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Pubertal development and risk of premenstrual disorders in young adulthood

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STUDY QUESTION: Is pubertal timing associated with risk of premenstrual disorders (PMDs) in young adulthood?

SUMMARY ANSWER: Late pubertal development is associated with decreased premenstrual symptom burden and risk of PMDs in young adulthood.

WHAT IS KNOWN ALREADY: PMDs, including premenstrual syndrome and premenstrual dysphoric disorder, may begin during the teenage years. Few risk factors in early life have been identified for PMD development.

STUDY DESIGN, SIZE, DURATION: A prospective cohort study of 6495 female participants during 1996–2013.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We included participants from the Growing Up Today Study (GUTS). Pubertal development was indicated by the timing of menarche, breast and pubic hair growth. Self-reported age at menarche was longitudinally assessed at enrollment (in 1996/2004 for GUTS I/II) and onwards, and classified as early (age $\leq$ mean $-$ SD, 11.64 years), normative and late menarche (age $\geq$ mean $+$ SD, 13.95 years). Timing of pubic hair and breast growth were assessed multiple times during follow-up via Tanner scales, and classified into early, normative and late development according to mean $\pm$ SD. Using a validated questionnaire based on the Calendar of Premenstrual Experiences, we assessed premenstrual symptoms and identified probable cases of PMDs in 2013. We examined the associations of timing of pubertal development with premenstrual symptom score and disorders using multivariable linear and logistic regressions, respectively.

MAIN RESULTS AND THE ROLE OF CHANCE: In 2013 (mean age = 26), 1001 (15.4%) individuals met criteria for a PMD. An inverse association was found between age at menarche and premenstrual symptom z-score (β −0.05 per year, 95% CI −0.07 to −0.03) and risk of PMDs (odds ratio (OR) 0.93 per year, 95% CI 0.88 to 0.99). Compared to individuals with normative menarche, individuals with late menarche had a lower risk of PMDs (OR 0.73, 95% CI 0.59 to 0.91), while individuals with early menarche had comparable odds (OR 0.98, 95% CI 0.81 to 1.18). Moreover, early growth of pubic hair was associated with increased premenstrual symptoms (z-score β 0.09 per year, 95% CI 0.02 to 0.17) and PMD risk (OR 1.28, 95% CI 1.04 to 1.56), independent of age at menarche. No associations were noted for breast development.

LIMITATIONS, REASONS FOR CAUTION: One major limitation is some misclassification of menarche due to recall. We, however, showed robust association among participants who were premenarcheal at baseline.

WIDER IMPLICATIONS OF THE FINDINGS: Our findings suggest that pubertal timing, particularly timing of menarche, is inversely associated with the risk of developing premenstrual symptoms in young adulthood, and that women with later menarche have significantly lower risk of PMDs. Information on PMDs should be provided to teenage girls and their parents. If these findings are confirmed in independent populations, prevention strategies and early detection programs may be considered for women with early pubertal development.

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Introduction

Premenstrual disorders (PMDs), including premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD), are characterized by mood and somatic symptoms cyclically occurring in the days before menstruation (Yonkers and Simoni, 2018). PMS manifests both as mood and somatic symptoms, while PMDD is primarily dominated by mood symptoms with significant functional impairment (Yonkers and Simoni, 2018). With estimated prevalence of 20–30% for PMS and 2.1–6.4% for PMDD, PMDs affect millions of women around the world and have a profound impact on quality of life (Cohen *et al.*, 2002; Qiao *et al.*, 2012; Chumpalova *et al.*, 2020). Although the peak age of seeking healthcare is in the late 20s, the symptoms of PMDs may in fact begin during the teenage years (Robinson and Swindle, 2000). Cross-sectional studies have shown that PMDs in adolescents occur as frequently as in adults (Steiner *et al.*, 2011). A handful of adulthood risk factors have been identified for PMDs, including dietary factors (e.g. low calcium and B vitamins) (Bertone-Johnson *et al.*, 2005; Chocano-Bedoya *et al.*, 2011), obesity (Bertone-Johnson *et al.*, 2010) and smoking (Bertone-Johnson *et al.*, 2008). Except for childhood emotional and physical abuse (Bertone-Johnson *et al.*, 2014a), little is known regarding what early-life factors may play a role in the development of PMDs, particularly for those emerging after adolescence.

Although the etiology of PMDs is not fully understood, exposure to fluctuating sex hormones clearly contributes, as PMDs do not precede menarche (Yonkers and Simoni, 2018). The elevation and cyclicity of hormones in puberty modulate the sensitivity of the neuroendocrine system, which may lead to premenstrual symptoms in some individuals (Rubinow and Schmidt, 2018). Emerging evidence also supports that pubertal timing plays an important role in adolescent neurodevelopment through sex hormones (Goddings *et al.*, 2019). It is thus plausible that earlier and/or later exposure to the elevation and cyclicity of hormones (e.g. early/late menarche) might predispose individuals to differential risk of PMDs. So far, most studies have employed cross-sectional designs and retrospectively collected information on menarche, which have yielded conflicting results on the association between menarche and PMDs (Cohen *et al.*, 2002; Lee *et al.*, 2006; Silva *et al.*, 2008; Zegeye *et al.*, 2009; Issa *et al.*, 2010; Czajkowska *et al.*, 2015; Yoshimi *et al.*, 2019). We are not aware of studies investigating other indicators of pubertal timing, such as pubic hair and breast growth. Leveraging a large-scale prospective cohort in the USA, here we examined the association of pubertal development (including timing of menarche, pubic hair and breast growth) with subsequent risk of PMDs in young adulthood.

Materials and methods

Study design

The Growing Up Today Study (GUTS) is a prospective cohort study which includes 15 044 girls and 12 761 boys residing across 50 US states who were children of participants in the Nurses' Health Study II (NHS II) (Rockett *et al.*, 2001). Children recruited in the first phase (GUTS I; N = 16 882) were aged 9–14 years at enrollment in 1996, while aged 9–16 years at enrollment in 2004 in the second phase (GUTS II; N = 10 923). Briefly, a letter was sent to ~40 000 nurses participating in the NHS II who had at least one child aged 9–14 years in 1996, inviting their child/children to participate. If the nurse mother consented, an invitation letter and baseline questionnaire were sent to their child/children (~27 000 (68%)); of those invited 68% of girls (N = 9039) and 58% of boys (N = 7843) returned a completed questionnaire.

A similar approach was taken to recruit participants for GUTS II in 2004, when ~21 000 NHS2 participants who gave birth between 1989 and 1993 were sent invitations. Consent was received from 17 280 (82%) women and completed questionnaires were ultimately received from 68% of girls (N = 6005) and 58% of boys (N = 4918).

Participants were followed through questionnaires annually during 1996–2001 and then every 2/3 years through 2013. Beginning with the 2013 questionnaire cycle, the two cohorts were combined and are now followed together as the GUTS cohort. The response rate for each questionnaire cycle has ranged from 55% to 87% among girls. A total of 7896 girls responded to the questionnaire in 2013, when PMDs were assessed. Girls who missed all items in the assessment of pubertal development (N = 29) or PMDs (N = 1372) were excluded, yielding a final cohort of 6495 participants. Characteristics were highly comparable between included and excluded participants, including timing of menarche. Early menarche was experienced by 15.8% of included participants vs. 15.1% of non-respondents, while mean age at menarche was 12.8 vs. 12.7 years (Supplementary Table SI).

This study was approved by the Institutional Review Board of the Brigham and Women's Hospital. At enrollment, mothers provided informed consent and the children assented by completing baseline questionnaires.

Pubertal development

We used the timing of menarche, pubic hair and breast growth as proxies to study pubertal development. According to the Tanner stages (Marshall and Tanner, 1969), both pubic hair and breast growth

are classified into five stages. Pubic hair growth stages range from no hair (Stage P1; i.e. prepuberty) to hair outside of triangle (Stage P5), whereas breast growth ranges from flat appearance (Stage B1; i.e. prepuberty) to areola flattens down (Stage B5). Typically, pubertal development follows the order of P2> B2> B3> P3> P4> B4> menarche> P5> B5 (Marshall and Tanner, 1969).

Menarche

Age at menarche was longitudinally assessed on all questionnaires during 1996–2003 in GUTS I and 2004–2008 in GUTS II. At enrollment, 3484 (53.9%) girls were reported as premenarchal and 1783 (27.5%) girls had menarche in the past 2 years. During follow-up, the girls were repeatedly asked 'Have you started having menstrual periods?' and 'If yes, age when periods began', by reporting age in years and calendar month at menarche. We derived age at menarche from these serial questionnaires by using the first report whenever possible. If month was never reported, we imputed it as 6 months after the reported integer age. Overall, 6348 (97.7%) participants reported age at menarche which was normally distributed with a mean of 12.79 (SD, 1.16) years. It was further categorized into early (≤1 SD below the sample mean; i.e. ≤11.64 years), normative (within 1 SD from the mean; i.e. >11.64 to <13.95 years) and late menarche (≥1 SD above the mean; i.e. ≥13.95 years).

Pubic hair and breast growth

Using the Tanner scales (Marshall and Tanner, 1969), both pubic hair and breast growth were longitudinally assessed via diagrams during 1996–1998 in GUTS I, while pubic hair growth was additionally reported in 1999 in GUTS I and during 2004–2008 in GUTS II. Participants who reported P5/B5 at baseline were excluded from corresponding analyses (N = 1010 and 219, respectively) as such development had ended before enrollment. We always took the first report for each stage and discarded downstage reports across questionnaires. Overall, 5387 (82.9%) and 3761 (94.0%) participants reported at least once for pubic hair and breast stage, respectively. We classified timing of pubic hair and breast growth into early (if age at any stage from P2/B2 to P5/B5 was ≤1 SD below the sample mean), normative (within 1 SD from the mean) and late development (≥1 SD above the mean). Age at each stage is normally distributed and the mean and SD (along with cutoffs in Supplementary Table SII) of each stage are largely comparable to the US population (Sun *et al.*, 2002).

Premenstrual disorders

PMDs were assessed in 2013 using a questionnaire based on the Calendar of Premenstrual Experiences (Mortola *et al.*, 1990); a similar version has been successfully used in NHS II (Bertone-Johnson *et al.*, 2007). Briefly, participants were provided with a list of 8 affective and 19 physical/behavioral symptom items and asked if each was experienced in 'most months of the year for at least several days before [their] menstrual period begins' and if so, to rate the severity as none, mild, moderate or severe. We scored each symptom from 1 to 4, summed a total score (range 27–108), and converted to z-score for premenstrual symptoms. While 91% of participants completed all items, symptoms with missing information were imputed by using a mean score of other symptoms reported by this individual (<1% of participants missed >5 out of 27 symptoms).

Participants further rated overall severity for their symptoms and whether their symptoms caused relationship problems with family/partner or friends/coworkers, poor work/school performance and increased desire to be alone, in categories of none/minimal, mild, moderate and severe. Individuals were classified as having a PMD if they met four criteria (Bertone-Johnson *et al.*, 2007): (i) ≥1 physical/behavioral symptoms and ≥1 affective symptoms; (ii) overall symptom severity of moderate/severe, or impact on life activities/relationships as moderate/severe, or ≥1 affective symptoms rated as severe; (iii) symptoms beginning within 14 days, and ending within 7 days, of the start of menses; and (iv) symptoms absent in the week after menses. The criteria were validated in a cross-sectional study by using daily symptom diaries (Bertone-Johnson *et al.*, 2014b).

PMDs were further grouped as PMS or probable PMDD (Bertone-Johnson *et al.*, 2009); criteria for the latter included (i) ≥1 of 4 severe affective symptoms including irritability/anger, mood swings/tearful, depression and anxiety; (ii) ≥5 of 11 symptom groups including the 4 above and hypersensitivity, desire for aloneness, insomnia, difficulty concentrating, fatigue, food cravings and/or other physical symptoms; and (iii) impact on life activities/relationships as moderate/severe. We aimed to specifically examine PMDs associated with pubertal development, which is typically completed by the end of adolescence. We thus classified PMDs according to the symptom onset below or above age 20, by asking at what age their symptoms generally began (since the first period, in the teens, 20s or 30s).

Covariates

Race, maternal marital status and use of multivitamin were reported at baseline, while paternal educational level was reported by mothers in 1999 in NHS II. Physical activity at baseline was estimated as total metabolic equivalent (MET) hours per week spent in activities of moderate to vigorous intensity (≥4 MET) (Ainsworth *et al.*, 2011). Average number of weekly hours spent in each qualifying activity was multiplied by its MET, and the products were summed to calculate weekly MET-hours. Baseline BMI was calculated using self-reported height and weight, and categorized into underweight, normal, overweight and obese according to the extended International Obesity Task Force (Cole and Lobstein, 2012). Information on adult BMI, smoking, alcohol drinking, parity and use of hormonal contraceptives was extracted from 2010/2011 questionnaires. Experiences of childhood abuse (including emotional, physical and sexual abuse) at age <11 years were surveyed in 2007 in GUTS I (Opoliner *et al.*, 2014).

Anxiety and depression are common comorbidities (Kim *et al.*, 2004). We defined anxiety as a self-reported diagnosis of anxiety or use of minor tranquilizers, both surveyed in 2013. Depression was defined as a total score >11 using the 10-item Center for Epidemiologic Studies Depression scale (Opoliner *et al.*, 2014), a self-reported diagnosis of depression, or use of antidepressants, all queried in 2013.

Statistical analysis

We estimated βs and 95% CIs for the associations of timing of menarche with premenstrual symptoms in z-score using linear regression. We analyzed age at menarche as a continuous variable, and compared early/late menarche with normative menarche. Similarly, we estimated odds ratios (ORs) and 95% CIs of PMDs by using logistic regression. To reduce potential misclassifications of menarche or PMDs, we

performed separate sensitivity analyses by restricting to girls premenarchal at baseline, to girls who reported months for age at menarche and to participants who had natural and typical menstrual cycles and did not use hormonal contraceptives. To illustrate the relationships with timing, we also assessed the associations of total symptom score with age at menarche in years.

To shed light on subtypes, we analyzed the associations of timing of menarche with PMS and probable PMDD, symptom onset before and after age 20, as well as with and without psychiatric comorbidity, using multinomial logistic regression which regresses exposures on outcomes with more than two levels. The direct estimates from this model are relative risk ratios (equivalent to ORs) (Kwak and Clayton-Matthews, 2002). We further tested the difference between estimates of PMD subtypes using Wald test. In an additional analysis, we examined associations between age at menarche and severity of specific premenstrual symptoms, and corrected for multiple comparisons using Bonferroni correction. For the identified symptoms, we further examined associations with age at menarche by year.

BMI and physical activity are highly correlated with menarche (Bertone-Johnson *et al.*, 2010), while pubertal development pattern might be different between the GUTS I and II cohorts. We therefore examined effect modification of these factors on studied associations.

We examined the correlations of menarche, pubic hair and breast growth (as categories) using Kendall's tau coefficients. As additional pubertal markers, we analyzed pubic hair and breast growth by comparing premenstrual symptoms and PMD risk among women with early/late development to that among women with normative development.

We developed different models based on *a priori* hypotheses on potential confounders and mediators (Bertone-Johnson *et al.*, 2005, 2008, 2010; Chocano-Bedoya *et al.*, 2011). We adjusted for cohort membership and demographic characteristics (year of birth and race) in Model 1; further adjusted for potential confounders associated with both pubertal development and PMDs (baseline BMI, physical activity, paternal educational level, maternal marital status and use of multivitamin) in Model 2; and additionally adjusted for risk factors for PMDs (recent smoking, alcohol drinking and use of hormonal contraceptives) in Model 3. We performed an additional analysis of menarche by adjusting for childhood abuse (limited to GUTS I) as Model 4. Physical activity was treated as continuous, while others were categorized as showed in Table I. In analyses of pubic hair/breast growth, we also applied additional adjustment for age at menarche.

Data were prepared in SAS (version 9.4) and analyzed in Stata (version 12.1). $P < 0.05$ was considered for statistical significance.

Results

In 2013 (mean age = 26 ± 3.5 years; Supplementary Fig. S1), 1001 (15.4%) individuals met criteria for a PMD. Among them, 694 (69.3%) reported symptom onset before age 20. Compared to individuals without PMDs, individuals with a PMD were less physically active at baseline, and were more likely to smoke and less likely to use hormonal contraceptives in 2010/11 (Table I). Individuals with PMDs were more likely to report comorbid anxiety and depression symptoms.

Menarche

Across different multivariable models, we found a robustly inverse association between age at menarche and total premenstrual symptom z-score (β −0.05 per year, 95% CI −0.07 to −0.03, $P < 0.001$, in the full model; Table II). Specifically, compared to individuals with normative age at menarche, higher premenstrual symptom score was noted in individuals with early menarche (β 0.07, 95% CI 0.00 to 0.14, $P = 0.045$), whereas lower symptom score was suggested for late menarche (β −0.07, 95% CI −0.14 to 0.00, $P = 0.05$). Moreover, we observed an inverse association of age at menarche with PMDs (OR 0.93 per year, 95% CI 0.88 to 0.99, $P = 0.03$). The association was most notable for late menarche, which was associated with lower risk of PMDs (OR 0.73, 95% CI 0.59 to 0.91, $P = 0.006$); in contrast, individuals with early menarche did not have higher risk of PMDs (OR 0.98, 95% CI 0.81 to 1.18, $P = 0.81$). Additional adjustment for childhood abuse did not modify the associations in GUTS I (Supplementary Table SIII). Greater effect sizes were observed in analyses limited to girls who were premenarchal at baseline, whereas largely comparable results were yielded when excluding imputed months at menarche, and when restricting to individuals with natural and normal menstrual cycles (Supplementary Table SIV).

By analyzing age at menarche by year, such a pattern was also confirmed for premenstrual symptom score (Fig. 1). Although PMD risk was inversely associated with age at menarche beyond 11 years, no risk increase was found when age at menarche was <11 years.

In subtype analyses, largely similar associations were found between probable PMDD and PMS, as well as between disorders with and without comorbidity (Table III). Stronger associations of age at menarche and late menarche were noted for early-onset PMDs (symptoms onset <age 20) compared to associations with disorders emerging afterwards (P for difference < 0.05; Table III). We also showed that age at menarche was inversely associated with premenstrual nausea, acne, diarrhea/constipation, fatigue, anxiety/nervousness (βs from −0.04 to −0.06; corrected $P < 0.05$; Supplementary Table SV). A similar pattern was noted for these identified symptoms by age at menarche analyzed with indicator variables for each age category (<11, yearly from 11 to 14 and ≥15 years; Supplementary Fig. S2). In stratified analyses, the associations of age at menarche with risk of PMDs were largely comparable across cohort membership, baseline and adult BMI, and physical activity (Supplementary Table SVI).

Pubic hair and breast growth

Pubic hair and breast growth were highly correlated ($r = 0.572$, $P < 0.001$), and both were moderately correlated with timing of menarche (pubic hair: $r = 0.328$, $P < 0.001$; breast: $r = 0.348$, $P < 0.001$). Compared with normative pubic hair development, early development was associated with higher premenstrual symptom z-score (β 0.11, 95% CI 0.04 to 0.18, $P = 0.001$; Table IV), while late development appeared associated with a non-significantly lower symptom score (β −0.03, 95% CI −0.10 to 0.04, $P = 0.39$). Similarly, higher risk of PMDs was observed in individuals with early pubic hair development (OR 1.32, 95% CI 1.09 to 1.61, $P = 0.005$), whereas individuals with late development displayed no increased risk of PMDs. Additional adjustment for age at menarche minimally altered associations. A weak inverse association was suggested between timing of breast

Table I Age-standardized characteristics of women with and without premenstrual disorders, N (standardized %[a]) or mean ± SD; Growing Up Today Study, 1996–2013.

	Women without premenstrual disorders	Women with premenstrual disorders
Total number	5494	1001
Age at menarche, years	12.81 ± 1.17	12.68 ± 1.09
Age at survey in 2013, years	26.0 ± 3.5	25.7 ± 3.5
Year of birth		
1981–1985	2467 (44.9)	399 (39.9)
1986–1990	1986 (36.1)	410 (41.0)
1991–1995	1041 (18.9)	192 (19.2)
Cohort membership		
GUTS I	3419 (61.6)	582 (61.6)
GUTS II	2075 (38.4)	419 (38.4)
Race		
White	5143 (93.6)	940 (93.8)
Others	351 (6.4)	61 (6.2)
Baseline assessment[b]		
Maternal marital status		
Not married	427 (7.8)	79 (7.8)
Married	4851 (88.3)	878 (87.8)
Unknown	216 (3.9)	44 (4.4)
Paternal educational level		
High school or below	1575 (28.6)	309 (30.9)
College	1732 (31.6)	319 (31.8)
Postgraduate	1838 (33.5)	304 (30.5)
Unknown	349 (6.3)	69 (6.9)
Use of multivitamin		
No	3121 (56.8)	570 (57.0)
Yes	2373 (43.2)	431 (43.0)
BMI		
Underweight	595 (10.8)	80 (8.0)
Normal	3966 (72.2)	723 (72.1)
Overweight	754 (13.7)	160 (16.1)
Obese	179 (3.3)	38 (3.9)
Moderate/vigorous physical activity (MET*hours/week)	77.4 ± 55.9	75.0 ± 55.0
Recent assessment[c]		
Smoking		
Never	4343 (79.0)	716 (71.7)
Former	293 (5.4)	79 (7.5)
Current	858 (15.6)	206 (20.8)
Alcohol drinking		
No	1484 (27.1)	280 (27.3)
Monthly	1910 (34.7)	312 (31.4)
Weekly	1598 (29.1)	298 (29.8)
Daily	502 (9.1)	111 (11.6)
Parity		
0	4754 (86.6)	848 (84.5)
1+	370 (6.7)	69 (7.3)
Unknown	370 (6.8)	84 (8.2)
Use of hormonal contraceptives		
No	2696 (49.1)	553 (55.1)
Yes, with menstruation	2101 (38.2)	293 (29.4)
Yes, without menstruation	327 (5.9)	71 (7.3)
Unknown	370 (6.8)	84 (8.2)
Childhood abuse (GUTS I only)		
No	2690 (48.5)	421 (44.7)
Yes	727 (13.1)	161 (16.9)
Unknown	2 (0.04)	0
Comorbidities[d]		
Anxiety[e]		
No	4613 (84.0)	759 (75.8)
Yes	881 (16.0)	242 (24.2)
Anxiety diagnosis		
No	4663 (84.9)	771 (77.1)
Yes	831 (15.1)	230 (22.9)
Use of minor tranquilizers		
No	5324 (96.9)	950 (94.9)
Yes	170 (3.1)	51 (5.1)
Depression[f]		
No	3879 (70.6)	555 (55.6)
Yes	1615 (29.4)	446 (44.4)
Depression diagnosis		
No	4491 (81.8)	736 (73.5)
Yes	1003 (18.2)	265 (26.5)
Use of antidepressants		
No	4838 (88.1)	845 (84.3)
Yes	656 (11.9)	156 (15.7)
CES-D Scale		
<11	4862 (88.5)	776 (77.8)
>11	632 (11.5)	225 (22.2)

CES-D, Center for Epidemiologic Studies Depression; GUTS, Growing Up Today Study; MET, metabolic equivalent of task; N, number.

[a]Percentages of categorical characteristics (except for year of birth) were standardized by year of birth (yearly).

[b]Characteristics were assessed at or around the enrollment (i.e. 1996/1997 in GUTS I and 2004/2005 in GUTS II) except for paternal educational level (in 1999).

[c]Characteristics were assessed 2–3 years before the endpoint (i.e. 2010 in GUTS I and 2011 in GUTS II). If information of smoking or alcohol drinking was not available, data from questionnaires in 2007/2008 were obtained for GUTS I/GUTS II.

[d]Comorbidities were assessed in 2013 in both GUTS I and GUTS II.

[e]Anxiety included self-reported diagnosis and use of minor tranquilizers.

[f]Depression included self-reported diagnosis, use of antidepressants and the CES-D Scale scored >11.

Table II. Associations of menarche timing with subsequent risks of premenstrual symptoms (in z-score) and premenstrual disorders, β (95% CI) or OR (95% CI); Growing Up Today Study, 1996–2013.

	Age at menarche, year	Early menarche	Normative menarche	Late menarche
Premenstrual symptoms				
Women, N	6348	1025	4370	953
Score, mean (SD)	0.000 (0.999)	0.096 (1.027)	−0.002 (1.000)	−0.090 (0.956)
Model 1 β (95% CI)[a]	−0.06 (−0.08 to −0.04)*	0.09 (0.03–0.16)*	0.00	−0.09 (−0.16 to −0.02)*
Model 2 β (95% CI)[b]	−0.05 (−0.07 to −0.03)*	0.07 (0.00–0.14)*	0.00	−0.07 (−0.14 to 0.00)
Model 3 β (95% CI)[c]	−0.05 (−0.07 to −0.03)*	0.07 (0.00–0.14)*	0.00	−0.07 (−0.14 to 0.00)
Premenstrual disorders				
Events, N (%)	986 (15.5)	168 (16.4)	705 (16.1)	113 (11.9)
Model 1 OR (95% CI)[a]	0.91 (0.86–0.97)*	1.01 (0.84–1.21)	1.00	0.70 (0.56–0.86)*
Model 2 OR (95% CI)[b]	0.94 (0.88–1.00)*	0.98 (0.81–1.18)	1.00	0.74 (0.60–0.92)*
Model 3 OR (95% CI)[c]	0.93 (0.88–0.99)*	0.98 (0.81–1.18)	1.00	0.73 (0.59–0.91)*

Early menarche was defined as age at menarche ≤ mean − SD, whereas late menarche was age ≥ mean + SD.
N, number; OR, odds ratio.
[a]In Model 1, the estimates were adjusted for year of birth and cohort membership in linear and logistic regressions for premenstrual symptoms and disorders, respectively.
[b]In Model 2, the estimates were additionally adjusted for race, baseline BMI (categorical), moderate/vigorous physical activity, paternal educational level, maternal marital status and use of multivitamin.
[c]In Model 3, the estimates were additionally adjusted for smoking, alcohol drinking, parity and use of hormonal contraceptives.
*$P < 0.05$.

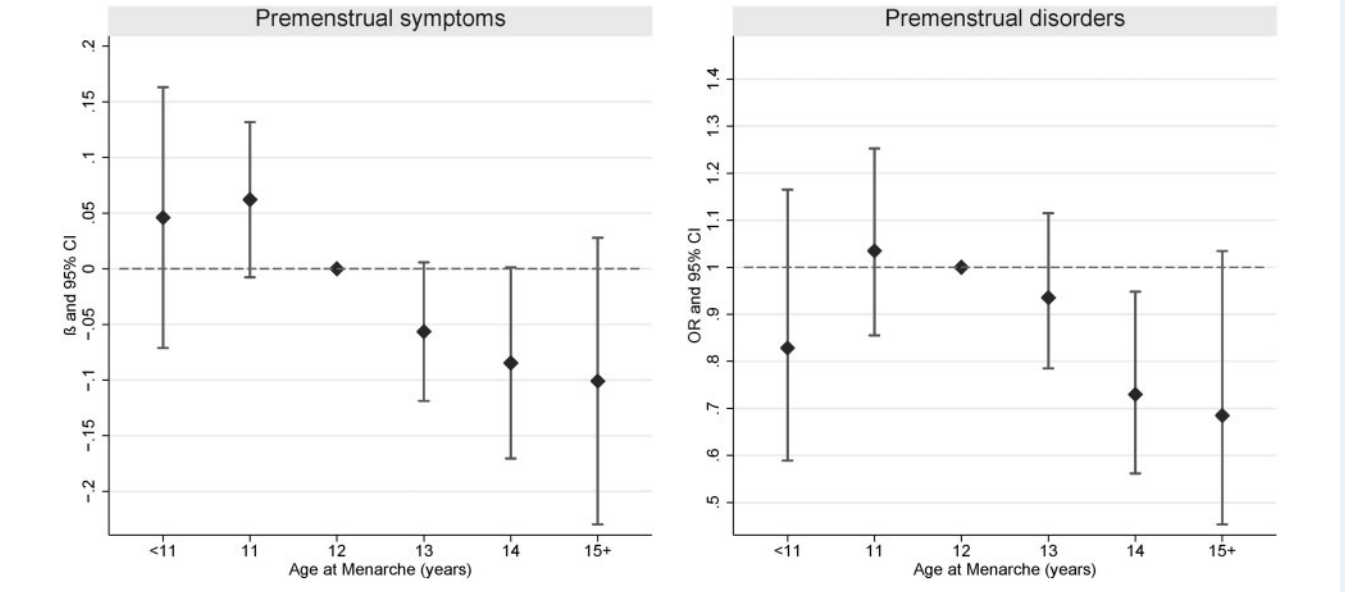

Figure 1. Associations of age at menarche with subsequent risks of premenstrual symptoms (in z-score) and disorders. Growing Up Today Study, 1996–2013. Age at menarche of 12 years was set as the reference. The estimates were adjusted for year of birth, cohort membership, race, baseline BMI (categorical), moderate/vigorous physical activity, paternal educational level, maternal marital status, and use of multivitamin, smoking, alcohol drinking, parity and use of hormonal contraceptives. OR, odds ratio.

Table III Associations of menarche with subtypes of premenstrual disorders, RRR (95% CI); Growing Up Today Study, 1996–2013.

	Age at menarche, year	Early menarche	Normative menarche	Late menarche
By severity[a]				
PMS				
Events, N (%)	846 (13.3)	144 (14.0)	602 (13.8)	100 (10.5)
RRR (95% CI)[b]	0.93 (0.87–1.00)	0.98 (0.81–1.20)	1.00	0.75 (0.60–0.95)
PMDD				
Events, N (%)	140 (2.2)	24 (2.3)	103 (2.4)	13 (1.4)
RRR (95% CI)[b]	0.93 (0.79–1.09)	0.93 (0.59–1.47)	1.00	0.63 (0.35–1.13)
P for difference[c]	0.960	0.811	–	0.568
By symptom onset				
<Age 20				
Events, N (%)	685 (10.8)	129 (12.6)	495 (11.3)	61 (6.4)
RRR (95% CI)[b]	0.87 (0.81–0.94)*	1.06 (0.86–1.31)	1.00	0.57 (0.43–0.76)*
Age 20+				
Events, N (%)	301 (4.7)	39 (3.8)	210 (4.8)	52 (5.5)
RRR (95% CI)[b]	1.08 (0.97–1.20)	0.77 (0.54–1.11)	1.00	1.11 (0.80–1.53)
P for difference[c]	<0.001	0.126	–	0.002
By comorbidity[d]				
No				
Events, N (%)	505 (8.0)	89 (8.7)	358 (8.2)	58 (6.1)
RRR (95% CI)[b]	0.93 (0.85–1.01)	1.04 (0.81–1.33)	1.00	0.73 (0.54–0.98)*
Yes				
Events, N (%)	481 (7.6)	79 (7.7)	347 (7.9)	55 (5.8)
RRR (95% CI)[b]	0.94 (0.86–1.02)	0.92 (0.71–1.19)	1.00	0.74 (0.55–1.01)
P for difference[c]	0.881	0.469	–	0.924

Early menarche was defined as age at menarche < mean − SD, whereas late menarche was age > mean + SD.
PMDD, premenstrual dysphoric disorder; PMS, premenstrual syndrome; RRR, relative risk ratio.
[a]PMS and PMDD were mutually exclusive.
[b]The estimates were adjusted for year of birth, cohort membership, race, baseline BMI (categorical), moderate/vigorous physical activity, paternal educational level, maternal marital status, use of multivitamin, alcohol drinking, parity and use of hormonal contraceptives.
[c]We used Wald test to examine the difference between estimates of subtypes.
[d]Comorbidity included anxiety and depression.
*$P < 0.05$.

development and premenstrual symptom score, whereas no association was observed with PMDs.

Discussion

In this large-scale prospective cohort of participants in the USA, we showed a consistently inverse association of age at menarche with occurrence of subsequent premenstrual symptoms and risk of PMDs in young adulthood. Moreover, stronger associations were noted for early-onset PMDs which accounts for near 70% of identified PMDs, while comparable associations were suggested for probable PMDD and PMS. We also illustrated similar associations of timing of pubic hair growth with premenstrual symptoms and PMDs.

Mixed results have been reported on the association between timing of menarche and PMDs. Four studies reported that individuals with PMDs appeared to have a younger age at menarche than individuals without these conditions (Lee *et al.*, 2006; Zegeye *et al.*, 2009; Issa *et al.*, 2010; Yoshimi *et al.*, 2019). However, none of these results were statistically significant, except for those in one study that did not adjust for any confounders. In contrast, one study indicated a positive association between age at menarche and PMDs (Czajkowska *et al.*, 2015), whereas two studies suggested a U-shaped association (i.e. increased risk in individuals with either early or late menarche) (Cohen *et al.*, 2002; Silva *et al.*, 2008). Most studies were cross-sectional and retrospectively collected information on timing of menarche in late adolescence/adulthood, whereas the only prospective cohort included two follow-ups at age of 13 and 15 (Silva *et al.*, 2008). This may have introduced some recall bias. Moreover, these studies assessed PMDs using a range of tools. Some used unvalidated or unknown tools, which may have increased the likelihood of misclassification on symptom experience and led to over-estimated prevalence (Lee *et al.*, 2006; Silva *et al.*, 2008; Zegeye *et al.*, 2009; Issa *et al.*, 2010).

With prospectively and annually collected data on menarche, standardized assessment of PMDs and adjustment for most known

Table IV. Associations of pubic hair and breast growth with subsequent risks of premenstrual symptoms (in z-score) and disorders, β (95% CI) or OR (95% CI); Growing Up Today Study, 1996–2013.

	Early development	Normative development	Late development
Pubic hair growth			
Women, N	1180	3005	1127
Premenstrual symptoms			
Score, mean (SD)	0.098 (1.047)	−0.028 (0.975)	−0.077 (0.979)
β (95% CI)[a]	0.11 (0.04–0.18)*	0.00	−0.03 (−0.10–0.04)
β (95% CI)[b]	0.09 (0.02–0.17)*	0.00	−0.01 (−0.09–0.06)
Premenstrual disorders			
Events, N (%)	218 (18.5)	438 (14.6)	161 (14.3)
OR (95% CI)[a]	1.32 (1.09–1.61)*	1.00	1.00 (0.82–1.23)
OR (95% CI)[b]	1.28 (1.04–1.56)*	1.00	1.03 (0.83–1.27)
Breast growth			
Women, N	716	2236	741
Premenstrual symptoms			
Score, mean (SD)	0.058 (1.058)	−0.036 (0.987)	−0.133 (0.976)
β (95% CI)[a]	0.05 (−0.04–0.14)	0.00	−0.06 (−0.15–0.03)
β (95% CI)[b]	0.03 (−0.06–0.13)	0.00	−0.04 (−0.14–0.05)
Premenstrual disorders			
Events, N (%)	118 (16.5)	321 (14.4)	96 (13.0)
OR (95% CI)[a]	1.02 (0.79–1.33)	1.00	1.00 (0.76–1.32)
OR (95% CI)[b]	0.94 (0.72–1.23)	1.00	1.10 (0.83–1.46)

Pubic hair growth was assessed in 1996–1999 in GUTS I and 2004, 2006, 2008 in GUTS II. Breast growth was measured in 1996–1998 in GUTS I. Early development was defined as age at any Tanner stage 2–5 of pubic hair/breast growth ≤ mean − SD, whereas late development was age at any Tanner stage 2–5 ≥ mean + SD.
[a]The estimates were adjusted for year of birth, cohort membership, race, baseline BMI (categorical; if applicable), moderate/vigorous physical activity, paternal educational level, maternal marital status, use of multivitamin, alcohol drinking, parity and use of hormonal contraceptives.
[b]The estimates were additionally adjusted for age at menarche.
*$P < 0.05$.

risk factors, ours is the first study, to our knowledge, to clearly illustrate the inverse association between age at menarche and premenstrual symptoms as well as PMDs. The association, although not completely linear, is particularly strong and consistent across analyses of premenstrual symptoms. The relationship with PMD risk is, however, weaker and complicated (i.e. no increased risk in individuals with early menarche), likely due to a combined effect of lower power and residual misclassification of age at menarche. Indeed, the linear trend is more pronounced in girls who were prospectively followed for menarche since enrollment (i.e. premenarcheal girls at baseline). Consistently, we showed a similar pattern between pubic hair growth and PMDs. Although pubic hair development is primarily dependent on adrenal androgen production, it commonly co-occurs with other pubertal markers (Abreu and Kaiser, 2016). Collectively, these findings lend some support to the potential role of pubertal timing in PMD development. However, we did not observe clear association between breast development and PMD risk, although a weak trend was indicated for premenstrual symptoms. It is also not implausible that the influence of pubertal timing is stronger on premenstrual symptoms than that on PMD, which is at the higher end of the symptom spectrum.

One might speculate that individuals with early menarche experienced a greater cumulative number of ovulatory cycles and more exposures to cyclic hormone fluctuations by a given age, and therefore are more prone to PMDs than individuals with late menarche. This is, however, not supported by our findings of stronger associations of timing of menarche with early-onset PMDs (i.e. symptoms emerged <age 20). One may also postulate that the association between menarche and PMDs is partly driven by comorbid depression, which is positively associated with early menarche (Galvao *et al.*, 2014). We, however, showed very similar associations for PMDs with and without comorbidities.

An alternative explanation is that certain childhood lifestyle may influence both pubertal timing and PMD development. For instance, rigorous physical activity may be associated with late menarche (Moisan *et al.*, 1991), and therefore associated with decreased risk of PMDs. Although vitamin D-deficiency in childhood may be associated with early menarche (Villamor *et al.*, 2011), the association of vitamin D level in adulthood with PMDs has been less consistent (Abdi *et al.*, 2019). It is also possible that girls who experienced childhood abuse were are more likely to have early menarche (Boynton-Jarrett *et al.*, 2013), and therefore increased risk of PMDs (Bertone-Johnson *et al.*, 2014b). Nevertheless, we have adjusted for these known risk factors or their proxies for PMDs and observed similar results. This suggests that our findings are unlikely to be explained by these factors, although we cannot rule out residual confounding. Time-

varying diet pattern and physical activity before puberty and abuse between age 11 and puberty should be adjusted for in future studies. Additionally, it is not implausible that pubertal timing is biologically linked to PMDs. Evidence suggest that neurotransmitter gamma-aminobutyric acid subtype A ($GABA_A$) receptor may play an important role in PMD development (Yonkers and Simoni, 2018), whereas the gradual activation of $GABA_A$ receptors expressed on gonadotropin-releasing hormone neurons may be key to pubertal onset and development (Herbison, 2016). Future research on $GABA_A$ receptors might help explain the link between pubertal development and PMDs. Because both premenstrual symptoms and menarche timing are heritable (Jahanfar *et al.*, 2011; Day *et al.*, 2017), it is also possible that they share common genes. Future research is needed to unravel the underlying mechanisms.

Our study had several limitations. First, some misclassification of menarche, especially early menarche, may have persisted, as 46.1% of participants had already experienced menarche at baseline. Reassuringly, data suggest that age at menarche is recalled accurately when the recall interval is <2 years (Koo and Rohan, 1997), which applies to >80% of our participants. Also, robust associations were observed in analyses limited to girls premenarcheal at baseline. Greater misclassification is expected for pubic hair/breast growth, particularly for late development, as we assessed Tanner stage at the time of survey completion, rather than when the stage began. This may partly explain the complicated pattern noted for late public hair/breast growth. Classification errors may also exist for B2/B3, which is preferably assessed by breast palpation, especially for overweight girls. This may explain the overall null association with breast development. Moreover, individuals may have different sensitivity in noticing or reporting symptoms, which could lead to some misclassification of PMDs. However, we would expect this to be non-differential with respect to pubertal timing and only to attenuate findings, rather than explain observed associations. Furthermore, by necessity, we excluded a significant number of participants who did not provide data on PMDs in 2013, due to the reduced participation rate 18 years after the baseline. While bias could emerge if loss-to-follow-up varied by exposure status, we found that baseline characteristics and age at menarche were largely comparable between participants included in the analysis and women not providing information on PMDs in 2013. Thus, it is unlikely that participation was differentially related to both timing of menarche and PMDs. Last, only 68% of invited girls were enrolled in GUTS. Differences in characteristics of girls who joined vs. did not join may limit the generalizability of our findings to other populations. For instance, our participants were mostly white and from middle/upper income-level households. Future studies based on more racially and socioeconomically diverse populations are warranted.

In conclusion, our findings suggest that the timing of pubertal development, particularly timing of menarche, is inversely associated with premenstrual symptom burden and PMD risk in young adulthood. Information on PMDs should be provided to teenage girls and their parents. If these findings are confirmed in independent populations, prevention strategies and early detection programs may be considered for women with early pubertal development.

Supplementary data

Supplementary data are available at *Human Reproduction* Online.

Data availability

The data underlying this article were provided the Growing Up Today Study (GUTS) by permission. Data will be shared on request to the corresponding author with permission of GUTS.

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Authors' roles

Conception and design of study: D.L. and E.R.B.-J.; obtaining of funding: D.L. and R.M.T.; acquisition of data: D.L. and E.R.B.-J.; analysis of data and drafting of article: D.L. and E.R.B.-J.; Interpretation of data and critical revision for intellectual content: D.L., J.A., R.B., R.M.T., U.A.V. and E.R.B.-J.; and final approval of version to be published: D.L., J.A., R.B., R.M.T., U.A.V. and E.R.B.-J.

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Conflict of interest

None declared.

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