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# Pubertal timing is associated with white matter microstructure and mental health during adolescence

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## Abstract

# Background

Puberty is a period of increased risk for mental health problems, particularly among early maturing youth. However, underlying neurobiological mechanisms remain unclear. This study examined longitudinal associations between pubertal timing, white matter (WM) microstructure and mental health.

# Methods

The analytical samples between comprised 6,370 and 3,350 participants from the Adolescent Brain Cognitive Development Study. Pubertal timing was estimated by regressing chronological age from pubertal development scores. Mixed-effects models tested associations between pubertal timing and WM restriction spectrum imaging (RSI) metrics (hindered normalized total [HNT], restricted normalized isotropic [RNI], normalized directional [RND] diffusion), and mental health. Significant WM tracts were examined as potential mediators.

# Results

Earlier pubertal timing was associated with lower HNT and higher RNI in both sexes, particularly within limbic and projection tracts, mediating higher depressive and somatic symptoms in females. In males alone, earlier timing was associated with lower RND in commissural and limbic tracts but higher RND in a projection tract. WM change analysis showed that earlier pubertal timing in males was associated with greater decreases in HNT and greater increases in RNI and RND over time across multiple tracts, mediating links to lower attention and social difficulties. In females, earlier timing was associated with greater increases in RNI and smaller increases in RND.

# Conclusion

Earlier pubertal timing was associated with sex-specific alterations in WM microstructure that partially explained links to mental health. While WM alterations mediated risk for internalising symptoms in females, they mediated lower attention and social difficulties in males, highlighting divergent neurodevelopmental pathways.

## Introduction

Adolescence, the transitional phase between childhood and adulthood, is a developmentally sensitive period with profound physical, cognitive, social and emotional changes. While most individuals successfully progress through adolescence, there is a sharp rise in the prevalence of mental health problems during this period [1, 2]. This emergence of mental health problems has drawn attention to the

role of pubertal development. In particular, early pubertal timing, defined as maturation occurring earlier than that of sex- and age-matched peers, has been consistently linked with increased risk for mental health problems, particularly internalising problems such as depression and anxiety [3–7].

This vulnerability may arise in part from pubertal hormonal influences on brain development during adolescence [8, 9]. Converging neuroimaging evidence demonstrates that adolescence is marked by continued refinement of white matter (WM) architecture extending into early adulthood [10], driven by coordinated processes including myelination, axonal remodelling, and synaptic pruning [11–13]. These microstructural changes support the maturation of distributed neural circuits implicated in emotional, cognitive, and behavioural regulation, processes that are highly relevant to the emergence of adolescent psychopathology.

Building on this framework, neuroimaging studies have illustrated WM changes as adolescents progress through puberty, including the microstructure of association and limbic tracts such as the superior and inferior longitudinal fasciculi and the uncinate fasciculus - pathways that support language, visuospatial processing, and emotion regulation [14–16]. However, studies directly examining individual differences in pubertal timing, rather than pubertal stage, remain limited, and findings are mixed. For example, one study identified higher fractional anisotropy (FA) and lower mean diffusivity (MD) in select tracts in earlier maturing females [17], whereas another study with a large-sample failed to identify significant associations between pubertal timing and diffusion tensor imaging (DTI) metrics across major WM pathways [18]. This scarcity of WM studies examining the effects of pubertal timing, as opposed to pubertal stage, has also been noted in a recent systematic review of puberty and brain development [19].

These inconsistencies may reflect limitations of conventional DTI metrics, which lack the specificity to identify underlying WM features, and are sensitive to fibre crossings and tissue heterogeneity [20]. More advanced diffusion models, including neurite sensitive approaches have illustrated changes to WM microstructure during puberty, particularly in association and commissural tracts [21–23]. One such neurite-sensitive approach, restriction spectrum imaging (RSI), decomposes the diffusion signal into restricted directional (RND), restricted isotropic (RNI), and hindered (HNT) diffusion compartments. These compartments are thought to reflect oriented neurite structures, isotropically restricted intracellular diffusion, and extracellular diffusion, respectively, providing greater microstructural specificity than conventional DTI metrics. Across adolescence, RND and RNI generally increase, while HNT decreases, consistent with ongoing WM maturation [24]. However, there has not been any prior research into how RSI metrics are associated with pubertal status or timing. Further, a recent systematic review suggested that no existing study has examined the interplay between pubertal timing, WM microstructure, and mental health outcomes, underscoring a critical gap that the current study directly addresses [25].

These limitations are compounded by the predominance of cross-sectional designs, with limited and mixed longitudinal evidence [26–30]. While some longitudinal studies have failed to identify associations between pubertal development and changes in WM microstructure [29, 30], others have demonstrated

region- and sex-specific associations between pubertal development and WM maturation [27]. Most longitudinal studies have also relied on conventional DTI metrics [26–29] with limited application of advanced diffusion models [30]. Critically, no longitudinal studies have directly examined whether pubertal timing relates to changes in WM microstructure and subsequent mental health problems.

To address these gaps, the current study aimed to characterise the early and developmental consequences of pubertal timing for white matter (WM) microstructure and mental health. First, prospective WM analyses examined whether pubertal timing in late childhood predicted WM microstructure assessed at a subsequent (single) timepoint in early adolescence, which was in turn related to later mental health problems, providing insight into the early neural correlates of maturation. Second, prospective WM change analyses investigated whether pubertal timing in late childhood was associated with subsequent longitudinal changes in WM microstructure across two timepoints in early adolescence, and whether these changes predict later mental health problems, thereby capturing neurodevelopmental mechanisms.

## Methods

# Participants

The current study used data from the ABCD Study [31] which consists of ~ 11,868 participants aged between 9–10 years at baseline (52% male). The ABCD Study is an ongoing longitudinal study of adolescent development in the United States, with annual behavioural and biennial imaging data collection across 21 sites.

In the current study, participants were included in the dataset based on ABCD recommended diffusion MRI quality control criteria. Of this dataset, those with missing non-imaging data, biologically implausible body mass index (BMI) values and diffusion MRI harmonisation issues were excluded (see Fig. S1 for details).

## Prospective WM Analysis Sample

In the prospective WM analyses, data was used on puberty from baseline to wave 6 to estimate timing at ~ 10.5 years of age, WM microstructure from the 2-year follow-up (at ~ 12 years of age), and mental health problems from 3-year follow-up (at ~ 13 years of age). The 3-year timepoint was selected as the earliest available mental health assessment following the WM microstructure measurement, minimising the interval between brain and mental health assessment while preserving the study's prospective temporal design. Refer to Fig. 1a for a visual representation.

After applying inclusion and exclusion criteria, the final prospective WM sample consisted of 6,370 participants (54% male; Fig. S1). Detailed demographic characteristics across study waves are presented in Table S1.

## Prospective WM Change Analysis Sample

In the prospective WM change analyses, data was used on puberty from baseline to wave 6 to estimate timing at ~ 10.5 years of age, WM microstructure from the 2-year and 4-year follow-up to examine WM change from ~ 12 to ~ 14 years of age, and mental health problems from 5-year follow-up (~ 15 years of age). This timepoint was chosen as the earliest available mental health assessment following the second WM measurement. Refer to Fig. 1b for a visual representation.

The final prospective WM change sample included 3,350 participants (55% male; Fig. S1). Detailed demographic characteristics across study waves are presented in Table S2.

To assess potential selection bias arising from these exclusions, baseline characteristics of the full cohort were compared against the final analytic sample (Table S4 for the prospective WM sample; Table S5 for the prospective WM change sample).

## Measures

# Pubertal Developmental Scale (PDS)

The PDS measures the physical characteristics of pubertal maturation, including growth spurt, skin change, and pubic hair growth for both males and females; vocal modification and facial hair growth in males; and breast development and menarche in females using a 4-point Likert scale. An overall PDS score is calculated by averaging the 5 physical characteristics for each sex [32]. Although both self- and parent-reported PDS were available, the current study used the parent-reported measure due to potentially lower accuracy from young adolescents [33].

# Mental health problems

Mental health problems were assessed using the parent-reported raw Child Behavior Checklist (CBCL) scores [34]. All eight CBCL subscales were examined in this study: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behaviour, and aggressive behaviour.

## Covariates

Details regarding covariates included in the analyses (i.e., race/ethnicity, area deprivation index and BMI) are provided in the supplementary materials.

## MRI acquisition and preprocessing

White matter microstructure was assessed using restriction spectrum imaging (RSI) derived from diffusion MRI. Further details of MRI acquisition and preprocessing are provided in supplementary

methods. RSI metrics included restricted isotropic diffusion (RNI), restricted directional diffusion (RND), and hindered normalized diffusion (HNT), reflecting neurite density, axonal organisation, and extracellular diffusion respectively. WM tracts were defined using AtlasTrack probabilistic segmentation, and mean RSI values were extracted within each tract (see Table S3 & Supplementary Methods).

# Statistical analysis

# Pubertal timing estimation

The PDS, measured from baseline to 6-year follow-up, was used to calculate pubertal timing. Pubertal timing was estimated using a linear mixed-effects model in R Statistical Software (v4.4.2; R Core Team 2021) using the *lme4* package [35]. Predicted PDS scores were modelled as a function of age and age², with a random intercept for participant ID (PDS ~ age + age² + (1|ID)). Age was centred at 10.5 years (to ensure that estimated timing was below the youngest age at the 2-year MRI assessment), and separate models were fit for males and females. The estimated random intercepts, extrapolated at age 10.5, indexed pubertal timing with higher values reflecting earlier-than-average development relative to same-sex peers.

# Analytical Overview

All statistical analyses followed a hierarchical structure with three levels of covariate adjustment and were fit separately for males and females. The unadjusted model included only the predictor of interest together with random intercepts for site and family, to account for clustering of participants within sites and relatedness among siblings. The minimally adjusted model, which served as the primary model for interpretation, additionally controlled for race/ethnicity and SES, and included dMRI motion when WM metrics were the outcome. This model was prioritised because it adjusts for key demographic confounders while minimising the risk of overadjustment from variables that may lie on the causal pathway between pubertal timing, brain development, and mental health problems [36]. The fully adjusted model further included BMI assessed at mean age ~ 10.95 (1 year follow-up wave). Primary results from the minimally adjusted model are presented in the main text, while estimates from the unadjusted and fully adjusted models are reported in the Supplementary Information (Fig. S4 & S5). To account for multiple comparisons, associations involving WM tracts were corrected separately for each RSI metric using the Benjamini-Hochberg false discovery rate (FDR-corrected $p < 0.05$).

# Prospective WM analysis

Analyses were conducted using linear mixed-effects models, with separate models for each WM tract and metric. As a first step, we examined normative age-related changes in WM microstructure (refer to Supplementary Information Results section and Fig. S2 & S3). Next, the primary models examined the association between pubertal timing and WM microstructure (i.e., WM ~ timing).

# Prospective WM change analysis

Prospective WM change analysis, followed an analogous framework but focused on WM change. For each WM tract, an annualised change score was computed as the difference between values at the 4-year and 2-year follow-ups divided by the corresponding difference in age. Linear mixed-effects models were then used to assess the association between pubertal timing and subsequent WM change (i.e., WM change ~ timing).

# Pubertal timing, WM microstructure, and mental health

Mediation analyses were conducted to assess whether WM microstructure mediated associations between pubertal timing and CBCL outcomes. First, we examined associations between timing and CBCL outcomes using linear mixed effects models, with separate models for each outcome (i.e., CBCL ~ timing). Because CBCL outcomes were positively skewed, they were modelled using a Poisson distribution.Only WM tracts and CBCL outcomes (refer to Supplementary Information 'Results' section) showing significant associations with pubertal timing in the 'minimally adjusted' models were included in mediation analyses, with separate models for each tract (per metric). Mediation models additionally adjusted for baseline CBCL scores to account for prior mental health problems. Analyses were conducted using the *brms* package in a joint Bayesian framework [37], with each WM tract as a Gaussian mediator and the corresponding CBCL outcome as a Poisson outcome (priors, sampling, and convergence checks are reported in the Supplementary Methods). Indirect effects were estimated by multiplying posterior samples of the pubertal timing→WM path (a-path) and the WM→CBCL path (b-path), generating a posterior distribution whose 95% credible interval provided the inferential basis for mediation [38]. The robustness of the indirect effects were further tested using a stricter 99% interval, computed from the same posterior draws as the primary 95% intervals. Indirect effects whose 99% interval also excluded zero were considered robust.

## Results

# Association between pubertal timing and white-matter microstructure

# Prospective WM analyses

Figure 2 illustrates tract-wise associations between pubertal timing and WM microstructure. Across both sexes, earlier pubertal timing was associated with lower HNT and higher RNI diffusion. These effects were the strongest in limbic tracts for HNT and in both limbic and projection tracts for RNI. In males, earlier pubertal timing was associated with lower RND in the corpus callosum (CC), forceps major (Fmaj), and bilateral fornix (Fx), but higher RND in the left inferior longitudinal fasciculus (ILF). No significant RND associations were observed in females.

# Prospectivc WM change analyses

Prospective WM change analyses revealed stronger and more widespread associations in males than in females. In males, earlier pubertal timing was associated with greater decreases in HNT and greater increases in RNI and RND across multiple tracts, with effects most prominent in commissural, limbic, and projection pathways, indicating widespread alterations in both extracellular and intracellular diffusion properties (Fig. 3 & S6). In females, earlier pubertal timing was associated with greater increases in RNI across a small number of tracts and smaller increases in RND, particularly in the bilateral inferior fronto-occipital fasciculi (IFO) (Fig. 3 & S7).

# Mediation analyses

Pubertal timing was associated with depressive and somatic problems in females at the 3rd year follow-up, and social and attention problems in males at the 5th year follow-up (see Supplementary Results and Fig. S8). WM metrics identified above were examined as potential mediators of these associations.

# Prospective WM mediation

There were significant indirect effects of pubertal timing on later mental health problems via WM microstructure in females alone (based on 95% credible intervals). Higher RNI in the left CgC and CgH, and right ATR and pSCS mediated associations between earlier pubertal timing and greater depressive problems. Additionally, higher RNI in the bilateral ATR and CC, right SIFC, and left UNC mediated associations between earlier pubertal timing and greater somatic problems (Fig. 4 & S9). Two of these nine effects, both for somatic problems (bilateral ATR), remained robust at the 99% interval (Fig. S9).

# Prospective WM change mediation

There were significant indirect effects of pubertal timing on later mental health problems through changes in WM microstructure in males alone (based on 95% credible intervals). Greater decreases in HNT across 12 tracts and seven tracts mediated associations between earlier pubertal timing and lower attention and social difficulties, respectively. Greater increases in RNI across three tracts and nine tracts mediated associations between earlier pubertal timing and lower attention and social difficulties, respectively. Additionally, greater increases in RND in the right pSLF and tSLF mediated the association between earlier pubertal timing and lower attention problems (Fig. 5, S10 & S11). Twenty-two of these 33 effects remained robust at the 99% interval: 10 of 17 for attention problems and 12 of 16 for social difficulties, including all seven HNT effects for social difficulties (Fig. S10 & S11).

## Discussion

The current study examined the associations between pubertal timing and WM using neurite sensitive restriction spectrum imaging (RSI), and tested whether pubertal timing–related microstructural differences mediated the associations with subsequent mental health problems. Overall, earlier pubertal timing was associated with widespread alterations in WM microstructure and its development during early adolescence, with evidence that effects differed by sex. These microstructural differences were

most evident in RSI compartments of limbic and projection tracts, and were partially implicated in pathways linking earlier pubertal timing to mental health problems.

# Associations between pubertal timing and white-matter microstructure

Across both sexes, earlier pubertal timing was associated with lower HNT and higher RNI across multiple WM tracts. This diffusion profile, characterised by lower extracellular diffusion and greater intracellular restricted diffusion, is consistent with previous findings using alternate diffusion methods [17, 27]. Importantly, these effects were not spatially uniform but were most prominent within limbic and projection tracts, including pathways connecting subcortical and cortical regions implicated in affective processing and regulatory control [39]. Limbic tracts such as the cingulum and fornix, as well as projection pathways including thalamic radiations, are known to undergo substantial reorganisation during early adolescence and are particularly sensitive to hormonal influences [19, 40]. The patterns of lower HNT and higher RNI were also identified with increasing age in our analyses (see Supplementary 'Results' and Fig. S2) and in prior research [24], suggesting that earlier pubertal timing may be associated with a relative acceleration of these developmental processes. Although this pattern likely reflects normative neurobiological maturation occurring earlier rather than atypical development per se, this temporal shift may have functional consequences. Specifically, earlier maturation of these tracts may alter their coordination with other brain systems whose development are more strongly shaped by age and experiences rather than pubertal processes, potentially leading to asynchrony in network-level communication and increasing vulnerability to mental health problems.

In contrast to the HNT and RNI, associations between pubertal timing and RND were only observed in males, with mixed directionality across tracts. RND is thought to reflect directionally-constrained intracellular diffusion and may be particularly sensitive to axonal coherence, calibre, and fibre organisation [41]. Although RND showed positive age-related associations across all tracts, earlier pubertal timing was associated with lower RND in commissural and limbic tracts but higher RND in the ILF, suggesting that pubertal timing may differentially influence the pace or pattern of axonal maturation across WM systems. Specifically, earlier timing may reflect accelerated maturation in the ILF, while associations in commissural and limbic tracts may indicate altered or less coherent axonal development relative to normative age-related increases. These male-specific effects may reflect differential sensitivity of axonal refinement processes to sex hormones, particularly androgens, which have been implicated in shaping axonal growth, pruning, and myelination trajectories [40, 42].

# Effects of pubertal timing on white-matter change

Analyses revealed more pronounced and widespread associations between pubertal timing and WM microstructural change in males than in females. Earlier pubertal timing in males predicted greater reductions in HNT alongside greater increases in RNI and RND across multiple tracts, indicating greater increase in intracellular diffusion compartments relative to extracellular diffusion over early

adolescence. In males, these effects were most prominent in commissural, limbic, and projection pathways, suggesting that pubertal timing influences both interhemispheric integration and cortical-subcortical connectivity. Notably, these patterns were generally consistent with normative age-related developmental effects observed across the same tracts, suggesting that earlier pubertal timing may reflect accelerated WM maturation in males. In females, associations were more localised, with earlier timing linked to microstructural change primarily in association pathways, namely the bilateral IFO, potentially reflecting earlier consolidation of specific long-range connectivity patterns. Unlike the male findings, these effects were not paralleled by significant age-related changes in the same tracts, making it difficult to determine whether they reflect accelerated normative maturation or more tract-specific developmental variation. These sex-specific effects are consistent with prior work linking pubertal timing to WM development, though the present findings extend this literature in important ways. Previous studies have linked earlier pubertal timing with increased WM organisation in projection and association tracts [17, 30], although null findings have also been reported, potentially due to limited pubertal variability or reduced sensitivity of conventional DTI metrics [29].

# Pubertal timing, mental health, and neurobiological mechanisms

Mediation analyses indicated that pubertal timing–related differences in white-matter microstructure partly accounted for associations with mental health outcomes. Among females, earlier pubertal timing was associated with greater depressive and somatic symptoms via altered microstructural properties within limbic and corticostriatal pathways, characterised by increased RNI. These tracts, including the cingulum and thalamic radiations, play central roles in emotion regulation, interoceptive processing, and stress responsivity, and undergo substantial reorganisation during early adolescence [14, 27, 43]. While the indirect effects for depressive symptoms should be interpreted cautiously as they were not robust to more stringent credible intervals, the overall pattern suggests that earlier pubertal maturation may be accompanied by advanced or temporally shifted microstructural organisation within affective salient networks, which is associated with heightened internalising symptom burden [44].

In contrast, among males, changes in WM microstructure mediated associations between earlier pubertal timing and lower attention and social difficulties. These effects were characterised primarily by greater decreases in HNT and increases in RNI and RND across widespread commissural, projection, and association pathways, including the corpus callosum, corticospinal tracts, superior longitudinal fasciculus, IFO, and corticostriatal projections. Collectively, these tracts support cognitive control, attentional regulation, sensorimotor integration, and social-cognitive processing, and continue to mature substantially across adolescence [14, 45]. The pattern of greater reductions in extracellular diffusion alongside increases in intracellular diffusion compartments may reflect accelerated or more efficient WM maturation in earlier maturing males, potentially supporting improved attentional and social functioning during early adolescence. These findings are consistent with past studies suggesting that puberty may differentially shape developmental adaptation depending on sex, developmental context, and the neural systems undergoing maturation [14, 46].

Taken together, the mediation findings revealed distinct developmental pathways linking pubertal timing to mental health outcomes in males and females. Earlier pubertal timing was associated with greater internalising symptoms in females, but lower attention and social difficulties in males. One potential explanation is that the implicated pathways differed substantially between sexes: mediation effects in females were concentrated within limbic and corticostriatal circuits involved in emotion regulation and stress responsivity, whereas effects in males were observed across widespread association, projection, and commissural pathways supporting cognitive control, attentional processes, and social functioning. These findings suggest that accelerated maturation may not be uniformly beneficial or detrimental, but rather its consequences depend on both the neural systems and the developmental context in which maturation occurs. More broadly, the contrasting patterns observed in males and females highlight the need for sex-specific developmental frameworks in both research and public health practice. As, pubertal timing has shifted earlier at the population level in many countries [47], a more nuanced understanding of pubertal maturation may help identify adolescents who are most likely to benefit from additional support, while recognising that earlier maturation may confer both vulnerabilities and potential advantages depending on the individual and developmental domain under consideration.

# Strengths and Limitations

A key strength of the present study is the use of RSI metrics, which allows dissociation of extracellular and intracellular diffusion processes to reveal nuanced associations that are not readily detectable using conventional DTI measures. This highlights the potential utility of RSI for advancing our mechanistic understanding of adolescent brain development and its relevance for socioemotional development and mental health outcomes. A few limitations should be noted. Pubertal timing (PDS) and mental health (CBCL) relied on parent report rather than self- or clinician-report, which may limit precision and introduce informant bias, particularly underestimating internalising symptoms that are less externally observable. We also cannot rule out residual confounding that may have influenced findings, such as individual-level childhood adversities.

The final samples differed from excluded participants in sex and race/ethnicity (both samples) and in age, BMI, and SES (prospective WM sample; Tables S4, S5). Although age, race/ethnicity and SES were accounted for and analyses were stratified by sex, the samples may not fully represent the original cohort. Finally, the median age of onset for anxiety and mood disorders is 17 (IQR 9–25 and 31 (IQR 21–46), respectively [2]; thus, a substantial share of pubertal timing effects on internalising risk may only emerge following the window of measurement in this study.

Thus, important future directions for clarifying the influence of pubertal timing on neurodevelopmental trajectories and psychiatric risk includes using additional imaging waves to model non-linear trajectories, accounting for further confounds such as childhood adversities, and examining mental health outcomes in later adolescence.

# Conclusions

This study demonstrates that pubertal timing is associated with distinct patterns of WM microstructure during early adolescence, as indexed by RSI metrics, and that these differences show meaningful associations with mental health problems. While WM alterations partially account for some pubertal timing-mental health associations, effects were modest. Associations also varied by sex, indicating differences in how pubertal timing relates to neurodevelopmental trajectories. These findings highlight puberty as a key period of neurobiological reorganisation and underscore the importance of considering developmental stage.

## Declarations

# Declaration of Competing Interest

The authors declare no competing interests.

# Author Contribution

S.B., N.V., T.J.S. and S.W. conceptualised and designed the study. S.B. processed the data, performed the statistical analyses, prepared all figures and tables, and wrote the main manuscript text. N.V., T.J.S. and S.W. supervised the project and provided guidance on study design, analysis and interpretation of the findings. A.B., S.C.L. and S.A. contributed to the analysis and interpretation of the findings through regular discussion. All authors reviewed the manuscript.

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# Data Availability

Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive Development (ABCD) Study, held in the NIH Brain Development Cohorts Data Sharing Platform. This is a multisite longitudinal study designed to recruit more than 10,000 children age 9-10 and follow them over 10 years into early adulthood. The ABCD Study is supported by the National Institutes of Health and additional federal partners under award numbers U01DA041048, U01DA050989, U01DA051016, U01DA041022, U01DA051018, U01DA051037, U01DA050987, U01DA041174, U01DA041106, U01DA041117, U01DA041028, U01DA041134, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051038, U01DA041148, U01DA041093, U01DA041089, U24DA041123, U24DA041147. A full list of supporters is available at Federal Partners – ABCD Study. A listing of participating sites and a complete listing of the study investigators can be found at the Complete ABCD Roster. ABCD consortium investigators designed and implemented the study and/or

provided data but did not necessarily participate in the analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators. The ABCD data repository grows and changes over time. The ABCD data used in this report came from NIMH Data Archive Digital Object Identifier (DOI): 10.15154/z563-zd24. DOIs can be found at https://nda.nih.gov/study.html?id=2313.

# References


1. Piao J, Huang Y, Han C, Li Y, Xu Y, Liu Y, He X (2022) Alarming changes in the global burden of mental disorders in children and adolescents from 1990 to 2019: a systematic analysis for the Global Burden of Disease study. Eur Child Adolesc Psychiatry 31(11):1827–1845. https://doi.org/10.1007/s00787-022-02040-4
2. Solmi M, Radua J, Olivola M, Croce E, Soardo L, Salazar de Pablo G, Fusar-Poli P (2022) Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. Mol Psychiatry 27(1):281–295. https://doi.org/10.1038/s41380-021-01161-7
3. Conley CS, Rudolph KD, Bryant FB (2012) Explaining the Longitudinal Association between Puberty and Depression: Sex Differences in the Mediating Effects of Peer Stress. Dev Psychopathol 24(2):691–701. https://doi.org/10.1017/S0954579412000259
4. Ge X, Natsuaki MN (2009) In Search of Explanations for Early Pubertal Timing Effects on Developmental Psychopathology. Curr Dir Psychol Sci 18(6):327–331. https://doi.org/10.1111/j.1467-8721.2009.01661.x
5. Graber JA (2013) Pubertal timing and the development of psychopathology in adolescence and beyond. Horm Behav 64(2):262–269. https://doi.org/10.1016/j.yhbeh.2013.04.003
6. Hamilton JL, Hamlat EJ, Stange JP, Abramson LY, Alloy LB (2014) Pubertal timing and vulnerabilities to depression in early adolescence: differential pathways to depressive symptoms by sex. J Adolesc 37(2):165–174. https://doi.org/10.1016/j.adolescence.2013.11.010
7. Hamlat EJ, Snyder HR, Young JF, Hankin BL (2019) Pubertal Timing as a Transdiagnostic Risk for Psychopathology in Youth. Clin Psychol Sci 7(3):411–429. https://doi.org/10.1177/2167702618810518
8. Blakemore S, Burnett S, Dahl RE (2010) The role of puberty in the developing adolescent brain. Hum Brain Mapp 31(6):926–933. https://doi.org/10.1002/hbm.21052
9. Goddings A-L, Beltz A, Peper JS, Crone EA, Braams BR (2019) Understanding the Role of Puberty in Structural and Functional Development of the Adolescent Brain. J Res Adolescence 29(1):32–53. https://doi.org/10.1111/jora.12408
10. Bethlehem RaI, Seidlitz J, White SR, Vogel JW, Anderson KM, Adamson C, Alexander-Bloch AF (2022) Brain charts for the human lifespan. Nature 604(7906):525–533. https://doi.org/10.1038/s41586-022-04554-y
11. Cooke BM, Woolley CS (2009) Effects of prepubertal gonadectomy on a male-typical behavior and excitatory synaptic transmission in the amygdala. Dev Neurobiol 69(2–3):141–152.

https://doi.org/10.1002/dneu.20688

12. Laube C, van den Bos W, Fandakova Y (2020) The relationship between pubertal hormones and brain plasticity: Implications for cognitive training in adolescence. Dev Cogn Neurosci 42:100753. https://doi.org/10.1016/j.dcn.2020.100753
13. Liu, Y., Rutlin, M., Huang, S., Barrick, C. A., Wang, F., Jones, K. R., … Ginty,D. D. (2012). Sexually Dimorphic BDNF Signaling Directs Sensory Innervation of the Mammary Gland. *Science (New York, N.Y.)*, *338*(6112), 10.1126/science.1228258. https://doi.org/10.1126/science.1228258
14. Asato MR, Terwilliger R, Woo J, Luna B (2010) White Matter Development in Adolescence: A DTI Study. Cereb Cortex (New York NY) 20(9):2122–2131. https://doi.org/10.1093/cercor/bhp282
15. Herting MM, Maxwell EC, Irvine C, Nagel BJ (2012) The Impact of Sex, Puberty, and Hormones on White Matter Microstructure in Adolescents. Cereb Cortex 22(9):1979–1992. https://doi.org/10.1093/cercor/bhr246
16. Menzies L, Goddings A-L, Whitaker KJ, Blakemore S-J, Viner RM (2015) The effects of puberty on white matter development in boys. Dev Cogn Neurosci 11:116–128. https://doi.org/10.1016/j.dcn.2014.10.002
17. Chahal R, Vilgis V, Grimm KJ, Hipwell AE, Forbes EE, Keenan K, Guyer AE (2018) Girls' pubertal development is associated with white matter microstructure in late adolescence. NeuroImage 181:659–669. https://doi.org/10.1016/j.neuroimage.2018.07.050
18. MacSweeney, N., Allardyce, J., Edmondson-Stait, A., Shen, X., Casey, H., Chan, S.W. Y., … Whalley, H. C. (2023). The role of brain structure in the association between pubertal timing and depression risk in an early adolescent sample (the ABCD Study®):A registered report. *Developmental Cognitive Neuroscience*, *60*, 101223. https://doi.org/10.1016/j.dcn.2023.101223
19. Piekarski DJ, Colich NL, Ho TC (2023) The effects of puberty and sex on adolescent white matter development: A systematic review. Dev Cogn Neurosci 60:101214. https://doi.org/10.1016/j.dcn.2023.101214
20. Figley CR, Uddin MN, Wong K, Kornelsen J, Puig J, Figley TD (2022) Potential Pitfalls of Using Fractional Anisotropy, Axial Diffusivity, and Radial Diffusivity as Biomarkers of Cerebral White Matter Microstructure. Front NeuroSci 15:799576. https://doi.org/10.3389/fnins.2021.799576
21. Chahal R, Delevich K, Kirshenbaum JS, Borchers LR, Ho TC, Gotlib IH (2021) Sex Differences in Pubertal Associations with Fronto-accumbal White Matter Morphometry: Implications for Understanding Sensitivity to Reward and Punishment. *NeuroImage*, *226*, 117598. https://doi.org/10.1016/j.neuroimage.2020.117598
22. Genc S, Seal ML, Dhollander T, Malpas CB, Hazell P, Silk TJ (2017) White matter alterations at pubertal onset. NeuroImage 156:286–292. https://doi.org/10.1016/j.neuroimage.2017.05.017
23. Genc S, Raven EP, Drakesmith M, Blakemore S-J, Jones DK (2023) Novel insights into axon diameter and myelin content in late childhood and adolescence. Cereb Cortex (New York NY) 33(10):6435–6448. https://doi.org/10.1093/cercor/bhac515

24. Palmer, C. E., Pecheva, D., Iversen, J. R., Hagler, D. J., Sugrue, L., Nedelec, P.,… Dale, A. M. (2022). Microstructural development from 9 to 14 years: Evidence from the ABCD Study. *Developmental Cognitive Neuroscience*, *53*, 101044. https://doi.org/10.1016/j.dcn.2021.101044
25. Kretzer, S., Lawrence, A. J., Pollard, R., Ma, X., Chen, P. J., Amasi-Hartoonian,N., … Dazzan, P. (2024). The Dynamic Interplay Between Puberty and Structural Brain Development as a Predictor of Mental Health Difficulties in Adolescence: A Systematic Review. *Biological Psychiatry*, *96*(7), 585–603. https://doi.org/10.1016/j.biopsych.2024.06.012
26. Herting MM, Gautam P, Spielberg JM, Kan E, Dahl RE, Sowell ER (2014) The role of testosterone and estradiol in brain volume changes across adolescence: A longitudinal structural MRI study. Hum Brain Mapp 35(11):5633–5645. https://doi.org/10.1002/hbm.22575
27. Herting MM, Kim R, Uban KA, Kan E, Binley A, Sowell ER (2017) Longitudinal changes in pubertal maturation and white matter microstructure. Psychoneuroendocrinology 81:70–79. https://doi.org/10.1016/j.psyneuen.2017.03.017
28. Ho TC, Colich NL, Sisk LM, Oskirko K, Jo B, Gotlib IH (2020) Sex differences in the effects of gonadal hormones on white matter microstructure development in adolescence. Dev Cogn Neurosci 42:100773. https://doi.org/10.1016/j.dcn.2020.100773
29. Frere, P. B., Vetter, N. C., Artiges, E., Filippi, I., Miranda, R., Vulser, H., …Lemaître, H. (2020). Sex effects on structural maturation of the limbic system and outcomes on emotional regulation during adolescence. *NeuroImage*, *210*, 116441. https://doi.org/10.1016/j.neuroimage.2019.116441
30. Genc S, Malpas CB, Gulenc A, Sciberras E, Efron D, Silk TJ, Seal ML (2020) Longitudinal patterns of white matter fibre density and morphology in children are associated with age and pubertal stage. Dev Cogn Neurosci 45:100853. https://doi.org/10.1016/j.dcn.2020.100853
31. Casey, B. J., Cannonier, T., Conley, M. I., Cohen, A. O., Barch, D. M., Heitzeg,M. M., … ABCD Imaging Acquisition Workgroup. (2018). The Adolescent Brain Cognitive Development (ABCD) study: Imaging acquisition across 21 sites. *Developmental Cognitive Neuroscience*, *32*, 43–54. https://doi.org/10.1016/j.dcn.2018.03.001
32. Petersen AC, Crockett L, Richards M, Boxer A (1988) A self-report measure of pubertal status: Reliability, validity, and initial norms. J Youth Adolesc 17(2):117–133. https://doi.org/10.1007/BF01537962
33. Rasmussen, A. R., Wohlfahrt-Veje, C., Tefre de Renzy-Martin, K., Hagen, C. P., Tinggaard,J., Mouritsen, A., … Main, K. M. (2015). Validity of self-assessment of pubertal maturation.*Pediatrics*, *135*(1), 86–93. https://doi.org/10.1542/peds.2014-0793
34. Achenbach TM, Rescorla L (2001) Child behavior checklist for ages 6–18. University of Vermont Burlington, VT
35. Bates D, Mächler M, Bolker B, Walker S (2015) Fitting Linear Mixed-Effects Models Using lme4. J Stat Softw 67:1–48. https://doi.org/10.18637/jss.v067.i01
36. Schisterman EF, Cole SR, Platt RW (2009) Overadjustment Bias and Unnecessary Adjustment in Epidemiologic Studies. Epidemiol (Cambridge Mass) 20(4):488–495.

https://doi.org/10.1097/EDE.0b013e3181a819a1

37. Bürkner P-C (2017) brms: An R Package for Bayesian Multilevel Models Using Stan. J Stat Softw 80:1–28. https://doi.org/10.18637/jss.v080.i01
38. Gelman A, Jakulin A, Pittau MG, Su Y-S (2008) A weakly informative default prior distribution for logistic and other regression models. Annals Appl Stat 2(4):1360–1383. https://doi.org/10.1214/08-AOAS191
39. Casey BJ, Heller AS, Gee DG, Cohen AO (2019) Development of the Emotional Brain. Neurosci Lett 693:29–34. https://doi.org/10.1016/j.neulet.2017.11.055
40. Herting MM, Sowell ER (2017) Puberty and structural brain development in humans. Front Neuroendocr 44:122–137. https://doi.org/10.1016/j.yfrne.2016.12.003
41. White NS, Leergaard TB, D'Arceuil H, Bjaalie JG, Dale AM (2012) Probing tissue microstructure with restriction spectrum imaging: Histological and theoretical validation. Hum Brain Mapp 34(2):327–346. https://doi.org/10.1002/hbm.21454
42. Perrin, J. S., Hervé, P.-Y., Leonard, G., Perron, M., Pike, G. B., Pitiot, A., …Paus, T. (2008). Growth of White Matter in the Adolescent Brain: Role of Testosterone and Androgen Receptor. *The Journal of Neuroscience*, *28*(38), 9519–9524. https://doi.org/10.1523/JNEUROSCI.1212-08.2008
43. Lebel C, Deoni S (2018) The Development of Brain White Matter Microstructure. NeuroImage 182:207–218. https://doi.org/10.1016/j.neuroimage.2017.12.097
44. Ordaz, S. J., LeMoult, J., Colich, N. L., Prasad, G., Pollak, M., Popolizio, M.,… Gotlib, I. H. (2017). Ruminative brooding is associated with salience network coherence in early pubertal youth. *Social Cognitive and Affective Neuroscience*, *12*(2), 298–310. https://doi.org/10.1093/scan/nsw133
45. Luna B, Padmanabhan A, O'Hearn K (2010) What has fMRI told us about the Development of Cognitive Control through Adolescence? Brain Cogn 72(1):101–113. https://doi.org/10.1016/j.bandc.2009.08.005
46. Giedd, J. N., Clasen, L. S., Lenroot, R., Greenstein, D., Wallace, G. L., Ordaz,S., … Chrousos, G. P. (2006). Puberty-related influences on brain development. *Molecular and Cellular Endocrinology*, *254–255*, 154–162. https://doi.org/10.1016/j.mce.2006.04.016
47. Farello G, Altieri C, Cutini M, Pozzobon G, Verrotti A (2019) Review of the Literature on Current Changes in the Timing of Pubertal Development and the Incomplete Forms of Early Puberty. Front Pead 7:147. https://doi.org/10.3389/fped.2019.00147

# Figures

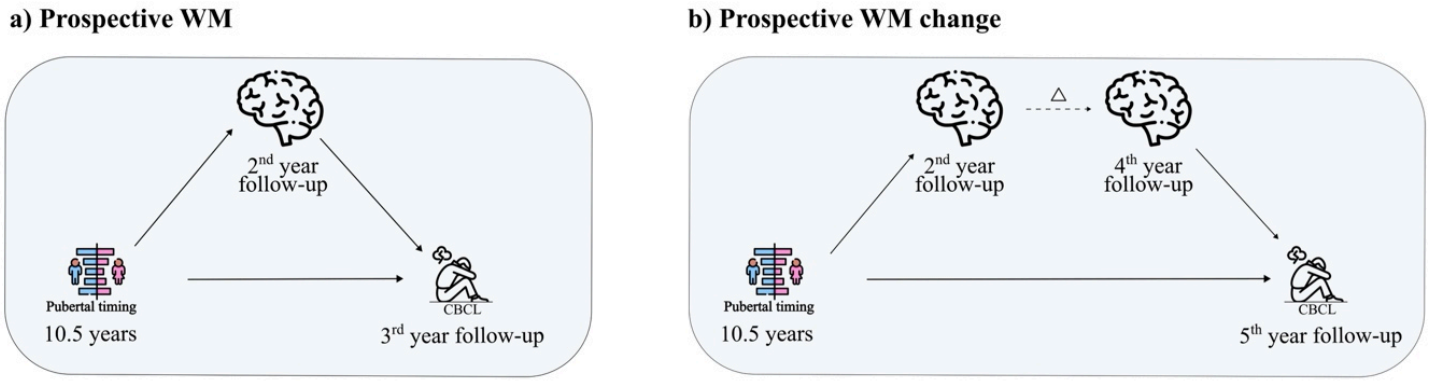


**Figure 1**

Schematic of study design illustrating prospective WM and prospective WM change analyses.

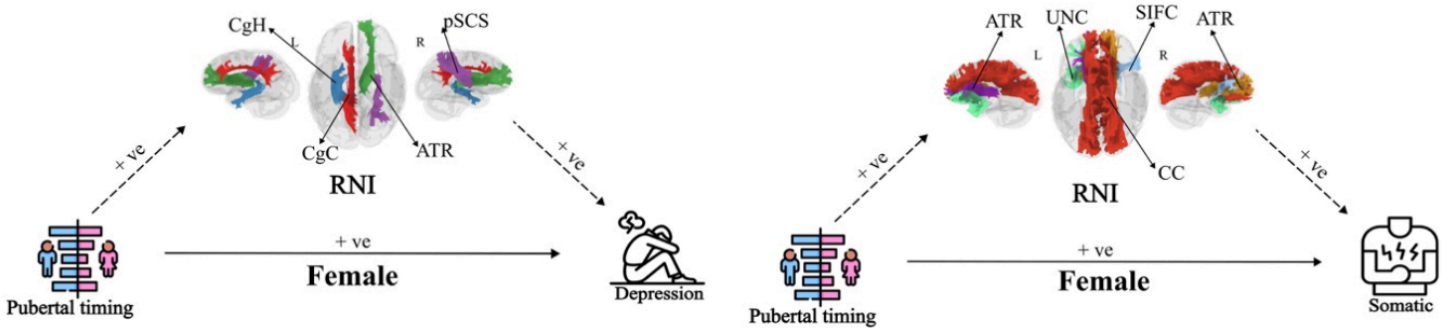


**Figure 4**

Prospective WM mediation analyses of pubertal timing, white matter (WM) microstructure, and mental health problems. Only mediation pathways reaching statistical significance are shown. Arrows represent the direct effect of pubertal timing on mental health outcomes. Abbreviations: RNI- restricted isotropic diffusion; L- left; R- right

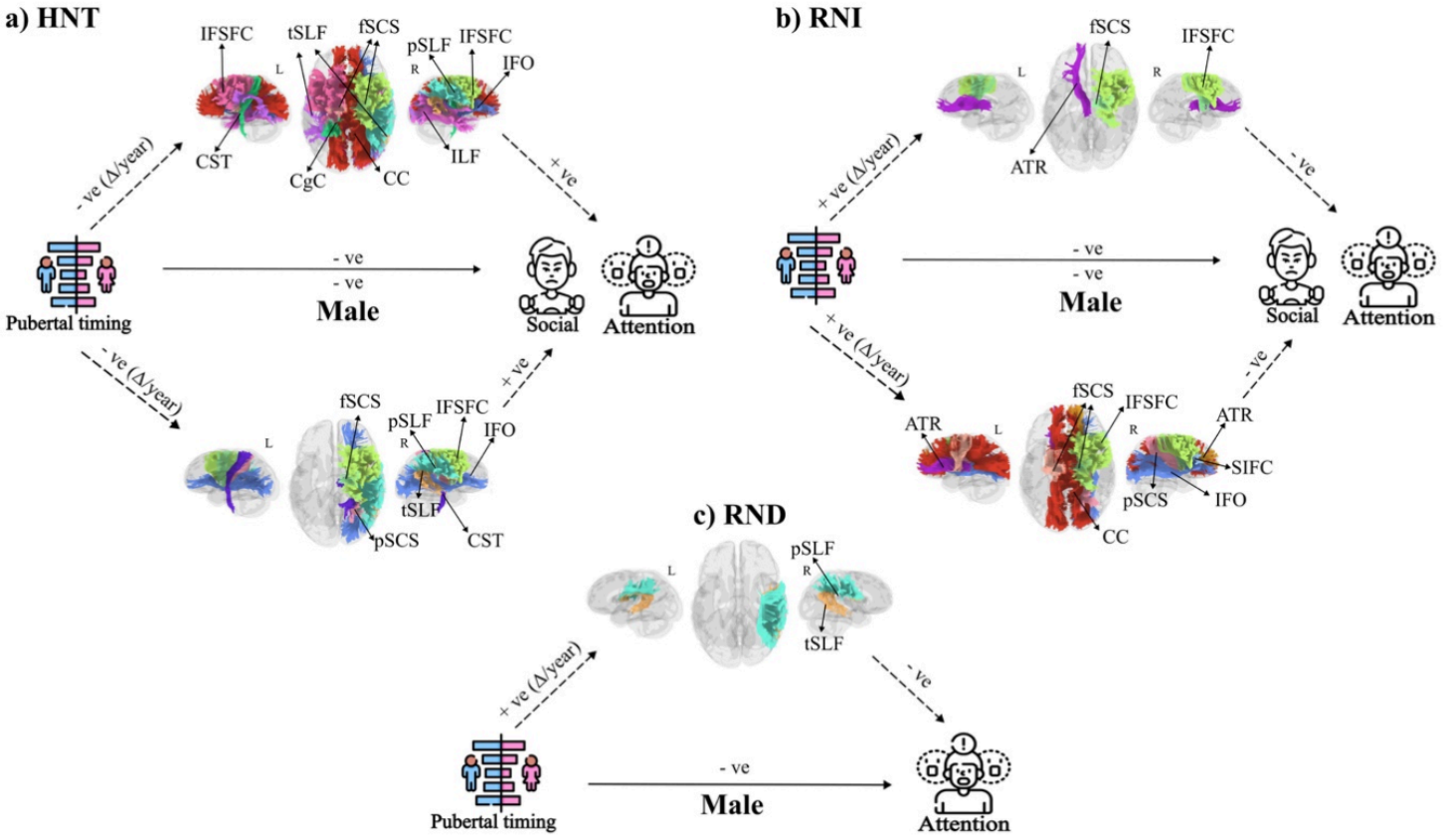


**Figure 5**

Prospective WM change mediation analyses of pubertal timing, white matter (WM) microstructure change, and mental health problems. Only mediation pathways reaching statistical significance are shown. Arrows represent the direct effect of pubertal timing on mental health outcomes. Abbreviations: HNT- hindered normalized total diffusion; RND- restricted directional diffusion; RNI- restricted isotropic diffusion; L- left; R- right

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