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A Randomized Clinical Trial Of Immediate versus Delayed Spectacles for Moderate Hyperopia in 1- and 2-Year-Olds

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Abstract

Objective: Two strategies were compared for managing moderate hyperopia without manifest strabismus among 1- and 2-year-old children: 1) immediate prescription of glasses vs 2) observation without glasses unless reduced distance visual acuity (VA), reduced stereoacuity, or manifest strabismus.

Design: Prospective randomized clinical trial

Participants: 130 children 1 to 2 years old with hyperopia between +3.00 diopters (D) and +6.00D spherical equivalent (SE) in at least one eye, anisometropia 1.50D SE and astigmatism 1.50D based on cycloplegic refraction, and no manifest strabismus.

Methods: Participants were randomly assigned to glasses (1.00D less than full cycloplegic hyperopia) versus observation and followed every 6 months for 3 years. Glasses were prescribed to

* A full list of participating study group members appears in the Acknowledgments e-Supplement.

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This article contains online-only material. The following should appear online-only: Tables 5, 6

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those assigned to observation if they met pre-specified deterioration criteria of distance VA or near stereoacuity below age norms, or development of manifest strabismus.

Main Outcome Measure: At the 3-year primary outcome examination, participants were classified as failing the randomized management regimen if distance VA or stereoacuity were below age norms, or manifest strabismus was observed (each with and without correction in trial frames, confirmed by masked retest, irrespective of whether deterioration had occurred previously), or if strabismus surgery had been performed.

Results: Of the 106 (82%) participants completing the 3-year primary outcome examination, failure occurred in 11 (21%) of 53 in the glasses group and 18 (34%) of 53 in the observation group (difference = -13%; 95% CI = -31% to 4%; $p=0.14$). The reasons for failure in the glasses and observation groups were reduced stereoacuity in 6 (11%) and 16 (30%) respectively, reduced VA in 3 (6%) and 4 (8%), and manifest strabismus in 5 (9%) in each group. Fifty-eight percent (95% CI = 46% to 70%) in the observation group, and 33% (95% CI = 22% to 46%) in the glasses group met deterioration criteria (requiring glasses if not wearing).

Conclusion: For 1- and 2-year-olds with uncorrected moderate hyperopia (+3.00D to +6.00D SE), our estimates of failure, after 3 years of 6-monthly follow-up, are inconclusive, and consistent with either a small to moderate benefit or no benefit of immediate prescription of glasses compared with careful observation (with glasses only if deteriorated).

Précis

Visual acuity, stereoacuity, and strabismus outcomes were consistent with either a small to moderate benefit or no benefit of immediate glasses compared with careful observation (glasses if deteriorated), in 1- to 2-year-olds with moderate hyperopia.

Moderate hyperopia is associated with the development of manifest strabismus and amblyopia in children,¹⁻¹⁰ and there is consensus that optical correction should be prescribed for such children.¹¹⁻¹⁵ In contrast, for children with moderate hyperopia without strabismus or amblyopia, there is less consensus among pediatric eye care professionals regarding whether optical correction should be prescribed.¹⁶ For example, a survey by Lyons et al¹⁶ found that for a 2-year-old child with hyperopia greater than +3.00D without strabismus or amblyopia, 65% of optometrists would prescribe glasses compared with 25% of ophthalmologists.

The rationale for proactively correcting moderate hyperopia in an asymptomatic child is to facilitate the development of normal visual acuity (VA) and reading function, and to potentially prevent the development of esotropia, amblyopia, or asthenopia. However, some believe there is no harm in waiting, and argue that parents may avoid the expense and inconvenience of having their child wear glasses as long as strabismus, amblyopia, or other symptoms are not present. Some proponents of waiting also have concern regarding the potential negative effects of wearing refractive correction on emmetropization.¹⁷ Others cite evidence that partial correction of hyperopia does not impede emmetropization,^{2, 18-20} with most emmetropization being completed by the end of the first year of life,^{21, 22} and high hyperopia persisting.^{18, 21, 23, 24}

Previous studies comparing partial correction with no glasses for moderate hyperopia have reported conflicting results regarding whether or not prescription of glasses influences the development of manifest strabismus or amblyopia.^{2, 25-27} Furthermore, these studies suffered from potential sources of bias such as lack of masking, high loss to follow-up, and unclear handling of missing data.^{2, 25-28} The purpose of the present randomized clinical trial was to compare VA and stereoacuity outcomes, and the rates of development of manifest strabismus after a 3-year follow-up period in 1- and 2-year-olds with moderate hyperopia [spherical equivalent (SE) +3.00D to +6.00D] who were prescribed 1) immediate glasses versus 2) observation without glasses unless reduced VA, reduced stereoacuity, or manifest strabismus was present at one of the 6-monthly follow-up visits. In addition, change in refractive error was compared between groups.

Methods

The study was supported through a cooperative agreement with the National Eye Institute of the National Institutes of Health and was conducted according to the tenets of the Declaration of Helsinki by the Pediatric Eye Disease Investigator Group at 39 academic- and community-based clinical sites. The protocol and Health Insurance Portability and Accountability Act-compliant informed consent forms were approved by institutional review boards, and a parent or guardian of each study participant gave written informed consent. An independent data and safety monitoring committee provided study oversight. The study is listed on www.clinicaltrials.gov (identifier, NCT01515475; accessed August 6, 2018). The full study protocol is available on the Pediatric Eye Disease Investigator Group website (www.pedig.net; accessed August 6, 2018).

Eligibility Exam and Criteria

Children 1 to <3 years of age were assessed by a pediatric ophthalmologist or pediatric optometrist, and were offered enrollment if they had moderate hyperopia of +3.00D to +6.00D SE in at least one eye, with astigmatism ≤ 1.50 D in each eye and SE anisometropia ≤ 1.50 D by cycloplegic refraction and no manifest strabismus at distance (3m) and near (33cm) by cover-uncover test. Children with a history of manifest strabismus or prior optical correction for hyperopia were excluded. Additional eligibility criteria are listed in Table 1. Prism and alternate cover testing was also assessed at eligibility and dynamic retinoscopy was an optional test, because not all investigators performed it routinely. Information regarding ADHD diagnosis and treatment, and family history of amblyopia and/or strabismus also was collected.

Treatment

Participants were randomly assigned with equal probability, using a permuted block design stratified by clinical site, to either prescribed glasses or observation [with glasses prescribed only if confirmation of pre-specified deterioration criteria (Table 2)]. Those randomized to glasses were provided a partial hyperopic correction (i.e., partial plus; glasses with the sphere cut symmetrically by 1.00D from the cycloplegic refraction) and the full astigmatism (magnitude and axis) correction at enrollment to be worn full time for the duration of the study. A partial plus correction was prescribed because there is some evidence that partial

correction of hyperopia does not impede emmetropization,^{2, 18-20} and most pediatric eye care professionals usually prescribe less than the full cycloplegic refraction for hyperopia in the absence of strabismus or amblyopia.¹⁶ Participants were not prescribed any other treatment unless there was confirmation of one or more deterioration criteria (Table 2). Participants who met deterioration criteria continued to return for study follow-up visits but were released to best clinical care at investigator discretion, which included providing partial plus glasses (as specified below) for those not already wearing, and full plus correction for any participant who developed manifest esotropia.

Follow-up Testing Procedures and Data Collection

Participants assigned to glasses were contacted two weeks after the enrollment exam to ensure that the glasses were received and to encourage adherence. A short course of bilateral cycloplegia could be prescribed if a participant was not compliant with glasses wear and the investigator believed that the participant needed assistance relaxing his/her accommodation to adapt to the glasses. Any prescribed bilateral cycloplegia was to be discontinued at least two weeks prior to any study visit.

Follow-up visits occurred every 6 months (± 1 month) for 3 years, with the primary outcome examination at 3 years (± 1 month). For those in glasses, the prescription was verified by lensometry and adherence to glasses wear was estimated based on a discussion with the parent [not at all ($< 1\%$), poor ($> 1\%$ to $< 26\%$), fair (26 to 50%), good (> 50 to 75%), or excellent (> 75 to 100%)] at each follow-up visit. All testing was completed by a study-certified examiner (pediatric optometrist, pediatric ophthalmologist, or certified orthoptist).

At non-primary outcome 6-month follow-up visits, each participant was initially assessed by an unmasked examiner. Distance (3m) and near (33cm) ocular alignment were assessed using the cover-uncover test, simultaneous prism and cover test (if tropia present), and the prism and alternate cover test in the randomized optical correction, defined as no refractive correction in the observation group and hyperopic correction (as defined above) in the glasses group. The participant's current glasses were worn for testing provided lensometry verified they contained the appropriate correction, otherwise trial frames were used. In participants ≥ 3 years of age at the time of the follow-up visit, the examiner also tested 1) near stereoacuity at 33cm using the Randot Preschool Stereotest (Stereo Optical Co., Inc., Chicago, IL) and 2) distance VA in each eye without cycloplegia using the Amblyopia Treatment Study HOTV[®] VA testing protocol.²⁹ For these participants, the order of testing was 1) stereoacuity, 2) alignment, and 3) VA. The parent was also asked, "Do you have concerns with your child's vision or ability to see well close up?" If one or more deterioration criteria (Table 2) appeared to be met or there was parent reported concern during unmasked testing (and the participant had not previously met deterioration criteria), a masked exam was subsequently performed to determine whether or not deterioration criteria were met.

For participants who failed one or more components by initial unmasked testing or for parental concern, masked testing of VA, stereoacuity, and/or ocular alignment was performed on the same day, or within 2 weeks, by an examiner unaware of treatment assignment (only the components failed on unmasked testing were retested). All masked

testing was performed with partial plus correction in trial frames and again without trial frames. In cases of parental concern that would warrant starting treatment in the absence of suspected deterioration, all age-appropriate areas were assessed by the masked examiner (alignment for all participants, VA and stereoacuity if ≥ 36 months of age). The participant was classified as having met deterioration criteria if confirmed by masked examination, when tested in the management strategy assigned at randomization (with correction in trial frames if assigned to glasses, without trial frames if assigned to observation). Guidelines for glasses prescribed post deterioration were: hyperopia not undercorrected by more than +1.00D SE, full correction of anisometropia, and astigmatism correction within 0.50D of full correction. For those participants who developed a manifest esotropia, full cycloplegic hyperopic correction was provided regardless of group.

At the 3-year primary outcome visit, participants were assessed to determine if they met the study “failure” criteria (Table 3). A masked examiner assessed VA, stereoacuity, and ocular alignment first in trial frames using the appropriate hyperopic correction (1D sphere less than cycloplegic refraction, full plus if previously prescribed full plus) and second without refractive correction. If any failure criteria (Table 3) were met at the 3-year primary outcome exam, with the exception of prior strabismus surgery, that visual condition was retested to confirm or refute failure. For participants with manifest strabismus at near while wearing correction, cover testing at near was also performed with +3.00D lenses over the distance correction. If failure criteria were confirmed both with and without correction and the cycloplegic refraction obtained at the end of the examination indicated a change from the most recent cycloplegic refraction (>0.75 D sphere, >0.75 D cylinder, >0.75 D in SE anisometropia or axis change of ≥ 6 degrees when cylinder is $>+1.00$ D), a new refractive correction was provided. These participants returned 4 weeks later, at which time any failed criterion was retested in trial frames using the new refractive correction; participants were only classified as failed if the criterion was again failed in the new refractive correction.

Primary Outcome

The primary outcome for this study was failure 3 years after randomization (Table 3), both with and without the appropriate hyperopic correction in trial frames (if confirmed by a retest). We defined failure as ultimately “doing harm” to VA, stereoacuity, or ocular alignment, evidenced by reduced VA, reduced stereoacuity or manifest strabismus that was not immediately reversed by hyperopic correction. Therefore, participants were assessed for potential failure both with and without optical correction at the primary outcome visit, and failure was declared (Table 3) only if criteria were met both with and without correction, confirmed by a retest. If reduced VA, reduced stereoacuity or manifest strabismus was not present under both conditions, with and without distance refractive correction, or only partial testing was completed (e.g., if components of testing or required re-testing was not completed, such that failure was not confirmed), failure was not declared.

Statistical Analysis

The sample size of 286 was chosen to provide 90% power to detect a difference in failure rates at 3 years given expected 3-year failure rates of 10% and 25% in the glasses and the observation groups respectively, and a type I error rate of 5%.

The primary analysis was a treatment group comparison of the proportion of participants meeting failure criteria 3 years after randomization using Barnard's test.³⁰ The treatment group difference in failure rates and the 95% confidence interval (CI) were calculated. The primary analysis was limited to participants who completed the 3-year visit within 3 months prior to target visit date and up to 6 months after the target visit date. Participants were not considered as a failure for the primary analysis if only partial testing was completed (e.g., if some testing or required re-testing was not completed, such that failure was not confirmed). Alternative approaches to the primary analysis are specified in Table 8.

Secondary analyses included treatment group comparisons of the best test or retest outcomes at 3 years with or without trial frames (VA, stereoacuity, and manifest strabismus), binocular near VA, and change in refractive error over the 3-year period. VA measurements were converted from Snellen equivalents to logMAR (logarithm of the minimum angle of resolution) lines for analysis. Stereoacuity was evaluated as a continuous outcome by converting seconds of arc scores to logarithm of seconds of arc values (in parentheses) as follows: 40 (1.60), 60 (1.78), 100 (2.00), 200 (2.30), 400 (2.60), 800 (2.90); participants with no detectable (nil) stereoacuity were assigned a value of 1600 (3.20).

Primary and secondary analyses followed a modified intent-to-treat principle, with no imputation of data for participants who missed the 3-year visit. Participants were analyzed based on randomized treatment assignment. To control for the inflation in type I error rate due to testing multiple hypotheses, statistical significance in secondary analyses was defined as $p < 0.01$. Analyses were conducted using SAS software version 9.4 (Cary, NC).

Results

Baseline Characteristics

Between February 2012 and August 2014, 130 participants were randomly assigned to the glasses group (N=65) or to the observation group (N=65). After 31 months, recruitment was stopped due to slow enrollment; 53% of the planned sample size had been enrolled. Baseline characteristics were similar in the two groups (Table 4).

Visit Completion and Treatment Adherence

The primary outcome examination was completed by 53 (82%) participants in the glasses group and 53 (82%) in the observation group (Figure 1). Compared with the 106 participants who completed the 3-year visit, the 24 participants who did not were more likely to be female (71% vs. 48%) and non-white (37% vs 15%), but appeared similar with regard to age, family history of amblyopia and strabismus, refractive error, anisometropia, and astigmatism (Table 5, available at www.aaojournal.org).

Parents of children in the glasses group reported that glasses were worn more than 75% of the time in 47% at 6 months, 43% at 12 months, 63% at 18 months, 66% at 24 months, 77% at 30 months, and 76% at 36 months (Table 6). On average, glasses were worn between 50% and 75% of the time both prior to and after meeting deterioration criteria.

There were six deviations to the protocol with respect to treatment. One participant in the glasses group and three in the observation group received non-protocol treatment in the absence of meeting deterioration criteria. Two participants in the observation group did not receive glasses upon meeting deterioration criteria.

Primary Outcome (Failure at 3 years)

At the 3-year primary outcome exam, 11 (21%; 95% CI = 11% to 34%) of 53 participants in the glasses group and 18 (34%; 95% CI = 22% to 48%) of 53 in the observation group met failure criteria (difference = -13%; 95% CI = -31% to 4%; $p=0.14$). Reasons for failure are listed in Table 7. Additional approaches to the primary analysis yielded similar results (Table 8). Results for subgroup analyses are reported in Table 9. Unfortunately, dynamic retinoscopy was not completed in enough children to allow subgroup analysis by accommodative response. Two participants in the glasses group and three in the observation group failed due to manifest strabismus at near. When tested with +3.00 lenses over the distance correction, manifest strabismus was still present at near for 2 participants in the glasses group and 1 in the observation group. Regarding the 2 participants in the observation group whose manifest strabismus was not present at near with the addition of a +3.00 lenses, one also met failure criteria for strabismus at distance and reduced stereoacuity, and the other also met failure criteria for stereoacuity (not tested with +3.00D lenses).

Deterioration Prior to 3 Years

The cumulative proportion of participants meeting deterioration criteria (in their assigned treatment, Table 2) was 62% (95% CI=49% to 74%; Figure 2) in the observation group and 34% (95% CI=23% to 48%) in the glasses group. A somewhat greater proportion of deterioration in the observation group was expected, due to the expected development of esotropia in a small number of cases, but “failure” was defined distinct from “deterioration,” as described. Although all the participants in the observation group who deteriorated (62%) should have been prescribed glasses, only 94% of these were actually prescribed glasses prior to the 3-year outcome exam. Reasons for deterioration are listed in Table 10.

Participants who met deterioration criteria (Table 2) during 3 years of follow-up were only classified as meeting failure criteria (Table 3) if one or more criteria were met *at* the 3-year outcome examination (confirmed by a re-test) or they had strabismus surgery during the course of the study. In the observation group, failure at 3 years was more likely to occur in those who met deterioration criteria prior to 3 years compared with those who did not (50% vs. 10%; difference=40%; 99% CI = 5% to 66%; $p=0.002$). In the glasses group, failure at 3 years was observed in 37% who met deterioration criteria prior to 3 years and 12% who did not (difference=25%; 99% CI = -6% to 58%; $p=0.03$).

Secondary Analyses

No statistically significant treatment group difference was observed for any of the following factors at 3 years based upon the best of test or retest with or without trial frames: distance VA, binocular near VA, best stereoacuity, proportion of participants with amblyopia, proportion of participants with manifest strabismus; or change in hyperopic refractive error (Tables 11, 12, 13).

Only 5 participants were reported to have a measurable esophoria at near at enrollment, 4 of these measured 2pd by prism and alternate cover testing (PACT) and one 20pd by PACT. Four of these 5 participants completed the primary outcome exam; 3 of the participants with 2pd esophoria did not meet failure criteria, whereas the one participant who was enrolled with 20pd near esophoria did meet failure criteria. In 10 of 130 participants, PACT was not recorded. No conclusions can be made from such small numbers.

Regarding the use of cycloplegic drops to relax into the hyperopic prescription, we had somewhat incomplete data (due to a change in data forms partway through the study), but we recorded 7 participants assigned to immediate prescription of glasses who were prescribed cycloplegic drops for this purpose.

Discussion

In this randomized clinical trial, distance VA, stereoacuity, and ocular alignment outcomes were compared after 3 years, between 1- and 2-year-old children with moderate hyperopia (SE +3.00D to +6.00D) who were managed with immediate glasses versus observation without glasses unless there was reduced VA, reduced stereoacuity, or manifest strabismus. Failure was defined as “doing harm” to VA, stereoacuity, or ocular alignment, at three years and therefore failure was assessed both with and without refractive correction, and confirmed by retest. Failure was observed in 21% in the glasses group and 34% in the observation group at the 3-year primary outcome visit. This apparent difference between treatment groups was not statistically significant; the 95% confidence interval of the difference ranged from 31% in favor of glasses to 4% in favor of observation, consistent with either a small to moderate benefit of glasses or no difference between the two treatment groups. Considering secondary outcomes, there were no statistically significant differences in mean distance VA, mean near VA, mean stereoacuity, proportion with amblyopia, proportion with manifest strabismus, or mean change in hyperopic refractive error.

Comparing our results with the previous literature, Ingram et al²⁵ studied 12-month-old children (n=306) with hyperopia of +2.00D or more and/or anisometropia of +1.00D or more. Children were randomly assigned to partial plus glasses or no treatment, and assessed at 3.5 years of age, finding similar proportions of strabismus (15% versus 21%) and similar proportions of children with 20/40 or better VA in the worse-seeing eye (91% in each group). Ingram et al²⁶ subsequently studied 6-month-old children (n=372) with +4.00D of hyperopia, randomly assigning them to glasses or no glasses, and found no difference in the rate of strabismus development (24% versus 26% respectively) by 3.5 years of age and no difference in final VA between the groups (92% vs 87% being 20/40 or better in worse-seeing eye). In a contrasting study, Atkinson et al² randomly assigned 9-month-old children with +3.50D of hyperopia to glasses or no glasses and reported, at 4 years of age, a lower proportion of children developed strabismus (6.3% vs. 21%, respectively) and reduced visual acuity (28.6% vs. 68%, respectively) in those who wore glasses compared with those who did not, but these analyses by Atkinson were not intention-to-treat analyses. In a second study by the same group,²⁷ children age 11 months of age with hyperopia of at least +4.00D were assigned to glasses or no glasses in a quasi-random fashion by year of study. In contrast to their first study,² the Atkinson group reported no difference in the proportion of

children who developed strabismus between the glasses group and non-glasses group [21% (12 of 58) vs 11% (2 of 18)], whereas the difference in proportion who developed reduced visual acuity was similar to their first study, (38% in those assigned to the glasses group versus 67% in those assigned to no-glasses).²⁷

The differences in estimates of failure due to manifest strabismus and reduced VA between our present study and the studies of Ingram^{25, 26} and Atkinson^{2, 27} are likely due to differences in study design and potential sources of bias in the four prior studies, such as lack of masking, high loss to follow-up, and unclear handling of missing data.²⁸ The children enrolled in our present study were older (1 to 3 years of age versus 6 to 12 months of age) and our primary outcome was based on a masked examination, both with and without correction in trial frames, to assess whether “harm” had been done to VA, stereoacuity, or ocular alignment. In our study, failure was only declared if a criterion was met both with and without optical correction, confirmed by a retest. A number of participants in our study were not considered to have failed because failure was not confirmed (i.e. one or more components of testing or required re-testing were not completed). It is likely that these differences in study design resulted in our overall estimates of failure being lower in our study than those for Ingram^{25, 26} and Atkinson.^{2, 27} Considering the results of our present study along with those previous studies, it still remains unclear whether or not there is definitive benefit to prescribing hyperopic spectacles prophylactically to 1- and 2-year-old children with moderate hyperopia (+3.00 to +6.00).

Regarding deterioration during follow-up, a higher proportion of deterioration would be expected with observation, because, for example, a proportion of children with moderate uncorrected hyperopia will develop accommodative esotropia, which would then be treated with glasses. Furthermore, if a particularly high proportion of children in the observation group deteriorated during follow up, that might influence the practitioner to always prescribe glasses prophylactically regardless of the 3-year outcomes of the present study. We found 33% of children deteriorated with glasses, whereas 58% deteriorated with observation. Although failure at 3 years (criteria met and confirmed with and without correction in trial frames) was more likely in children who deteriorated during the 3 years of follow-up (criteria met and confirmed in assigned management strategy), at least half of the children who deteriorated prior to 3 years were not classified as failure at 3 years (50% observation, 63% glasses), recognizing that failure and deterioration were deliberately defined differently in the present study. Regardless of the difference in definitions, the proportion of deterioration in both groups, and proportion of failure in both groups, suggests that it is important to follow these young children with moderate hyperopia closely.

Regarding emmetropization, we found little reduction of hyperopia occurred in either group, with no significant difference between the two groups. This may be attributed to the age of our participants (1 to <3 years); it has been reported that partial correction of hyperopia does not impede emmetropization,^{2, 18-20} that emmetropization during the first year is rapid,^{21, 22, 31-34} with most emmetropization being completed by the end of the first year of life,^{21, 22} and with high hyperopia persisting.^{18, 21, 23, 24}

The main limitation of the present study was slow recruitment resulting in closure of enrollment before the planned sample size was reached. We did not collect specific data on the reasons for slow recruitment, but informal discussions with participating investigators suggested that children who presented for eye examinations were frequently ineligible due to manifest strabismus. The smaller-than-planned sample size resulted in wider confidence intervals around our estimate of effect, which, in turn, resulted in more than anticipated uncertainty in our conclusions; our results are consistent with both a small to moderate benefit of glasses and also consistent with no benefit of immediate glasses. In addition, VA and/or stereoacuity may not have been normal at enrollment, which we were unable to assess because of the children's young age. Our lack of sufficient dynamic retinoscopy data is a weakness, because some providers recommend using assessment of accommodative response by dynamic retinoscopy to determine whether hyperopic patients should be treated. Deterioration criteria were also not reassessed in children wearing glasses who deteriorated but had a change in refraction. Therefore, the proportion of those who met deterioration criteria in glasses due to a change in refractive error is not known. Our results are generalizable only to children meeting the eligibility criteria for the present study, specifically those 1 to <3 years of age with +3.00 D to +6.00 D hyperopia, 1.50D anisometropia and/or astigmatism, and no measurable manifest strabismus who present to pediatric eye care professionals, and to children who are followed according to our protocol of follow-up visits at 6-month intervals. We did not perform community screening for hyperopia, and so our results may not be generalizable to such populations. Other considerations regarding the cost:benefit of glasses and the effect of the hyperopic correction on asthenopia, reading performance, social development, or intellectual development were not addressed in our study.

In conclusion, for 1- to <3-year-old children with uncorrected moderate hyperopia (+3.00 to +6.00D SE), estimates of failure for manifest strabismus, reduced distance VA, or reduced stereoacuity after 3 years of 6-month follow-up visits are inconclusive, and consistent with either a small to moderate benefit or no benefit (reduced failure rate) of immediate glasses compared with careful observation (glasses only if deteriorated). A larger study would be needed to determine a more precise estimate of the treatment effect and whether one management strategy is better than the other. Regardless of initial treatment approach, the moderate to high proportion of deterioration and subsequent moderate proportion of failure at 3 years indicate the need for eye care professionals to closely follow 1 to <3-year-old children with moderate hyperopia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Visit Completion by Treatment Group.

Diagram showing flow of participants through the study. One participant in the glasses group and one in the observation group completed the 36-month visit but did not complete the required follow-up visit after receiving a new glasses prescription.

Figure 2. Kaplan-Meier Estimates of Deterioration in Observation Group

Table 1:**Eligibility Criteria**

The following criteria must be met for the patient to be enrolled in the study:

- 1** Age 12 to <36 months
- 2** Spherical equivalent refractive error between +3.00 and +6.00 (by cycloplegic refractions) in either eye
- 3** Astigmatism 1.50D in both eyes
- 4** Spherical equivalent anisometropia 1.50D
- 5** Gestational age 32 weeks
- 6** Investigator is willing to prescribe glasses per protocol or observe hyperopia untreated for 3 years unless specific criteria for deterioration (Table 2) are confirmed
- 7** Parent understands the protocol and is willing to accept randomization to either glasses or no glasses initially, and is willing to wear glasses as prescribed or accept that glasses will not be prescribed by the investigator unless specific deterioration criteria (Table 2) are confirmed
- 8** Parent has phone (or access to phone) and is willing to be contacted by Jaeb Center staff
- 9** Relocation outside of area of an active PEDIG site for this study within the next 36 months is not anticipated.
- 10** No measurable manifest strabismus at distance (3 meters) or near (1/3 meter) by cover/uncover testing. Heterophoria is eligible.
- 11** No previously documented strabismus (parental report must be confirmed by investigator)
- 12** No clinical evidence of manifest or latent nystagmus
- 13** No prior treatment of refractive error with glasses or contact lenses unless duration of glasses or contact wear was one week or less and occurred more than 2 months prior to enrollment
- 14** No prior intraocular, refractive, or extraocular surgery
- 15** No prior treatment for amblyopia
- 16** No prior therapy for vergence/accommodation
- 17** No parental concerns over learning or development
- 18** No ocular co-morbidity that may reduce visual acuity
- 19** No symptoms of blur or asthenopia
- 20** No developmental delay, diagnosed by pediatrician or Individualized Education Program (IEP)
- 21** No known neurological anomalies (e.g. Cerebral palsy, Down syndrome)

Table 2:

Deterioration Criteria (prior to 3-year outcome; assessed in randomized correction, and requiring confirmation)

Deterioration

The participant was considered to have met deterioration criteria if ANY of the following criteria were met while wearing randomized correction by an unmasked examiner at a protocol-specified or non-protocol mandated visit after randomization but prior to the 3-year outcome exam, and confirmed by a retest performed by a masked examiner.

- 1 Any measurable manifest strabismus detected by cover/uncover test in primary gaze at distance (3 meters) or at near (1/3 meter)
 - 2 Distance VA below age norms^{35, 36} in either eye (see below)
 - 3 2 logMAR lines of IOD if VA is 20/25 or worse in the better-seeing eye (applies to IOD in either with or without correction but not one eye with and the other without)
 - 4 3 logMAR lines of IOD if VA is 20/20 or better in the better-seeing eye (applies to IOD in either with or without correction but not one eye with and the other without)
 - 5 Stereoacuity at near by Randot Preschool Stereoacuity test³⁷ below age normal values (see below)
 - 6 Non-protocol treatment is received in the absence of meeting deterioration criteria
-

Age Normal Values for Stereoacuity³⁷ and VA^{35, 36}

<i>Age range</i>	<i>Stereoacuity Level Needed to Meet Deterioration Criteria (arcsec)</i>	<i>VA Level Needed to Meet Deterioration Criteria</i>
36-47 months (3 years)	800 or worse	20/63 or worse
48-59 months (4 years)	400 or worse	20/50 or worse
60-71 months (5 years)	400 or worse	20/40 or worse
72-83 months (6 years)	200 or worse	20/40 or worse
84 months (7 years)	100 or worse	20/32 or worse

VA = visual acuity; logMAR = logarithm of minimum angle of resolution; IOD = interocular difference; arcsec = seconds of arc

Table 3:

Failure Criteria (3-year outcome; assessed with and without trial frames, requiring failure and confirmation in both)

Failure (primary outcome)^a

The participant was considered to have met failure criteria if ANY of the following criteria (with the exception of strabismus surgery prior to the 3-year outcome exam) were met during testing by a masked examiner at the 3-year examination both with and without trial frames (without prism or bifocal), and the criteria was confirmed by a retest, with and without trial frames.

- 1 Any measurable manifest strabismus in primary gaze at distance (3 meters) or at near (1/3 meter) not correctable with distance refractive correction alone
- 2 Strabismus surgery prior to the 36-month outcome exam
- 3 Distance VA below age norms^{35, 36} in either eye (see below)
- 4 2 logMAR lines of IOD if VA is 20/25 or worse in the better-seeing eye (applies to IOD in either with or without correction but not one eye with and the other without)
- 5 3 logMAR lines of IOD if VA is 20/20 or better in the better-seeing eye (applies to IOD in either with or without correction but not one eye with and the other without)
- 6 Stereoacuity at near by Randot Preschool Stereoacuity test³⁷ below age normal values (see below)

Age Normal Values for Stereoacuity and VA³⁵⁻³⁷

<i>Age range</i>	<i>Stereoacuity Level Needed to Meet Failure Criteria (arcsec)</i>	<i>VA Level Needed to Meet Failure Criteria</i>
36-47 months (3 years)	800 or worse	20/63 or worse
48-59 months (4 years)	400 or worse	20/50 or worse
60-71 months (5 years)	400 or worse	20/40 or worse
72-83 months (6 years)	200 or worse	20/40 or worse
84 months (7 years)	100 or worse	20/32 or worse

VA = visual acuity; logMAR = logarithm of minimum angle of resolution; IOD = interocular difference; arcsec = seconds of arc

^a Participants were not considered as a failure for the primary analysis if only partial testing was completed (e.g., if specific components of testing or required re-testing were not completed, such that failure was not confirmed).

Table 4:**Baseline Characteristics of Enrolled Participants**

	Glasses (N=65)		Observation (N=65)	
	N	%	N	%
Sex: Female	33	51	35	54
Race/Ethnicity				
Asian	1	2	0	0
Black/African American	2	3	3	5
Hispanic	7	11	8	12
White	53	82	52	80
Other	2	3	2	3
Age at Enrollment				
1 year	42	65	42	65
2 years	23	35	23	35
Mean (SD), years	1.8 (0.6)		1.8 (0.6)	
Family History of Amblyopia^a	21	32	20	31
Family History of Strabismus^b	26	40	25	38
Diagnosis of ADHD	0	0	0	0
SE Refractive Error: More hyperopic eye				
+1.00 to <+2.00D	0	0	0	0
+2.00 to <+3.00D	0	0	0	0
+3.00 to <+4.00D	25	38	20	31
+4.00 to <+5.00D	19	29	27	42
+5.00 to <+6.00D	20	31	13	20
+6.00 to <+7.00D	1	2	5	8
Mean (SD), SE	+4.32 (0.85)		+4.37 (0.87)	
SE Refractive Error: Less hyperopic eye				
+1.00 to <+2.00D	0	0	1	2
+2.00 to <+3.00D	4	6	2	3
+3.00 to <+4.00D	26	40	27	42
+4.00 to <+5.00D	22	34	21	32
+5.00 to <+6.00D	13	20	11	17
+6.00 to <+7.00D	0	0	3	5
Mean (SD), SE	+4.04 (0.85)		+4.07 (0.90)	
Anisometropia				
0.00 to <+0.50	47	72	46	71
+0.50 to <+1.00	13	20	12	18
+1.00 to +1.50	5	8	7	11
Mean (SD), SE	+0.28 (0.38)		+0.30 (0.39)	
Astigmatism: More astigmatic eye				
0.00 to <+0.50	36	55	29	45

	Glasses (N=65)		Observation (N=65)	
	N	%	N	%
+0.50 to <+1.00	18	28	19	29
+1.00 to +1.50	11	17	17	26
Mean (SD), SE	0.40 (0.48)		0.49 (0.48)	
Astigmatism: Less astigmatic eye				
0.00 to <+0.50	41	63	39	60
+0.50 to <+1.00	17	26	13	20
+1.00 to +1.50	7	11	13	20
Mean (SD), SE	0.27 (0.38)		0.37 (0.47)	

ADHD = Attention-Deficit/Hyperactivity Disorder; D = diopters; SD = standard deviation; SE = spherical equivalent

^aFamily history of amblyopia was not reported for 3 (5%) participants in glasses group and 2 (3%) in observation group.

^bFamily history of strabismus was not reported for 2 (3%) participants in glasses group.

Table 7:

Failure Criteria Met at 3 Years

	Glasses (N=53)		Observation (N=53)	
	N	%	N	%
3-Year Failure Status^a				
Failure	11	21	18	34
Not failure	42	79	35	66
Difference in Failure Proportions (glasses minus observation) with 95% Confidence Interval	-13% (-31% to 4%)			
Barnard's Exact Test for Difference in Proportions	p=0.14			
Reasons for Failure at 3-Year Exam^b				
Stereoacuity	6	11	16	30
Strabismus ^c	5	9	5	9
Visual acuity	3	6	4	8

^a Failure criteria had to be met and confirmed with and without trial frames.

^b Failure criteria may have been met for more than one reason. Denominator is the number of participants who completed the study.

^c Three participants in the glasses group and two in the observation group received strabismus surgery prior to the 3-year visit. These participants are included in the table.

Table 8:

Primary Outcome and Alternative Statistical Approaches

Analysis Approach ^a	Difference (Glasses – Observation Group)	95% CI
Primary Analysis^b No imputation for missing data.	–13%	–31% to 4%
Excluding 3-year exams completed outside the protocol window (36 ±2 months, N=11) ^b	–12%	–30% to 6%
Failure based on meeting failure criteria on the first or single test (not including results of retest, and not excluding participants who did not have a retest). ^b	–17%	–35% to 2%
Multiple imputation Three-year failure status imputed for the following participants with incomplete data at 3 years: <ul style="list-style-type: none"> • 36-month visit not completed (N=24) • An initial assessment or required retest was not performed and the available data indicate that the participant is a failure (considered not failing in primary outcome analysis; N=11) • A required 37-month visit was not completed (classified as not failing in primary outcome analysis; N=2) 	–17%	–35% to 0%
Include age at the 36-month visit as an adjustment covariate in the model. ^{b,c}	–11%	–28% to 6%

CI = confidence interval

^aFor analyses other than the primary analysis, the modification to the analysis is specified.

^bParticipants were included in analysis if at least one test of visual acuity, stereoacuity, or ocular alignment was obtained (one or more parameters). The outcome determination was based on all available data for visual acuity, stereoacuity, and ocular alignment, i.e. test and retest when available. If a required test or retest was not completed for a parameter, the participant was classified as not meeting failure criterion (or criteria) for that parameter.

^cBarnard's exact test does not allow for the adjustment of covariates. Binomial regression was used to compare failure rates in treatment groups.

Table 9:

Failure at 3 Years by Treatment Group According to Subgroups of Baseline Factors

	Glasse			Observation		
	N Failed	Total N	% Failed	N Failed	Total N	% Failed
Race						
Non-white	0	7	0	4	9	44
White	11	46	24	14	44	32
Gender						
Female	4	24	17	10	27	37
Male	7	29	24	8	26	31
Family History of Amblyopia						
Yes	4	16	25	6	17	35
No	7	37	19	12	36	33
Family History of Strabismus						
Yes	5	20	25	7	22	32
No	6	33	18	11	31	35
Anisometropia						
0.00 to 0.50D	8	39	21	14	36	39
0.50 to <1.00D	2	9	22	1	11	9
1.00 to 1.50D	1	5	20	3	6	50
Mean SE Refractive Error at Enrollment (D) ^a						
+2.50 to +4.00D ^b	2	23	9	6	19	32
+4.00 to +5.00D	5	17	29	7	20	35
+5.00 to +6.06D ^c	4	13	31	5	14	36

D = diopters

^aMean of refractive errors in the left and right eyes^bParticipants were eligible if moderate hyperopia (+3.00D to +6.00D SE) was reported in at least one eye. Refractive error in the less hyperopic eye was less than +3.00D in seven participants who completed the 3-year primary outcome visit.^cParticipants were eligible if moderate hyperopia (+3.00D to +6.00D SE) was reported in at least one eye. Refractive error in the more hyperopic eye was greater than +6.00D in three participants who completed the 3-year primary outcome visit.

Table 10:

Deterioration Criteria Met (Prior to 3 Years)

	Glasses (N=65)		Observation (N=65)	
	N	%	N	%
Kaplan-Meier Estimate of Cumulative Deterioration Rate	20	33	36	58
Reasons for Deterioration^a				
Stereoacuity	6	9	10	15
Strabismus	6	9	15	23
Visual acuity	9	14	10	15
Treatment due to parental concern	0	0	3 ^b	5
Treatment prescribed against protocol	1 ^c	2	3 ^d	5

^aDenominator is the number of enrolled participants.^bOne participant was prescribed patching for concerns of strabismus, one prescribed glasses for concerns of poor vision, and another prescribed glasses, but no reason for parental concern was provided.^cParticipant prescribed patching for concerns of amblyopia.^dOne participant was prescribed patching for concerns of amblyopia. Two prescribed glasses; no reason was provided.

Table 11:

Visual Acuity at 3 Years

	Glasses (N=53)	Observation (N=53)
Mean distance VA in better-seeing eye (logMAR) ^{a,b}	0.06	0.12
Difference in means (99% CI)	-0.05 (-0.12 to 0.01)	
Test for difference in means ^{c,h}	p=0.02	
Mean distance VA in worse-seeing eye (logMAR) ^{a,b}	0.16	0.23
Difference in means (99% CI)	-0.07 (-0.19 to 0.05)	
Test for difference in means ^{c,h}	p=0.15	
Proportion who failed to meet age-normal VA at distance ^e	3 (6%)	4 (8%)
Difference in percentages (99% CI)	-2% (-18% to 14%)	
Test of difference in percentages ^{d,h}	0.79	
Proportion with amblyopia at distance ^f	7 (13%)	9 (17%)
Difference in percentages (99% CI)	-4% (-24% to 16%)	
Test of difference in percentages ^{d,h}	p=0.68	
Mean Binocular near VA (logMAR) ^{b,g}	0.09	0.12
Difference in means (99% CI)	-0.03 (-0.10 to 0.04)	
Test for difference in means ^{c,h}	p=0.25	

VA = visual acuity; CI = confidence interval; logMAR = logarithm of minimum angle of resolution

^a Evaluated the best of the values reported with and without trial frames, during initial assessment and retest

^b Converted Snellen equivalents to logMAR equivalents (in parentheses) as follows: 20/16 (-0.1), 20/20 (0), 20/25 (0.1), 20/32 (0.2), 20/40 (0.3)

^c An analysis of covariance model, adjusting for age at the 3-year visit, was used to compare mean visual acuity between treatment groups.

^d Barnard's exact test was used to compare proportions between treatment groups.

^e Participants were classified as failing to meet age-normal visual acuity if, for either eye, distance visual acuity was below age-normal values both with and without trial frames, during initial assessment and re-test.

^f Participants were classified as having amblyopia if any of the following criteria were met: 1) the intraocular difference was ≥ 2 logMAR lines of IOD if VA is 20/25 or worse in the better-seeing eye, 2) the intraocular differences was ≥ 3 logMAR lines of IOD if VA is 20/20 or better in the better-seeing eye, or 3) VA less than age normal in each eye (presumed bilateral amblyopia). These values differ from Table 5, because failure was only declared if retest confirmed failure.

^g Assessment completed in randomized correction.

^h Results are considered statistically significant if p < 0.01.

Table 12:

Proportion with Manifest Strabismus and Stereoacuity at 3 Years

	Glasses (N=53)	Observation (N=53)
Proportion with manifest strabismus	5 (9%)	5 (9%)
Difference in percentages (99% CI)	0% (-17% to 17%)	
Test of difference in percentages ^{a,f}	-	
Mean stereoacuity ^{b,c}	2.2	2.3
Difference in means (99% CI)	-0.1 (-0.4 to 0.1)	
Test for difference in means ^{d,f}	p=0.15	
Proportion who failed to meet age-normal stereoacuity ^e	6 (11%)	16 (30%)
Difference in percentages (99% CI)	-19% (-40% to 2%)	
Test of difference in percentages ^{a,f}	p=0.02	

CI = confidence interval

^aBarnard's exact test used to compare proportions between treatment groups.^bEvaluated the best of the values reported with and without trial frames, during initial assessment and retest..^cConverted seconds of arc to logarithm of seconds of arc (in parentheses) as follows: 40 (1.60), 60(1.78), 100 (2.00), 200 (2.30), 400 (2.60), 800 (2.90), Nil (3.20)^dAn analysis of covariance model was used to compare mean change in stereoacuity between treatment groups. The analysis controlled for age at the 3-year visit and anisometropia at the most recent visit.^eParticipants were classified as failing to meet age-normal stereoacuity if near stereoacuity was below age-normal values both with and without trial frames, during initial assessment and re-test.^fResults are considered statistically significant if p 0.01.

Table 13:

Change in Refractive Error from Baseline to 3 Years

	Glasses (N=53)	Observation (N=53)
Mean change in SE refractive error from baseline to 3 years (more hyperopic eye) ^a	+0.15	−0.01
Difference in means (99% CI)	0.16 (−0.51 to 0.84)	
Test for difference in means ^{b,c}	p=0.53	
Mean change in SE refractive error from baseline to 3 years (less hyperopic eye) ^a	+0.30	+0.08
Difference in means (99% CI)	0.22 (−0.43 to 0.86)	
Test for difference in means ^{b,c}	p=0.38	

CI = confidence interval; SE = spherical equivalent

^aPositive values indicate a shift in the hyperopic direction.^bAn analysis of covariance model adjusting for refractive error at enrollment was used to compare mean change in refractive error between treatment groups.^cResults are considered statistically significant if p < 0.01.