Clinical and Epidemiologic Research

The Association Between Menarche and Myopia: Findings From the Korean National Health and Nutrition Examination, 2008–2012

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Purpose. The purpose of this study was to analyze the relationship between age at menarche and myopia in Korean adult females.

Methods. A total of 8398 women of at least 19 years of age, who participated in the Korean National Health and Nutrition Examination Survey from 2008 to 2012, underwent a refractive examination using an autorefractor. The association between age at menarche and the severity of myopia was evaluated using a four-level multinomial logistic regression analysis.

Results. The prevalence of myopia was 61.77% (95% confidence interval [CI], 60.46–63.08), including 40.02% with low, 15.46% with moderate, and 6.29% with high myopia. The mean age at menarche was 14.09 ± 0.03 years. Age at menarche was inversely associated with the severity of myopia. In fully adjusted models, older age at menarche decreased the risk of moderate myopia (odds ratio [OR], 0.93; 95% CI, 0.86–0.99; $P = 0.0261$), and high myopia (OR, 0.85; 95% CI, 0.77–0.95; $P = 0.0012$).

Conclusions. Later age at menarche is associated with a decreased risk of moderate and high myopia. The effects of female sex hormones on ocular structures and growth spurts may mediate this relationship between age at menarche and myopia.

Keywords: myopia, menarche, Korean National Health and Nutrition Examination

Myopia is one of the most common ophthalmological disorders whose prevalence has been increasing.[1,2] Myopes suffer physically and psychologically from wearing spectacles or contact lenses, and the associated large healthcare costs also are burdensome on society.[3] Indeed, high myopia is often associated with disorders, such as myopic macular degeneration, retinal detachment, and glaucoma, which all lead to severe visual impairment.[4]

Myopia is understood as a multifactorial disease. Genetic and environmental factors have been associated with its progression.[5–17] The role of genetic factors on myopia has been supported by evidence of heritability through twin studies, and several genes have been suggested as candidate susceptibility genes for myopia.[5–7] Ethnicity,[8–10] a high level of education,[11–13] minimal outdoor activity,[13–15] and excessive close work[13,16] all have been found to impact the development of myopia. Various epidemiological studies also have reported a higher prevalence of myopia in females than males,[8,10,17,18] although the exact reasons remain unknown.

Myopia mostly progresses in adolescence, especially during growth spurts.[19] Several studies have shown evidence supporting the relationship between myopia and body growth.[20–22] Yip et al.[20] described a significant association between the peak velocity of height and the peak velocity of myopia progression in Singaporean children aged 6 to 14. Another study indicated that body height increment was positively correlated with ocular axial length elongation, but not with myopia progression rate in Taiwanese children aged 7 to 9 years after adjusting for age and sex.[21] The association between body height or pubertal maturation and subfoveal choroidal thickness also was reported in Copenhagen girls.[22] In females, growth spurts are closely associated with the time of menarche, which is a milestone of puberty.[23] Therefore, studying the relationship between age at menarche and myopia may clarify the effects of sex and physical growth on the development of myopia. This study analyzed data from the Korean National Health and Nutrition Examination Survey (KNHANES), which was conducted from 2008 to 2012, to evaluate the association between age at menarche and the severity of myopia.

Methods

Study Participants

The KNHANES is a cross-sectional, nationally representative survey of the South Korean population conducted by the Korean Ministry of Health and Welfare using a stratified, multistage clustered probability sampling design. From 2008 to 2012, 45,811 subjects participated in the health interview survey and the health examination survey. Of these participants, the number of female participants of at least 19 years of age was 19,708. Among these, 16,345 participants underwent autorefraction. We excluded 6044 subjects who had cataracts, pseudophakia, aphakia, and a previous history of refractive surgery, which can considerably influence refractive error. Subjects whose data were incomplete for the history of menarche ($n = 563$) as well as those missing data regarding potential confounders of myopia, such as height, weight, residential area, economic status, level of education, level of parental education, sunlight exposure, and level of vitamin D ($n = 1340$) were excluded from this study. As a result, data from 8398 female participants, representative of 10,117,923 Korean females, were analyzed. The Institutional Review Board of the Samsung Medical Center approved the present study, which was conducted in accordance with the Declaration of Helsinki.

Examinations and Variable Definitions

The KNHANES consisted of the health interview survey, health examination survey, and nutrition survey. We obtained data from the health interview and health examination surveys; data regarding the medical histories and socioeconomic conditions included age at menarche. Participants responded to an open-ended question about age at menarche: "At what age did you have your first menstrual period (menarche)?" The question about sun exposure was closed-ended: "What is the average amount of time that you have been exposed to direct sunlight per day without wearing sunglasses or a cap since the age of 19?" The possible responses included: "less than 5 hours," or "5 hours or more" in KNHANES IV (2008–2009) and "less than 2 hours," "2–5 hours," or "5 hours or more" in the KNHANES V (2010–2012). All participants underwent noncycloplegic autorefraction of both eyes using Topcon KR8800 autorefractor (Topcon, Tokyo, Japan) with the fogging technique to reduce instrument myopia and patient accommodation. The mean of three consecutive measurements was recorded for each eye. The spherical equivalent (SE) refractive error was calculated as the sphere + 1/2 cylinder. Myopia was defined as a SE less than or equal to –0.50 diopters (D). For the degree of myopia, we considered four levels as follows: (1) nonmyopia defined as a SE greater than –0.50 D; (2) low myopia defined as less than or equal to –0.50 and greater than –3.0 D; (3) moderate myopia defined as less than or equal to –3.0 D and greater than –6.0 D; and (4) high myopia defined as less than or equal to –6.0 D.[24]

The variables analyzed in this study were defined and categorized as follows. Residence was categorized as either urban or rural based on the address of the subjects. Economic status levels were divided into four groups: lowest, lower middle, higher middle, and highest quartile. Educational level was divided into four groups: elementary school graduate or less, middle school graduate, high school graduate, and undergraduate or higher. Sun exposure level was divided into two groups: an average of less than 5 hours and an average of 5 hours or more.

Statistical Analysis

The SEs of the right and left eyes were highly correlated in Pearson's correlation analysis ($r = 0.925$, $P < 0.001$). Thus, this study analyzed data from the left eye.

To test the association between the degree of myopia and population characteristics, univariable analysis was conducted based on analysis of covariance (ANCOVA) and Pearson's χ^2 test for continuous and categorical variables, respectively. Focusing on the association between age at menarche and myopia, we used a multinomial logistic regression with "nonmyopia" as the reference level. For this association, we considered three models. The first was a univariable model with only age at menarche. The second model was adjusted for sex, age, height, weight, and astigmatism. The third model further included area of residence, economic status, level of education, level of parental education, vitamin D level, and sun exposure time as potential risk factors for myopia. In the multinomial logistic regression models, *P* values and 95% confidence interval (CI) for odds ratio (OR) were corrected using Bonferroni's method. Survey weights were calculated to account for survey year, stage of selection, and nonresponse. All *P* values were two-sided, and *P* values less than 0.05 were considered statistically significant. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Results

General Characteristics of the Subjects

The characteristics of 8398 enrolled subjects according to the degree of myopia are summarized in Table 1. The study participants were aged 39.25 ± 0.18 years (95% CI, 38.90–39.60). The mean height and weight were 158.91 ± 0.09 cm (95% CI, 158.73–159.08) and 57.90 kg (95% CI, 57.64–58.16), respectively. The mean astigmatism was –0.73 D (95% CI, –0.75 to –0.71). The percentage of those living in an urban area was 49.68%. Of the participants, 46.55% had an education level of undergraduate or higher and parental education level of undergraduate or higher was recorded for 13.31% of them. Of those surveyed, 92.48% reported average sunlight exposure of less than 5 hours, and the mean serum level of vitamin D was 15.99 ± 0.12 ng/mL (95% CI, 15.76–16.23).

Among the baseline characteristics, age ($P < 0.0001$), height ($P < 0.0001$), weight ($P = 0.0443$), astigmatism ($P < 0.0001$), residence area ($P = 0.0116$), economic status ($P = 0.0038$), education level ($P < 0.0001$), parental education level ($P < 0.0001$), sun exposure time ($P < 0.0001$), and level of vitamin D ($P < 0.0001$) were significantly different among the groups stratified according to degree of myopia.

Prevalence of Myopia

The weighted prevalence of myopia was 61.77% (95% CI, 60.46–63.08), including a prevalence of 40.02% (95% CI, 38.59–41.45) for low myopia (mean, −1.31 D; 95% CI, −1.34 to −1.28), 15.46% (95% CI, 14.39–16.54) for moderate myopia (mean, –4.25 D; 95% CI, –4.31 to –4.19), and 6.29% (95% CI, 5.62–6.96) for high myopia (mean, –7.84 D; 95% CI, –8.07 to –7.61). The mean SE of all participants was −1.56 ± 0.03 D (95% CI, −1.63 to −1.50).

Association Between Menarche and Myopia

The mean age at menarche was 14.09 ± 0.03 years (95% CI, 14.04–14.14) and the age of menarche onset ranged from 8 to 26 years. However, most participants (99.1%) reported their menarche onset occurred between the ages of 10 and 19 years. Distributions of age at menarche and spherical equivalent are presented in the Figure. According to the degree of myopia, the mean age at menarche was 14.70 years (95% CI, 14.61–14.79) in the nonmyopia group, 13.90 years (95% CI, 13.82–13.97) in the low myopia group, 13.45 years (95% CI, 13.33–13.57) in the moderate myopia group, and 13.18 years (95% CI, 13.01–13.35) in the high myopia group ($P < 0.0001$). According to the univariable multinomial logistic regression analysis (model 1), age at menarche was strongly associated with the degree of myopia. Positive 1-year increments in age at menarche were associated with a 20% decrease in the risk of low myopia (OR, 0.80; 95% CI, 0.76–0.83), a 31% decrease in the risk of moderate myopia (OR, 0.69; 95% CI, 0.65–0.73), and a 37% decrease in the risk of high myopia (OR, 0.63; 95% CI, 0.57–

Table 1. Characteristics of the Study Population According to Spherical Equivalent ($n = 8398$)

Variables	Nonmyopia $n = 3510$	Low Myopia $n = 3211$	Moderate Myopia $n = 1184$	High Myopia $n = 493$	*P* Value	Total $n = 8398$
Spherical equivalent, diopters	0.29 (0.26, 0.32)	−1.31 (−1.34, −1.28)	−4.25 (−4.31, −4.19)	−7.84 (−8.07, −7.61)	<0.0001	−1.56 (−1.63, −1.50)
Astigmatism, diopters	−0.56 (−0.59, −0.54)	−0.68 (−0.71, −0.65)	−0.96 (−1.02, −0.90)	−1.42 (−1.53, −1.32)	<0.0001	−0.73 (−0.75, −0.71)
Age, y	45.17 (44.64, 45.70)	37.21 (36.75, 37.68)	32.94 (32.19, 33.68)	31.73 (30.76, 32.70)	<0.0001	39.25 (38.90, 39.60)
Height, cm	157.76 (157.51, 158.01)	159.34 (159.09, 159.59)	159.95 (159.57, 160.32)	160.58 (159.96, 161.19)	<0.0001	158.91 (158.74, 159.08)
Weight, kg	58.11 (57.74, 58.49)	58.10 (57.66, 58.55)	57.10 (56.45, 57.74)	57.33 (56.19, 58.48)	0.0443	57.90 (57.64, 58.16)
Area of residence					0.0116	
Urban area	47.73 (45.07, 50.38)	49.21 (46.36, 52.07)	53.51 (49.94, 57.08)	55.17 (51.03, 59.31)		49.68 (47.31, 52.06)
Rural area	52.27 (49.62, 54.93)	50.79 (47.93, 53.64)	46.49 (42.92, 50.06)	44.83 (40.69, 48.97)		50.32 (47.95, 52.69)
Economic status					0.0038	
Lowest	11.46 (10.06, 12.86)	7.89 (6.61, 9.17)	8.51 (6.50, 10.53)	7.03 (3.47, 10.60)		9.3 (8.35, 10.24)
Lower middle	26.74 (24.79, 28.69)	27.52 (25.43, 29.61)	26.04 (22.68, 29.39)	22.47 (18.11, 26.84)		26.68 (25.22, 28.13)
Upper middle	31.18 (29.20, 33.15)	33.55 (31.41, 35.70)	31.83 (28.66, 35.00)	36.43 (31.24, 41.61)		32.56 (31.14, 33.98)
Highest	30.62 (28.48, 32.76)	31.04 (28.84, 33.23)	33.62 (30.12, 37.12)	34.07 (28.9, 39.24)		31.47 (29.81, 33.13)
Level of education					<0.0001	
Elementary school or less	16.07 (14.55, 17.60)	4.26 (3.49, 5.03)	0.86 (0.28, 1.44)	0.67 (0.08, 1.26)		8.02 (7.3, 8.75)
Middle school graduate	14.91 (13.54, 16.28)	6.85 (5.80, 7.90)	1.51 (0.72, 2.29)	1.93 (0.60, 3.26)		8.8 (8.04, 9.55)
High school graduate	39.57 (37.50, 41.64)	39.53 (37.31, 41.76)	28.44 (25.18, 31.71)	20.39 (16.43, 24.34)		36.63 (35.18, 38.07)
Undergraduate or higher	29.44 (27.56, 31.33)	49.36 (47.05, 51.67)	69.2 (65.82, 72.58)	77.01 (72.81, 81.21)		46.55 (44.99, 48.12)
Level of parental education					<0.0001	
Elementary school or less	54.57 (52.43, 56.71)	37.78 (35.70, 39.87)	26.13 (23.01, 29.25)	19.4 (15.18, 23.62)		41.24 (39.84, 42.64)
Middle school graduate	16.51 (14.97, 18.06)	21.22 (19.37, 23.06)	17.44 (14.96, 19.92)	17.03 (13.07, 20.99)		18.57 (17.54, 19.61)
High school graduate	19.96 (18.30, 21.62)	28.18 (26.14, 30.21)	36.60 (32.99, 40.21)	36.79 (31.68, 41.90)		26.88 (25.64, 28.12)
Undergraduate or higher	8.96 (7.74, 10.18)	12.82 (11.38, 14.26)	19.83 (17.02, 22.64)	26.78 (22.09, 31.48)		13.31 (12.28, 14.34)
Sun exposure					<0.0001	
<5 h/d	90.09 (88.78, 91.41)	93.30 (92.22, 94.38)	95.03 (93.59, 96.46)	95.51 (93.52, 97.49)		92.48 (91.72, 93.24)
≥5 h/d	9.91 (8.59, 11.22)	6.70 (5.62, 7.78)	4.97 (3.54, 6.41)	4.49 (2.51, 6.48)		7.52 (6.76, 8.28)
Serum vitamin D concentration, ng/ml	16.78 (14.46, 17.10)	15.70 (15.41, 15.98)	15.17 (14.76, 15.59)	15.10 (14.60, 15.61)	<0.0001	15.99 (15.76, 16.23)

Data are expressed as weighted means or weighted frequency (%) with 95% CI.

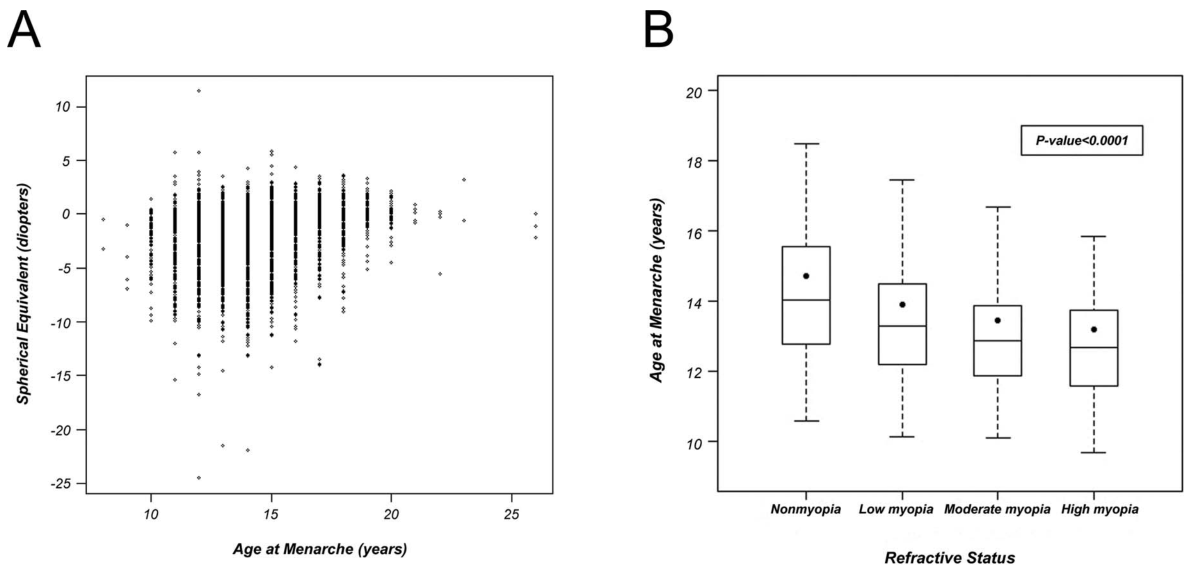

Figure. Age at menarche and refractive status in the KNHANES, 2008–2012. (**A**) Scatter plot of age at menarche and spherical equivalent. (**B**) Box plot of age at menarche according to the degree of myopia. The *bottom* and *top* of the box represent the 25th and 75th percentile, respectively, and the *band* near the *middle* of the box is the median. The *ends* of the *whiskers* represent the 2.5th percentile and the 97.5th percentile. *Dots* within *box* represent the mean value.

0.68; all $P < 0.0003$; Bonferroni's correction). In an adjusted model of age, height, weight, and astigmatism (model 2), age at menarche still was significantly related to the degree of myopia ($P = 0.0009$ for low, $P < 0.0003$ for myopia, and $P < 0.0003$ for high myopia). In the fully adjusted logistic regression model (model 3), 1-year increments in age at menarche were associated with a 4% decrease in the risk of low myopia (OR, 0.96; 95% CI, 0.92–1.00; $P = 0.0909$), a 7% decrease in the risk of moderate myopia (OR, 0.93; 95% CI, 0.86–0.99; $P = 0.0261$), and a 15% decrease in the risk of high myopia (OR, 0.85; 95% CI, 0.77–0.95; $P = 0.0012$; Table 2).

Discussion

Several epidemiological studies have reported a relationship between female hormone exposure and eye disease. The Blue Mountain eye study found that a late age at menarche increased the risk of nuclear cataracts,[25] and less intrinsic estrogen exposure increased the risk of age-related macular degeneration.[26] The Rotterdam study reported that a single year of intrinsic estrogen exposure resulted in a 5% decreased risk of open angle glaucoma.[27] Interestingly, one epidemiological study in a rural Indian population aged 40 years and older analyzed potential associations between female reproductive factors and eye diseases, and reported that menarche onset older than 14 years of age elicited protective effects against myopia and cataracts, but increased the risk of macular degeneration after adjusting for age, diabetes, body mass index (BMI), and pseudoexfoliation.[28] However, there were no further descriptions of the associations between reproductive factors and myopia.

In this study, there was a negative association between age at menarche and the severity of myopia, and later age at menarche significantly lowered the risk of moderate and high myopia. To our knowledge, this is the first study to analyze the relationship between age at menarche and the severity of myopia after adjusting for various confounding factors of myopia.

The mechanisms responsible for the association between female hormones and ocular conditions are not fully understood. However, recent studies have shown the presence of sex hormone receptors in multiple areas of the human eye, including the ciliary body, iris, lens, retina, and pigment epithelial cell, and these receptors have been shown to have roles in the development of various ocular pathologies.[29]

Table 2. Univariable and Multivariable Multinomial Logistic Regression Analyses for the Association Between Age at Menarche and Severity of Myopia in Korean Adults

	Age at Menarche					
	Model 1		Model 2		Model 3	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Nonmyopia	Reference		Reference		Reference	
Low myopia	0.80 (0.76, 0.83)	<0.0003	0.93 (0.89, 0.98)	0.0009	0.96 (0.92, 1.00)	0.0909
Moderate myopia	0.69 (0.65, 0.73)	<0.0003	0.87 (0.81, 0.93)	<0.0003	0.93 (0.86, 0.99)	0.0261
High myopia	0.63 (0.57, 0.68)	<0.0003	0.79 (0.71, 0.88)	<0.0003	0.85 (0.77, 0.95)	0.0012

Model 1, univariable model. Model 2, age, height, weight, and astigmatism were adjusted. Model 3, age, height, weight, astigmatism, area of residence, economic status, level of education, level of parental education, sun exposure, and vitamin D level were adjusted. *P* values were corrected by Bonferroni's correction due to multiple testing.

Current clinical research also supports the hypothesis of the effects of hormones on myopia.[30,31] Chen et al.[30] investigated polymorphisms in sex hormone genes and the risk of high myopia. They found certain interactions between sex and gene polymorphisms affected the sex hormone levels and were associated with the risk of high myopia. An additional study showed significant negative associations between myopia and the second-to-fourth-digit ratio, favoring a causal role of prenatal sex steroids on eye growth and the development of myopia.[31]

There are several possible mechanisms by which earlier female sex hormone exposure may cause progression of myopia. In a previous animal study, estrogen showed an influence on nitric oxide production,[32] which was involved in the signal cascade of visual regulation of ocular growth.[33] Estrogen also is known to regulate matrix metalloproteinases (MMPs) in the human RPE.[34] Scleral MMPs are involved in the remodeling of scleral extracellular matrix and myopia development.[35] Considering estrogen receptors were founded not only in RPE, but also in multiple areas of the human eye, including the sclera,[29] it is supposed that early estrogen exposure is related to myopia progression, possibly due to scleral remodeling through MMPs. Female sex hormones also modulate the biochemical properties and curvature of the cornea.[36] Another possible explanation is that growth spurts during puberty are associated with the progression of myopia. Research from Singapore reported that earlier growth spurts result in an earlier peak of myopia progression compared to later onsets of growth spurts.[20] The pediatric globe is distensible, with more flexible scleral collagen fibers compared to adults.[37,38] Thus, earlier progression of myopia may lead to more marked myopia. Recently, the relationship between body height and subfoveal choroidal thickness in girls aged 11 to 12 years was reported.[22] Choroidal thickness was increased with height and tended to be thicker in girls in advanced puberty. Although the rate of increase in height, which is better parameter to describe puberty, was not determined, the results suggest ocular structure change during puberty. However, additional experimental and clinical studies are required to determine the actual mechanistic association between myopia and menarche.

There are several limitations to this study. The study was cross-sectional in design and did not provide a causality assessment. The study also had potential recall bias associated with self-reported menarche timing, although menarche is a memorable event in a woman's life. Several studies have assessed the recall accuracy of age at menarche in adult women.[39,40] Cooper et al.[40] evaluated the reliability of self-reported age at menarche in middle age compared to that recorded in adolescence in a prospective cohort study. The validity of self-reported age at menarche was moderate, with 43.6% of participants recalling the exact age, although 85.2% of participants reported age at menarche within 1 year of the age recorded in adolescence.[40] In the present study, the differences in mean age at menarche between the nonmyopia group and other myopia groups ranged from 0.8 to 1.52 years. However, the actual recorded age of menarche can vary by approximately 1 year due to subjective recall error, according to a previous study.[40] Given the fact that the nonmyopic group is older than myopic groups on average, it is possible that the recall error rate in the older group may be higher. Thus, further prospective studies are required to confirm our findings. Third, the refractive error was measured without cycloplegia and an ocular axial length examination was not performed in KNHANES. While autorefraction was measured with the fogging technique to reduce instrument myopia and patient accommodation, there may have been some degree of overestimation of myopia in young nonpresbyopic participants.[41] Fourth, we could not analyze data regarding the parental history of myopia, age of onset of myopia, and history of retinopathy of prematurity, which could have potentially confounded the results, because this information was not available. The timing of onset of myopia and age at menarche must be considered in the interpretation of our findings. Further studies controlling for all these possible confounders are needed. Finally, sun exposure time was obtained via a closed-ended question in KNHANES. The possible responses were "less than 5 hours" or "5 hours or more" in KNHANES IV (2008–2009) and "less than 2 hours," "2–5 hours," or "5 hours or more" in KNHANES V (2010–2012). Thus, we adopted a cut-off of 5 hours and divided the participants into two groups. However, 5 hours might be a high cut-off value for sun exposure time, considering the result that 64% of Northeast Asian Austrians aged 18 to 80 years reported less than 1 hour of daily sun exposure.[42] In the current study, more than 92% of the subjects reported less than 5 hours of daily sun exposure on average. The reasons for low sun exposure time might be associated with the characteristics of the participants in this study. First, Asian women tend to avoid direct sun exposure.[42,43] Second, subjects with cataracts or a history of cataract surgery, which can considerably influence refractive error, were excluded in this study. This could have affected the low sun exposure time in this data set, as sun exposure is an important risk factor for cataracts.[44] Moreover, sun exposure data in KNHANES relates to the adulthood experience, when myopia progression would have slowed or stopped. Therefore, we did not further analyze the association between sun exposure and myopia, although sun exposure was significantly different among groups. Recently, several studies have reported an association between myopia and sun exposure in adults.[41,45] In the Western Australian Raine Cohort Study, the prevalence of myopia was associated with ocular sun exposure measured by conjunctival ultraviolet autofluorescence in young adults.[45] Another study also reported that longer sun exposure decreased the risk of myopia in the Korean population aged 40 years and older.[41] The relationship between sun exposure and myopia is another interesting topic that requires further investigation. Despite these limitations, to our knowledge this is the first study to evaluate the relationship between age at menarche and myopia using nationally representative data with a large sample size.

In conclusion, later age at menarche is associated with a decreased risk of moderate and high myopia. The actions of female sex hormones on ocular structures and growth spurts may mediate this relationship between age at menarche and myopia.

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