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## Increased intermittent exotropia in preschool children: a comparison in eastern China at a 5-year interval

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| Complete List of Authors: | Wang, Yue; The First Affiliated Hospital with Nanjing Medical University, Ophthalmology; Nanjing Medical University  
Zhao, Andi; The First Affiliated Hospital with Nanjing Medical University, Department of Ophthalmology; Nanjing Medical University  
Zhang, Xiaohan; Wuxi Children's Hospital, Ophthalmology  
Huang, Dan; The First Affiliated Hospital with Nanjing Medical University, Department of Child Healthcare  
Zhu, Hui; The First Affiliated Hospital with Nanjing Medical University, Department of Ophthalmology; Nanjing Medical University  
Sun, Qigang; Maternal and Child Healthcare Hospital of Yuhuatai District Nanjing China, Ophthalmology  
Yu, JiaJia; Wuxi No. 2 People's Hospital  
Chen, Ji; Maternal and Child Healthcare Hospital of Yuhuatai District Nanjing China, Ophthalmology  
Zhao, Xiaoyan; The Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, Ophthalmology  
Li, Rui; The First Affiliated Hospital with Nanjing Medical University, Department of Ophthalmology; Nanjing Medical University  
Han, Shu; Soochow University Affiliated Children's Hospital, Ophthalmology  
Dong, Weiyi; Fourth School of Clinical Medicine of Nanjing Medical University  
Ma, Fanfei; Fourth School of Clinical Medicine of Nanjing Medical University  
Chen, XueJuan; The First Affiliated Hospital with Nanjing Medical University, Department of Ophthalmology; Nanjing Medical University  
Liu, Hu; The First Affiliated Hospital with Nanjing Medical University, Department of Ophthalmology; Nanjing Medical University |
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Title page

Increased intermittent exotropia in preschool children: a comparison in eastern China at a 5-year interval

Yue Wang\textsuperscript{1,2\dagger}, Andi Zhao\textsuperscript{1,2\dagger}, Xiaohan Zhang\textsuperscript{3\dagger}, Dan Huang\textsuperscript{4}, Hui Zhu\textsuperscript{1,2}, Qigang Sun\textsuperscript{5}, JiaJia Yu\textsuperscript{6}, Ji Chen\textsuperscript{5}, Xiaoyan Zhao\textsuperscript{7}, Rui Li\textsuperscript{1,2}, Shu Han\textsuperscript{8}, Weiyi Dong\textsuperscript{9}, Fanfei Ma\textsuperscript{9}, Xuejuan Chen\textsuperscript{1,2\ast}, Hu Liu\textsuperscript{1,2\ast}

\textsuperscript{\dagger} Yue Wang, Andi Zhao and Xiaohan Zhang Andi Zhao contributed equally to the study and they should be regarded as joint first authors.

\textsuperscript{1}Department of Ophthalmology, The First Affiliated Hospital with Nanjing Medical University, Nanjing 210029, China;

\textsuperscript{2}Nanjing Medical University, Nanjing 211166, China;

\textsuperscript{3}Department of Ophthalmology, The Affiliated Wuxi Children's Hospital of Nanjing Medical University, Wuxi 214000 China;

\textsuperscript{4}Department of Child Healthcare, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China

\textsuperscript{5}Department of Ophthalmology, Maternal and Child Healthcare Hospital of Yuhuatai District, Nanjing, China

\textsuperscript{6}Department of Ophthalmology, Wuxi No. 2 People's Hospital, Wuxi, China

\textsuperscript{7}Department of Ophthalmology, The Affiliated Changzhou No.2 People’s Hospital of Nanjing Medical University, Changzhou 213164, China;

\textsuperscript{8}Department of Ophthalmology, Children's Hospital of Soochow University, Suzhou 215025, Jiangsu, China
*The Fourth School of Clinical Medicine of Nanjing Medical University, Nanjing 210029, China

*To whom correspondence should be addressed:

Hu Liu & Xuejuan Chen

Department of Ophthalmology, the First Affiliated Hospital with Nanjing Medical University, 300 Guangzhou Road, Nanjing 210029, China.

Email address: liuhu@njmu.edu.cn and chenxuejuan@vip.163.com

Tel: +86 (25) 68136470, Fax: +86 (25) 68136470

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ABSTRACT

Objective: To update strabismus data and evaluate changes in prevalence and patterns among preschoolers in eastern China over a period of five years.

Design: Nanjing Eye Study, a longitudinal population-based study.

Setting: Recruitment and testing in kindergartens in Yuhuatai District, Nanjing.

Participants: 2,300 eligible children.

Main outcome measures: Comprehensive ocular examinations were conducted in 1986 children aged 48 to < 60 months in Nanjing Eye Study (NES, 2016 to 2017), including visual acuity, ocular alignment, refractive error and ocular structures evaluation. The prevalence rate and pattern of strabismus were calculated and compared to those from the Nanjing Pediatric Vision Project (NPVP, 2011 to 2012) in the same age children of the same area using the same diagnostic criteria.

Results: The overall prevalence rate was 5.56% (95% CI 4.54% to 6.57%) for strabismus in NES. The prevalence rate was not significantly different from that in NPVP (p = 0.40). The subtype proportion of strabismus underwent changes. The prevalence of intermittent exotropia (IXT) significantly increased in NES (2.78% vs. 4.69%, p = 0.001), whereas the prevalence of constant exotropia was only one-tenth of that in NPVP (1.17% vs. 0.15%, p < 0.001). Significant pattern change was observed in IXT, where convergence insufficiency type (2.90% vs. 27.17%) increased and exceeded divergence excess type (20.29% vs. 11.96%) to be the second common type (p < 0.001).

Conclusion: The prevalence of strabismus appeared stable in children aged 48 to < 60
months in eastern China at a 5-year interval. The prevalence of IXT increased significantly, and convergence insufficiency type became more prevalent in IXT patients. Timely IXT detection and intervention are important among preschoolers.

**Key words:** strabismus; intermittent exotropia; vision care; preschool children

**Strengths and limitations of this study**

As a part of Nanjing eye study (NES), this study is a population-based study, comprising 1986 preschoolers aged 48 to <60 months.

Strabismus was identified based on the comprehensive eye examination on every preschooler by a trained team.

This report updated the strabismus epidemiological data among preschoolers in eastern China and compared them to those from the Nanjing Pediatric Vision Project (NPVP), which was conducted five years ago.

Both NPVP and NES had high participating rates (> 80%) and used the same diagnostic criteria as MEPEDS, allowing a direct comparison between them to evaluate changes in strabismus in Chinese preschool children.

The prevalence estimate might be biased due to poor cooperation of young children and recall bias on strabismus history.
INTRODUCTION

Strabismus is a common ocular disorder in childhood, which can lead not only to cosmetic impairment but also to loss of binocularity and depth perception. The negative influences of this early-onset visual developmental disorder can persist into adulthood if left untreated. Identifying strabismus at an earlier age may prevent the development of strabismic amblyopia as well as improve the chance of restoring binocularity, highlighting the importance of early detection and timely interventions of strabismus. And an accurate estimate of the strabismus epidemiology would provide guidance for children strabismus screening and control in early age.

So far, several population-based studies, including Baltimore Pediatric Eye Disease Study (BPEDS), Multiethnic Pediatric Eye Disease Study (MEPEDS), the Strabismus, Amblyopia and Refractive Error in Singapore (STARS) Study and Vision in Preschoolers (VIP) study, reported the prevalence rate of strabismus vary from 1% to 4.6% in preschoolers and revealed the disparities of prevalence and pattern in different world regions and ethnic populations. However, these cross-sectional studies only captured a snapshot of the ocular disorder at a single point of time. Due to changes in the natural environment, social economy, people’s lifestyle as well as vision care system, studies for evaluating their change over time in prevalence and characteristics of ocular diseases are needed to help obtain valuable feedback for ongoing vision care efforts, bringing the next stage targeted approaches and improvement directions. This will help us to accomplish objectives for eliminating the main causes of all preventable and treatable blindness set forth in “Vision 2020”.8
From 2011 to 2012, we conducted the Nanjing Pediatric Vision Project (NPVP) to assess the prevalence and associated risk factors of amblyopia, strabismus, and vision disorders in 5,667 preschoolers aged 36-72 months. Among total of 2,486 children aged 48 to < 60 months involved, we found the strabismus prevalence rate of 4.99%. In 2016, Nanjing Eye Study (NES) was carried out in the same age children and the same area using the same study procedure and diagnostic criteria. In this study, we assessed the prevalence of strabismus and its subtypes in NES and compared them with NPVP. The aim of this study is to update the prevalence rate of strabismus and evaluate its changes among preschoolers in eastern China over a 5-year period.
METHODS

Study design and population

NES is a population-based cohort eye study, which is targeted at longitudinally observing the initiation and progression of childhood ocular diseases by establishing a systematic database in eastern China. Of all children in Yuhuatai District, those who were born between September 2011 and August 2012 and on the point of entering a kindergarten, were invited to take part in this study to have a comprehensive eye examination annually. Data in the present study was obtained from 2016 to 2017 when these children were 48 - < 60 months old. Among 2300 eligible preschoolers, 1986 (response rate 83.5%) children participated in this study. NPVP was a cross-sectional, population-based cohort study conducted from 2011 to 2012. Of all participants, 2486 children aged 48 to < 60 months were involved in the present study for comparison. The study was approved by the Ethics Committee, Nanjing Medical University and followed the tenets of the Declaration of Helsinki.

Ocular examination

In both NES and NPVP, a comprehensive eye examination was performed on participants by a team composed of trained ophthalmologists and optometrists using similar protocols as MEPEDS, including anthropometric parameters, ocular biometric parameters, distance visual acuity, anterior segment, refractive error, stereoacuity test and ocular alignment and motility. The Hirschberg light reflex test was performed to assess ocular alignment at a distance of 33 cm, followed by the cover-uncover test and the alternate cover test with fixation targets at distance of 33 cm and 6 m, with or
without correction (if wore). Monocular and binocular ocular movements were examined at nine diagnostic positions of gaze. An alternate prism cover test was used to detect the degree of eye misalignment of participants suspected with strabismus. Once strabismus was suspected, a prism cover test was used to detect the degree of eye misalignment. If the participant was suspected with IXT, one eye was covered with thick gauze to break tenacious proximal fusion between the two eyes for at least 30 min, and then an alternate prism cover test was performed to assess the degree of exotropia.

Definitions

Strabismus was defined if any tropia was present at distance or near, with or without spectacles and then classified according to the primary direction (esotropia, exotropia, vertical) of the tropia. Strabismus is considered as constant if constant at both near and distance fixation, otherwise it is considered as intermittent. Intermittent exotropia was defined as an intermittent exodeviation of at least 10 prism diopters (PD) at a distance. According to the Burian’s classification, IXT is classified into four subtypes based on the difference between the distant (6m) and the near (33cm) angles of deviation: “basic type” (difference < 10PD), “convergence weakness type” (near angle minus distant angle ≥ 10PD), “pseudo divergence excess type” (distant angle minus near angle ≥ 10PD but < 10PD after 30 min monocular patching), and “true divergence excess type” (distant angle minus near angle ≥ 10PD even after patching). In this study, all IXT suspects had one of their eyes patched before the alternative prism cover test. Therefore,
the “pseudo divergence excess type” was counted in the “basic type” category in this analysis.

Microstrabismus was defined as a deviation of less than 10 prism diopters, in addition to binocular vision. Children with history of strabismus or treatment were regarded as strabismic.

**Statistical analyses**

Statistical analyses were performed using the IBM SPSS V13.0 (www.ibm.com). All statistical tests were two-sided, and P < 0.05 was considered statistically significant. T-test was used to compare means. Prevalence rates strabismus and its subtypes were calculated for NES and NPVP and compared between two studies using chi-square test and fisher’s exact test. The 95% confidence intervals (CI) for prevalence rates were calculated using normal approximation.

**Patient and public involvement**

Patients and the public were not involved in any aspects of the study, including the development of study question, study design, conduct of the study and dissemination of results.

**RESULTS**

**Prevalence of strabismus in NES and comparison with NPVP**

In NES, a total of 1,986 children aged 48 to < 60 months underwent ocular examinations, of them, 25 were excluded due to incomplete data. The detailed characteristics of participants had been described in previous published articles.10,11 A total of 109 children were diagnosed with strabismus in NES with an overall
prevalence of 5.56% (95% CI 4.54% to 6.57%). The prevalence of concomitant esotropia and concomitant exotropia was 0.56% (95% CI 0.23% to 0.89%) and 4.84% (95% CI 3.89% to 5.79%), respectively (Table 1). There was no statistical gender difference in overall strabismus prevalence (5.95% vs. 5.08%, p = 0.40), concomitant esotropia (0.74% vs. 0.34%, p = 0.36); or concomitant exotropia (5.02% vs. 4.63%, p = 0.69).

Among 109 strabismic preschoolers in NES, two presented normal ocular alignment but with strabismus surgery histories (1 esotropia and 1 exotropia preoperative). In terms of pattern of strabismus, 11 had concomitant esotropia, 95 had concomitant exotropia, 1 had pure vertical strabismus (superior oblique muscle palsy), and 2 had special forms of strabismus (1 Duane syndrome and 1 Brown syndrome). Four exotropia cases were combined with vertical deviation (3.7%, 4/109). The most frequent strabismus type was IXT (84.4%; 92/109), followed by constant esotropia (10.1%; 11/109), constant exotropia (2.8%; 3/109) and special forms of strabismus (1.8%; 2/109), and vertical deviation (0.9%; 1/109) accounted for the least (Figure 1).

Comparison between NES and NPVP

Table 2 showed comparisons of the characteristics of strabismic children between NPVP and NES. The prevalence of strabismus (p = 0.40) and exotropia-esotropia ratio (p = 0.33) were similar in two studies. Statistically significant difference was observed between two studies in the pattern of horizontal strabismus (p < 0.001), driven by lower prevalence of constant exotropia in NES than NPVP (0.15% vs. 1.17%, p < 0.001) and higher prevalence of IXT in NES than NPVP (4.69% vs. 2.78%, p = 0.001). The
proportion of subtype of IXT was different between two studies (p < 0.001), with convergence weakness accounted for larger proportion in NES than NPVP (27.2% vs. 2.9%, p < 0.001). Twenty of 109 (18.4%) NES strabismic children were reported having previous treatment, which was similar to NPVP (16.9%, p = 0.78). Treatment rate was higher in NES than NPVP for esotropia (90.9% vs. 47.1%, p = 0.04) while remained stable for exotropia (10.5% vs. 12.2%, P = 0.71). The mean spherical equivalent refraction (SER) of strabismic children was 0.97 ± 1.86 D in NES and 1.72 ± 1.78 D in NPVP. Statistically significant differences in SER were found in strabismic children between two studies, with strabismic children in NPVP having more hyperopic SER than in NES (P = 0.003).
DISCUSSION

In this population-based study, we reported an overall prevalence rate 5.56% for strabismus in children aged 48 to < 60 months in eastern China. The overall concomitant esotropia and exotropia prevalence rates are 0.56% and 4.84%, respectively, with IXT as the most common type of strabismus. Compared with the NPVP study that we carried out five years ago with same study protocol in the same area, no significant difference was found in the prevalence of amblyopia or strabismus. However, the prevalence of IXT has significantly increased in NES, whereas the prevalence of constant exotropia is only one-tenth of that reported in NPVP.

Both NPVP and NES had high participating rates (> 80%) and used the same diagnostic criteria as MEPEDS, allowing a direct comparison between them to evaluate changes in strabismus in Chinese preschool children. Our data showed that the prevalence of strabismus appeared stable over the past 5 years. An Israeli investigation found a decline in the prevalence of young adulthood strabismus from 1974 to 1994, which might be due to a better diagnosis and treatment in the pediatric population.16 Taken into consideration that our analyses did not exclude those who had been successfully treated, we believed that our results tended to reflect the natural change in strabismus experience in this area. Our previous study found a rate of reduced UCVA increased significantly in a five-year interval, which was likely due to the influence of some environmental risk factors, such as more use of mobile devices.10 Conversely, the steady trend in strabismus rate in the present study indicated that genetic factors might play a more important role in the advert of strabismus in early life.

The prevalence of strabismus in NPVP or NES in 48 to < 60-month-old children was
similar to those reported in other studies. However, exotropia-esotropia ratio was the highest among those investigations (Table 3), which is in line with the high exotropia-esotropia ratio reported by several studies based on East Asian populations. This ratio has increased over the past 5 years, from 5.8 to 8.6, but no significant difference was found. Nevertheless, the subtype proportion in exotropia underwent an obvious transition. An increase in the proportion of patients with IXT was observed while constant exotropia became less common in NES. A previous Hong Kong study reported a similar increasing trend in IXT accompanied by an apparent decline in esotropia. On the contrary, the prevalence of esotropia appeared stable in our study. Hong Kong study attributed this change to the increasing prevalence of myopia.17-20 We observed a declining trend in SER that strabismic children in the NES were less hyperopia than NPVP. Given that myopia is not the predominant refractive error in strabismic preschoolers,21 this explanation may not be appropriate in our study. Taken together opposite change in IXT and constant exotropia, we inferred that regular vision screening and timely intervention might reduce the risk of deterioration of IXT and thus drop constant exotropia share. In addition, improved pregnant and prenatal care might play a role as well.22 23 It is noteworthy that the prevalence of esotropia was lower than that reported in other studies (Table 3) and had a slight decrease over the past 5 years. Besides the contributions by widespread ethnic and regional disparity, early significant hyperopia correction likely played a role in preventing children with hyperopia from developing esotropia in this population.

The basic type was found to be the most common IXT subtype in both NPVP and NES.
Notably, proportion of convergence insufficiency increased and exceeded divergence excess to be the second major type of IXT in NES. So far, few population-based studies had studied the subtypes of IXT. Since the increased prevalence of IXT had been found in this area, investigations on causes and characteristics are of great importance to broaden our understanding of IXT. Chia et al. in their hospital-based study, reported that divergence excess IXT was the major subtype. However, lacking patching in Chia’s methodology might over-estimate the amount of divergence excess cases. All children in NPVP and NES suspected with IXT had one of their eyes patched before examinations and thus increased the accuracy of IXT classification by weakening the influence of tenacious proximal fusion. Consistent with our study, a Korean hospital-based investigation also found convergence insufficiency was the second common subtype in IXT. The reason for pattern changes in IXT is unknown, future investigation on causes and characteristics in IXT is warranted.

NPVP and NES had similar treatment rates for strabismus, almost one in five strabismic children had treatment before our examination. So far, few studies directly reported treatment rates, making comparison difficult. Although no significant difference between NES and NPVP was found in the overall treatment rate, a significant increase in esotropia treatment rate was found. Vision screening in preschoolers from the Yuhuatai district had been performed earlier than other communities in China. Early detection and timely referral had achieved good outcomes, which would be a likely explanation for the rise in esotropia treatment rate. Given early diagnosis and treatment are associated with a better outcome in strabismus, more efforts ought to be paid on
comprehensive screening, timely referral and standardized correcting.

The strengths of this study including the large sample of 48 to < 60-month-old preschoolers in two studies from the same area that followed standardized protocols for comprehensive eye examinations, and used the same diagnostic criteria, allowing us to reliably assess the prevalence changes in amblyopia and strabismus in 5-year interval. However, our study has some limitations. Firstly, poor cooperation of these very young children may lead to underestimate the overall prevalence of strabismus. Secondly, data on the history of strabismus came from questionnaires responded by parents, which could have recall biases.

**Conclusion**

In summary, the NES found an overall prevalence rate of 5.56% for strabismus in children aged 48 to < 60 months in eastern China. The prevalence of strabismus appeared stable but the pattern of strabismus underwent significant changes over the past 5 years comparable to our previous NPVP study. The prevalence of IXT increased significantly, and the high exotropia-esotropia ratio was the most noteworthy feature in this area. More vision screening and care efforts should be paid on IXT detection and intervention in the future.
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Contributors Liu H and Chen X designed the study. Wang Y, Zhang X and Zhao A wrote the main manuscript text. Wang Y, Zhang X and Li R prepared tables. Wang Y, Zhang X, Huang D, Han S, Zhu H and Zhao X performed data interpretation and analysis. Wang Y, Zhang X, Sun Q, Chen J, Yu J, Dong W and Ma F performed the ocular examinations.

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Competing interests None declared.

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Table 1. Prevalence and characteristics of strabismic children in NES

| Characteristics               | Without strabismus, N | With strabismus, N | Prevalence (%) (95%CI) |
|-------------------------------|-----------------------|--------------------|------------------------|
| **Gender**                    |                       |                    |                        |
| Any strabismus                |                       |                    |                        |
| Male                          | 1011                  | 64                 | 5.95 (4.54 to 7.37)    |
| Female                        | 841                   | 45                 | 5.08 (3.63 to 6.52)    |
| Overall                       | 1852                  | 109                | 5.56 (4.54 to 6.57)    |
| **Concomitant esotropia**     |                       |                    |                        |
| Male                          | 1067                  | 8                  | 0.74 (0.23 to 1.26)    |
| Female                        | 883                   | 3                  | 0.34 (0 to 0.72)       |
| Overall                       | 1950                  | 11                 | 0.56 (0.23 to 0.89)    |
| **Concomitant exotropia**     |                       |                    |                        |
| Male                          | 1021                  | 54                 | 5.02 (3.72 to 6.33)    |
| Female                        | 845                   | 41                 | 4.63 (3.24 to 6.01)    |
| Overall                       | 1866                  | 95                 | 4.84 (3.89 to 5.79)    |
| **Types**                     |                       |                    |                        |
| Concomitant strabismus        | 1855                  | 106                | 5.41 (4.40 to 6.41)    |
| Esotropia                     | 1950                  | 11                 | 0.56 (0.23 to 0.89)    |
| Constant                      | 1950                  | 11                 | 0.56 (0.23 to 0.89)    |
| Intermittent                  | 1961                  | 0                  | 0                      |
| Exotropia                     | 1866                  | 95                 | 4.84 (3.89 to 5.79)    |
| Constant                      | 1958                  | 3                  | 0.15 (0 to 0.33)       |
| Intermittent                  | 1869                  | 92                 | 4.69 (3.76 to 5.63)    |
| Basic                         | 1905                  | 56                 | 2.86 (2.12 to 3.59)    |
| Convergence insufficiency     | 1936                  | 25                 | 1.27 (0.77 to 1.87)    |
| Divergence excess             | 1950                  | 11                 | 0.56 (0.23 to 0.89)    |
| Microtropia                   | 1961                  | 0                  | 0                      |
| Vertical deviations           | 1960                  | 1                  | 0.05 (0 to 0.15)       |
| Special forms of strabismus   | 1959                  | 2                  | 0.10 (0 to 0.24)       |

N, number.
Table 2. Comparison of strabismic children aged 48 – < 60 months in NPVP and NES populations

| Characteristics                                      | NPVP     | NES     | P       |
|------------------------------------------------------|----------|---------|---------|
| Gender, N (%)                                        |          |         | 0.98    |
| Male                                                 | 73 (58.9%) | 64 (58.7%) |         |
| Female                                               | 51 (41.1%) | 45 (41.3%) |         |
| Prevalence of strabismus                             | 4.99     | 5.56    | 0.40    |
| Prevalence of concomitant esotropia                  | 0.68     | 0.56    | 0.61    |
| Prevalence of concomitant exotropia                  | 3.94     | 4.84    | 0.14    |
| Prevalence of constant exotropia                     | 1.17     | 0.15    | <0.001  |
| Prevalence of IXT                                    | 2.78     | 4.69    | 0.001   |
| XT:ET ratio                                          | 5.8:1    | 8.6:1   | 0.33    |
| Subtypes of concomitant horizontal strabismus, N (%) |          |         | <0.001* |
| Constant esotropia                                   | 14 (12.2%) | 11 (10.4%) |         |
| Intermittent esotropia                               | 3 (2.6%)  | 0 (0)   |         |
| Constant exotropia                                   | 29 (25.2%) | 3 (2.8%)  |         |
| IXT                                                  | 69 (60.0%) | 92 (86.8%) |         |
| Subtypes of IXT, N (%)                               |          |         | <0.001  |
| Divergence excess                                    | 14 (20.3%) | 11 (12.0%) |         |
| Convergence weakness                                 | 2 (2.9%)  | 25 (27.2%) |         |
| Basic                                                | 53 (76.8%) | 56 (60.8%) |         |
| Mean SER in strabismic children, D                   | 1.720 ± 1.779 | 0.971 ± 1.863 | 0.003   |
| History of strabismus treatment, N (%)               |          |         | 0.78    |
| Yes                                                  | 21 (16.9%) | 20 (18.4%) |         |
| No                                                   | 103 (83.1%) | 89 (81.6%) |         |
| History of esotropia treatment, N (%)                 |          |         | 0.041*  |
| Yes                                                  | 8 (47.1%)  | 10 (90.9%) |         |
| No                                                   | 9 (52.9%)  | 1 (9.1%)  |         |
| History of exotropia treatment, N (%)                 |          |         | 0.71    |
| Yes                                                  | 12 (12.2%) | 10 (10.5%) |         |
| No                                                   | 86 (87.8%) | 85 (89.5%) |         |

NPVP, Nanjing Pediatric Vision Project; NES, Nanjing Eye Study; N, number; IXT, Intermittent exotropia; XT, exotropia; ET, esotropia; SER, Spherical equivalent refraction; D, degree.

Bold print represents statistical significance.

*Fisher’s exact test.
Table 3. Prevalence of Amblyopia and Strabismus in Children aged 48 to <60 months from Population-Based or Large Cohort Studies

| Study     | Conducting year | Country | Ethnicity           | Sample size | prevalence of strabismus | XT | ET | IX | XT:ET |
|-----------|-----------------|---------|---------------------|-------------|--------------------------|----|----|----|--------|
| MEPEDS    | 2003-2011       | US      | Hispanic/Latino     | 539         | 3.9                      | 2.0| 1.5| NA | 1.4:1  |
|           |                 |         | African American    | 549         | 4.1                      | 2.0| 2.0| NA | 1:1    |
|           |                 |         | Non-Hispanic White  | 271         | 4.0                      | 1.4| 2.5| NA | 1:1.8  |
|           |                 |         | Asian               | 288         | 6.2                      | 3.1| 3.1| NA | 1:1    |
|           |                 |         | White               | 201         | 3.4                      | 2.0| 1.0| NA | 2:1    |
| BPEDS     | 2003-2007       | US      | African American    | 261         | 2.3                      | 0.7| 1.5| NA | 1:2    |
|           |                 |         | White               |             | 0.7                      | 0  | 3  | NA | 2:1    |
| STARS     | 2006-2008       | Singapore | Chinese           | 602         | 1.1                      | 1.1| 0  | NA | NA     |
|           |                 |         |                     |             | 1.1                      | 7  | 7  |     |        |
| NPVP      | 2011-2012       | China   | Chinese             | 2486        | 4.9                      | 3.9| 0.6| 2.7| 5.8:1  |
|           |                 |         |                     |             | 4.9                      | 3.9| 0.6| 2.7| 5.8:1  |
| NES       | 2016-2017       | China   | Chinese             | 1961        | 5.5                      | 4.8| 0.5| 4.6| 8.6:1  |
|           |                 |         |                     |             | 5.5                      | 4.8| 0.5| 4.6| 8.6:1  |

MEPEDS, Multiethnic Pediatric Eye Disease Study; BPEDS, Baltimore Pediatric Eye Disease Study; STARS, Strabismus, amblyopia and refractive error in Singapore; SPEDS, Sydney Pediatric Eye Disease Study; NPVP, Nanjing Pediatric Vision Project; NES, Nanjing Eye Study; NA, Not applicable.
Figure legend

Figure 1. The proportion of subtypes of strabismus in NES and in NPVP.
Figure 1. The proportion of subtypes of strabismus in NES and in NPVP.

206x125mm (144 x 144 DPI)
Prevalence of strabismus among preschool children in eastern China and comparison at a five-year interval: a population-based cross-sectional study

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Prevalence of strabismus among preschool children in eastern China and comparison at a five-year interval: a population-based cross-sectional study

Yue Wang†, Andi Zhao†, Xiaohan Zhang†, Dan Huang, Hui Zhu†, Qigang Sun, JiaJia Yu, Ji Chen, Xiaoyan Zhao, Rui Li†, Shu Han, Weiyi Dong, Fanfei Ma, Xuejuan Chen†, Hu Liu†

† Yue Wang, Andi Zhao and Xiaohan Zhang contributed equally to the study and they should be regarded as joint first authors.

1 Department of Ophthalmology, The First Affiliated Hospital with Nanjing Medical University, Nanjing 210029, China;
2 Nanjing Medical University, Nanjing 211166, China;
3 Department of Ophthalmology, The Affiliated Wuxi Children's Hospital of Nanjing Medical University, Wuxi 214000 China;
4 Department of Child Healthcare, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China
5 Department of Ophthalmology, Maternal and Child Healthcare Hospital of Yuhuatai District, Nanjing, China
6 Department of Ophthalmology, Wuxi No. 2 People’s Hospital, Wuxi, China
7 Department of Ophthalmology, The Affiliated Changzhou No.2 People’s Hospital of Nanjing Medical University, Changzhou 213164, China;
8 Department of Ophthalmology, Children's Hospital of Soochow University, Suzhou 215025, Jiangsu, China
The Fourth School of Clinical Medicine of Nanjing Medical University,
Nanjing 210029, China

*To whom correspondence should be addressed:

Hu Liu & Xuejuan Chen

Department of Ophthalmology, the First Affiliated Hospital with Nanjing Medical University, 300 Guangzhou Road, Nanjing 210029, China.

Email address: liuhu@njmu.edu.cn and chenxuejuan@vip.163.com

Tel: +86 (25) 68136470, Fax: +86 (25) 68136470

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ABSTRACT

Objective: To update strabismus data and evaluate changes in prevalence and patterns among preschoolers in eastern China over a period of five years.

Design: Nanjing Eye Study, a longitudinal population-based study.

Setting: Recruitment and testing in kindergartens in Yuhuatai District, Nanjing.

Participants: 2,300 eligible children.

Main outcome measures: Comprehensive ocular examinations were conducted in 1986 children aged 48 to < 60 months in Nanjing Eye Study (NES, 2016 to 2017), including visual acuity, ocular alignment, refractive error and ocular structures evaluation. The prevalence rate and pattern of strabismus were calculated and compared to those from the Nanjing Pediatric Vision Project (NPVP, 2011 to 2012) in the same age children of the same area using the same diagnostic criteria.

Results: The overall prevalence rate of strabismus in NES was 5.56% (95% CI 4.54% to 6.57%), which was not significantly different from that in NPVP (4.99%, 95% CI 4.13% to 5.84%, p = 0.40). The prevalence of subtype of strabismus underwent significant changes, with significant increase in intermittent exotropia (IXT) in NES (2.78% vs. 4.69%, p = 0.001), and significant decrease in constant exotropia (1.17% vs. 0.15%, p < 0.001). Significant pattern change was observed in IXT, where proportion of convergence insufficiency type (2.90% vs. 27.17%) increased and exceeded divergence excess type (20.29% vs. 11.96%) to be the second common type (p < 0.001).

Conclusion: The prevalence of strabismus appeared stable in children aged 48 to < 60
months in eastern China at a 5-year interval. The prevalence of IXT increased significantly, and convergence insufficiency type became more prevalent in IXT patients. Timely detection and intervention of IXT are important among preschoolers.

**Key words:** strabismus; intermittent exotropia; vision care; preschool children
Strengths and limitations of this study

Studies for evaluating changes over time in prevalence and characteristics of strabismus in preschool children are rare, this study updated strabismus data in eastern China and reported changes.

This study is a large population-based study, comprising 1986 preschoolers aged 48 to <60 months.

High participating rates (> 80%), same standard procedure and diagnostic criteria applied in the same age children of the same area, allowing a direct comparison between two studies.

The prevalence estimate might be biased due to poor cooperation of young children and history of strabismus treatment recalled by parents could be subject to recall bias.
INTRODUCTION

Strabismus is a common ocular disorder in childhood, which can lead not only to cosmetic impairment but also to loss of binocularity and depth perception.\textsuperscript{1-5} The negative impact of this early-onset visual developmental disorder can persist into adulthood if left untreated.\textsuperscript{6} Identifying strabismus at an earlier age may prevent the development of strabismic amblyopia as well as improve the chance of restoring binocularity, highlighting the importance of early detection and timely interventions of strabismus.\textsuperscript{7} Study of the strabismus epidemiology would provide useful data for guiding the strabismus screening and control at early age.

So far, several population-based studies, including Baltimore Pediatric Eye Disease Study (BPEDS),\textsuperscript{8} Multiethnic Pediatric Eye Disease Study (MEPEDS),\textsuperscript{9,10} the Strabismus, Amblyopia and Refractive Error in Singapore (STARS) Study\textsuperscript{11} and Vision in Preschoolers (VIP) study,\textsuperscript{12} reported the prevalence rate of strabismus vary from 1% to 4.6% in preschoolers and revealed the disparities of prevalence and pattern in different world regions and ethnic populations.\textsuperscript{7-11} However, these cross-sectional studies only captured a snapshot of the ocular disorder at a single point of time. Due to changes in the natural environment,\textsuperscript{13} social economy,\textsuperscript{14,15} lifestyle as well as vision care system,\textsuperscript{16} studies for evaluating changes over time in prevalence and characteristics of ocular diseases are needed to help obtain valuable feedback for ongoing vision care efforts, bringing the next stage targeted approaches and improvement directions. This will help us accomplish goals for eliminating the main causes of all preventable and treatable blindness set forth in “Vision 2020”.\textsuperscript{17}
In Nanjing Pediatric Vision Project (NPVP) we carried out in 2011 to 2012, the strabismus prevalence rate was 4.99%.\textsuperscript{18} In 2016, Nanjing Eye Study (NES) was conducted in the children of same age and at the same area using the same study procedure and diagnostic criteria. In this study, we assessed the prevalence of strabismus and its subtypes in NES and compared them with NPVP. The aim of this study is to update the prevalence rate of strabismus and evaluate its changes among preschoolers in eastern China over a 5-year period.
METHODS

Study design and population

NES is a population-based cohort eye study, designed to longitudinally evaluate the initiation and progression of childhood ocular diseases by establishing a systematic database in eastern China. Of all children in Yuhuatai District, children born between September 2011 and August 2012 and on the point of entering a kindergarten, were invited to participate in this study to undergo a comprehensive eye examination annually. Data presented in the present study were obtained from 2016 to 2017 when these children were 48 - < 60 months old. Among 2300 eligible preschoolers, 1986 (response rate 83.5%) children participated in this study. This study complied with the tenets of the Declaration of Helsinki. Ethics committee approval was obtained from the Ethics Committee of the First Affiliated Hospital with Nanjing Medical University (2017-SR-205). Written informed consent was obtained from the parents or legal guardians of all participants. Oral assent was obtained from all children right before the examination.

Ocular examination

In both the NES and NPVP, a comprehensive eye examination was performed on children by a team composed of trained ophthalmologists and optometrists using similar protocols as MEPEDS, including anthropometric parameters, ocular biometric parameters, distance visual acuity, anterior segment, refractive error, stereoacuity test and ocular alignment and motility. The Hirschberg light reflex test was performed to assess ocular alignment at a distance of 33 cm, followed by the cover-uncover test and
the alternate cover test with fixation targets at distance of 33 cm and 6 m, with or without correction (if wore). Monocular and binocular ocular movements were examined at nine diagnostic positions of gaze. An alternate prism cover test was used to detect the degree of eye misalignment of children suspected with strabismus. Once strabismus was suspected, a prism cover test was used to detect the degree of eye misalignment. If the child was suspected with intermittent exotropia (IXT), one eye was covered with thick gauze to break tenacious proximal fusion between the two eyes for at least 30 min, and then an alternate prism cover test was performed to assess the degree of exotropia.

**Inclusion and exclusion criteria**

Only children aged 48 to <60 months who were able to complete ocular alignment test were included in this analysis and considered as the general study population.

**Definitions**

Strabismus was defined if any tropia was present at distance or near, with or without spectacles and then classified according to the primary direction (esotropia, exotropia, vertical) of the tropia. Strabismus is considered as constant if constant at both near and distance fixation, otherwise it is considered as intermittent. Intermittent exotropia was defined as an intermittent exodeviation of at least 10 prism diopters (PD) at a distance. According to the Burian’s classification, IXT is classified into four subtypes based on the difference between the distant (6m) and the near (33cm) angles of deviation: “basic type” (difference < 10PD), “convergence weakness type” (near angle minus distant angle ≥ 10PD), “pseudo divergence excess type” (distant angle minus near angle ≥
10PD but < 10PD after 30 min monocular patching), and “true divergence excess type”
(distant angle minus near angle ≥ 10PD even after patching). In this study, all IXT
suspects had one of their eyes patched before the alternative prism cover test. Therefore,
the “pseudo divergence excess type” was counted in the “basic type” category in this
analysis. Microstrabismus was defined as a deviation of less than 10 prism diopters, in
addition to binocular vision. Children with history of strabismus or treatment were
regarded as strabismic.

**Statistical analyses**

Statistical analyses were performed using the IBM SPSS V13.0 (www.ibm.com). All
statistical tests were two-sided, and P < 0.05 was considered statistically significant. T-
test was used to compare means. Prevalence rates of strabismus and its subtypes were
calculated for NES and NPVP separately and compared between two studies using chi-
square test or fisher’s exact test. The 95% confidence intervals (CI) for prevalence rates
were calculated using normal approximation.

**Patient and Public Involvement**

Patients and the public were not involved in any aspects of the study, including the
development of study question, study design, conduct of the study and dissemination
of results.
RESULTS

Prevalence of strabismus in NES and comparison with NPVP

Ultimately, 1,961 (1961/1986, 98.7%) children with complete data were included in statistical analysis sample. The detailed characteristics of children had been described in previous published articles.\textsuperscript{19, 20}

A total of 109 children were diagnosed with strabismus in NES with an overall prevalence rate of 5.56% (95% CI 4.54% to 6.57%). The prevalence of concomitant esotropia and concomitant exotropia was 0.56% (95% CI 0.23% to 0.89%) and 4.84% (95% CI 3.89% to 5.79%), respectively (Table 1). There was no statistical gender difference in overall strabismus prevalence (5.95% vs. 5.08%, \(p = 0.40\)), concomitant esotropia (0.74% vs. 0.34%, \(p = 0.36\)); or concomitant exotropia (5.02% vs. 4.63%, \(p = 0.69\)).

Among 109 strabismic preschoolers in NES, two presented normal ocular alignment but with strabismus surgery histories (1 esotropia and 1 exotropia preoperative). In terms of pattern of strabismus, 11 had concomitant esotropia, 95 had concomitant exotropia, 1 had pure vertical strabismus (superior oblique muscle palsy), and 2 had special forms of strabismus (1 Duane syndrome and 1 Brown syndrome). Four exotropia cases were combined with vertical deviation (3.7%, 4/109). The most frequent strabismus type was IXT (84.4%; 92/109), followed by constant esotropia (10.1%; 11/109), constant exotropia (2.8%; 3/109) and special forms of strabismus (1.8%; 2/109), and vertical deviation (0.9%; 1/109) accounted for the least (Figure 1).
Comparison between NES and NPVP

Table 2 showed comparisons of the characteristics of strabismic children between NPVP and NES. The prevalence of strabismus (p = 0.40) and exotropia-esotropia ratio (p = 0.33) were similar between two studies. Statistically significant difference was observed between two studies in the pattern of horizontal strabismus (p < 0.001), driven by lower prevalence of constant exotropia in NES than NPVP (0.15% vs. 1.17%, p < 0.001) and higher prevalence of IXT in NES than NPVP (4.69% vs. 2.78%, p = 0.001). The proportion of subtype of IXT was different between two studies (p < 0.001), with convergence weakness accounted for larger proportion in NES than NPVP (27.2% vs. 2.9%, p < 0.001). Twenty of 109 (18.4%) NES strabismic children were reported having previous treatment, which was similar to NPVP (16.9%, p = 0.78). Treatment rate was higher in NES than NPVP for esotropia (90.9% vs. 47.1%, p = 0.04) while remained stable for exotropia (10.5% vs. 12.2%, P = 0.71). The mean (± standard deviation) spherical equivalent refraction (SER) of strabismic children was 0.97 ± 1.86 Diopters (D) in NES and 1.72 ± 1.78 D in NPVP and their difference are statistically significant (P = 0.003).
DISCUSSION

In this population-based NES study, we reported an overall prevalence rate 5.56% for strabismus in children aged 48 to < 60 months in eastern China. The overall concomitant esotropia and exotropia prevalence rates are 0.56% and 4.84%, respectively, with IXT as the most common type of strabismus. Compared with our NPVP study conducted five years ago using the same study protocol in the children of the same area as the NES study, no significant difference was found in the prevalence of strabismus. However, the prevalence of IXT was significantly higher in NES, whereas the prevalence of constant exotropia was only one-tenth of that reported in NPVP.

Both NPVP and NES had high participating rates (> 80%) and used the same diagnostic criteria as MEPEDS, allowing a direct comparison between them to evaluate changes in strabismus in Chinese preschool children. Our data showed that the prevalence of strabismus appeared stable over the past 5 years. An Israeli investigation found a decline in the prevalence of young adulthood strabismus from 1974 to 1994, which might be due to a better diagnosis and treatment in the pediatric population.23 Taken into consideration that our analyses did not exclude those who had been successfully treated, we believed that our results tended to reflect the natural change in strabismus experience in this area. Our previous study found that the rate of reduced UCVA increased significantly in a five-year interval, which was likely due to the influence of some environmental risk factors, such as more time on the mobile devices.19 Conversely, the steady trend in strabismus rate in the present study indicated that genetic factors
might play a more important role in the advert of strabismus in early life.

The prevalence of strabismus in NPVP or NES in 48 to < 60-month-old children was similar to those reported in other studies. However, exotropia-esotropia ratio was the highest in NES (8.6:1) and NPVP (5.8:1) among those investigations (Table 3), which is in line with the high exotropia-esotropia ratio reported by several studies based on East Asian populations.\textsuperscript{11 24 25} This ratio has increased over the past 5 years, from 5.8 in NPVP to 8.6 in NES, but their difference was not significant. Nevertheless, the subtype proportion in exotropia underwent substantial change. An increase in the proportion of patients with IXT was observed while constant exotropia became less common in NES. A previous Hong Kong study reported a similar increasing trend in IXT accompanied by an apparent decline in esotropia. On the contrary, the prevalence of esotropia appeared stable in our study. Hong Kong study attributed this change to the increasing prevalence of myopia.\textsuperscript{26} We observed a declining trend in SER in that strabismic children in the NES were less hyperopic than NPVP (0.97 vs. 1.72 D, \(p = 0.003\)). Given that myopia is not the predominant refractive error in strabismic preschoolers,\textsuperscript{27} this explanation may not be appropriate in our study. Taken together opposite change in the prevalence of IXT and constant exotropia, we speculated that regular vision screening and timely intervention might reduce the risk of deterioration of IXT and thus drop constant exotropia share. In addition, improved pregnant and prenatal care might play a role as well \textsuperscript{28 29}. It is noteworthy that the prevalence of esotropia was lower than that reported in other studies (Table 3) and had a slight decrease over the past 5 years. Besides the contributions by widespread ethnic and
regional disparity, early significant hyperopia correction likely played a role in preventing children with hyperopia from developing esotropia in this population.

The IXT was found to be the most common subtype in both NPVP and NES. Notably, proportion of convergence insufficiency increased and exceeded divergence excess to be the second major type of IXT in NES. So far, few population-based studies had studied the subtypes of IXT. Since the increased prevalence of IXT had been found in this area, investigations on causes and characteristics are of great importance to broaden our understanding of IXT. Chia et al. in their hospital-based study, reported that divergence excess IXT was the major subtype. However, lacking patching in Chia’s methodology might over-estimate the amount of divergence excess cases. All children in NPVP and NES suspected with IXT had one of their eyes patched before examinations and thus increased the accuracy of IXT classification by weakening the influence of tenacious proximal fusion. Consistent with our study, a Korean hospital-based investigation also found convergence insufficiency was the second common subtype in IXT. The reason for pattern changes in IXT is unknown, future investigation on causes and characteristics in IXT is warranted.

NPVP and NES had similar treatment rates for strabismus, almost one in five strabismic children received treatment before our examination. So far, few studies directly reported treatment rates, making comparison with other studies difficult. Although no significant difference between NES and NPVP was found in the overall treatment rate, a significant increase in esotropia treatment rate was found. Vision screening in preschoolers in the Yuhuatai district was performed earlier than other communities in
China. Early detection and timely referral had achieved good outcomes, which would contribute to the rise in the treatment rate of esotropia. Given early diagnosis and treatment are associated with a better outcome in strabismus, more efforts ought to be made on comprehensive screening, timely referral and treatment.

The strengths of this study including the large and population-based sample of 48 to < 60-month-old preschoolers in two studies from the same area that followed standardized protocols for comprehensive eye examinations, and used the same diagnostic criteria, allowing us to reliably assess the change in prevalence in strabismus at a 5-year interval.

This study had a few limitations. Firstly, poor cooperation of these very young children may lead us to underestimate the prevalence rate of strabismus. Secondly, history of treatment and pattern of strabismus with previous treatment were determined by medical records or recalled by parents, the latter is thus subject to recall bias.

**Conclusion**

In summary, the NES found an overall prevalence rate of 5.56% for strabismus in children aged 48 to < 60 months in eastern China. The prevalence of strabismus appeared stable but the pattern of strabismus underwent significant changes over the past 5 years comparable to our previous NPVP study. The prevalence of IXT increased significantly, and the high exotropia-esotropia ratio was the most noteworthy feature in this area. More efforts on vision screening should be made on IXT detection and intervention in the future.
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Contributors Liu H and Chen X designed the study. Wang Y, Zhang X and Zhao A wrote the main manuscript text. Wang Y, Zhang X and Li R prepared tables. Wang Y, Zhang X, Huang D, Han S, Zhu H and Zhao X performed data interpretation and analysis. Wang Y, Zhang X, Sun Q, Chen J, Yu J, Dong W and Ma F performed the ocular examinations.

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Competing interests None declared.

Patient consent Written informed consent was obtained from the parents or legal guardians of all participants. Oral assent was obtained from all children before the examination.

Ethics approval This study was approved by the ethics committee of the First Affiliated Hospital with Nanjing Medical University (2017-SR-205) in accordance with the Declaration of Helsinki principles.

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**Data sharing statement** All data relevant to the study are included in the article or uploaded as supplementary information.

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Table 1. Prevalence and characteristics of strabismus in children in NES (N = 1961)

| Characteristics          | Without strabismus, N | With strabismus, N | Prevalence rate (95%CI) |
|--------------------------|-----------------------|--------------------|-------------------------|
|                          |                       |                    |                         |
| **Gender**               |                       |                    |                         |
| Any strabismus           |                       |                    |                         |
| Male                     | 1011                  | 64                 | 5.95 (4.54 to 7.37)     |
| Female                   | 841                   | 45                 | 5.08 (3.63 to 6.52)     |
| Overall                  | 1852                  | 109                | 5.56 (4.54 to 6.57)     |
| **Concomitant esotropia**|                       |                    |                         |
| Male                     | 1067                  | 8                  | 0.74 (0.23 to 1.26)     |
| Female                   | 883                   | 3                  | 0.34 (0 to 0.72)        |
| Overall                  | 1950                  | 11                 | 0.56 (0.23 to 0.89)     |
| **Concomitant exotropia**|                       |                    |                         |
| Male                     | 1021                  | 54                 | 5.02 (3.72 to 6.33)     |
| Female                   | 845                   | 41                 | 4.63 (3.24 to 6.01)     |
| Overall                  | 1866                  | 95                 | 4.84 (3.89 to 5.79)     |
| **Types**                |                       |                    |                         |
| Concomitant strabismus   | 1855                  | 106                | 5.41 (4.40 to 6.41)     |
| Esotropia                | 1950                  | 11                 | 0.56 (0.23 to 0.89)     |
| Constant                 | 1950                  | 11                 | 0.56 (0.23 to 0.89)     |
| Intermittent             | 1961                  | 0                  | 0                       |
| Exotropia                | 1866                  | 95                 | 4.84 (3.89 to 5.79)     |
| Constant                 | 1958                  | 3                  | 0.15 (0 to 0.33)        |
| Intermittent             | 1869                  | 92                 | 4.69 (3.76 to 5.63)     |
| Basic                    | 1905                  | 56                 | 2.86 (2.12 to 3.59)     |
| Convergence insufficiency| 1936                  | 25                 | 1.27 (0.77 to 1.87)     |
| Divergence excess        | 1950                  | 11                 | 0.56 (0.23 to 0.89)     |
| Microtropia              | 1961                  | 0                  | 0                       |
| Vertical deviations      | 1960                  | 1                  | 0.05 (0 to 0.15)        |
| Special forms of strabismus | 1959              | 2                  | 0.10 (0 to 0.24)        |

N, number.
Table 2. Comparison of strabismic children aged 48 – < 60 months in population of NPVP (N = 2486) and NES (N = 1961)

| Characteristics                                | NPVP           | NES           | P    |
|------------------------------------------------|----------------|---------------|------|
| Gender, N (%)                                  |                |               |      |
| Male                                           | 73 (58.9%)     | 64 (58.7%)    | 0.98 |
| Female                                         | 51 (41.1%)     | 45 (41.3%)    |      |
| Prevalence of strabismus                       | 4.99%          | 5.56%         | 0.40 |
| Prevalence of concomitant esotropia            | 0.68%          | 0.56%         | 0.61 |
| Prevalence of concomitant exotropia            | 3.94%          | 4.84%         | 0.14 |
| Prevalence of constant exotropia               | 1.17%          | 0.15%         | <0.001 |
| Prevalence of IXT                              | 2.78%          | 4.69%         | 0.001 |
| XT:ET ratio                                    | 5.8:1          | 8.6:1         | 0.33 |
| Subtypes of concomitant horizontal strabismus, N (%)<0.001*| | | |
| Constant esotropia                             | 14 (12.2%)     | 11 (10.4%)    |      |
| Intermittent esotropia                         | 3 (2.6%)       | 0 (0)         |      |
| Constant exotropia                             | 29 (25.2%)     | 3 (2.8%)      |      |
| IXT                                            | 69 (60.0%)     | 92 (86.8%)    |      |
| Subtypes of IXT, N (%)<0.001                   |                |               |      |
| Divergence excess                              | 14 (20.3%)     | 11 (12.0%)    |      |
| Convergence weakness                           | 2 (2.9%)       | 25 (27.2%)    |      |
| Basic                                          | 53 (76.8%)     | 56 (60.8%)    |      |
| Mean SER in strabismic children, D             | 1.720 ± 1.779  | 0.971 ± 1.863 | 0.003 |
| History of strabismus treatment, N (%)         |                |               | 0.78 |
| Yes                                            | 21 (16.9%)     | 20 (18.4%)    |      |
| No                                             | 103 (83.1%)    | 89 (81.6%)    |      |
| History of esotropia treatment, N (%)<0.041*   |                |               |      |
| Yes                                            | 8 (47.1%)      | 10 (90.9%)    |      |
| No                                             | 9 (52.9%)      | 1 (9.1%)      |      |
| History of exotropia treatment, N (%)          |                |               | 0.71 |
| Yes                                            | 12 (12.2%)     | 10 (10.5%)    |      |
| No                                             | 86 (87.8%)     | 85 (89.5%)    |      |

NPVP, Nanjing Pediatric Vision Project; NES, Nanjing Eye Study; N, number; IXT, Intermittent exotropia; XT, exotropia; ET, esotropia; SER, Spherical equivalent refraction; D, diopter

Bold print represents statistical significance.

*Fisher’s exact test.
| Study    | Year of study | Country | Ethnicity                  | sample size | Prevalence rate (%) of strabismus | XT:E T |
|----------|---------------|---------|----------------------------|-------------|-----------------------------------|--------|
| MEPEDS   | 2003-2011     | US      | Hispanic/Latino            | 539         | 3.90% 2.04% 1.5% NA               | 1.4:1  |
|          |               |         | African American           | 549         | 4.19% 2.00% 2.00% NA              | 1:1    |
|          |               |         | Non-Hispanic White         | 271         | 4.06% 1.48% 2.58% NA              | 1:1:8  |
|          |               |         | Asian                      | 288         | 6.25% 3.13% 3.13% NA              | 1:1    |
| BPEDS    | 2003-2007     | US      | White                      | 201         | 3.48% 2.00% 1.00% NA              | 2:1    |
|          |               |         | African American           | 261         | 2.30% 0.77% 1.53% NA              | 1:2    |
| STARS    | 2006-2008     | Singapore | Chinese                  | 602         | 1.17% 1.17% 0% NA                 | NA     |
| NPVP     | 2011-2012     | China   | Chinese                   | 2486        | 4.99% 3.94% 0.68% 2.78%          | 5.8:1  |
| NES      | 2016-2017     | China   | Chinese                   | 1961        | 5.56% 4.84% 0.56% 4.69%          | 8.6:1  |

MEPEDS, Multiethnic Pediatric Eye Disease Study; BPEDS, Baltimore Pediatric Eye Disease Study; STARS, Strabismus, amblyopia and refractive error in Singapore; SPEDS, Sydney Pediatric Eye Disease Study; NPVP, Nanjing Pediatric Vision Project; NES, Nanjing Eye Study; NA, not applicable.
Figure legend

Figure 1. The proportion of subtypes of strabismus in NES and in NPVP.
Figure 1. The proportion of subtypes of strabismus in NES and in NPVP.

364x210mm (144 x 144 DPI)
## STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

| Item No | Recommendation                                                                 | Page No |
|---------|---------------------------------------------------------------------------------|---------|
| **Title and abstract**                                                   | (a) Indicate the study’s design with a commonly used term in the title or the abstract | 1, 3 |
|         | *(b) Provide in the abstract an informative and balanced summary of what was done and what was found* | 3-4 |
| **Introduction**                                           | Explain the scientific background and rationale for the investigation being reported | 6 |
| **Objectives**                                             | State specific objectives, including any prespecified hypotheses | 7 |
| **Methods**                                                | Present key elements of study design early in the paper | 8 |
| Study design                                               | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 8 |
| Setting                                                   | 5 |
| Participants                                               | (a) Give the eligibility criteria, and the sources and methods of selection of participants | 9 |
| Variables                                                 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 8-9 |
| Data sources/ measurement                                  | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 8 |
| Bias                                                      | Describe any efforts to address potential sources of bias | 9 |
| Study size                                                | Explain how the study size was arrived at | 8 |
| Quantitative variables                                     | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 8-9 |
| Statistical methods                                        | (a) Describe all statistical methods, including those used to control for confounding | 10 |
|                                                          | (b) Describe any methods used to examine subgroups and interactions | N/A |
|                                                          | (c) Explain how missing data were addressed | N/A |
|                                                          | (d) If applicable, describe analytical methods taking account of sampling strategy | N/A |
|                                                          | (e) Describe any sensitivity analyses | N/A |
| **Results**                                                | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 11 |
| Participants                                               | (b) Give reasons for non-participation at each stage | 11 |
|                                                          | (c) Consider use of a flow diagram | N/A |
| Descriptive data                                           | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 11 |
|                                                          | (b) Indicate number of participants with missing data for each variable of interest | N/A |
| Outcome data                                               | Report numbers of outcome events or summary measures | 11-12 |
Main results 16  
(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included.  
(b) Report category boundaries when continuous variables were categorized.  
(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. 

Other analyses 17  Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses. N/A

Discussion
Key results 18  Summarise key results with reference to study objectives. 13
Limitations 19  Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. 16
Interpretation 20  Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. 13-16
Generalisability 21  Discuss the generalisability (external validity) of the study results. N/A

Other information
Funding 22  Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. 18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.