



Original article

Age at menarche predicts age at onset of major affective and anxiety disorders

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ABSTRACT

Background: Menarche age has been associated inconsistently with the occurrence, timing or severity of major depressive disorder (MDD), but rarely studied in women with bipolar (BDs) or anxiety disorders. **Methods:** We investigated women patients at a Sardinian mood disorder center for associations of age at menarche with age at illness onset for major affective or anxiety disorders, year of birth, and other selected factors, using bivariate comparisons and multivariate regression modeling.

Results: Among women ($n = 1139$) with DSM-IV MDD ($n = 557$), BD-I ($n = 223$), BD-II ($n = 178$), or anxiety disorders ($n = 181$), born in 1904–1998, of mean age 42.9 years, menarche age averaged 12.8 [CI: 12.7–12.9] years. Illness onset age averaged 30.9 [30.1–31.8] years, ranking: BD-I, 25.8; anxiety disorders, 28.0; BD-II, 30.3; MDD, 34.1 years. Menarche age declined secularly over birth years, and was associated with younger illness-onset, having no or fewer siblings, more psychiatrically ill first-degree relatives, living in rural environments, being suicidal, substance abuse, and being unemployed. Earlier menarche and earlier illness-onset were significantly associated for onset age groups of ≤ 20 , 20–39, and > 40 years. Menarche age versus diagnosis ranked: BD-II $<$ BD-I $<$ anxiety disorders $<$ MDD.

Conclusions: Age at menarche in Sardinia, as elsewhere, has declined over the past decades. It was strongly associated with age at onset of bipolar and anxiety, as well as major depressive disorders across the age range, suggesting sustained effects of biological maturational factors.

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1. Introduction

In many countries, average age at menarche falls within a limited range (11–14 years), but with some differences between regions and ethnic groups. International average age at menarche in general populations samples is 12.8 [CI: 12.5–13.0] years [1–15]. Studies from several countries have found a consistent secular decline in age at menarche throughout the past century [1,5,6,10,12–14,16–21], including a study reporting data from the end of the 18th century to 1981 [22].

Relatively early age at menarche has been associated with several psychopathological conditions. These include overall worse mental health indicated by multiple morbidity indices [23], as well as anxiety disorders [24–28], abuse of alcohol or other substances [25,29–31], conduct or oppositional-defiant disorder

[24], disruptive or violent behavior [32], eating disorders [30,33] and attention-deficit hyperactivity disorder (ADHD) [34], as well as cyclothymic or depressive temperaments in women diagnosed with bipolar disorder (BD) [35]. In contrast, later menarche has been associated with later onset of schizophrenia [36] and its more favorable clinical outcome [37].

Findings concerning an association between age at menarche and depression are inconsistent. Some studies found a significant association of early menarche and early onset of major depressive disorder (MDD) [30,37–42]; another did not [43]. In addition, greater risk of depression [35,44], and more severe depression sometimes were associated with earlier menarche [44–46], but not in certain ethnic subgroups, including African-American and Hispanic women in the US [47]. Moreover, menarche itself has been proposed as a possible triggering factor for depressive disorders [48,49].

Studies addressing associations of menarche age with BD have been rare. Among 50 women, BD began before menarche in 32% and in another 18% (total, 50%) within a year after menarche [50],

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whereas recurrent, endogenous MDD began before or at menarche in only 3% of 70 women [51]. Early menarche was more prevalent among women diagnosed with BD or MDD than among healthy women: menarche at or before age 11 was found in 25.7% of women with mood disorders (27.8% with BD, 23.3% with MDD) versus only 13.9% of healthy controls ($\chi^2 = 25.9$; $P < 0.0001$) [51]. Seemingly inconsistently, however, earlier menarche was found in patients with onset of BD *after* age 16 more than with earlier illness onset [52].

This background indicates a striking paucity of studies of menarche age in relation to age at onset of specific mood disorders, particularly BD. Accordingly, we studied the relationship of age at menarche to age at illness onset among women diagnosed with DSM-IV BD-I or BD-II or MDD, compared to anxiety disorders, and considered covariates, and considered an expected secular trend in age of menarche. We hypothesized that earlier menarche would be associated with earlier illness onset, would decline over birth years, and might be associated with indicators of less successful adaptation.

2. Methods

The study sample included all women diagnosed clinically with a major affective (BD-I, BD-II, or MDD) or anxiety disorder, with diagnoses updated to meet DSM-IV-TR criteria, evaluated and followed at the Lucio Bini Mood Disorders Center in Cagliari, Sardinia. We analyzed information from systematic clinical assessments of consecutive patients between 1976 and September 2015. All subjects underwent diagnostic and follow-up evaluations by the same mood-disorders expert (LT), based on semi-structured interviews at intake as well as during prospective, clinical follow-up. Diagnoses were updated to meet DSM-IV-TR criteria after the year 2000. Written informed consent was obtained for collection and analysis of patient data to be presented anonymously in aggregate form, in accordance with the requirements of Italian law and following review by a local ethical committee. Data management complied with US federal Health Insurance Portability and Accountability Act (HIPAA) regulations pertaining to confidentiality of patient records. Required data were entered into a computerized database (by LD, MP, GS, and LT) in coded form to protect subject identity; all authors participated in literature searching, data analysis and reporting.

Age at menarche (within six months) and estimated age at onset of illness were recorded routinely; included subjects had defined ages both at menarche and illness-onset. Analyses of the relationships of these measures and other factors of interest used standard bivariate comparisons of age at menarche with categorical (linear regression [slope or β]) and continuous measures (by ANOVA methods [F]), both tested with t -scores. Factors significantly associated with menarche age in bivariate analyses were subjected to multivariable linear regression modeling (to generate slope (β) functions and their 95% confidence intervals [CI]). For regression analyses of age at menarche versus birth year, we compared findings with data limited to subjects who had reached menarche by age 20 (the observed maximum age in the entire sample), so as to avoid biasing toward earlier menarche among younger women. In addition, for analyses of illness onset age versus age at menarche, we compared results with all subjects included to results limited to subjects with onset age ≤ 40 years and born before 1976. We also analyzed the age at menarche for three different age classes (< 20 , 20 – 39 , and ≥ 40 years) for illness-onset to compare possible differences in younger versus older women. We also applied Bayesian analysis (*sensitivity, specificity, and positive predictive value*) for the correlation of age at menarche and age at illness onset.

Data are presented as means \pm standard deviation (SD) or with (CI), or as medians with inter-quartile range (IQR); regression models are presented with slope functions (β) with their CI. Analyses employed commercial software: Statview.5 (SAS Institute, Cary, NC; for spreadsheets) and Stata.12 (StataCorp, College Station, TX) for analyses.

3. Results

3.1. Characteristics of study subjects

The study involved 1139 women subjects born between 1904 and 1998, of mean age at intake at the study site of 42.9 [CI: 41.9–43.8] years. DSM-IV psychiatric diagnoses were:

- unipolar MDD ($n = 557$; 48.9%);
- BD-I ($n = 223$; 19.6%);
- anxiety disorders ($n = 181$; 15.9%);
- BD-II ($n = 178$; 15.6% of subjects).

Age (years) at intake to the study site was lower in patients with anxiety disorders than those with mood disorders, but similar across mood disorders: anxiety disorders (40.1 [37.8–42.3]), BD-I (46.1 [44.1–48.2]), MDD (48.0 [46.5–49.5]), and BD-II (50.8 [48.6–53.0]).

Age at menarche in this sample of Sardinian women averaged 12.8 [CI: 14.7–12.9] (median: 13.0 [IQR: 12.0–14.0]; range: 7–20) years, overall, and was similar to the overall average for Italy, of 12.4 years [3,4]. Age at menarche was similar among the four diagnoses, ranking:

- BD-I (12.7 [CI: 12.5–12.9]);
- anxiety disorders (12.8 [12.5–13.0]);
- BD-II (12.8 [12.6–13.1] years);
- MDD (12.8 [12.7–13.0]).

Age at onset for the four disorders overall averaged 30.9 [CI: 30.0–31.8] years, and ranked by diagnosis as: BD-I (25.8 [24.2–27.4] years), anxiety disorders (28.0 [26.0–30.0]), BD-II (30.3 [28.4–32.2]), MDD (34.1 [32.7–35.5] years).

3.2. Association of age at menarche with year of birth

We confirmed and extended an internationally reported secular decline of age at menarche over the years of birth (1904–1995; Table 1A). In particular, menarche age averaged 13.7 [CI: 13.1–14.4] years in women born in 1904–1925, and 12.2 [11.8–12.6] years for those born in 1985–1995 (selected to account for the highest age at menarche of 20 years encountered in the entire sample); this 1.51-year decline in menarche age over 69 years (2.19%/year, or 2.59 months per decade) is highly significant ($t = 4.48$, $P < 0.0001$).

3.3. Association of age at menarche with age at illness onset

There was a notable, highly significant, overall correlation of younger age at menarche with earlier onset of major mood or anxiety disorders (slope, $\beta = 1.64$ [CI: 1.09–2.15]; $t = 5.89$, $P < 0.0001$; Table 1A; Fig. 1). Owing to concern for potentially biased sampling of onset ages among patients sampled either at young ages or with late onsets, we repeated this analysis including only women who experienced illness onset before age 40 and were at least 40 years old when evaluated (born before 1976). Again, there was a highly significant correlation of earlier onset age with earlier menarche (slope [β] = 0.694 [CI: 0.320–1.07]; $t = 3.64$, $P < 0.0001$).

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