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Original Article

Early menarche is a risk factor of short stature in young Korean female: Epidemiologic study

Running title: Early menarche is a risk factor of short stature

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What is already known on this topic?

In European countries, age at menarche was positively associated with final adult height and negatively associated with body mass index.

What this study adds?

This is the first study to show that early menarche is a risk factor of short adult stature in Korean female. The OR for short stature in female with early menarche was 2.62 after adjusting for mother's height.

Abstract

Objective: We investigated the association between age at menarche and adult height (and body mass index; BMI) in young Korean female. We also investigated whether early menarche (<12years) is a risk factor of short stature and obesity in young Korean female.

Methods: We analyzed data for 1148 female aged 18–30 years (612 pairs of mothers and daughters) from the 6th Korea National Health and Nutrition Examination Survey (KNHANES IV) (2013–2015).

Results: Among 1148 female, 256(22.3%) female had early menarche. Female grew approximately 0.445 cm shorter when menarche occurred 1 year earlier. The prevalence of short stature (≤153cm)

and obesity(BMI≥25) was higher in female with early menarche compared with later menarche(short stature: 10.5% vs. 6.4%, obesity; 20.7% vs. 13.1%, all P < 0.001). In multivariate regression, the odds ratio (OR) of short stature was 2.62(95%CI 1.26-5.44) adjusting for current age and mother's height. However, the OR of obesity was 1.74(0.98-3.07) after adjusting for age and mother' BMI.

Conclusion: The final height for female is influenced by age of menarche. Early menarche increased the risk of adult short stature in young Korean female.

Keywords: Early menarche; short stature; adult height; Obesity; KNHANES

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Introduction

Age of menarche is known to be influenced by several factors, such as gene, ethnicity, geography, and socioeconomic status, especially nutritional status(1-4). Several studies including ours have found relationship between early menarche age (<12years) and the risk of obesity, insulin resistance, metabolic syndrome, nonalcoholic fatty liver disease, diabetes, and cardiovascular disease in adulthood(5-9). Thus, by managing the risk factor of early menarche, metabolic disease of adulthood can be prevented in pediatric age.

Short stature is typically defined as an adult height that is more than two standard deviations below the mean for age and sex(10). In developed countries, this typically includes adult men who are shorter than 166 cm and adult women who are shorter than 153 cm. Several factors might cause short adult height. Multiple familial genes, surrounding environments, and the interplay of those factors are main factors. Besides, short adult height can be caused by abnormal conditions, such as genetic disease like Turner syndrome, prolonged chronic disease, malnutrition, prolonged treatment with certain drugs like steroid, and hormone deficiency such as growth hormone. It may also occur by early fusion of growth plates earlier than normal when precocious puberty occurs (11).

In Europe and USA, women with earlier menarche reached shorter adult height compared to women who had menarche at a later age were observed (12, 13, 14). Furthermore, in Asian countries including Korea, female age of menarche has decreased continuously and rapidly recently (5, 15, 16).

The aim of this study is to investigate whether final adult height is associated with the age at menarche in Korean young female. We also assessed whether an independent association exists between early menarche and short adult stature (or obesity) in Korean female. For this purpose, we use individual data of 12,537 female who participated in the KNHANES-VI.

Methods

This study uses the 6th Korea National Health and Nutrition Examination Survey (KNHANES-VI) (2013–2015) data. KNHANES-VI is a cross-sectional survey with multi-staged, stratified sampling design and nationally representative data conducted by the Division of Chronic Disease Surveillance, Korea Centers for Disease Control and Prevention (17). Written informed consent was secured by all of the participants before the study had begun, and the KNHANES was conducted following after ethical approval by the Institutional Review Board of the Korea Centre for Disease Control and Prevention.

Among the 12,537 female who participated in KNHANES-VI, we selected data of 1148 young female aged 18 to 30 years old, menarchial age and their anthropometric variable. We acquired mother's height and weight data of 612 female. Weight was determined to the nearest 0.1 kg on a medical balance (GL-6000-20, CAS, Seoul, Korea) and height was measured to the nearest 0.1 cm with a wall-mounted stadiometer (Seca 220, Seca, Hamburg, Germany). Body mass index (BMI) was calculated by dividing the weight by the height squared (kg/m^2). Korean female's height remained near plateau at age 16 according to 2017 Korean National Growth Charts (18).

"Age of menarche" is defined as age of the first menstrual period, and the definition is established by using questionnaire. The question was open-ended: "At what age did you have your first menstrual period (menarche)?" The age of 11 years represents 11.00–11.99 years old. We defined early menarche as <12 years old. If the height of female is less than ≤ 153 cm (≤5 percentile), we defined as "short stature" and obese if BMI was ≥25 based on Asian criteria(19). Household income as a surrogate marker of socioeconomic state was assessed as categorical variables: low(1Q), lower middle(2Q), upper middle(3Q), and high(4Q) in KNHANES.

Statistical analysis

Data related to anthropometric measurements and other covariates were stratified by early menarche and later menarche. Differential between early menarche and later menarche was compared to the data from student's t-test and chi-square test. Continuous variables are reported as mean ± standard deviation (SD), and categorical variables are reported as percentages (%). Linear regression analysis was used to evaluate the predictors of subject's height as a dependent variable using age at menarche as predictive variables, controlling current age. For the assessment of odds ratios (ORs) of short stature (or obesity) according to early menarche, multivariable logistic regression was used. The ORs including 95% confidence interval (CI), between early menarche and short stature (or obesity) were calculated before and after adjusting for age, and other confounders. In final analysis,

household income was excluded as there was no significant difference of prevalence of short stature among that quartile. All statistical analyses were performed by using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). P values <0.05 were considered significant.

Results

The characteristics of the study subjects were divided according to early menarche or later menarche are summarized in Table 1. The current age of total subjects was 23.5±3.5 years, the mean age of menarche was 12.7±1.6 years, the mean height was 161.6±5.8(138-179)cm, and the mean BMI was 21.6±3.7(15-49) kg/m^2.

Among 1148 female, 256(22.3%) female had early menarche and 892 had later menarche. Early menarche group are younger current age(22.9±3.4, P = 0.001), shorter height(160.4±5.1, P < 0.001), higher BMI(22.4±3.8, P < 0.001) than later menarche group(23.7±3.5, 161.9±6.0, 21.3±3.5). They also had higher prevalence of short stature (10.5 vs. 6.4%) and obesity(20.7 vs.13.1%)(Fig 1). However, there was no difference in prevalence affected by household income.

In subgroup, subjects with mother's anthropometric data(n=612), the mean age of the mothers was 50.3±4.6 years, and the mean age at menarche was 14.3±1.7 years. The difference of age, age of menarche, height and BMI between mother and daughter was 27.5±3.5 years, 1.5±2.0(-4 to 8) years, 4.4±5.9(-20 to 23) cm, and 2.5±3.9 kg/m^2. There was no difference in mother's age, height, weight and BMI between early menarche and later menarche group. There was also no difference in prevalence of short stature and obesity of mothers'.

The subjects' height and BMI according to age at menarche are depicted in Fig 2. In linear regression, female grew approximately 0.445 cm shorter when menarche occurred 1 year earlier: subject's height(cm) = subject's age at menarche(year) x 0.445 - subject's age(year) x 0.03+156.56(R^2 = 0.014; P < 0.001). The ORs for short stature and obesity in female with early

menarche compared to the later menarche are summarized in Table 2. The crude OR for short stature in female with early menarche was 1.73. The OR decreased to 1.71 after adjusting to current age (Model 1), and increased to 2.62 after further adjusting for mother's height (Model 2). Here, the Exp(B) of mother's height was 0.799(95%CI 0.742-0.860). The OR for obesity in female with early menarche was 1.73. The OR increased to 1.79 after adjusting to current age (Model 1), and further decreased to 1.74 (95%CI 0.98-3.07) after adjusting to age and mother' BMI (Model 2).

Discussion

In this study, we found that each year of advance in age of menarche was associated with 0.445cm final height loss in young Korean female. We also found female with early menarche had a 10.5% chance of having short adult stature, which was 2.62-fold higher than those with later menarche. In addition, the OR for obesity in female with early menarche was 1.73 compared to those with later menarche.

The prevalence of early menarche has increased dramatically in Korea. In this study, the percentage of subjects who experienced menarche before the age of 12 years is 22.3 %, while the percentage of subjects' mother with early menarche is 2.5%, which is nine times higher than that of their mothers'. Like other countries from mid-20th century, South Korea has shown rapid decrease of female age in menarche, and this is probably due to remarkable improvements in nutrition and living conditions (13, 20). In our previous study, the mean age of menarche decreased rapidly over time, from 15.62±1.88 years for female born between 1950 and 1954, to 13.11±1.52 years for those born between 1980 and 1984, to 12.60±1.14 years for those born between 1990 and 1994(5). This trend might be due to changes in the socioeconomic environment, mainly due to the changes in nutritional status(13). The nutrition state of South Korea rapidly improved after Korean Civil War. South Koreans rapidly accepted western culture especially in dietary habit after the 1988 Olympic Games, while North Korean refugees still showing the age of female menarche around 16.0±2.1 years

(2018). Nutrition, in particular, appears to play an important role in the onset of menarche. There are great amount of reports that girls with higher body weight, higher body mass index, and more body fat reach their menarche earlier (13, 21, 22). It has been suggested that 'Critical weight' is needed for menarche based on observation of children to reach at an earlier age of menarche (23, 24). Furthermore, other factors such as birth weight, prenatal nutrition, dietary component, and exposure to endocrine disruptors, have been suggested as likely contributory factor of earlier pubertal development and early menarche (25-27). The other suggested reason for increasing prevalence of early menarche in Korean girl is rapid increasing prevalence of central precocious puberty (CPP). CPP can cause early menarche in girls and result in short adult stature due to early epiphyseal fusion (11). The annual incidence of CPP in girls had significantly increased from 3.3 to 50.4 per 100,000 girls during 2004 to 2010 in Korea(28). The incidence of girls diagnosed with CPP has markedly increased in 21th century and much higher compared to 40 year ago in Denmark(29).

In this study, 10.5% of female with early menarche had a short stature. The OR of short stature was 2.62-fold after adjusting current age and mother's height in female youth with early menarche compared to those with later menarche. In a crude manner, for each year of delay in age at menarche in Korean female, she will grow approximately 0.445 cm taller in her final height. This finding agrees with other countries studies (12, 21, 30, 31). According to the European Prospective Investigation into Cancer and Nutrition (EPIC) study, based on 286,205 women from nine European countries, women grew approximately 0.35 cm taller when menarche occurred 1 year later (range by country: 0.13–0.50 cm) (12). Furthermore, a 1-year increase in the age of menarche caused an increase in standing height, leg length, and trunk height of 0.76, 0.41, and 0.35 cm, respectively in USA birth cohort (31).

The pathogenesis of this may be explained by the earlier closure of epiphyseal growth plates due to the increase in ovarian estrogens (32, 33). Low dose of estrogen induces the stimulation of the GH-IGF-I axis and a pubertal growth spurt in early puberty. However, high dose of estrogen binding to its receptors in growth plate cartilage might cause early epiphyseal fusion by advancing growth plate senescence (33). A delay in menarche allows continued growth of long bones before the epiphyseal fusion, which prevent loss of adult height. GnRHa treatment in girls with CPP could improve final adult height and made the age of menarche close to that of the general population. The height gain, achieved after GnRH analog treatment in children with CPP, depends on the age of onset of puberty and onset of treatment as reviewed by Bereket A(34).

In this study, the OR for obesity in female with early menarche was 1.73. However, after adjusting the age and mother' BMI, we failed to find an association between early menarche and obesity (p=0.058). The most plausible reason for this might be relatively small number of subjects analyzed. Additionally, socioeconomic factors assessed in our study failed to demonstrate an association with adult short height. This finding agrees with previous Korean study and supports the notion that the socioeconomic factor is not an independent predictor of age at menarche or final height in well-developed countries(35, 36).

The major strength of the present study is based on the large national representative study population. However, this study has some limitations. First, the cross-sectional nature of the study prohibits making conclusions regarding to the existence of a causal relationship despite of preceding age of menarche to adult height. Second, we could not adjust other confounders such as the fathers' height and birth weight, which might influence subject's adult height. Recent studies showed an association between lower birth weight and early menarche (26). Finally, the age at menarche was reported by crude recall. It was known that age at menarche based on recall data is not very accurate, especially when the time between menarche and current age is more than 3 years

(37). However, other study have shown high correlations (R=0.67 to 0.79) between age at menarche by recall during middle-age and the original childhood data(38).

In conclusion, we found that early menarche is a risk factor of short adult stature and obesity in young Korean female. To our knowledge up to now, this is the first study to show that early menarche is a risk factor of short adult stature in Korean female. Some female might result in short adult stature despite within normal height during childhood and adolescent but due to earlier growth plates fusing. In the view of rapidly increasing prevalence of early menarche, knowledge of pubertal beginning, progression tempo, and age at menarche is important in identifying female at risk. Further long term cohort investigations are needed to fully explain these causal relationships.

Ethics

Ethics Committee Approval:

Informed Consent:

The Research Ethics Committee of the Korea Centers for Disease Control approved the study protocol (No: 2013-07CON-03-4C, 2013-12EXP-03-5C), and all participants or their parents signed a written informed consent form.

The IRB of KIRAMS confirmed exemption of the study.

Authorship Contributions

Surgical and Medical Practices:

Concept: Jung Sub Lim

Design: Sol Kang, Jung Sub Lim

Data Collection or Processing: Yoon Mo Kim, Jun Ah Lee, Dong Ho Kim,

Analysis or Interpretation: Sol Kang, Jung Sub Lim

Literature Search: Sol Kang, Jung Sub Lim

Writing: Sol Kang, Jung Sub Lim, Jun Ah Lee

Conflict of Interest: No conflict of interest

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Figure 1. Prevalence of short stature and obesity according to early and later menarche

* Female with early menarche had higher prevalence of short stature (10.5 vs. 6.4%) and obesity (20.7 vs.13.1%)

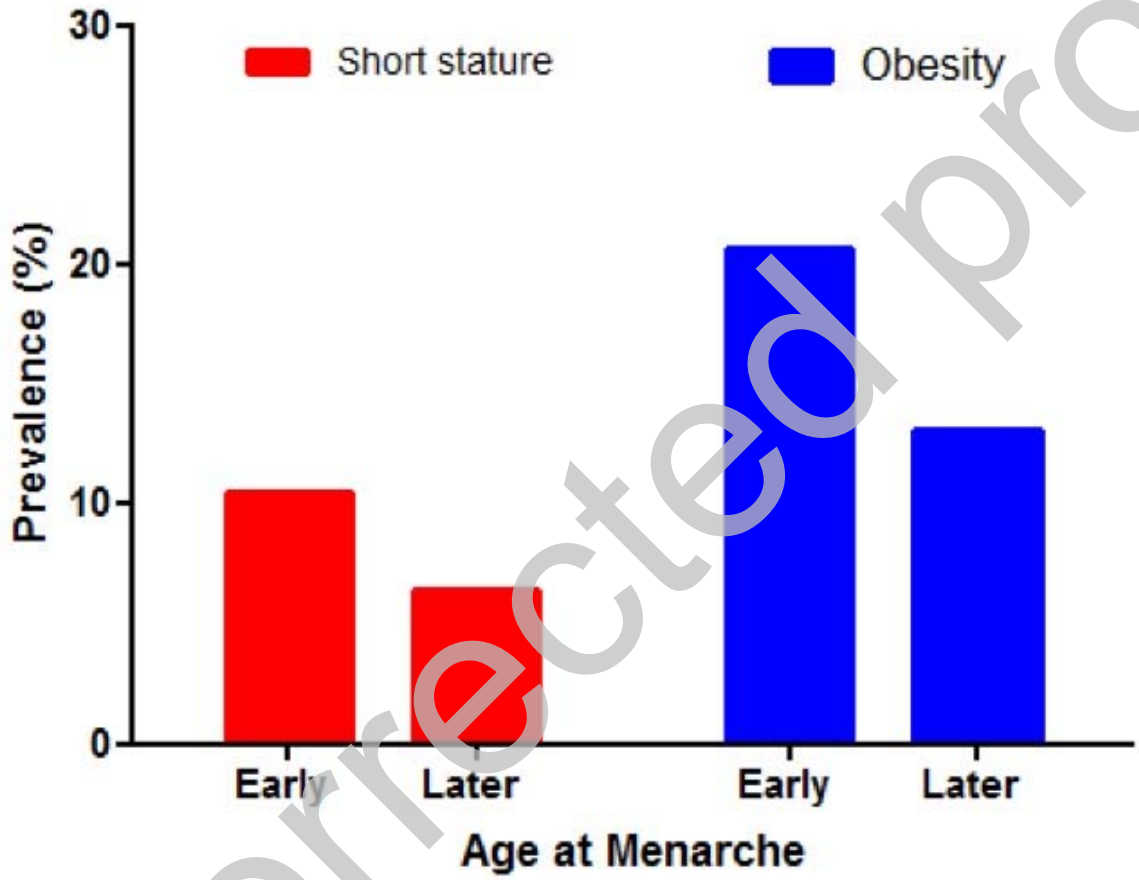
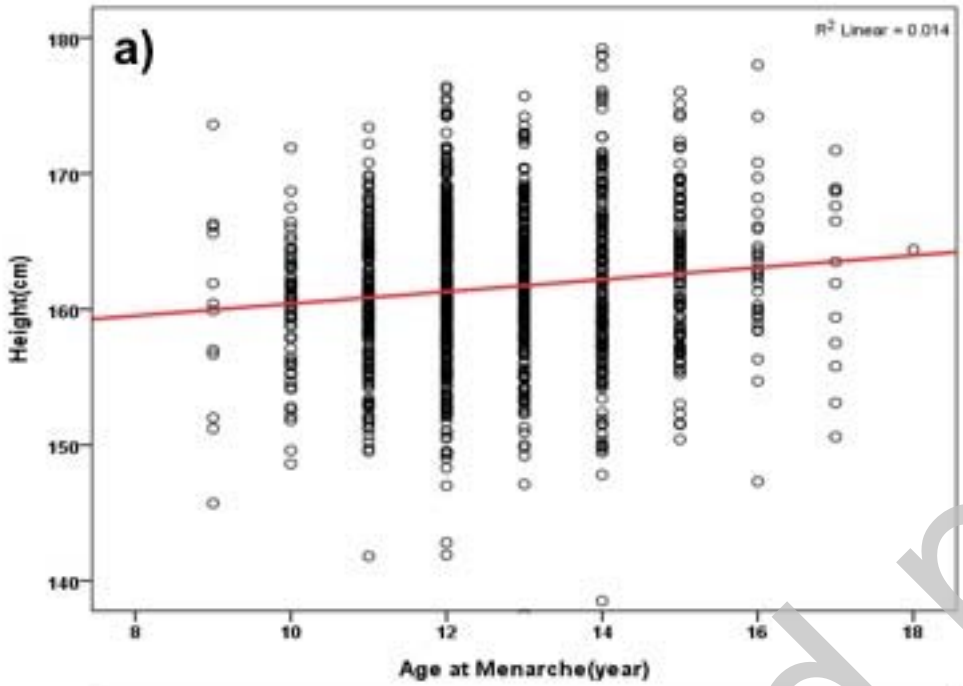


Figure 2. Subjects' height and Body mass index according to age at menarche

*Female grew 0.445 cm shorter when menarche occurred 1 year earlier



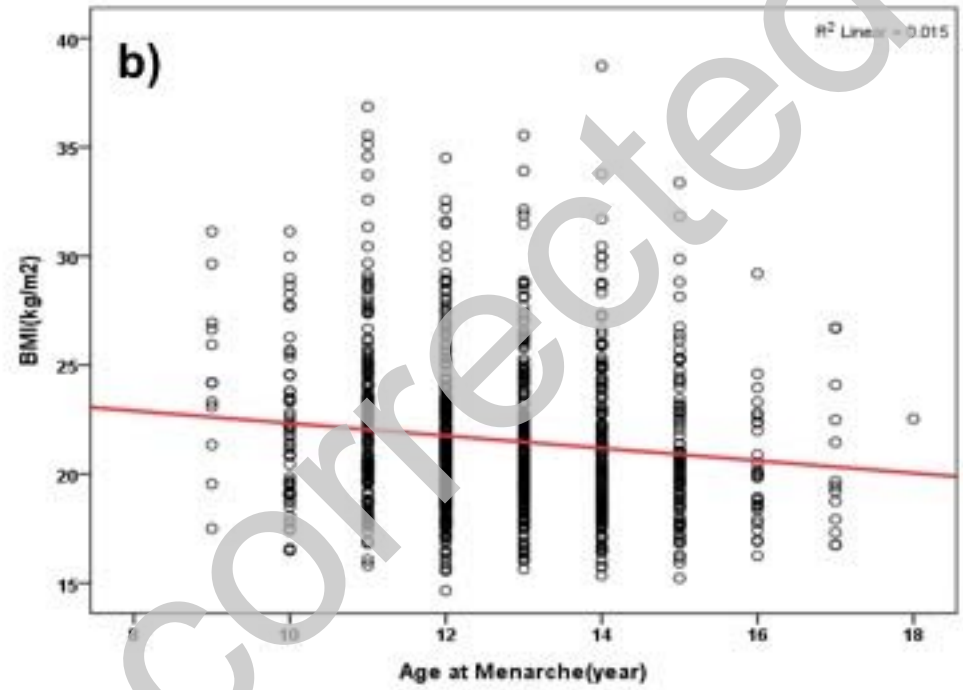


Table 1 Characteristics of the subjects stratified by age at menarche

	Age at menarche		
Characteristics	Early menarche (< 12 years)	Later menarche(≥12 years)	P-value
Subjects			
Number	256	892	
Age of menarche (years)	10.7±0.6	13.2±1.2	<0.001
Age at time of survey (years)	22.9±3.4	23.7±3.5	0.001
Height (cm)	160.4±5.1	161.9±6.0	<0.001
Weight (kg)	57.6±10.5	56.0±9.9	0.026
Body mass index (kg/m2)	22.4±3.8	21.3±3.5	<0.001
Household income			
low(1Q)	0.9%	8.7%	0.077
lower middle(2Q)	22.6%	28.3%	
upper middle(3Q)	29.9%	32.0%	
high(4Q).	38.9%	30.9%	
Mother			
Number	131	481	
Mother's Age of menarche (years)	13.8±1.5	14.4±1.7	<0.001
Mother's Age at time of survey (years)	50.0±3.4	50.3±3.5	0.479
Mother' height (cm)	157.6±4.4	157.6±5.5	0.933
Mother' weight (kg)	58.6±7.2	58.6±8.2	0.968
Mother' Body mass index (kg/m2)	23.6±2.7	23.6±3.2	0.921
Daughter- Mother' height (cm)	3.3±5.3	4.7±6.0	0.009

* Short stature is defined by below the 5th percentile of Korean female aged 20–30 (16). ǂ Obesity was defined as BMI≥25 kg/m^2.

* Differences between early menarche (< 12 years) and later menarche (≥12 years) were compared using Student's t-test for continuous variables and chi-square test for %.

Table 2 Odds ratios for short stature and obesity between early menarche and the reference group

	Early menarche (< 12 years)		Later menarche (≥12 years)
	OR	95% CI	
Short stature *	1.73	1.07-2.79	1.00
Model 1 age	1.71	1.06-2.78	1.00
Model 2 age+ mother's height	2.62	1.26-5.44	1.00
Obesity ǂ	1.73	1.21-2.45	1.00
Model 1 age	1.79	1.25-2.58	1.00
Model 2 age+ mother's BMI	1.74	0.98-3.07	1.00

* Short stature is defined by below the 5th percentile of Korean female aged 20–30 [16]. ǂ Obesity was defined as BMI≥25 kg/m^2.

* Odds ratios of short stature and obesity of early menarche compared with later menarche, multivariate logistic regression was used.

Abbreviations: BMI: body mass index, CI: confidence interval, OR: odds ratio

Model 1: results were adjusted for current age (in years).

Model 2: results were adjusted for age (in years), mother's height (or BMI)