

Shanghai Child and Adolescent Large-scale Eye Study

- High Myopia Registration Implementation Plan

(Internal Information)

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Hospital

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1. introduction

1.1 Overview of myopia and high myopia

Myopia is the most common eye disease in the world ^[1]. Among them, the incidence and prevalence of myopia are highest in developed countries and regions in East and Southeast Asia ^[2-8]. It is predicted that by 2050, global myopia patients would reach 5 billion, 1 billion of which were high myopia ^[9]. In developed countries and regions in East and Southeast Asia, the prevalence of myopia in high school graduates is as high as 80% to 90% ^[2]. A study in Taiwan showed that more than 80% of adolescents suffered from myopia when they graduated from high school, 10% of whom were high myopia ^[10]. Another study which focused on university students in Shanghai showed that 95.5% of college students suffered from myopia, and 19.5% of them were high myopia ^[11]. In stark contrast, the prevalence of myopia in the same age in western developed countries is between 20% and 40% ^[2, 12-14]. In less developed countries and regions of the world, the incidence of myopia in young people is about 5% to 10% ^[15-18] due to the low level of education.

At present, the etiology and pathogenesis of myopia and high myopia are still unclear. Environmental and genetic factors are involved in the development of myopia and high myopia. Among them, the level of education and outdoor activity time are closely related to the development of myopia and high myopia. At present, most studies believe that the higher the education level, the higher the incidence of myopia and the deeper the degree of myopia ^[19-21]. In addition, most studies suggest that outdoor activities was a protective factor for myopia, and increasing outdoor activity time could reduce the incidence of myopia ^[22-25]. Also, some studies have shown that the age of onset of myopia was closely related to high myopia ^[26-27]. Furthermore, genes

may also be closely related to the occurrence of myopia and high myopia. At least 19 myopic loci ^[28] have been identified through family studies and twin studies till now. With the completion of the Human Genome Project, genome-wide association analysis technology is becoming more and more mature, and more and more related genes and mutation sites have been elucidated ^[28], but the pathogenic genes of myopia are still not completely clear. In addition, the genes related to pathological myopia and fundus lesions are currently unclear. In recent studies, high myopia and pathological myopia are not strictly differentiated (pathological myopia is defined by diopter or axial length alone). Therefore, genes related to pathological myopia need further research, in order to judge whether high myopia and pathological myopia are two different diseases at genetic level or different states controlled by the same genes.

1.2 Relationship between high myopia and pathological myopia

The fundus of patients with high myopia is often accompanied by a series of pathological changes, such as posterior scleral staphyloma, retinal choroidal atrophy, lacquer crack, choroidal neovascularization, macular hemorrhage, Fuchs plaque, retinal palpebral fissure, retinal tear, retinal detachment. These pathological changes are important causes of decreased vision and even blindness. Some studies have shown that macular degeneration caused by myopia has become a major cause of blindness and low vision ^[29-32]. In Jing'an District of Shanghai, high myopia with macular degeneration has leapt to the first place in adult blindness ^[29]. A study in Beijing showed that pathological myopia has become the leading cause of blindness and visual impairment in the 40-49 age group ^[30].

Although high myopia is closely related to pathological myopia, and most patients with pathological myopia are highly myopic, high myopia is not equivalent to pathological myopia. The change of diopter and axial length do not fully reflect the characteristics of pathological myopia. Some patients with high myopia have no definite fundus lesions, and some non-high myopia patients may also have posterior scleral staphyloma, retinochoroid atrophy and other complications. At present, Ohno-Matsui K et al define pathological myopia as: myopic macular degeneration ≥ 2 (diffuse retinochoroid atrophy), or additional lesions (lacquer cracks, CNV, Fuchs plaque), or posterior scleral staphyloma^[33]. In this definition of pathological myopia, we focus on fundus lesions caused by myopia, and do not emphasize diopter and axial length.

At present, there are still many unknowns about the relationship between high myopia and pathological myopia. The process of developing simple high myopia in children and adolescents as pathological myopia is still unclear. Does high myopia eventually evolve into pathological myopia? Are pathological myopia and high myopia different stages of the same disease or two different diseases? Which fundus changes can predict the occurrence of pathological myopia? These problems need further exploration.

1.3 Morphology and visual function changes in fundus of children with high myopia

At present, there are few studies on the changes of fundus morphology and visual function in children with high myopia. And long-term follow-up studies are also lacking.

Morphological studies suggest that the common fundus changes in children with high myopia include β -PPA, optic disc tilt, etc., but the incidence of posterior scleral staphyloma and retinochoroid atrophy is low in childhood ^[34-35]. Furthermore, some studies have suggested that diffuse retinohoroid atrophy around the optic disc in childhood could easily develop into pathological myopia ^[36] in adulthood. In addition, thinning of the retina, choroid, and sclera is also present in children with myopia and high myopia ^[37-40]. In addition to the fundus of the posterior pole, there are also multiple lesions ^[41-44] in the peripheral fundus. Some studies considered that peripheral fundus lesions such as lattice-like degeneration, non-compressive whitening, and retinal tears are more common in children with high myopia ^[42].

Corresponding to structural changes, there are also changes in micro-field and electrophysiology of patients with high myopia ^[45-52]. However, there is few studies focusing on children and adolescents with high myopia ^[49-50], and no long-term follow-up studies has been reported. There are still many unknowns in the early morphological changes, evolution process and visual function of high myopia, which deserve further exploration.

1.4 The direction of this research

- A. Follow-up study of morphological changes in the fundus of children with high myopia;
- B. Follow-up study of visual function changes in children with high myopia;
- C. Etiological studies related to high myopia in children;
- D. Follow-up study of quality of life, psychology, behavior, and social interactions in children with high myopia.

2. Goal and design

2.1 Research objectives

- A. To observe the fundus changes in the posterior pole (morphology, thickness, asymmetry, blood flow density, etc) with the myopia progression.
- B. To observe morphological changes in choroid and peripheral region of retina with myopia progression.
- C. To observe changes of visual function (contrast sensitivity, Microperimetry, etc) with myopia progression.
- D. To detect the susceptibility genes related to high myopia and myopic fundus changes; to test the levels of Vitamin D, riboflavin, TGF, IGF, FGF, etc.
- E. To observe the changes of living quality, psychology, behavior and social activities of high myopic children.

2.2 Research design

Prospective cohort study. After completing the baseline survey, the planned follow-up frequency is once a year.

2.3 Research cycle

2018.06~2038.06 (at least).

2.4 Expected results

- A. Registration completed a study of high myopia research for children and adolescents covering around 3,000 people;
- B. Establish a database information management system and workflow SOP file for the study of high myopia registration in children and adolescents;
- C. Further clarify the changes in the retinal, choroidal and scleral

tissue structures, blood flow density, etc. in the macular area and the optic disc;

- D. Revealing the changes of the retina, choroid and other tissues in the peripheral area with the progression of myopia;
- E. To clarify the relationship between changes in the fundus structure and changes in visual function in the posterior pole;
- F. Further clarify the etiology and pathogenesis of high myopia, pathological myopia and myopic fundus lesions, and identify the relationship between high myopia and pathological myopia;
- G. From the perspectives of society, behavior and psychology, the effects of high myopia and pathological myopia on children and adolescents will be fully demonstrated.

3. Research object

3.1 General characteristics of the research object

Based on the refraction development archive system that has been constructed in Shanghai, the list of children and adolescents with high myopia was selected from the database of children's refractive development archives information in Shanghai. Children of different ages with high myopia must meet the following conditions:

- (1) 4-5 years old, equivalent spherical error ≤ -4.0 D;
- (2) 6-8 years old, equivalent spherical error ≤ -6.0 D;
- (3) 9-18 years old, equivalent spherical error ≤ -8.0 D.

3.2 Sample size

A total of 1.25 million children and adolescents are currently registered, 4,006 (0.32%) of which meet the entry requirements. Among the 4~5 year olds, there are 815 people with $SE \leq -4D$; 842 people with $SE \leq -6$ D among the 6~8 year olds; 2349 people with $SE \leq -8D$ among the people aged 9 and over. Taking into account the 50% non-response

and the proportion of the exclusion, the initial registration number is about 2,000.

3.3 Source of study object

Children and adolescents who meet the inclusion criteria in the Shanghai Children's Refractive Development Archives Information Database System.

3.4 Inclusion criteria

- A. Children and adolescents between the ages of 4 and 18 years old, $SE \leq -4$ D under 5 years old, $SE \leq -6$ D at 6-8 years old, $SE \leq -8$ D over 9 years old;
- B. No eye disease, good general condition, can cooperate with the examiner;
- C. Obtaining the consent of the child and his/her guardian;
- D. Long-term residence in this city, there is no plan to move out of this city in the short term.

3.5 Exclusion criteria

- A. Amblyopia (best corrected visual acuity (BCVA) less than 0.8 for children over 6 years old, BCVA less than 0.63 for children 6 years old and younger) and strabismus;
- B. Secondary myopia, genetic disease or connective tissue-related myopia;
- C. Moderate or severe ptosis;
- D. Congenital cataract, glaucoma;
- E. Other fundus diseases other than myopic related fundus lesions;
- F. Intraocular or refractive surgery history;
- G. The refractive medium is turbid, and it is impossible to take a

clear fundus image;

- H. Unable to cooperate with fundus image shooting and other examination;
- I. Do not receive cycloplegia or have contraindications;
- J. Poor overall condition, unable to follow up for a long time;
- K. The child or the guardian refuses to participate in the research;
- L. Other cases in which the researcher judges that it is not suitable for participation in the study.

4. Data collection

4.1 Preparatory work

- A. Establish Shanghai Children and Adolescents High Myopia Registration Information System and Workflow: a set of information function modules including appointment, real-time collection of exam data, online feedback of exam results, daily consultation contact and data management analysis. And then establish the workflow SOP file;
- B. Train physicians, optometrists and other relevant staff responsible for the research;
- C. Print promotional materials, questionnaires, informed consent forms and examination flow charts;
- D. Contact the children and adolescents in the Shanghai Children's Refractive Development Archives Information Database System through their school and use science lectures, WeChat official accounts, Weibo (Chinese version of Twitter), paper leaflets to promote the harm of high and pathological myopia to children, adolescents and their parents, as well as introduction of the content of this study, the participants' benefits and potential risks;
- E. Sign an informed consent form to collect information on the

participants;

F. The appointment is registered through the information system.

4.2 Examination process

The brief process is as follows: Identity information registration > height, weight > naked eye vision & wearing vision > axial length > intraocular pressure > slit lamp anterior segment examination > Microperimetry (selected) > cycloplegia > Autorefraction and subjective refraction > Pentacam, SS-OCT(Topcon), wide-angle OCT/OCTA(Zeiss-9000), fundus color photography + autofluorescence(Topcon), Ultra wide Angle fundus photography (Optos), mfERG (optional), wavefront aberrations > blood sample collection / saliva specimens > fill out the questionnaire.

The specific flow chart is as follows.

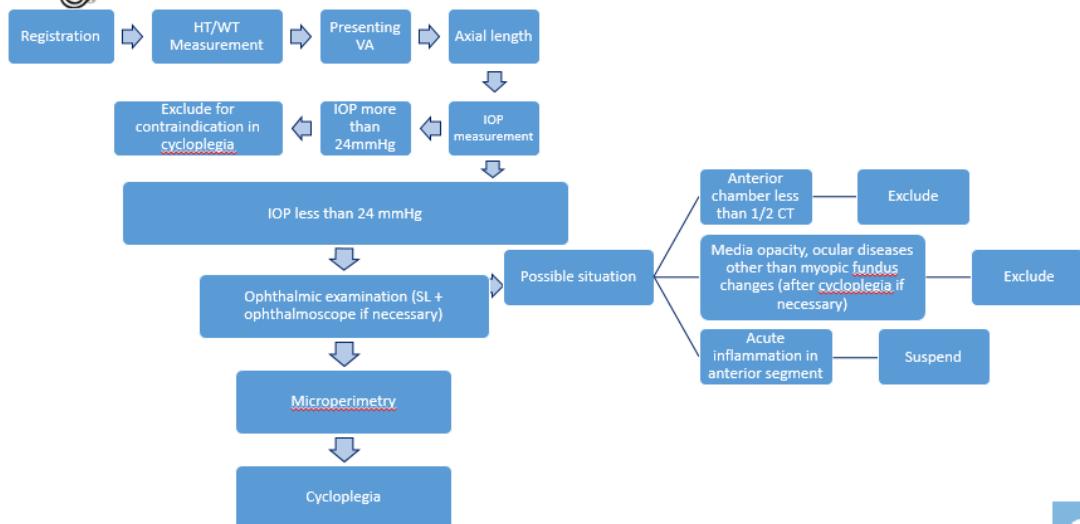
4.3 Ophthalmology inspection project operation rules

4.3.1 Vision test

The eyesight examination used the ETDRS visual acuity chart (LCD backlit lamp, WH0701, Guangzhou Xieyi Weishikang), the test distance was 4 meters, and the visual target at 20/20 was the same height as the eye of the examinee. The recognition time of each visual target is 2~3s; the eye of the subject is required to be opened normally for examination, and the blinking, hoeing, neck stretching and peeking are strictly prevented. Vision is converted to a decimal count record. Visual acuity examination includes two parts: uncorrected visual acuity (UCVA) and corrected visual acuity (CVA). Children who are not wearing glasses are only examined by UCVA, and children who wear glasses are required to check CVA after completing the UCVA test.



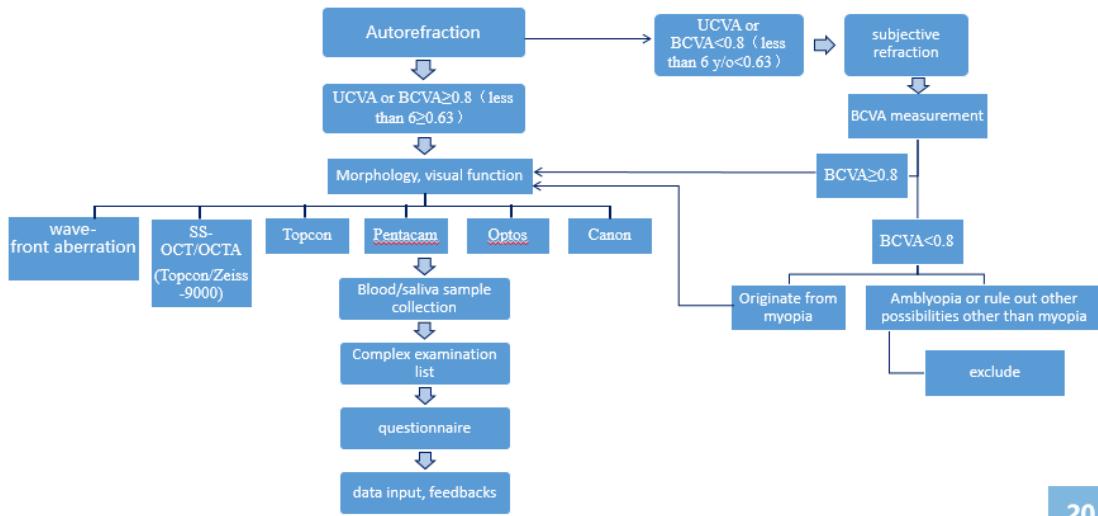
4.2 Examination process (before cycloplegia)



19



4.2 Examination process (after cycloplegia)



20

Check flow chart

4.3.2 Axis measurement

The axial measurement was performed using an IOL Master (version 5.02, Carl Zeiss Meditec, Germany). Simulated eye calibration was needed before measurement. Each eye was measured repeatedly for 3 times, and the difference was less than 0.02 mm each time. For those who still have large fluctuations in multiple measurements, the examiner needs to record it.

4.3.3 Intraocular pressure measurement

Intraocular pressure was measured using a non-contact tonometer (NT-4000, Nidek, USA). Each eye was repeatedly measured 3 times and averaged, and the difference between each two was less than 5 mmHg. Those with an intraocular pressure higher than 24 mmHg should be recorded and added for visual field examination.

4.3.4 Ophthalmologist examination

Ophthalmologist examinations included anterior segment slit lamp examination (66 Vision. Tech, Suzhou) and ophthalmoscopy examination (66 Vision. Tech, Suzhou). The examination of the anterior segment slit lamp includes the eyelid, conjunctiva, cornea, anterior chamber, iris, pupil, lens and anterior vitreous body, which is completed by our senior ophthalmologist. For patients with peripheral anterior chamber depth less than 1/2 corneal thickness, or acute inflammation of the anterior segment of the eye and other related diseases, it is not suitable for cycloplegia afterwards. It should be registered by the examining physician and suspended or excluded from the study. In addition, the ophthalmologist should use corneal reflection, occlusion-de-covering, etc. to determine whether the

subject has strabismus (hidden strabismus or strabismus). Those who were strabismus should be excluded from the study. For those suspected of having fundus diseases, ophthalmoscopy (direct ophthalmoscope or 90D) can be performed after cycloplegia, and the nature of fundus disease is judged by an ophthalmologist. Participants with myopia-related fundus lesions can be registered and included in the study, while participants with other fundus lesions need to be excluded after recorded. Those who had other organic eye diseases were also excluded after recording.

4.3.5 Microperimetry

Microperimetry examinations were performed in the darkroom and needed to be performed prior to OCT and fundus photographic examinations to avoid influence by bright light. Microperimetry was performed using an MP1 micro-perimeter (MP-1, Nidek, Japan), and the Goldman III, 4-2-1 mode was selected to detect retinal light sensitivity within 10 degrees of the macula. There were a total of 40 stimulation points (1°-8 stimulation points, 3°-16 stimulation points, 5°-16 stimulation points), and the stimulation intensity of each point is from 20 decibels (dB) (equivalent to 20 asb) to 0 dB (Equivalent to 400 asb) change. Initial stimulation intensity is 16 dB and stimulation duration is 100 ms. The background light is white, 4asb. All participants will receive at least 5 light stimuli before the formal test, making them familiar with the examination process and minimizing the impact of learning effects. The test procedure is as follows: the infrared fundus camera takes a fundus shot (45° field of view) and transmits it to the video monitor. The fixation target and the stimulation point are projected onto the retina by the liquid crystal display. The eyeball automatic tracking system tracks the

position of the retina in real time to ensure each stimulation point in the predetermined retinal position. Every 60 s system will project a super-threshold stimulus on the physiological blind spot to monitor the false positive reaction. If a false positive reaction occurs, it needs to be re-examined. This item is optional for children under 10 years old.

4.3.6 Cycloplegia

The cycloplegia procedure is as follows: 1 drop of 0.5% proparacaine (Alcaine, Alcon) is added to the conjunctival sac of each eye, and 2 drops of 1% cyclopentolate are added to each eye after 15 seconds. (Cyclogyl, Alcon), 5 minutes apart. After each drip, ask the participant to press the inner canthus for a few seconds gently and try to take the head back posture. The last drop of cyclopentolate was instilled into the conjunctival sac for 30 minutes to check for light reflection. If the light reflection disappeared and the pupil diameter was greater than 6 mm, cycloplegia was considered complete. If the light reflection still exists, add a third drop of cyclopentate, and re-examine the light reflection and pupil diameter after 20 minutes. If there was still light reflection, the inspector needs to record this. During cycloplegia, if the participant has symptoms of ocular discomfort, the ophthalmologist should carefully examine it and give an appropriate treatment.

4.3.7 Measurement of refractive state and corneal radius of curvature (CR)

The refractive status and CR measurements were performed using an automated computer refractometer (KR-8900, Topcon, Japan), which was performed after ciliary muscle paralysis. Simulated eye calibration

needed before measurement. Each eye was repeatedly measured three times to average, and if any two results differ by more than 0.5 D, the measurement needed to be repeated. If there were still significant differences in the results of multiple measurements, the examiner needed to record it.

4.3.8 Subjective optometry

Children who do not wear glasses have a UCVA of less than 0.8 (less than 0.63 for children 6 years of age and younger) or children with glasses have a CVA of less than 0.8 (children under 6 years of age and below 0.63) need to finish a subjective optometry after cycloplegia in order to measure the best corrected visual acuity (BCVA). If the BCVA is less than 0.8 (less than 0.63 for children aged 6 and under), or the degree of compliance during the examination is poor, the examiner should record it. If the BCVA is less than 0.8 (children under 6 years of age and below is less than 0.63), further examination by an ophthalmologist is required to determine whether the inclusion conditions are still met.

4.3.9 Pentacam

Pentacam (OCULUS Optikgeratic GmbH, Germany) was examined after cycloplegia. Measurements include corneal diameter and curvature, anterior chamber depth and volume, anterior chamber angle, pupil diameter, crystal thickness, etc. Shooting requirements: Image quality display "OK", crystal thickness value is available. This item is optional for children under 6 years old.

4.3.10 SS-OCT (Topcon)

SS-OCT (DRI OCT Triton, Topcon, Tokyo, Japan) was examined after

cycloplegia. OCT location: Macular + optic disc area. Shooting mode: 12*9 mm 3D scan mode (4 overlap) / Line scan (64 overlap) + 9 mm radial scan mode (16 overlap, follow up mode) + optic disc area 9 mm radial scan mode (16 overlap, follow up mode) + macular area 7*7 mm 3D scan mode (4 overlap) + optic disc area 6*6 mm 3D scan mode (4 overlap). Shooting requirements: input spherical error, cylinder, axis length, corneal curvature radius correction magnification before shooting; image signal of strength 3D scan mode is not less than 50, radial scan mode is not lower than 60, peripheral image avoids mirror flip as much as possible. When shooting the disc area, we need to manually adjust the shooting center to the center of the disc. If the image quality is affected by blinking or eye movement during shooting, you need to re-shoot. If you still can't meet the requirements, you need to record it. SS-OCT comes with a fundus color photograph. The shooting position is required to be consistent with the SS-OCT scanning position and to avoid eyelids, eyelashes and hair occlusion. Dark areas are avoided in the image, and the image quality is not less than 90. This item is optional for children under 6 years old.

4.3.11 Wide angle OCT/OCTA (Zeiss)

Wide-angle OCT/OCTA examinations were performed after cycloplegia. OCT/OCTA location: macular + optic disc area. Shooting mode: 12*12mm, 15*9mm angio mode; 16mm loop sweep mode (horizontal and vertical directions) a total of 8 scans. Shooting requirements: communicate more with the subject; the forehead and chin must be close to the instrument. If the image quality is affected by blinking or eye movement during shooting, you need to re-shoot. This item is optional for children under 6 years old.

4.3.12 Fundus photography + autofluorescence

Fundus photography + autofluorescence was performed after cycloplegia. Shooting content: pseudo color eye fundus + spontaneous fluorescent fundus. Shooting requirements: The exposure intensity is 30ws and 300ws respectively and it needs to focus on the split line and rotate the upper refractive compensation button. If you find the participant not completely cycloplegic, please take another drop of cyclopentolate, otherwise there will be a dark area. This item is recommended for final inspection as the exposure is too bright.

4.3.13 Ultra wide-angle fundus photography (Optos)

Optos ultra-wide-angle fundus photography was performed after cycloplegia. Shooting content: pseudo color eye fundus + spontaneous fluorescent fundus. Shooting requirements: the same as color fundus photography.

4.3.14 mfERG

mfERG (RETIscan, 3.15 version, Roland, Germany) was examined after cycloplegia. After 0.5% topical anesthesia with procarbaine hydrochloride, the contact lens was placed on the cornea, the ground electrode was placed in the middle of the forehead, and the reference electrode was placed on the lateral iliac crest to correct refractive error. The stimulator has an average brightness of 102 cd/m² (4~200 cd/m²), a contrast ratio of 99%, and stimulates the retina with a center of about 30° around the macula. There are 61 hexagons, each of which is six. The edge is flipped in black and white under the control of the binary m sequence. Each stimulation cycle time is 47 s, stimulating 6 cycles. This item is optional for children under 10 years old.

4.3.15 Wavefront aberration

When the corneal topography and wavefront aberrations are measured, the subject's eyes are enlarged, and the operator or assistant pulls the upper eyelid if necessary.

4.4 Collection of blood/saliva specimens

5 ml of Blood/saliva specimens were collected. Blood/saliva specimens are temporarily stored in a portable refrigerator on site and transferred to a -80 °C deep-temperature refrigerator as soon as possible. The detection of serum riboflavin and related cytokine levels will be carried out in the Ophthalmology Laboratory of the Shanghai General Hospital affiliated to Shanghai Jiao Tong University.

4.5 Questionnaire

The questionnaire is divided into 5 parts:

- A. General information, including birth status (maternal pregnancy status, premature birth history, feeding status, etc.), family status (family history of myopia, family economic status, parental education level, parental physical condition, etc.), growth and development status, living and learning status (living environment, dietary status, sleep status, academic burden, academic performance, etc.), past medical history (including systemic and eye diseases);
- B. Quality of life for children with high myopia (NEI-VFQ-25 scale);
- C. High myopia children's psychology (NEI-VFQ-25 scale, depression self-assessment SDS, anxiety self-assessment table SAS, self-esteem scale SES);
- D. High myopia child behavior (NEI-VFQ-25 scale);
- E. Social interaction for children with high myopia (NEI-VFQ-25

scale).

The questionnaire is completed by the parent or guardian. Children and adolescents aged 10 or older are required to complete additional questionnaires to conduct self-evaluation on quality of life, psychology, behavior and social interaction. The questionnaires are mainly filled in online. For parents or children who are not convenient to fill out the questionnaire online, a paper-based questionnaire can be issued and collected after completion.

5. Organization and quality control of research

5.1 Drafting, revision and finalization of the plan

- A. The program was drafted by the Shanghai Eye Disease Prevention and Control Center. The draft is reviewed by the expert group, and the draft is discussed, revised, and finalized in the form of a seminar. The research plan was implemented after approval by the ethics committee.
- B. In the process of research implementation, if major revisions to the research plan are required, they must be submitted to the ethics committee for approval before further implementation.

5.2 Research institute

- A. The Shanghai Municipal Health Bureau and the Shanghai Municipal Education Bureau are responsible for the coordination of major issues.
- B. Shanghai third-level eye disease prevention and control system (city-district (county)-community) jointly guarantees the implementation of research
- C. The Shanghai Eye Disease Prevention and Control Center is the only municipal-level eye disease prevention and control institution in

Shanghai. It leads the city's 16 districts and counties and more than 240 community-level eye care institutions to jointly develop eye care services.

D. The Shanghai Eye Disease Prevention and Control Center can provide sufficient human resources for the research. Most of the inspection teams are staff members of the hospital and have extensive clinical experience. In addition, the Shanghai Eye Disease Prevention and Control Center has extensive experience in recruiting temporary volunteers.

5.3 Quality control and supervision

A. All participants in the study are required to be trained before the study is officially launched. The training content is printed as a work manual and distributed to researchers. The clinician, optometrist or technician who participates in the examination needs to learn the corresponding part of the work requirements, procedures, instrument use and operation specifications before going to work. After the passing examination, the official examination can be carried out. For items that are responsible by multiple people, it is necessary to complete the consistency test before the study is officially carried out to ensure that the results between different examiners are comparable.

B. All inspectors are only able to know the relevant parameters necessary for the inspection items they are responsible for, and remain blind for other irrelevant parameters.

C. The instrument should be calibrated before the start of the work on each inspection day.

D. Researchers responsible for quality control should regularly check the inspection data of each inspection post. The quality control

standards refer to the operating rules on the work manual. For those who have higher failure rate, they need to re-train and pass the examination before they can re-employ.

- E. Follow-up content and criteria were consistent with baseline. The equipment for follow-up examination is as close as possible to the baseline, and the examiner is as consistent as possible. If inspection instrument must be replaced due to the upgrad, the comparability of the old and new instruments should be evaluated.
- F. The follow-up interval was as consistent as possible.
- G. The reliability and validity of the questionnaire needs to be assessed before use.

5.4 Data entry, analysis and deletion

- A. The online data system is researched and developed by professional information technology companies, used to check real-time data entry, questionnaire filling, etc. The accuracy and completeness of the data is automatically determined by the data system.
- B. The entry of non-electronic data is done independently by two people.
- C. Data deletion and analysis were performed independently by two statisticians.

6. Statistical Analysis

6.1 Descriptive statistics

- A. Continuity variables: sample size, mean, standard deviation, minimum, maximum, quartile
- B. Classification variable or grade variable: frequency distribution

6.2 statistical methods

- A. Continuous variables: The normality test uses the Kolmogorov-

Smirnov test. If the normal distribution is satisfied, the t test or one-way ANOVA is used; if the normal distribution is not satisfied, the Mann-Whitney U test or the Kruskal Wallis test is used. The two-two comparison between groups was performed using the Bonferroni method.

- B. Categorical variable: chi-square test.
- C. Correlation analysis: simple linear regression and stepwise multiple linear regression, using nonlinear regression if necessary.

6.3 Statistical significance

All differences were statistically defined as $P < 0.05$ (bilateral)

6.4 Subgroup analysis

Subjects will be assigned to different subgroups for subgroup analysis based on age, gender, diopter, axial length, fundus structure, and functional changes.

6.5 Interim analysis

Baseline data (2018) and follow-up data for every 3 years are used for analysis and reporting.

7. Ethical issues

7.1 Ethics committee

The study will be carried out after the approval of the Shanghai General Hospital Ethics Committee and strictly abide by the Helsinki Declaration.

7.2 Protect the privacy of participants

In order to protect the privacy of the children and adolescents in

the test, when the research materials are provided to other organizations, the subject code or initials should be used instead of their ID number or real name. In addition, the researcher and the relevant staff involved in the research must keep the privacy information of the children and adolescents in the test confidential.

8. Funds and insurance

8.1 funds

Before the start of the study, funds were raised by the Shanghai Eye Disease Prevention and Control Center.

8.2 Compensation and insurance

If the subject is compromised by participating in the study and the damage is directly related to the research content, the research sponsor will provide the victim with the necessary treatment and compensation.

Research sponsors need to purchase commercial insurance for children and adolescents involved in the study and temporary workers involved in the study.

9. References

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