Supplementary Online Content


Trial protocol
A school-based randomized trial of the protective effect of time outdoors on the development of school myopia in Chinese children

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1. SCIENTIFIC ABSTRACT

Myopia is one of the most prevalent visual disorders affecting both children and adults. It imposes significant costs for optical or surgical correction, and uncorrected refractive errors may impose significant burden on children in terms of low vision, social capability and education achievement. Given the high prevalence of myopia in Chinese school-children, there is now an urgent need to define public health interventions capable of preventing the development of myopia, or slowing the progression of this disease. Recent studies have shown that less myopic refractive error is associated with more time spent on outdoor sport or other outdoor activities. However, cross-sectional or longitudinal studies, of the kind so far reported, were not able to demonstrate a causal effect of engagement in outdoor activities, because there was neither control group nor any intervention. This requires a controlled clinical trial. With a very high prevalence of myopia, China is an ideal location for such a trial. We propose to enroll 1,500 Grade 1 children from primary schools in Guangzhou, with the total number of 12 schools, 6 in each arm. This cohort will be drawn from an annual medical health checkup cohort that involve 30 primary schools in Guangzhou run by the Guangzhou Students’ Health Care Institute. Promoting outdoor activities will be implemented by adding one class session (approximately 40-45 minutes) of scheduled outdoor activities every day in school curricula and encouraging parents to engage their children in outdoor pursuits at leisure time and weekend. The refractive status, ocular biometry, and academic performance of the students will be investigated over the three-year follow-up period.

2. INTRODUCTION

2.1 Specific aims of project
The purpose of the proposed project is to assess whether outdoor activities are effective in preventing the development of juvenile-onset myopia in Chinese children. Specifically, we intend:

1. To determine if increased engagement in outdoor activities reduces the development of myopia in Chinese school children.
2. To identify the risk factors associated with the development and progression of juvenile-onset myopia.
3. To characterize the interaction between refractive error and education.

2.2 Background and relevance

Myopia, one of the most prevalent visual disorders affecting both children and adults {Resnikoff, 2004 #776}, is also the second leading cause of blindness {Resnikoff, 2008 #779}. An uncorrected refractive error may impose significant burdens on children in terms of social capability and educational achievement. Nowadays, uncorrected refractive error is receiving increasing global recognition as a significant cause of avoidable visual impairment, and has been included as one of the major eye diseases in the WHO Vision 2020 initiative {Pizzarello, 2004 #763}. It is imperative to plan corresponding public health strategies.

It has been well recognized that the incidence and progression rates of myopia are high in East Asians, particularly in those of Japanese {Watanabe, 1999 #1532} and Chinese ancestry {He, 2004 #639} {Zhao, 2000 #882} {Fan, 2004 #362} {Saw, 2005 #1533}. Furthermore, the prevalence and progress of myopia are greater in children with myopic parents {Mutti, 2002 #302} {Kurtz, 2007 #670}. This evidence is consistent with the idea that genetic factors may contribute a lot in the pathogenesis of
myopia. However, myopia is generally believed to have a multifactorial etiology, resulting from a combination of genetic and environmental factors, including those responsible for the urban-rural difference of myopia progression in people with similar genetic backgrounds {He, 2004 #639} {He, 2007 #637}.

Although near work has long been considered as an important environmental risk factor for the development of myopia, because of the obvious association between near work and accommodation {Goss, 2000 #1534}, previous detailed cross-sectional investigations revealed limited association between near-work time and myopia {Mutti, 2002 #302} {Saw, 2002 #798}. However, higher levels of outdoor activities have been shown to be possibly protective for myopia {Rose, 2008 #343} {Mutti, 2002 #302}. This association has been further demonstrated in longitudinal data in the Orinda longitudinal study {Jones, 2007 #659}. A recent study on 6 and 12 year-old Australian children has found that the protective effect might come from the total time spent outdoors rather than the sport per se {Rose, 2008 #343}.

However, these studies did not provide evidence that increased time spent outdoors can be used to reduce the incidence and progression of myopia, which requires a control group and an intervention, calling for a scientifically designed Controlled Clinical Trial that is able to comprehensively evaluate the effect of outdoor activities.

3. STUDY DESIGN

3.1 Study site and sample identification

Guangzhou, the capital city of Guangdong province, is the economic, cultural, and academic center of South China. According to a population census in 2008, it has a
The Guangzhou metropolitan region has been chosen for the survey because of its relatively stable population and representative demographic and socioeconomic characteristics, and because of the extensive data already available on prevalence of myopia in children and adults {He, 2004 #639}. Residents are of Han ethnicity (Chinese), and cover a wide socioeconomic spectrum.

In China, children normally start their formal primary school education at the age of 6 to 7. Before that, kindergarten or preschool attendance is voluntary. Since the 9-year compulsory education policy was introduced by the Chinese government in July 1986, school attendance rates have been increasing and are now very high. Thus, a sample representing the general population of Guangzhou children aged 6 to 7 can be drawn directly from school populations. Considering the period during which myopia develops and progresses significantly, the need of a high retention rate of the study cohort (younger students in primary schools are not likely to change schools) and the feasibility of comparison with data from other studies, primary school children at Grade 1 (aged 6 to 7) will be chosen.

The Guangzhou Students’ Health Care Institute takes the responsibility of performing annual medical health checkup for students in 30 primary schools in Guangzhou city. Participants in the proposed trial will be recruited from these schools.

### 3.2 Study sample size calculation

The cluster size is approximately 120, being the approximate number of students of Grade 1 in each school. The intra-class correlation coefficient (ICC) is assumed to be 0.01 and the precise matching of schools on the basis of visual acuity data allows a
low estimate of the inflation factor (IF) of 0.01. Based on an incidence rate in the control group of around 10% per year from Grade 1 to 4 {He, 2004 #639}, enrolling 6 schools in each are with a total of approximately 1,500 students, will provide sufficient power to detect a reduction of about 50% incidence for the intervention compared to the control arm.

3.3 School matching and randomization

All the schools will be stratified by the prevalence and progression of normal version (uncorrected visual acuity ≥ 20/25), using Guangzhou Students’ Health Care Institute established data. Here, prevalence refers to the percentage of students with normal visual acuity and progression refers to the decrease of prevalence from Grade 1 to Grade 6. A total of 6 strata will be established. In each stratum, two schools will be randomly selected and allocated to intervention arm and control arm.

3.4 Recruitment and informed consent

Once the school matching and randomization procedure complete, 6 schools in the intervention arm will be awarded the title of “Myopia Prevention Trial Model School”. With the assistance of the Guangzhou Education Bureau and the Guangzhou Students’ Health Institute, information sessions will be conducted for school principals and teachers. Before the baseline data collection, written informed consent will be obtained for all participants from either parents or guardians. Further attempts will be made by contacting the parents once if they initially refuse to give consent.

3.5 Intervention

For schools in the intervention arm, one class session of outdoor activity per day will
be added after the last class in the afternoon (approximately 4:00-5:45 pm). An outdoor activity program brochure will be distributed to participating classes, which includes guidelines, suggestions for outdoor activities, and sample schedules. Head teachers will be responsible for organizing the supervising outdoor classes.

In addition, parents and families will be encouraged to engage their children in a variety of outdoor pursuits such as sports and picnic in their spare time including weekend. Children will be provided with school bags with special outdoor logos. Parents will be provided with periodical newsletters.

Control schools will continue with their normal patterns of activity.

3.6 Quality control and validation test

In order to maximize intervention compliance, study staff will go, at random, to two of the six intervention schools each day to inspect the outdoor classes, without prior notice. Details of compliance will be recorded. Those with low compliance will be warned and given instructions to change.

4. FIELD WORK PROCEDURES

4.1 Baseline examinations

At the baseline visit, all of the measurements will be performed. The family questionnaires and risk factor questionnaires will be issued and later collected by the teacher after being satisfactorily completed by parents. Information sessions for parents are organized in each school in order to make sure the parents fully understand the project and understand how to respond correctly on the questionnaire.
The design of examinations and procedures of this study is based on the Guangzhou Twin Study {He, 2006 #1030}. Non-contact (IOLMaster) technology will be used to record ocular biometric measures. Protocols for the various procedures are outlined below.

1. Anthropometry

The children’s weight, height, blood pressure, waist–hip ratio, arm circumference and triceps skin fold thickness will be measured.

2. Visual Acuity

Distance visual acuity will be measured using an ETDRS chart (Precision vision, Villa Park, Illinois, USA) with standard illumination. Visual acuity measurement is performed at a distance of 4 meters. Uncorrected visual acuity will be measured for all children. If spectacles are normally worn or worn at presentation, visual acuity will also be measured with corrections. If the child presents with glasses, the power of the lenses will also be measured. If the presenting visual acuity is worse than 6/12 in either eye, the visual acuity testing will be repeated for each eye (one eye at a time), to determine the best-corrected visual acuity using the autorefraction result and necessary refinement. The protocol used in the Refractive Error Study in Children (RESC) study will be applied.

3. Cover test and ocular dominance

Cover-uncover tests will be used to identify any tropia. Ocular dominance will be assessed using the hole-in-the-card test. In the test, children view a centrally placed
target set at 6 m away through a 3-cm hole in a card held with both hands at arm’s length. The right eye of each child will be covered. If the target disappears, then they will be identified as fixing with the right eye. If it does not disappear, the left eye will be identified as the dominant eye.

4. Noncycloplegic autorefraction
Noncycloplegic autorefraction will be performed before cycloplegia induced with cyclopentolate. Auto-refraction (Nikon Retinomax autorefractor) is taken on both eyes by experienced optometrists. An auto-refractor is used to obtain three consecutive, reliable readings after cycloplegia. The child is required to sit in front of the auto-refractor and look at the target, which is designed to minimize accommodation. Measures are taken on the right eye first, followed by the left eye after cycloplegia. The reliability of each measure is indicated by an automatic numeric assessment provided by the auto-refractor.

5. Cycloplegia
Cycloplegia will be induced with three drops of 1% cyclopentolate administered at 0, 5th, 20th minute to each eye, respectively. The light reflex and pupil dilation will be checked after an additional 15 minutes. Dilation and light reflex status will be recorded and full cycloplegia will be justified if the pupil dilates to 6 mm or greater and the light reflex is absent.

6. Ocular Biometric Measurements by IOL Master
During the waiting time for the pupil dilation, IOL Master is used to measure the axial length of both eyes. Five measures are taken for each eye. The axial length
measurement is based on the mean of these five values if the desired precision (i.e., <0.1 mm) is achieved. Prior to the beginning of data collection, study examiners should demonstrate good consistency of axial length measurements suggesting that these measures are reliable.

7. Cycloplegic auto-refraction

Cycloplegic auto-refraction is selected as the measure of refractive error because of its accuracy, reliability, and objectivity, thus allowing for standardization of measurements over time within and across schools. The same protocol used in noncycloplegic autorefraction will be applied.

8. Subjective Refraction

Subjective refraction will be performed on children with an uncorrected visual acuity 20/40 or worse, using autorefraction values as a starting reference, in order to exclude the children with amblyopia.

9. Direct ophthalmoscopic examination

Ophthalmoscope will be used to exam the anterior segment, lens, vitreous and fundus, specific abnormalities will be recorded.

When all examinations were completed, reading glasses were provided to children with cycloplegia free of charge to minimise difficulties with nearwork associated with cycloplegia. The reading glasses were collected by head teachers after three days.

4.2 Summary flow chart
All testing will follow the order as above starting with the body measurements. The final part of the visit is the direct ophthalmoscopic examination. The flow chart summarizing the clinical measurement process is shown in Annex II. The flow chart showing the overall procedure of the trial is shown in Annex I.

4.3 Follow-up Examinations

Follow-up examinations will be performed annually. Examinations for follow-up visits will be exactly the same as the baseline visit with the same examiner and the same set of equipment with proper calibration.

4.4 Related information collection

The related information will be collected using questionnaires and some tests.

1. Family Questionnaire

Questionnaires for parents on their ethnicity, socioeconomic status, education level, occupations, refractive status, family history of ocular conditions and other related information will be administered. Children's learning behavior in home will be reported in this questionnaire.

2. School/Class Curricula Questionnaire

The grade leader teacher/head teacher of each class involved will be asked to fill out a questionnaire about the curriculum (e.g., school days, school holidays) and attach the curriculum schedule.

3. Learning Behavior Questionnaire
Children’s learning behavior including class rank, performance in class, homework accomplishment etc will be reported by the head teacher of each class. This questionnaire will be administrated annually.

4. Risk Factors Questionnaire

Parents will also be asked to complete the questionnaire on children’s near work and outdoor activities. This questionnaire will record the detailed activities typically in weekdays and weekends, the responses regarding the time spent on activities will be validated against a 24-hour clock. The questionnaire applied in our study is a standard questionnaire developed by a group of myopia researchers convened by the World Health Organization in Singapore, which has been adopted in several on-going WHO-sponsored longitudinal studies on myopia in children (e.g.: the RESC studies).

5. School Achievement

Standardized exams (literature + math) will be organized for the involved students every academic year.

6. Constitution

The Students’ Health Care Institute will collect data on the physical health parameters every year, such as 100 meter run, jump on spot. The test protocol and standard for evaluation are uniform in the 30 schools.

5. DATA ENTRY AND ANALYSIS

Study personnel will be trained and certified before collecting study data. Data processing is centralized and concurrent. Two independent, certified data entry
personnel will input data into two separate files, which will be compared by an adjudication program.

5.1 Data source: Guangzhou Outdoor Activity Longitudinal (GOAL) Study baseline and annual follow-up data.

5.2 Study population
- Definition: all participants in the GOAL Study.
- Number of participants: Grade 1 students in 12 primary schools in Guangzhou;
- Duration of study: 2010 (baseline) to 2013 (3rd follow up year).
- Inclusion/exclusion criteria: all participants in the GOAL study, excluding those with ocular conditions (e.g. amblyopia, tropia) and other systemic conditions (e.g. mental retardation).

5.3 Study measurements
- All participants attended annual follow-up examination every year.
- Ocular examinations: visual acuity, cover-uncover tests, cyclopegic auto-refraction, ocular biometry.
- Questionnaires: family socio-economic status, family myopic status, parental education, children’s learning behaviours and daily activities.
- Other examinations: height, weight, arm circumference, triceps skin fold thickness.

5.4 Data cleaning
- Examination forms and questionnaires are reviewed for accuracy and completeness before data entry at the Zhongshan Ophthalmic Centre.
- Measurement data ranges, frequency distribution and consistency among related measurements are checked with data cleaning programs.
One eye per child will be included in data analysis (right eye). If data for right eye are not available, data for left eye will be used.

Missing data: missing data are due to students missing follow-up examinations. Mixed model will be used to handle missing data.

5.5 Data definition

- **Primary outcome**: cumulative increase in percentage of incident myopia in the intervention and control arms over 3 years.
- **Secondary outcome**: changes in mean SER and AL over 3 years.
- **Definition and derivation**: myopia should be defined as a SER (sphere + ½ cylinder) of at least -0.5 dioptres (D). Incident myopia is defined as myopia detected in those who were not myopic at baseline.

5.6 Sequence of planned analyses, including:

- Descriptive analysis for baseline data (t-test, Mann-Whitney test or Chi-square tests, where applicable).
- Differences in cumulative incident myopia in the two arms (Chi-square tests or mixed model).
- Changes in SER and AL between intervention and control arms (mixed effect models with covariates adjustments; treatment assignment, time and [treatment×time] will be included as fixed effects); intention-to-treat principles will be applied.
- Descriptive analysis for time spent outdoors outside school hours at baseline and follow-up visits (t-test or Mann-Whitney test, where applicable)

5.7 Analysis software: Stata (Version TBD)
6. QUALITY ASSURANCE

Data quality and integrity will be assured by the following measurements:

1. All of the data collection protocols are standardized throughout study documentation, uniform study protocols and forms, study personnel are trained and certified before examination and collecting study data;

2. The responses regarding the time spent on activities of the Risk Factor Questionnaire will be validated against a 24-hour clock, and obviously inaccurate answers will be checked by telephone interviews;

3. In the intervention group, teachers who are responsible for supervising the outdoor activity time will be given some extra pay. Other incentives will be given to children annually if needed. Interviews with the Risk Factor Questionnaire will be performed annually to compare changes in the patterns of activity of the children.
Stratify schools by prevalence and progression of low VA

Match schools in pairs

Enrollment and Conformed consent

Baseline Examinations

Outdoor Intervention

Compliance Supervision

Follow-up visit (1 year ×3)

Baseline Examinations

No Intervention

No Compliance Supervision

Follow-up visit (1 year ×3)
ANNEX II

SUMMARY FLOW CHART OF FIELD EXAMINATIONS
Examination Enrolment
   ↓
Anthropometry
   ↓
Visual Acuity
   ↓
*Cover test and ocular dominance
   ↓
Non-cycloplegic auto-refraction
   ↓
Dilation with 1% Cyclopentolate
   ↓
**Ocular Biometric Measurements
   ↓
Auto-refraction
   ↓
Subjective Refraction
   ↓
Slit-lamp examination

* Only performed in baseline examination

** Some uncompleted anthropometry measurements can be performed when waiting
for the pupil dilation