Review Article

Strategies to control myopia in children: a review of the findings from the Anyang Childhood Eye Study

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Abstract: Myopia in children remains a major public health problem worldwide, especially in some Asian countries such as China, Singapore and Japan. Although many interventions have been attempted, few has been proven to be effective in controlling onset and progression of myopia in children. Environmental factors, genetic susceptibility or ethnic differences can affect the efficacy of these interventions. However, many questions remain unclear and even controversial for controlling myopia. China has the biggest population with myopia, especially for children myopia. Thus, it is of importance to present what achievements Chinese scientists have made in the field of myopia control in children. We summarize the current findings on myopia control in children from the Anyang Childhood Eye Study, including epidemiological data, clinical trials, systematic reviews and meta-analyses, and compare them with studies in other countries to find potential clues for controlling myopia in children.

Keywords: Children myopia; time outdoors; near work; Chinese eye exercises; spectacles

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By 2050, it has been estimated that 49.8% of the world population will have myopia, 9.8% will have high myopia and 1 billion people with high myopia may suffer from vision loss (1). The rapid increase in myopia, especially in high myopia, indicates that myopia is no longer just a problem refractive errors that can be easily corrected by wearing spectacles, but will significantly impact vision due to ocular complications related to myopia of high degree (2,3). Seeking for strategies on slowing myopia onset and progression in children is of vital importance in order to reduce the total population with high myopia. It is even more urgent for China to control myopia, because it has the biggest population with myopia in the world.

In China, the earlier population-based study on children myopia originated from the Refractive Error Study in Children (RESC) surveys and was carried out in Shunyi district, Beijing, northern China in 2000 (4), which reported a 2-year progression on myopia in school-age children (5). Later, He *et al.* reported the refractive error and visual impairment in both urban (6) and rural (7) children in southern China, and conducted the Guangzhou Twin Eye Study to identify the genetic and environmental determinants of ocular diseases including myopia (8,9).

Since 2011, the Anyang Childhood Eye Study (ACES) was conducted in Anyang city, central China, to evaluate gene-environmental interaction effects on myopia by following 2,893 grade 1 students and 2,267 grade 7 students every year (10). In July 2017, the ACES finished the 6th observation of these children and became the biggest cohort study on myopia, amblyopia (11,12), strabismus (13) and ocular parameters (14-19) in Chinese children. Meanwhile, the ACES group also performed some randomized controlled trials on intervention measures to clarify their effect on controlling myopia in children.

Time outdoors

In recent years, more and more epidemiological evidences support the idea that time outdoors, maybe sunlight, is protective against myopia in children (20). Dopamine (21) or vitamin D (22) may mediate the protective effect of time outdoor on myopia. Irrespective of the mechanism involved, it is uncertain whether time outdoors also block myopia progression (20). A novel classroom with four walls made of glass has been reported to be able to increase light intensity inside the classroom without leading to significant discomfort (23). Studying the long-term effect of this form of classroom on retarding myopia progression in children is clearly worthwhile.

In 2015, Li *et al.* followed 1,997 12-year-old children from the Anyang Childhood Eye Study for 2 years and found that greater time outdoors was associated with slower axial elongation in nonmyopic teenagers (−0.036 mm/y, P=0.009), but not in existing myopes (−0.005 mm/y, P=0.595) (24). A little later, He *et al.* reported a clinical trial among 6-year-old children conducted in Guangzhou with 952 in the intervention group and 951 in the control group. They found that additional 40 minutes outdoor activity every day reduced myopia incidence by −9.1% (P<0.001) and slowed myopia progression by only 0.17 D (P=0.04) over 3 years (25). The amount of 0.17 D during 3 years was very small and clinically insignificant (26), and supported the findings from the ACES that more time outdoor is effective in children without myopia, but not in children with existing myopia. Therefore, strategies to prevent myopia onset and slow myopia progression in children should be differentiated. For example, time outdoors should be increased in preschool children who have no myopia.

Near work

Different from time outdoors, there are few epidemiological evidences supporting that near work is risk factor for myopia (27). Some scholars proposed that measurement of near work amount by questionnaire is far from accuracy due to recall bias and wide variation in near work. On the other hand, the ACES showed continuous reading, distance of near work, habits of reading and writing are associated with myopia in children, indicating that visual behaviors and environments are important factors mediating the effects of near work on myopia in children (28).

Instruments for logging near work distance were initially developed by Leung *et al.* in Hong Kong (29). Now, some more powerful instruments that can document distance, angle, light level and duration of near work have been manufactured by Chinese scientists and been commercially available (30). The instrument can be attached to a spectacle frame and can connect with a smartphone in real time. This sort of instrument should enable the collection of big data on myopia in children that is more precise than that which can be obtained via questionnaires.

Chinese eye exercises

It has been more than half a century since Chinese eye exercises became a community ritual and a living habit of Chinese children since 1963. As a form of massage on periocular acupoints related to traditional Chinese medicine (TCM), Chinese eye exercises are thought to be able to protect vision and prevent myopia in children. Some scholars think Chinese eye exercises is not effective for controlling myopia in children, while some argue that myopia prevalence in Chinese children may have been much higher had children not perform the exercises. In short, there is no strong evidence to support or against Chinese eye exercises for its effect on myopia control in children.

In 2015, Li and Kang *et al.*, part of the Tongren team led by Ningli Wang, finished the first randomized controlled trial (RCT) on evaluating the effect of Chinese eye exercises (31). A total of 190 children aged 10–14 years with emmetropia to moderate myopia were divided into three groups: standard Chinese eye exercises group (trained by doctors of TCM); sham point eye exercises group (instructed to massage on non-acupoints); and eyes closed group (asked to close their eyes without massage). Only 5 minutes of standard Chinese eye exercises significantly alleviated the accommodative lag (0.10 D, P=0.04) compared with other two groups (−0.03 D and 0.07 D). The proportion of children with reduced accommodative lag was also significantly higher in the standard Chinese eye exercises group (54.0%, P=0.03) than the other two groups (32.8% and 34.9%).

Despite the design with a short-term outcome measure, this first RCT on Chinese eye exercises proved its effect on alleviating accommodative lag, which has been associated with myopia progression in children (32,33). Moreover, the authors from the ACES group found that children who performed high quality exercises had a slightly lower myopia progression of 0.15 D than the children who did not perform the exercises, over a period of 2 years (34). The amount of 0.15 D seems to be small and nonsignificant. However, it is comparable to that of 0.17 D by additional 40 minutes time outdoors over 3 years (25).

It should be noted that Chinese eye exercises are performed for only 5–10 minutes by Chinese students every day, and most Chinese students do not perform it accurately. As a kind of massage, the exercise is also weaker than acupuncture. It is worthwhile to evaluate whether Chinese eye exercises can produce similar effect size of controlling myopia in children like time outdoors if it can be administered for longer time, such as 40 minutes, over a longer period.

Lenses

Spectacles are often used to correct myopia to give better distance vision. Traditionally, spectacle lenses use single-vision designs. However, some lenses with special designs, such as bifocal or multifocal, which are used for correcting presbyopia, have been used in attempts to control myopic progression in children. The evidence from meta-analysis showed that multifocal spectacles with powers ranging from +1.50 to +2.00 D produce statistically significant decreases in myopia progression in school-aged children compared with single-vision spectacles (35). Moreover, Asian children, predominantly East Asian children, appeared to have greater benefit from intervention with multifocal lenses than Caucasian children. Studies on soft contact lenses using design concentric ring bifocal and peripheral add multifocal designs confirm that it is the design of bifocal or multifocal, not the modality of spectacles or contact lenses, that is important for clinically effective control of myopia in children (36).

Bifocal or multifocal lenses, incorporating under correction around center of lenses for achieving better near vision, raise an issue on whether single-vision lenses designed with under correction can also slow myopia progression. To date, there were only two randomized controlled trials published on this issue. Chung *et al.* (37) and Adler *et al.* (38) found that under correction of myopia with respective amount of +0.75 D and +0.50 D enhanced rather than inhibited myopia progression in children. However, these two studies were conducted in Malaysia and in Israel, respectively. A randomized controlled trial (FUMET) conducted in Chinese children (39), who usually spend more time on near work and less time outdoors, is expected to show whether ethnic difference also exist in the effect of under correction of myopia.

Interestingly, data from the Anyang Childhood Eye Study showed that myopic children with under correction of myopia by wearing spectacles did not present with faster myopia progression than children with full correction over 1 year (40). Furthermore, the data showed that myopic children with no correction had significantly slower myopia progression (–0.76 D *vs.* –1.03 D, $P<0.01$) and less axial elongation (0.47 *vs.* 0.51 mm, $P<0.01$) than children with full correction over 2 years (41). Moreover, myopia progression decreased significantly with an increasing amount of under correction in Anyang children. This is the first report in myopic children to support previous findings from animal model of lens-induced myopia (LIM) that myopic defocus slows myopia progression (42), and indicate that stronger or longer signal of myopic defocus may be needed in human beings for producing effective inhibition of eye growth than in animals (43). Further analysis from the Anyang data may reconfirm whether feedback control theory applies to myopia progression in children, namely continuous correction of myopia will open the feedback loop resulting in linear progression that increases myopia (44).

Relative peripheral refraction

In recent years, relative peripheral hyperopia has been proposed to play an important role in refractive development supported from evidence from both human being (45,46) and animal studies (47-49). Chinese children wearing single-vision spectacles did show increasing peripheral hyperopic defocus (50), however, the spectacles designed to reduce peripheral hyperopic defocus failed to slow myopia progression in Chinese children in a randomized controlled trial compared with single-vision spectacles (51). Later, in a controlled trial without randomization, contact lenses designed to reduce peripheral hyperopic defocus did appear to slow myopia progression in Chinese children by 33% over 1 year (–0.57 D *vs.* –0.86 D; 0.27 *vs.* 0.40 mm) compared with single-vision spectacles (52).

In a longitudinal study on Singapore Chinese children, data with mean duration of 1.26 years showed that baseline peripheral refraction did not predict subsequent onset of myopia or influence the myopia progression (53). Data from the Anyang Childhood Eye Study showed that myopic children in mainland China have relative peripheral hyperopia, while hyperopic and emmetropic children have relative peripheral myopia (54). However, data over 2 years from the ACES reconfirmed that relative peripheral hyperopia does not predict development nor progression of myopia in Chinese children (55). This calls into question the efficacy of treatments that aim to slow progression of myopia in children by "treating" relative peripheral hyperopia.

Ethnic difference

Currently, it has been widely recognized that atropine and orthokeratology are two promising interventions on controlling myopia in children (56). Moreover, summarized evidence showed that Asian children benefit more from these interventions than Caucasian children (57,58). Are Asian children more sensitive to such interventions on myopia? In other words, does ethnic difference in effect of these interventions exists among myopic children with different ethnicities? This issue has not been adequately addressed because both environmental and genetic factors are involved, and it is not easy to clarify their respective contribution.

Numerous reports have proved that East Asian children, have a higher prevalence of myopia than children of other ethnicities (1,59,60). Not only ocular anatomical factors (61,62), environmental factors (63) and genetic factors (64-66), but also gene-environmental interaction (67) may contribute to this significant difference. Despite of these, environmental factors may offer scope for most promising intervention on myopia in near future. Using a questionnaire derived from the Sydney Childhood Eye Study, the Anyang Childhood Eye Study found that Chinese children spent significantly more time on near work than European Caucasian children, but were similar to East Asian children living in Australia (28,68). It is suggested that in future trials near work should be measured, for example using wearable instruments, to accurately evaluate its effect on intervention. Moreover, genetic susceptibility should also be considered, such as APLP2 which has been proven to regulate myopia development in both human and mice (67).

In addition, it is promising that control based on function-related myopia genes may be applied for controlling early-onset high myopia in children with the development of genome-engineering techniques (69). Recently, Jin *et al.* found some *de novo* mutations in early-onset high myopia in children (−6.0 D before the age of 6) using trio-based exome sequencing, and further proved that *BSG* mutation had function impact on myopic phenotype of elongated axial length (70). Although early-onset high myopia is obviously different from school myopia, which is most common in children and is generally thought to be mainly affected by environmental change (71), these findings remains meaningful because acquired high myopia is increasing in Chinese young adults (72) and methods for preventing visual impairment due to high myopia are eagerly anticipated (73).

Summary

As the country with biggest population of myopia, China has put much efforts into controlling myopia although there are increasing numbers of early onset myopia and high myopia. At public health level, school-based interventions to reduce educational pressure and increase time outdoors or sunlight exposure for children, especially for preschool children, are worthwhile to prevent onset of myopia. Low concentration atropine and orthokeratology, which have been reported to be effective in controlling myopia in children, however, have not been evaluated in children living in China by randomized controlled trial. Meanwhile, more strategies with stronger effect on slowing myopia progression, and most importantly, preventing sight-threatening ocular complications associated with high myopia or pathological myopia, are required. A cocktail method consisting of two or more interventions, as well as consideration of gene susceptibility, might produce the maximum effect for controlling myopia in children.

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Footnote

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