Research article

The levelling-off of the secular trend of age at menarche among Italian girls

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A B S T R A C T

Objective: The main aim of this study was to verify whether the secular trend stopped in Italy by comparing the results of a 1990–2000 birth cohort versus a 1980–1990 birth cohort of Italian young women. The results were used to speculate about age at menarche as adaptive response to non-genetic factors.
Methods: In 2016, a study was set on 413, 18-to-26 year-old women (1990–2000 birth cohort) attending two Italian Universities by web-based, self-reported questionnaires. Previously in 2000, a research including 3,783 high school female students (1980–1990 birth cohort) was led. The age at menarche distribution was performed by Kaplan-Meier analysis. The comparison between the findings of the two birth cohorts was performed by Wilcoxon sum-rank test. Mixed models analysis was applied to evaluate the effect of cohort and socio-economic status on age at menarche.
Results: 1990–2000 cohort's age at menarche median was 12.44y (95%CI 12.37; 12.59y). There was no significant difference with age at menarche of the previous cohort (p = 0.56). Consistently, the advance of age at menarche in comparison to the mothers' one was not significantly different between the two cohorts (-0.27y±0.10y vs -0.25y±0.03y, p = 0.33). The socio-economic level was not significantly associated with menarcheal age.
Conclusions: The findings of this study confirm that, like in other developed countries, the advance of age at menarche has stopped in Italy, consistently with the stop of the improvement of socio-economic conditions. Further studies are needed to explore the differential effect of each non-genetic factor to outline future scenarios of human sexual maturation.
Trial registration: the Comitato Etico per la Sperimentazione Clinica (CESC) della Provincia di Padova of the Veneto Region (Italy), n°3993/U16/16.

1. Introduction

In the last centuries, girls from several countries encountered a decline in their age of pubertal maturation. Many studies documented that the most convenient marker for the timing of puberty in girls (i.e., age at menarche) underwent a decrease of about 4–5 years from the beginning of the 19th century (about 17 years old) to the middle of the 20th century (<13 years old) [1]. At today, mean/median age at

menarche, as available in the literature, ranges between 12 and 14 years (Figure 1) [2, 3, 4, 5].

In this regard, the so-called secular trend, about the decline of the age at menarche, has been demonstrated, but highly variable rates of decline have been reported between and within many countries. In nine Western European countries, the decline of age at menarche ranged from 1 to 4 months per decade [6]. More recent findings confirmed the high variability between countries as follows: in poor and developing countries in

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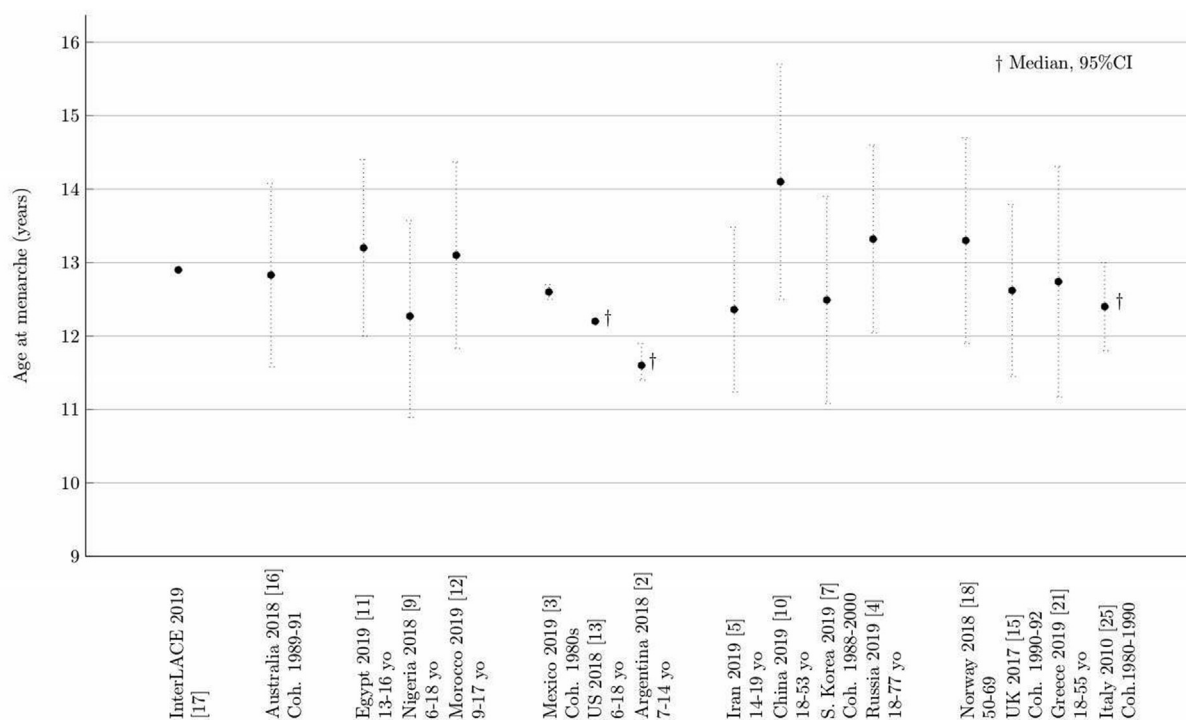 *E-mail address:* egle.perissinotto@unipd.it (E. Perissinotto).

Figure 1. Mean/median age at menarche with 95%CI from more recent researches, by Country. † Median (95%CI) are shown when mean (95%CI) was not provided in the paper.

Africa or in South-East Asia [7, 8, 9, 10, 11, 12], the trend seems to be still ongoing – as well as in the US, Canada, Australia and the UK [13, 14, 15, 16]; in Spain, Denmark, Belgium, Norway, and Sweden, data showed lower rates of decline [17, 18]; meanwhile in France [19], Germany [20], Greece [21], and the Netherlands [22] the secular trend looks like to have stopped.

The main cause of the decline was identified in the improved health and nutritional status experimented worldwide for the socio-economic development started at the end of the 19th century [23].

Consistently, evidence from the literature largely supported this association, using the socio-economic status [SES] [24] as a proxy for both the accessibility to food and better living conditions: in fact, until the mid-1950s, in industrialized countries, age at menarche was lower in girls with higher SES; yet, since then, age at menarche in Caucasian girls with lower SES became comparable to the one of girls with higher SES. These observations get along with the followings: (*i*) faster rates of decline in age at menarche are currently still seen among less advantaged populations, or population sub-groups, where the mean age at menarche is higher; (*ii*) slower rates (or a complete absence of decline) are seen among those sub-groups with long-standing improved SES.

As far as Italy is concerned, the results from a population-based study on adolescents (1980–1990 birth cohort) suggested that the secular trend of the age at menarche was levelling off [25]. The study showed no difference in age at menarche among SES levels, meanwhile other well-known covariates (e.g., geographical area, Body Mass Index [BMI], maternal age at menarche) confirmed their association with menarche onset.

That said, since the SES improvement topped off in Italy in the period 1980–2010, we believed that an update of the age at menarche in the birth cohort 1990–2000 should confirm the stop of the secular trend in Italy.

To verify this hypothesis, the aim of the study was to estimate the age at menarche of girls born in Italy between the 1990s and 2000s and to compare it with previous results regarding the 1980–1990 cohort of

birth. Moreover, the results helped speculating about age at menarche as an adaptive response to non-genetic factors.

2. Methods

2.1. Birth cohort 1990–2000

A cohort study was conducted in 2016 on a sample of 18-to-26 year-old female medical students attending at two Italian Universities (Pavia and Padova). Students were given information about the research and its aims during short conferences at the University and by means of a free-access website on the Internet. The young women who were interested in the research were invited to sign an informed consent before receiving the credentials to access the web-based platform, known as RedCap, where to fill in the self-reported questionnaires [26].Personal computers, tablets, smartphones could be used to fill in the questionnaires, as such as academic informatics facilities. Inclusion criteria were to be female, aged 18–26 years, and to have had menarche. Among the 1,419 eligible students, 413 (29%) voluntarily adhered; of these 413, 85% resided in the University areas (Northern Italy), while 15% came from other Italian regions.

The cohort study design included:

a) Baseline data collection
  - I phase – General questionnaire regarding baseline characteristics. The questionnaire collected information about demography and health details, any chronic diseases, lifestyles and psychological characteristics, menstrual cycle features and its disorders, and drug and non-drug treatments. A certain number of questions aimed to detect symptoms of dysmenorrhoea, dysphoria, anxiety and depression. The students and their mothers' age at menarche was registered and all data were self-reported.
  - II phase - The features of 3 consecutive menstrual cycles, such as: physical, psychic and psychosomatic traits, headache and

treatments of symptoms day-by-day for 10 days after the beginning of the menstrual flow.
b) 3 years data collection

    Three follow-up phases, each year for 3 years, starting from baseline. The questionnaires were the same as the first administered.

All participants were informed about the nature, purpose and procedures of the study, and the written informed consent was obtained from each student. The study was developed in line with the principles of the Helsinki Declaration and approved by the Comitato Etico per la Sperimentazione Clinica (CESC) di Padova of the Veneto Region (Italy), n°3993/U16/16.

In the present study, baseline information about the students and their mothers' age at menarche were analyzed, as well as students' demographic, socio-economic and health status.

Girls' mean (SD) age at survey was 21.3y (2.17y), ranging from 18y to 26y. With regard to mothers'data, birth years ranged in 1950–1978, mother mean age (SD) was 51.9y (4.6y) with age ranging from 38y to 66y.

2.2. Birth cohort 1980–1990

In 2000, the same research group had conducted a multicentre, cross-sectional study among a large number of Italian high-school girls, by means of a self-administered questionnaire, in 16 cities all throughout Italy. Study design and methods were reported elsewhere [25]. Briefly, the questionnaire was filled in at school in the presence of the teachers. The questionnaire included questions about girls' demography, anthropometry, date of menarche, regularity of menses, behavioural habits and physical activity, as well as questions regarding their parents. The high-school girls could ask their parents and siblings about the information the questionnaire requested about them (e.g., parents' educational level, mothers' age at menarche, etc.). Moreover, the questionnaire included questions regarding menstrual and premenstrual complaints, and the psychological self-perceived experience of menses. The study of the 1980–1990 cohort was designed in accordance with the Helsinki Declaration; all participants were informed about the nature, purpose and procedures of the study, and written informed consent was obtained from the students and their legal guardians. According to the Italian regulations on observational research at that time, the study was exempted to institutional ethics committee approval.

As a result, 3,783 girls voluntarily participated in this study.

In the present study, the results from the cohort 1980–1990 study, regarding girls' and mothers' age at menarche and their socio-economic level, were used.

Girls' mean (SD) age at survey was 17.1y (1.35y), ranging from 13y to 21y. Referring to mothers' data, birth years ranged from 1938 to 1969, mothers' mean age (SD) was 45.2y (5.0y) with age ranging from 31y to 62y.

In studying both the cohorts, with the aim to reduce the probability of a possible forward telescoping bias [27], more questions were asked the participants about the time of the event. One question asked the absolute time (month, day, year), but other questions about the associative memory chain helped to locate the event in the remote time (How old were you at menarche? What school and year did you attend at menarche?).

2.3. Statistical analysis

The Hollingshead index, based onto parents' education and employment, was applied to both the birth cohorts [28]. Consistently with the previous study [25], the total SES score was categorized into 4 levels: 0–4 was considered low; 5–8 middle; 9–12 high; and 13–14 very high. The normality of the distribution of quantitative variables was verified by the Sapiro-Wilk test. The quartiles of age at menarche, and their 95%

Confidence Intervals [CI] as well, were estimated by the Kaplan-Meyer survival analysis. The comparison between the median age at menarche of the two birth cohorts was obtained by using the Wilcoxon sum rank test. The log-rank test was applied to verify the difference among the sub-groups distributions of age at menarche. Adjusted mean values for age at menarche and p values for significance of differences between sub-groups were obtained by applying mixed models analysis with fixed effects (cohorts and SES levels).

To estimate the secular trend taking into account of paired data in the dyad daughter-mother, a new variable was created by using the difference between the girl's and her mother's age at menarche and expressed as a decimal year. As that variable was not normally distributed, the comparison between the differences in the dyad between the two birth cohorts was obtained by using the Wilcoxon sum rank test, meanwhile the comparison of the entire distributions was applied by means of the Kolmogorv Smirnov asymptotic test for two samples. The adjusted effects of the cohort and the SES score on the difference between the girl's and mother's age at menarche were obtained by means of nonparametric mixed models, after transforming in ranks the values of the dependent variables (age at menarche and the difference of age at menarche in the dyad daughter-mother, in two separate models). For each model, multiple comparisons were performed by using the Sheffe' test.

With the sole aim to roughly estimate the mean age at menarche per decade in Italy, the mean age at menarche was computed for mothers and girls by birth decades (from mothers' data:1938–1949, 1950–1959, 1960–1969, 1970–1979; from girls' data 1980–1989 and 1990–2000), without taking into account paired data. In this analysis, data were analysed as a whole, even though the accuracy of mothers' and girls' age at menarche may be biased by different reporting bias.

All the statistical analyses were performed using R, ver3.6.0 [29]. Data are available at reasonable request at https://doi.org/10.17632/rvmrbsc8vc.1.

3. Results

A total of 413, 18-to-26-year-old females compiled the questionnaire in 2016. As Figure 2 shows, the median value of the age at menarche resulted being 12.44 years (95%CI = 12.37; 12.59). Median menarche onset was not significantly different from the median onset of the 1980–1990 cohort (12.40, 95%CI = 12.34; 12.46, p = 0.56). However, the distribution of age at menarche of the two cohorts significantly differed (log-rank p = 0.02), due to a number of subjects with very high menarcheal age. Therefore, in the 1990–2000 cohort, the variability of the menarche onset was slightly higher than the one of the 1980–1990 cohort (standard deviation and coefficient of variation % [CV%]: 1.50y, 12.0% and 1.28y, 10.2%, respectively). Consequently to lower sample size and higher variability, the estimated precision of quartiles was lower in the cohort 1990–2000 (Figure 3). As shown in Table 1, even in the 1990–2000 cohort, menarcheal age was not significantly different by SES levels with values comparable with those of the cohort 1980–1990. No difference was found between mothers' age at menarche (12.8 ± 0.08 vs 12.7 ± 0.03, p = 0.09). Moreover, the girls' mean advance in age at menarche was substantially the same in the two cohorts (-0.27y ± 0.10y vs -0.25y ± 0.03y, p = 0.33). The adjusted p levels showed no significant effect of the cohort (p = 0.20) and the socio-economic level (p = 0.69).

Only for a descriptive purpose of observed data, when the mothers' and girls' age at menarche was analysed without taking into account for paired data, the rough mean age at menarche (SD) by birth decade, in our Italian cohorts, was: 1938–1949 12.8y (1.50y), 1950–1959 12.6y (1.53y), 1960–1969 12.6y (1.61y), 1970–1979 12.7y (1.72y), 1980–1989 12.4y (1.28y), and 1990–2000 12.5y (1.50y).

4. Discussion

The results of the present study confirmed that in Italy the secular decline of the age at menarche has finally stopped, with a substantially
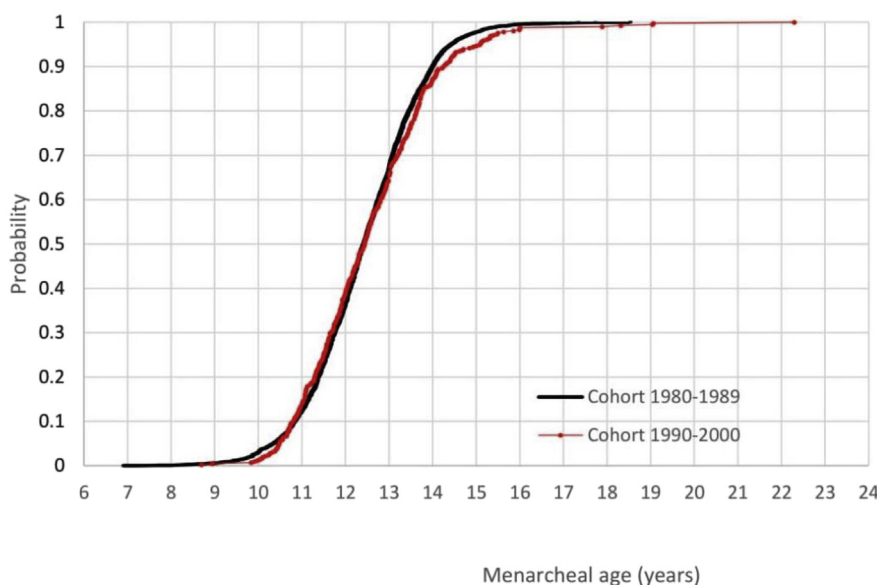
Figure 2. Probability distribution of the age at menarche, in the two Italian cohorts.
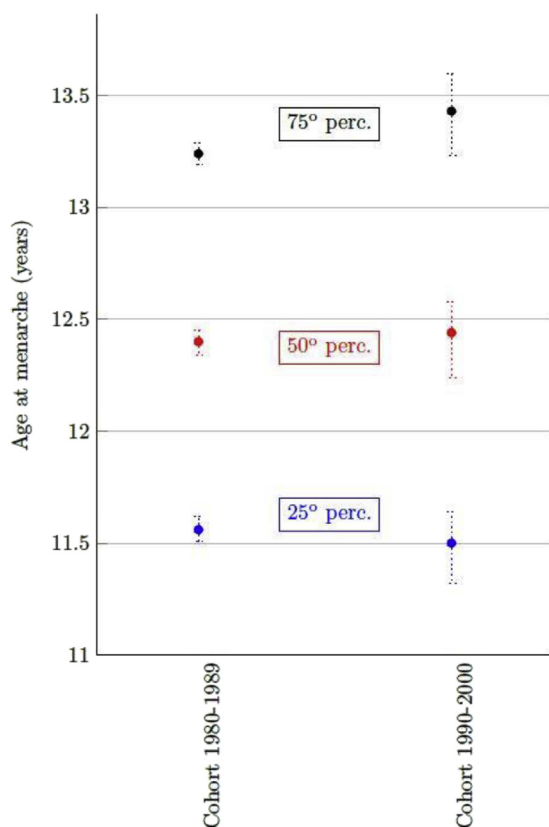

Figure 3. Percentiles (25°, 50° and 75°) with 95%CI of the age at menarche in the two Italian cohort.

stable median value of 12.4 years. Moreover, the SES categories and the age at menarche resulted independent. Accordingly, the advance of the girls' age at the first period in comparison with their mothers' one was stable (about a quarter of year). This result was expected given that girls' age at menarche was stable and the mothers' birth decades largely overlap in the two study cohorts, as reported in the method section (1938–1969 vs 1950–1978). The inclusion criteria of the present research (in particular, the age – up to 26 years old – and the presence of

menarche) justify the higher variability of the age at menarche in comparison to that from the 1980–1990 cohort, where only adolescents were included [25]. In fact, the 1990–2000 birth cohort study design allowed the inclusion of young women with late or very late menarche, consequently the distribution of menarcheal age was slightly asymmetric on the right tail. Actually, also the presence of a possible forward telescoping bias might justify a major proportion of girls with late or very late menarche in the 1990–2000 cohort. As they had older ages, the time distance from menarche was higher and, due to the telescoping bias, the more remote events might be perceived as more recent than they are [27].

Allowing that the real age at menarche was unknown in this study, we could only indirectly explored this bias by testing the linear association between the age at survey and the age at menarche. Actually, only in the 1980–1990 cohort, age at survey resulted significantly and positively associated with menarcheal age (data not shown), even though this association would likely depend on the study design, which includes only secondary school girls who have already had menarche. The absence of that a relationship in the 1990–2000 cohort would suggest that the possible forward telescoping bias is limited, so making the physio-pathological origin of its outliers probable.

The findings of the present study raised the question whether there is a sort of biological threshold for the age at menarche. Since the timing of puberty is a multifactorial process, in non-pathological conditions (e.g., precocious puberty) the value of 12.4 years is far from being intended as an absolute limit. As widely accepted, in fact, genetic and environmental factors mainly concur to the timing of the pubertal development. Genetic and environmental differences among countries, and even areas, can be accounted for the great variability of non-pathological sexual maturation timing worldwide.

Recent studies confirmed that the timing of puberty is a highly polygenic childhood trait and more than hundreds of independent, genome-wide significant signals for age at menarche have been identified [30, 31, 32, 33, 34]. In fact, ethnic and geographical differences modulate human genome variants and polymorphisms, thus reflecting on variability of the local timing of sexual maturation: approximately half of the phenotypic variation in the timing of menarche is likely due to genetic factors, at least in girls living in developed countries [35].

Ong et al. [36] suggested that time at menarche might be genetically established, with wide variation within the same population and between populations, but an inadequate nutritional status at early ages might act slowing the timing of the pubertal maturation process. As to say, if the

Table 1. Estimated mean values ±standard error (SE) of age at menarche and difference between girl's and mother's age, by cohort and by social levels.

	n	COHORT 1980–1990 mean ± SE†	n	COHORT 1990–2000 mean ± SE†	p*	p**	Cohort effect‡ adjusted p	Social Score effect‡ adjusted p
A) Girls'age at menarche								
Total	3783	12.40 ± 0.03	413	12.53 ± 0.07	0.56	0.33		
by Social Score							0.91	0.24
Low	175	12.44 ± 0.10[a]	10	11.58 ± 0.39[a]				
Middle	1155	12.36 ± 0.04[a]	63	12.71 ± 0.15[a]				
High	1493	12.42 ± 0.03[a]	189	12.39 ± 0.09[a]				
Very high	650	12.49 ± 0.05[a]	151	12.66 ± 0.10[a]				
B) Mothers'age at menarche								
Total	3214	12.7 ± 0.03	330	12.8 ± 0.08	0.08	0.20		
C) Difference between girl's and mother's age at menarche								
Total	3214	-0.25 ± 0.03	330	-0.27 ± 0.10	0.33	0.09		
by Social Score							0.20	0.69
Low	145	-0.17 ± 0.15[a]	8	-0.52 ± 0.60[a]				
Middle	984	-0.27 ± 0.05[a]	55	-0.11 ± 0.23[a]				
High	1315	-0.21 ± 0.05[a]	149	-0.41 ± 0.14[a]				
Very high	549	-0.24 ± 0.07[a]	118	-0.10 ± 0.15[a]				

*p values from Wilcoxon sum ranked test.

**p values from Kolmogorov Smirnov asymptotic test.

† Mean values and Standard Error (SE) were obtained by applying Mixed Models with cohort and SES score as fixed effects.

‡ adjusted p values from nonparametric Mixed Models with fixed effects entering the dependent variable values (age at menarche or difference between girl's and mother's age at menarche) as ranks.

[a] Differences between means of ranked values were never statistically significant by using Scheffe's adjusted p for multiple comparisons, with separate Mixed Models for age at menarche and difference between girl's and mother's age at menarche.

environment permits an adequate growth in healthy children, the chronology of pubertal development will respect the timing defined by genetics; otherwise, it will be delayed. The impressive reduction of the variability of age at menarche observed over the centuries in most population is taken as support for this theory [1]. In fact, the reduction of the nutritional braking effect makes the pure effect of genetics clearer.

Assuming this reasoning as correct, worldwide the decline of menarcheal age should stop only when children nutritional status (or generically, food availability) will be adequate, and it could be now for most industrialized countries.

As Papadimitriou claimed [23], despite the obvious limitations, Gluckman and Hanson discovered that in Prehistorical times age at menarche was between 7 and 13 years – very similar to the contemporary age [37]. Nowadays, in Italy, in physiological conditions, about 90% of girls have their first cycle between 10 and 14 years (Figure 2).

Since it is difficult to claim that there are the same environmental conditions that there were thousands years ago, it could be said that a genetic timing of the age at menarche does stand and, at the same time, in the latest centuries, we are experiencing a restoration of the biological timing as an adaptive response to modified environmental conditions. In fact, the major food availability in the last century is a direct consequence of the technological development, which enhanced quality, quantity and distribution of food production, even though global data show substantial variation in consumption by nation and population worldwide [38].

The enhanced nutrient bioavailability in food particularly fits the nutrient requirement increased in infancy, childhood and adolescence, improving growth in earlier ages. In summary, a higher disposal of food is relevant for several health outcomes – largely positive for maternal and child health outcomes but, at the same time, mostly negative for some non-communicable diseases in adulthood.

Simultaneously, in this new situation, in which exaggerated consumption of resources and global pollution occur, the interaction with new environmental elements other than food, might play a significant role on the biology of sexual maturation.

Among others, chemical and not-chemical contaminants could hamper through epigenetic processes. Recently, Street M.E. and colleagues [39] claim that numerous xenobiotic chemicals, once released into the environment at relevant concentrations as the product of human activities, do have the potential to disrupt the endocrine system of wildlife and humans. Approximately 1,000 chemical products (plasticisers as phthalates and bisphenol, flame-retardants, alkyl phenols, metals and dioxins, polycyclic aromatic hydrocarbons, and pesticides, etc.) are recognized as potential endocrine-disruptor chemicals. Consequently, the exposition to several chemicals' effect might cause negative, immediate and transgenerational effects. For example, atrazine delays puberty in both males and females [40], meanwhile polychlorinated biphenyls have been associated with earlier menarche [41].

To reinforce this evidence, very recently researchers wonder on the potential effect of common pollutants such as Perfluorooctanesulfonic acids [PFAS] on pubertal timing [42, 43]. Consistent results support the gender-specific associations between exposure to PFAS and pubertal development, even though further studies are needed to clarify the mechanism linking the two factors. Ernst et al. [43] have suggested that the increased risk of childhood obesity in both sexes after pre- or post-birth exposure to PFAS might explain this relationship.

Still: another critical effect onto the age at menarche can be related to the seasonal events. In the past, several studies indicated that the onset of menarche may be conditioned by seasons and various hypotheses were formulated: photoperiod, latitude, temperature, psychosocial stress, ultraviolet radiation doses, etc. Actually, in our previous study on Italian adolescents, we found that seasonality of age at menarche was bimodal (peaks in summer and autumn) [44]. Accounting the effects acted by temperature, sun exposition and stress, it is plausible to think that also dramatic climatic changes would interfere with the natural sexual maturation leading to unexpected breakaways from the genetically determined sexual maturation time.

Finally, a heavier ecological footprint during the industrial centuries caused a growing environmental pressure on human genome and on its

expression during life – the so-called epigenetics – but, as of today, its effects are unpredictable.

4.1. Limits

The main criticism of the present study is the comparability of the results from the two birth cohorts. In fact, the previous study included girls attending secondary high school, while the present research recruited university students (mean age at data collection: 17.1y vs 21.9y). The main drawback could depend on a differential recall bias between the two populations, with possible less accurate self-reported age at menarche for the university students due to a larger time between their menarche and the age at the data collection. Actually, a moderate to high validity (r = 0.66–0.83) appears in most studies regarding the self-reported age at menarche, especially when comparing actual age at menarche with recalled age at menarche later in life [45, 46, 47]. Moreover, Lundblad and Jacobsen [48] suggested no systematic difference in self-reported age at menarche over time. Based on these elements, and in consideration that median values of age at menarche are not affected by potential outlier data, the impact of the potential recall bias on the results was limited.

Another potential criticism in the representativeness of the 1990–2000 cohort could be due to the use of a electronic questionnaire in the data collection. Actually, it might have attracted a more computer literate population among the university students. In any case, the effect of this potential bias is difficult to describe both on the representativeness of the university sample and the comparison between the two cohorts.

However, due to the voluntary base of participation in the cohort 1990–2000, the selection bias is likely. First, the University students' SES score may be higher than the one of the young population; second, the sample might include young women who are more sensitive to the research topic; third, the eligible population of the present study is regional, and not national as in the previous research; fourth, known and unknown confounding factors might be differently distributed in the two cohorts.

In regards of the first point, in the last decades, nationally in Italy, the economic improvement was largely diffuse with the expansion of SES levels labelled as middle and high. Moreover, in Italy the education is free and compulsory up until 16 years old, while Universities fees are often affordable and state subsidies are available for those in need. Therefore, nowadays, the impact of the socio-economic factors on the young population (menstrual) health is likely attenuated in Italy. Actually, had been a bias, an earlier age at menarche would be expected for University students. In any case, in the present study, the statistical comparison of age at menarche between the two cohorts was adjusted on the SES levels of the girls.

As for the second point, the selection bias cannot be excluded; yet, by recruiting medical students, it was expected that they would be more sensitive and observant to provide correct clinical information. In any case, again, the statistical comparison was applied to median values, that are robust to extreme cases.

Considering the third point, the prestigious Universities included in the study attract students from many Italian areas and, from a genetic point of view, the present study only have a slightly higher prevalence of students coming from northern areas than the previous cohort (data not shown). We did not found that difference relevant for the results. In the present study, in fact, about 85% of the respondents came from Northern Italy vs 71% in the previous study.

As for the last point, more non-genetic variables could affect age at menarche. The more relevant was the socio-economic level, as expression of quality of health and lifestyle. It was included as a covariate in the statistical analyses. Other factors, such as BMI, were not considered in the study because clinically non-comparable in the two cohorts. Actually, while in the adolescent cohort the BMI value was likely to represent the nutritional condition in childhood, the same was not applicable for young women. Other non-genetic factors relevant for the study (e.g. potential

endocrine disruptors) are unobserved (and someway unobservable). We did not have the possibility to adjust the statistical analysis for these potential confounding factors. However, since the diffusion of similar exposures occurred nationally during the past three decades in Italy, this made us confident they might be similarly distributed in the two cohorts.

Finally, the findings of the present study on the levelling-off of the secular trend of age at menarche in Italy seem to agree with the literature regarding several European and Western countries.

5. Conclusion

The findings of this study confirm that, like in other EU and developed countries, the advance of age at menarche has stopped in Italy, consistently with the stop of the improvement of socio-economic conditions. We speculate that, by analogy, recent dramatic changes in climate, pollutants and living conditions due to human activities may have an impact onto sexual maturation inducing adaptative changes in pubertal timing. Further studies are needed to explore the differential effect of each non-genetic factor to delaine future scenarios of human sexual maturation.

Declarations

Author contribution statement

G. Piras: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

L. Bianchin and V. De Sanctis: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

M. Bozzola, S. Bernasconi, G, Bona, G. Lorenzoni, F. Buzi, F. Rigon and G. Tonini: Conceived and designed the experiments; Performed the experiments; Wrote the paper.

E, Perissinotto: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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