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Update on Age at Menarche in Italy: Toward the Leveling Off of the Secular Trend

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Abstract

Purpose: To update the information on age at menarche in the Italian population and to verify the influence of genetic, nutritional, and socioeconomic factors on menarcheal age. Recent studies suggest that the magnitude of the secular trend toward an earlier age at menarche is slackening in industrialized countries.
Methods: This multicenter study was conducted on a large, population-based sample of Italian high school girls (n = 3,783), using a self-administered questionnaire. The questionnaire was used to gather information on the girls, including demography, anthropometry, menarcheal date, regularity of menses, behavioral habits, and physical activity. The questionnaire was also used to gather information on parents, including demography and mothers' and sisters' menarcheal ages. The median age at menarche and its 95% confidence interval were estimated by means of Kaplan-Meier survival analysis. To identify the independent predictive factors of age at menarche, multivariate mixed-effects models were applied.
Results: The median age at menarche of the subjects was 12.4 years (95% confidence interval: 12.34–12.46). The girls had their first menses approximately one-quarter of a year (median–0.13) earlier than did their mothers ($p < .0001$). Among all variables, parents' birth area, body mass index, family size, and the mother's menarcheal age were significantly and independently associated with age at menarche.
Conclusions: This study confirmed the reduction in the trend toward earlier menarche in Italy. The results also confirmed that genetic and nutritional factors are strong markers for early menarche. Currently, socioeconomic factors do not seem to play as significant a role as in the past.

Keywords: Menarcheal age; Pediatrics; Socioeconomic factors; BMI; Mother's menarcheal age

Menarche is a milestone in human sexual development and a substantial landmark of female puberty. Although age at menarche depends on recognized endocrinological mechanisms, many genetic [1–5] and environmental factors,

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including socioeconomic status [5–10] and family size [4,11,12], are also thought to influence the onset of puberty. Nevertheless, the causative model has not yet been fully elucidated. Additional studies are needed, as knowledge of reproductive physiology is important for health planning, particularly for promoting menstrual education, dealing with the perceived discomforts of menstruation, and menstrual disorders.

Previous studies on menarcheal age have principally dealt with two main aspects: 1) the secular trend that shows a decreasing age at menarche in industrialized countries and 2) the relationship of age at menarche to long-term health risks. Early menarcheal activation is a well-known risk factor for breast carcinogenesis [13] and may also increase the risk of ischemic heart disease [14]. Age at menarche is thought to be related to Alzheimer's disease [15], osteoporosis [15], higher adult body mass index (BMI), and obesity [16].

Secular evolution has led to increased weight and stature during childhood [5,9,15,17–19] and to a downward trend in the mean age at menarche, from about 16 to 13 years, although there have been some differences in various countries [15]. Several studies have now suggested that this trend has been slowing down during the last decade in most industrialized countries [5,15,20], but that it is still ongoing in other countries [7,8,11,21,22]. Moreover, published data have suggested that body weight and nutritional status play a role in the timing of pubertal development [23–29]. Determining the current normal physiological age range for onset of menstruation is therefore important for diagnosing precocious versus delayed puberty and for collecting a detailed menstrual history.

The aims of this cross-sectional, population-based study were to provide the mean age at menarche, verify the secular trend, and evaluate the factors, including genetic, nutritional, social, and behavioral characteristics, that may be associated with age at menarche in a large sample of Italian high-school girls.

Methods

Sample selection and participants

This multicenter study was conducted among a large number of Italian high-school girls, by means of a self-administered anonymous questionnaire, in 13 cities in northern Italy (Brescia, Bolzano, Ferrara, Modena, Novara, Padova, Parma, Pavia, Reggio Emilia, Torino, Trieste, Verona, and Vicenza) and three in southern Italy (Foggia, Lecce, and Taranto). An equal allocation strategy was used by sampling about 5% of the scholastic population in each city. Two to five high schools were randomly selected in each city, depending on the size of the scholastic population. The girls attending the schools came either from the cities or from their outskirts, and only those who had reached menarche were selected for the study.

The questionnaire was prepared by a pediatric endocrinologist and a pediatric neuropsychiatrist from the Pediatric Unit of the University of Padua, who also trained the investigators from the other cities regarding the use of this questionnaire. The questionnaire was validated by the Department of Pediatrics of the same university, and the research was approved by the local ethical committee. The questionnaire was divided into three parts. The first part included questions on the girls' demography (birth date and place, place of residence, family unit size, number of siblings, and birth order), anthropometry (height and weight), date of menarche, regularity of menses, behavioral habits (cigarette and alcohol consumption), and physical activity, as well as questions on the parents' demography (birth date and place, education, and occupational status) and their mothers' and sisters' age at menarche. The second part included questions on their premenstrual and menstrual complaints. The third part included questions on the psychological self-perceived experience of menses.

In each school, the local investigator explained the aims of the survey and the questionnaire to the science teachers, who, in turn, explained and handed the questionnaire to their students to fill out. Informed written consent was obtained from the students and their parents/guardians. The part of the questionnaire that dealt with the girl's information was filled out by each student at school, and the girls were asked to indicate as accurately as possible the date of their first menstrual bleeding (at least the month and the year) or to not answer if they did not know. The questions regarding the girls' parents and siblings were answered at home by the girls and their mothers.

Of the 6,924 questionnaires that were administered, 4,992 (71%) were collected. The respondent rate was not statistically different among the cities, where it ranged from 68% to 76% ($p = .41$).

The present study analyzed data only from the first part of the questionnaire. Among the 4,992 questionnaires, 4,892 students included information about birth date, and 3,782 (77%) of them indicated the complete data of their first menses. In addition, 777 (16%) did not remember the date of their first menses, 1 (0.02%) reported only the month and the year, and 332 (7%) reported only the year. When the day was missing, the event was considered to have happened halfway through the month. When both day and month were missing, the subject was excluded from the study. In the end, the analyzed data set included 3,783 students who reported both their birth date and their menarcheal date. Age at menarche was expressed as a decimal year. In contrast to the nonresponding subjects or those who did not provide adequate information, the subjects who were included in the analysis were significantly younger (17.1 vs. 17.4 years, $p = .0001$), and a significantly higher proportion were physically active (51.5% vs. 45.3%; $p = .0004$). No significant difference was found between responders and nonresponders with regard to living area, BMI, socioeconomic level, and parents' birth area.

To estimate the secular trend, the difference between the menarcheal ages of the girl and her mother was calculated and expressed as a decimal year.

Body mass index (kg/m^2) was analyzed both as a quantitative and categorical variable (<18.5 was considered underweight; 18.5–25, normal; 25–30, overweight; and >30, obese).

The categorization of socioeconomic class was based on parents' education and occupation through application of the Hollingshead index [30]. Both education and occupation were scored on a scale from 0–4, where 0 was the lowest level and 4, the highest. The educational and occupational scores were summed, and the total scores were categorized into four levels: 0–4 was considered low; 5–8, middle; 9–12, high; and 13–14, very high.

The parents' birth place was dichotomized into North or South, with isles included in the latter group, and these designations were used as a proxy for the geographical genotype.

Physical activity was classified as follows: no–low indicated <2 hours/week; moderate, 2–6 hours/week; and high, >6 hours/week.

Statistical analysis

Descriptive analyses were performed on quantitative and qualitative variables for the total sample.

Observed percentiles were evaluated for the age at menarche on the total sample and on specific subgroups that were identified by the demographic, physical, and behavioral characteristics. The same analyses were performed to describe the difference between the girl's and her mother's age at menarche.

Kaplan-Meier survival analysis was applied to estimate the median time at menarche and its 95% confidence interval (95% CI). The normality of quantitative variables was verified by the Shapiro-Wilk test.

In evaluating the effects of covariates on menarcheal age, the design effect was considered nesting schools within cities and considering subjects clustered at the city level. Age at menarche was evaluated by means of the multiple regression mixed models using the SAS MIXED procedure with restricted maximum likelihood method, in which covariates were fixed effects and cities were random effects. For each level of the covariates, the mean values and standard errors of menarcheal age were obtained by the models including one covariate at a time. Multiple comparisons were performed using Sheffé test. Variance due to individuals was accounted by including cities as a random categorical variable into the models. The covariance parameter estimates were performed with their confidence intervals at 95% using the Wald method. Intracluster correlation coefficients were calculated by the ratio of city variance and total variance. The multivariate model included the variables that were statistically associated with the age at menarche in the analysis using one covariate at a time as fixed effect. To estimate the goodness to fit of the model, the R^2 estimate for the corresponding fixed-effects model was used.

To confirm the results, a model was applied to estimate the adjusted odds ratios (ORs) and 95% CIs for early menarche (<12 years) by testing the same independent variables. When age at menarche was considered as a binary response (<12/≥12 years), the SAS procedure NLMIXED was applied to fit the nonlinear model with random effects.

The significance level was fixed at 0.05, and all tests were two-tailed. All the analyses were performed using the SAS statistical software release. 9.1 (SAS Institute, Cary, NC).

Results

The demographic and clinical characteristics of the 3,783 girls included in this study are described in Table 1. Mean age at interview was 17.1 years (standard deviation [SD] = 1.4; range = 15–21). Among the included respondents, 3,218 subjects (87.6%) came from northern Italy; of these, 2,186 (60.7%) had parents who were both also from the North. The mean age at menarche was 12.4 years (SD = 1.3), and the median age was 12.4 years (95% CI = 12.34–12.46). The proportion of different menarcheal ages, as estimated by survival analysis, is shown in Figure 1. A comparison of the estimated age at menarche in the northern and southern part of Italy from the 1930s to 2000s (resulting from the present study) is shown in Figure 2. The studies included in the comparison derived from a selection of Italian studies evaluating retrospectively age at menarche [31]. Detailed observed percentiles of the sample population as a whole and subdivided according to geographical area, nutritional status, and family size are shown in Table 2. For the girls from northern Italy, the median age at menarche was 12.44 years (95% CI = 12.38–12.49), and for the girls from southern Italy, the median age at menarche was 12.10 years (95% CI = 12.00–12.28). No relationship was observed between menarcheal age and social level, physical activity score, or birth order (data not shown).

For the total sample, mothers' menarcheal age was significantly and positively associated with the girls' age at menarche ($r = 0.30$; $p < .0001$). With regard to the difference between the age at menarche of girls and their mothers (Table 2), the results indicated that the girls had their first menses about one-quarter of a year (median–0.13) earlier than their mothers had ($p < .0001$). The difference was smaller for girls living in northern Italy (median–0.07 year, $p < .0001$) and greater for those living in southern Italy (median–0.36, $p < .0001$).

The results of the multivariate analysis that evaluated the independent predictive role of the variables that were statistically associated with age at menarche are shown in Table 3. In the model, the within-city covariance was about 0.02 (95% CI = 0.01–0.11), the residual covariance was about 1.35 (95% CI = 1.29–1.43), and the intracluster correlation coefficient was about 2%. The predictive strength of the corresponding marginal model (only fixed-effects), as

Table 1
Sample population characteristics

	n	%	Mean±SD
Age at interview (years)	3,783		17.1±1.4
<16	644	17.0	
16	1,077	28.5	
17	1,122	29.7	
18	705	18.6	
19	167	4.4	
>19	68	1.8	
Geographical area	3,675		
North	3,218	87.6	
South	457	12.4	
Parents	3,599		
Both North	2,186	60.7	
One North and one South	651	18.1	
Both South	762	21.2	
BMI (kg/m^2)	3,549		20.3±2.5
<18.5	823	23.2	
18.5–20.0	967	27.3	
20.0–25.0	1,600	45.1	
25.0–30.0	140	3.9	
>30.0	19	0.5	
Family size (n)	3,736		4.0±0.9
≤3	967	25.9	
4	1,972	52.8	
≥5	797	21.3	
Social score	3,473		9.5±3.1
Low	175	5.0	
Middle	1,155	33.3	
High	1,493	43.0	
Very high	650	18.7	
Physical activity	3,783		
No–low	1,834	48.5	
Moderate	1,580	41.8	
Intense	369	9.7	

expressed by R^2, was 14%. In the linear regression model, the mother's menarcheal age alone explained about 10% of the total variance. Living area was the only variable that was not confirmed to have an independent association with the age at menarche.

The independently associated covariates identified by the multivariate linear model were confirmed by the application of the multivariate nonlinear model for binary response, using early menarche (<12 years) as the dependent variable. The adjusted ORs for early menarche are shown in Table 3. For parents' birth area, subjects whose parents were born in southern Italy showed a significantly higher OR for early menarche in comparison with those whose parents were both born in northern Italy (OR = 1.14, 95% CI = 1.01–1.29). The higher family size showed to reduce the probability of early menarche (OR = 0.88, 95% CI = 0.78–0.99), whereas each BMI unit corresponded to an increase of 0.14 in the risk of early menarche (OR = 1.14, 95% CI = 1.11–1.18). One additional year at mother's menarcheal age reduced of about one-third the probability of early menarche for the girl (OR = 0.70, 95% CI = 0.66–0.74).

Discussion

In our research, we studied the age at menarche in a large sample of Italian girls attending secondary school. We collected data on clinical, epidemiological, and psychological features of menses, and investigated the first two aspects.

The date of first menses was retrospectively collected from girls who had already had their first menses. The information was self-reported by girls, with the help of a structured questionnaire. This methodology has several advantages. First, it is easy to execute, which allows a useful sample size to be collected. Second, even though memory bias is possible, several studies have shown that the results from such questionnaires are reliable when the data collection is close to the menarcheal event [32–35]. The mean age of the studied girls was 17.19 years (SD = 1.42), and only 6.2% of the girls were older than 18 years. This indicated a very short time between the event and the data collection. The results indicated that the median age for all the girls at menarche was 12.40 years. Comparison of our results with previous studies on the Italian population or on other countries [3,5,15,22,36] suggests that, at present, the secular trend has slowed. In the United States and northern Europe between the 19th and 20th centuries, the decrease in age at

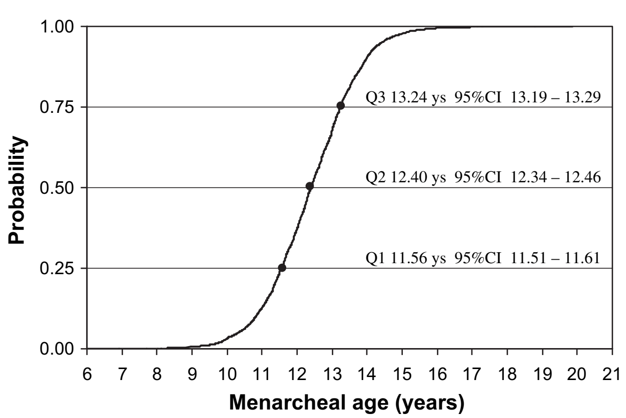

Figure 1. Menarcheal age among Italian girls estimated by survival analysis.

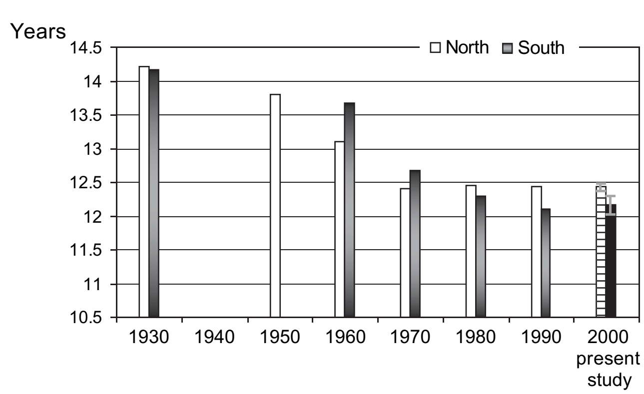

Figure 2. Secular trend for age at menarche in northern and southern Italy. Grey vertical lines represent 95% CI for the results of the present survey. Data for previous studies are from Rigon and Bianchin [31].

Table 2
Mean menarcheal age (±SE) in decimal year according to geographical components, nutritional status, and family size.* The difference in comparison to mothers' age at menarche is also shown.

		Mean±SE†	Observed percentiles						
			5	10	25	50	75	90	95
Total sample population		12.4±0.05	10.3	10.8	11.6	12.4	13.2	14.0	14.4
Area	Northern Italy	12.4[a]±0.05	10.4	10.9	11.6	12.4	13.3	14.0	14.5
	Southern Italy	12.2[b]±0.08	10.2	10.7	11.2	12.1	13.0	13.7	14.2
Parents	Both from North	12.5[a]±0.05	10.4	10.9	11.6	12.5	13.3	14.0	14.5
	North and South	12.4[a]±0.07	10.1	10.9	11.6	12.4	13.2	14.0	14.4
	Both from South	12.3[b]±0.07	10.3	10.7	11.3	12.2	13.1	13.8	14.2
BMI (kg/m^2)	<18.5	12.8[a]±0.07	10.8	11.2	12.0	12.8	13.6	14.2	14.7
	18.5–20.0	12.5[a]±0.06	10.5	10.9	11.7	12.5	13.3	14.0	14.4
	20.0–25.0	12.3[c]±0.06	10.2	10.7	11.4	12.3	13.1	13.9	14.2
	25.0–30.0	11.8[d]±0.11	9.8	10.4	11.0	11.7	12.8	13.6	13.9
	>30.0	11.6[d]±0.29	9.5	9.5	10.4	11.5	12.6	13.0	14.1
Family size (persons)	≤3	12.3[a]±0.06	10.2	10.7	11.4	12.3	13.2	13.9	14.4
	4	12.4[b]±0.05	10.4	10.9	11.6	12.4	13.2	14.0	14.4
	≥5	12.5[b]±0.06	10.3	10.9	11.5	12.5	13.3	14.0	14.4
Mothers' population		12.7±0.06	10.0	11.0	12.0	13.0	14.0	15.0	15.0
Age at menarche difference (girl–mother)		−0.32‡±0.07	−3.1	−2.35	−1.21	−0.13	0.79	1.78	2.32

* Social status and physical activity were not significantly associated with menarcheal age.
† Mean values and standard errors were obtained by the PROC MIXED with cities as random effect. For each stratifying variables, mean values with different superscript letters (a,b,c,d) are statistically different ($p < .5$). Significance was evaluated by means of the MIXED procedure with cities as random effect and the covariate as fixed effect.
‡ Paired data, $p < .001$.

menarche was about 0.3 years per decade [15]. Since then, the rate of decrease in age at menarche has progressively slackened and, in a few cases, the direction of the change has actually been inverted [3,5,22]. The trend of decreasing age at menarche in the same time period was also observed in Italy [31], with a decrease of about 0.3 year per decade. This study suggests that, in Italy, there is currently a decrease of about 0.1 year per decade and at least a similar age at onset of menarche since 1970. The latter result is largely consistent with findings from other countries [16,19,23], and it would suggest that, in Italy, the secular trend of menarcheal age is probably coming to a halt.

Our results are comparable to those produced by previous studies on Italian girls [31,37], confirming that the clinical criteria for normality of menarcheal age in Italy ranges from 10 to 15 years, as this interval includes about 95% of the entire distribution. The slackening in the onset of menarche may also validate the findings by Danubio et al [37], who suggested that the threshold for early onset of puberty is 8 years old for girls from northern Italy and 7.5 years old for girls from southern Italy. In actuality, longitudinal studies are required to verify whether the secular trend in Italy has a different effect on telarche and menarche, as has been suggested by other authors [26,27,29].

In the present study, the effect of the genetic component on age at menarche was explored on the basis of parents' geographical birth area. As illustrated in Tables 2 and 3, this component has an independent effect on menarcheal age, even after adjusting for the other covariates. This result is in agreement with the findings of previous studies

Table 3
Results of multivariate linear and non linear regression analysis*, in which geographical and familial characteristics are the independent factors

Parameters	Age at menarche as continuous response multivariate linear model for clustered data ($R^2 = .14$)			Age at menarche as binary response (<12 years) (multivariate nonlinear model for clustered data)	
	Estimate	SE	p	OR	95% CI
Parents (both from North = 0, North and South = 1, both from South = 2)	−0.07	0.03	.03	1.14	1.01–1.29
BMI (kg/m^2)	−0.08	0.009	<.0001	1.14	1.11–1.18
Family size (no. persons)	0.06	0.03	.01	0.88	0.78–0.99
Mother's age at menarche (years)	0.23	0.01	<.0001	0.70	0.66–0.74

* In the first model, the girl's menarcheal age is the dependent variable, whereas adjusted odds ratios (95% CI) for early menarche (<12 year) were computed by the model for binary response. The linear regression model was obtained by the MIXED procedure. Covariates were fixed effects and cities were random effect. The R^2 estimate was obtained by means of the corresponding fixed-effects model. The nonlinear regression model was obtained by the NLMIXED procedure. Covariates were fixed effects and cities were random effects.

[1,10,15,27,36,37], and it confirms the role of genetic components, even after the geographical migration of parents.

As shown by the results, when the city random effects were taken into account, the environmental component (expressed by the girls' place of residence) did not show to independently associate with the menarcheal age. This suggests that the environmental effects are implicit in the within cities correlation.

In our study, the girls' nutritional condition was expressed by the BMI value, which was calculated from self-reported weight and stature at the time of the survey. We are aware that BMI can only be considered a proxy, especially given that it generally overestimates the nutritional condition at the menarcheal age, but we consider the effect of memory bias on the data to be worse. We assumed that, in nonpathological individual growth, nutritional conditions track from childhood BMI to adulthood. As we were interested in the relationship between variables and not in the true BMI value at menarcheal age, we assumed BMI at the survey time to be a reliable surrogate.

According to published reports, improved nutritional condition is considered to be the main independent factor causing the decrease in age at menarche. As in many countries, the nutritional conditions in Italy have already reached an optimal level, and it is possible that this could cause the secular trend toward an earlier age at menarche to slacken [5,8,15,22]. Our results confirm the significant advance in age at menarche of overnourished girls, and we share with other authors [16] the idea that the relationship between childhood BMI and age at menarche is not likely to be causal, as both early menarche and increased BMI might be the consequence of a predisposition to insulin resistance.

Previous studies on the role of family size, birth order, and family socioeconomic status indicated that girls living in larger families have menarche at older ages. Ulijaszek et al [20] and Padez et al [21] confirmed this result, but, whereas Ulijaszek et al found birth order to be unrelated to menarcheal age, Padez et al [21] suggested that first-born girls had menses earlier. In the latter study, they also found parents' educational level and occupation were unrelated to the age at menarche.

Our study showed that larger family size corresponded with a significantly later age at menses, whereas socioeconomic level and physical activity seemed to be unrelated to menarcheal age. The lack of association between socioeconomic level and age at menarche could be differently interpreted. On one hand, the girls whose parents had a high education might have had lower weight, and, in actuality, their BMIs were significantly lower than those of the other girls (data not shown). This lower BMI would correspond to a lower fat mass, and, as a higher fat mass is thought to be related to an advance in the age at menses [23,25], the sexual maturity of the girls whose parents had a high education might have been delayed. On the other hand, the feminine scholastic population that was included in the study belongs to the middle and upper social classes, given that the social level of the Italian population improved after World War II. The lack of inclusion of girls belonging to the lower class may have prevented the identification of class-based differences in age at menarche. The significant correlation that was found between the girls' and mothers' age at menarche is largely in accordance with data from the literature [2,4,11,12,15,22].

Overall, our model could only explain 14% of the total variance in age at menarche. This is not surprising because, as outlined by Dorn [38], the mechanisms of pubertal timing are still not fully understood and new efforts have to be made to develop satisfactory models of the interactions between physiological, behavioral, environmental, and genetic data.

This study has some limitations mainly due to methodological issues: the only inclusion of postmenarcheal girls and the comparison with former studies. For the first point, a systematic underestimation of age at menarche may have occurred. Actually, the range of the girls' age (15–21 years) suggests that only a very limited number of premenarcheal girls might be excluded. We must take into account, as indicated by the literature and confirmed by our data, that more than 95% of the girls have menarche before they are 15. In addition, the study included girls of older ages and this should have limited the bias by capturing retrospectively the information on age at menarche for girls maturing the latest. The accuracy of estimates of menarcheal age based on recall information has been discussed in the literature. Data analysis methods have been proposed [33] to handle censored (girls that have not yet started menstruating) and missing data (girls who have started but forgot when) to produce more efficient parameter estimates. With reference to our study, the efficiency concerns were not very relevant as the sample size was very large [33]. With regard to the second methodological point, the comparison of up-to-date results with previous researches is challenging because of biases due to unmanageable differences (methodology in data collection, study design, data analysis) related to the studies heterogeneity. To minimize those biases, only surveys with the same methodological approach (retrospective studies with recalled age at menarche) were included for the comparison with our data.

In conclusion, our results suggest that Italian girls' age at menarche seems to have stabilized during the last decades and that the secular trend toward an earlier age at menarche is reducing. This study identified the conditions that contribute to enhanced age at menarche, namely, later menarcheal age of the mother and larger family size, and of those that contribute to decreased age at menarche, namely, a high BMI and having parents born in southern Italy.

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