Accelerated Pubertal Development as a Transdiagnostic Mechanism linking Childhood Trauma with Multiple Forms of Adolescent-Onset Psychopathology

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Abstract

Although early life adversity (ELA) increases risk for psychopathology, mechanisms linking ELA with the onset of psychopathology remain poorly understood. Conceptual models have argued that ELA accelerates development. It is unknown whether all forms of ELA are associated with accelerated development or whether early maturation is a potential mechanism linking ELA with the onset of psychopathology. We examine whether two distinct dimensions of ELA – threat and deprivation – have differential associations with pubertal timing in girls, and evaluate whether accelerated pubertal timing is a mechanism linking ELA with the onset of adolescent psychopathology.

Data were drawn from a large, nationally representative sample of 4,937 adolescent girls. Multiple forms of ELA characterized by threat and deprivation were assessed along with age at menarche (AAM) and onset of DSM-IV fear, distress, externalizing, and eating disorders.

Greater exposure to threat was associated with earlier AAM (B=-0.1, p=0.001). Each one-year increase in AAM was associated with reduced odds of fear, distress, and externalizing disorders post-menarche (ORs=0.74-0.85). Earlier AAM significantly mediated the association between exposure to threat and post-menarche onset of distress (proportion mediated=6.2%), fear (proportion mediated=16.3%), and externalizing disorders (proportion mediated=2.9%).

Accelerated pubertal development in girls may be one transdiagnostic pathway through which threat-related experiences confer risk for the adolescent onset of mental disorders. Early pubertal maturation is a marker that could be used in both medical and mental health settings to identify trauma-exposed youth that are at risk for developing a mental disorder during adolescence in order to better target early interventions.

Introduction

Early life adversity (ELA) refers to a broad set of negative experiences in childhood that are likely to require psychological or neurobiological adaptation and that represent a deviation from the expected early environment (McLaughlin, 2016). Exposure to ELA is associated with increased risk for psychopathology across the life-course (Green et al., 2010; McLaughlin et al., 2012). Despite the robust link between ELA and psychopathology, mechanisms linking ELA to the onset of psychopathology remain poorly understood. One potential mechanism is accelerated pubertal timing (one's stage of pubertal development relative to age-matched peers), given that exposure to ELA is associated with earlier pubertal onset (Ellis & Garber, 2000; Graber, Brooks-Gunn, & Warren, 1995), especially in girls (Joinson, Heron, Lewis, Croudace, & Araya, 2011; Mendle, Harden, Brooks-Gunn, & Graber, 2010). Although accelerated pubertal timing is associated with risk for a diverse set of mental disorders (Ullsperger & Nikolas, 2017), little research has directly examined whether early onset of puberty is a mechanism explaining elevated risk for psychopathology in youth who have experienced ELA (see Belsky, Ruttle, Boyce, Armstrong, & Essex, 2015; Mendle, Leve, Van Ryzin, & Natsuaki, 2014; Negriff, Saxbe, & Trickett, 2015 for work that has explored this idea). Accordingly, this study empirically examines alterations in pubertal timing as a mechanism through which ELA exposure confers risk for the onset of psychopathology during adolescence.

Extensions of life history theory to humans have posited that certain types of ELA may accelerate pubertal timing, in order to maximize reproduction prior to mortality (Belsky, Steinberg, & Draper, 1991; Ellis, Figueredo, Brumbach, & Schlomer, 2009). Specifically, ELA characterized by environmental harshness (e.g. trauma, violence exposure) is thought to accelerate pubertal timing (Belsky, 2012a; Ellis et al., 2009). Recent conceptual models have highlighted the importance of distinguishing between ELA experiences characterized by threat (i.e., experiences involving trauma/threat of harm to the child, such as abuse and exposure to violence) versus deprivation (i.e., experiences involving an absence of expected environmental inputs, such as physical and psychosocial neglect and food insecurity)

(Humphreys & Zeanah, 2015; McLaughlin & Sheridan, 2016; McLaughlin, Sheridan, & Lambert, 2014; Sheridan & McLaughlin, 2014). Experiences involving threat and deprivation have increasingly been shown to have unique consequences in the domains of emotion, cognition, and neural development (Busso, McLaughlin, & Sheridan, 2016; Dennison et al., 2017; Everaerd et al., 2016; Lambert, King, Monahan, & McLaughlin, 2017; Rosen, Sheridan, Sambrook, Meltzoff, & McLaughlin, 2018; Sheridan, Peverill, Finn, & McLaughlin, 2017), although it is unknown whether they have differential associations with pubertal timing. Harshness maps on well to the threat dimension of ELA, suggesting that experiences of threat may accelerate pubertal timing (Sung et al., 2016). However, it is unclear how experiences of deprivation align with life history theory; whereas nutritional deprivation/food insecurity and famine are thought to delay pubertal timing to ensure maximal bioenergetic resources should reproduction occur (Prebeg & Bralic, 2000; Rogol, Clark, & Roemmich, 2000; van Noord & Kaaks, 1991), specific predictions about psychosocial neglect are lacking. Determining whether accelerated pubertal timing is associated with exposure to ELA generally or with particular dimensions of ELA may help to elucidate specific psychobiological mechanisms underlying these associations (McLaughlin, 2016).

To date, few studies have empirically examined whether different dimensions of ELA have distinct associations with pubertal timing. Prior work examining the effects of specific types of adversity suggests that child abuse and family composition (such as absence of a biological father/presence of a step-father) are associated with earlier pubertal timing, particularly in females (i.e. Belsky et al., 2007; Ellis & Garber, 2000; Noll et al., 2017; Ryan, Mendle, & Markowitz, 2015). Less work has examined deprivation and pubertal timing (Belsky, 2012b; Ellis, 2004). Existing work typically finds no association between psychosocial neglect and pubertal timing (Mendle, Leve, Van Ryzin, Natsuaki, & Ge, 2011; Reid et al., 2017; Ryan et al., 2015), although two studies found an association between material deprivation as measured by socioeconomic status (SES) and accelerated pubertal timing (James-Todd, Tehranifar, Rich-Edwards, Titievsky, & Terry, 2010; Sun, Mensah, Azzopardi, Patton, & Wake, 2017). In contrast, studies of war and famine suggest that

severe deprivation can delay pubertal development (Prebeg & Bralic, 2000; van Noord & Kaaks, 1991). A central issue in most prior work on this topic is a failure to assess and adjust for co-occurring forms of ELA. Such an approach is critical when evaluating potential specificity in associations with pubertal timing, because experiences of ELA are highly co-occurring (Kessler et al., 2010; McLaughlin, Green, Gruber, et al., 2012). In a smaller community sample, we found that whereas exposure to threat-related ELA was associated with advanced pubertal stage, exposure to deprivation was associated with delayed pubertal stage, after controlling for experiences of threat (Sumner, Colich, Uddin, Armstrong, & McLaughlin, 2018). Inconsistencies in the prior literature exploring associations between ELA and pubertal timing may be due, in part, to lack of consideration of how different dimensions of environmental experience uniquely influence these associations.

Here we evaluate whether distinct dimensions of ELA—specifically, experiences of threat and deprivation—have differential associations with pubertal timing and whether accelerated pubertal timing is a mechanism linking ELA with the onset of psychopathology during adolescence. We examine these questions among a nationally representative sample of females, using age at menarche (AAM) as our marker of pubertal timing. We hypothesized that exposure to threat would be associated with earlier AAM. Given mixed findings regarding associations between deprivation and pubertal development, we did not expect to find associations between psychosocial and material deprivation and AAM. Building on prior work demonstrating that ELA and accelerated pubertal timing are associated with adolescent psychopathology (McLaughlin et al., 2012; Platt, Colich, McLaughlin, Gary, & Keyes, 2017), we expected that the association between exposure to threat and adolescent-onset mental disorders would be mediated by earlier AAM.

Methods

Sample

Data were from the National Comorbidity Survey Adolescence Supplement (NCS-A). As described elsewhere (Kessler, Avenevoli, Costello, et al., 2009b, 2009a) the NCS-A data were collected from 2001-2004. Adolescents aged 13-18 were interviewed face-to-face in

dual-frame household and school samples. See Supplementary Materials for more detail on sample selection.

The NCS-A sample includes 10,148 participants and 5183 females (51.1%). We focus here only on girls given the literature suggesting that the association between ELA and pubertal timing is stronger in girls, and because pubertal timing was measured only by AAM and no similar measure was available for males. Females with missing responses for AAM (n=83; 1.6%) and those who had not begun menstruating (n=163; 3.1%) were excluded from the analyses. The final sample size included is 4937 participants. See Table 1 for sample demographics.

Measures

Early Life Adversity. Exposure to ELA was assessed using both child interviews and parent self-administered questionnaires of 11 types of childhood adversity. Following prior work in this sample (McLaughlin, Green, Gruber, et al., 2012; Platt et al., 2018), threat-related adversities included 6 specific adversities including physical abuse, witnessing domestic violence, sexual assault, witnessing or being the victim of violence in the community, and emotional abuse. Deprivation-related adversities included 5 specific adversities including physical and psychosocial neglect, financial insecurity (i.e., family received money from a government assistant program), food insecurity, low parental education attainment (less than a high school degree), and household poverty (ratio of household income to poverty level <1.5). All adversities were coded dichotomously. We created a composite score for each dimension of adversity (threat and deprivation) by summing across all child- or parent-reports for each type of adversity. See Supplementary Materials for more information about measurement of ELA. We included poverty and low parental education as indicators of deprivation in our models, consistent with earlier work in this sample (Platt et al., 2018) and based on extensive evidence demonstrating that children from families with low parental education and/or income experience reductions in cognitive and social stimulation than children from higher-SES families (Bradley, Corwyn, Burchinal, McAdoo, & Garcia Coll, 2001; Duncan & Magnuson, 2012). However, poverty has also been

conceptualized as a risk factor for, rather than a direct marker of, deprivation (McLaughlin et al., 2014; Sheridan & McLaughlin, 2014). Results were consistent when we removed poverty and parental education from our deprivation composite, and we retain them in final models.

We evaluated whether associations of ELA with AAM and mental disorders were due to experiencing any threat or deprivation experience, and whether the effects were due to cumulative exposure to ELAs, measured by a count of the number of threat and deprivation experiences[a].

Age at menarche. AAM was assessed via self-report. Girls were asked the age at which they had their first period, in whole year increments. Responses ranged from 6-17 years of age (mean=12.10 years of age, median=12.0 years of age)[b]. AAM was modeled as a continuous variable. Interview-based assessments of AAM in adolescence have been shown to be acceptably reliable (Dorn, Sontag-Padilla, Pabst, Tissot, & Susman, 2013).

Mental Disorders. Adolescents were administered a modified version of the CIDI, a fully structured, valid and reliable interview administered by trained interviewers that assesses both lifetime and past-year DSM-IV disorders (Kessler, Avenevoli, Green, et al., 2009; Kessler & Üstün, 2004). Age-of-onset of each disorder was assessed using procedures shown experimentally to improve the accuracy of these reports (Knäuper, Cannell, Schwarz, Bruce, & Kessler, 1999). We used this information to determine whether a disorder onset was pre- or post-menarche. We examined fifteen adolescent disorders, and conducted a confirmatory factor analysis to reduce the data to four disorder groups based on prior work in this sample: fear disorders (panic disorder with/without agoraphobia, agoraphobia without panic disorder, social phobia, specific phobia), distress disorders (major depressive disorder/dysthymia, generalized anxiety disorder, post-traumatic stress disorder), externalizing disorders (oppositional defiant disorder, conduct disorder, alcohol abuse, drug abuse, tobacco abuse, [with or without dependence]), and eating disorders (anorexia,

[a] 22.4% of the sample experienced both a threat and deprivation-related adversity.
[b] Given the wide range of age of menarche reported by this sample, we also ran analyses excluding the 20 participants (0.004 % of the sample) with AAM > or < 3 SD from the mean. Our results hold after removing these participants.

bulimia, binge eating; McLaughlin et al., 2012; McLaughlin, Costello, Leblanc, Sampson, & Kessler, 2012; Platt et al., 2017). This model fit the data well (CFI=0.94; RMSEA=0.029; Hu & Bentler, 1999).

Each disorder onset was classified as having occurred pre- or post-menarche. Participants could have experienced both a pre-menarche and post-menarche disorder in the same disorder group (for example, a participant could have experienced specific phobia at age 4 (pre-menarche) and social phobia at age 14 (post-menarche).

Covariates. Models adjusted for age, race/ethnicity, body mass index (BMI), and pre-menarche onset disorders and SES (for models that did not include deprivation). See Supplementary Materials for more details.

Data Analysis. We first used linear regression to estimate associations between ELAs and menarche age. Second, we used logistic regression to estimate the associations of ELAs with post-menarche disorder onset, separately for fear, distress, externalizing, and eating disorders. Third, we used logistic regression to estimate the associations between menarche age and post-menarche disorder onset for each disorder group. We tested a mediation model only when there was a significant association between ELA and AAM, and AAM and a disorder group. We implemented the mediation analysis by fitting linear regression models to estimate the distribution of the mediator given the observed exposure and covariate values, and logistic regression models to estimate the distribution of the outcome given the observed exposure, mediator, and covariate values. These fitted models were used to estimate the indirect pathway parameters, interpreted as the log odds of developing a post-menarche disorder for each ELA a participant experienced, mediated by a one-year change in AAM (see Supplementary Materials for details). Robust standard errors were computed to estimate 95% confidence intervals, using quasi-Bayesian Monte Carlo methods based on normal approximation (Imai, Keele, & Tingley, 2010).

Sensitivity Analyses. Timing of exposure was assessed for most threat-related adversities, but none of the deprivation-related adversities. We did not incorporate information on timing of exposure into our main analyses because we did not want to

introduce a systematic difference between how threat and deprivation-related adversities were assessed. However, in order to ensure findings do not reflect reverse causality, we ran sensitivity analyses excluding instances of sexual abuse, physical abuse, witnessing domestic violence and witnessing or being the victim of violence in the community that occurred post-menarche. The direction and significance of our results were unchanged in these models, which are reported in the Supplementary Materials.

We also did not have information on maternal age at menarche, which is associated with child age at menarche and could be a genetic confounder of the association of the association of both ELA with age at menarche and age at menarche with post-menarche psychopathology. To address this. we conducted a sensitivity analysis that included maternal age at birth of the respondent as a proxy for maternal age at menarche as a covariate in (see Supplementary Materials). The pattern of findings was unchanged when maternal age at birth was included as a covariate.

Finally, given that the threat composite included six indicators and the deprivation composite included only five, we wanted to ensure that the reduced range in the deprivation composite was not responsible for our results. To do so we created a standardized score (M=0, SD=1) of each composites, consistent with prior work (Sumner, Colich, Uddin, Armstrong, & McLaughlin, 2018). Using these composites did not change the direction or significance of our results (see Supplementary Materials).

Results

Early Life Adversity and Age at menarche

We first examined whether exposure to any threat- or deprivation-related adversity predicted AAM and found no significant associations (Table 2, Model 1). We next examined whether the number of threat or deprivation experiences was associated with AAM (Table 2, Model 2). Here, a greater number of threat-related exposures was associated with earlier AAM (B=-0.1, SE=0.03, *p*=0.001; Figure 1a). The number of deprivation exposures was not associated with AAM (B=0.01, SE=0.03, p=0.63; Figure 1b). See Supplemental Table S1 for estimates for all individual indicators of threat and deprivation.

Early Life Adversity and Post-Menarche Mental Disorders

Exposure to any threat-related adversity was associated with elevated odds of post-menarche onset of distress (OR=4.27), fear (OR=2.21), externalizing (OR=4.83) and eating disorders (OR=2.83; Table S2; Model 1). Deprivation was not associated with any post-menarche disorder groups. We next examined how the number of threat-related or deprivation-related experiences predicted post-menarche disorder onset (Table S2; Model 2). Experiencing a greater number of threat-related ELAs was associated with elevated odds of post-menarche distress (OR=1.7), fear (OR=1.35), externalizing (OR=1.82), and eating disorders (OR=1.49). Exposure to a greater number of deprivation-related adversities was associated with elevated odds of post-menarche externalizing disorders (OR=1.2). See Table S2 (Model 3) for ORs for all individual indicators of threat and deprivation-related forms of adversity.

Age At Menarche and Post-Menarche Mental Disorders

We conducted four separate logistic regressions to evaluate whether AAM was associated with post-menarche onset of each disorder group. Earlier AAM was associated with elevated odds of experiencing post-menarche distress (OR=0.75), fear (OR=0.74), and externalizing disorders (OR=0.85), but not eating disorders (OR=0.98; Table 3).

Mediation Results

We tested whether AAM mediated the association between threat-related ELA and post-menarche disorder onset (Figure 2; Table S3). We observed a significant indirect effect of cumulative threat-related ELAs on distress (OR=1.003, 95% CI=1.002,1.004; proportion mediated=6.2%), fear (OR=1.003, CI=1.002,1.004; proportion mediated=16.3%), and externalizing disorders (OR=1.002, CI=1.001,1.003; proportion mediated=2.9%) through earlier AAM. These results can be interpreted as the increased log odds of each disorder group for each experience of threat-related ELA, mediated by a one-year decrease in menarche onset, and indicate that accelerated pubertal timing is a mediator of the association between threat-related ELA and adolescent-onset mental disorders.

Discussion

We provide novel evidence that a specific *dimension* of ELA (i.e., threat but not deprivation) is associated with earlier AAM in females, and that this accelerated pubertal timing is a transdiagnostic mechanism contributing—in part—to the association between ELA and onset of mental disorders in adolescence. Specifically, experiences of threat, but not deprivation, were associated with earlier AAM. Earlier AAM, in turn, was associated with increased odds of experiencing an onset of distress, fear, and externalizing disorders post-menarche. Critically, we demonstrate that earlier AAM partially mediates the association between threat-exposure in childhood and the onset of post-menarche distress, fear, and externalizing disorders. These findings suggest that accelerated pubertal development may be one potential pathway through which trauma exposure confers risk for psychiatric disorders in adolescent females.

Extensions of life history theory to humans has posited that exposure to environmental harshness (i.e. threat) in childhood accelerates maturation, in order to increase the likelihood of reproduction prior to potential mortality (Rickard, Frankenhuis, & Nettle, 2014). Our evidence is consistent with this theory, as a greater number of threat-related experiences in childhood was associated with earlier AAM. They also replicate recent findings from our lab demonstrating that threat-related adversities are associated with accelerated pubertal development, whereas deprivation-related adversities are associated with delayed pubertal development (Sumner et al., 2018). The mechanisms through which ELA influences pubertal timing remain unknown. One possibility is that ELA provides an early signal to the organism of the type of environment they are likely to experience, which allows the development of an appropriate phenotype for that environment; the neurobiological mechanisms that could mediate this type of early forecasting remain unknown, but most likely involve the hypothalamic-pituitary-adrenal (HPA) axis (Negriff et al., 2015; Saxbe et al., 2014). Alternatively, increasing evidence suggests that ELA—particularly experiences of threat—are associated with accelerated cellular and epigenetic aging (Sumner et al., 2018; Wolf et al., 2017). Recent models argue that internal markers of aging provide a signal to the reproductive system that accelerates sexual maturation in

response to advanced biological aging (Nettle, Frankenhuis, & Rickard, 2013; Rickard et al., 2014). Finally, evidence from animal models suggests that ELA influences epigenetic programming which in turn, signals the onset of pubertal development (Cameron, 2011; Cameron et al., 2008). Future research is needed to directly evaluate these mechanisms.

In contrast, we found no evidence for an association between deprivation and altered pubertal timing. Life history theory posits that deprivation of bioenergetics resources could result in delayed maturation and later AAM (Ellis et al., 2009). It is likely that deprivation in our modern context is not the same as deprivation in our evolutionary past. Although food insecurity is common in the U.S. and associated with youth psychopathology (McLaughlin et al., 2012), caloric intake may be sufficient to support metabolic processes even in individuals who experience food insecurity and nutrient deficiency in the US (Barrett, 2010). It is possible that more extreme forms of deprivation in contexts where food scarcity is associated with significantly decreased caloric intake may be more strongly associated with pubertal timing, particularly delayed onset of puberty, consistent with prior studies of war-related famine (Prebeg & Bralic, 2000; van Noord & Kaaks, 1991). These findings highlight the importance of considering the nature of the exposure when exploring the developmental consequences of ELA. Future research should carefully distinguish between the effects of threat- and deprivation-related adversities on pubertal timing.

Accelerated life history strategies stemming from early environmental circumstances may be adaptive in terms of reproductive fitness but appear to have deleterious consequences for mental health. We provide novel evidence that accelerated pubertal timing is a mechanism contributing to the strong association between threat-related ELA and post-menarche onset of fear, distress, and externalizing disorders, after controlling for important confounders such as race/ethnicity, BMI, SES, and pre-menarche mental disorders. These findings suggest that accelerated pubertal timing may be one pathway through which exposure to trauma increases risk for mental disorders in girls. Although prior work has shown that certain types of adversity are associated with pubertal timing (Mendle, Ryan, & McKone, 2016; Natsuaki, Leve, & Mendle, 2011) and that adversity is associated with onset

of mental disorders in adolescence and adulthood (Green et al., 2010; Kessler et al., 2010; McLaughlin et al., 2012), prior literature exploring pubertal timing as a mediator of the effect of adversity on mental health has been limited and results are mixed (Belsky et al., 2015; Mendle et al., 2014; Negriff et al., 2015). This may reflect that prior studies have examined single types of adversity (sexual abuse; Mendle et al., 2014) or a composite measure of adversity that includes both experiences of threat and deprivation (Belsky et al., 2015; Negriff et al., 2015). We demonstrate that accelerated pubertal timing explains a significant proportion of the association only between trauma-related adversities and post-menarche mental disorder onsets, particularly fear (16.3%) and distress (6.2%) disorders. The association between early puberty and psychopathology is often attributed to discrepancies between physical and cognitive development (Ge & Natsuaki, 2009; Mendle, 2014). Accelerated physical maturation may place females in a social context that they are not prepared to handle in terms of their social-cognitive development, either presenting opportunities for engagement in age-inappropriate risk-taking behaviors or creating psychological distress. Accelerated pubertal timing is also associated with heightened stress reactivity in adolescents (Natsuaki et al., 2009) and altered neural responses to emotional stimuli (Whittle et al., 2015). However, understanding of the neurobiological mechanisms linking accelerated pubertal timing to psychopathology remains limited (Byrne et al., 2016) and represents a critical direction for future research.

Several limitations of this study highlight key directions for future research. First, we focused solely on AAM as a metric of pubertal timing. Menarche occurs relatively late in the pubertal process and does not provide information on the tempo or pace of pubertal progression (Marceau, Ram, Houts, Grimm, & Susman, 2011). Use of AAM as a metric of pubertal timing also prevented us from studying males. Future research should explore potential sex differences in these associations. Additionally, we assessed AAM in whole-year increments, which may limit the precision of our estimates. Second, the timing of ELA could influence pubertal timing (Parent, Franssen, Fudvoye, Gérard, & Bourguignon, 2015). Information on timing of exposure was unavailable for all deprivation-related adversities in

the NCS-A, precluding us from examining timing of exposure as a predictor of AAM and limiting our ability to establish clear temporal sequencing of ELA occurring prior to AAM. However, timing of exposure was available for most threat-related adversities. In a sensitivity analysis, we demonstrate that threat-related adversities occurring prior to menarche predict both AAM and post-menarche onset of mental disorders with no change in the direction or significance of our results (see Supplementary Materials). This bolsters our confidence in the finding that pre-menarche trauma is associated with earlier AAM and increased risk of post-menarche mental disorders. It will be important to replicate these patterns in longitudinal studies with greater information on timing of adversity exposure. Third, ELAs were coded dichotomously and we did not take into account the severity of specific adversities. Given the nature of the survey data collected from this large, nationally-representative sample, this was not feasible. Future research should explore how severity and timing of ELAs influence pubertal timing and AAM. An alternative explanation for the association of ELA with pubertal timing is the heritability/intergenerational transmission of pubertal timing (de Vries, Kauschansky, Shohat, & Phillip, 2004; Towne et al., 2005). It is plausible that mothers who experience earlier onset of puberty reproduce at an earlier age and/or expose their offspring to a more adverse environment. Sensitivity analyses including maternal age at birth as a covariate did not alter the pattern of findings, but future research should explore how maternal age at menarche influences the associations of ELA, child age at menarche, and psychopathology. Finally, self-reports of age of onset (of ELA, age at menarche, and psychopathology) are subject to recall bias. Because these biases are likely to be non-systematic, this would make our findings conservative estimates of the true associations.

Finally, we note that associations between AAM and psychiatric disorders are complicated by the fact that both the exposure and the outcomes have a natural course that is developmentally linked. By defining the outcome in our analyses as post-menarche disorders, which is necessary to establish temporality, we are also introducing some selection processes. Such selection will be minimal for disorders with later average ages of onset (e.g. MDD [mean age=12.35], alcohol/drug/tobacco abuse [14.60/14.55/14.50], eating

disorders [13.19]), but caution should be applied for disorders with earlier ages of average onset. For example, the average onset age of specific phobia in these data is 6.13 (SD=2.51). Those girls with onset of specific phobia after menarche (mean age 12) may be different in terms of etiology and phenomenology of disorder than girls with onset of specific phobia pre-menarche. However, we addressed the potential for selection to explain our results by controlling for pre-menarche disorders.

We demonstrate that earlier age at menarche may be one pathway through which ELA, particularly threat-related experiences, leads to later psychopathology in a population-representative sample of females. These findings have relevance for pediatric health practice. Specifically, early menarche is an easily assessed marker that can be measured non-intrusively that can identify females who may be at risk for later psychopathology. Both medical and mental health professionals can use these findings to guide preventative and early interventions in trauma-exposed youth who may be showing signs of early pubertal onset, in order to mitigate the subsequent development of psychopathology.

Key Points

- Mechanisms linking early life adversity with the onset of psychopathology remain poorly understood.
- It is unknown whether all forms of ELA are associated with accelerated development, and whether accelerated development is a mechanism linking ELA with psychopathology.
- We found that experiences characterized by threat (but not deprivation) are associated with earlier age at menarche in females and that earlier age at menarche partially mediates the association between threat-exposure in childhood and the onset of distress, fear, and externalizing disorders.
- These findings suggest that early age at menarche may be one pathway through which threat-related ELA leads to later psychopathology.
- Early menarche is an easily assessed marker that could be used to identify trauma-exposed individuals at heightened risk for the development of psychopathology.

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Figure Legends

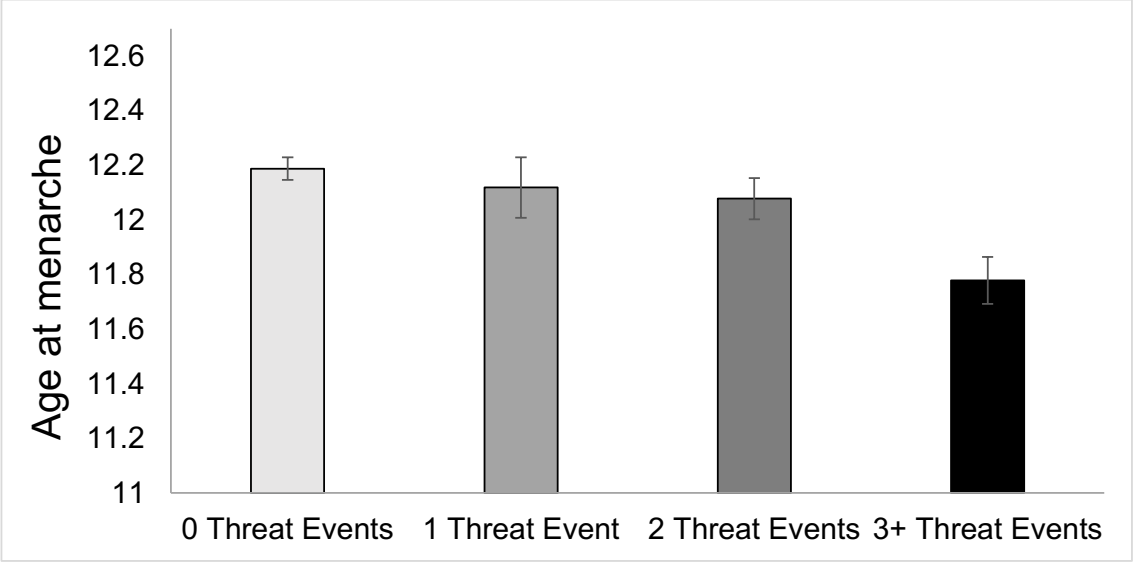
Figure 1A. Adjusted age at menarche for individuals who experienced 0, 1, 2, or 3+ threat-related early life adversity experiences. Model adjusted for age, race/ethnicity, and deprivation-related ELA. Error bars represent standard errors.

Figure 1B. Adjusted age at menarche for individuals who experienced 0, 1, 2, or 3+ threat-related early life deprivation experiences. Model adjusted for age, race/ethnicity, and threat-related ELA. Error bars represent standard errors.

Figure 2. Total and indirect effect of threat-related ELA exposure on onset of mental disorder (separate models for distress, fear, and externalizing disorders) through age at menarche. Model adjusted for age, race/ethnicity, SES, and pre-menarche disorder.

Figure 1.

A.


Age at menarche
12.6
12.4
12.2
12
11.8
11.6
11.4
11.2
11
0 Threat Events
1 Threat Event
2 Threat Events
3+ Threat Events

B.

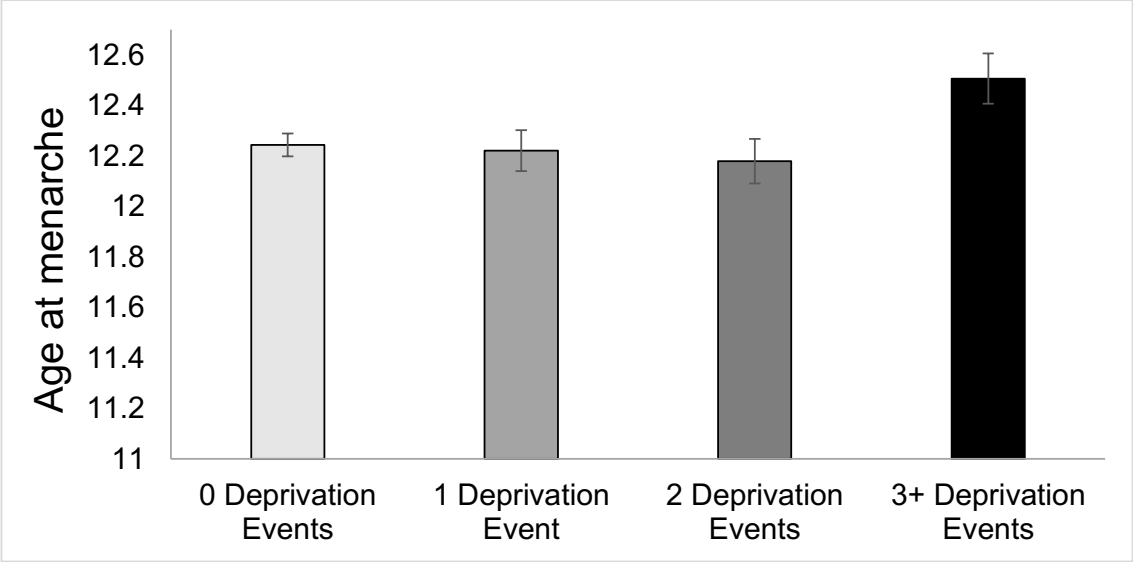

Age at menarche
12.6
12.4
12.2
12
11.8
11.6
11.4
11.2
11
0 Deprivation Events
1 Deprivation Event
2 Deprivation Events
3+ Deprivation Events

Figure 2.

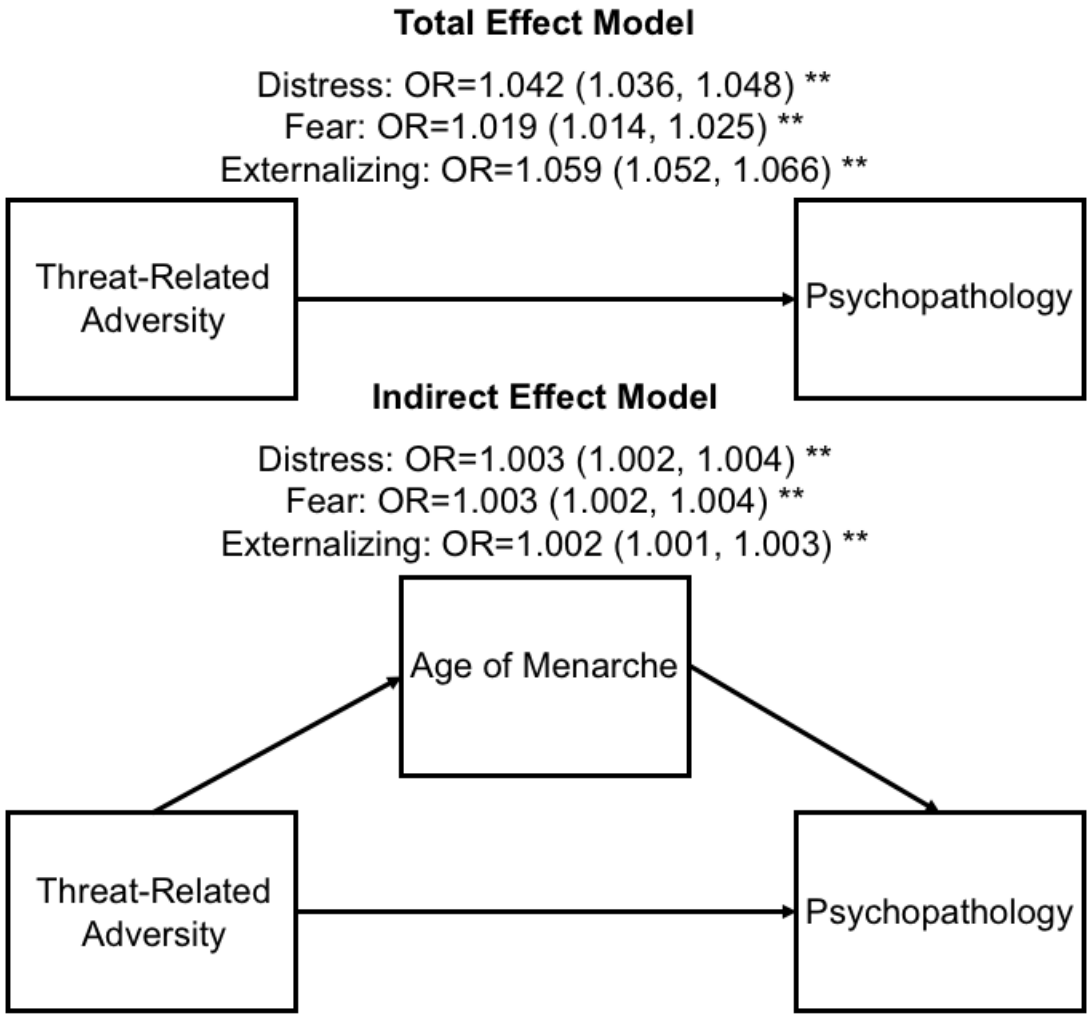

Total Effect Model
Distress: OR=1.042 (1.036, 1.048) **
Fear: OR=1.019 (1.014, 1.025) **
Externalizing: OR=1.059 (1.052, 1.066) **
Threat-Related Adversity
Psychopathology
Indirect Effect Model
Distress: OR=1.003 (1.002, 1.004) **
Fear: OR=1.003 (1.002, 1.004) **
Externalizing: OR=1.002 (1.001, 1.003) **
Age of Menarche
Threat-Related Adversity
Psychopathology

Table 1. Participant characteristics.

	Mean (*SD*)	Range	% (*n*)
Demographics			
Age, years	15.25 (1.47)	13-18	
Age at menarche, years	12.10 (1.26)	6-17	
Race/ethnicity, %			
White			55.58 (2744)
Black			19.71 (973)
Latino			18.31 (904)
Other			6.40 (316)
Parent income to poverty ratio	6.13 (7.97)	0-142.06	
Parent Education, %			
< High school graduate			16.16 (798)
High school graduate			30.18 (1490)
Some college			19.61 (968)
College graduate or advanced degree			34.05 (1681)
Early-life adversity exposure			
Threat exposure composite	0.66 (1.06)	0-6	
Physical Abuse			3.93 (194)
Domestic Violence			11.14 (550)
Sexual Assault			9.86 (487)
Violent Victimization			9.64 (476)
Witnessing Violence			11.06 (546)
Emotional Abuse			6.83 (337)
Deprivation exposure composite	0.64 (0.86)	0-5	
Poverty (ratio of household income to poverty level <1.5)			16.89 (834)
Parent Education (< high school graduate)			16.16 (798)
Financial Insecurity			16.95 (837)
Food Insecurity			13.02 (643)
Neglect			0.75 (37)
Mental Disorders			
Pre-menarche Distress Diagnosis			5.73 (283)
Post-menarche Distress Diagnosis			11.00 (543)
Pre-menarche Fear Diagnosis			28.9 (1427)
Post-menarche Fear Diagnosis			8.14 (402)

Pre-menarche Externalizing Diagnosis	3.48 (172)
Post-menarche Externalizing Diagnosis	15.03 (742)
Pre-menarche Eating Diagnosis	1.52 (75)
Post-menarche Eating Diagnosis	5.00 (427)

Note. SD=standard deviation

Table 2. Regression parameters for associations of childhood adversity and age at menarche.

	Estimate	St. Error	*t*	*p*
Model 1				
Intercept	12.226	0.043	283.748	< 0.001***
Any Threat (0/1)	-0.106	0.078	-1.347	0.187
Any Deprivation (0/1)	-0.048	0.064	-0.754	0.456
BMI	-0.215	0.024	-8.872	< 0.001***
age	0.113	0.018	6.196	< 0.001***
race				
Black	-0.187	0.053	-3.523	0.001**
Hispanic	-0.203	0.069	-2.936	0.006**
other	0.014	0.117	0.116	0.908
Model 2				
Intercept	12.195	0.046	266.977	< 0.001***
Threat Count	-0.098	0.026	-3.813	0.001 ***
Dep Count	0.014	0.029	0.482	0.633
BMI	-0.215	0.024	-8.817	< 0.001***
age	0.116	0.018	6.357	< 0.001***
race				
Black	-0.184	0.052	-3.540	0.001**
Hispanic	-0.213	0.067	-3.175	0.003**
other	0.003	0.120	0.025	0.980

* p < 0.05 ** p < 0.01 *** p < 0.001

Table 3. Odds ratios for associations of age at menarche and post-menarche mental disorders.

	Distress Disorders	Fear Disorders	Externalizing Disorders	Eating Disorders
	OR (95 % CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
(Intercept)	3.857 (0.995, 16.430)	2.521 (0.481, 13.214)	1.861 (0.528, 6.564)	0.047 (0.008, 0.267)
Age at Menarche	0.746 (0.653, 0.854) ***	0.737 (0.647, 0.840) ***	0.845 (0.763, 0.936) **	0.979 (0.858, 1.117)
BMI	1.098 (0.915, 1.318)	0.995 (0.864, 1.147)	1.058 (0.945, 1.184)	1.020 (0.846, 1.231)
age	1.370 (1.267, 1.481) ***	1.189 (1.056, 1.339) **	1.552 (1.418, 1.698) ***	1.170 (1.016, 1.348) *
race				
Black	0.897 (0.627, 1.284)	1.336 (0.869, 2.055)	0.475 (0.313, 0.721) *	1.374 (0.835, 2.260)
Hispanic	1.095 (0.702, 1.709)	1.228 (0.721, 2.091)	0.668 (0.435, 1.026)	2.376 (1.149, 4.910) *
other	0.745 (0.423, 1.313)	1.088 (0.617, 1.916)	0.941 (0.562, 1.576)	1.044 (0.508, 2.145)
Income	0.992 (0.980, 1.005)	1.001 (0.982, 1.020)	0.992 (0.973, 1.001)	0.999 (0.985, 1.013)
Parental Education				
High school	0.908 (0.595, 1.388)	1.050 (0.687, 1.603)	0.881 (0.674, 1.152)	0.988 (0.726, 1.344)
Some college	1.198 (0.799, 1.795)	1.062 (0.635, 1.774)	0.764 (0.505, 1.115)	1.365 (0.573, 3.248)
College	1.034 (0.714, 1.497)	0.702 (0.424, 1.161)	0.511 (0.388, 0.673) ***	1.025 (0.648, 1.621)
Pre-Menarche Disorder	2.121 (1.288, 3.492) **	1.877 (1.300, 2.711) **	5.447 (2.923, 10.150) ***	1.553 (0.353, 6.834)

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

Supplementary Materials

Sample

The NCS-A household sample (n=879) included adolescents recruited from households that participated in the National Comorbidity Survey Replication (NCS-R), a national household survey of adult mental disorders (Kessler et al., 2004), and had a response rate, conditional on adult NCS-R participation, of 86.8%. The remaining adolescents (n=9,244) were recruited from a representative sample of schools in NCS-R sample areas (response rate 82.6%, conditional on school participation). The proportion of initially selected schools that participated in the NCS-A was low (28.0%), but replacement schools were recruited and carefully matched to the original schools. No bias in estimates of prevalence or correlates of mental disorders was found when household sample respondents from non-participating schools were compared with school sample respondents from replacement schools (Kessler et al., 2009a). Cases were weighted for variation in within-household probability of selection in the household sample and residual discrepancies between sample and population socio-demographic and geographic distributions. The household and school samples were then merged with sums of weights proportional to relative sample sizes adjusted for design effects in estimating disorder prevalence. Weighting procedures are detailed elsewhere (Kessler et al., 2009b, 2009a). The weighted socio-demographic distributions of the NCS-A sample closely approximate those of the Census population.

Study participants received $50 for their participation and written informed consent and assent were obtained from both parents and adolescents, respectively, in accordance to the procedures approved by the Human Subjects Committees of Harvard University and the University of Michigan.

Early Life Adversity

Information about ELA was obtained through both child-interviews and parent self-administered questionnaires (SAQ). Either parent or child report was considered an endorsement of an ELA event. Physical and emotional abuse of the child was assessed

using a modified version of the Conflict Tactics Scale.(Straus, 1979) Sexual assault was assessed with questions from the Composite International Diagnostic Interview (CIDI) about sexual assault, attempted rape, and rape (Kessler & Üstün, 2004). Neglect was assessed with a battery of questions used in investigations of child welfare that ask about experiences with inadequate supervision, age-inappropriate chores, and not having adequate food, clothing or medical care (Courtney, Piliavin, Grogan-Kaylor, & Nesmith, 1998). Domestic violence was assessed using the modified Conflict Tactics Scale. Economic adversity was assessed with questions in the SAQ including household income, parental education attainment, whether the respondent's family had received welfare or other government assistance or often did not have enough money to pay for basic necessities of living. See (McLaughlin et al., 2012) for more detail on how adversities were coded.

Although information on timing of ELA was not available for all forms of adversity considered in our analysis, timing information was available on several adversities included in the threat composite. We did not incorporate timing information into our main analyses because it was not available for any of the forms of adversity included in the deprivation composite, and we did not want to introduce a systematic difference in how threat- and deprivation-related adversities were assessed. However, for the purposes of ensuring that reverse causality did not explain the findings (i.e., earlier age of menarche contributing to increased risk for experiencing some forms of adversity, such as sexual assault), we ran sensitivity analyses excluding cases of sexual abuse, physical abuse, witnessing domestic violence and witnessing or being the victim of violence in the community that occurred post-menarche.

A total of 22.4% of our sample experienced both threat- and neglect-related experiences. This level of co-occurrence should not be a problem with statistical modeling of adversities in the same model to isolate the relative effects of each. We have used similar approaches in prior work in this and other population-based samples examining the associations of childhood adversities with first onset and persistence of psychiatric disorders (Green et al., 2010; McLaughlin et al., 2010, 2012). In those papers, 12 separate adversities

were entered into a single model to isolate the unique contributions of each on disorder onset and persistence. Many other studies of childhood adversity have used a similar approach. Within a large, representative sample such as this with wide variability in exposure to various adversities, co-occurrence of exposures at the level we see in these data is easily addressed with statistical control. Examining these types of adverse experiences in a large, nationally representative sample allows for generalization of the findings to the broader population.

Covariates

Models were adjusted for a series of potential confounding variables shown to impact both age at menarche and onset of psychiatric disorder in adolescence, including age at survey response, race/ethnicity (non-Hispanic white [reference group], non-Hispanic Black, Hispanic, other), body mass index (BMI; measured by self-reported height and weight) and family socioeconomic status (SES; determined by both parent income to poverty ratio and highest parental education attainment [coded into 4 categories: less than high school graduation (reference group), high school graduation, some college, college graduate or advanced degree]). As SES is included in our measure of deprivation, we included SES as a covariate only in models examining the effects of threat in isolation (i.e., the association between pubertal timing and disorder onset; final mediation models). BMI was modeled as a continuous variable, standardized according to established procedures for adolescents (Cole, Faith, Pietrobelli, & Heo, 2005; Kakinami, Henderson, Chiolero, Cole, & Paradis, 2014), using the SAS macro available here: https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm. We also conducted sensitivity analyses with maternal age at birth as a covariate.

Data Analysis

We investigated whether there was a significant indirect effect of cumulative ELA events on post-menarche psychiatric disorder through age at menarche. The mediation models were comprised of a model to estimate the conditional distribution of the mediator given the exposure and the set of observed covariates, and an outcome model to estimate

the conditional distribution of the outcome given the exposure, mediator, and covariates. The mediation analysis proceeded in two steps. First, we specified two statistical models: the mediator model estimated the conditional distribution of the mediator given the exposure and the set of observed covariates, and the outcome model estimated the conditional distribution of the outcome given the exposure, mediator, and covariates. The assumptions necessary for unbiased estimation of mediation models include no residual confounding of either the exposure-mediator pathway and the exposure-outcome pathway. In our models, we assumed that the same covariate set could cause confounding in both pathways, therefore we included the same covariates in both mediation and outcome models. An additional assumption is no exposure-mediator interaction. None of the tests for multiplicative interaction were statistically significant (data not shown).

Each model's fitted objects comprised the main inputs to the mediate function, which computed both the direct and mediated parameter estimates in the total mediation model (Imai, Keele, & Tingley, 2010). This approach overcomes the limitation of the standard mediation methods. These methods allow for a greater flexibility of statistical models, including binary and count dependent variables (Imai, Keele, Tingley, & Yamamoto, 2014; Tingley, Yamamoto, Hirose, Keele, & Imai, 2014). A second advantage of this approach is that standard errors are computed using quasi-Bayesian Monte Carlo methods based on normal approximation, which allowed for the estimation of 95% confidence intervals around both the direct and mediated parameter estimates (Imai et al., 2010).

All statistical analyses were conducted in R (version 3.3.2). Mediation models were completed using the "mediation" package (Tingley et al., 2014). The "survey" package (Lumley, 2004, 2017) was used to adjust for the complex survey design.

Sexual Assault and Age At Menarche

When examining the individual impact of each type of ELA on age at menarche, we found the strongest association between childhood sexual assault and earlier age at menarche. These findings contribute to a relatively consistent literature suggesting that childhood sexual assault leads to earlier pubertal timing, especially in females (Boynton-

Jarrett et al., 2013; Brown, Cohen, Chen, Smailes, & Johnson, 2004; Herman-Giddens, 1988; Noll et al., 2017). This association has been demonstrated in both smaller, high-risk populations (females in foster care and females referred by child protective services; Mendle, Leve, Van Ryzin, Natsuaki, & Ge, 2011; Noll et al., 2017) as well as in larger, nationally representative sample, similar to the sample used in this current analysis (National Longitudinal Study of Adolescent Health; Mendle, Ryan, & McKone, 2016). However, the mechanism accounting for this association is not well understood. It is possible that there is something specific about how childhood sexual assault influences development of the hypothalamic pituitary adrenal (HPA) and hypothalamic pituitary gonadal (HPG) axes, that in turn, advance the onset of puberty in adolescent females. It is equally plausible that there is something psychologically unique about the nature of the stress of sexual assault that may in turn exacerbate associations between stress and pubertal timing. Most likely it is a combination of both of these mechanisms (Trickett, Noll, & Putnam, 2011; Trickett & Putnam, 1993) and future work should explore these potential mechanisms in conjunction.

Sensitivity Analyses

Deprivation Composite Without Poverty

We included poverty as an indicator of deprivation in our models, consistent with earlier work in this sample (Platt et al., 2018) and based on extensive evidence demonstrating that children from families with low income experience reductions in cognitive and social stimulation than children from higher-SES families (Bradley, Corwyn, Burchinal, McAdoo, & Garcia Coll, 2001; Duncan & Magnuson, 2012). However, poverty has also been conceptualized as a risk factor for, rather than a direct marker of, deprivation (McLaughlin, Sheridan, & Lambert, 2014; Sheridan & McLaughlin, 2014). To ensure that we had not diluted our deprivation composite by including poverty as an indicator, we re-ran our analyses without poverty or financial insecurity in the deprivation composite. When we poverty and financial insecurity from the deprivation count, deprivation remained unassociated with age at menarche (B=0.038, SE=0.047, p=0.429).

Removing poverty and financial insecurity from our composite measure of deprivation also did not change the direction or significance of our findings linking deprivation-related adversity to post-menarche mental disorders. Exposure to deprivation (excluding poverty and financial insecurity) was not associated with odds of post-menarche onset of distress (OR=1.05, 95% CI=0.72, 1.52), fear (OR=0.96, 95% CI=0.71, 1.29), or eating disorders (OR=1.15, CI=0.84, 1.59), consistent with our findings when parental education was included in the composite. However, without poverty and financial insecurity, deprivation is no longer associated with increased odds of post-menarche onset of externalizing disorders (OR=1.24, 95% CI=0.95, 1.61).

Deprivation Composite Without Parental Education

Although low levels of parental education are reliably associated with reductions in cognitive stimulation among children (Bradley, Corwyn, Burchinal, McAdoo, & Garcia Coll, 2001; Duncan & Magnuson, 2012; Gilkerson et al., 2017; Rosen et al., (Under review)), parental education is a proxy for deprivation rather than a direct measure. To ensure that we had not diluted our deprivation composite by including parent education as an indicator, we re-ran our analyses without parental education in the deprivation composite. When we removed parental education from the deprivation count, deprivation remained unassociated with age at menarche (B=0.002, SE=0.032, *p*=0.932).

Removing parental education from our composite measure of deprivation also did not change the direction or significance of our findings linking deprivation-related adversity to post-menarche mental disorders. Exposure to deprivation (excluding low levels of parental education) was not associated with odds of post-menarche onset of distress (OR=1.24, 95% CI=0.93, 1.64), fear (OR=1.06, 95% CI=0.83, 1.35), or eating disorders (OR=1.12, CI=0.81, 1.53), consistent with our findings when parental education was included in the composite. Deprivation remained associated with increased odds of post-menarche onset of externalizing disorders (OR=1.23, 95% CI=1.03, 1.47).

Threat Composite Without Sexual Assault

There is strong evidence that sexual abuse or assault in early childhood precedes the onset of early puberty (Mendle, Leve, Van Ryzin, Natsuaki, & Ge, 2011b; Noll et al., 2017; Trickett et al., 2011), there is also evidence to suggest that early puberty may be a risk factor for later sexual abuse (Chen, Rothman, & Jaffee, 2017). Therefore, in order to alleviate concerns about the possibility of post-menarche sexual assault driving our findings, we have conducted additional analyses. To ensure that the associations of threat-related adversities with age at menarche still hold without sexual abuse, we re-ran our models using a threat composite without sexual assault (still including physical abuse, witnessing domestic violence, witnessing or being the victim of violence in the community, and emotional abuse). Indeed, threat-related adversities (excluding sexual assault) remain significantly associated with earlier age at menarche (B=-0.09, SE=0.03, p=0.007). Similarly, threat-related adversities (excluding sexual assault), still significantly predict the post-menarche onset of all four disorder classes: distress (OR=1.72, 95% CI=1.47, 2.01), fear (OR=1.37, 95% CI=1.20, 1.57), externalizing (OR=1.86, 95% CI=1.64, 2.11) and eating disorders (OR=1.57, 95% CI=1.35, 1.83).

Constraining Analysis to Pre-Menarche Threat-Related Adversities

We excluded cases of sexual abuse, physical abuse, witnessing domestic violence and witnessing or being the victim of violence in the community that occurred post-menarche and re-ran all analyses in order to ensure that reverse causality was not driving the results. Indeed, threat-related adversities that occurred pre-menarche were still significantly associated with earlier age at menarche (B=-0.10, SE=0.05, p=0.04) and deprivation-related adversities (that we don't have timing information for) remained unassociated with age at menarche (B=-0.004, SE=0.03, p=0.88). Threat-related adversities that occurred pre-menarche still significantly predict the post-menarche onset of all four disorder classes: distress (OR=1.88, 95% CI=1.50, 2.36), fear (OR=1.33, 95% CI=1.09, 1.62), externalizing (OR=2.09, 95% CI=1.73, 2.53) and eating disorders (OR=1.72, 95% CI=1.37, 2.16).

Furthermore, using only pre-menarche threat-related adversities did not alter the results of our mediation analyses. We still observe a significant indirect effect of cumulative

threat-related ELAs on distress (OR=1.004, 95% CI=1.002,1.010; proportion mediated=5.7%), fear (OR=1.003, CI=1.001,1.010; proportion mediated=15.0%), and externalizing disorders (OR=1.002, CI=1.001,1.005; proportion mediated=2.6%) through earlier age at menarche.

Maternal Age at Birth as a Covariate

Including maternal age at birth did not change the direction or significance of the findings linking ELA to age at menarche. When using threat and deprivation counts to predict age at menarche, threat count was still strongly associated with age at menarche (B=-0.11, SE=0.04, *p*=0.003). Maternal age at birth was not related to age at menarche in this model (B=0.002, SE=0.006, *p*=0.764).

Including maternal age at birth similarly did not change the direction or significance of our findings linking age at menarche to post-menarche mental disorders. Exposure to threat-related adversity was still associated with elevated odds of post-menarche onset of distress (OR=0.75, 95% CI=0.67, 0.84), fear (OR=0.72, 95% CI=0.58, 0.88) and externalizing disorders (OR=0.86, 95% CI=0.76, 0.97), but not eating disorders (OR=0.96, 95% CI=0.78, 1.18). Greater maternal age at birth was significantly associated with decreased risk for externalizing disorders only (OR=0.96, 95% CI=0.93, 1.00).

These results suggest that maternal age at birth, a proxy for maternal age at menarche, is not a confounding variable in the associations among early adversity (particularly threat-related adversities), age at menarche, and post-menarche mental disorders.

Standardized Scores for Threat and Deprivation

Given that the threat composite included six indicators and the deprivation composite included only five, we wanted to ensure that the reduced range in the deprivation composite was not responsible for our results. To do so we created a standardized score (M=0, SD=1) of each composites, consistent with prior work (Sumner, Colich, Uddin, Armstrong, & McLaughlin, 2018). Using these composites did not change the direction or significance of our results. Indeed, the standardized score for threat-related adversities remained

significantly associated with earlier age at menarche (B=-0.10, SE=0.03, p<0.001) and the standardized score for deprivation-related adversities was unrelated to age at menarche (B=0.01, SE=0.03, p=0.63). Similarly, the standardized score for threat-related adversities predicted post-menarche onset of all four disorder classes: distress (OR=1.77, 95% CI=1.53, 2.05), fear (OR=1.37, 95% CI=1.20, 1.56), externalizing (OR=1.89, 95% CI=1.66, 2.14) and eating disorders (OR=1.53, 95% CI=1.29, 1.81). The standardized score for deprivation-related adversities predicted the post-menarche onset of externalizing disorders (OR=1.17, 95% CI=1.03, 1.33) but not distress (OR=1.11, 95% CI=0.89, 1.37), fear (OR=1.02, 95% CI=0.87, 1.21), or eating disorders (OR=1.04, 95% CI=0.84, 1.27).

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Table S1. Regression parameters for associations of all types of childhood adversity and age at menarche.

	Estimate	St. Error	*t*	*p*
Model 3				
Intercept	10.560	0.261	40.400	< 0.001***
Physical Abuse	-0.195	0.171	-1.141	0.265
Domestic Violence	-0.145	0.087	-1.660	0.110
Sexual Abuse	-0.341	0.163	-2.087	0.048 *
Violent Victimization	-0.101	0.169	-0.595	0.558
Witnessing Violence	0.168	0.114	1.465	0.156
Emotional Abuse	0.230	0.123	1.868	0.074
Poverty	-0.008	0.060	-0.130	0.898
Parental Education				
High school	-0.006	0.074	-0.081	0.936
Some college	-0.104	0.067	-1.554	0.133
College	-0.034	0.091	-0.371	0.714
Financial Insecurity	-0.007	0.078	-0.089	0.929
Food Insecurity	0.022	0.054	0.413	0.684
Neglect	-0.260	0.354	-0.734	0.470
BMI	-0.215	0.023	-9.209	< 0.001***
age	0.119	0.018	6.544	< 0.001***
race				
Black	-0.236	0.054	-4.366	< 0.001***
Hispanic	-0.239	0.079	-3.016	0.006 **
other	-0.012	0.121	-0.103	0.919

* p < 0.05 ** p < 0.01 *** p < 0.001

Table S2. Odds ratios for associations of childhood adversity and post-menarche mental disorders.

	Distress Disorders	Fear Disorders	Externalizing Disorders	Eating Disorders
	OR (95 % CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Model 1				
Intercept	0.070 (0.051, 0.088) ***	0.047 (0.033, 0.066) ***	0.097 (0.077, 0.122) ***	0.027 (0.019, 0.039) ***
Any Threat	4.272 (3.041, 6.001) ***	2.205 (1.601, 3.026) ***	4.831 (3.653, 6.388) ***	2.826 (1.786, 4.471) ***
Any Deprivation	1.017 (0.732, 1.413)	1.258 (0.434, 3.648)	2.182 (0.494, 9.635)	2.002 (0.519, 7.718)
BMI	1.116 (0.949, 1.313)	1.059 (0.923, 1.215)	1.070 (0.968, 1.182)	0.991 (0.819, 1.199)
age	1.289 (1.195, 1.390) ***	1.136 (1.002, 1.289)	1.473 (1.357, 1.599) ***	1.126 (0.973, 1.303)
race				
Black	0.754 (0.507, 1.121)	1.375 (0.878, 2.152)	0.425 (0.278, 0.649) ***	1.183 (0.728 1.923)
Hispanic	0.950 (0.630, 1.434)	1.275 (0.807, 2.016)	0.659 (0.441, 0.985)	2.037 (1.074, 3.900) *
other	0.678 (0.378, 1.217)	1.067 (0.618, 1.845)	0.978 (0.514, 1.859)	0.959 (0.471, 1.955)
Pre-Menarche Disorder	1.180, 0.641, 2.172)	1.647 (1.163, 2.332) **	3.004 (1.684, 5.361) ***	1.097 (0.247, 4.877)
Model 2				
Intercept	0.075 (0.058, 0.096) ***	0.048 (0.035, 0.067) ***	0.103 (0.081, 0.130) ***	0.028 (0.019, 0.042) ***
Threat Count	1.710 (1.488, 1.966) ***	1.345 (1.188, 1.522) ***	1.816 (1.611, 2.048) ***	1.494 (1.274, 1.751) ***
Dep Count	1.124 (0.875, 1.444)	1.029 (0.851, 1.244)	1.204 (1.041, 1.393) *	1.044 (0.822, 1.326)
BMI	1.126 (0.954, 1.330)	1.065 (0.927, 1.225)	1.081 (0.983, 1.188)	1.003 (0.821, 1.225)
age	1.300 (1.199, 1.409) ***	1.138 (1.011, 1.281) *	1.494 (1.378, 1.619) ***	1.127 (0.980, 1.297)
race				
Black	0.664 (0.447, 0.987)	1.323 (0.812, 2.156)	0.349 (0.229, 0.531) ***	1.114 (0.682, 1.819)
Hispanic	0.909 (0.623, 1.323)	1.269 (0.843, 1.912)	0.609 (0.437, 0.850) **	2.030 (1.199, 3.746) *
other	0.614 (0.334, 1.126)	1.038 (0.593, 1.819)	0.898 (0.472, 1.746)	0.933 (0.443, 1.965)
Pre-Menarche Disorder	0.944 (0.463, 1.923)	1.646 (1.166, 2.323) **	2.791 (1.580, 4.932) **	1.102 (0.228, 5.321)

Model 3				
Intercept	0.001 (0.00, 0.004)***	0.007 (0.001, 0.039) ***	0.000 (0.000, 0.001) ***	0.000 (0.000, 0.001) ***
Physical Abuse	1.052 (0.528, 2.094)	1.392 (0.608, 3.187)	1.180 (0.597, 2.332)	1.332 (0.662, 2.682)
Domestic Violence	1.291 (0.885, 1.883)	0.890 (0.570, 1.389)	1.806 (1.108, 2.942) *	1.834 (1.132, 2.971) *
Sexual Assault	1.982 (1.166, 3.369) *	1.477 (0.838, 2.603)	0.7614 (0.431, 1.344)	0.768 (0.436, 1.351)
Violent Victimization	2.070 (1.258, 3.406) **	1.760 (1.018, 3.043)	5.716 (3.137, 10.415) ***	5.800 (3.166, 10.627) ***
Witnessing Violence	1.674 (1.010, 2.776)	0.912 (0.516, 1.612)	1.545 (0.983, 2.428)	1.523 (0.960, 2.417)
Emotional Abuse	1.903 (0.884, 4.094)	1.725 (1.043, 2.853) *	1.924 (1.114, 3.322) *	2.085 (1.252, 3.475) **
Poverty	1.167 (0.837, 1.628)	0.907 (0.575, 1.431)	1.093 (0.729, 1.639)	1.083 (0.733, 1.602)
Parental Education				
High school	1.078 (0.681, 1.706)	1.126 (0.725, 1.748)	0.967 (0.694, 1.348)	0.957 (0.685, 1.339)
Some college	1.372 (0.880, 2.138)	1.117 (0.728, 1.714)	0.766 (0.501, 1.171)	0.787 (0.520, 1.191)
College	1.373 (0.916, 2.060)	0.761 (0.472, 1.225)	0.591 (0.413, 0.845) **	0.585 (0.413, 0.828) **
Financial Insecurity	1.434 (1.009, 2.039)	1.256 (0.948, 1.664)	1.241 (0.894, 1.723)	1.306 (0.939, 1.818)
Food Insecurity	1.429 (0.894, 2.285)	0.929 (0.531, 1.628)	1.183 (0.826, 1.695)	1.205 (0.832, 1.745)
Neglect	1.135 (0.175, 7.368)	0.833 (0.257, 2.696)	1.512 (0.149, 15.315)	1.638 (0.180, 14.944)
BMI	1.131 (0.954, 1.341)	1.052 (0.923, 1.200)	1.052 (0.960, 1.153)	1.042 (0.949, 1.145)
age	1.294 (1.190, 1.408) ***	1.137 (1.016, 1.273) *	1.503 (1.389, 1.628) ***	1.496 (1.377, 1.625) ***
race				
Black	0.794 (0.552, 1.144)	1.428 (0.885, 2.304)	0.414 (0.277, 0.619) ***	0.400 (0.271, 0.590) ***
Hispanic	1.041 (0.711, 1.524)	1.272 (0.843, 1.918)	0.565 (0.392, 0.816) **	0.566 (0.390, 0.820) **
other	0.674 (0.370, 1.227)	1.073 (0.614, 1.875)	0.897 (0.467, 1.724)	0.886 (0.4537, 1.732)
Pre-Menarche Disorder	0.878 (0.427, 1.805)	1.616 (1.161, 2.249) **	2.577 (1.472, 4.511) **	1.929 (0.623, 5.975)

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

Table S3. Effect of threat-related ELA exposure on post-menarche mental disorder through age at menarche.

	Indirect Effect	Direct Effect	Total Effect	Proportion Mediated
	OR (95 % CI)	OR (95% CI)	OR (95% CI)	
Distress Disorders	1.003 (1.002, 1.004) ***	1.039 (1.033, 1.044)***	1.042 (1.036, 1.048)***	0.062 (0.039, 0.092)
Fear Disorders	1.003 (1.002, 1.004) ***	1.016 (1.011, 1.022)***	1.019 (1.014, 1.025)***	0.163 (0.104, 0.258)
Externalizing Disorders	1.002 (1.001, 1.003)***	1.057 (1.050, 1.065)***	1.059 (1.052, 1.066)***	0.029 (0.014, 0.051)
Eating Disorders	1.000(1.000, 1.001)	1.015 (1.011, 1.018)***	1.015 (1.011, 1.019)***	0.020 (-0.016, 0.059)