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ORIGINAL ARTICLE

Pubertal timing, menstrual irregularity, and mental health: results of a population-based study

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Abstract Reproductive events have a significant impact on women's lives. The aim of this study was to analyze the effects of age at menarche and current menstrual irregularity on psychological well-being and psychopathology. Data were collected in the context of the Finnish population-based Health 2000 study with self-administered questionnaires, a home interview, and a clinical health examination. The Beck Depression Inventory (BDI-21), the General Health Questionnaire-12 (GHQ-12), and the Composite International Diagnostic Interview (M-CIDI) were used to assess psychopathology. The relationships between age at menarche and current menstrual flow irregularity vs. BDI-21 and GHQ-12 scores and M-CIDI diagnoses were studied among 4,391 women aged 30 years and over. Negative, nonsignificant associations were found between age at menarche and BDI-21 and GHQ-12 scores. Young age at menarche was associated with increased risks of any recent mental disorder (OR=0.894, $p<0.01$), major depressive episode (OR=0.900, $p<0.05$), major depressive disorder (OR=0.888; $p<0.05$), and anxiety disorder (OR=0.892; $p<0.05$). Menstrual irregularity was associated with BDI-21 ($p<0.001$) and GHQ-12 ($p<0.05$) scores, but not with any recent psychiatric diagnosis. Age at menarche and menstrual irregularity have an influence on mental health, particularly on mood and anxiety symptoms. Reproductive features (age at menarche and menstrual irregularity) should be paid attention to during psychiatric evaluations.

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Introduction

Reproductive events, including pregnancy, puerperium, and menopausal transition have a significant impact on women's lives. The onset of menarche may itself have a dramatic effect on adolescent girls, being the most memorable sign of pubertal development (and the last sign of its completion). The following reproductive life is characterized and influenced by the rhythm of the menstrual cycle and by its related hormonal fluctuations. Any abnormalities in this rhythmicity may affect a variety of aspects in women's lives. In particular, there seems to be a reciprocal influence between mental health and reproductive features such as the menstrual cycle phase and menstrual flow regularity (Akdeniz 2010). A higher number of admissions to a psychiatric ward occur during the menstrual period than at other times of the menstrual cycle (Luggin et al. 1984), and a premenstrual mood worsening, sometimes leading to a well-defined premenstrual syndrome or to a premenstrual dysphoric disorder (PMDD), is also well-known (Johnson 1987). Moreover, completed and attempted suicides are more common in the early menstrual and luteal phases (Baca-Garcia et al. 2000; Saunders and Hawton 2006; Leenaars et al. 2009).

The widely shown gender difference in the epidemiology of many psychiatric disorders, first of all of mood disorders (Paykel 1991; Lehtinen and Joukamaa 1994; Marcus et al. 2005), is much clearer soon after puberty. It is thereby plausible to hypothesize that puberty may itself be related to psychiatric issues. Many studies have dealt with the question of a possible relationship between pubertal timing and mental health and psychosocial functioning, with the general conclusion that an early pubertal timing is associated with higher

level of psychopathology and poorer social adjustment in adolescent girls (Patton et al. 1996; Lien et al. 2006). In a review on this topic, Mendle et al. (2007) came to the conclusion that an early pubertal timing in adolescent girls might be a risk factor for many behavioral, psychosocial, and psychiatric problems. Early pubertal timing (i.e., early menarche) contributes, interacting with genetic, cultural, and social factors, to an increased risk of depressive disorders, eating disorders, substance abuse, anxiety and psychosomatic symptoms, risky sexual behavior, and poorer educational level in adolescent girls (Mendle et al. 2007). The way how puberty affects mental health is partly mediated by gonadal hormones, known to increase the levels of arousal, excitability, emotional lability, and reactivity (Angold et al. 2003). In fact, estrogens contribute to regulate many neurotransmitter systems (serotonin, noradrenaline, dopamine), and progesterone participates in the control of the opioidergic, serotoninergic, cholinergic, and GABAergic systems as well (Rubinow et al. 1998; Genazzani et al. 2007; Pluchino et al. 2009). Additionally, estrogen and progesterone receptors are expressed in the brain regions involved in circadian regulations (suprachiasmatic nucleus and anteroventral periventricular nucleus) (de la Iglesia and Schwartz 2006).

Whether the detrimental effects of an early pubertal timing in girls are confined to adolescence or persist later in adulthood is not clear. A recent cohort study reported a general attenuation of the negative consequences of early puberty in young adult women (Copeland et al. 2010). Nevertheless, early pubertal timing in women was found to be associated with higher lifetime prevalence of psychiatric disorders and with a slightly poorer psychosocial functioning in young adulthood (Stattin and Magnusson 1990; Graber et al. 2004). On the contrary, Bisaga et al. (2002) found that late (but not early) menarche was significantly associated with a higher risk of depressive symptoms. These inconsistencies among the studies may be due to recall bias, which makes it particularly difficult to evaluate the effects of the age at menarche, especially late in adulthood. Indeed, in cross-sectional studies, age at menarche is retrospectively collected and relies entirely on women's report. Even though menarche is, per se, a significant event in women's lives, nevertheless there is a well-known lack of consistency between age at menarche as reported in adolescence and in middle age (Cooper et al. 2006).

Bisaga et al. (2002) also reported menstrual cycle abnormalities (in particular, secondary amenorrhea and irregular cycles) to be related with higher odds of depressive disorder symptoms and eating disorder symptoms. However, there is a lack in the literature concerning the effects of menstrual irregularity on mental health in middle-aged women (from young adulthood to perimenopause).

In general, the results are contradictory, and, to the best of our knowledge, there is a lack of data from representative population-based samples. Therefore, the aim of this study was to analyze the long-term effects of menstrual functioning, focusing on age at menarche and menstrual irregularity, on psychological well-being and psychopathology on a large nationwide sample of adult women.

Material and methods

The data were collected in connection with the Health 2000 Survey, a cross-sectional, nationwide, population-based study carried out in Finland in 2000 to 2001. By means of a stratified and clustered sampling procedure, a representative sample of the general population aged 30 years and over was obtained. More details about the study design and methodology have already been described elsewhere (Heistaro 2008). Data collection consisted of a home interview followed by a clinical health examination; additionally, a total of four self-administered questionnaires were given to be filled and returned. A modified version of the Beck Depression Inventory-21 (BDI-21) (Raitasalo 1995) and the General Health Questionnaire-12 (GHQ-12) (Goldberg et al. 1978) were included in the self-administered questionnaires. In connection with the health examination, the Composite International Diagnostic Interview (M-CIDI) (Wittchen et al. 1998), a structured mental health interview, was carried out to assess the mental health in the previous 12 months.

Approval for the survey was obtained from the Ethics Committee of the National Public Health Institute (1999) and from the Ethics Committee for Research in Epidemiology and Public Health at the Hospital District of Helsinki and Uusimaa (2000). Written informed consent was obtained from all participants.

Reproductive health

Information about reproductive health features was obtained in the interviews with questions inquiring into menstrual features (age at menarche, menstrual flow regularity, menopausal age, and causes), infertility, contraception, and hormone therapy in perimenopause and postmenopause. Age at menarche was assessed via the question "How old were you when your periods started?" The question concerning menstrual flow regularity ("Do you have periods nowadays…") was asked only to women younger than 55 years (and who had had no hysterectomy), with possible answers "regularly", "irregularly", or "none". Current use of hormonal contraception (oral contraceptives or hormonal intrauterine device) was assessed among women aged 30–54 years ("Do you at the moment take contraceptive pills?" and "For birth-control, are you at the moment using a hormonal intrauterine device?"). Lifetime experience of infertility was assessed via the question "Have you had such time periods, when you have tried to get a

child, but have not succeeded or to succeed has taken over 12 months?" Women were considered postmenopausal if the time from the last period was 12 or more months; perimenopausal if it was between 6 and 12 months or if the woman was using hormone therapy (and the periods have not ended before starting hormone therapy); and premenopausal if the time since the last period was less than 6 months.

Mental health

The presence and severity of current depressive symptoms was assessed via a modified version of the 21-item BDI (Raitasalo 1995), a reliable and commonly used self-reported inventory validated by Beck et al. (1979) to assess depression, inquiring specifically into depressive, cognitive, and somatic symptoms. Psychological well-being was assessed with the 12-item GHQ, a broadly used questionnaire introduced by Goldberg et al. (1978) to evaluate the common mental state, with particular attention to the areas of depression and anxiety. The GHQ provides a view of the general mental health in the previous 4 weeks. At the end of the health examination, a structured diagnostic interview developed by the World Health Organization was carried out: the Munich computerized version of the CIDI (M-CIDI) was used (Wittchen et al. 1998). The M-CIDI interview was administered by trained interviewers, allowing them to assess the presence, onset, and recency of psychiatric disorders in the 12 months prior to the interview. For the purpose of this study, we focused on major depressive episode (MDE), major depressive disorder (MDD), dysthymic disorder, any anxiety disorder, alcohol abuse, and dependence. "Any current psychiatric diagnosis" was defined as meeting the criteria for at least one full diagnosis in the past 12 months (excluding cases with missing data at one or more of the diagnoses inquired about). BDI-21 and GHQ-12 total scores were considered only for the cases with a valid answer at each item; each BDI and GHQ item score was calculated for all the participants with a valid answer at that item.

Statistical analyses

For the purpose of this study, "age at menarche" was used as a continuous variable, while "menstrual flow regularity" was converted into a binary variable (menstrual regularity vs. menstrual irregularity or no cycle). A bivariate analysis was performed to study differences between groups using menstrual irregularity as the grouping variable. The χ^2 test was used to compare frequencies and Fisher's exact test was selected when expected frequencies were less than five. For continuous variables, comparison of means was carried out using Student's t test. A p value<0.05 was considered significant.

The existence of partial correlations (age as controlling variable) between both BDI-21 score and GHQ-12 score vs. age at menarche and menstrual irregularity or no cycles, respectively, was investigated. Partial correlations with each BDI and GHQ items were also tested.

Multivariable analysis was performed, using generalized linear models, to identify those predictors that had a statistically significant association with BDI-21 (and each BDI item) score and GHQ-12 (and each GHQ item) score. Age group (30–54 years vs. >54 years), professional status, marital status, education level, current psychiatric diagnosis (as assessed via the M-CIDI), and age at menarche were entered in a first model as predictors. Logistic regression was performed to identify the predictors of any current psychiatric diagnosis (M-CIDI).

Analyses on menstrual irregularity were limited to the age group 30–54 years. Generalized linear models and logistic regressions were calculated in three progressively selected subpopulations: first, all the women aged 30–54 years and not currently using hormonal contraception were considered. In a second model, the analyses were limited to women aged 30–54 years, not currently using hormonal contraception and with no lifetime infertility. Lastly, only women aged 30–54 years, not currently using hormonal contraception, with no lifetime infertility and who were also premenopausal were included in the third model.

Cases with missing data concerning one or more variables were omitted from the analyses. Descriptive and multivariable analyses were performed using SPSS/PASW software (version 18.0) (SPSS Inc., Chicago, IL, USA).

Results

We had information about 4,391 women aged 30 years and over (mean age 56.2 years; SD 17.2; range 30–99); background information is reported in Table 1. A complete M-CIDI interview was available for 3,165 women (response rate 72.1 %); 502 women (15.9 %) met full diagnostic criteria for at least one psychiatric diagnosis within the 12 months prior to the interview. A reliable BDI-21 score was available for 3,467 women (response rate 79.0 %), and 3,606 women returned a complete GHQ-12 (response rate 82.0 %). In the age group 30–54 years, the response rates for M-CIDI, BDI-21 and GHQ-12 were, respectively, 80.5 % ($n=1,859$), 86.0 % ($n=1,987$), and 87.5 % ($n=2,022$).

Age at menarche

The mean age at menarche among women aged 30 years and over was 13.6 years ($n=3,690$; range 8–20; SD 1.6). Significant negative correlations were found between age at menarche and both BDI-21 score and GHQ-12 score as well

Table 1 Characteristics of the participants and comparison between women with menstrual irregularity vs. women with regular menstrual flows

	Women aged 30 years or over (n=4,391)		Women aged 30–54 years (n=2,310)			
			Menstrual irregularity (n=608)		No menstrual irregularity (n=1,286)	
	n	%	n	%	n	%
Professional status						
Full-time employed	1,685	41.4	411	67.6	918	71.4
Part-time employed	232	5.7	54	8.9	91	7.1
Students, retired, unemployed/laid off, homemakers	2,141	52.6	141	23.2	270	21.0
Other	14	0.3	2	0.3	7	0.5
Marital status*						
Married/cohabitants	2,451	60.2	435	71.5	986	76.7
Divorced/separated, widowed, single	1,620	39.8	173	28.5	300	23.3
Education level***						
Basic education	1,161	28.7	127	9.9	102	16.8
Vocational/high school education	2,454	60.6	929	72.2	419	69.0
University education	436	10.8	230	17.9	86	14.2
Hormonal contraception**	–	–	234	18.3	152	25.0
Lifetime infertility	571	15.1	244	19.0	125	20.6
M-CIDI diagnosis	502	15.9	103	19.0	203	17.7
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
BDI-21 total score***	3,467	8.0 (7.3)	580	7.6 (7.6)	1,223	5.9 (6.6)
GHQ-12 total score	3,606	2.0 (3.0)	590	2.0 (2.9)	1,238	1.7 (2.7)
Age at menarche (years)	3,690	13.6 (1.6)	605	13.2 (1.4)	1,282	13.1 (1.4)
Age (years)***	4,391	56.2 (17.2)	608	45.5 (7.0)	1,286	40.0 (6.4)**

BDI-21 Beck Depression Inventory, *M-CIDI* Composite International Diagnostic Interview, GHQ-12 General Health Questionnaire

* Chi-squared or t test significant at $p<0.05$

** Chi-squared or t test significant at $p<0.01$

*** Chi-squared or t test significant at $p<0.001$

as several BDI and GHQ items. A significant negative correlation was also found between age at menarche and any current psychiatric diagnosis as assessed with the M-CIDI (Table 2).

In generalized linear models, no significant associations were found with BDI-21 score or GHQ-12 score when controlling for age group, marital status, education level, professional status, and current psychiatric diagnosis (Table 3). However, age at menarche was significantly negatively associated with the BDI items *past failure* (B=−0.027; 95 % CI=−0.045 to −0.009; $p<0.01$), *self disappointment* (B=−0.012; 95 % CI=−0.024 to −0.001; $p<0.05$), *lost interest in people* (B=−0.014; 95 % CI=−0.024 to −0.003; $p<0.05$), and *feelings of looking ugly* (B=−0.019; 95 % CI=−0.034 to −0.004; $p<0.05$), and with the GHQ items *strain* (B=−0.019; 95 % CI=−0.036 to −0.002; $p<0.05$), *feelings of depression* (B=−0.028; 95 % CI=−0.045 to −0.010; $p<0.01$), and *unhappiness* (B=−0.015; 95 % CI=−0.028 to −0.001; $p<0.05$). Moreover, positive associations with the BDI items *tiredness* (B=0.015; 95 % CI=0.002 to 0.028; $p<0.05$) and *lost interest in sex* (B=0.023; 95 % CI=0.002 to 0.044; $p<0.05$) were found. In multiple logistic regression analysis, the risk of *any recent psychiatric diagnosis*, and in particular of *MDE*, *MDD*, and *anxiety disorder* was significantly negatively associated with the age at menarche (Table 3).

Menstrual irregularity

When asked about their menstrual flow regularity, 1,286 (67.9 %) women aged 30–54 years reported having regular menstrual cycles, 289 (15.3 %) irregular cycles, and 319 (16.8 %) having no cycles (data missing for 416). At the time of the interview, 393 of them (20.7 %, missing data for 415) were using hormonal birth controls, and 418 (20.2 %; missing data for 241) reported previous infertility. Regarding their

Table 2 Correlations between BDI-21 scores, GHQ-12 scores, and M-CIDI diagnoses vs. age at menarche (30 years and over) and menstrual irregularity (30–54 years) after controlling for age

	Age at menarche		Menstrual irregularity	
BDI-21	*n*	*r*	*n*	*r*
Total score	3,396	−0.055**	1,803	0.092***
Sadness	3,393	−0.045**	1,800	0.081**
Future hopeless	3,389	−0.032	1,797	0.022
Past failure	3,392	−0.060***	1,799	0.061**
Dissatisfaction	3,402	−0.045**	1,799	0.053*
Worthlessness	3,380	−0.041*	1,798	0.067**
Punishment feelings	3,323	−0.047**	1,781	0.039
Self-disappointment	3,379	−0.041*	1,796	0.052*
Uselessness	3,392	−0.038*	1,798	0.048*
Suicidal ideation	3,375	−0.040*	1,796	0.045
Crying	3,396	−0.030	1,801	0.052*
Irritability	3,389	0.004	1,800	0.037
Lost interest in people	3,403	−0.056**	1,799	0.048*
Indecisiveness	3,395	−0.037*	1,802	0.059*
Looking ugly	3,357	−0.059**	1,789	0.065**
Impaired working capability	3,371	−0.033	1,797	0.053*
Earlier waking	3,393	−0.039*	1,801	0.043
Tiredness	3,394	0.002	1,798	0.031
Lost appetite	3,408	0.016	1,804	0.030
Lost weight	3,375	−0.001	1,794	−0.010
Worries about one's health	3,392	−0.019	1,801	0.074**
Lost interest in sex	3,341	0.000	1,794	0.102***
GHQ-12	*n*	*r*	*n*	*r*
Total score	3,464	−0.047**	1,828	0.049*
Impaired concentration	3,425	−0.006	1,823	0.053*
Sleep lost over worries	3,480	−0.023	1,829	0.018
Feelings of usefulness	3,435	−0.051**	1,820	0.070**
Impaired decision making	3,475	−0.041*	1,828	0.001
Strain	3,473	−0.048**	1,830	0.014
Overcoming difficulties	3,474	−0.023	1,830	0.034
Impaired enjoyment	3,474	−0.029	1,829	0.010
Impaired problem-coping	3,467	−0.012	1,826	0.010
Feelings of depression	3,482	−0.052**	1,830	0.061**
Loss of self-confidence	3,480	−0.032	1,829	0.055*
Feelings of worthlessness	3,484	−0.007	1,828	0.062**
Unhappiness	3,464	−0.049**	1,822	0.009
M-CIDI	*n*	*r*	*n*	*r*
Any psychiatric diagnosis	3,117	−0.043*	1,687	0.029
Alcohol abuse	3,191	0.002	1,720	−0.005
Alcohol dependence	3,183	0.003	1,717	−0.016
Major depressive episode	3,197	−0.024	1,725	0.014
Dysthymic disorder	3,195	−0.026	1,724	0.011
Major depressive disorder	3,197	−0.029	1,725	0.016
Anxiety disorder	3,131	−0.033	1,691	0.029

* Correlation significant at $p<0.05$

** Correlation significant at $p<0.01$

*** Correlation significant at $p<0.001$

Table 3 Associations between BDI-21 score, GHQ-12 score, and M-CIDI diagnoses vs. age at menarche

	Age at menarche		
	n	*B*	95 % CI
BDI-21 total score[a]	3,066	−0.128	−0.278 to 0.022
GHQ-12 total score[a]	3,061	−0.035	−0.100 to 0.030
M-CIDI[b]	*n*	OR	95 % CI
Any psychiatric diagnosis	3116	0.890	0.831 to 0.952**
Alcohol abuse	3,190	0.930	0.636 to 1.359
Alcohol dependence	3,182	0.954	0.825 to 1.102
MDE	3,196	0.895	0.810 to 0.989*
Dysthymic disorder	3,194	0.880	0.748 to 1.035
MDD	3,196	0.883	0.798 to 0.977*
Anxiety disorder	3,130	0.879	0.789 to 0.980*

* Significant at $p<0.05$

BDI-21 Beck Depression Inventory, *CI* confidence interval, *M-CIDI* Composite International Diagnostic Interview, *GHQ-12* General Health Questionnaire, *MDD* major depressive disorder, *MDE* major depressive episode, *OR* odds ratio

** Significant at $p<0.01$

[a] Adjusted for age group, marital status, education level, professional status, and current psychiatric diagnosis

[b] Adjusted for age group, marital status, education level, and professional status

reproductive status, 1,612 women aged 30–54 years (78.7 %) were classified as premenopausal, 54 (2.6 %) as perimenopausal and 381 (18.6 %) as postmenopausal (missing data for 263). Results of the bivariate analyses are reported in Table 1.

Significant positive correlations were found between menstrual irregularity (or no cycles) and BDI-21 score and GHQ-12 score. Some of the BDI and GHQ items also significantly correlated with menstrual irregularity (Table 2). No correlation was found between age at menarche and menstrual irregularity ($r=-0.003$; $p=0.900$).

Menstrual irregularity or absence of cycles was significantly positively associated with BDI-21 score (controlling for age, marital status, education level, professional status, and current psychiatric diagnosis) in women younger than 55 years and not using hormonal contraception, even after excluding those with lifetime infertility problems (Table 4). However, the associations were lost after further limiting the analysis to premenopausal women (not using contraception and without lifetime infertility) only. Additionally, menstrual irregularity was constantly associated with GHQ-12 score, irrespectively of the above-mentioned sample limitations (Table 4). Among premenopausal women not using contraception and without lifetime infertility, menstrual irregularity (or absence of menstrual cycles) was also significantly associated with the BDI items *lost interest in people* ($B=0.084$; 95 % CI=0.007 to 0.160; $p<0.05$), *worries about one's health* ($B=0.126$; 95 % CI=0.034 to 0.219; $p<0.01$), and *lost interest in sex*

Table 4 Associations between BDI-21 scores, GHQ-12 scores, and M-CIDI diagnoses vs. menstrual irregularity (30–54 years group)

	M1			M2			M3		
	n	*B*	95 % CI	*n*	*B*	95 % CI	*n*	*B*	95 % CI
BDI-21 total score[a]	1,310	1.069	0.281 to 1.857**	1,023	1.274	0.372 to 2.177**	875	1.036	−0.031 to 2.102
GHQ-12 total score[a]	1,311	0.359	0.022 to 0.695*	1,024	0.477	0.097 to 0.857*	875	0.481	0.025 to 0.936*
M-CIDI[b]	*n*	OR	95 % CI	*n*	OR	95 % CI	*n*	OR	95 % CI
Any psychiatric diagnosis	1,319	1.220	0.872 to 1.709	1,030	1.235	0.832 to 1.832	878	1.450	0.910 to 2.312
Alcohol abuse	1,350	0.874	0.169 to 4.518	1,057	1.435	0.252 to 8.178	900	2.458	0.446 to 13.543
Alcohol dependence	1,347	0.942	0.470 to 1.885	1,055	1.016	0.420 to 2.456	898	1.197	0.434 to 3.303
MDE	1,356	1.383	0.870 to 2.198	1,060	1.181	0.689 to 2.025	903	1.246	0.655 to 2.371
Dysthymic disorder	1,354	1.063	0.408 to 2.766	1,058	1.260	0.402 to 3.949	901	1.970	0.605 to 6.416
MDD	1,356	1.393	0.871 to 2.228	1,060	1.163	0.673 to 2.011	903	1.182	0.610 to 2.292
Anxiety disorder	1,324	1.187	0.710 to 1.983	1,033	1.432	0.796 to 2.574	880	1.742	0.882 to 3.442

M1. sample 30–54 years, not using contraception, *M2. sample* 30–54 years, not using contraception and with no lifetime infertility, *M3. sample* 30–54 years, premenopausal, not using contraception and with no lifetime infertility, *BDI-21* Beck Depression Inventory, *CI* confidence interval, *M-CIDI* Composite International Diagnostic Interview, *GHQ-12* General Health Questionnaire, *MDD* major depressive disorder, *MDE* major depressive episode, *OR* odds ratio

* Significant at $p<0.05$

** Significant at $p<0.01$

[a] Adjusted for age, marital status, education level, professional status, and current psychiatric diagnosis

[b] Adjusted for age, marital status, education level, and professional status

($B=0.163$; 95 % CI=0.046 to 0.280; $p<0.01$). In logistic regression analysis, no significant associations were found with any current psychiatric diagnosis.

Discussion

The main findings of this work were the associations between young age at menarche and higher risk of *any recent psychiatric diagnosis*, in particular of *MDE*, *MDD*, and *anxiety disorder*, as well as with some depressive and anxiety symptoms at the BDI-21 and GHQ-12 assessments. Moreover, women reporting current menstrual irregularity tended to have higher BDI-21 and GHQ-12 scores, i.e., worse mood and psychological well-being. These results indicate that menstrual-related features (in specific, young age at menarche and menstrual irregularity) may have an impact, though marginal, on mood symptoms and psychological well-being even in adulthood, with only partial attenuation of the widely reported mood detrimental effects of early puberty in adolescent girls.

In our study, we were able to detect a number of significant associations between young age at menarche and depressive or anxiety symptoms at the BDI-21 (past failure, self-disappointment, lost interest in people, and feeling of looking ugly) and GHQ-12 (strain, feelings of depression, and unhappiness) evaluations. These results are suggestive of possible negative effects of an early pubertal timing, in line with most of the literature on this topic. In a cross-sectional survey, Patton et al. (1996) showed higher levels of depression and anxiety in postmenarchal than in premenarchal girls; also, the authors found an association with recency of the menarche, with higher rates of psychopathology when the time from menarche was longer. Similarly, higher levels of psychological (internalizing and externalizing) symptoms were detected among early-maturing than among late-maturing girls and boys (Kaltiala-Heino et al. 2003). Moreover, Lien et al. (2006) reported an inverse linear relation between age at menarche and level of mental distress, suggesting pubertal timing as a risk indicator for psychopathology in girls.

Three main hypotheses have been proposed to explain how an early pubertal transition might affect psychosocial and behavioral functioning (Mendle et al. 2007), namely, the *psychosocial*, the *selection*, and the *biological* models. While the psychosocial model highlights the social pressure and changes a girl has to deal with after her development, the selection model focuses on the social and environmental outcomes of early puberty. According to the biological model, the pubertal hormonal changes have a central role in increasing arousal, excitability, emotional lability and reactivity, and negative affect (Angold et al. 2003), thus leading to impulsive and risky behaviors. Early-maturing girls experience high estradiol levels at an earlier age and for a longer time than their late-maturing peers. Moreover, the maturity process from childhood to adulthood follows a "non-linear" pattern, which,

in turn, leads to suboptimal behavioral choices and consequently to risky (e.g., suicidal) behavior, especially in early puberty, when judgment and self-regulatory skills are not yet well-developed (Graber et al. 1997; Dahl 2004; Casey et al. 2008).

Our results are also suggestive of a limited, but noteworthy persistency, of the detrimental sequelae of early puberty throughout adulthood. Only a few recent studies have addressed the adverse effects of early pubertal timing into adulthood. Graber et al. (2004) analyzed the effects of the age at menarche on young women (24 years) who had previously been interviewed during adolescence, comparing early, on-time, and late maturers. They found that early-maturing women had significantly higher lifetime (but not current) prevalence rates of psychiatric disorders than on-time-maturing women. Moreover, early-maturing women had significantly poorer psychosocial functioning in adulthood when compared with their on-time-maturing counterparts. Copeland et al.'s work (2010) supports the "attenuation hypothesis", i.e., that the effects of early puberty attenuate in adulthood. However, the authors also found a subgroup of early maturers (those who had conduct problems during adolescence) at greatest risk of depression in young adulthood. Both Garber's and Copeland's studies limited their analyses to samples of young women, with the oldest aged, respectively, 24 and 21 years. Our study examines the effects of pubertal timing in a larger perspective, facing the question if its effects would last across the entire life span. This is particularly meaningful nowadays and in Western cultures, where the (social and psychological) transition into adulthood is progressively postponed and where the 20–25-year age group can still be considered relatively close to the adolescence transition. From our findings, it seems that the younger the age at menarche is, the higher the risk of a psychiatric diagnosis is (in specific, of MDE, MDD, and anxiety disorder) also later in the adulthood. However, we cannot rule out that these results have been partly biased by other confounding factors (including other reproductive events and chronic somatic illness) as well as by a recall bias in the age at menarche. Among these confounding factors, the presence of PMDD has to be taken into account. In fact, it cannot be ruled out that the depressive symptoms detected in our study are rather expression of the mood deterioration that occurs in a subset of women in the weeks before the onset of the menstruations. In fact, a nonirrelevant proportion (1 to 7 %, or even higher) of women in fertile age, and more commonly those with regular menstrual cycles, are estimated to suffer from PMDD (Halbreich et al. 2003; Wittchen et al. 2002).

Interestingly enough, only specific items in the BDI-21 and GHQ-12 evaluation resulted to be significantly associated with the age at menarche after adjustment for possible confounding factors. In particular, in a more general mental health evaluation, as in the GHQ-12, the items expression of depressive rather than anxiety state (i.e., feelings of depression and unhappiness) resulted to be significantly associated with young age at menarche, suggesting that an early pubertal timing may more prominently influence mood. However, when using a more specific dimensional approach, as the BDI-21, especially the items related to self-dislike were associated with the age at menarche. Thus, it could be hypothesized that, as an early menarche means an early (role) transition into puberty and therefore into adulthood, this could, at some degree, interfere with the personal, social, and educational development, which, in turn, leads to an impaired self-perception, with no or little repercussion on other, more somatic dimensions of depression, such as appetite, weight, sleep, and work performance.

In this study, women reporting current menstrual irregularity or no cycles scored significantly worse at the BDI scale than women reporting regular menstrual flows. Also, menstrual irregularity resulted to be associated with higher GHQ-12 score and, to a lesser extent, BDI-21 score after adjustment. These results allow saying that menstrual abnormalities have a negative effect on mood, enhancing the severity of depressive symptoms. This is consistent with the findings reported by Bisaga et al. (2002), i.e., an association between irregular cycles and depressive symptoms. However, the comparability of the studies is limited by the different characteristics of the samples, first of all, age of participants (high school girls in Bisaga et al.). Nevertheless, in our study, women with menstrual irregularity did not have significantly higher risks of any recent psychiatric diagnosis. This is partly consistent with the findings reported by Barron et al. (2008), i.e., a generally lower prevalence of psychiatric disorders in pregnant women with reports of irregular cycles than in those with regular cycles. In particular, Barron et al. (2008) found a significantly lower risk of a current anxiety disorder in women with menstrual irregularity. Again, our results are not exactly comparable because of Barron et al.'s selection of pregnant women. Their sample was divided into three age/reproductive phase groups (women aged 36 years or older being classified as perimenopausal). In fact, when limiting our analysis to premenopausal women, only a few significant results were found. As known, perimenopause is a risky period for the onset or relapse of depressive disorders and symptoms (low mood, irritability, difficult concentration). A hypothesis for this phenomenon is that the female brain needs to quickly adapt to the irregular and unpredictable hormonal fluctuations typical of the menopausal transition (Deecher et al. 2008), and menstrual irregularity is itself an easily detectable marker of hormonal fluctuations. The brain inability in this adaptation process may contribute to an increased vulnerability to depressive symptoms in a subgroup of women. However, some of the associations (e.g., the ones with the GHQ-12 score and with some BDI-21 items) remained significant even after limiting the analyses to premenopausal women only, suggesting that factors other than the transition to menopause mediate the

associations between menstrual irregularity and depressive mood. As an example, menstrual irregularity may also be an expression of infertility, which, in turn, is associated with psychiatric disorders, in particular with dysthymic and anxiety disorders (Klemetti et al. 2010). However, even when restricting the study population to women without history of infertility, the results did not change. In addition, the associations between menstrual features and mental health could be partly mediated by the influence of clock genes. Gonadal hormones are known to modulate circadian systems (de la Iglesia and Schwartz 2006), and clock genes can, in turn, contribute to the etiology of mood disorders (Albrecht 2010). Mutations in the clock genes may cause an alteration of sleep and emotional behavior, partly due to their role in the modulation of the dopaminergic and serotoninergic transmissions as well as in the response to evening signals such as the melatonin ones (Albrecht 2010; Partonen 2012). Reciprocally, the suprachiasmatic nucleus (the pacemaker of circadian rhythms) regulates the rhythmic secretion of gonadotropins and gonadal hormones. Gonadotropin-releasing hormones are shown to have a circadian rhythm in the expression of clock genes. This evidence suggests that circadian clocks play a significant role in reproduction and fertility. In particular, it has been shown that clock genes expressed in the gonads and other reproductive tissues regulate the sensitivity to gonadotropins in the ovaries as well as the production of progesterone and testosterone by the gonads (Sellix and Menaker 2011).

This study has some methodological shortcomings. Firstly, it is a cross-sectional study with a retrospective data collection. This may constitute a recall bias for some variables, as menstrual regularity and age at menarche, the latter relying only on participants' recall. Cooper et al. (2006) showed that there seems to be a moderate agreement between the age at menarche as reported in adolescence and as reported in middle age. However, using a stratification procedure according to age group (30–54 years vs. >54 years) may have partly limited the recall bias. Also, the definition of menstrual regularity in this study relies on women's reports only, and not on objective measurements; consequently, it may be affected by the woman's subjective perception. Information about menstrual cycle length was not available. Also, it has to be acknowledged that the information on the use of hormonal contraception was not complete as participants were not asked about the use of other birth control methods, such as patches and rings. Another limitation arises from the self-reported quality of mood and psychological well-being assessment. Nevertheless, the validity and reliability of the BDI-21 and GHQ-12 scales have been widely demonstrated. Furthermore, a structured interview administered by trained nurses was used to assess the presence of current psychiatric diagnoses, although the presence of lifetime psychiatric diagnoses was not included in the assessment. Similarly, the presence of a PMDD diagnosis was not assessed in connection with the CIDI evaluation. Lastly, the retrospective design of the study precludes any causal conclusions. In spite of the above limitations, strengths of this study include the nationwide, population-based characteristic of the sample and the good response rate. A relatively good generalization of the results is thereby allowed.

Conclusion

The study findings are in keeping with a marginal influence of menstrual features on mental health, particularly on mood and anxiety symptoms. Attention should be paid to assessing psychopathology when seeing patients with early menarche or with menstrual irregularity. Conversely, inquiring about reproductive features (age at menarche and menstrual irregularity) should be part of any psychiatric evaluations.

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Conflicts of interest The authors declare that they have no conflict of interests.

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