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The influence of age at menarche on cross-sectional geometry of bone in young adulthood

Maja Šešelja^{a,*}, Ramzi W. Nahhas^a, Richard J. Sherwood^{a,b,c}, Wm. Cameron Chumlea^{a,b,d}, Bradford Towne^{b,d}, and Dana L. Duren^{a,e}

^aDivision of Morphological Sciences and Biostatistics, Lifespan Health Research Center, Department of Community Health, Wright State University Boonshoft School of Medicine, USA

^bDepartment of Pediatrics, Wright State University Boonshoft School of Medicine, USA

^cDepartment of Orthodontics, School of Dental Medicine, Case Western Reserve University, USA

^dDivision of Epidemiology, Lifespan Health Research Center, Department of Community Health, Wright State University Boonshoft School of Medicine, USA

^eDepartment of Orthopaedic Surgery, Sports Medicine and Rehabilitation, Wright State University Boonshoft School of Medicine, USA

Abstract

Elucidating the somatic and maturational influences on the biomechanical properties of bone in children is crucial for a proper understanding of bone strength and quality in childhood and later life, and has significant potential for predicting adult fracture and osteoporosis risks. The ability of a long bone to resist bending and torsion is primarily a function of its cross-sectional geometric properties, and is negatively impacted by smaller external bone diameter. In pubescent girls, elevated levels of estrogen impede subperiosteal bone growth and increase endosteal bone deposition, resulting in bones averaging a smaller external and internal diameter relative to boys. In addition, given a well-documented secular trend for an earlier menarche, the age at which the rate of subperiosteal bone deposition decreases may also be younger in more recent cohorts of girls.

In this study we examined the relationship between pubertal timing and subsequent bone strength in girls. Specifically, we investigated the effects of age at menarche on bone strength indicators (polar moment of inertia and section modulus) determined from cross-sectional geometry of the second metacarpal (MC2) using data derived from serial hand-wrist radiographs of female participants (N=223) in the Fels Longitudinal Study, with repeated measures of MC2 between the ages of 7 and 35 years. Using multivariate regression models, we evaluated the effects of age at menarche on associations between measures of bone strength in early adulthood and the same measures at a prepubertal age. Results indicate that later age at menarche is associated with stronger adult bone (in torsion and bending) when controlling for prepubertal bone strength (R^2 ranged between 0.54 and 0.70, $p < 0.001$). Since cross-sectional properties of bone in childhood may have long lasting implications, they should be considered along with pubertal timing in assessing risk for future fracture and in clinical recommendations.

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*Corresponding author at: Division of Morphological Sciences and Biostatistics, Department of Community Health, 3171 Research Boulevard, Boonshoft School of Medicine, Wright State University, Kettering, OH 45420, USA. Fax: +1 937 775 1456. maja.seselja@wright.edu (M. Šešelja).

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Keywords

Bone geometry; Children; Menarche; Bone strength; BMI

Introduction

Bone strength depends on its material properties, including bone mineral content (BMC), bone mineral density (BMD), and the spatial distribution of bone tissue (i.e., bone geometry) [1]. Resistance to the principal loads that cause fracture (e.g., bending and torsion) is primarily a function of a long bone's cross-sectional geometric properties [2]. In general, larger external bone diameters provide greater strength in bending and torsion than smaller external bone diameters, when all else is held equal (e.g., amount of cortex, BMD, BMC). Significant sex differences in bone diameter exist, with girls tending to have bones of smaller external diameter than boys, regardless of overall body size (i.e., height or weight) [3–6]. These sex differences arise during puberty, when exposure to estrogen promotes subperiosteal bone deposition in boys [7] but has the opposite effect in girls, where estrogen suppresses subperiosteal bone deposition and promotes endosteal bone deposition [3,5,6]. As a result, girls tend to have bones with both a smaller external diameter and a smaller medullary cavity, and possibly greater density [8], than boys [4,5,9,10]. From this it can be inferred that: 1) a later onset of exposure to estrogen in girls provides more time for periosteal bone deposition; 2) the result of this delayed exposure includes long bones with an increased external diameter; 3) increased external diameter ultimately leads to bones with higher strength under bending and torsion. Thus, it is plausible that among girls with equal prepubertal bone size, those with later age at menarche (i.e., later exposure to elevated estrogen) would have larger adult bone diameter than their peers with an earlier age at menarche.

Examination of the relationship between age at menarche and bone strength is particularly timely given the reported secular trend for younger age at menarche [11–16]. If menarche affects subperiosteal bone deposition as posited, the age at which subperiosteal bone deposition rate decreases may be occurring earlier as well. The resulting bone geometry could lead to lower bone strength, tracking into adulthood, and a greater proportion of women at risk for fracture. While many researchers have examined the relationship between age at menarche and BMD and BMC [17–34], the specific effects of age at menarche on cross-sectional geometric properties of bone remain largely unexplored.

Materials and methods

Study sample

Participants included in the current analysis are derived from the Fels Longitudinal Study, a large longitudinal study of human growth, development and body composition change over the life span, which has been running continuously since 1929 [35]. The sample consisted of 223 female participants between the ages of 7 and 35 years who had at least one hand-wrist radiograph taken between age 7 years and the time of menarche, and at least one radiograph taken between the ages of 18 and 35 years. Fels Longitudinal Study participants were born primarily in Southwest Ohio or neighboring states, and are predominantly Caucasian (~98%). Participants in the current analysis were born between 1929 and 1988, and the year of birth was used for assessment of secular trends. Participants were not selected for any disease or bone-related trait, and therefore represent normal variation in such traits. For the age range of interest (7–35 years), the examination protocol was to see participants every 6 months until age 18 or until they reach skeletal maturity, and every 2 years thereafter [36]. Each study exam included collecting measures of body habitus (e.g., stature, weight, and

BMI), a hand-wrist radiograph, and a detailed health history (including menstrual history) via questionnaire. A maximum of 197 participants were included in any one analysis, though the number varied depending on the age range used in determining premenarcheal bone strength (Table 1). All data collection protocols were approved by the Wright State University Institutional Review Board.

Bone strength measurements

Quantitative measures of bone geometry were obtained from the second metacarpal of the left hand in each individual from antero-posterior radiographs. The second metacarpal is the most cylindrical bone in the hand and can be assumed to have bone evenly distributed about its axis [3,37]. As it is free from weight-bearing stress that would influence bone morphology, it has been widely used in biomedical investigations of bone health [3,37–44]. The radiographs were digitized using a Vidar DosimetryPRO Advantage Radiographic Scanner, and analyzed with a dedicated image processing program written for this purpose in MatLab v.7.7.0.471 [45]. The program first determined diaphyseal length and maximum length (diaphysis + epiphysis) of MC2 along the long axis of the bone. Then, using pixel properties reflecting radiolucency (the differences between light and dark pixels representing cortical bone and medullary cavity, respectively), the program determined external bone diameter and medial and lateral cortical thicknesses perpendicular to the long axis at midshaft of the maximum bone length (Fig. 1A). All measurements were recorded in millimeters. Each radiograph was reviewed for accuracy of measurement placement and adjusted, if necessary, before the data were entered into a database. The radiographs were reviewed by two assessors, and a subset was reviewed by both assessors to assess inter-observer error. Inter-observer repeatability, expressed as Lin's concordance correlation coefficient [46], ranged from 0.93 to 0.99, with the mean measurement differences between 0.008 mm and 0.023 mm (N=256). Intra-observer repeatability ranged between 0.95 and 0.99, with the mean differences between 0.001 mm and 0.04 mm (N₁=261, N₂=248).

Two indicators of bone strength were calculated for the study presented here; polar moment of inertia (J) and section modulus (Z). J represents torsional rigidity of bone along an axis perpendicular to the plane of the cross-section [47]. In case of a hollow cylinder, J is equal to twice the value of the second moment of area (I), or bending rigidity, along an axis in the plane of the cross-section. Z represents the ratio of the polar moment of area and the radius of the bone, and is also a measurement of bending rigidity. Assuming a cylindrical cross-section, J and Z were calculated from measurements described above using the following formulae [2]: $J = \pi \cdot (T^4 - t^4)/32$, and $Z = J/(T/2)$, where T is the external bone diameter and t is the diameter of the medullary cavity (external diameter minus total cortical thickness) at the midshaft of maximum bone length (Figs. 1B and 2).

Statistical analyses

We used multivariate regression to test for associations between J and Z values in adulthood and age at menarche, adjusting for premenarcheal J and Z values, premenarcheal body mass index (BMI), and birth year (to account for any secular trend in bone strength). We also considered age-squared at menarche, as well as interactions between age at menarche terms and childhood bone strength (model formulae are given in Tables 2 and 3). Nominally significant ($p < 0.10$) covariates were retained in the models. For each model, an overall model F-test was conducted and R^2 was calculated. In all the regression models, bone strength (adult and childhood J and Z) was log-transformed in order to normalize the adult response variables and reduce the influence of outliers in the childhood predictor variables. Additionally, all covariates were centered at their mean value (or mean of log values for childhood J and Z). The analyses were carried out using PROC GLM in SAS software v9.2 [48].

We considered two approaches to modeling the relationship between adulthood and childhood bone strength. In both, an average of bone strength values between the ages of 18 and 35 years was used as the adult bone strength variable. The first approach we employed controls for childhood bone properties at a specific prepubertal age. This approach is prospective and easily translates to a clinical setting. To make our models applicable to a wide range of ages for timing of the premenarcheal bone strength measure, we considered five models. Each model controlled for childhood bone properties at a different premenarcheal age (the average of measurements in the age range 7 to <8 years, 8 to <9 years, 9 to <10 years, 10 to <11 years, or 11 to <12 years). Girls who had already experienced menarche were excluded from the models controlling for bone strength at subsequent ages.

The second approach controls for bone properties at a premenarcheal maturational stage, such as Tanner B2 (e.g., [20]), or at a certain time interval relative to menarche or another maturational marker, such as age at peak height velocity (PHV) [49]. This approach is retrospective and can be less clinically applicable because it is limited to peripubertal girls, who will likely experience menarche in the very near future, thus reducing the window for potential intervention to improve bone strength. For comparison, and because the retrospective approach has been used in previous studies, we adapted this approach to our data to examine differences in outcome attributable to analytical method. Because Tanner staging was not available in this sample, we used an average of prepubertal bone strength values recorded between one and two years before menarche as the premenarcheal bone strength value. This interval was chosen as it is in the range of the Tanner B2 stage, and it includes the age at PHV [50].

Results

Prospective models

Descriptive statistics of the prospective samples, including sample size, mean, standard deviation and range for observed age at menarche, BMI, and adult and childhood bone strength indicators, for each model are shown in Table 1. Table 1 also includes the mean, standard deviation and range for bone strength variables on the natural log scale.

Tables 2 and 3 present the estimated regression parameters for the significant covariates in the prospective models for adult polar moment of inertia (J) and section modulus (Z), respectively, each along with model R^2 values and overall p-values. Graphic representations of these models, showing the relationship between adult bone strength and age at menarche at different levels of childhood bone strength (while controlling for all significant covariates), are shown in Fig. 3. In each panel of Fig. 3, the lines represent the regression of adult bone strength on age at menarche at childhood bone strength values at the mean, and at the mean $\pm$ one standard deviation.

Results of the multivariate regression modeling of adult J showed that all of our prospective models are statistically significant (F-test $p < 0.001$), and account for 55% to 70% of the variability in adult bone strength. The models predicting adult Z are all statistically significant as well (F-test $p < 0.001$), and account for 59% to 65% of the variability in adult bone strength. Adult J and Z are both, in general, positively associated with age at menarche. One of the most substantial components of bone strength measured by J and Z is the external diameter of bone (T; see *Bone strength measurements*). Like J and Z, adult external bone diameter exhibits a positive relationship with age at menarche when controlling for childhood bone diameter (r^2 for different models between 0.55 and 0.67, $p < 0.001$). Given equal childhood bone diameter, later age at menarche provides an additional augmentative effect resulting in a larger adult bone diameter.

The positive effect of later age at menarche on J and Z is clearly present for individuals with average to high childhood bone strength, but the effect is less clear for individuals with relatively low childhood bone strength. Statistically, the attenuation of the age of menarche effect for those with lower childhood bone strength is due to the presence of a significant interaction with childhood bone strength (see the 9 and 11-year old models in Table 2 and Fig. 3). We suspect that, in fact, there either is an interaction or not regardless of at what age one measures prepubertal bone strength, and the presence of an interaction in some models but not others is due to either Type I or Type II error. In any case, all five models consistently indicate a significant positive association between age at menarche and adult bone strength for girls with average to high childhood bone strength in our sample. This association may also be true for girls on the lower end of childhood bone strength in our sample, but our results are not conclusive for those girls.

In our dataset, participant birth years span almost six decades, so it is possible that there is an underlying secular trend (either in age at menarche, BMI, or a previously unidentified secular trend in bone strength) influencing our results. In this sample of girls, birth year and age at menarche are not significantly correlated (p-values between 0.15 and 0.91 for different models). Additionally, birth year in our sample is not significantly correlated with childhood bone strength (p-values between 0.17 and 0.98 for different models) but is weakly correlated with childhood BMI in 7-year-olds ($r=0.16$, $p=0.03$) and 9-year-olds ($r=0.14$, $p=0.05$). Childhood BMI was significantly and negatively associated with adult bone strength (both J and Z) after controlling for the other covariates. After controlling for all other covariates, birth year is a significant ($p = 0.011$) and negative predictor of adult J only when controlling for childhood J at age 8 years, whereas for adult Z it is a significant negative predictor in the 8-year old model ($p=0.035$), and marginally significant in the 10-year old ($p = 0.087$) and 11-year old models (0.057). However, in all instances, its absolute contribution to adult bone strength is small (Tables 2 and 3).

Retrospective models

Descriptive statistics for the retrospective sample, providing the mean $\pm$ standard deviation (range) for each variable, and the natural log values for bone strength variables are shown in Table 4. Regression coefficients for the retrospective models for adult J and Z are shown in Table 5. These models accounted for 63.1% and 60.8% of the variability in adult J and Z, respectively. When controlling for average childhood J in the period between one to two years before menarche, adult J has a curvilinear relationship with age at menarche, with later age at menarche associated with, in general, lower adult J (see Fig. 4A). Birth year and BMI were significant negative predictors of adult J (see Table 5). Similar results were obtained for Z (see Table 5 and Fig. 4B).

Discussion

Menarcheal timing has lasting effects on the female skeleton. Our principal finding using a prospective analysis shows that, for a majority of girls, a later age at menarche is associated with an increase in external bone diameter and a concomitant increase in bone strength under bending and torsion. A later age at menarche appears to be particularly beneficial for adult bone strength in girls of average and high childhood bone strength in our sample, regardless of age at which childhood bone strength is measured. For girls on the lower end of the childhood bone strength distribution in our sample, the effect of age at menarche is less clear (Fig. 3).

Previous work examining the effects of age at menarche on bone strength has generally focused on bone mineral content (BMC) and density (BMD), rather than bone geometry, with differing results [17–34]. Most studies report that late menarche is associated with

lower BMD [17–22,24,28,29,32–34] and higher fracture risks for different skeletal sites [23,25,26,30,31] (but see [27,51]). While this may seem at odds with our results for bone strength, we believe the two outcomes are mutually compatible. If early exposure to estrogen at menarche halts periosteal expansion (and limits cross-sectional strength) in early puberty, but mineralization continues, the pattern of bone deposition may be altered [52,53]. Increased endosteal deposition after menarche compensates in part for the reduced periosteal expansion in girls. This configuration, however, does not benefit bending and torsional strength of the bone as much as does periosteal expansion. Thickening the cortex through endosteal expansion (if the external diameter cannot be increased) improves bone strength, but is less biomechanically beneficial than increasing the external diameter of bone (e.g., by delaying exposure to estrogen), even when cortical thickness is held constant (Fig. 2). The exponentiation of bone diameter values (both T and t) to the fourth power in calculations of polar moment of inertia and section modulus means that even small increases in the external diameter of bone due to a later age at menarche exponentially increase both measures of bone strength.

Endosteal expansion of bone after menarche is anatomically and physiologically limited by the necessary functions of the medullary cavity. It is also possible that new bone mineralization in postmenarcheal girls with early age at menarche could increase the BMD and BMC of bone. This may, at least in part, explain why some studies find skeletal benefits to a late menarche (increased BMD/BMC), and some studies show skeletal benefits to early menarche (bending/torsional strength).

Prospective vs. retrospective modeling

Another explanation of divergent conclusions in the literature regarding the effect of age at menarche on bone strength is the differing approaches to statistical modeling used in each study. The primary statistical model presented here is prospective and, in controlling for premenarcheal values of the outcome, it utilizes bone strength measures at a specific prepubertal chronological age, regardless of age at menarche. Other studies have used a more retrospective approach, controlling for bone measures at a certain time point relative to a maturational marker, such as breast development or age at PHV.

To examine the differences between modeling approaches in our own data, we conducted analyses using the retrospective criteria. Using this retrospective approach, we found that age at menarche and bone strength were negatively associated (i.e., later age at menarche was associated with lower adult bone strength). This result is the opposite of what we found using the prospective approach. This discrepancy, however, stems from the fact that these two models statistically condition on childhood bone strength in two very different ways. The prospective model controls for childhood bone strength at a specific chronological age, whereas the retrospective model controls for childhood bone strength at a specific time point relative to a sexual maturation event, but does not include information on chronological age. Fig. 5 presents these two scenarios in two hypothetical individuals and serves to illustrate a possible reason why the prospective and retrospective approaches/models result in different conclusions regarding the relationship between age at menarche and adult bone strength.

In the prospective approach, the model is conditioned on childhood bone strength at a specific age, but subjects are not equally distant from menarche, as some girls will experience it earlier, and some later. Fig. 5A illustrates a hypothetical girl with earlier menarche (point of flexion in the figure) who started with the same premenarcheal bone strength at age 8 years as another hypothetical girl with later menarche. Assuming the rate of increase in bone strength diminishes at menarche (i.e., greater estrogen exposure), the girl with later menarche ends up with higher adult bone strength, ostensibly because she had more time before menarche for increasing bone diameter and bone strength.

In the retrospective approach, our model is conditioned on childhood bone strength at a specific number of years prior to menarche, but subjects are of different chronological ages. Fig. 5B presents one of the possible scenarios where early age at menarche could be seen to have a positive effect on cross-sectional bone strength in two hypothetical girls. Here, bone strength is measured (and is equal) at the same number of years before menarche, but each girl is measured at a different chronological age since age at menarche differs between them. In both girls, the event of menarche (point of flexion in the figure) slows the rate of increase in bone strength by the same degree. The girl with earlier menarche has higher adult bone strength, and the girl with later menarche has lower adult bone strength. However, in this model, the difference in adult bone strength is heavily based on a higher premenarcheal bone strength at any given chronological age in the girl with earlier menarche, and not necessarily because of the timing of menarche.

The prospective and retrospective modeling approaches are equally valid mathematically but, biologically, they seem to contradict one another. Age at menarche is either positively or negatively associated with adult bone strength, given childhood bone strength. The contradiction is resolved with a better understanding of what the models are conditioned on, how the pre-menarcheal age for bone strength measures is determined, and how that may influence the results. In the prospective model, when evaluating the effects of menarcheal timing on bone strength, girls are compared at the same age with similar bone strength and we prospectively determine which girl ends up with higher adult bone strength. This approach accounts for chronological age, bone strength at that age, and age at menarche. The retrospective model, however, controls for bone strength at a certain time point relative to the age at menarche, but does not account for chronological age. This leads to a comparison of girls of different chronological ages whose developmental timing is already known to be different, which makes them less comparable to each other than are the girls in the prospective model. Since childhood growth in normal children is largely a function of age, and to a lesser extent of sexual maturation, omitting chronological age when evaluating the effects of subsequent maturational events on childhood bone growth may introduce bias into the interpretation. Moreover, the retrospective approach may be less clinically applicable, as it applies only to peripubertal girls who would experience menarche in the near future, reducing the possible intervention window regarding geometric properties of bone. The prospective approach, on the other hand, can be applied to girls of any age regardless of their pubertal status, and provides a greater window of opportunity for potential intervention to increase cross-sectional bone strength given the predicted outcome.

Secular trends

Secular trends have been noted in a variety of maturational milestones in the U.S. and worldwide [11,12,35,54]. It is, therefore, possible that there is an underlying secular trend influencing our results, such as changes in age at menarche over the course of the 20th century [11–16], or a previously unrecognized secular trend in childhood or adult bone strength. Using a large sample of girls participating in the Fels Longitudinal Study, Demerath et al. [14] found a 3–6 month decrease in the mean age at menarche starting in the 1980s. In our smaller Fels dataset, birth year is not significantly correlated with age at menarche. Given our need for a matched measure of bone strength in adulthood, our sample did not include many girls who entered puberty in or after the 1980s, the timeframe in which Demerath et al. detected the trend. We nonetheless felt it was prudent to test for secular trend in our sample.

In our sample, in only a few models is birth year significantly associated with adult bone strength, and even then its contribution to the adult bone strength outcome is very small. Likewise, birth year is not significantly correlated with childhood bone strength, and is weakly correlated with childhood BMI. Birth year, when used as a predictor, also does not

have a large impact on adult bone strength. Thus, there does not appear to be a consistent secular trend in bone strength during the 59-year birth year span captured in this sample.

In addition to the potential factors affecting the relationship between menarche and bone strength already discussed, the effects of BMI on bone strength and quality are another important consideration. In children, higher BMI generally has a positive effect on BMC and different measures of BMD [55–57], but the relationship between higher BMI and cortical thickness and density is less straightforward [55]. Furthermore, higher adiposity generally has a negative impact on bone strength, including bone geometry [55,56,58,59]. In the current study, higher childhood BMI is associated with lower adult torsional and bending bone strength when controlling for prepubertal bone strength and age at menarche. Given the increasing proportion of overweight children in the United States, further studies focusing on the effects of BMI on various aspects of bone quality and strength are highly warranted.

Pubertal timing and bone strength are each under genetic influence [60–62]. Studies of genetic underpinnings of skeletal traits frequently show heritabilities of 50–65% [37,63,64], with the other proportion of trait variance due to the environment. In this sense, the term “environment” typically encompasses any number of non-genetic unmeasured covariates, such as diet or nutrition, physical activity, or hormonal influences. Because menarche directly contributes to one of these unmeasured environmental influences, namely hormones (e.g., estrogen), it is difficult to identify independent genetic influence on the two, versus shared genetic underpinnings (pleiotropy). Nevertheless, covariation between these two traits, whether it is genetic in origin or not, is an important consideration. This is especially true given the secular trend in menarche (discussed above) and the implications for lifelong skeletal health.

Conclusion

Our analyses demonstrate that later age at menarche may be beneficial for bone strength under bending and torsion. A likely mechanism for this is the delayed exposure to estrogen and longer period available for subperiosteal bone expansion in girls with later menarche. Therefore, although late menarche may result in lower BMC or BMD, at the same time it leads to bones of greater diameter, and consequently greater bone strength. Furthermore, based on our results, the strength of bone in childhood is a key predictor of adult bone strength, as measured by its cross-sectional geometric properties. Thus, any factors that negatively affect subperiosteal bone deposition in childhood (including early menarche), leading to bones of a smaller external diameter, have consequences into adulthood.

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Fig. 1. Bone measurements of the second metacarpal. (A) TL=total length, DL=diaphyseal length, x=total midshaft, y=minimum shaft, z=diaphyseal midshaft. After Duren et al. [37].

Fig. 2.

Changes in bone strength due to the thickening of the cortex by one unit (left) or widening the external diameter by one unit (right) relative to a hypothetical initial cross-section (center).

Fig. 3.

Results of the prospective models. (A) Adult polar moment of inertia J (y-axis) relative to age at menarche (x-axis), while controlling for all other covariates using the prospective models. (B) Adult section modulus Z (y-axis) relative to age at menarche (x-axis), while controlling for all other covariates using the prospective models. The black lines represent the mean $\pm$ standard deviation for childhood bone strength values (dashed line = mean, dotted line = + 1SD, solid line = - 1SD). The analyses were performed with logtransformed bone strength variables, which were reverted to the original scale for these graphs.

Fig. 4.

Results of the retrospective models. (A) Adult polar moment of inertia J (y-axis) relative to age at menarche (x-axis), while controlling for all other covariates using the retrospective model. (B) Adult section modulus Z (y-axis) relative to age at menarche (x-axis), while controlling for all other covariates using the retrospective model. The black lines represent the mean $\pm$ standard deviation for childhood bone strength values (dashed line=mean, dotted line=+1SD, solid line=-1SD). The analyses were performed with logtransformed bone strength variables, which were reverted to the original scale for these graphs.

Fig. 5.

Prospective versus retrospective models. The effects of prospective versus retrospective modeling are presented for two sets of hypothetical girls of equal premenarcheal bone strength, but different age at menarche (solid line=earlier menarche; dashed line=later menarche; gray line=age at which childhood bone strength was measured; flexion point in each line indicates age at menarche and the concomitant slowing of bone strengthening). (A) The prospective model conditions on bone strength at the same age. (B) The retrospective model conditions on bone strength at the same number of years before menarche. The result is a different conclusion regarding the relationship between age at menarche and adult bone strength.

Table 1

Summary statistics for the prospective model samples, providing the mean±standard deviation (range) for each variable.

Pre-pubertal age	N	Birth year	Age at menarche ^a	Childhood BMI	Childhood J	Log childhood J	Childhood Z	Log childhood Z	Adult J	Log adult J	Adult Z	Log adult Z
7–7.9	176	1952 ±13 (1930–1987)	13.0 ±1.1 (9.8–16.1)	15.5 ±1.8 (12.3–25.3)	107.4 ± 35.9 (39.5–221.2)	4.6 ± 0.3 (3.7–5.4)	36.1 ± 8.9 (17.0–62.9)	3.6 ± 8.9 (2.8–4.1)	352.2 ± 106.2 (157.3–737.4)	5.8 ± 0.3 (5.1–6.6)	89.5 ± 19.9 (48.9–157.1)	4.5 ± 0.2 (3.9–5.1)
8–8.9	187	1954 ±15 (1930–1988)	12.9 ±1.2 (9.0–16.1)	16.0 ±2.0 (12.6–25.3)	128.5 ± 41.7 (50.2–251.1)	4.8 ± 0.3 (3.9–5.5)	41.4 ± 10.0 (20.6–69.0)	3.7 ± 0.2 (3.0–4.2)	351.0 ± 103.0 (146.7–737.4)	5.8 ± 0.3 (5.0–6.6)	89.4 ± 19.3 (46.5–157.1)	4.5 ± 0.2 (3.8–5.1)
9–9.9	198	1954 ±15 (1929–1988)	13.0 ± 1.2 (10.1–16.1)	16.5 ±2.2 (11.7–23.4)	149.6 ± 48.6 (54.6–301.5)	4.9 ± 0.3 (4.0–5.7)	46.4 ± 11.3 (21.8–80.0)	3.8 ± 0.2 (3.1–4.4)	348.9 ± 103.3 (146.7–737.4)	5.8 ± 0.3 (5.0–6.6)	88.9 ± 19.5 (46.5–157.1)	4.5 ± 0.2 (3.8–5.1)
10–10.9	154	1958 ±15 (1929–1988)	13.0 ±1.1 (11.0–16.1)	17.2 ± 2.5 (12.5–24.9)	177.2 ± 53.4 (56.0–351.3)	5.1 ± 0.3 (4.0–5.9)	52.9 ± 11.9 (22.0–88.3)	3.9 ± 0.2 (3.1–4.5)	345.1 ± 94.5 (146.7–684.6)	5.8 ± 0.3 (5.0–6.5)	88.4 ± 17.8 (46.5–148.3)	4.5 ± 0.2 (3.8–5.0)
11–11.9	133	1956 ±15 (1929–1987)	13.4 ±0.9 (12.0–16.1)	17.4 ± 2.6 (12.9–27.8)	193.4 ± 60.0 (67.6–362.7)	5.2 ± 0.3 (4.2–5.9)	56.5 ± 13.0 (25.4–91.1)	4.0 ± 0.2 (3.2–4.5)	340.0 ± 93.9 (146.7–709.3)	5.8 ± 0.3 (5.0–6.6)	87.4 ± 17.9 (46.5–153.4)	4.5 ± 0.2 (3.8–5.0)

^aAge at menarche changes in each model due to different sample sizes.

Regression coefficients β (and their p-values), coefficients of determination (R^2) and significance for each model for the adult polar moment of inertia (J) model (NS = not significant). Each covariate is centered at its mean (see Table 1). The regression formula is:

Table 2

$$\begin{aligned} \log(Adult\ J) = & \beta_0 + \beta_1 (\log(childhood\ J)) \\ & + \beta_2 (age\ at\ menarche) \\ & + \beta_3 (\log(childhood\ J) \times age\ at\ menarche) \\ & + \beta_4 (childhood\ BMI) + \beta_5 (birth\ year) . \end{aligned}$$

Prepubertal age	N	β_0 Intercept	β_1 $\log(Childhood\ J)$	β_2 Age at menarche	β_3 $\log(ChildhoodJ) \times age\ at\ menarche\ interaction$	β_4 Childhood BMI	β_5 Birth year	R^2	Overall model F-test p value
7-7.9	176	5.820 p<0.001	0.711 p<0.001	0.038 p=0.005	NS	-0.017 p=0.041	NS	0.606	p<0.001
8-8.9	186	5.819 p<0.001	0.695 p<0.001	0.035 p=0.007	NS	-0.019 p=0.011	-0.002 p=0.034	0.554	p<0.001
9-9.9	198	5.821 p<0.001	0.734 p<0.001	0.031 p=0.012	0.76 p=0.054	-0.019 p=0.003	NS	0.619	p<0.001
10-10.9	154	5.808 p<0.001	0.730 p<0.001	0.028 p=0.050	NS	-0.014 p=0.020	NS	0.615	p<0.001
11-11.9	129	5.804 p<0.001	0.797 p<0.001	0.038 p=0.020	0.157 p=0.005	-0.002 p=0.057	NS	0.702	p<0.001

Regression coefficients β (and their p-values), coefficients of determination (R^2) and significance for each model for section modulus (Z) (NS = not significant). Each covariate is centered at its mean (see Table 1). The regression formula is:

$$\begin{aligned} \log (Adult\ Z) = & \beta_0 + \beta_1 (\log (childhood\ Z)) \\ & + \beta_2 (age\ at\ menarche) \\ & + \beta_3 (\log (childhood\ Z) \times age\ at\ menarche) \\ & + \beta_4 (childhood\ BMI) + \beta_5 (birth\ year) . \end{aligned}$$

Table 3

Prepubertal age	N	β_0 Intercept	β_1 $\log(\text{Childhood } Z)$	β_2 Age at menarche	β_3 $\log(\text{Childhood } Z) \times \text{age at menarche}$ interaction	β_4 Childhood BMI	β_5 Birth year	R^2	Overall model F-test p value
7–7.9	176	4.470 p<0.001	0.708 p<0.001	0.028 p=0.006	NS	-0.013 p=0.046	NS	0.595	p<0.001
8–8.9	186	4.470 p<0.001	0.692 p<0.001	0.025 p=0.009	NS	-0.015 p=0.011	-0.001 p=0.035	0.545	p<0.001
9–9.9	198	4.471 p<0.001	0.729 p<0.001	0.022 p=0.015	0.076 p=0.055	-0.014 p=0.003	NS	0.611	p<0.001
10–10.9	154	4.461 p<0.001	0.721 p<0.001	0.021 p=0.049	NS	-0.009 p=0.036	-0.001 p=0.087	0.612	p<0.001
11–11.9	133	4.458 p<0.001	0.794 p<0.001	0.028 p=0.024	0.155 p=0.007	-0.009 p=0.041	-0.001 p=0.057	0.692	p<0.001

Summary statistics for the retrospective sample, providing the mean±standard deviation (range) for each variable, and the natural log values for bone strength variables used in the regression models (for both J and Z).

Table 4

	N	J	Log J	Z	Log Z	Age at menarche	Birth year	Childhood BMI
Child	223	208.0 ± 58.4 (60.7–376.0)	5.3 ± 0.3 (4.1–5.9)	59.7 ± 12.6 (23.9–93.5)	4.1 ± 0.2 (3.2–4.5)		1955 ± 16 (1929–1988)	17.6 ± 2.5 (12.7–27.5)
Adult	223	347.4 ± 94.9 (146.7–709.3)	5.8 ± 0.3 (5.00–6.6)	88.7 ± 18.00 (46.5–153.4)	4.5 ± 0.2 (3.8–5.0)	12.9 ± 1.2 (9.0–16.1)	1955 ± 16 (1929–1988)	

Regression coefficients β (and their p-values), coefficients of determination (R^2) and significance of the retrospective regression models for J and Z. Each covariate is centered at its mean (see Table 4). The regression formula is:

$$\begin{aligned} \log(\text{Adult bone strength}) = & \beta_0 \\ & + \beta_1 (\log(\text{premenarcheal bone strength})) \\ & + \beta_2 (\text{age at menarche}) \\ & + \beta_3 ((\text{age at menarche})^2) \\ & + \beta_4 (\log(\text{premenarcheal bone strength}) \times \text{age at menarche}) \\ & + \beta_5 (\text{childhood BMI}) + \beta_6 (\text{birth year}). \end{aligned}$$

Table 5

Bone strength indicator	N	β_0 Intercept	β_1 $\log(\text{Premenarcheal bone strength})$	β_2 Age at menarche	β_3 (Age at menarche) ²	β_4 $\log(\text{Premenarcheal bone strength}) \times$ age at menarche interaction	β_5 Childhood BMI	β_6 Birth year	R ²	Overall model F-test p value
log(J)	223	5.826 p<0.001	0.757 p<0.001	-0.068 p<0.001	-0.013 p=0.043	0.073 p=0.058	-0.015 p=0.002	-0.002 p=0.020	0.631	p<0.001
log(Z)	223	4.475 p<0.001	0.752 p<0.001	-0.051 p<0.001	-0.010 p=0.046	0.072 p=0.065	-0.011 p=0.002	-0.001 p=0.018	0.617	p<0.001