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Original Contribution

Prepubertal Internalizing Symptoms and Timing of Puberty Onset in Girls

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Stressful environments have been associated with earlier menarche. We hypothesized that anxiety, and possibly other internalizing symptoms, are also associated with earlier puberty in girls. The Lessons in Epidemiology and Genetics of Adult Cancer From Youth (LEGACY) Girls Study (2011–2016) included 1,040 girls aged 6–13 years at recruitment whose growth and development were assessed every 6 months. Prepubertal maternal reports of daughter's internalizing symptoms were available for breast onset ($n = 447$), pubic hair onset ($n = 456$), and menarche ($n = 681$). Using Cox proportional hazard regression, we estimated prospective hazard ratios and 95% confidence intervals for the relationship between 1 standard deviation of the percentiles of prepubertal anxiety, depression, and somatization symptoms and the timing of each pubertal outcome. Multivariable models included age, race/ethnicity, study center, maternal education, body mass index percentile, and family history of breast cancer. Additional models included maternal self-reported anxiety. A 1–standard deviation increase in maternally reported anxiety in girls at baseline was associated with earlier subsequent onset of breast (hazard ratio (HR) = 1.22, 95% confidence interval (CI): 1.09, 1.36) and pubic hair (HR = 1.15, 95% CI: 1.01, 1.30) development, but not menarche (HR = 0.94, 95% CI: 0.83, 1.07). The association of anxiety with earlier breast development persisted after adjustment for maternal anxiety. Increased anxiety in young girls may indicate risk for earlier pubertal onset.

breast development; cohort study; girls; internalizing symptoms; puberty

Abbreviations: BCFH, breast cancer family history; BMI, body mass index; CI, confidence interval; HR, hazard ratio; LEGACY, Lessons in Epidemiology and Genetics of Adult Cancer From Youth; TS, Tanner stage.

Age at onset of breast development, a common indicator of puberty onset, has become younger in recent decades, although the average age at menarche has remained stable (1, 2). Earlier puberty in girls is associated with a variety of adverse physical and mental health outcomes (1, 3, 4). Thus, it is important to understand the factors that contribute to pubertal onset and progression, particularly those potentially amenable to intervention. Several factors, such as obesity and genetics, play a role, but the factors contributing to variation in pubertal developmental timing are not fully understood (1, 2, 4).

Stress has been associated with the timing of pubertal development in girls, although this area of research is complex, with varied definitions of stress (1, 5). Most evidence to date is based on the association of systems-level factors such as socioeconomic status, familial characteristics, and number of adverse childhood events with the timing of the development of pubertal characteristics, usually menarche (1, 5). Although stressful environments involving inadequate nutrition are associated with pubertal delays, adverse psychosocial conditions may accelerate pubertal development (1, 5).

Few studies have examined individual indicators of stress. Earlier menarche has been associated prospectively with higher scores of socioemotional difficulties at age 7 years (6) and retrospectively with recalled anxiety or a combined

measure of anxiety and depression in late childhood (7). To our knowledge, no study to date has prospectively assessed the relationship of anxiety and other internalizing symptoms (related to anxiety and depression) in prepubertal girls with the timing of the appearance of characteristics indicating pubertal onset (i.e., breast and pubic hair development). Understanding the relationship between psychosocial factors and pubertal development is relevant because it may enhance the ability to identify girls at risk of earlier puberty and indicate modifiable targets of intervention.

Therefore, we assessed the relationship between symptoms of anxiety, depression, and somatization (i.e., the manifestation of depression and/or anxiety as physical symptoms), as well as a composite score of internalization, in prepubertal girls participating in the Lessons in Epidemiology and Genetics of Adult Cancer From Youth (LEGACY) Girls Study (8) and the timing of subsequent development of pubertal characteristics (i.e., pubic hair and breast development and menarche). We hypothesized that higher scores for anxiety and potentially other symptoms of internalizing, as reported by mothers before the appearance of pubertal signs, would be associated with earlier pubertal development. We also investigated whether increased self-reported maternal stress, anxiety, and depression, as well as family functioning and communication, were associated with pubertal timing in daughters, because these factors may independently influence pubertal timing and/or influence maternal reporting of pubertal signs.

METHODS

Study sample

The LEGACY Girls Study is a prospective cohort of 1,040 girls enrolled at 5 study sites in the United States (New York City, New York; Philadelphia, Pennsylvania; Salt Lake City, Utah; San Francisco Bay area, California) and Canada (Toronto, Ontario) from 2011 through 2013 (8, 9). These are the 5 North American sites of the Breast Cancer Family Registry cohort of breast cancer families (10, 11). Girls with a breast cancer family history (BCFH) were recruited through Breast Cancer Family Registry participants, local cancer registries, and cancer genetics and oncology clinics. Girls, usually without a BCFH, were also recruited through local pediatric practices, friend referrals, social media, and community outreach. Girls were primarily between the ages of 6 and 13 years at recruitment and 51% had a BCFH, defined as breast cancer in a first- or second-degree relative. The mother was the participating guardian for 97% of the girls. For this study, which relied on maternal reports, we excluded the 3% of girls without a participating mother.

Questionnaires and measurements were administered at baseline and every 6 months thereafter. The current analysis includes prospective follow-up data collected through August 2016. Mothers provided written informed consent for themselves and their daughters. Daughters also provided written informed assent according to local institutional standards. The study was approved by the institutional review boards of the collaborating institutions.

Of the 1,040 girls in the cohort, 861 (83%) had internalizing symptom data reported by their mothers as described later in this section ($n = 697$ mothers, some with multiple daughters participating, also reported information on their own symptoms and family functioning). Information was missing on breast development for 3 girls and on pubic hair development for 12 girls. No girls were missing menarche information. Analyses of each outcome excluded girls who had already experienced the outcome at baseline (thus, there was no left censoring), leaving 447 girls in the analyses of breast development onset ($n = 320$ subsequently started breast development; $n = 120$ were censored), 456 girls in the analyses of pubic hair onset ($n = 271$ subsequently started pubic hair development; $n = 185$ were censored), and 681 in the analyses of menarche ($n = 294$ subsequently started menstruating; $n = 387$ were censored). Although girls reported on their own development and some psychosocial characteristics from the age of 10 years, by this age, 40% of girls had begun breast development. Therefore, to avoid bias associated with restricting analysis to girls with later pubertal onset, we used maternal reports, because these were available across all ages.

Growth and development

We assessed pubertal development by questionnaire every 6 months. Mothers assessed their daughters' stages of breast and pubic hair development using the Sexual Maturation Scale (12) that shows drawings of the 5 Tanner stages (TS) (13). Breast TS2 and pubic hair TS2 indicate the onset of breast and pubic hair development, respectively (13). We previously found maternal reports of breast onset using this approach to be highly reliable ($\kappa = 0.73$) and valid (sensitivity = 77%; specificity = 94%) in a subset of girls in the LEGACY Study who also had clinical breast TS (14). Where applicable, mothers reported their daughter's age at menarche in half-year intervals. We were not able to examine pubertal tempo (i.e., the timing of progression through pubertal stages) because we did not have sufficient follow-up for the different outcomes within the same individual. Height and weight were measured twice every 6 months by trained research staff using a stadiometer and a digital scale. We used the averages to calculate body mass index (BMI), defined as weight (kg) divided by square of height (m^2), and calculated the percentiles for age using the 2000 US Centers for Disease Control and Prevention growth charts (15). Models included the baseline BMI percentile.

Psychosocial measures

As previously described (16), mothers completed behavioral surveys before other baseline study assessments. These surveys included maternal report of girls' functioning using the Behavioral Assessment System for Children-2, a tool used in clinical assessment of child behavior and emotion. Mothers completed the Internalizing Composite Scale, which includes subscales for anxiety, depression, and somatization, with established criteria for clinical at-risk status ($t \geq 60$) (17). We used the individual scores for each subscale

as well as the internalizing composite scale score. (17). Percentiles were used as in our previous work (16). Maternal anxiety and depression symptoms were assessed using the Hospital Anxiety and Depression Scale (18, 19). Mothers also reported on their stress using the Perceived Stress Scale (20) and on family functioning and communication using the general function and communication subscales of the McMaster Family Assessment Device (21, 22).

Statistical analysis

We examined associations of psychosocial measures with timing of pubertal outcomes using multivariable Cox proportional hazards regression (23). Follow-up time was calculated from the date of baseline behavioral assessment in prepubertal girls to the midpoint between the date when the mother last reported TS1/premenarche and the date when the mother first reported TS2/menarche. Girls who did not transition to TS2 or menarche during follow-up were censored at date of last follow-up. We adjusted models for aspects of our study design (study center; BCFH), variables known to be strongly associated with pubertal development (age at baseline, race/ethnicity, baseline BMI percentile), and an indicator of socioeconomic status (maternal education). We previously observed an association between BCFH and the timing of breast development onset in this cohort (9). We evaluated maternal age at menarche as a potential confounder, but we excluded it from final models because there was little impact on estimates. We used a robust variance estimator to account for familial clustering arising from the participation of siblings within the cohort.

The Cox proportional hazards assumption was assessed by testing for interactions between predictors and log-transformed time and by evaluating plots of smoothed and scaled Schoenfeld residuals over time. We found no evidence that the proportional hazards assumption was violated. We conducted sensitivity analyses using subgroup analyses in girls younger than 8 years at baseline (reducing enrichment for later pubertal onset), by race/ethnicity (non-Hispanic White girls and girls of all other race/ethnicities), and in the subset of girls with available clinical breast TS information. We also conducted sensitivity analyses examining associations using Weibull regression with interval censoring, rather than censoring at the midpoint, for girls who transitioned from TS1/premenarche to TS2/menarche between follow-up dates. This method requires more assumptions than does Cox proportional hazards regression, assuming the functional form of the baseline hazard in addition to assuming proportional hazard functions (24).

Finally, we conducted sensitivity analyses using age as the time scale. Both the Weibull regression and using age as the time scale produced estimates consistent with our primary analysis (data not shown). In the results, we present hazard ratios and 95% confidence intervals for each pubertal event associated with a 1–standard deviation change in the psychosocial factor. Statistical significance was defined as $P < 0.05$ for a 2-sided test. All analyses were conducted using Stata 15.1 (StataCorp LP, College Station, Texas).

RESULTS

Study population characteristics for each outcome are shown in Table 1. Overall, the girls demonstrated an average amount of internalizing symptoms as reported by their mothers (mean percentile scores close to 50). Mothers also did not have elevated scores of stress, anxiety, or depression overall. As expected, there were moderate correlations among all the scores (Web Table 1, available at https://academic.oup.com/aje). As described in *Methods*, internalizing is a composite of anxiety, depression, and somatization and, therefore, highly correlated with these subscales. The BMI percentile was not correlated with any psychosocial measures.

Higher overall internalizing in the daughters, as reported by the mothers, was significantly associated with earlier onset of breast development, after adjustment for age at assessment, race/ethnicity, study center, maternal education, BMI percentile, and BCFH (Table 2). This relationship appeared to be largely driven by the association with the anxiety component of internalizing. There was a similar, but not statistically significant, association between earlier breast development and anxiety scores that were clinically high, which occurred in 56 girls (12.5%; hazard ratio (HR) = 1.23, 95% confidence interval (CI): 0.89, 1.71). Higher anxiety scores in the daughters were also associated with earlier onset of pubic hair, but not earlier menarche (Table 2). When the analysis was restricted to the subset of girls who were younger than 8 years at baseline, the associations with age at onset of breast development were slightly stronger (Table 3). Menarche cannot be examined in this age group because it is rare within our window of follow-up time.

We conducted several additional analyses to explore whether maternal psychological state could explain the association between anxiety in girls and pubertal timing. There was some evidence that mothers' self-reports of their own anxiety was associated with earlier onset of breast development in their daughters (Table 4); however, after the inclusion of the maternal report of the daughter's anxiety and maternal self-reported anxiety in the same model, the association with maternal anxiety was weaker (HR = 1.09, 95% CI: 0.95, 1.25), whereas the association with maternal report of daughter's anxiety symptoms remained statistically significant (HR = 1.17, 95% CI: 1.01, 1.35). There was little consistent evidence for associations between stress, anxiety, and depression in the mother, or family communication and functioning, and the development of pubertal characteristics in the daughter (Table 4, Web Tables 2 and 3). There was no statistical evidence for multiplicative interaction between anxiety in mothers and daughters in relation to the onset of breast development ($P = 0.57$). We assessed the association of anxiety in daughters with the timing of breast development onset separately for those with mothers who had baseline anxiety scores below the median and those with scores equal to or greater than the median. The results were virtually identical (HR = 1.18, 95% CI: 0.97, 1.44; and HR = 1.19, 95% CI: 0.99, 1.44, respectively).

When we examined internalizing symptoms in the subset of girls with clinical breast TS information, we observed

Table 1. Baseline Characteristics in Each Analytic Subcohort of Girls Assessed Before the Onset of the Development of Pubertal Characteristics, the Lessons in Epidemiology and Genetics of Adult Cancer From Youth Girls Study (*n* = 1,040), 2011–2016

Characteristic	Breast Development (*n* = 447)			Pubic Hair Development (*n* = 456)			Menarche (*n* = 681)		
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
Race/ethnicity									
Non-Hispanic White	316	70.7		326	71.5		469	68.9	
Other	131	29.3		130	28.5		212	31.1	
Study center									
Philadelphia, PA	66	14.8		68	14.9		110	16.2	
New York, NY	78	17.5		76	16.7		112	16.5	
Salt Lake City, UT	89	19.9		88	19.3		118	17.3	
Toronto, ON, Canada	76	17.0		82	18.0		117	17.2	
San Francisco Bay area, CA	138	30.9		142	31.1		224	32.9	
Maternal education									
Some college or less	93	20.8		99	21.7		151	22.2	
Bachelor's degree	179	40.0		182	39.9		261	38.3	
Graduate degree	170	38.0		170	37.3		263	38.6	
Missing	5	1.1		5	1.1		6	0.9	
Breast cancer family history									
None	235	52.6		228	50.0		349	51.3	
Second degree only	133	29.8		148	32.5		206	30.3	
First degree	79	17.7		80	17.5		126	18.5	
Daughter's age at behavioral assessment, years			8.6 (1.6)			8.6 (1.5)			9.4 (1.9)
Body mass index percentile			41.0 (28.2)			44.3 (29.5)			45.4 (29.7)
Maternal-reported internalizing symptoms in girls[a]									
Anxiety			45.9 (28.9)			45.4 (29.1)			46.9 (29.3)
Depression			53.3 (27.3)			52.6 (27.3)			52.5 (26.9)
Somatization			46.4 (30.9)			46.4 (30.7)			46.6 (31.0)
Internalizing			47.5 (29.4)			47.1 (29.7)			47.9 (29.4)
Maternal self-reported internalizing symptoms									
Stress[b]			4.8 (2.7)			4.9 (2.7)			4.8 (2.7)
Anxiety[c]			7.0 (3.6)			7.0 (3.7)			6.9 (3.7)
Depression[c]			3.3 (2.7)			3.4 (2.8)			3.2 (2.8)
Family communication[d]			17.9 (3.8)			18.1 (3.6)			18.0 (3.8)
Family functioning[d]			21.4 (5.3)			21.7 (5.2)			21.4 (5.3)

Abbreviations: CA, California; NY, New York; ON, Ontario; PA, Pennsylvania; SD, standard deviation; UT, Utah.

[a] Anxiety, depression, and somatization data from the internalizing subscales of the Behavior Assessment System for Children-2 (percentiles). Internalizing is a composite of the other scales.

[b] Perceived Stress Scale score.

[c] Hospital Anxiety and Depression Scales scores.

[d] General function and communication subscales of the McMaster Family Assessment Device.

similar results, albeit with less precision given the smaller subset (Web Table 4). The relationship between internalizing symptoms in girls and pubertal outcomes was generally similar in non-Hispanic White girls and in all other groups combined, although the estimates for the latter group were imprecise (Web Table 5). There was no statistical evidence for any multiplicative interactions between internalizing symptom and race/ethnicity.

Table 2. The Association of Maternal-reported Internalizing Symptoms With the Timing of Subsequent Development of Pubertal Characteristics in All Girls Recruited Before Pubertal Onset, the Lessons in Epidemiology and Genetics of Adult Cancer From Youth Girls Study (n = 1,040), 2011–2016

Symptom in Girls	Breast Development[a]			Pubic Hair Development[b]			Menarche[c]		
	HR[d]	95% CI	*P* Value	HR[d]	95% CI	*P* Value	HR[d]	95% CI	*P* Value
Anxiety[e]	1.22	1.09, 1.36	<0.001	1.15	1.01, 1.30	0.04	0.94	0.83, 1.07	0.35
Depression[e]	1.05	0.92, 1.19	0.49	1.09	0.96, 1.24	0.16	1.02	0.91, 1.15	0.73
Somatization[e]	1.13	1.01, 1.27	0.04	1.06	0.93, 1.21	0.38	1.02	0.91, 1.15	0.70
Internalizing[e]	1.17	1.04, 1.32	0.01	1.12	0.98, 1.28	0.10	0.99	0.88, 1.12	0.90

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] n = 447; no. of events = 320; cumulative days of follow-up = 293,741.
[b] n = 456; no. of events = 271; cumulative days of follow-up = 343,183.
[c] n = 681; no. of events = 294; cumulative days of follow-up = 601,318.
[d] HR is for a 1–standard deviation change in the psychosocial factor adjusted for age at assessment, race/ethnicity, study center, maternal education, body mass index percentile, breast cancer family history.
[e] Anxiety, depression, and somatization data from the parent-reported internalizing subscales of the Behavior Assessment System for Children-2 (percentiles). Internalizing is a composite of the other scales.

DISCUSSION

Consistent with our hypothesis, we found that maternally reported anxiety symptoms in daughters before any pubertal sign and, to a lesser extent, other internalizing symptoms were associated with earlier onset of pubic hair and breast development at subsequent follow-up visits. The observed hazard ratio of 1.22 translates into breast development occurring approximately 3 months earlier, on average, in girls in the top quartile of anxiety scores (which equates approximately with 1 standard deviation above the mean) compared with girls in the lowest quartile. These associations were stronger in girls who were younger than 8 years at recruitment, a group that would be more broadly representative because it is less weighted toward girls with later pubertal onset. The associations with early breast development were not explained by maternal anxiety and were evident after accounting for other factors, including the daughter's race/ethnicity and BMI percentile, maternal education, and the presence of a BCFH. We did not find any association of maternally reported internalizing symptoms with subsequent menarche.

The first sign of puberty in girls is the onset of breast development and/or the appearance of pubic hair (25), with menarche generally occurring a few years later. The age of pubertal onset can vary considerably between individual girls (26, 27). There is accumulating evidence that, in developed countries over recent decades, the onset of

Table 3. Association of Maternal-Reported Internalizing Symptoms With Timing of Subsequent Development of Pubertal Characteristics[a] in Girls Aged < 8 Years and Prepubertal at Recruitment in the Lessons in Epidemiology and Genetics of Adult Cancer From Youth Girls Study (n = 1,040), 2011–2016

Symptom in Girls	Breast Development[b]			Pubic Hair Development[c]		
	HR[d]	95% CI	*P* Value	HR[d]	95% CI	*P* Value
Anxiety[e]	1.40	1.11, 1.76	0.01	1.23	0.94, 1.61	0.13
Depression[e]	1.28	1.03, 1.58	0.02	1.09	0.86, 1.40	0.47
Somatization[e]	1.23	0.98, 1.53	0.07	1.08	0.82, 1.42	0.58
Internalizing[e]	1.37	1.10, 1.72	0.01	1.16	0.89, 1.51	0.27

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Menarche could not be evaluated because few girls younger than 8 years reached menarche.
[b] n = 181; no. of events = 93; cumulative days of follow-up = 160,913.
[c] n = 183; no. of events = 64; cumulative days of follow-up = 179,762.
[d] HR is for a 1–standard deviation change in the psychosocial factor adjusted for age at assessment, race/ethnicity, study center, maternal education, body mass index percentile, breast cancer family history.
[e] Anxiety, depression, and somatization data from the parent-reported internalizing subscales of the Behavior Assessment System for Children-2 (percentiles). Internalizing is a composite of the other scales.

Table 4. Association of Maternal Self-Report of Internalizing Symptoms and Family Functioning With Subsequent Timing of Breast Development Onset in All Girls Recruited Before Onset, Mothers (n = 821) From the Lessons in Epidemiology and Genetics of Adult Cancer From Youth Girls Study, 2011–2016

Symptom in Mothers and Families	No.	Events	Days of Follow-up	HR[a]	95% CI	
Stress[b]	323	243	207,186	1.06	0.93, 1.21	0.41
Anxiety[c]	324	245	207,894	1.14	1.00, 1.30	0.05
Depression[c]	323	243	207,400	1.02	0.89, 1.16	0.82
Family communication[d]	314	237	202,823	1.11	0.97, 1.28	0.14
Family functioning[d]	319	242	204,972	1.10	0.96, 1.26	0.16

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] HR is for a 1–standard deviation change in the psychosocial factor adjusted for daughter's age at assessment, race/ethnicity, study center, maternal education, body mass index percentile, breast cancer family history.

[b] Perceived Stress Scale score.

[c] Hospital Anxiety and Depression Scales scores.

[d] General function and communication subscales of the McMaster Family Assessment Device.

breast development is occurring earlier, whereas the age at menarche has remained stable (1, 2). Earlier pubertal signs in girls are an issue of concern because they have been associated with several adverse psychosocial and cardiometabolic health outcomes (1, 3, 4). Early breast development has been associated with an approximate 20% increased breast cancer risk, independent of age at menarche (28). However, most epidemiologic studies of pubertal timing and health outcomes have been focused on the relationship of menarche timing with health outcomes rather than pubertal onset.

Many factors contribute to the variation in pubertal timing in girls. Genetics plays a role (2) but cannot account for secular trends. Obesity contributes to earlier pubertal onset, but other factors are likely involved (1, 2, 4). Although energetic stress associated with severe malnutrition is associated with delayed puberty, environments related to psychosocial stress are associated with earlier pubertal development (1). The underlying theory for this relationship is the evolutionary benefit from earlier puberty and reproduction in girls growing up in adverse conditions, as long as there are sufficient resources for physical development and reproduction (5, 29). Consistent with this theory is that adverse socioeconomic and/or family circumstances are associated with earlier puberty in girls (1, 3). Psychosocial stress in girls may mediate the relationship between adverse environments and pubertal timing (30).

In nearly all studies to date on the relationship between stress and pubertal timing in girls, only external stressors were considered; how girls respond was not. In a small study of 28 girls aged 12–15 years at assessment, recalled anxiety or anxiety combined with depression were associated with earlier menarche, but the retrospective nature of that study is a major limitation, because recalled psychological state could be influenced by current state (7). In the prospective Millennium Cohort Study of 5,839 girls, maternally reported socioemotional difficulties at age 7 years were associated with menarche by age 11 years (6). To our knowledge, there are no studies on the relationship of anxiety and other internalizing symptoms in prepubertal girls and the timing of pubertal onset.

It is interesting that in our prospective study, prepubertal anxiety was associated with earlier puberty onset but not with menarche, despite greater statistical power for the latter outcome. This result suggests the psychosocial status of girls is primarily associated with earlier, but not later, stages of pubertal development. That association is not consistent with evolutionary theory, by which an earlier transition to full reproductive status in stressful conditions would be expected (3). However, in a study of 114 girls and boys, among children with low parental supportiveness, those exhibiting a high level of sympathetic nervous system reactivity had more rapid pubertal development, defined by TS, specifically before age 12.5 years, compared with children with low reactivity, but differences diminished with age (31). Some individuals may develop more rapidly only at early or later stages (31).

The key strength of our study is the prospective design that allowed us to examine the relationship of psychosocial factors in girls before the appearance of pubertal signs with subsequent pubertal developmental milestones. We found no evidence for differences by race/ethnicity, although we were limited by statistical power. Most mothers (78%) had a bachelor's or graduate degree, limiting the socioeconomic diversity of our cohort. Our cohort was enriched for girls with a BCFH, which could alter the prevalence of internalizing symptoms, but we have not observed differences in the prevalence of internalizing symptoms in girls with and those without a BCFH (16) The girls had mean percentile internalizing symptom scores close to 50% and the proportion with clinically high values of anxiety symptoms, 12.5%, was within the broad range of anxiety prevalence observed in other populations (32) and consistent with the 12.6% prevalence of clinical anxiety in a recent, large, community-based sample (33).

The main limitation of the study is that mothers provided information on both the psychological and pubertal status

of the daughters, albeit using different instruments and at different times, which allowed us to assess a temporal relationship. The literature is variable regarding the consistency of mother versus child reports of anxiety symptoms. In general, the agreement is low to moderate and mothers often under-report symptoms (32, 33). In the girls aged ≥10 years in the LEGACY Girls Study who reported their own anxiety and depression symptoms, the percentile scores were moderately correlated with the maternally reported scores (Spearman ρ = 0.45 and 0.41, respectively, both with $P < 0.001$). The psychological status of mothers can influence the agreement, but the reported direction of this influence is quite variable (32, 33). It is important to note that our finding of an association between mother-reported child anxiety symptoms and breast development onset did not differ by self-reported anxiety in the mothers. By age 10 years, many girls had started showing the first signs of puberty; thus, our outcomes relied on maternal report. With respect to the assessment of pubertal status, we have previously shown good reliability of maternal reports in our cohort within a subset of girls who also had standardized clinical assessment of breast development (14). We also observed similar findings when we used clinical breast TS as the outcome within this subset, indicating that it is unlikely that our findings are explained by biased maternal reporting. We did not perform clinical examination of pubic hair, but we note that the mother-daughter agreement for pubic hair onset in girls ≥10 years was moderate to good ($\kappa = 0.69$), and in reports of the limited studies on the topic, authors suggest self-staging may be more reliable than maternal reporting for this outcome (14). Measurement error may have attenuated the associations we observed, but research is needed using multi-informant approaches for psychosocial measures and clinical assessment of pubertal characteristics (32, 33) to confirm and expand on our findings.

We cannot exclude the possibility of reverse causality, where anxiety increased as a result of early hormonal changes before the physical signs of puberty. The temporality of events could be examined in research incorporating sequential measurements of hormone metabolites, which can be assessed in urine samples.

Our results suggest that girls who show signs of anxiety before the first signs of puberty are more likely to enter puberty at an earlier age, although more work is needed to confirm this finding. The findings are consistent with the concept that psychosocial stress is associated with earlier puberty in girls (3), but we provide an additional perspective to previous work that linked exposure to stressful environments, such as low socioeconomic status and high familial conflict, to earlier pubertal development (1, 5). Our results suggest the ability of young girls to cope with stress, manifested by the presence or absence of internalizing symptoms, may be relevant to the onset of puberty. This finding lends support to screening and treating youth for anxiety (34), which do not require the use of medications, because there are other evidence-based interventions to reduce youth anxiety (34, 35). As indicated by our results, such interventions may not only benefit stress and coping but may also have the incremental benefit of reducing the risk of earlier pubertal onset and the associated psychological and physical effects.

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