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The association between menarche and myopia and its interaction with related risk behaviors among Chinese school-aged girls: a nationwide cross-sectional study

Original Article

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Abstract

Nearly 80% of new cases of myopia arise between 9 and 13 years old when puberty development also progresses rapidly. However, little is known about the association between myopia and puberty. We aim to evaluate the association between myopia and menarche, the most important puberty indicator for girls, and to test whether menarche could modify the effects of myopia-related behaviors. The participants came from two consecutive national surveys conducted in 30 provinces in mainland China in 2010 and 2014. We included 102,883 girls (61% had experienced menarche) aged 10–15 years. Risk behaviors for myopia which included sleep duration, homework time, and outdoor activity were measured by self-administrated questionnaire. Myopia was defined according to a validated method, and its relationships with menarche status and behaviors were evaluated by robust Poisson regression models based on generalized estimated equation adjusting for cluster effect of school. We found that postmenarche girls were at 13% (95% confidence interval: 11%–16%) higher risk of myopia than premenarche girls, after adjusting for exact age, urban–rural location, survey year, and four behavioral covariates. Short sleep duration (<7 h/d), long homework time (>1 h/d) and low frequency of weekend outdoor activity tended to be stronger (with higher prevalence ratios associated with myopia) risk factors for myopia in postmenarche girls than in premenarche girls, and their interaction with menarche status was all statistically significant ($P < 0.05$). Overall, our study suggests that menarche onset may be associated with increased risk of myopia among school-aged girls and could also enhance girls' sensitivity to myopia-related risk behaviors.

Introduction

Myopia has emerged as a major global public health concern[1] with its rapidly increasing prevalence[2,3] and heavy economic burden.[4,5] East Asians, including Chinese,[6] showed the highest prevalence of myopia worldwide, reaching 69% at 15 years of age, which is more than two times higher than other ethnicities.[2]

Once myopia presents, progression can continue irreversibly throughout childhood, and particularly result in high myopia which could significantly increase the risk of future pathologic ocular changes.[7] Consequently, preventing the onset of myopia is of great public health significance. It is widely accepted that myopia onset usually results from eye growth that leads to elongated axial length, but the inner regulatory mechanism remains unclear.[1,8] Given that nearly 80% myopia develops during early and medium puberty (about 9~13 years),[9] we can postulate that puberty development might contribute to myopia onset via regulating axial growth. This hypothesis is supported by the study of Yip *et al* which found that boys and girls with earlier puberty defined by height spurt also experienced earlier age of axial growth and myopia onset.[10] However, another two cohort studies showed that height growth only explained less than 0.5% of myopia development.[11,12] Therefore, indicators of puberty other than height spurt might explain the association between myopia and puberty.

Menarche is a milestone in girls' sexual maturity and one of the most important indicators of puberty.[13] About half of the variation of age at menarche is contributed by genetic factors.[14] An earlier age at menarche could also be contributed by many environmental and behavioral factors, such as high body mass index, low physical activity, high animal protein intake, family stressors (e.g., single parenting), and exposure to endocrine-disrupting chemicals.[14,15] Earlier menarche is associated with increased risk of many diseases in adulthood, such as reproductive

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cancers, metabolic syndrome, and cardiovascular diseases,[16,17] but evidence about its relationship with myopia is controversial. In the study by Yip *et al*, no significant association was found between age of menarche and age of axial growth or myopia onset.[10] By contrast, two cross-sectional studies in India and South Korea, respectively,[18,19] found that earlier age at menarche could increase the risk of myopia in adulthood. Yip *et al* may suffer from selection bias and low statistical power because it only included 1779 children from three schools in Singapore.[10] Meanwhile, recall bias could be a big problem in the Indian and South Korean studies,[18,19] considering that their age of menarche and myopia-related covariates were all collected in adulthood. Accordingly, we need more studies with large sample sizes and good measures of menarche status to clarify the role of menarche onset in myopia acquisition. In addition, such evidence from China, the country with largest myopic population is still absent.[6] The Chinese National Survey on Student's Constitute and Health (CNSSCH), a national survey of school-aged children, provides us with a great opportunity to address this question and suggest potential etiologies for myopia development.

Based on previous studies, we hypothesize that for girls of the same age those who have experienced menarche are more likely to be myopic than those who have not. This is equivalent to the statement that earlier menarche onset is associated with the higher risk of myopia. On the other hand, minimal outdoor activity,[20] excessive near-vision requiring work,[21] and insufficient sleep[22] are suggested as the main alterable or intervenable risk factors for myopia, but little is known about how their impacts on myopia can be modified by other factors such as menarche status. Due to the potential rapid axial growth along with body growth during puberty,[9] growth of axial length might become more sensitive to behavioral risk factors. As a result, the association between behavioral risk factors and developing myopia might increase during puberty growth. In other words, we hypothesized that menarche onset might enhance the adverse impacts of behavioral risk factors on myopia. Testing this hypothesis will help us to develop more targeted preventive strategies.

Methods

Study population

Data were extracted from the 2010 to 2014 cycles of the CNSSCH, a series of cross-sectional national surveys among school-aged children in China with identical stratified random cluster sampling procedure in each cycle.[23,24] The CNSSCH covered 30 of the 31 mainland provinces, excluding Tibet. In each province, three cities or regions at different levels of economic development ("upper," "moderate," and "low") were chosen. In each city or region, an equal number of primary and secondary schools were randomly selected from both rural and urban areas. Children aged 7–18 clustered by classroom were randomly chosen from these schools, ensuring that each sex × age combination in each city/region included at least 100 children. The CNSSCH only included children of Han ethnicity (all purely of Chinese ancestry), the dominant ethnicity accounting for 92% of population in mainland China.[21]

Exposure measure

Individual menarche data were collected by the status quo method.[25] Girls aged 9 years or above in each CNSSCH were interviewed by a school nurse or female physician and asked whether or not menarche had occurred. This study only extracted data of school girls aged 10–15 years, to ensure enough sample sizes for both premenarche and postmenarche girls in each age. Because almost all school girls of that age have some knowledge of menstrual periods from school health education, a dichotomous response (yes/no) for menarche status could be easily obtained. The school nurses or physicians were well trained to explain menstruation to young girls, so that it could be distinguished from other potential sources of bleeding.

Outcome measure

Myopia in this study was defined according to unaided distance visual acuity (VA) and subjective refraction method.[6,23] The unaided distance VA for both eyes was measured by certified optometrists using a retro illuminated logMAR chart with tumbling-E optotypes (Precision Vision, Denver Colorado). Reduced VA was defined as distance VA worse than 6/6 or 1.0.

Only for those eyes with reduced VA, subjective refraction was used to detect the refractive status. Participants' distance VA was measured again wearing positive or negative diopter spherical lens of ±0.75 D. Compared with the unaided distance VA, if the distance VA wearing positive lens reduced ≥1 line, and the distance VA wearing negative lens improved ≥1 line, then the examined eye would be defined as "myopia"; if the result was reversed, then the examined eye would be defined as "hyperopia." Any other situation would be defined as "other eye diseases." If one of the two eyes was defined as myopia, then the participant was defined as having myopia.[23]

Reduced VA is a good surrogate of myopia, having a sensitivity of 84.0% and a specificity of 88.8% in a study on Singapore school-aged children.[26] These two figures were even higher in another study among 12-year-old adolescents from Sydney.[27] Theoretically, reduced VA plus subjective refraction method in this study could make the diagnosis more accurate because it distinguishes myopia from hyperopia and other kinds of reduced VA. According to the validation trial conducted by our collaborators (see Supplementary Materials for detail), this definition of myopia in CNSSCH achieved a sensitivity of 91.9% and a specificity of 83.6%, taking the most common examination definition of myopia[3] (spherical equivalent refractive error measured by cycloplegic refraction ≤ −0.50 D) as the gold standard.

Other measures

Participants in the cycles of 2010 and 2014 CHSSCH were asked to complete a self-administered questionnaire in the classroom with the guidance of trained investigators. The questionnaire was designed by a panel of experts in their respective fields. Pilot studies were carried out to test if the questionnaire could be understood and answered accurately by the students. Prior to filling in the questionnaire, students were informed that all their answers would be kept strictly confidential and would have no bearing on their grades. The questionnaire included questions about sleep duration, homework time, and frequency of weekend outdoor activity. Age by years and age by days were both calculated according to participants' date of birth and date of physical examination in the survey. Data entry was done with double entry and verification by trained investigators using an identical software developed by the Chinese Ministry of Education and followed an identical protocol at each site. All data from each site were double-checked before submitting to national data center. We also obtained provincial population size in 2010 and 2014 from the China Statistical Yearbook, to ensure that all regression analyses were weighted by population.[23]

Table 1. Comparison of the myopia prevalence between premenarche and postmenarche girls aged 10–15 years, 2010–2014 CNSSCH [n(%)]

	2010			2014		
Age (years)	Pre	Post	*P*-value	Pre	Post	*P*-value
10	7841(46.3)	235(58.7)	<0.001	7512(47.9)	536(54.1)	0.006
11	7003(52.4)	1490(62.8)	<0.001	6175(54.4)	2228(63.6)	<0.001
12	4238(54.7)	4421(60.7)	<0.001	3483(56.7)	5143(65.1)	<0.001
13	1613(56.1)	7120(68.8)	<0.001	1124 (62.8)	7617(71.0)	<0.001
14	374(60.7)	8336(71.9)	<0.001	261(64.8)	8530(75.8)	<0.001
15	96(74.0)	8648(75.3)	0.760	47(68.1)	8812(77.5)	0.124
Total	21165(51.2)	30250(69.9)	<0.001	18602(52.9)	32866(72.3)	<0.001
Standardized* total	**21165(57.4)**	**30250(66.4)**	**NA**	**18602(59.1)**	**32866(67.9)**	**NA**

CNSSCH, Chinese National Survey on Students' Constitute and Health. Standardized by age with each age had the same weight; NA, not applicable.

Table 2. The association between myopia and menarche status among Chinese school girls aged 10–15 in 2010 and 2014

	Model 1			Model 2			Model 3		
Survey year	n	PR (95%CI)	*P*-value	n	PR (95%CI)	*P*-value	n	PR (95%CI)	*P*-value
2010	50,004	1.36(1.31, 1.42)	<0.001	50,004	1.17(1.13, 1.21)	<0.001	47,911	1.13(1.09, 1.17)	<0.001
2014	48,652	1.36(1.31, 1.41)	<0.001	48,652	1.16(1.13, 1.19)	<0.001	47,892	1.14(1.11, 1.17)	<0.001
2010 and 2014	98,656	1.36(1.33, 1.40)	<0.001	98,656	1.17(1.15, 1.20)	<0.001	95,803	1.13(1.11, 1.16)	<0.001

PR, prevalence ratio; 95% CI, 95% confidence interval. All the three models adjusted for the cluster effect of school and weighted by provincial population. Model 1 is univariate model; model 2 adjusted for exact age (age by days); model 3 adjusted for exact age, urban–rural location, sleep duration per day, homework time per day, and frequency of outdoor activity at weekend, and survey year (if using both 2010 and 2014 dataset).

Statistical analysis

A total of 102,883 girls aged 10–15 with complete data of age, visual examination, and menarche status were included in the descriptive analyses. We compared the prevalence of myopia between premenarche and postmenarche girls in different ages and survey years using chi-square tests. Considering the design effect of cluster sampling by school, we used robust Poisson regression models based on generalized estimated equation (Poisson-GEE) to detect the association between menarche status and myopia. The regression analyses were weighted by provincial population, to make the results be more representative of China.[23] This model adjusted for the cluster effect of school and estimate the prevalence ratios (PRs) which is an unbiased estimator of relative risk in cross-sectional studies.[28–30] Calculating PRs could avoid the problem that odds ratios (ORs) would overestimate the relative risk when the prevalence is higher than 10%.[28–30] The regression analysis was based on subset 1 and subset 2. Subset 1 ($N = 98{,}656$) was based on the descriptive sample ($N = 102{,}883$), excluding participants with hyperopia and other eye diseases, and participants without information of school code in 2010 and 2014 CNSSCH. While subset 2 ($N = 95{,}803$) was extracted from subset 1 excluding girls without full answer of any one of the three variables from questionnaire in 2010 and 2014 CNSSCH.

In all regression models, the dependent variable was myopia (1 = myopia, 0 = nonmyopia), and the independent variable was menarche status (1 = postmenarche, 0 = premenarche). Because both the proportion of myopic girls and postmenarche girls increased rapidly with age, age was the major confounder and was controlled as precisely as possible to avoid residual confounding.[2,25] We developed three models. Model 1 was a univariate model; model 2 adjusted for exact age (age by days); model 3 additionally adjusted for urban–rural location, survey year, sleep duration per day, homework time per day, and frequency of outdoor activity on weekends. The PRs and their 95% CI were estimated for each model. A two-sided P value < 0.05 was considered statistically significant. The interaction effects between menarche status and the behavioral factors on myopia were evaluated by sequentially adding one interaction term at a time. The data cleaning and descriptive analysis was completed with SPSS (version 20.0, IBM, Chicago, Illinois, USA); all regression analyses were completed by *geeglm* function of *geepack* package (version 1.2-1) in R (version 3.3.1).[31]

Results

Myopia prevalence among pre-menarche and post-menarche girls

The myopia prevalence among postmenarche girls was consistently higher than premenarche girls, with the age weighted prevalence 66.4%(postmenarche) vs. 57.4%(premenarche) in 2010 and 67.9% vs. 59.1% in 2014. The difference was statistically significant ($P < 0.05$) in 10 of the 12 age-group x survey year combinations (Table 1).

The association between menarche status and myopia

According to the robust Poisson-GEE regression analysis, postmenarche girls were at a 36% higher risk of being myopic than premenarche girls (PR = 1.36, 95%CI:1.33–1.40). After adjustment for age by days, the PRs (95%CI) reduced to 1.17(1.15, 1.20). Further adjusting for urban–rural location, survey year, and four behavioral factors, postmenarche girls still had a 13% (95%CI: 11%–16%)higher risk of being myopic than premenarche girls (Table 2).

Age seems to be the most important confounder among all covariates. After adjusting for exact age, further adjusting for

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Table 3. The association between myopia and menarche status when adjusting for different covariates

Adjusted variable	PR (95%CI)	*P*-value	*P*-value for difference
Unadjusted model	1.36(1.33, 1.40)	<0.001	<0.001
Exact age	1.17(1.15, 1.20)	<0.001	Reference
Exact age + urban–rural location	1.15(1.13, 1.18)	<0.001	0.278
Exact age + sleep duration	1.17(1.14, 1.20)	<0.001	0.829
Exact age + homework tome	1.16(1.14, 1.19)	<0.001	0.601
Exact age + weekend outdoor activity frequency	1.17(1.14, 1.20)	<0.001	0.950
Exact age + survey year	1.16(1.14, 1.19)	<0.001	0.654

PR, prevalence ratio; 95% CI, 95% confidence interval. *P*-values for difference were estimated by fixed-effect meta-regression, which tested whether the difference between different models was statistically significant.

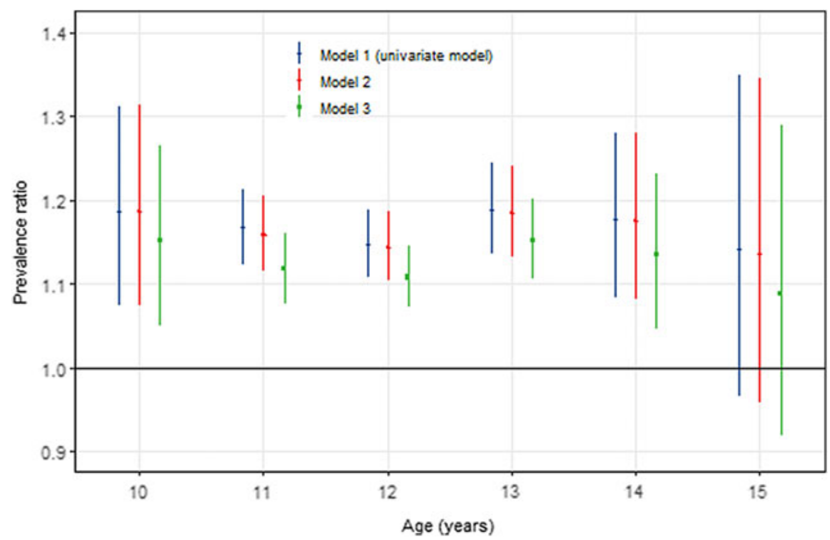

Fig. 1. The association between myopia and menarche status, stratified analyses by age.
Note: All the three models adjusted for the cluster effect of school. Model 1 is univariate model; model 2 adjusted for exact age (age by days); model 3 adjusted for exact age, urban–rural location, sleep duration per day, homework time per day, and frequency of outdoor activity at weekend and survey year.

any other covariates did not change the effect estimate significantly (all *P*-values for difference > 0.05) (Table 3). The menarche–myopia associations were generally consistent among all ages between 10 and 15, and the nonsignificant results in 15 year olds might be explained by the small sample size of premenarche girls (Fig. 1).

The interaction effects on myopia between menarche status and behavioral risk factors

The effects of short sleep duration (<7 h/d vs. ≥9 h/d), long homework time (>1 h/d vs. <0.5 h/d), and low frequency of weekend outdoor activity (very low, low, and moderate vs. high) on myopia tended to be stronger in postmenarche girls (with higher PRs), and their interactions with menarche status were all statistically significant ($P < 0.05$, Table 3).

Multicollinearity diagnostics

The covariates in the regression models were correlated with each other, with the highest correlation coefficient (0.72) shown between age by day and menarche status (**Supplementary Table S2**). As age increased, more girls experienced menarche onset, and girls slept less, did less outdoor activity but had longer homework time. However, the multicollinearity in models in Tables 2 & 4 is not a statistical concern even applying the strictest threshold (**Supplementary Table S3**).

Discussion

Our results indicate that menarche onset produced a 13% increase in the risk of myopia during adolescence after controlling for age and other potential confounders. Moreover, menarche onset may also enhance girls' sensitivity to some myopia-related risk behaviors, such as insufficient sleep, long homework time, and low frequency of outdoor activity.

Menarche is a milestone of female puberty that every girl would experience, but different girls may experience it at different ages.[13] Meanwhile, myopia onset and its progression usually stop when adolescents enter adulthood.[1] According to our findings, the earlier the girls reach menarche, the longer before adulthood they will be at increased risk of myopia and increased sensitivity to other myopia-related risk factors. As a result, those girls would be at higher risk of being myopic once they become adults, because of their longer and enhanced exposure to those risk factors before adulthood. This has been verified by previous studies,[18,19] which found that earlier menarche was associated with higher risk of adulthood myopia. Also, those girls tend to have earlier onset of myopia, leaving more time for low myopia to progress to high myopia before adulthood. This could explain why earlier menarche was also increased risk of adulthood high myopia[19] which is more clinically important than low and moderate myopia due to its pathological impact (e.g., glaucoma, retinal detachment, and macular degeneration).[7] Given the secular downward trend of median

Table 4. The interaction effects of menarche status and four behavioral factors on myopia

	Premenarche ($N = 36473$)		**Postmenarche** ($N = 59330$)		
	n	PR (95%CI)[a]	n	PR (95%CI)	Interaction P-value[b]
Sleep duration per day					
<7 h	3749	0.98(0.94, 1.03)	19562	**1.05(1.02, 1.08)**	**<0.001**
7–8 h	7365	**1.04(1.01, 1.07)**	20879	**1.04(1.00, 1.07)**	0.196
8–9 h	13407	1.01(0.98, 1.04)	13290	1.02(0.99, 1.05)	0.287
≥9 h	11952	Reference	5599	Reference	NA
Homework time per day					
<0.5 h	3614	Reference	2710	Reference	NA
0.5–1 h	16472	1.01(0.97, 1.06)	13124	**1.05(1.01, 1.08)**	0.063
1–2 h	11683	**1.08(1.04, 1.13)**	22074	**1.11(1.07, 1.15)**	**0.008**
2–3 h	3694	**1.09(1.04, 1.15)**	14739	**1.15(1.11, 1.19)**	**<0.001**
≥3 h	1010	**1.08(1.01, 1.15)**	6683	**1.16(1.12, 1.21)**	**<0.001**
Weekend outdoor activity frequency					
Very low	9646	0.97(0.93, 1.00)	19044	**1.05(1.03, 1.07)**	**<0.001**
Low	6219	1.03(0.99, 1.08)	10457	**1.07(1.04, 1.09)**	**0.001**
Moderate	17039	0.98(0.94, 1.02)	24464	**1.03(1.01, 1.05)**	**0.001**
High	3569	Reference	5365	Reference	NA

a. Adjusted for age by days, urban–rural location, survey year, and the other two behavioral factors in this table; b. evaluated by adding a interaction term (e.g., sleep × menarche) to the models.

age at menarche among Chinese girls from 13.41 in 1985 to 12.47 in 2010,[25] our findings might be increasingly important in China.

The results of our study are consistent with the Indian study and South Korean study but not consistent with the study by Yip *et al* which claims that among many indicators of puberty including menarche, only the timing of height spurt related to the timing of myopia onset. Compared to the first two studies, our study has the advantage that the menarche status and the covariates were gathered by well-trained nurses or physicians in participants' adolescence rather than in adulthood, so the recall bias is minimized. In comparison with the study by Yip *et al*, the major strength of our study is the availability of a large, nationwide sample whose selection bias tends to be minimal. Moreover, two independent national datasets (2010 and 2014 CNSSCH) were used to test our hypothesis and the results were consistent. In summary, our study adds an important population-based evidence for the association between menarche and myopia, which may provide some implications for the etiology of myopia.

The mechanism underlying the association between menarche and myopia is still unclear. Human menarche onset is regulated by complex neuroendocrine pathways.[14,32] Briefly, it starts from the activation of Kiss-1 neurons in human hypothalamus that produces kisspeptin, a protein that could activate the hypothalamic gonadotropin-releasing hormone (GnRH) neurons. GnRH neurons then activate the GnRH secretory system, leading to secretion of GnRH which stimulates the pituitary to secret luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH stimulate the production of estradiol (a kind of estrogen) and progesterone, and the maturation and release of eggs from the ovaries. Estradiol and progesterone promote the growth of endometrium of uterus to prepare for the menarche onset. Circulation estradiol before menarche was found to drive the activation of Kiss-1 neurons. Therefore, the increased level of estrogen along with menarche might explain the association between myopia and early menarche.[19] However, this is not supported by two case-control studies, which did not find that myopic girls had a higher serum estrogen than nonmyopic girls.[33,34] The rapid increase of insulin-like growth factor-1 (IGF-1) level along with menarche[35,36] may be another explanation of the menarche–myopia association. IGF-1 increases around menarche, possibly as a result of the increased insulin resistance and body fat during puberty onset.[37] IGF-1 in the brain contributes to the menarche onset by activating the GnRH neuron and possibly the Kiss-1 neuron.[38] IGF-1 in scleral fibroblasts contributes to axial elongation of the eye and thus the development of myopia.[39–41] The IGF-1 gene polymorphisms has been associated with both myopia[42] and the age at menarche,[43] suggesting a shared molecular pathway of myopia and menarche.

In this study, we found that insufficient sleep, low frequency of weekend outdoor activity, and long homework time were all risk factors for myopia among girls aged 10–15. In previous studies, no protective effects of indoor physical activity on myopia have been observed,[44,45] while the outdoor activity has been demonstrated to prevent myopia in cohort studies and randomized clinical trials.[20,45,46] The homework time is an indicator of near work exposure.[21] Therefore, our results were consistent with previous studies on outdoor activity,[20] near work,[21] and sleep duration.[22] Moreover, we found the effects of these risk factors on myopia were stronger or only statistically significant in postmenarche girls, implying that girls after menarche are more sensitive to these risk factors. This suggests that differentiated recommendations of sleep duration, outdoor activity, and homework time should be made for school-aged girls according to their menarche status. For example, for two nonmyopic girls at a similar age, where one has reached menarche while one has not, in order to prevent myopia onset, the postmenarche girl should undertake outdoor activity and study break more intensively than the premenarche girl because of her higher sensitivity to inadequate outdoor activity and long homework time.

The effects of these behavioral factors and their interaction with menarche status may also be explained by IGF-1. First, outdoor activity could retard axial elongation by increasing the dopamine secretion in human eyes.[46,47] IGF-1 may mediate dopamine's effect, because high levels of dopamine could suppress the IGF-1 level.[48] Second, near work may also impose its impact on axial growth by upregulating the IGF-1 receptor in retinal pigment epithelium according to an animal study.[40] Third, short sleep duration could greatly increase the risk of being insulin resistant,[49] which could increase the serum level of IGF-1.[39] Although the IGF-1 system seems to be a sound explanation for our results, this hypothesis needs to be tested with further clinical and experimental studies.

There are several limitations of our study. First, the definition of myopia is not the most widely used one, and may lead to a nondifferential outcome misclassification, which might well underestimate the effect of menarche. However, in such a large national sample, the current screening method is acceptable given its efficiency and high sensitivity and specificity (Supplementary Table S1). Furthermore, in the context of Chinese schools, where nearly 90% of vision impairment is due to uncorrected myopia, using unaided VA as a surrogate for myopia may be justified.[23,50] Further studies with standard measurement of myopia are warranted to confirm our findings. Second, this is not a cohort study and the causal relationship between exposure and outcome cannot be established with certainty. Prospective studies might be helpful to definitively establish causality, although myopia is unlikely to affect the timing of menarche. Third, due to the limitation of the survey and its data, we only have one indicator of puberty for girls. We cannot exclude the possibility that the effect of menarche status might be caused by other unmeasured pubertal indicators such as breast development, since these indicators are highly correlated with each other. However, menarche is one of the most significant indicators of female puberty, so its association with myopia provides important information on the effect of puberty development on myopia. Also, menarche is the easiest pubertal indicator to identify, so public health strategies based on this indicator are more practical to implement. Finally, we do not have a suitable puberty indicator for boys, such as the break of voice, thus our study is limited to girls and further studies are warranted for boys.

In conclusion, among Chinese girls aged 10–15, earlier menarche appears to be associated with a higher risk of myopia. Menarche onset could also increase girls' sensitivity to several behavioral risk factors for myopia, which might have some implications for the prevention of myopia.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S204017442000077X

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Conflicts of Interest. None.

Ethical Standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on population-based cross-sectional studies and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the Medical Research Ethics Committee of Peking University Health Science Center (application number: IRB00001052-18002).

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