Published in final edited form as:

Cochrane Database Syst Rev. ; 8: CD007738. doi:10.1002/14651858.CD007738.pub2.

Spectacle correction versus no spectacles for prevention of strabismus in hyperopic children

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Abstract

Background—Hyperopia (far-sightedness) in infancy requires accommodative effort to bring images into focus. Prolonged accommodative effort has been associated with an increased risk of strabismus (eye misalignment). Strabismus makes it difficult for the eyes to work together and

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Citation: Jones-Jordan L, Wang X, Scherer RW, Mutti DO. Spectacle correction versus no spectacles for prevention of strabismus in hyperopic children. *Cochrane Database of Systematic Reviews* 2014, Issue 8. Art. No.: CD007738. DOI: 10.1002/14651858.CD007738.pub2.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

may result in symptoms of asthenopia (eye strain) and intermittent diplopia (double vision), and makes near work tasks difficult to complete. Untreated strabismus may result in the development of amblyopia (lazy eye). The prescription of spectacles to correct hyperopic refractive error is believed to prevent the development of strabismus.

Objectives—To assess the effectiveness of prescription spectacles compared with no intervention for the prevention of strabismus in infants and children with hyperopia.

Search methods—We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2014, Issue 4), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to April 2014), EMBASE (January 1980 to April 2014), PubMed (1966 to April 2014), the *metaRegister of Controlled Trials* (*mRCT*) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictpr/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 3 April 2014. We also searched the Science Citation Index database in September 2013.

Selection criteria—We included randomized controlled trials and quasi-randomized trials investigating the assignment to spectacle intervention or no treatment for children with hyperopia. The definition of hyperopia remains subjective, but we required it to be at least greater than +2.00 diopters (D) of hyperopia.

Data collection and analysis—Two review authors independently extracted data using the standard methodologic procedures expected by The Cochrane Collaboration. One review author entered data into Review Manager and a second review author verified the data entered. The two review authors resolved discrepancies at all stages of the review process.

Main results—We identified three randomized controlled trials (855 children enrolled) in this review. These trials were all conducted in the UK with follow-up periods ranging from one to 3.5 years. We judged the included studies to be at high risk of bias, due to use of quasi-random methods for assigning children to treatment, no masking of outcomes assessors, and high proportions of drop-outs. None of the three trials accounted for missing data and analyses were limited to the available-case data (674 (79%) of 855 children enrolled for the primary outcome). These factors impair our ability to assess the effectiveness of treatment.

Analyses incorporating the three trials we identified in this review (674 children) suggested the effect of spectacle correction initiated prior to the age of one year in hyperopic children between three and four years of age is uncertain with respect to preventing strabismus (risk ratio (RR) 0.71; 95% confidence interval (CI) 0.44 to 1.15). Based on a meta-analysis of three trials (664 children), the risk of having visual acuity worse than 20/30 at three years of age was also uncertain for children with spectacles compared with those without spectacle correction irrespective of compliance (RR 0.87; 95% CI 0.60 to 1.26).

Emmetropization was reported in two trials: one trial suggested that spectacles impede emmetropization, and the second trial reported no difference in the rate of refractive error change.

Authors' conclusions—Although children who were allocated to the spectacle group were less likely to develop strabismus and less likely to have visual acuity worse than 20/30 children

allocated to no spectacles, these effects may have been chance findings, or due to bias. Due to the high risk of bias and poor reporting of included trials, the true effect of spectacle correction for hyperopia on strabismus is still uncertain.

BACKGROUND

Description of the condition

Hyperopia, also known as far-sightedness or long-sightedness, is a condition that arises when the image produced by light rays is focused behind the retina. In hyperopia, vision is blurred and requires accommodative effort to produce a clear image. Should the level of hyperopia be too great, accommodation will not be sufficient to overcome the amount of hyperopia without increasing the risk of strabismus and the eventual development of amblyopia (lazy eye), as well as resulting in symptoms such as blurry vision. Prolonged accommodative effort can result in strabismus, a condition commonly known as crossed eyes (also known as squint) (Babinsky 2013). Among full-term infants, one expects to see low to moderate levels of hyperopia that generally resolve as the child's vision emmetropizes (normalizes) (Goldschmidt 1969), which occurs, in large part, by nine to 12 months of age (Mutti 2004). A certain proportion of children have such high levels of hyperopia that the vision may not reach normal levels. Ingram 2000 found up to 9% of children retained at least +4.0 diopters (D) of hyperopia at six months old, and estimated that approximately 20% of these children may develop some type of visual problem. Atkinson 1996 estimated that infants with at least +3.50 D of hyperopia were 13 times more likely to develop strabismus by four years of age than infants with less hyperopia, and they are six times more likely to have decreased vision than those infants with less hyperopia or emmetropia or 'normal' vision. While most hyperopic eyes will eventually emmetropize, strabismus and subsequent amblyopia present a real danger to children whose eyes do not normalize. Amblyopia is a loss of vision for which eyeglasses and contact lenses may not restore full vision, though early treatment of children with refractive correction, patching, or drug therapy has been successful (Li 2009; Taylor 2011; Taylor 2012). Amblyopia that has not been identified or treated eventually may lead to vision loss (Holmes 2006). Children with amblyopia also are believed to be at a higher risk of losing vision in the unaffected eye when compared with the general population (Tomilla 1981; van Leeuwen 2007). Because of the more serious consequences of amblyopia, seeking ways to limit the development of strabismus can decrease one of the contributing factors for amblyopia.

After refractive error, strabismus is the next leading cause of eye problems among infants and young children, and has been reported to occur in 3.7% to 5.3% of children (Cotter 1997). If the strabismic child is not given appropriate treatment, strabismus can lead to the development of amblyopia or prevent the development of binocularity, which is the ability of the eyes to work together to produce a single image (Cotter 1997). Strabismus can manifest in different ways. When the eye turns inward to the nose, this condition is called an esotropia, while the eye turning outward is known as exotropia. Sometimes the tropia can be vertical (up or down). Together these are types of manifest strabismus, where the deviation of the eye can be intermittent or constant in frequency. When the strabismus is accommodative in nature and involves an esotropia rather than an exotropia, it is termed accommodative esotropia. Accommodative esotropia results from high levels of hyperopia,

an AC/A ratio (accommodative convergence/accommodation ratio that defines how much accommodative convergence occurs for a unit of accommodative response) that is too high, or the two factors working together. Onset is frequently between the ages of two and three years (Donahue 2007). The ability to do near tasks is compromised, with intermittent diplopia (double vision) and asthenopia (eyestrain) among other reported symptoms (Cotter 1997). About 10% to 20% of children with +4.0 D or more of hyperopia develop accommodative esotropia (Atkinson 1996; Dobson 1989). More recent, cross-sectional data from the Multi-Ethnic Pediatric Eye Disease and Baltimore Pediatric Eye Disease Studies showed that even at +2.0 D of hyperopia, there was a sixfold increase in the odds of esotropia (Cotter 2011). About half of the children with esotropia become amblyopic according to Donahue 2007.

Description of the intervention

Hyperopia is often treated with a spectacle correction to remove or reduce the need for accommodation to view distance and near targets (Donahue 2007; Rubin 2006), and, thus, may help to prevent the development of strabismus (Rubin 2006). No other interventions have been proposed to manage hyperopic infants in an effort to prevent the development of strabismus (AOA 2008).

How the intervention might work

Treatment of hyperopia with the intention of preventing accommodative esotropia is a topic of disagreement. Using a spectacle correction to reduce the need for accommodation when fixating at distance (i.e. reducing the accommodative effort needed to bring an image into focus) is a proposed treatment. In addition, reduced stimulation of accommodative convergence is an added benefit. The angle of existing esotropia will be reduced or perhaps eliminated. The expectation is that removing accommodative strain will allow regular binocular vision to develop during emmetropization, allowing for a decrease and eventual cessation of the spectacle correction (Rubin 2006). Although spectacle correction may be critical to prevent the development of esotropia, spectacles may prevent normal emmetropization. Atkinson 2000 found that any lag in the emmetropization of infants wearing a partial correction (undercorrection) for hyperopia at nine or 18 months had disappeared by three years, and that these children had similar refractive errors to children who were untreated. Others, however, found that children with a spectacle correction for their hyperopia did not emmetropize (Ingram 2000; Mulvihill 2000; Repka 1989). It is speculated that emmetropization is affected by the absence of accommodative demand that comes about from wearing a full spectacle correction (Birch 2005; Mutti 2009). As a result of this speculation, some ophthalmologists adopt a partial correction of the hyperopia in order to reduce the need for accommodation while providing some signal for emmetropization.

Why it is important to do this review

The conversion rate to amblyopia is high among children with esotropia, threatening long-term visual health and productivity. Hyperopia, in itself, presents a strain on the visual system causing symptoms such as blurred vision and asthenopia, as well as possibly adversely affecting the learning and academic growth of the highly hyperopic child. The

spectacle prescription is meant to correct the hyperopia to reduce the accommodative effort required to bring images into focus. It reduces stimulation of accommodative convergence as an added benefit. Whether reduced stimulation of accommodative convergence with spectacles lowers the risk of future strabismus is an important but unanswered question. However, if we treat every hyperope with spectacles, we could be treating 80% to 90% of these children unnecessarily (Birch 2005). Because of the differing evidence regarding the effectiveness of treating these children with spectacles and the concerns about interference with emmetropization, straightforward recommendations are difficult to make. To that end, high-quality data describing the effects, if any, of treatment with spectacles, and the level of treatment required to be effective, are necessary.

OBJECTIVES

To assess the effectiveness of prescription spectacles compared with no intervention for the prevention of strabismus in infants and children with hyperopia.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized and quasi-randomized controlled trials for this review.

Types of participants

We included trials with children from three months old to four years old at entry, with an age of primary outcome assessment at or before seven years of age. We based the risk of development of strabismus on the criteria defined by the included study, which were: a) levels of hyperopia greater than +2.0 D in both meridians with a high AC/A ratio or b) levels of hyperopia +4.0 D or greater. High hyperopia for the purposes of this review constituted the level at which the prescription of spectacles would be recommended. This level varies given differing beliefs about what constitutes high hyperopia, but frequently is considered between +3.50 D and +4.0 D of refractive error. The study investigators must have diagnosed hyperopia by cycloplegic retinoscopy. The AC/A ratio could have been measured by the heterophoria method using the increase in phoria (deviation of the eye) when measured between distance and near and adjusted for the interpupillary distance (IPD), or the gradient method using distance and near points and introducing graded spectacle lenses to calculate the AC/A ratio. High AC/A ratio interpretation differs depending on the method used. For the heterophoria method, a 10 prism-diopter difference was the cut point for high AC/A ratio, while for the gradient method we considered greater than 5:1 as high. We also considered differing levels of high AC/A, as defined by the studies. We had no gender restrictions. We excluded studies that included children with existing strabismus, amblyopia, or other ocular pathology.

Types of interventions

We included trials in which spectacle correction for any level of hyperopia greater than +2.00 D was compared with no spectacle correction. We also planned, when available, to

include trials that used a sham correction in the control group and trials that had compared full hyperopic spectacle correction with partial hyper-opic spectacle correction.

Types of outcome measures

Primary outcomes—The primary outcome was the proportion of children with manifest strabismus, as defined by study investigators, in the spectacle correction group compared with the proportion of children with strabismus in the no treatment group after a treatment period of a minimum of three years. Strabismus was commonly identified by one of the following methods: unilateral cover test, or the Hirschberg test (with or without spectacle correction), in conjunction with the 4-D prism test for suppression or microtropia. We considered other clinically meaningful treatment periods as reported by included studies in this review.

We considered manifest strabismus as a dichotomous variable and did not attempt to stratify outcomes according to final deviation or visual acuity (VA), or whether or not participants wore spectacles at the time of final assessment.

Secondary outcomes—Planned secondary outcomes for comparison of interventions were amblyopia, defined as a difference of three lines of VA between eyes, and stereoacuity as defined by the study using the appropriate criteria for the test chosen (i.e. Randot Stereoacuity Test or a similar measure); however, there were no data reported for these outcomes. Should later studies include these outcomes, we will consider them in updates. When reported from studies, we also considered how outcome results (such as strabismus and VA) were affected when accounting for compliance with spectacle correction. We also considered change in refractive error, as a measurement of the interference of emmetropization, and we defined it as the expected change anticipated to achieve emmetropization, given the level of refractive error at baseline, both continuously and as the proportion of children who did not achieve a refractive error in the emmetropic range. We considered quality of life measures though none was available at this time. We made a post-hoc decision to assess the proportion of participants with inadequate VA (worse than 20/30) as an intermediate assessment of the natural development of vision as the included trials did not evaluate either amblyopia or stereoacuity.

Search methods for identification of studies

Electronic searches—We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2014, Issue 4), Ovid MED-LINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to April 2014), EMBASE (January 1980 to April 2014), PubMed (1966 to April 2014), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictpr/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 3 April 2014.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), PubMed (Appendix 4), *mRCT* (Appendix 5), ClinicalTrials.gov (Appendix 6), and the ICTRP (Appendix 7).

Searching other resources—We searched reference lists of included studies to identify any additional inclusions. We also used the Science Citation Index-Expanded database (September 2013) to identify additional studies that may have cited trials that we included in this review. We did not handsearch journals or conference proceedings.

Data collection and analysis

Selection of studies—Two review authors independently reviewed titles and abstracts resulting from the literature searches, according to the inclusion criteria stated above. We classified the records as 'definitely relevant', 'possibly relevant', or 'definitely not relevant'. After adjudication, we retrieved the full-text reports for records classified as 'definitely relevant' or 'possibly relevant' by both review authors and then assessed the studies for inclusion, labeling each study as 'include' or 'exclude'. We did not need to contact trial authors of studies for further clarification as all studies could be included or excluded after examining the full-text reports. We excluded studies labeled as 'exclude' by both review authors after the review of full-texts and documented the reasons for exclusion. We resolved any disagreements through discussion at all stages of the study selection process.

Data extraction and management—Two review authors independently extracted data using a form based on templates developed and piloted by the Cochrane Eyes and Vision Group. One review author entered data into Review Manager (RevMan 2012), and a second review author verified the data entered. We resolved discrepancies in data extraction and data entry by discussion.

Assessment of risk of bias in included studies—Two of the review authors independently assessed the included studies for sources of bias according to the guidelines in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011), and resolved disagreements through discussion. We evaluated the studies for the following criteria: sequence generation and allocation concealment (selection bias), masking of participants/personnel (performance bias), masking of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. We reported our judgment for each criterion as 'low risk', 'high risk', or 'unclear risk' of bias. We did not contact study investigators for the present review. We will contact the trial authors of the studies included in future updates for additional information on issues that are unclear from information available in the original reports. In case of failure to communicate with the primary investigators, or if there is no response within four weeks, we will assess the risk of bias on the basis of the available information and will update it as more information becomes available.

1. We reported adequacy of sequence generation and allocation concealment. Methods of sequence generation that we considered to be at low risk of bias included use of random number tables, computer-generated randomization, and coin tosses. We considered any

method of allocation concealment that provided reasonable confidence that the investigators concealed the allocation sequence from participating physicians and participants (children and parents) to be at low risk of bias (such as centralized randomization and use of sequential opaque envelopes).

2. We assessed masking (blinding) of participants and personnel in the included studies. Although masking is not possible when spectacles are compared with no spectacles, masking is possible if the comparison of spectacles was with sham spectacles or partial spectacle correction.

3. We noted masking (blinding) of outcome assessors by study outcome or group of outcomes (e.g. primary and secondary outcomes) in the included studies.

4. For incomplete outcome data, we examined the proportion of participants lost to follow-up, reasons for loss to follow-up, and methods of analysis. We assessed whether follow-up for treatment and control arms were similar and whether there were missing data for outcomes of interest. We considered studies to be at low risk of bias when there were no missing data or when missing data were correctly imputed and when the reasons for missing data were adequately addressed. We plan to note the method of data imputation if reported in any future included studies.

5. We assessed risk of bias for selective outcome reporting. We considered a study to be at low risk of bias when trial authors reported all prespecified outcomes of interest in the published report in the same manner as described in the study protocol. We considered the risk of bias to be unclear whenever the protocol was not available. Whenever the published report described different outcomes in the protocol and published report, or when the protocol was not available, different outcomes were reported in the Methods and Results section, we considered the trial as having high risk of bias.

6. We examined included studies for other sources of bias and considered studies at low risk of bias when there was no evidence of research misconduct, no potential for bias based on study methodology, and the study was not stopped early due to evidence of harm or benefit.

Measures of treatment effect—We calculated a summary risk ratio (RR) with corresponding 95% confidence interval (CI) for dichotomous outcomes, including the primary outcome of the presence or absence of strabismus at three years and secondary outcomes of the presence or absence of emmetropization and VA above a clinically meaningful cut-point (i.e. 20/30 or worse). We planned to calculate summary RRs for the presence or absence of amblyopia and stereopsis. For continuous outcomes (e.g. change in refractive error to determine if emmetropization had occurred), we calculated mean differences (MD) with corresponding 95% CIs in changes from baseline when reported by included studies as well as the MD at a time point. For continuous outcomes, reported for spectacle compliant, spectacle noncompliant, and control groups separately, we averaged the means and standard deviations (SD) in order to calculate effect estimates for the as-randomized analyses (spectacle compliant and noncompliant versus controls).

Unit of analysis issues—The unit of analysis was the child, as strabismus is a malfunction of the binocular system. If cross-over trials are included in updates, we will attempt to extract or request from the investigators data that account appropriately for the cross-over design. If we are unable to retrieve these data, we will incorporate statistical techniques to approximate a paired analysis as outlined in Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2011).

Dealing with missing data—We did not contact primary authors of included studies to provide missing data such as SDs and intention-to-treat data. We did not impute missing data and we analyzed data as available.

Assessment of heterogeneity—We calculated the I^2 statistic (%) to determine the percentage of variation in effect estimates due to heterogeneity and not chance; a value above 50% suggested substantial statistical heterogeneity. We also examined the result of the χ^2 test for heterogeneity and the degree of overlap in CIs of included studies. Poor overlap also may suggest heterogeneity. We assessed clinical and methodologic heterogeneity by examining variations in participant characteristics, inclusion/exclusion criteria, and methods of assessment of primary and secondary outcomes.

Assessment of reporting biases—The small number of studies included in each meta-analysis prevented a meaningful interpretation of funnel plots. If studies are added to the meta-analyses in updates, we will examine funnel plots to assess reporting biases when 10 or more studies are included in a meta-analysis. We will use this method in conjunction with study characteristics or other factors that may contribute to asymmetry of the funnel plot.

Data synthesis—In the protocol of this review, we stated that we would not combine results in meta-analysis when the I^2 statistic suggested substantial statistical heterogeneity (i.e. I^2 greater than 50%) (Jones 2009). However, because we considered the included trials were similar clinically and methodologically, we combined the results in meta-analyses for strabismus and VA outcomes. We used a random-effects model for all analyses.

Subgroup analysis and investigation of heterogeneity—We further evaluated heterogeneity through subgroup analyses of children with high levels of hyperopia (+3.50 D or greater) at baseline. We may include additional subgroup analyses with strictly hyperopia versus hyperopia and additional risk factors as we include new studies in updates.

Sensitivity analysis—We conducted analyses based on the available case data for participants as randomized (assigned treatment group). We will consider the impact of excluding industry-funded studies and unpublished studies if we include such studies in updates.

RESULTS

Description of studies

We presented studies included in this review in the Characteristics of included studies table. We described excluded studies in the Characteristics of excluded studies table.

Results of the search

As of April 2014, the electronic searches resulted in 175 titles and abstracts and 24 references from trial registries for initial review. After we removed duplicates, we screened 186 records from which we identified 14 reports for full-text review (Figure 1). Of these 14 records, we selected for inclusion three reports discussing one trial (Atkinson 1996), four reports discussing a second trial (Ingram 1990), and one report from a third trial (Ingram 1985), investigating spectacle correction in hyperopic children between three and four years of age. We also identified one reference from ClinicalTrials.gov as an ongoing study and we describe it in the Characteristics of ongoing studies table. We excluded the remaining five studies.

We entered each of the references corresponding to the three included trials into the Science Citation Index Expanded database, which resulted in 215 additional citations (as of September 2013). We did not consider any of these citations as potentially relevant and did not review any full-text articles from these records.

Included studies

Participant selection—All three included trials enrolled children between six and 12 months of age (Atkinson 1996; Ingram 1985; Ingram 1990). There were 855 children enrolled across all three trials. To account for the broad inclusion criteria with respect to minimum eligible hyperopia levels, which ranged from +2.00 D (Ingram 1985) to +4.00 D (Atkinson 1996; Ingram 1990), we conducted prespecified subgroup analyses in which we analyzed treatment outcomes for children with hyperopia less than +3.50 D and hyperopia +3.50 D or more separately. This analysis made it possible to evaluate treatment effects in children within a similar range of hyperopia at baseline.

Interventions—All trials included in this review assigned children to receive spectacle correction or no spectacle correction. Table 1 provides a description of the parameters used for prescribing spectacle correction that differed between studies. Trial investigators used a consistent prescription of 2 D less than the participant's current refraction in two trials (Ingram 1985; Ingram 1990), while spectacle correction was influenced to a certain degree by the amount of hyperopia in the other trial (Atkinson 1996). The studies were similar in their follow-up protocols, as well as referrals for strabismus treatment should an incident case have appeared. Investigators of all trials modified spectacle prescriptions as necessary in response to refractive error changes.

Outcomes—Two trials reported using the cover test to assess the presence of strabismus (Atkinson 1996; Ingram 1990). VA was assessed using Cambridge Crowding Cards in one trial with failure defined as worse than 20/40 (i.e. 6/12) (Atkinson 1996). Two trials also used the Sheridan Gardiner test (Atkinson 1996; Ingram 1990), and one trial used the Snellen test (Ingram 1990). We considered that the methods used to measure both the presence of strabismus and VA were consistent across the three included trials to allow quantitative summary meta-analyses of these outcomes.

Two of the three trials evaluated emmetropization (Atkinson 1996; Ingram 1990). The trials used different methods to determine whether the child's vision had emmetropized, which may not necessarily measure the actual developmental changes in the eye, and effect estimates may not be comparable across trials. One trial recorded the mean refractive error at baseline and follow-up in both “fixing eyes” and “non-fixing eyes”, and also set a cut-point of greater than +3.5 D in any meridian to determine whether emmetropization had not occurred (Ingram 1990). The other trial analyzed the change in the most hyperopic meridian, which was not always the same at each follow-up examination (Atkinson 1996). Outcome examiners in two trials determined compliance with treatment (Ingram 1985; Ingram 1990). Investigators of the other trial considered children who wore the prescribed spectacles for greater than 50% of waking hours as compliant based on parent interviews and questionnaires (Atkinson 1996).

We conducted a final assessment of strabismus and VA outcomes when children were between three and four years of age in all three trials.

None of the trials assessed the presence of amblyopia, or measured stereoacuity or quality of life in these children.

Funding sources—One trial was funded by regional sources, the Medical Research Council of Great Britain and a grant from the East Anglia Regional Health Authority (Atkinson 1996). Ingram 1985 and Ingram 1990 did not report funding sources.

Excluded studies—We reviewed and excluded five studies. One study did not investigate the use of spectacle correction as an intervention (Althaus 1994). The other four studies were not randomized or quasi-randomized trials (Anker 2004; MacEwen 2008; Nischal 2008; Roth 1989).

Risk of bias in included studies

Figure 2 presents summary information on the risk of bias for the trials included in this review.

Allocation—We judged Ingram 1990 to be at low risk of bias for random sequence generation because the study investigators used a “random number table” to generate the random sequence. We judged Atkinson 1996 to be at high risk of bias because some of the infants were alternately assigned to the treated or untreated group. Ingram 1985 did not specify the method for randomization, therefore, we judged the risk to be unclear.

None of the three trials provided sufficient details describing how participants were allocated to treatment groups and we judged them to have an unclear risk of bias for allocation concealment.

Masking of participants and personnel (performance bias)—All studies compared spectacles versus no spectacles. Because no sham or control spectacles were used, we judged performance bias as high in all included studies.

Masking of outcome assessors (detection bias)—None of the three trials addressed masking of people who assessed VA and strabismus. Thus, we assess all studies as having an unclear risk of bias.

Incomplete outcome data—We judged all included trials to be at high risk of bias for incomplete outcome data. Atkinson 1996 did not adequately outline the number of participants from the baseline visit onward and the numbers reported in the results were inconsistent among analyses; thus, the data available did not allow us to determine the number of participants who dropped out. Ingram 1990 did not clearly identify participants allocated to the treatment and no treatment groups, and was not specific about the participants dropping out. Ingram 1985 did not specify how many participants were allocated to each group or the number of participants lost to follow-up according to treatment group. The study authors reported 149 eligible children did not enter the study but did not explain why.

Selective reporting—We judged two trials to be at unclear risk of bias for selective reporting because we did not identify study protocols (Atkinson 1996; Ingram 1990). We judged Ingram 1985 to be at high risk of bias due to a change in the study outcome because of concerns regarding the ability to measure VA and amblyopia in 3.5 year olds correctly.

Other potential sources of bias—We did not identify other potential sources of bias for the three trials.

Effects of interventions

See: **Summary of findings for the main comparison**

Presence of strabismus—All three trials contributed data to conduct as-randomized analyses for the presence of strabismus. All studies reported available data only, comprising 674 children and not accounting for 181 children (21%) with missing data. The reason for missing data was mainly due to drop-out or participants.

When we combined the three included trials (674 children) into a summary meta-analysis based on as randomized data, spectacle correction led to a 29% reduction in the risk of developing strabismus after three years of age compared with no correction (RR 0.71; 95% CI 0.44 to 1.15; $I^2 = 52\%$) (Analysis 1.1; Figure 3). The RR for the subgroup of 485 children with hyperopia +3.50 D or greater (using a subset of children from Ingram 1985 and children from the remaining studies) was 0.81 (95% CI 0.50 to 1.31; $I^2 = 49\%$) (Analysis 1.1; Figure 3).

Visual acuity—All three trials contributed data to conduct as-randomized analyses for VA. All studies reported available data only, comprising 664 children and not accounting for 191 children (22%) with missing data.

For the purposes of assessing VA, we considered vision worse than 20/30 (i.e. 6/9) to be inadequate. Based on a meta-analysis of three trials (664 children), the RR of worse than 20/30 VA at three to four years of age was 13% lower for children assigned to spectacles

compared with children without spectacle correction irrespective of compliance (RR 0.87; 95% CI 0.60 to 1.26; $I^2 = 22\%$) (Analysis 1.2; Figure 4). If we consider only those children who had at least +3.50 D of hyperopia at baseline from Ingram 1985, the summary meta-analysis (three trials, 475 children) revealed an RR of 0.83 (95% CI 0.54 to 1.29; $I^2 = 43\%$) (Analysis 1.2; Figure 4).

Emmetropization—Two trials reported emmetropization (Atkinson 1996; Ingram 1990). Given the variety of methods used to evaluate emmetropization, we could not conduct summary meta-analyses of this outcome. Instead, we have provided a narrative summary of the results from the two trials individually.

When dichotomized with refractive error +3.5 D or greater at follow-up, indicating emmetropization had not occurred, one trial (287 children) showed a RR of 1.32 (95% CI 0.97 to 1.80) when comparing 60 of 144 children in the spectacle group with 45 of 143 children in the control group for which emmetropization had not occurred (Ingram 1990). When evaluating the mean change in refractive error from baseline to final follow-up (mean of 3.2 years), there was a mean difference of 0.22 D (95% CI -0.20 to 0.64) in the “fixing eye” between 100 children in the spectacle group (mean change -1.12 D, SD 1.65) and 89 children in the control group (mean change -1.34 D, SD 1.30) among children without strabismus at the follow-up visit. Among children with strabismus, the MD was -0.24 D (95% CI -0.96 to 0.48) between 47 children in the spectacle group (mean change -0.40 D, SD 2.13) and 53 children in the control group (mean change -0.16 D, SD 1.40) (Ingram 1990).

The other trial reported no difference between the spectacle group and control group after accounting for compliance with treatment (Atkinson 1996). At three years of age, the refractive error in the most hyperopic meridian was +3.4 D in the spectacle group and +3.1 D in the control groups. Using SDs inferred in the text describing the results for each group, the difference in the mean refractive error between 44 children in the spectacle group (mean +3.4 D, SD 1.4) and 37 children in the control group (mean +3.1 D, SD 1.5) was 0.3 D (95% CI -0.34 to 0.94). The trend was similar when we accounted for compliance with a refractive error of +3.3 D in the spectacle compliant group. The investigators reported a statistically nonsignificant difference in refractive error at three years for both of the above comparisons.

DISCUSSION

Summary of main results

We included three trials in this review from which 674 hyper-opic children provided follow-up data to determine the effects of spectacle correction for preventing strabismus. All trials allocated infants between the ages of six and 12 months to a spectacle treatment group or an untreated group and evaluated the presence of strabismus and assessed VA and emmetropization between three and four years of age. Based on our assessment of these trials, spectacle correction was not associated with a lower risk of developing strabismus or improved VA in infants with hyperopia. Two studies considered the potential adverse effect of spectacle treatment, the inhibition of emmetropization. The results from one trial suggested that spectacles impede emmetropization (as defined by an increase in risk of

remaining hyperopic) (Ingram 1990); a second trial reported no difference in the rate of refractive error change (Atkinson 1996). We observed several potential biases in the design (no use of a proper randomization sequence and no masking of those who assessed treatment outcomes) and conduct (large proportion of participants lost to follow-up as well as incomplete compliance with the intervention) of the three included trials. Although children who were allocated to the spectacle group were less likely to develop strabismus, this may have been a chance finding, or due to bias. Due to high risks of bias and poor reporting of included trials, the true effect of spectacle correction for hyperopia on strabismus is still uncertain.

Overall completeness and applicability of evidence

Clinically, the three included studies were not substantially heterogeneous. For presence of strabismus, although there appeared to be some statistical heterogeneity across trials, the confidence intervals of individual studies overlapped and the I^2 value was around our pre-specified threshold of 50% ($I^2 = 52\%$). Thus we combined the findings in a meta-analysis. For visual acuity worse than 20/30, the statistical heterogeneity was not substantial ($I^2 = 22\%$). We combined the findings in a meta-analysis for presence of strabismus at three to four years of age and VA worse than 20/30. We saw additional methodologic variation in the way investigators of two trials evaluated emmetropization, preventing meta-analysis of this outcome. In both trials, the amount of refractive error change that occurred seemed to result in incomplete emmetropization (i.e. the resulting refractive error had not reached a “normal” level).

It is important to consider children similar in risk and possible etiology because highly hyperopic children are thought to be less likely to emmetropize (Mutti 2009), and therefore are likely to benefit from treatment. In subgroup analyses, we considered only those children with at least +3.50 D hyperopia at baseline. The subgroup analyses did not show that wearing spectacles decreased the risk of developing strabismus or of poor VA in children who were highly hyperopic.

One potential issue when considering these trials is the possible impact the time of treatment initiation may have had. Ingram 1985 began with infants that were one year old, but in a subsequent study (Ingram 1990), treatment initiation was moved to six months of age because they suspected the sensitive period was earlier. Atkinson 1996 enrolled infants between six and eight months of age. Therefore, comparing varying ages may be obscuring the possibility that a sensitive period may exist.

The trials used similar treatments (spectacles) and controls (untreated) and the amount of correction was reasonably consistent across the three trials (Table 1). Both Ingram 1985 and Ingram 1990 used a +2.00 D decrease in the refractive correction for spectacle prescription as opposed to the +1.00 D decrease in refractive correction used by the other trial (Atkinson 1996).

Assessing treatment compliance is difficult to ascertain given the potential for recall bias. Determining what constitutes compliance is also a problem. It is possible that there is a certain amount of time that spectacles should be worn in order to have a clinically

meaningful effect. Each study used a different assessment of compliance. Ingram 1990 simply stated that “some children obviously wore the glasses consistently, but it was apparent that some wore them irregularly and others not at all” as their definition of compliance. It appears that Ingram 1985 used something similar to classify participants as compliant. Atkinson 1996 questioned the parent and classified a child as compliant whenever the parent indicated that the child wore the spectacles at least 50% of the time. One option for a future trial would be one that assesses treatment groups assigned to varying wearing times (i.e. four hours per day, eight hours per day, 12 hours per day) compared with a no correction group to allow for the determination of an effect of the amount of time correction was worn.

In terms of the outcomes, all trials used similar assessments at a similar time, so comparing them was reasonable; however, the data contributing to this review, given the potential attrition bias mentioned above, do not provide a reliable assessment of the effect of spectacle correction. All of the studies were conducted in the UK, limiting the potential sample from which to draw. The reports did not include any information regarding race, gender, or other socioeconomic variables, neither was family history, a known risk factor for the development of strabismus, reported.

Quality of the evidence

All trials had a high degree of uncertainty in the presence of potential biases due to insufficient descriptions of important methodologic design issues. One trial used alternate assignment for participants to treatment groups, so we judged the risk of bias as high. One trial used a random number table to generate random sequence, so we judged the risk as low. The other trial did not specify the method for randomization. None of the three trials indicated how treatment assignments were allocated to ensure investigators and study participants did not have prior knowledge of their treatment assignment. We judged all three trials at high risk of performance bias as they all compared spectacles versus no treatment. None of the three trials specified masking of people assessing VA and strabismus, so the risk of detection bias remains unclear. We considered all three trials included in this review to be at a high risk of bias for incomplete outcome data (Figure 2). Due to the high loss to follow-up in all trials and lack of details regarding missing participant data, the data were not complete and do not provide an accurate estimate of the overall treatment effect of spectacle correction for preventing strabismus.

Potential biases in the review process

Two review authors independently reviewed titles and abstracts and full-text reports of potentially eligible trials, and extracted data and assessed risk of bias for all trials included in this review, which should have minimized review bias. During the review process, we added a post-hoc secondary outcome for VA. We are aware of no other potential biases in the review process.

Agreements and disagreements with other studies or reviews

To our knowledge, no authors have completed any other systematic reviews on the subject of this review. One retrospective, observational study of hyperopic children identified in a

preschool screening found no statistically significant difference between the percentage of children who developed amblyopia among children who received some type of spectacle correction and children who did not (21% with spectacle correction versus 38% with no spectacle correction); however, the study authors concluded the results were consistent with a benefit of spectacle correction on reducing amblyopia risk. However, only 16 children received no treatment so the sample size was insufficient to support inferences (Colburn 2010). Current preferred practice guidelines show uncertainty with regard to when to prescribe spectacles for hyperopic children due to the lack of empirical data. The American Optometric Association Optometric Clinical Practice Guidelines suggest that in the absence of amblyopia or strabismus practitioners begin treating hyperopia in children from birth to 10 years of age at levels of hyperopia of +5.0 D or greater, with consideration made for other coexisting factors that are relevant in the clinician's judgment. They recommend a partial prescription with monitoring (AOA 2008). The American Academy of Ophthalmology Pediatric Ophthalmology/Strabismus Panel has issued age-tiered guidelines for prescribing correction for hyperopia. In children under one year of age with no manifest deviation, they recommend correction beginning at +6.0 D of hyperopia. For children ages one to two years, they recommend prescribing spectacles for hyperopia of +5.0 D or greater, and for children ages two to three years of age, they recommend refractive correction for +4.50 D and greater of hyperopia (AAO 2012).

Leat presented several recommendations for prescribing spectacle correction based upon all literature evaluating potential treatment effects in hyperopic children (Leat 2011). Based on the expected distribution of refractive error at various ages, the trial author recommended partial correction when the refractive error fell outside the normal range of the age group. After one year of age, a partial prescription was suggested starting at +3.50 D of hyperopia. Based upon the guidelines, recommendations, and the results of this review, there is uncertainty in the benefit of spectacle correction and the preferred amount of correction, which is another area that warrants investigation in order to be able to assess the efficacy of spectacle treatment for the prevention of strabismus. There is also some variation in the level of hyperopia at which to prescribe spectacle correction, although the guidelines agree that there is a level that is 'high' hyperopia beyond which refractive error is unlikely to resolve on its own.

AUTHORS' CONCLUSIONS

Implications for practice

The limited number of trials, all with potentially significant risk of bias affecting the treatment effect estimates, makes it impossible to draw firm conclusions regarding the most appropriate course of action with respect to spectacle correction for preventing the development of strabismus in hyperopic infants. Although children who were allocated to the spectacle group were less likely to develop strabismus, this may have been a chance finding or due to bias. Because of the high/unclear risk of bias of included trials, the true effect of spectacle correction for hyperopia on strabismus is still uncertain. The suggestion of positive effects on later visual acuity remains inconclusive until further clinical trial

results are available. The information is, at best, equivocal from the trials that have been reported in the literature.

Implications for research

More clinical trials with attention to proper study design are needed to provide a better foundation for determining the effect of spectacle correction to prevent strabismus in hyperopic children. Properly randomizing participants to either a treatment or control group and careful concealment of the treatment allocation has been lacking in research completed to date. In addition, participants need to be followed adequately and every attempt must be made to schedule final outcome visits for these children. Highly hyperopic children make up a very small percentage of the infant population, so minimizing loss to follow-up in these trials is necessary to achieve adequate power. Estimating sample size with adjustment for attrition is also recommended. An adequately powered clinical trial is likely to require multiple sites in order to address the issue of incidence of strabismus with and without spectacle correction for hyperopia. Although the three included trials were published more than 15 years ago and the clinical evidence demonstrated was uncertain, the ongoing trial Hyperopia Treatment Study 1 (HTS1) might be able to provide more information on this topic in the future. With similar entry criteria and interventions to previous studies, this study will benefit from controlled methodology. In future updates of this review, we will include the trial in our meta-analysis when sufficient data are available.

Future research should carefully consider the issue of compliance to spectacle wear in these infants. Because of their age, education and encouragement of the parents is key to increasing the percentage who comply with the treatment. Alternatives to make it easier to keep the babies in their correction (glasses straps, contact lenses, etc.) should make it easier for parents to comply as well. As the effectiveness of treatment depends on actually receiving the treatment, this area is worth considerable effort prior to launching a trial.

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Comparison 1

Spectacle correction versus no spectacle correction

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of strabismus at 3-4 years of age	3	674	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.44, 1.15]
1.1 Children with hyperopia < 3.5 D at ages 6-12 months	1	189	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.14, 1.05]
1.2 Children with hyperopia ≥ 3.5 D at ages 6-12 months	3	485	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.50, 1.31]
2 Visual acuity worse than 20/30 at 3-4 years of age	3	664	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.60, 1.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Children with hyperopia < 3.5 D at ages 6-12 months	1	189	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.31, 5.86]
2.2 Children with hyperopia ≥ 3.5 D at ages 6-12 months	3	475	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.54, 1.29]

Characteristics of excluded studies [ordered by study ID]

Atkinson 1996	
Methods	<p>Initially 3166 children were screened, which was approximately 74% of the total eligible infant population. Of those screened, 9.3% were identified for additional follow-up</p> <p>Number randomized (total and per group): total: 177 children; number in each group was not reported</p> <p>Number analyzed (total and per group): outcome data on strabismus were available from 124 hyperopic infants (+4.0 D): “spectacles” (n = 68) and “untreated” (n = 56) outcome data on visual acuity were available for 114 hyperopic infants (+4.0 D): “spectacles” (n = 55) and “untreated” (n = 59)</p> <p>Infants provided outcome data that were analyzed 2 different ways: 1. “treated group” (n = 48): children who were offered treatment and complied by wearing their correction, compared with children who were “not treated” (n = 76): children who did not comply with wearing their correction in addition to children not offered correction 2. “offered treatment” (n = 68): including both compliers and noncompliers randomized to the “spectacle” group compared with children “not offered treatment” (n = 56)</p> <p>Losses to follow-up: number lost to follow-up not reported, no sufficient baseline information to calculate number lost to follow-up from the number with follow-up data available</p> <p>Unit of randomization: individual</p> <p>Unit of analysis: strabismus: individual child; visual acuity: individual child (pass/fail)</p>
Participants	<p>Country: the screening population consisted of children living in Cambridge, UK</p> <p>Age: children initially were screened at 6-8 months of age; eligible children identified from screening were followed up within 9 months of age</p> <p>Gender: not reported</p> <p>Inclusion/exclusion criteria: infants attending well-baby visits ages 6-8 months were referred for follow-up if the photorefraction revealed marked hyperopia, myopia, or anisometropia or if significant strabismus or any ocular pathology was evident</p> <p>Equivalence of baseline characteristics: not reported</p> <p>Diagnoses in participants: the screening procedure included cycloplegia with 1% cyclopentolate, isotropic photorefraction; infants identified to have hyperopia (> +3.5 D), myopia (-2.0 D), anisometropia (1.5 D difference between corresponding axes), strabismus, or any other ocular pathology from photorefraction were followed up with retinoscopy</p>
Interventions	<p>Intervention 1: spectacle correction:</p> <ul style="list-style-type: none"> • sphere: 1.0 D less than least hyperopic meridian (corrections under 1.5 D were not prescribed) • cylinder: up to 2 years of age - half of astigmatic error if over 2.5 D; at 2.0-3.5 years - half of any astigmatic refractive error; over 3.5 years - full correction <p>Prescriptions were checked frequently, at which time the child's wearing of the spectacles was monitored by close, sympathetic questioning of the parents</p> <p>Intervention 2: no spectacle correction</p> <p>Length of follow-up: planned: repeated follow-up visits at regular intervals through 4 years of age actual: not reported</p>
Outcomes	<p>Incidence of strabismus was diagnosed with the cover test. Single-letter acuity was measured with the Sheridan-Gardiner test at 3 m and Cambridge Crowding Cards with spectacle correction worn as appropriate. Emmetropization was evaluated by measuring the refractive error in the most hyperopic meridian</p> <p>Intervals at which outcome assessed: repeated follow-up visits at 4- to 6-month intervals</p> <p>Adverse effects: not reported</p>
Notes	<p>Type of study: published</p> <p>Funding: Medical Research Council of Great Britain, and a grant from the East Anglia Regional Health Authority</p> <p>Declaration of interest: not mentioned</p> <p>Study period: children born in 1981-1983 were screened and followed up until 7 years of age</p> <p>Subgroup analyses: according to compliance with wearing spectacles</p>

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Spectacle correction was tested as a preventive intervention by randomly assigning infants in the hyperopic group to 'spectacles' and 'non-spectacles' groups" "Infants identified as having significant hyperopia but with no meridian greater than +6D were alternately assigned to the treated or untreated group"
Allocation concealment (selection bias)	Unclear risk	Assignment by alternation allows next assignment to be known
Masking of participants and personnel	High risk	Participants and personnel were not masked, which could have been attempted with use of sham spectacles
Masking of outcome assessors (detection bias)	Unclear risk	Masking of outcome assessors was not specified
Incomplete outcome data (attrition bias) All outcomes	High risk	The study did not report baseline numbers for each treatment group. The numbers reported in the results were inconsistent between analyses, which did not allow us to determine the number of participants who dropped out
Selective reporting (reporting bias)	Unclear risk	The protocol was not available
Other bias	Low risk	No other sources of bias identified
Ingram 1985		
Methods	Number randomized (total and per group): 306 children entered the trial untreated group: 154 spectacle-treated group: 152 Number analyzed (total and per group): 265 children untreated group: 136 spectacle-treated group: 129 Losses to follow-up: 41 Unit of randomization: individual Unit of analysis: squint - individual child; visual acuity - single eye with the lowest visual acuity	
Participants	Country: the population consisted of children from the towns of Kettering and Rushden in the UK Age: not reported Gender: not reported Inclusion/exclusion criteria: the refractive criteria for entry into the trial were bilateral spherical hypermetropia (+2.0 DS) or anisometropia (+1.0 D sphere or cylinder), or both Equivalence of baseline characteristics: not reported Diagnoses in participants: children from the general study population underwent refraction after cycloplegia with 1% cyclopentolate or 1% atropine. The refractive criteria for entry into the trial were bilateral spherical hypermetropia (+2.0 D sphere) or anisometropia (+1.0 D sphere or cylinder), or both	
Interventions	Intervention 1: spectacle correction: "the prescription of the glasses was based on the cycloplegic retinoscopy with 2.00 D subtracted from each meridian of each eye. Spectacles were prescribed until refraction came within normal limits, that is, < +2.00 DS right and left, < +1.50 D cyl, < 1.00 DS or cyl anisometropia" Intervention 2: no spectacles If strabismus (squint) was detected during follow-up, children were given conventional treatment. Additional occlusion was also offered to both groups throughout follow-up Length of follow-up: planned: until 3.5 years of age actual: 1-year outcomes reported	
Outcomes	Incidence of strabismus (squint) and visual acuity in the worse eye Intervals at which outcome assessed: every 3 months until the age of 3.5 years Other issues with outcome assessment: "The end result was to be decided on the basis of: (a) presence or absence of esotropia/intermittent esotropia; (b) presence or absence of amblyopia at the age of 3½. This has not proved possible in practice" "Therefore the end result has been recorded as the last known visual acuity of the eye with lower acuity, with spectacle correction if necessary, and after occlusion had been given and often some time after occlusion had stopped" Adverse effects: not reported	
Notes	Type of study: published Funding: not reported	

Ingram 1985

Declaration of interest: not mentioned
Study period: not reported
Subgroup analyses: according to compliance with wearing spectacles

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study only mentioned "the trial required that her child would be randomly allocated to wearing glasses or not, but that she had to decide whether she wished to enter the trial before the random decision for 'treatment' or 'no treatment' was taken." Method for random sequence generation was not specified
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not specified
Masking of participants and personnel	High risk	Participants and personnel were not masked, which could have been attempted with use of sham spectacles
Masking of outcome assessors (detection bias)	Unclear risk	Unknown as to whether the person who assessed visual acuity and strabismus was also the outcomes assessor
Incomplete outcome data (attrition bias) All outcomes	High risk	"Some of the children who were lost to follow-up moved from the area, but some information has been obtained from colleagues elsewhere in the UK. Others dropped out but reattended after a final recall about the age of 3½ years or returned spontaneously because of squint or poor performance at a school vision screening test. A final vision was recorded for 265 of the 306 children who originally entered the trial." The trial authors did not report the number of participants initially allocated to each treatment group, or the number of participants lost to follow-up according to treatment group. Study authors reported 149 eligible children did not enter the study but did not explain why
Selective reporting (reporting bias)	High risk	"The end result was to be decided on the basis of 1) presence or absence of esotropia/amblyopia at the age 3½. This has not proved possible in practice" Investigators reported the presence of esotropia/amblyopia that was recorded at last known visit
Other bias	Low risk	No other sources of bias identified

Ingram 1990

Methods	<p>Number randomized (total and per group): total: 372 children; number in each group was not reported Number analyzed (total and per group): results were reported for 289 children 3.5 years of age who were assessed for the presence of strabismus (squint) and visual acuity with cycloplegic refraction untreated group: 145 spectacle treated group: 144 Losses to follow-up: 56 children dropped out of the study early and others throughout follow-up for a total of 87 Unit of randomization: individual Unit of analysis: strabismus (squint): individual child; visual acuity: 'worse eye' of individual child</p>
Participants	<p>Country: children living within the boundaries of the Kettering and District Health Authority, and Market Harborough, UK Age: children born between July 1978 and July 1981 who were 6 months old at time of visit Gender: not reported Inclusion/exclusion criteria: +4.0 D meridional hypermetropia. 1 child was excluded because of congenital nystagmus Equivalence of baseline characteristics: not reported Diagnoses in participants: children within the general screening population undergoing retinoscopy with cycloplegia with 1% cyclopentolate refractions +4.0 D hypermetropia. A 'refraction' figure was calculated to determine the degree of hypermetropia by subtracting 1.75 D from 1-m retinoscopy in the most hypermetropic meridian</p>
Interventions	<p>Intervention 1: prescription glasses based on subtracting 2.0 D from each meridian of the retinoscopy Intervention 2: no glasses Additional treatment with spectacles, occlusion, operation as necessary was offered to children who developed squint throughout the follow-up period Length of follow-up:</p>

Ingram 1990	
	planned: not reported actual: through 3.5 years of age
Outcomes	The presence of strabismus (squint) was assessed by the cover test, and visual acuity measured on either the linear Sheridan-Gardiner or Snellen tests with correction if worn. Emmetropization was initially determined by dichotomizing refractive error, with $> +3.5$ D indicating emmetropization had not occurred. A secondary analysis of emmetropization included the change in the mean refractive error from baseline to follow-up Intervals at which outcome assessed: every 3 months Adverse effects: not reported
Notes	Type of study: published Funding: not reported Declaration of interest: not mentioned Study period: not reported Subgroup analyses: according to compliance with wearing spectacles

Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Using a table of random numbers, all cases with an odd number were prescribed glasses (2.00 D less than the retinoscopy figure for each meridian in each eye) for constant wear and those with even numbers were not prescribed glasses"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not specified
Masking of participants and personnel	High risk	Participants and personnel were not masked, which could have been attempted with use of sham spectacles
Masking of outcome assessors (detection bias)	Unclear risk	Unknown as to whether the person who assessed visual acuity and strabismus was masked
Incomplete outcome data (attrition bias) All outcomes	High risk	The investigators reported that 56 children dropped out of the study but not by treatment group. The investigators did not provide reasons for loss to incomplete outcome data. 87 children were unaccounted for the reporting of the results
Selective reporting (reporting bias)	Unclear risk	The protocol was not available
Other bias	Low risk	No other sources of bias identified

Characteristics of ongoing studies [ordered by study ID]

Study	Reason for exclusion
Althaus 1994	Did not investigate effects of spectacle correction
Anker 2004	Not a randomized or quasi-randomized trial
MacEwen 2008	Not a randomized or quasi-randomized trial
Nischal 2008	Not a randomized or quasi-randomized trial
Roth 1989	Not a randomized or quasi-randomized trial

DATA AND ANALYSES

Hyperopia Treatment Study 1	
Trial name or title	Hyperopia Treatment Study 1 (HTS1)
Methods	Randomized controlled trial
Participants	Inclusion criteria:

Hyperopia Treatment Study 1

	<ol style="list-style-type: none"> 1. age 12 to < 60 months 2. refractive error between +3.00 D and +6.00 D SE (by cycloplegic refraction) in either eye 3. astigmatism < 1.50 D in both eyes 4. spherical equivalent anisometropia +1.50 D 5. for children 36 to < 60 months of age: normal visual acuity for age - uncorrected monocular visual acuity in both eyes of 20/50 or better for age 36 to < 48 months and 20/40 or better for age 4 years without cycloplegia using the ATS-HOTV® visual acuity testing protocol; no amblyopia - zero (0) or 1 logMAR line interocular difference in uncorrected visual acuity without cycloplegia using the ATS-HOTV® visual acuity testing protocol; normal near stereoacuity for age using the Randot Preschool Stereoacuity test (see section 3.4, Table 2 of the trial protocol) 6. gestational age > 32 weeks 7. investigator is willing to prescribe glasses per protocol or observe the hyperopia untreated for 3 years unless specific criteria for deterioration outlined in section 3.4 of the protocol are confirmed 8. 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 outlined in section 3.4 of the protocol are confirmed 9. parent has telephone (or access to telephone) and is willing to be contacted by Jaeb Center staff 10. relocation outside of area of an active Pediatric Eye Disease Investigator Group site for this study within the next 36 months is not anticipated <p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. any measurable heterotropia in primary gaze at distance (3 m) or at near (0.33 m) by cover/uncover testing 2. previous documented strabismus (parental report must be confirmed by investigator) 3. manifest or latent nystagmus evident clinically 4. previous treatment of refractive error with glasses or contact lenses 5. previous intraocular, refractive, or extraocular muscle surgery 6. previous amblyopia treatment 7. previous vergence/accommodative therapy 8. parental concerns over learning or development 9. ocular comorbidity that may reduce visual acuity 10. symptoms of blur or asthenopia 11. developmental delay diagnosed by pediatrician or individualized education program 12. known neurologic anomalies (e.g. cerebral palsy, Down syndrome) 13. inability to perform visual acuity ATS-HOTV testing if > 36 months of age
Interventions	For children in the glasses group, glasses will be prescribed at enrollment with the sphere cut symmetrically by 1.00 D and full cylinder correction. If a child in the observation group has confirmed deterioration, glasses will be prescribed with amount of correction at investigator discretion
Outcomes	<p>Primary outcome measures:</p> <ul style="list-style-type: none"> • proportion of participants with confirmation of failure criteria at 36 months <p>Secondary outcome measures:</p> <ul style="list-style-type: none"> • best visual acuity at 36 months • development of strabismus at 36 months • subgroup analysis by baseline factors at 36 months • observation group deterioration at 36 months • development of amblyopia at 36 months • near visual acuity at 36 months
Starting date	February 2012
Contact information	Ray Kraker or Chelsea Costa: 888-387-8686 pedig@jaeb.org
Notes	This study is currently recruiting participants (as of November 2013)

D: diopter.

ACKNOWLEDGEMENTS

We would like to thank Iris Gordon, Trials Search Co-ordinator, Cochrane Eyes and Vision Group (CEVG), for devising and conducting the electronic searches. We also thank Angela Chen, Barbara Hawkins, Valerie Kattouf, and the CEVG editorial team, especially Sue Elliott, Michael Marrone, and Kristina Lindsley, for their advice and assistance during the review process.

External sources

- National Eye Institute, National Institutes of Health, USA.

The Cochrane Eyes and Vision Group US Project is funded by Grant 1 U01 EY020522

- National Institute of Health Research (NIHR), UK.

Richard Wormald, Co-ordinating Editor for Cochrane Eyes and Vision Group (CEVG), acknowledges financial support for his CEVG research sessions from the Department of Health through the award made by the NIHR to Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology for a Specialist Biomedical Research Centre for Ophthalmology. The views expressed in this publication are those of the authors and not necessarily those of the Department of Health.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Strabismus

#2 strabism* or squint*

#3 MeSH descriptor Esotropia

#4 esotrop*

#5 MeSH descriptor Exotropia

#6 exotrop*

#7 hypertrop*

#8 hypotrop*

#9 cyclotrop*

#10 heterophor*

#11 esophor*

#12 exophor*

#13 hyperphor*

#14 hypophor*

#15 cyclophor*

#16 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)

#17 MeSH descriptor Hyperopia

#18 hyperop* or hypermetrop*

#19 far next sight*

#20 long next sight*

#21 farsight*

#22 longsight*

#23 (#17 OR #18 OR #19 OR #20 OR #21 OR #22)

#24 MeSH descriptor Eyeglasses

#25 spectacle* or glasses

#26 (#24 OR #25)

#27 (#16 AND #23 AND #26)

Appendix 2. MEDLINE (OvidSP) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp strabismus/
14. (strabism\$ or squint\$).tw.
15. exp esotropia/
16. esotrop\$.tw.
17. exp exotropia/
18. exotrop\$.tw.

19. hypertrop\$.tw.
20. hypotrop\$.tw.
21. cyclotrop\$.tw.
22. heterophor\$.tw.
23. exp esophoria/
24. esophor\$.tw.
25. exp exophoria/
26. exophor\$.tw.
27. hyperphor\$.tw.
28. hypophor\$.tw.
29. cyclophor\$.tw.
30. or/13-29
31. exp hyperopia/
32. (hyperop\$ or hypermetrop\$).tw.
33. (far adj1 sight\$).tw.
34. (long adj1 sight\$).tw.
35. farsight\$.tw.
36. longsight\$.tw.
37. or/31-36
38. exp eyeglasses/
39. (spectacle\$ or glasses).tw.
40. or/38-39
41. 30 and 37 and 40
42. 12 and 41

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville et al (Glanville 2006).

Appendix 3. EMBASE.com search strategy

- #1 'randomized controlled trial'/exp
- #2 'randomization'/exp
- #3 'double blind procedure'/exp
- #4 'single blind procedure'/exp
- #5 random*:ab,ti
- #6 #1 OR #2 OR #3 OR #4 OR #5
- #7 'animal'/exp OR 'animal experiment'/exp
- #8 'human'/exp
- #9 #7 AND #8
- #10 #7 NOT #9
- #11 #6 NOT #10
- #12 'clinical trial'/exp
- #13 (clin* NEAR/3 trial*):ab,ti
- #14 ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti
- #15 'placebo'/exp
- #16 placebo*:ab,ti
- #17 random*:ab,ti
- #18 'experimental design'/exp
- #19 'crossover procedure'/exp
- #20 'control group'/exp
- #21 'latin square design'/exp
- #22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
- #23 #22 NOT #10
- #24 #23 NOT #11
- #25 'comparative study'/exp

- #26 'evaluation'/exp
- #27 'prospective study'/exp
- #28 control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti
- #29 #25 OR #26 OR #27 OR #28
- #30 #29 NOT #10
- #31 #30 NOT (#11 OR #23)
- #32 #11 OR #24 OR #31
- #33 'strabismus'/exp
- #34 strabism*:ab,ti OR squint*:ab,ti
- #35 'convergent strabismus'/exp
- #36 esotrop*:ab,ti
- #37 'divergent strabismus'/exp
- #38 exotrop*:ab,ti
- #39 hypertrop*:ab,ti
- #40 hypotrop*:ab,ti
- #41 cyclotrop*:ab,ti
- #42 heterophor*:ab,ti
- #43 esophor*:ab,ti
- #44 exophor*:ab,ti
- #45 hyperphor*:ab,ti
- #46 hypophor*:ab,ti
- #47 cyclophor*:ab,ti
- #48 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43
OR #44 OR #45 OR #46 OR #47
- #49 'hypermetropia'/exp
- #50 hyperop*:ab,ti OR hypermetrop*:ab,ti
- #51 (far NEAR/1 sight*):ab,ti

#52 (long NEAR/1 sight*):ab,ti
 #53 farsight*:ab,ti
 #54 longsight*:ab,ti
 #55 #49 OR #50 OR #51 OR #52 OR #53 OR #54
 #56 'spectacles'/exp
 #57 spectacle*:ab,ti OR glasses:ab,ti
 #58 #56 OR #57
 #59 #48 AND #55 AND #58
 #60 #32 AND #59

Appendix 4. PubMed search strategy

1. ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomised[tiab] OR randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])
2. (strabism* OR squint*) NOT Medline[sb]
3. esotrop* NOT Medline[sb]
4. exotrop* NOT Medline[sb]
5. hypertrop* NOT Medline[sb]
6. hypotrop* NOT Medline[sb]
7. cyclotrop* NOT Medline[sb]
8. heterophor* NOT Medline[sb]
9. esophor* NOT Medline[sb]
10. exophor* NOT Medline[sb]
11. hyperphor* NOT Medline[sb]
12. hypophor* NOT Medline[sb]
13. cyclophor* NOT Medline[sb]
14. #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
15. (hyperop* OR hypermetrop*) NOT Medline[sb]

16. (far AND sight*) NOT Medline[sb]
17. (long AND sight*) NOT Medline[sb]
18. farsight* NOT Medline[sb]
19. longsight* NOT Medline[sb]
20. #15 OR #16 OR #17 OR #18 OR #19
21. (spectacle* OR glasses) NOT Medline[sb]
22. #14 AND #20 AND #21
23. #1 AND #22

Appendix 5. *metaRegister* of Controlled Trials search strategy

(Strabismus OR Esotropia OR Exotropia) AND (Hyperopia)

Appendix 6. [ClinicalTrials.gov](https://clinicaltrials.gov) search strategy

(Strabismus OR Esotropia OR Exotropia) AND (Hyperopia)

Appendix 7. ICTRP search strategy

(Strabismus OR Esotropia OR Exotropia) AND (Hyperopia)

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We intended to handsearch journals not included in electronic bibliographic databases, but did not conduct these searches in the implementation of the review. We decided searching CENTRAL was adequate to identify potentially eligible studies that we would have identified through handsearching. We also added a post-hoc secondary outcome for visual acuity. Although the protocol stated we would not conduct meta-analyses when the I^2 value was 50% or greater, we felt the included studies were similar with respect to clinical and methodologic factors to perform meta-analyses for strabismus and visual acuity outcomes.

PLAIN LANGUAGE SUMMARY

Glasses to prevent eye misalignment in far-sighted children

Review question

We compared the benefits and harms of wearing glasses to other interventions in far-sighted children to prevent the development of eye misalignment.

Background

Infants typically are born hyperopic, or far-sighted, and as they grow, their eyes typically grow to where they can see clearly. Some children, however, remain very far-sighted. Being far-sighted means that to focus on something up close the child must use a great deal of effort (called accommodation). This prolonged and repeated effort can cause symptoms, such as headaches, seeing double, and eyestrain, as well as cause difficulty doing things up close, such as reading. Children that remain far-sighted are more likely than children with normal vision to develop eye misalignment (called strabismus), commonly known as crossed eyes. Strabismus makes it difficult for the eyes to work together to focus. Children who develop strabismus are then more likely than children without strabismus to develop amblyopia. Amblyopia, commonly known as lazy eye, is a condition where the child cannot achieve normal visual acuity (clear vision). Amblyopia requires treatment to prevent long-term vision loss; however, even the use of glasses may not allow a child with amblyopia to have 20/20 vision. Doctors often prescribe glasses to prevent the development of strabismus in far-sighted children, but very little research has been done on the effectiveness of this treatment.

Study characteristics

We identified results from three randomized controlled trials (RCTs; clinical studies where people are randomly put into one of two or more treatment groups) to determine whether glasses were successful in reducing the occurrence of strabismus in far-sighted infants. The trials enrolled infants ages 12 months or younger and measured outcomes between the ages of three and four years. The three trials enrolled 855 infants and included about 79% of the infants in the final analyses of different outcomes. These trials were all conducted in the UK with follow-up periods ranging from one to 3.5 years. The evidence is current up to April 2014.

Key results

Combining the results of the three trials, we found the risk of strabismus with wearing glasses is uncertain. We identified several potential biases in the way these three trials were conducted. Given the high risk of bias and amount of missing data, it is possible the observed decrease in risk of developing strabismus may be an overestimate of the true effect. The evidence does not currently support the conclusion that glasses prevent strabismus in far-sighted children. More research is required to answer the question. In addition, the prescription of glasses, particularly glasses that correct all of the prescription (full correction), may prevent eyes from developing naturally and normalizing to clear visual acuity. Emmetropization (normalization of vision which usually occurs during the natural growth process) was reported in two trials: one trial

suggested that spectacles impede emmetropization, and the second trial reported no difference in the rate of refractive error change.

Quality of the evidence

The overall quality of the evidence was low, particularly due to improper trial design and high number of losses to follow-up.

Spectacle correction compared with no spectacles for infants or children with hyperopia						
Patient or population: infants or children with hyperopia Settings: all studies were done in the United Kingdom Intervention: spectacle correction Comparison: no spectacles						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No spectacles	Spectacles				
Incidence of strabismus at 3 to 4 years of age	Children with hyperopia <3.5 D at 6 months to 1 year		RR 0.71 (0.44 to 1.15)	874 (3 studies)	⊕○○○ ^{1,2,4} very low	-
	137 per 1000	97 per 1000 (60 to 158)				
	Children with hyperopia > 3.5 D at 6 months to 1 year					
	273 per 1000	194 per 1000 (120 to 314)				
Visual acuity worse than 20/30 at 3 to 4 years of age	Children with hyperopia <3.5 D at 6 months to 1 year		RR 0.87 (0.60 to 1.26)	664 (3 studies)	⊕○○○ ^{1,2,4} very low	-
	32 per 1000	28 per 1000 (19 to 40)				
	Children with hyperopia > 3.5 D at 6 months to 1 year					
	266 per 1000	231 per 1000 (160 to 325)				
*The basis for the assumed risk (e.g. the mean control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk Ratio; ⊕: degree of certainty						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						
¹ All studies at high or unclear risk of bias for allocation concealment and masking. ² Inconsistent results between risk groups for strabismus. ³ Wide confidence intervals for visual acuity. ⁴ Total population sample size and with wide confidence intervals indicates less than optimal information size.

Figure 1.
Study flow diagram as of 3 April 2014.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Masking of participants and personnel	Masking of outcome assessors (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Atkinson 1996	-	?	-	?	-	?	+
Ingram 1985	?	?	-	?	-	-	+
Ingram 1990	+	?	-	?	-	?	+

Figure 2.

Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Figure 3.

Forest plot of comparison: 1 Spectacle correction versus no spectacle correction, outcome:

1.1 Incidence of strabismus at three to four years of age.

Figure 4.

Forest plot of comparison: 1 Spectacle correction versus no spectacle correction, outcome:
1.2 Visual acuity worse than 20/30 at three to four years of age.

Review: Spectacle correction versus no spectacles for prevention of strabismus in hyperopic children

Comparison: 1 Spectacle correction versus no spectacle correction

Outcome: 1 Incidence of strabismus at 3-4 years of age

Review: Spectacle correction versus no spectacles for prevention of strabismus in hyperopic children

Comparison: 1 Spectacle correction versus no spectacle correction

Outcome: 2 Visual acuity worse than 20/30 at 3-4 years of age

Table 1

Spectacle prescription by study

Study	Spectacle treatment method
Atkinson 1996	Sphere: 1.00 D less than the least hyperopic meridian with no prescription given for < 1.50 D Cylinder: < 2 years old - half of the astigmatic error over 2.50 D; 2-3.5 years - half of the astigmatic error; > 3.5 years - full astigmatic error
Ingram 1985	Each meridian minus 2.00 D
Ingram 1990	Each meridian minus 2.00 D

D: diopter.