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# Developmental correlates of accelerated molar eruption in early childhood

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## Abstract

*Background.* Adversity has been linked to accelerated maturation. Molar eruption is a simple and scalable way to identify early maturation, but its developmental correlates remain unexplored. Thus, we examined whether accelerated maturation, as indexed by molar eruption, is associated with children's mental health or cognitive skills.

*Methods.* Molar eruption was evaluated from T2-weighted MRIs in 117 children (63 female, 4-7-years old). Parents reported on mental health with the Child Behavior Checklist. Children completed standardized assessments of fluid reasoning, working memory, processing speed, crystallized knowledge, and math performance. Relationships between molar eruption and developmental outcomes were examined using linear models, with age, gender, and stress risk as covariates.

*Results*. Earlier molar eruption was positively associated with children's externalizing symptoms ($P_{FDR}$ = .027), but not internalizing symptoms, and the relationship did not hold when controlling for stress risk. Earlier molar eruption was negatively associated with fluid reasoning ($P_{FDR}$ < .001), working memory ($P_{FDR}$ = .033), and crystallized knowledge ($P_{FDR}$ = .001). The association between molar eruption and both reasoning and crystallized knowledge held controlling for stress risk. Molar eruption also partially mediated associations between stress risk and both reasoning (proportion mediated = 0.273, $P$ = 0.004) and crystallized knowledge (proportion mediated = 0.126, $P$ = 0.016).

*Conclusions.* Accelerated maturation, as reflected in early molar eruption, may have consequences for cognitive development, perhaps because it constrains brain plasticity. Knowing the pace of a child's maturation may provide insight into the impact of a child's stress history on their cognitive development.

## Introduction

Children who mature too quickly are more likely to experience mental health challenges, including externalizing problems such as aggression and delinquency (1–3), and internalizing problems, including depression and anxiety disorders (4–8). Early adversity, including low socioeconomic status and exposure to adverse childhood experiences (ACEs), is a major risk factor for accelerated maturation of the body (9–15) and brain (16–20). According to evolutionary theories (21,22), accelerated development may represent an adaptive trade-off in harsh environments, as it can lead to earlier attainment of adult-like abilities and increased reproductive fitness, but at the cost of later health. Multiple theories have been put forth to explain the relationship between accelerated development and psychopathology (23). First, early-maturing children may show a mismatch between their and physical and social-cognitive development, leading peers and adults to place unwarranted expectations of socioemotional maturity onto early physically-maturing children (1,5,24). Second, early cortical thinning in brain regions that support functions such as emotion regulation (18) and attention (3) may disrupt the development of these skills. It is also possible that mental health symptoms like increased attention to threat (25) can contribute to faster maturation through physiological processes such as oxidative stress and inflammation (26,27). Finally, accelerated maturation and psychopathology could both be downstream effects of early adversity with no causal links between them.

Accelerated maturation has been measured in a number of ways, including pubertal timing and epigenetic age. Existing methods of detecting accelerated maturation can be costly and difficult to obtain at scale (e.g., DNA methylation), or cannot be detected until later in adolescence (e.g., pubertal timing). As a result, associations between early maturation and mental health or other important developmental outcomes in early childhood have been less well established (7). Identifying developmental risk earlier in childhood can provide opportunities for intervention before the full symptom consequences are realized. In response to these challenges, we have put forth a new scalable biomarker of accelerated maturation: molar eruption (28).

The first permanent molars erupt around age 6, before puberty begins, and are easier and less expensive to assess than epigenetic or brain age. Molar eruption is typically characterized through radiographs and dental exams obtained through routine dental care, and can also be captured in existing magnetic resonance imaging (MRI) datasets. Using MRI, we found that children from lower-income backgrounds and children with more ACEs show earlier permanent molar eruption than their more advantaged peers (28). We also observed differences in molar eruption timing by race/ethnicity (28,29), which are consistent with pervasive racial disparities in income and other contextual stressors that have roots in structural racism. We replicated associations between molar eruption and income in a large epidemiological dataset with dental exam data (30), and further showed that second molar eruption was correlated with menarche

status in girls (28). A recent unpublished finding supported the stress-sensitivity of dental milestones: children with higher salivary cortisol had lost more of their primary teeth (31). Thus, the timing of dental development may serve as an early indicator of a broad pattern of stress-accelerated maturation. It remains unknown, however, whether molar eruption is associated with important developmental outcomes.

In addition to mental health consequences, early maturation may have consequences for cognitive development. Complex cognitive skills including reasoning and working memory develop slowly, perhaps because the brain networks that support them require extended environmental input to reach optimal configurations (32,33). A faster pace of brain development may shorten windows of peak neuroplasticity, reducing the brain's sensitivity to future experiences (34). Reduced plasticity as a consequence of accelerated maturation may have negative implications for cognition and learning. In line with this hypothesis, slower structural brain development is associated with higher general intelligence (35). Additionally, one recent study found that children with a faster pace of epigenetic aging demonstrated lower scores on tests of verbal intelligence and perceptual reasoning (36). If accelerated molar eruption is indicative of a broader pattern of accelerated brain development following stress exposure, we may expect earlier molar eruption to be associated with lower cognitive skills.

In this study, we examine how accelerated maturation, as indexed by molar eruption, is associated with mental health and cognition in childhood. To test associations between maturation and mental health, we examine parent report of internalizing and externalizing symptoms. To test associations between maturation and cognition, we explore five cognitive tests: reasoning, working memory, processing speed, crystallized knowledge, and math performance. We examine associations between each developmental domain and molar eruption status characterized from T2-weighted MRI. We test associations between maturation and developmental outcomes with and without controlling for measures of stress risk. Additionally, we assess whether accelerated maturation mediates the relationship between stress risk and developmental outcomes. In sum, we examine whether molar eruption is a marker of developmental risk above and beyond stress exposure, as children differ in how their brains and bodies respond to stress (37).

## Methods and Materials

*Participants*. This study was approved by the Institutional Review Board at the University of Pennsylvania. All parents provided written informed consent. Children and parents were recruited from the greater Philadelphia area as part of two larger neuroimaging studies. Participants were recruited through advertisements on public transportation, partnerships with local schools, outreach programs, community family events, and social media ads. Participants were screened and excluded from the studies if they had a diagnosed psychiatric, neurological, or

learning disorder, were born more than six weeks premature, were adopted, or had any contraindications for MRI scanning. These exclusions were put into place because associations between the environment, molar eruption, and developmental outcomes might be different in children with diagnoses than they are in typically developing children.

*Molar Eruption.* A detailed description of the molar eruption scale and rating procedure, as well as example scans, can be found in McDermott et al. (2021). Molar eruption was rated from each subject's raw T2-weighted MRI scan by a dental student (K.H.) at the University of Pennsylvania School of Dental Medicine, in consultation with a faculty member (M.M.) with expertise in oral and maxillofacial radiology. They developed a novel scale for classifying molar eruption status in MRI, which was based on previous experience in dental imaging, and similar to other fine-grained dental scales (38), which rely on dental radiographs. The eruption status of each first permanent molar was rated on a scale from 1 (unerupted) to 4 (fully erupted; see Supplemental Methods for further information).

The eruption status of all four first molars was averaged to create a single continuous molar eruption variable that was used in analyses. We analyzed molar eruption data from 117 participants (54 male/63 female) between ages 4.05 and 7.32 years (28). This final sample size was obtained after excluding 3 subjects who had extremely delayed molar eruption (Cook's Distance > 4/N for the molar eruption by age regression), and restricting analyses to include only subjects within the range for which there was variability in molar eruption, as we preregistered (https://osf.io/2edyx). For visualization purposes (Figures 1 and 2) and inclusion in a zero-order correlation table (Table S2), we created an adjusted molar eruption variable by regressing age and gender on molar eruption status, and extracting the residuals. Positive molar eruption residuals indicate accelerated molar eruption relative to chronological age.

*Psychiatric Symptoms.* In one of the two neuroimaging studies included in the current sample, parents ($n$ = 80) completed the Child Behavior Checklist (CBCL) to identify behavioral and emotional problems (39,40). Parents of children under age 6 years old completed the preschool version of the CBCL, and parents of children ages 6 and above completed the school-age version of the CBCL. We initially preregistered analyzing the three 'AAA' subscales which are shared between the two CBCL versions: Aggressive Behavior, Anxious/Depressed, and Attention Problems (https://osf.io/2edyx). However, based on the distribution of the data (Figure S1), we decided to analyze the more commonly used internalizing and externalizing subscales, which we initially planned as exploratory analyses. T-scores for these composite scales were used in all analyses.

*Cognitive Assessment*. To assess cognition, we administered four subtests from the Wechsler Preschool & Primary Scale of Intelligence (WPPSI-IV) (41): Matrix Reasoning ($n$ = 116), Picture Memory ($n$ = 106), Bug Search ($n$ = 76), and Information ($n$ = 115). Missing subtest

scores are due to differences in study protocols, administration errors, or lack of child understanding or compliance. Children ages 5 and up also completed the Numeration subtest of the KeyMath-3 Diagnostic Assessment ($n$ = 80) (42). Matrix Reasoning is a measure of fluid reasoning that requires children to select missing pieces to complete a visual pattern. Picture Memory is a measure of working memory in which children must memorize and then identify pictures. Bug Search measures processing speed by requiring children to scan and mark simple visual information. Information consists of general, crystallized knowledge questions. Finally, Numeration measures the child's understanding of number concepts. Scaled scores were used in all analyses.

*Covariates*. Parents reported their child's date of birth, gender, race and ethnicity, family income, and exposure to Adverse Childhood Experiences (ACEs). Age and gender were included as covariates in all analyses of molar eruption, as molar eruption shows strong relationships with both (age: $\beta$ = 0.842, 95% CI [0.743, 0.942], $P$ < 0.001; gender: $\beta$ = 0.349, 95% CI [0.159, 0.539], $P$ < 0.001, controlling for age) (28). Poverty, ACEs, and racism-based stress are all environmental risk factors which can contribute to chronic stress and increase biological aging (28,43,44). In order to streamline analyses, we used exploratory factor analysis (EFA) to generate a single score representing stress risk, which we use as a covariate and as the exposure variable in mediation analyses.

Parents were asked to indicate each of the following race categories that applied to their child: American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; white; or Other. Parents were separately asked to indicate whether their child was Hispanic or Latino (Table S1). For our factor analysis, in order to capture risk for racism-based stress, we recoded race and ethnicity into two categories: a racial/ethnic majority group (non-Hispanic white; $n$ = 36, 31%) and a racial/ethnic minority group ($n$ = 81, 69%). Parents reported their total annual family income in one of 11 income bins (less than $5,000; $5000-$11,999; $12,000-$15,999; $16,000-$24,999; $25,000-$34,999; $35,000-$49,999; $50,000-$74,999; $75,000-$99,999; $100,00-$149,999; $150,000-$199,999; and $200,000 or greater). Annual family income was estimated as the median value of each income bracket. Family income in this sample ranged from $2,500 to $200,000 (Mean = $80,051, SD = $66,735, $n$ = 108; Table S1). For context, the median income of Philadelphia County during the years of this study was $49,127 (45). Parents completed the child version of the ACEs questionnaire (46), which asks parents about their child's lifetime experiences with ten types of experiences with household dysfunction, parent separation, abuse, and neglect. An ACEs score is calculated by summing the binary responses to each of the ten items. ACEs in this sample ranged from 0 to 7 (Mean = 1.0, SD = 1.3, $n$ = 111; Table S1). For the factor analysis, ACEs were grouped into three bins: 0 ACEs ($n$ = 52, 47%), 1 ACE ($n$ = 36, 32%), and 2 or more ACEs ($n$ = 23, 21%). It is possible that parents fail to report ACE exposure because they did not witness events, do not remember events, or do not want to disclose sensitive data to researchers. We minimize the last

possibility by allowing parents to complete questionnaires privately on iPads, and ensuring that they understand that data are de-identified. Despite these limitations, parent-report is the most standard way of reporting ACEs (47), and is less intrusive and time consuming than other possible methods, including requesting sensitive health and Child Protective Service records. Furthermore, the rates of exposure to ACEs that we observe in our data are consistent with the national prevalence of ACEs among children in this age range. Nationally, 65% of children under the age of 5 have experienced no ACEs, and 52% of children between the ages of 6 and 11 years have experienced no ACEs (48).

To generate a single variable capturing children's stress risk, we conducted a one-factor EFA of income, ACEs, and race (as a proxy for racism-based stress), using the 'psych' package in R (49). All three variables showed acceptable loadings onto the single factor (income: $\lambda = 0.92$, ACEs: $\lambda = -0.37$, race: $\lambda = 0.71$). Individual factor scores extracted from the EFA were reverse coded, so that a higher score represents greater purported stress risk (i.e., lower income, more ACEs, and non-white race). Greater stress risk was significantly associated with earlier eruption of the first permanent molars ($\beta = 0.163$, 95% CI [0.072, 0.254], $P = .001$).

*Statistical Analyses*. We examined associations between molar eruption and developmental outcomes using linear regression in R. All analyses included age and gender as covariates, as molar eruption shows strong relationships with both (28,29). Missing data were handled by complete case analysis within each model. First, we tested the association between CBCL internalizing and externalizing symptoms and molar eruption. We re-ran both regressions with the factor score of stress risk as a covariate. Next, we tested associations between each cognitive test and molar eruption, and again re-ran each regression with stress risk as a covariate. We report standardized effect sizes for independent variables, obtained by running the linear models after centering and scaling all variables. To correct for multiple comparisons, we used the Benjamini-Hochberg false discovery rate (FDR) (50). FDR correction was applied separately 1) across the two CBCL composite scales, 2) across all five cognitive tests. FDR correction was also applied separately for models with and without controlling for stress risk.

Next, we conducted mediation analyses to investigate whether molar eruption mediates the associations between the early environment and developmental outcomes. Because our data is cross-sectional and observational, we cannot draw causal conclusions from a mediation analysis; instead, we ran these analyses to understand whether accelerated maturation explains variance in the relationship between environmental measures and developmental outcomes. We used the R 'mediation' package for causal mediation analysis (51), with stress risk as the independent variable, and each cognitive test as the dependent variable. We first tested associations between stress risk and cognition, and then conducted mediation analyses for cognitive tests that were significantly related to stress risk. The *mediate()* function estimates the average causal mediation effect (ACME) and the average direct effect (ADE), which together sum to the total effect of the

independent variable on the dependent variable. The proportion mediated, which we report, represents the size of the ACME relative to the total effect.

**Results**

Children with accelerated molar maturation showed more externalizing symptoms (Table S3, Figure 1, $\beta$ = 0.545, 95% CI [0.117, 0.973], $P$ = .013, FDR-corrected $P$ = 0.027). Internalizing symptoms were not related to molar eruption (Table S3, Figure 1, $\beta$ = 0.283, 95% CI [-0.192, 0.758], $P$ = .239, FDR-corrected $P$ = 0.239). The association between molar eruption and externalizing symptoms was no longer significant after controlling for stress risk (FDR-corrected $P$ = 0.069).

Accelerated molar eruption was also associated with lower performance on tests of fluid reasoning (Table S4, Figure 2A, WPPSI-IV Matrix Reasoning, $\beta$ = -0.707, 95% CI [-1.052, -0.362], $P$ < .001, FDR-corrected $P$ < .001), working memory (Figure 2B, WPPSI-IV Picture Memory, $\beta$ = -0.459, 95% CI [-0.843, -0.075], $P$ = .020, FDR-corrected $P$ = 0.033), and crystallized knowledge (Figure 2D, WPPSI-IV Information, $\beta$ = -0.634, 95% CI [-0.984, -0.284], $P$ < .001, FDR-corrected $P$ = 0.001). Molar eruption was marginally associated with math performance (Figure 2E, KeyMath-3 Numeration, $\beta$ = -0.339, 95% CI [-0.696, 0.018], $P$ = .062, FDR-corrected $P$ = 0.078), and was not associated with processing speed (Figure 2C, WPPSI-IV Bug Search, $\beta$ = 0.049, 95% CI [-0.369, 0.468], $P$ = .816). Associations between molar eruption status and fluid reasoning held controlling for stress risk (Table S4, $\beta$ = -0.561, 95% CI [-0.916, -0.206], $P$ = .002, FDR-corrected $P$ = 0.011). Molar eruption was also associated with crystallized knowledge after controlling for stress risk ($\beta$ = -0.402, 95% CI [-0.738, -0.066], $P$ = .019, FDR-corrected $P$ = 0.049). Associations between molar eruption and working memory, math performance, and processing speed were not significant after adding stress risk to the models (Table S4).

Finally, we explored relationships among stress, cognition, and accelerated maturation by investigating whether molar eruption mediated associations between stress risk and cognition. Mediation was tested for developmental outcomes which were significantly related to the stress risk factor score. Stress risk was not associated with internalizing or externalizing behavior, or with processing speed ($P$s > 0.05). Higher stress risk was significantly related to performance on fluid reasoning ($\beta$ = -0.322, 95% CI [-0.498, -0.147], $P$ < .001), working memory ($\beta$ = -0.292, 95% CI [-0.478, -0.106], $P$ = .002), crystallized knowledge ($\beta$ = -0.473, 95% CI [-0.637, -0.309], $P$ < .001), and math performance ($\beta$ = -0.444, 95% CI [-0.646, -0.242], $P$ < .001), and thus we tested whether molar eruption mediated these associations. Molar eruption partially mediated the relation between stress risk and both fluid reasoning (proportion mediated = 0.273, $P$ = 0.004; Figure 3) and crystallized knowledge (proportion mediated = 0.126, $P$ = 0.016; Figure 3), but not

the relations between stress risk and working memory ($P$ = 0.172), or math performance ($P$ = 0.491).

## Discussion

Molar eruption timing, characterized by MRI, showed significant associations with mental health and cognition in early childhood. Specifically, children with earlier molar eruption demonstrated higher externalizing problems, and lower performance on assessments of fluid reasoning, crystallized knowledge, and working memory. Fluid reasoning and crystallized knowledge remained significantly related to molar eruption after controlling for a composite factor of stress risk variables, suggesting that understanding a child's maturational state may provide unique predictive power for the development of reasoning skills and acquisition of crystallized knowledge. Furthermore, molar eruption significantly mediated the associations between stress risk and both fluid reasoning and crystallized knowledge. Though we cannot draw causal conclusions using cross-sectional observational data, these findings are broadly consistent with the hypothesis that early adversity can accelerate maturational processes in the brain, leading to reduced plasticity, and negatively impacting cognition and learning.

We observed the strongest relationship between early maturation and fluid reasoning. There are multiple reasons why fluid reasoning may show the strongest relationship with accelerated development after controlling for stress exposure variables. Fluid reasoning may depend most strongly on generating novel ideas and thinking flexibly, and therefore may be most sensitive to overly stabilized neural networks. Fluid reasoning may also be less dependent than crystallized skills on income-related experiences other than stress, like language and explicit instruction. It is also possible that associations between accelerated development and domains of cognition will shift across development. Fluid reasoning predicts change over time in crystallized abilities and academic knowledge (52), and the strength of association between fluid reasoning and academic skills increases with age (53). Given this complex developmental cascade of cognitive skills, we may expect accelerated maturation to be predictive of different cognitive domains at different ages.

We did not find a significant association between molar eruption and either processing speed or math performance. Processing speed is supported by white matter maturation (54), as myelination increases action potential conduction speed. On the other hand, processing speed performance also relies on attention and inhibitory control (55), which can be impaired by early life stress (56). If accelerated structural brain development increases conduction speed but limits attentional control, there may be no observed association between accelerated maturation and processing speed. We also did not observe strong associations between molar eruption and math performance. Of note, the math assessment was only scaled for children ages 5 years and up, and processing speed was only administered to a subgroup of participants, and thus both subtests had

a reduced sample size. Math performance in this age range may also be more strongly driven by explicit instruction in the home that may vary by family income. Future longitudinal research is needed to explore whether associations between accelerated maturation and cognition vary across development.

Finally, we observed a significant association between molar eruption and children's externalizing problems, though this association did not hold when controlling for a composite factor capturing stress risk. This finding is in contrast with studies showing a correspondence between accelerated maturation and both internalizing and externalizing problems in adolescence (1,57–59). There are several possible explanations for our limited mental health findings. First, the CBCL was only administered in one of the two studies included in this sample, so analyses of mental health included a smaller sample than analyses of cognition. Second, we relied on parent report of child symptoms. Childhood externalizing behaviors are more salient to observers, and thus parents can be more reliable at reporting externalizing than internalizing problems (60). Further, the majority of psychiatric illnesses peak in onset in adolescence (61), and thus the mental health consequences of accelerated maturation may not emerge until later in development. Our results suggest that cognitive vulnerability associated with accelerated maturation may precede mental health vulnerability, though future longitudinal research is needed to further explore this developmental cascade.

This study has a number of limitations. First, our data are cross-sectional, and thus we cannot make conclusions about whether early maturation constrains cognitive development or mental health over time. Future longitudinal research is needed to illuminate co-occurring trajectories of physical maturation, cognitive development, and mental health. It is possible that poor mental health or cognitive difficulties lead to accelerated maturation (27), or that there are reciprocal interactions between the pace of maturation and health across the lifespan. Second, this study assessed a limited selection of cognitive measures. It is possible that accelerated maturation plays an adaptive or protective role for other skills that we did not measure, such as fear conditioning (62). Third, we cannot directly compare how molar eruption is related to mental health versus cognition, as the two sets of developmental outcomes were measured with different methods (parent-report versus direct assessment). Fourth, it is important to note that observed associations between molar eruption and cognition are neither diagnostic nor deterministic. Early maturation does not guarantee cognitive or mental health challenges, and future work is needed before conclusions can be drawn about the utility of dental development as a screening tool for cognitive risk. Molar eruption is also not the mechanism linking stress exposure and cognition, but rather a putative biomarker of the impact of a child's experiences on their development. Fifth, there may be other pathways besides psychosocial stress that link income, ACEs, and race with the timing of molar eruption. Finally, future research is needed to establish the mechanisms of accelerated dental development, and the extent to which molar eruption timing is predictive of accelerated maturation across other domains, such as epigenetic aging or brain age.

Despite these limitations, this work provides insight into the potential developmental consequences of accelerated maturation. Children vary greatly in how they perceive, internalize, and respond to stressors in their lives (37). Thus, knowing the pace or status of a child's maturation may reflect the developmental impact of their stress history above what can be measured by 'objective' questionnaires alone. There are several important future directions for this research. First, it is unknown to what extent a child's maturational trajectory is established early in life or even prenatally (63), or can be recalibrated across development. Understanding when a child's maturational trajectory is established, and perhaps whether there are variable sensitive periods across biological domains, may inform decisions about intervention timing. Though a reduced plasticity account may suggest that children who develop faster would be less responsive to interventions, some interventions have instead found that the most academically at-risk children benefit the most (64,65). Thus, it is important to understand whether children who are growing up more quickly are more, or less, likely to benefit from educational or psychosocial interventions. Overall, our results suggest that dental milestones may make an important contribution towards a holistic understanding of risk and resilience during child development.

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**Figure Legends**

**Figure 1.** Scatterplots show relationships between adjusted molar eruption and parent-reported (A) externalizing problems and (B) internalizing problems. Positive molar eruption residuals indicate accelerated molar eruption relative to chronological age and gender.

**Figure 2.** Scatterplots show relationships between adjusted molar eruption and scaled scores on cognitive tests of (A) fluid reasoning, (B) working memory, (C) processing speed, (D) crystallized knowledge, and (E) math performance. Positive molar eruption residuals indicate accelerated molar eruption relative to chronological age and gender.

**Figure 3.** Causal mediation analyses. Accelerated maturation, as indexed by molar eruption, partially mediates the associations between stress risk and both fluid reasoning and crystallized knowledge. ACME: average causal mediation effect; ADE: average direct effect.

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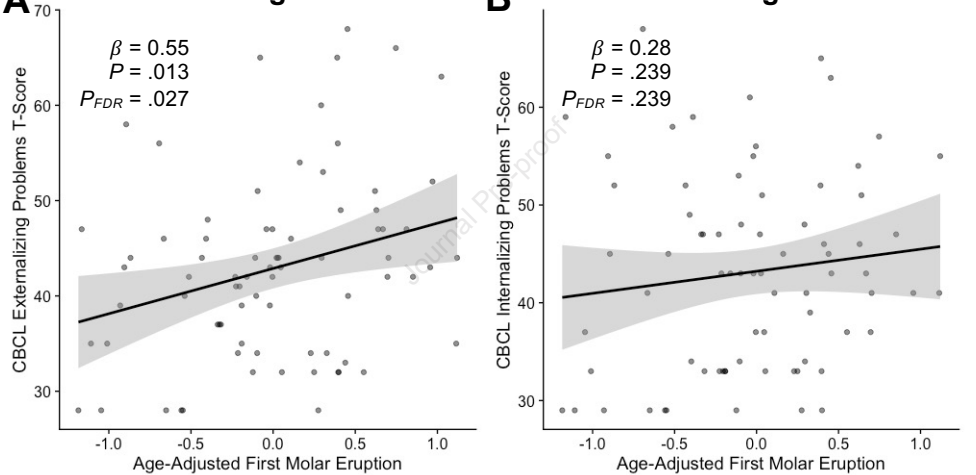
Journal Pre-proof


A
Externalizing Problems
β = 0.55
P = .013
PFDR = .027
CBCL Externalizing Problems T-Score
70
60
50
40
30
-1.0
-0.5
0.0
0.5
1.0
Age-Adjusted First Molar Eruption
B
Internalizing Problems
β = 0.28
P = .239
PFDR = .239
CBCL Internalizing Problems T-Score
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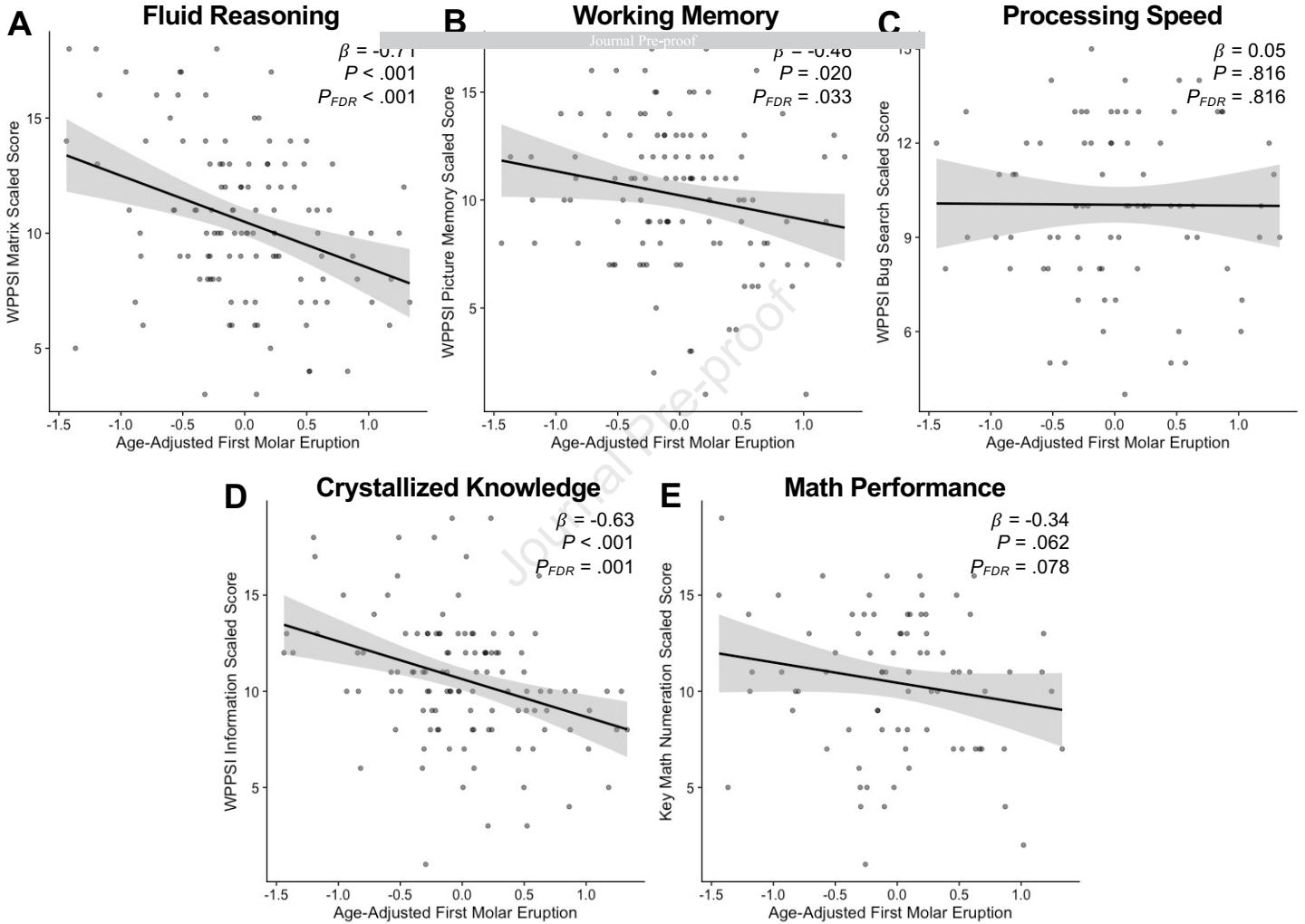
Age-Adjusted First Molar Eruption

Journal Pre-proof



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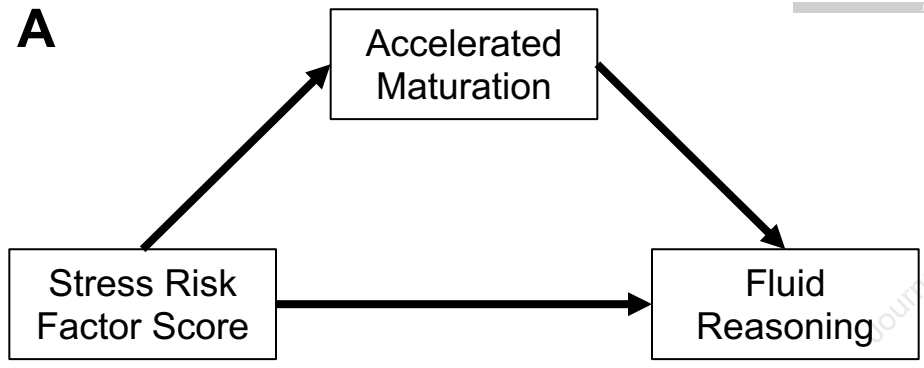
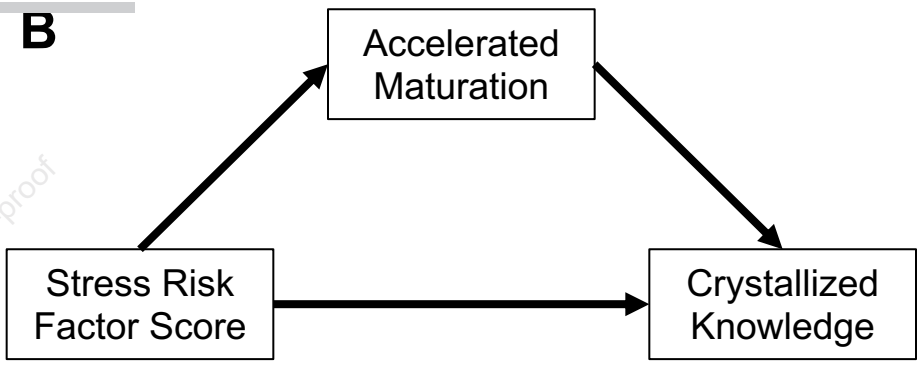



ACME = -0.090 (*P* = 0.003)
ADE = -0.235 (*P* = 0.012)
**Proportion mediated = 27%**




ACME = -0.061 (*P* = 0.016)
ADE = -0.402 (*P* < 0.001)
**Proportion mediated = 13%**