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## Interventions to slow progression of myopia in children

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### Abstract

**Background**—Nearsightedness (myopia) causes blurry vision when looking at distant objects. Highly nearsighted people are at greater risk of several vision-threatening problems such as retinal detachments, choroidal atrophy, cataracts and glaucoma. Interventions that have been explored to slow the progression of myopia include bifocal spectacles, cycloplegic drops, intraocular pressure-lowering drugs, muscarinic receptor antagonists and contact lenses. The purpose of this review was to systematically assess the effectiveness of strategies to control progression of myopia in children.

**Objectives**—To assess the effects of several types of interventions, including eye drops, undercorrection of nearsightedness, multifocal spectacles and contact lenses, on the progression of nearsightedness in myopic children younger than 18 years. We compared the interventions of interest with each other, to single vision lenses (SVLs) (spectacles), placebo or no treatment.

**Search methods**—We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2011, Issue 10), MEDLINE (January 1950 to October 2011), EMBASE (January 1980 to October 2011), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to October 2011), the *metaRegister* of Controlled Trials (*mRCT*) ([www.controlled-trials.com](http://www.controlled-trials.com)) and ClinicalTrials.gov (<http://clinicaltrials.gov>). There were no date or language restrictions in the electronic searches for trials. The electronic databases were last searched on 11 October 2011. We also searched the reference lists and Science Citation Index for additional, potentially relevant studies.

**Selection criteria**—We included randomized controlled trials (RCTs) in which participants were treated with spectacles, contact lenses or pharmaceutical agents for the purpose of controlling progression of myopia. We excluded trials where participants were older than 18 years at baseline or participants had less than  $-0.25$  diopters (D) spherical equivalent myopia.

**Data collection and analysis**—Two review authors independently extracted data and assessed the risk of bias for each included study. When possible, we analyzed data with the inverse variance method using a fixed-effect or random-effects model, depending on the number of studies and amount of heterogeneity detected.

## **Main results**—We included 23 studies (4696 total participants) in this review, with 17 of these

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### **DECLARATIONS OF INTEREST**

Jeffrey J Walline, OD, PhD was the Principal Investigator of the Contact Lens and Myopia Progression (CLAMP) Study which was an RCT to examine the effects of rigid gas permeable contact lenses (RGPCs) on myopia progression in children. Susan Cotter, OD, MS was the Principal Investigator on a trial evaluating pirenzepine ophthalmic gel for slowing myopia progression in children. Both studies were included in this review.

Jeffrey J. Walline received research funding, consulted for companies, received honoraria from companies, and has pending grants with companies, all relating to myopia and/or myopia progression. Susan Cotter's institution received grant funding for participation in the following NIH/NEI-funded multicenter study related to myopia: Correction of Myopia Evaluation Trial — 2 (COMET-2).

### **DIFFERENCES BETWEEN PROTOCOL AND REVIEW**

We modified the interventions under review compared with the published protocol. Single vision soft contact lenses (SVSCLs) are considered a control intervention and we did not study them as an active treatment intervention for the purposes of this review. We did not include studies that compared SVSCLs with single vision lenses (SVLs) (spectacles) in this review.

### **NOTES**

This protocol was previously published as 'Contact lenses for reducing myopia progression in children' by Walline J, Mathew M, Twelker JD.

studies included in quantitative analysis. Since we only included RCTs in the review, the studies were generally at low risk of bias for selection bias. Undercorrection of myopia was found to increase myopia progression slightly in two studies; children who were undercorrected progressed on average 0.15 D (95% confidence interval (CI) -0.29 to 0.00) more than the fully corrected SVLs wearers at one year. Rigid gas permeable contact lenses (RGPCs) were found to have no evidence of effect on myopic eye growth in two studies (no meta-analysis due to heterogeneity between studies). Progressive addition lenses (PALs), reported in four studies, and bifocal spectacles, reported in four studies, were found to yield a small slowing of myopia progression. For seven studies with quantitative data at one year, children wearing multifocal lenses, either PALs or bifocals, progressed on average 0.16 D (95% CI 0.07 to 0.25) less than children wearing SVLs. The largest positive effects for slowing myopia progression were exhibited by anti-muscarinic medications. At one year, children receiving pirenzepine gel (two studies), cyclopentolate eye drops (one study), or atropine eye drops (two studies) showed significantly less myopic progression compared with children receiving placebo (mean differences (MD) 0.31 (95% CI 0.17 to 0.44), 0.34 (95% CI 0.08 to 0.60), and 0.80 (95% CI 0.70 to 0.90), respectively).

**Authors' conclusions**—The most likely effective treatment to slow myopia progression thus far is anti-muscarinic topical medication. However, side effects of these medications include light sensitivity and near blur. Also, they are not yet commercially available, so their use is limited and not practical. Further information is required for other methods of myopia control, such as the use of corneal reshaping contact lenses or bifocal soft contact lenses (BSCLs) with a distance center are promising, but currently no published randomized clinical trials exist.

## PLAIN LANGUAGE SUMMARY

### Interventions to slow progression of nearsightedness in children

Nearsightedness (myopia) causes blurry vision when looking at distant objects. Approximately 33% of the population in the United States is nearsighted, and some Asian countries report that up to 80% of children are nearsighted. Several studies have examined a variety of methods (including eye drops, incomplete correction (known as 'undercorrection') of nearsightedness, multifocal lenses and contact lenses) to slow the worsening of nearsightedness.

In this review we included 23 clinical investigations of myopia treatments in children. Two studies investigated undercorrection of myopia; twelve studies investigated multifocal spectacles (progressive addition lenses (PALs) or bifocal spectacles); one study investigated bifocal soft contact lenses (BSCLs); one study investigated novel lenses designed to reduce peripheral hyperopic defocus (peripheral vision farsightedness) (i.e. lenses that help to focus peripheral vision as well as central vision); two studies investigated rigid gas permeable contact lenses (RGPCs); and six studies investigated pharmaceutical eye drops (five of these studies were of anti-muscarinic medications). There was one study that evaluated both multifocal lenses and pharmaceutical eye drops. In all studies the interventions of interest were compared with each other, single vision lenses (SVLs) (spectacles), single vision soft contact lenses (SVSCLs) or placebo. The follow-up period was at least one year for all studies.

The largest positive effects for slowing myopia progression were exhibited by anti-muscarinic medications (eye drops), but they either cause light sensitivity or blurred near vision, and are not yet available for use. Multifocal spectacles including PALs and bifocal spectacles were found to yield a small slowing of myopia progression. Undercorrection of myopia was found to increase myopia progression slightly, while RGPCLs were found to have no evidence of effect on myopic eye growth.

## BACKGROUND

### Description of the condition

Myopia, also known as nearsightedness, is a condition where near objects are seen clearly but distant objects appear blurred. In myopia, distant objects are focused in front of the retina instead of on it, as occurs in non-myopic individuals. Myopia occurs because the cornea or lens is too powerful or because the eyeball is longer than normal.

### Epidemiology

Myopia is an important cause of reduced vision in populations throughout the world and is one of the five immediate priorities for the 'Vision 2020' initiative by the World Health Organization (WHO) (Pararajasegaram 1998). Approximately 2% of the United States population is myopic at school entry (Blum 1959) and about 15% of the people entering high schools are myopic (Sperduto 1983). Racial and ethnic differences in magnitude and prevalence of myopia have been observed (Garner 1999; Lin 1999; Maul 2000; Voo 1998; Zhan 2000), both being greater in Asia than other parts of the world (Lin 1999; Zhan 2000).

Juvenile-onset myopia typically develops at approximately six to eight years of age and progresses at a rate of approximately 0.50 D (diopters) per year through 15 to 16 years (COMET Study; Fulk 2002; Goss 1987; Perrigin 1990). The progression of myopia is typically faster at younger ages (Braun 1996; Goss 1987; Goss 1990; Pärssinen 1989; Saw 2000), but myopia onset, progression, and stabilization vary widely among individuals (Braun 1996; Pärssinen 1989; Saw 2000). Similar proportions of boys and girls are affected by myopia and the degree of myopia is similar between the two genders (Zadnik 2003).

### Etiology and risk factors

Several factors have been suggested to have a role in the development of myopia. Many models estimate greater genetic effects than environmental effects for myopia (Chen 1985; Hammond 2001). Children with two myopic parents have greater axial lengths which indicates a higher risk of myopia than children with one or no myopic parents (Zadnik 1994). Environmental influences relate to prolonged reading or near work, which has been associated with increased myopia prevalence (Saw 2001; Young 1969). Myopic individuals exhibit a greater accommodative lag (poor focusing accuracy while looking at near objects) than emmetropes (those who do not require spectacles to see either distant or near objects clearly). This high lag of accommodation leads to blur, which may stimulate myopic eye growth (Gwiazda 1993; Gwiazda 1995). Fewer hours spent outdoors also has been associated with myopia (Jones 2007; Rose 2008).

## Presentation and diagnosis

The primary symptom of myopia is blurred distance vision. Children often present to an eye care practitioner after failing a vision screening at school or after a parent or teacher notices the child squinting or having difficulty seeing distant objects.

An eye care practitioner using autorefraction or retinoscopy may confirm the diagnosis of myopia objectively, or it can be confirmed by performing a subjective refraction, which requires responses from the child. In order to diagnose myopia in children, cycloplegic drops can be placed in the child's eyes, hindering his or her ability to focus the eyes so that an accurate prescription can be determined.

## Description of the intervention

Spectacles are often the initial treatment for children with myopia because they provide clear vision with few potential side effects. Spectacles for myopia correction use concave lenses that focus light more posteriorly, resulting in a clear image focused on the retina. Contact lenses are typically a secondary treatment option for children because they require greater dexterity and responsibility to care for them than spectacles. They also bear greater risks than spectacles that range from innocuous redness of the eyes to severe pain and vision loss due to corneal ulcers (Fonn 1988; MacRae 1991; Schein 1989).

Laser refractive surgery, such as Laser In Situ Keratomileusis (LASIK) or Photorefractive Keratectomy (PRK), causes a permanent flattening of the central corneal curvature by removing stromal tissue with a laser (Duffey 2003). Although it is frequently performed in adults (Shortt 2006), children's eyes are still developing and the myopia continues to change during adolescence, so surgery is not routinely performed in children.

Other forms of myopia correction, such as a lens placed inside the eye and clear rings placed in the cornea, also are not used routinely in children due to children's potential for myopia progression (Barsam 2010).

## How the intervention might work

In terms of slowing myopia progression, multifocal spectacles and undercorrection of myopic refractive error are thought to reduce accommodative error, which may act as a stimulus for increased eye growth. Myopic patients exhibit greater accommodative lag than non-myopic patients (COMET Study; Mutti 2006). Accommodative lag results in light focused behind the retina during near work, which may act as a signal to increase eye growth and result in myopia. If the accommodative error can be reduced with bifocals or undercorrection, then the stimulus for eye growth will be reduced and may slow myopia progression.

Cycloplegic agents were thought to reduce myopic progression by eliminating accommodation, but it has since been shown to be a local retinal effect that slows myopia progression (Troilo 1987). Anti-muscarinic receptor binding may lead to a biochemical change that slows eye growth, but the exact mechanism is unknown.

## Why it is important to do this review

Myopia has been reported to reach epidemic proportions in parts of the world (Park 2004). Strategies to control progression of myopia gain importance in the context of the ‘Vision 2020’ initiative by the WHO to eliminate preventable causes of blindness, including risks associated with high myopia, by the year 2020 (Pararajasegaram 1998). Interventions that have been explored for this purpose include bifocal spectacles, cycloplegic drops, intraocular pressure-lowering drugs, muscarinic receptor antagonists and contact lenses. In this review we systematically assessed the effectiveness of strategies to control progression of myopia in children.

## OBJECTIVES

The objective of this review was to assess the effects of interventions, including spectacles, contact lenses and pharmaceutical agents, for slowing myopia progression in children.

## METHODS

### Criteria for considering studies for this review

**Types of studies**—This review included randomized controlled trials (RCTs).

**Types of participants**—We included trials in which participants were treated with spectacles, contact lenses, or pharmaceutical agents for controlling progression of myopia. We excluded trials where participants were older than 18 years at the start of the trial. We also excluded trials that included participants with less than  $-0.25$  D spherical equivalent myopia at baseline. (The spherical equivalent is an optical measurement based on a mathematical calculation: the sum of the spherical power plus half the cylindrical power of the lens.)

**Types of interventions**—We included trials in which any of the following interventions for controlling progression of myopia were compared with single vision lenses (spectacles) or single vision soft contact lenses (SVSCLs) (control treatment), placebo or with each other.

1. Bifocal soft contact lenses (BSCLs), rigid gas permeable contact lenses (RGPCs) and corneal reshaping (orthokeratology) contact lenses.
2. Bifocal lenses (spectacles), progressive addition lenses (PALs) and undercorrection of myopia.
3. Pharmaceutical agents.

### Types of outcome measures

**Primary outcomes:** The primary outcome for this review was progression of myopia assessed as the mean change in refractive error (spherical equivalent) from baseline for each year of follow-up and measured using any method.

## Secondary outcomes

1. Mean change in axial length, measured by any method.
2. Mean change in corneal radius of curvature, measured by any method.

We analyzed the secondary outcomes for each year of follow-up when sufficient data were available. We included data as reported by each included study (i.e. data from one eye, from each eye individually or the average of both eyes) and pooled the results, regardless of how the data were analyzed in an individual study.

**Adverse effects:** We summarized the reported adverse effects related to the interventions as described in the included studies, including but not limited to blurry vision, red eyes, infections and conjunctival reactions.

**Economic data:** We documented reported cost-analyses and other data on economic outcomes when reported from the included trials.

**Quality of life measures:** We documented any quality of life information when reported from the included trials.

**Follow-up:** We reported outcomes for follow-up at one year, two years and as available throughout the study periods. We imposed no restrictions based on the length of follow-up.

## Search methods for identification of studies

**Electronic searches**—We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2011, Issue 10, part of *The Cochrane Library*, [www.thecochranelibrary.com](http://www.thecochranelibrary.com) (accessed 11 October 2011), MEDLINE (January 1950 to October 2011), EMBASE (January 1980 to October 2011), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to October 2011), the *metaRegister* of Controlled Trials (*mRCT*) ([www.controlled-trials.com](http://www.controlled-trials.com)) and ClinicalTrials.gov (<http://clinicaltrials.gov>). There were no date or language restrictions in the electronic searches for trials. The electronic databases were last searched on 11 October 2011.

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

**Searching other resources**—We searched the reference lists of identified trial reports to find additional trials. We used the Science Citation Index (assessed 1 November 2011) to find studies that had cited the identified trials. We contacted the primary investigators of identified trials for details of other potentially relevant trials not identified by the electronic searches, recently completed trials or ongoing trials. We did not conduct manual searches of abstracts of conference proceedings and optometry literature specifically for this review, as these sources are searched by the Cochrane Eyes and Vision Group and listed in CENTRAL.



## Data collection and analysis

**Selection of studies**—Two review authors, including at least one clinician (JJW, DOM, SAC, JDT) and one methodologist (SSV, KL), independently assessed the titles and abstracts of all reports identified by the electronic and manual searches as per the ‘Criteria for considering studies for this review’. The abstracts were classified as (1) definitely include, (2) unsure or (3) definitely exclude. We obtained and assessed the full-text of articles classified as (1) or (2) by at least one review author. After assessing the full-text we reclassified the studies as (A) include, (B) awaiting assessment or (C) exclude. A third review author resolved disagreements. The review authors were unmasked to the report authors, institutions and trial results during this assessment. For studies identified as (A), we included and assessed them further for study design and risk of bias. We contacted the authors of studies classified as (B) for clarification and reassessed these studies as per the inclusion criteria as further information became available. We excluded the studies in (C) and documented the reasons for exclusion in this review.

We initially included Cheng 2010, but after full-text review and data extraction we assessed it to be quasi-randomized and thus ineligible for the review. However, as we initially included the study we did not exclude it post hoc and instead conducted sensitivity analyses for inadequate randomization when applicable.

**Data extraction and management**—Two review authors independently extracted the data for the primary and secondary outcomes on to paper data collection forms developed by the Cochrane Eyes and Vision Group. We resolved discrepancies by discussion. We contacted primary investigators for missing data. One review author entered the data into Review Manager 5 (RevMan 2011) and a second review author verified the data entered.

**Assessment of risk of bias in included studies**—Two review authors independently assessed the sources of systematic bias in trials according to the methods described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements between authors through discussion.

We considered the following parameters:

- selection bias (random sequence generation, quality of allocation concealment);
- performance bias and detection bias (masking of participants, outcome assessors and data analyzers);
- attrition bias (completeness of follow-up and intention-to-treat (ITT) analysis);
- reporting bias; and
- other potential sources of bias (such as funding source).

For attrition bias, we considered whether or not reasons for losses to follow-up were comparable between treatment arms and whether or not all participants were analyzed as randomized. If studies reported that an ITT analysis was performed we assessed whether both a) participants in which no outcome was collected, and b) participants who received only some or none of their allotted treatment were included. We interpreted a true ITT



analysis to have been undertaken only when both of these criteria were fulfilled. We classified the risk of bias for each parameter as “low risk of bias”, “unclear risk of bias”, or “high risk of bias”. For example, studies using allocation concealment by centralized randomization and sequential opaque envelopes, (which provided reasonable confidence that the participating eye care providers and patients were not aware of the randomization sequence), were considered to be at low risk of bias. We contacted the authors of trials when additional information was needed to assess risk of bias. If the authors did not respond within an eight-week period we classified the trial based on the available information.

**Measures of treatment effect**—We reported mean differences (MDs) for continuous outcome measures and risk ratios (RRs) for dichotomous outcomes.

**Unit of analysis issues**—We included data from one eye, from each eye individually, or the average of both eyes, and pooled the results, regardless of how the data were analyzed. We sought advice from the Cochrane Eyes and Vision Group editorial base for analysis issues involving included trials with multiple treatment groups, cross-over design and cluster randomized designs.

**Dealing with missing data**—We contacted the authors of trial reports for any missing data. When we did not receive a response within eight weeks, we analyzed the studies based on available information. We will include any new information in future updates of the review.

**Assessment of heterogeneity**—We assessed statistical heterogeneity using the Chi<sup>2</sup> test and I<sup>2</sup> statistic. We considered a P value less than 0.05 as significant for the test of heterogeneity. We assessed the inconsistency of effect estimates across studies using the I<sup>2</sup> statistic.

**Assessment of reporting biases**—We assessed reporting biases based on communications with trial authors regarding any outcomes assessed but not reported.

**Data synthesis**—If the I<sup>2</sup> statistic was greater than 50%, (indicating a substantial degree of heterogeneity), we did not combine the study results in a meta-analysis; instead, we presented a tabulated summary. We examined the funnel plot for other sources of variation between studies when more than three studies were included in the analysis. When there was no substantial statistical or clinical heterogeneity we combined the results of included trials. We used a fixed-effect model for meta-analyses including three or fewer studies and a random-effects model for meta-analyses including four or more studies. We calculated the MD with 95% confidence intervals (CIs) for continuous outcomes. Change-from-baseline outcomes were combined in meta-analyses with studies reporting mean outcomes at annual measurement time points using the generic inverse variance (unstandardized) MD method as outlined in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

**Subgroup analysis and investigation of heterogeneity**—We undertook subgroup analyses for types of intervention modalities (i.e. bifocals, progressive addition lenses

(PALs) and specific pharmaceutical agents). In the future, if sufficient evidence becomes available, we will also conduct subgroup analyses according to age, degree of myopia at baseline and type of contact lens (soft versus hard).

**Sensitivity analysis**—We conducted a sensitivity analysis for meta-analyses in which more than three studies were included and when change-from-baseline outcomes were combined in analysis with mean outcomes at annual measurement time points. We combined studies using autorefraction in analysis with subjective refraction or when the analyses included the Cheng 2010 study. In the future, if sufficient evidence becomes available, we will conduct sensitivity analyses to determine the impact of excluding studies with lower methodological quality, unpublished studies and industry-funded studies. We also conducted sensitivity analyses to determine the effect on the primary outcome of inclusion of trials in which refraction was measured after administration of cycloplegic agents.

## RESULTS

### Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

**Results of the search**—We conducted an electronic literature search as of 11 October 2011 and identified 1310 unique records of journal articles and conference abstracts. After screening the titles and abstracts, we obtained full-text copies of 138 records for further review. Of those, we included 75 records (23 studies) and excluded 60 records (43 studies); one record was for an ongoing study and two records are awaiting classification. We handsearched the reference lists of included studies and used the Science Citation Index (1 November 2011) to identify additional studies. From the manual search, we identified 38 additional records not identified by the electronic search. Of these 38 records, there were 14 additional records to studies already included, two additional records to studies already excluded, 20 records that were excluded (from 18 studies), one record for a study already awaiting assessment, and one record for an ongoing study. Thus overall, we reviewed 176 potentially relevant full-text articles or conference abstracts of which we included 89 records (from 23 studies), excluded 82 records (from 61 studies), identified four records awaiting classification (from three studies), and identified one ongoing study (Figure 1).

**Included studies**—We included 23 RCTs in this review. The studies evaluated varying interventions, including spectacles, contact lenses and pharmaceutical agents (Table 1). The age range of children participating in the included studies was six to 18 years and no child had myopia less than  $-0.25$  D. The primary outcome of all included studies was the progression of myopia, measured as the change in refractive error (Table 2; Table 3; Table 4). Twenty-one studies (91%) measured refraction under cycloplegia, of which 16 used autorefraction. Only one study has not been published as a full report in a peer reviewed journal (Aller 2006). Three studies were funded primarily by industry (Aller 2006; PIR-205

Study; Tan 2005) and four studies were funded partially by industry (Cheng 2010; CLAMP Study; COMET Study; Hasebe 2008).

**Undercorrected versus fully-corrected spectacles**—Two studies compared the use of undercorrected spectacles with fully-corrected spectacles. In one study, 62 children in Israel aged six to 15 years old were randomized to receive spectacles blurred by +0.50 D or spectacles with full correction (Adler 2006). In the second study, 106 Malay and Chinese children were evenly randomized to receive spectacles undercorrected by approximately +0.75 D or fully-corrected spectacles (Chung 2002). The study periods were 18 months and two years, respectively.

**Multi-focal versus single vision lenses (spectacles)**—Twelve studies included in the review compared multi-focal spectacles with single vision lenses (SVLs) (spectacles) for slowing progression of myopia in children. Five of these studies directly compared bifocal spectacles to SVLs for slowing progression of myopia in children. One study, conducted in Tahlequah, Oklahoma, USA, randomized 32 children to receive either bifocals with +1.25 D addition or SVLs (Fulk 1996). The children were six to 13 years old and were followed for 18 months. Following this pilot study, the study authors initiated a larger study with slight modifications to the study design (Fulk 2002). For their second study, the study authors added another study center in Tulsa, Oklahoma, USA, enrolled 82 children aged six to 12 years, changed the addition for the bifocal lenses to +1.50 D, and extended the follow-up period to 30 months.

The third study comparing bifocals to SVLs was the Houston Myopia Control Study (Houston Study). The 207 children enrolled in the study (ages six to 15 years) were randomized to one of three treatment groups and followed for three years. The treatment groups included two intervention groups that received bifocals with either +1.00 D or +2.00 D addition, and a standard treatment group that received SVLs.

A study from central Finland enrolled myopic schoolchildren referred by local doctors and nurses after routine vision check-ups (Pärssinen 1989). In all, 240 children with a mean age of 10.9 years were randomized to one of three treatment groups and followed for three years. The first intervention group, the distant-use group, received minus lenses with full correction and were advised to use them for distance vision only and to read at the greatest distance possible. The second intervention group, the bifocal group, received clear plastic bifocal lenses with +1.75 D addition for continuous use. The third group was the reference group and received minus lenses with full correction for continuous use. The fifth study investigated the effect of bifocal lenses (+1.50 D) with or without a 3-prism diopters base-in prism in the near segment with single vision distance lenses for slowing the progression of myopia in Chinese Canadian children (aged eight to 13 years) (Cheng 2010). One hundred and fifty children were enrolled in the two-year study.

Four included studies directly compared the use of progressive addition lenses (PALs) to SVLs. The Correction of Myopia Evaluation Trial (COMET) was a three year, multi-center trial conducted in four major US cities (COMET Study). In all, 469 children aged six to 11 years were randomized to receive either multifocal lenses (no-line bifocals) with gradual and

progressive changes of power or SVLs with the same focal power throughout the lens area. Studies of 298 children from seven to 10.5 years of age and 178 children from seven to 13 years of age were completed in Hong Kong (Edwards 2002) and China (Yang 2009), respectively. The children in both studies, randomized to receive PALs or SVLs, were followed up for two years. A Japanese cross-over trial followed up children aged six to 12 years for 18 months after randomization to PALs or SVLs (Hasebe 2008). After 18 months, each child was switched to receive the alternate type of lens and followed up for another 18 months.

The Myopia Intervention Trial (MIT) included 227 Taiwanese children and investigated SVLs, PALs, and PALs in combination with atropine drops for controlling the progression of myopia (MIT study). The children, between six to 13 years of age, were randomized to one of three treatment groups and followed up for 18 months: 1) SVLs and eyedrop placebo; 2) PALs and eyedrop placebo; and 3) PALs and 0.5% atropine instilled once a day at bedtime.

A three-arm trial including interventions of bifocals, timolol maleate and SVLs was completed in Odense, Denmark (Jensen 1991). For two years, 159 schoolchildren with a mean age of 10.9 years were followed up after being randomized to one of three treatment groups. The bifocal group received bifocal lenses with +2.0 D addition for constant wear. The timolol group received one drop of 0.25% timolol maleate (an IOP reducing beta-blocker) in each eye twice daily in addition to SVLs for constant wear. The control group received only SVLs for constant wear.

In a study of 26 twin pairs, the combined use of bifocal lenses and tropicamide ophthalmic solution for controlling myopia progression was compared to the use of SVLs over a three and a half year period (Schwartz 1981). This Washington D.C. area study included monozygotic twin pairs between the ages of seven and 14 with similar myopia. For each twin pair, one twin was randomized to receive combined treatment of bifocal spectacles with +1.25 D addition and two drops of 1% tropicamide ophthalmic solution (a short-acting cycloplegic) instilled into each eye nightly; the other twin received standard spectacle correction.

A study of 78 children from eight to 18 years of age compared bifocal soft contact lenses (BSCLs) to SVSCLs for controlling myopia progression (Aller 2006). The children, from California, USA, were randomized to wear BSCLs or SVSCLs every day for one year.

**Spectacles to reduce peripheral hyperopic defocus versus single vision lenses (spectacles)**—One study compared three novel lenses designed to reduce peripheral hyperopic defocus (peripheral vision farsightedness) with SVLs in 210 Chinese children aged six to 16 years (Sankaridurg 2010). The novel lenses corrected for central vision as SVLs do, as well as peripheral vision using novel lens designs that had (1) a symmetrical, clear central aperture (20 mm) with increasing peripheral power to +1 D; (2) a symmetrical, clear central aperture (14mm) with increasing peripheral power to +2D; or (3) an asymmetrical, clear central aperture with increasing peripheral power to +1.9 D. The study

was planned for two years of follow-up, but was terminated at year one due to observing lower than expected progression in myopia among all study participants.

**Rigid gas permeable contact lenses versus single vision lenses**—Two studies included in the review compared rigid gas permeable contact lenses (RGPCs) to either SVSCLs or spectacles (SVLs). The Contact Lens and Myopia Progression (CLAMP) study was a three year trial to compare RGPCs to SVSCLs for controlling myopia in school-aged children (CLAMP Study). All the participants had to complete a run-in period successfully prior to enrolment to exclude those that could not adapt to rigid contact lenses. After the run-in period, 116 children aged eight to 12 were randomized to RGPC or SVSCL treatment groups. A study of 564 children in Singapore, aged six to 12 years, compared the use of RGPCs to SVL spectacles for controlling myopia over a two-year period (Katz 2003). After a three-month adaptation period, 383 participants remained in the study.

**Pharmaceutical agents versus control**—The use of topical ophthalmic solutions for the control of myopia progression was investigated in six studies. The Myopia Intervention Trial mentioned previously evaluated SVLs, PALs, and PALs in combination with atropine drops for controlling the progression of myopia (MIT study). The Atropine in the Treatment of Myopia (ATOM) Study enrolled 400 Singaporean children aged six to 12 years (ATOM study). Once each child was randomized to a treatment group, one eye of each child was randomized to receive treatment and the other eye served as a natural control. The atropine group applied one drop of 1% atropine sulfate nightly to the appropriate eye and the placebo group applied one drop of vehicle nightly to the appropriate eye. Follow-up for this study was two years.

Another study, completed in Taiwan, investigated the effectiveness of lower concentrations of atropine for controlling the progression of myopia in children aged six to 13 years (Shih 1999). Two hundred children were randomized to one of three atropine groups or to a control group: 1) daily drop of 0.5% atropine and advised to wear bifocal spectacles; 2) daily drop of 0.25% atropine and advised to wear slightly undercorrected SVLs; 3) daily drop of 0.1% atropine and advised to wear fully corrective SVLs; and 4) daily drop of 0.5% tropicamide. A three-arm trial of 247 children from Taiwan compared the use of topical eye drops for one year in controlling myopia progression (Yen 1989). The children aged six to 14 were randomized to one of three treatment groups: 1) 1% atropine drops every other night and bifocal spectacles prescribed after 2 weeks of treatment; 2) 1% cyclopentolate drops every night and SVLs prescribed if necessary; and 3) normal saline eye drops every night and SVLs prescribed if necessary.

Two studies compared the use of pirenzepine gel (an anti-muscarinic) to placebo gel for the control of myopia progression. The first study was a multi-center US study that enrolled 174 children eight to 12 years old, and followed them up for one year (PIR-205 Study). Children were randomized in a 2:1 ratio to apply either 2% pirenzepine ophthalmic gel or placebo gel twice a day. An additional year of follow-up was continued for children who completed the first year.

The final study was a three-arm, multi-center trial from Singapore, Hong Kong and Thailand (Tan 2005). For one year, 353 children aged six to 13 years were randomly treated with either 1) 2% pirenzepine gel applied twice daily (gel/gel); 2) placebo once daily and 2% pirenzepine gel once daily (placebo/gel); or 3) placebo gel twice daily (placebo/placebo).

**Excluded studies**—We excluded 61 studies from this review after full-text assessment. The complete list of studies and reasons for exclusion are shown in the Characteristics of excluded studies table. Our reasons for exclusion are based on four categories: (1) the study was not randomized, 43 studies; (2) the study interventions were not intended to control myopia progression, 10 studies; (3) the study interventions were not in the scope of this review, five studies; and (4) the study population was not eligible for this review, three studies. We excluded two RCTs from this review comparing SVSCLs with spectacles in myopic children and adolescents (ACHIEVE study; Horner 1999). We excluded these studies because SVSCLs and spectacles are not meant to control the progression of myopia. The purpose of the ACHIEVE study was to compare the effects of contact lens wear with spectacle wear on the children's self-perception.

### Risk of bias in included studies

**Allocation**—This review was limited to RCTs only. Twenty (87%) of the 23 included studies described the randomization procedure used to allocate patients to treatment groups and we judged them as having adequate sequence generation (Figure 2). Methods employed for adequate sequence generation included block randomization schemes, computer-generated randomization lists, independently prepared randomization lists or tables and flipping coins or drawing lots. Of these studies, we graded 19 to also have adequate allocation concealment. Methods considered to be at low risks of bias for this domain included using sequentially numbered sealed envelopes, calling a centralized coordinating center, or allocating the participants to treatment groups after being enrolled in the study. One study which used random number tables did not report whether or not allocation was concealed (Yen 1989).

We judged one study as having inadequate sequence generation and allocation concealment (Cheng 2010). Group assignments for this study were determined by selecting pieces of paper with patient numbers written on them from a container. The first 50 numbers pulled out were assigned to the control group, the second 50 to the bifocal group and the remaining 50 to the bifocal plus prism group. Since participants did not have equal chances of being assigned to all treatment groups once the first 50 numbers were drawn, we considered this method of sequence generation to be inadequate. Since treatment assignments were consecutive, there was inadequate allocation concealment as well.

The remaining two studies we considered to have unclear risks of bias for sequence generation and allocation concealment were Aller 2006 and Yang 2009. These studies stated that patients were randomized, but did not report further details on how randomization was implemented or whether concealment of allocation was done.

**Masking (performance bias and detection bias)**—We assessed the use of masking (blinding), for three types of roles: outcome assessors, study participants and data analysts.



Furthermore, we considered separately the masking of outcome assessors for primary (change in refractive error) and secondary (changes in axial length and corneal radius of curvature) outcomes. Adequate methods of masking outcome assessors involved having the patients examined by an investigator unaware of treatment assignments. This method was implemented for spectacle or contact lens studies by having the patients remove contact lenses and spectacles prior to being examined or distributing SVLs for all patients to wear during office visits. Use of coded, identical packaging was considered adequate masking for pharmaceutical studies. Overall, masking of primary outcome assessors was done for 17 (74%) of the 23 included studies (Figure 2). Of these 17 studies that masked primary outcome assessors, 14 of the studies were masked similarly for the secondary outcome assessors and three of the studies did not measure secondary outcomes related to this review.

We judged five included studies as not masking primary outcome assessors adequately. In a three-armed study comparing bifocal lenses or timolol with SVLs there was only one study investigator, who therefore could not be masked to treatment assignments (Jensen 1991). Refractive errors for this study were measured by cycloplegic autorefraction. In another three-armed trial comparing bifocals or distance-use spectacles with continuous-use spectacles, it was reported that the examining ophthalmologist did not look at the group assignment before the examination, but often, for different reasons, the group assignments were revealed (Pärssinen 1989). However, the three-year follow-up examinations were conducted by two different ophthalmologists, one of whom did not know the group assignments. Refractive errors for this study were measured by subjective cycloplegic refraction. The Houston Myopia Control Study included a team of masked observers (evaluation team) and a team of unmasked observers (patient care team) to measure outcomes in a trial of bifocal versus SVLs (Houston Study). Since the results presented in the final analysis of the primary outcome were from the non-masked group, we judged the study as having inadequate masking of primary outcome assessors. Refractive errors for this study's results were measured by subjective noncycloplegic refraction. There were two included studies that did not attempt to mask primary outcome assessors, one measured refractive errors by cycloplegic autorefraction (Cheng 2010) and the other measured refractive error by subjective cycloplegic refraction (Katz 2003). With the exception of the Houston Study, secondary outcome assessors were the same as the primary outcome assessors. Data for secondary outcomes in the Houston Study were collected by the masked evaluation team and, therefore we considered them to have a low risk of bias.

One study did not report masking of outcome assessors and we judged it to have an unclear risk of bias (Yen 1989). This used cycloplegic refraction, but did not specify whether it was autorefraction or subjective refraction.

Due to the interventions under investigation, masking of participants was not feasible for many of the studies included in this review. Participants from 18 (78%) of the 23 included studies could not be masked because of significant physical (e.g. contact lenses versus spectacles), functional (e.g. multifocal lenses versus SVLs), or performance (e.g. undercorrected versus fully-corrected spectacles) differences between the study interventions. The three studies evaluating pharmaceutical agents exclusively did mask participants adequately by distributing identically packaged, coded bottles (ATOM study;



PIR-205 Study; Tan 2005). One study reported masking participants, but we judged it as having an unclear risk of bias because it was not clear whether the two types of contact lenses under study, BSCLs versus SVSCLs, performed differently when used by the patients (Aller 2006). A second study also reported masking participants, but we judged it as having an unclear risk of bias because it was not clear whether the novel lens designs were noticeably different to participants when compared with the control SVLs (Sankaridurg 2010).

The final assessments for masking applied to the study data analysts. How data were handled and whether or not data analysts were masked to treatment groups was not reported in 10 (43%) of the 23 included studies. Two studies explicitly stated that masked investigators analyzed the data independently (Edwards 2002; Hasebe 2008). Additionally, study authors contacted for clarification replied that data analysts were masked for Cheng 2010, MIT study and Shih 1999. Although three studies stated that data were analyzed independently after the conclusion of the trial, we considered masking of data analysts to be unclear since the treatment assignments may have been accessible in the data (Adler 2006; Chung 2002; Yang 2009). One study could not be masked because there was only one investigator involved (Jensen 1991). Study authors of four studies informed us that data analysts were not masked (via email communications) (CLAMP Study; Katz 2003; PIR-205 Study; Tan 2005). We assessed studies in which data analysts were not masked or masking of data analysts was not reported, to have an unclear risk of bias for this parameter.

**Incomplete outcome data**—Attrition rates reported by the included studies varied from 0% to 61%. There were three studies that followed the intention-to-treat (ITT) analysis as defined by this review: 1) participants were analyzed in the intervention groups to which they were randomized, regardless of the intervention they actually received; and 2) all randomized participants were included in the analysis, even participants in which no outcome was collected. One study had follow-up data for all participants at the final follow-up visit (CLAMP Study) and two used statistical methods to account for all randomized patients by imputing values for missing data (COMET Study; Fulk 2002). The COMET Study used the last-observation-carried-forward method to impute data for the seven (1.5%) children who did not complete the study. The Fulk 2002 study imputed missing data for seven (8.5%) children that did not complete the study by assuming that they had “myopia progression equal to that of mean progression observed in the SVL group for the time period for which their data were missing.”

There were seven studies that analyzed participants in the intervention groups to which they were randomized, but did not include all randomized participants in the analysis due to attrition. In none of the studies were patients excluded from the analysis due to noncompliance, switching intervention groups or failure to adhere to treatment protocols. In four of these studies, outcome data were missing in both intervention groups, but drop-outs were balanced across groups and participants who dropped out were similar to those who remained (Chung 2002; Edwards 2002; Fulk 1996; Hasebe 2008). The attrition rate for each of these studies was between 6.5% and 15%. For these considerations we judged these four studies as having a low risk of bias due to minimal amounts of incomplete outcome data.

The other three studies had an unclear risk of attrition bias due to unbalanced drop-out rates

between treatment groups or because there were statistically significant differences between participants who dropped out compared with those who remained in the study (ATOM study; Katz 2003; Yang 2009).

We assessed one additional study to be at low risk of bias due to incomplete outcome data (Pärssinen 1989). In this study, one child who was randomized was excluded from the study because he was subsequently found to be ineligible (his sister had been included previously in a different group). Two other children moved from the area (less than 1% of the study population) and were excluded from the analyses due to missing data. The remaining participants were analyzed by their original treatment assignments. One study published only as an abstract reported the number of patients included in the analyses, but it was not clear whether this number represented the total number who were initially enrolled in the study and randomized to treatment (Aller 2006).

We judged the remaining 11 studies to have a high risk of bias due to incomplete outcome data. The percentage of missing data ranged from 4% to 61%. In all of these studies, a proportion of participants were excluded after randomization for not adhering to treatment protocol, having adverse events or withdrawing consent. In a study evaluating undercorrection with full-correction spectacles, participants were excluded for not wearing spectacles continuously (Adler 2006). A study comparing bifocal lenses with SVLs excluded patients from the analysis who were randomized to receive SVLs, but dropped out because their parents wanted them to receive bifocals (Cheng 2010). In another study evaluating bifocals and SVLs, noncompliant patients were dismissed from the study as were patients who were fitted with contact lenses without informing study personnel (Houston Study). One study excluded two participants for withdrawing due to having an adverse event or withdrawing consent, as well as seven participants who were lost to follow-up (Sankaridurg 2010). The other seven studies evaluated a pharmaceutical agent in at least one treatment arm (seven of the eight pharmaceutical studies included in this review). In five of these studies, participants were excluded for not using the eye drops or gel, or for not using them consistently (MIT study; PIR-205 Study; Shih 1999; Tan 2005; Yen 1989). Another study evaluating timolol plus SVLs versus bifocals or SVLs, excluded patients for switching to contact lenses or because they could not adapt to the bifocal lenses (Jensen 1991). In the last study, a co-twin study in which one twin received bifocal spectacles and 1% tropicamide ophthalmic solution and the other twin received SVLs, one twin pair was excluded from the study for noncompliance (Schwartz 1981).

In addition to excluding participants for non-adherence, two studies reported an imbalance in drop-out rates (PIR-205 Study; Tan 2005). The PIR-205 Study reported that there were significantly more drop-outs in the pirenzepine arm compared with the placebo arm, although three additional analytical methods used to impute missing values for those who discontinued the study found similar or more beneficial treatment effects for pirenzepine compared with analysis censoring the drop-outs. The Tan 2005 study also reported more drop-outs in the pirenzepine treated groups than the placebo only group. Although the difference was not statistically different, all the patients who dropped out because of adverse events received pirenzepine.

Two studies excluded participants for inefficacy of treatment (MIT study; Tan 2005). In the MIT study, two children were excluded from the study for having myopic progression greater than 2.00 D per year. One child was from the SVL group and one child was from the PAL group (none were from the atropine plus PAL group). One child was dropped from the placebo group of the Tan 2005 study for inadequate efficacy.

Finally, the study with the highest percentage of missing data enrolled 247 children, but data were missing for 151 (61%) children (Yen 1989). Reasons for missing data were not reported. The study authors stated that “patients who used the eye drops continuously for one year received another complete ophthalmologic examination” and “96 such patients were collected for evaluation, 32 in each group”. It was not clear whether the 96 patients analyzed included all the children who were examined at one year or a subset of those examined.

**Selective reporting**—All the studies included in this review reported outcomes related to the progression of myopia with at least one year of follow-up. Study specific outcomes used to measure progression of myopia included mean changes in refractive error, mean rate changes in refractive errors and mean differences (MDs) in refractive errors. We assessed seventeen (74%) studies to have a low risk of bias for selective reporting: eight studies reported results for study outcomes defined a priori (i.e. in a design and methods publication, baseline report or clinical trial registry); and nine studies reported results for the outcomes described in the methods section of each paper (Figure 2).

One study had an unclear risk of bias due to inadequate reporting for one of the two outcomes measured (Fulk 1996). For this study, the refractive error outcome was reported by treatment assignment, however, the axial length outcome was presented only as it correlated to myopia progression and results by treatment groups were not given.

We considered five studies to have a high risk of reporting bias. For one study only published as an abstract (Aller 2006), the study author’s website stated: “Full disclosure of the results is awaiting approval by the sponsor, but some results have already been published in abstract form” (Aller 2010). The results published in the abstract did not include all the study outcomes listed in the clinicaltrials.gov registry. Another study stated in its methods section that results would be discussed only if exceptional (Jensen 1991). There was one study in which not all outcomes described in the methods section were reported (Yen 1989) and one study in which all outcomes identified in the study methods were reported, but the number of participants included in the analyses were not consistent between outcomes (Katz 2003). In the final study, results were not reported for evaluation team (masked observers) measurements or for other secondary outcomes outlined in the design paper (Houston Study). The methods paper stated that an evaluation team report would be based on 1) cycloplegic retinoscopy, 2) non-cycloplegic autorefraction and 3) cycloplegic autorefraction performed by masked examiners. However, findings from masked examinations were not reported in the outcomes paper, and instead results were reported from the patient team (unmasked observers). Also secondary outcomes, such as change in axial length, were not reported.

**Other potential sources of bias**—We assessed eight (35%) studies to be free of other potential sources of bias, ten (43%) studies to have an unclear risk of bias and five (22%) studies to be at high risk of bias (Figure 2).

One study was a cross-over trial and we assessed this as having an unclear risk of bias since carry-over effects were not investigated and some participants who completed the first period dropped out during the second period (Hasebe 2008). Thus, we only used data from the first period to estimate treatment effects.

One study reported having imbalances between treatment groups at baseline in gender, corneal curvature and refractive error (Katz 2003). This study also had unequal losses to follow-up between treatment groups and by gender. In addition to these considerations and due to the 32% of participants who dropped out of the study between randomization and the end of the adaptation period, we judged this study to have a high risk of bias. Two other studies incorporated a pre-randomization administration of an intervention in their study designs (ATOM study; CLAMP Study). Run-in periods may enhance or diminish the effect of a subsequent, randomized, intervention; thus we assessed these studies as having an unclear risk of bias.

The CLAMP Study, along with seven other studies, was fully or partially funded by companies with financial interests in at least one of the interventions being studied. Of the eight included studies funded by industry, we considered seven to have an unclear risk of bias (Cheng 2010; CLAMP Study; COMET Study; Hasebe 2008; PIR-205 Study; Sankaridurg 2010; Tan 2005). We judged the eighth study to have a high risk of bias due to the author's note that "full disclosure of the results is awaiting approval by the sponsor" (Aller 2006; Aller 2010).

There were two additional studies with unclear risk of bias for other sources. One study reported that the study investigator was masked; however, there was only one study investigator and it was not reported who reviewed the participants' activities when they came in for follow-up or how the examiner remained masked at follow-up visits (Schwartz 1981). The other study did not report the unit of analysis for the results, such as the average of both eyes, the right eye only and the worse eye, etc. (Yang 2009).

We judged the remaining three studies to be at high risk of other sources of bias (Houston Study; Shih 1999; Yen 1989). In the Houston Study, outcomes were assessed by masked and unmasked personnel. Although the study protocol described presenting primary outcome data collected by the masked investigators, results were only published for data measured by unmasked subjective refraction without cycloplegic and sometimes measured by student examiners. In the Shih 1999 study, participants in different treatment groups were advised to wear differing types of spectacle lenses depending on the concentration of atropine received. The rationale for recommending different types of spectacles for different atropine doses (bifocals in the 0.5% group; undercorrected lenses in the 0.25% group; and fully corrective lenses in the 0.1% group) was not explained. In the Yen 1989 study it was unknown why equal numbers of participants dropped out of each group or how the equal numbers of

participants per group were selected for analysis (“96 such patients were collected for evaluation, 32 in each group”).

### Effects of interventions

We compared several interventions to SVL (spectacles) or SCLs in order to determine which treatments may best slow the progression of myopia in children. We pooled results for prespecified outcomes when appropriate; otherwise we reported study-specific results. For the primary outcome of this review, progression of myopia assessed as the mean change in refractive error (spherical equivalent) from baseline for each year of follow-up, negative mean differences (MDs) represented faster progression of myopia in the treatment group compared with progression in the control group. Thus, point estimates to the left of null on the forest plots favor the control group for this outcome. For axial length, negative MDs represent less axial elongation for treatment group participants compared with control group participants (point estimates to the left of null on the forest plots favor the treatment group for this outcome). The unit of analysis reported by each study is shown in Table 5.

**Undercorrected versus fully-corrected spectacles**—Two studies with a total of 142 participants compared spectacles that undercorrected myopia by approximately  $-0.50$  to  $-0.75$  D, with SVLs that fully corrected myopia (Adler 2006; Chung 2002).

**Change in refractive error (Analysis 1.1):** After one year, 72 children who were undercorrected progressed, on average,  $-0.15$  D (95% CI  $-0.29$  to  $0.00$ ) more than the 70 SVLs wearers (Figure 3). At two years, Chung 2002 reported faster progression of myopia from baseline for the undercorrection group compared with the full correction group (MD  $-0.23$  D, 95% CI  $-0.50$  to  $0.04$ ).

**Change in axial length (Analysis 1.2):** Changes in axial length were measured by Chung 2002. The undercorrected group showed greater axial elongation than the fully-corrected group at one year (MD  $0.05$  mm, 95% CI  $-0.01$  to  $0.11$ ) and at two years (MD  $0.06$  mm, 95% CI  $-0.04$  to  $0.16$ ).

**Change in corneal radius of curvature:** Changes in corneal radius of curvature were not measured by Adler 2006 and reported to be statistically non-significant during the two-year study by Chung 2002.

**Adverse effects:** Two participants who were undercorrected complained of blurred vision in the study by Adler 2006. No other adverse effects were reported by either Adler 2006 or Chung 2002.

**Multifocal spectacles versus single vision lens spectacles**—There were six studies that compared bifocal lenses (Cheng 2010; Fulk 1996; Fulk 2002; Houston Study; Jensen 1991; Pärssinen 1989) and five studies that compared progressive addition lenses (PALs) (COMET Study; Edwards 2002; Hasebe 2008; MIT study; Yang 2009) to SVLs to slow the progression of myopia in children. Eight studies were included in quantitative analysis and three studies did not provide adequate data for meta-analysis: one study did not report data for each year of follow-up (Hasebe 2008) and two studies reported outcomes as

rates of change per year based on varying follow-up times (Fulk 1996; Houston Study). Of the eight studies that we analyzed quantitatively, six studies reported mean changes from baseline and two reported final values (Edwards 2002; MIT study). Since the studies were randomized with no significant imbalances in potential confounders between groups at baseline, we pooled MDs based on changes from baseline with MDs based on final measurements, given the assumption that these measures address the same underlying intervention effects. With the exception of Pärssinen 1989, which measured refractive error by subjective cycloplegic refraction, the studies included in the analysis used cycloplegic autorefraction for refraction measurements. We included Cheng 2010 in the review following full-text assessment, but subsequently classified it as not being adequately randomized.

**Change in refractive error (Analysis 2.1; Analysis 2.2; Analysis 2.3):** At one year follow-up, the average progression was 0.16 D slower (95% CI 0.07 to 0.25) for 633 multifocal (+1.50 to +2.00 near addition) spectacle wearers than for 633 SVL wearers in seven studies (Figure 4). The effect, from a meta-analysis of only three to four trials in each comparison, was similar among PALs wearers (MD 0.17 D, 95% CI 0.10 to 0.24) and bifocal lens wearers (MD 0.16 D, 95% CI 0.01 to 0.32). One study with quantitative data did not report data at one year (Yang 2009). Excluding from the analysis the two studies with MDs based on final values did not influence the result significantly (MD 0.16 D, 95% CI 0.06 to 0.26). Excluding Pärssinen 1989, which used subjective refraction, from the analysis did not influence the result significantly (MD 0.19 D, 95% CI 0.10 to 0.27). Excluding Cheng 2010, which was not randomized adequately, from the analysis did not influence the overall result significantly (MD 0.14 D, 95% CI 0.08 to 0.19); however, when excluding Cheng 2010 from the analysis, the  $I^2$  for the bifocal subgroup was reduced from 74% to 0%.

Seven of the eight studies with quantitative data followed up participants for at least two years, of which four evaluated bifocal lenses and three evaluated PALs (Figure 5). Due to the amount of statistical heterogeneity ( $I^2 = 62%$ ), we did not include these studies in a meta-analysis. Qualitatively, at two years, four studies favored multifocal lenses over SVLs (Cheng 2010; COMET Study; Fulk 2002; Yang 2009); a further two studies favored multifocal lenses over SVLs, although the effect was not statistically significant (Edwards 2002; Jensen 1991); and one study favored SVLs over multifocal lenses, although the effect was not statistically significant (Pärssinen 1989).

Two of the eight studies with quantitative data followed up participants for three years (COMET Study; Pärssinen 1989). We did not combine these studies in a meta-analysis due to statistical heterogeneity ( $I^2 = 81.9%$ ). The COMET Study reported a significant MD of 0.19 D (95% CI 0.04 to 0.34) for PAL wearers compared with SVL wearers. Pärssinen 1989 reported a non-significant MD in the opposite direction for bifocal wearers compared with SVL wearers (MD -0.19, 95% CI -0.47 to 0.09).

Three studies not included in the meta-analyses showed mixed effects of multifocal lenses for slowing myopia progression. In a cross-over study of +1.50 PALs versus SVLs, children wearing PALs during the first 18-month treatment period showed significantly less progression than children wearing SVLs (MD 0.31 D, 95% CI 0.11 to 0.51); however, no



difference was observed between groups for the second 18-month period (MD 0.02 D, 95% CI -0.17 to 0.21) (Hasebe 2008). In an 18-month study of 14 children assigned to wear +1.25 bifocal lenses and 14 children assigned to wear SVLs, bifocal wearers progressed -0.39 D/year and SVL wearers progressed -0.57 D/year ( $P = 0.26$ ) (Fulk 1996). The authors noted that during the first year of the study the rate of progression was equal between groups, but during the last six months of the study the SVL group progressed more rapidly than the bifocal group. In a three-arm trial of +1.00 bifocals, +2.00 bifocals, and SVLs, no significant differences were observed between groups after three years of follow-up (Houston Study). The reported average change in refraction error per year during the three-year study for +1.00 bifocals was -0.36 D/year ( $n = 41$ ), +2.00 bifocals was -0.32 D/year ( $n = 44$ ) and SVLs was -0.34 D/year ( $n = 39$ ).

**Change in axial length (Analysis 2.4; Analysis 2.5; Analysis 2.6):** Five studies reported axial length outcomes, three of which reported results for one year follow-up (Cheng 2010; COMET Study; Edwards 2002). At one year the summary MD was -0.07 mm (95% CI -0.09 to -0.04) for 404 PAL wearers compared to 408 SVL wears. This was similar to the summary results after two years of follow-up (MD -0.05 mm, 95% CI -0.10 to -0.01) for two of these studies (COMET Study; Edwards 2002); Cheng 2010 did not report results for two years. After three years of follow-up participants in the COMET Study wearing PALs continued to have less axial elongation compared with participants wearing SVLs (MD -0.11 mm, 95% CI -0.17 to -0.05). Cheng 2010 and Edwards 2002 did not follow up participants at three years.

The three studies that did not report one year data showed treatment effects in the same direction as the studies included in the meta-analysis, although results were not significant in two studies. In a three-arm trial of PALs with or without atropine compared with SVLs, a pair-wise comparison showed participants who wore PALs without atropine had on average 0.10 mm (95% CI 0.00 to 0.20) less axial elongation compared with participants who wore SVLs at 18-months follow-up (MIT study). In the cross-over trial by Hasebe 2008, axial length was not measured at baseline; however, there was no significant difference in axial length between groups after the first 18-month study period (MD -0.08 mm, 95% CI -0.41 to 0.25) and no significant change in axial length was reported between groups after the second 18-month study period (MD -0.01 mm, 95% CI -0.09 to 0.07). In the third study, changes in axial length were not significantly different between bifocal wearers and SVL wearers after 30 months of follow-up (MD -0.09 mm, 95% CI -0.24 to 0.06) (Fulk 2002).

**Change in corneal radius of curvature (Analysis 2.7):** Changes in corneal radius of curvature outcomes were reported in three studies. Two studies only stated that differences were not significantly different between treatment and control groups (Edwards 2002; Hasebe 2008). In the COMET Study, neither horizontal measurements nor vertical measurements differed between groups after three years of follow-up (MD 0.00 D, 95% CI -0.15 to 0.15 and MD 0.00 D, 95% CI -0.14 to 0.14, respectively).

**Novel lens spectacles versus single vision lens spectacles—**One study, which included 210 participants, compared three novel lens designs with SVLs (Sankaridurg 2010). Each of the four study groups included 50 participants, with 10 additional



participants allocated to the most radical lens type (novel lens type II) in anticipation of higher attrition in this group. The study originally was planned for two years, but was terminated after the first year due to observing slower progression of myopia than expected for all participants.

**Change in refractive error (Analysis 3.1):** Refractive error was measured by cycloplegic autorefraction. At one year, there were no significant differences in myopia progression between novel lens types, either compared with each other or with SVLs.

**Change in axial length (Analysis 3.2):** At one year, there were no significant differences in axial length between novel lens types, either compared with each other or with SVLs.

**Change in corneal radius of curvature:** Corneal radius of curvature was not assessed by Sankaridurg 2010.

**Adverse effects:** Telephone questionnaires were conducted at one week post-distribution of lenses. At this time 2/50 participants in the type I group, 2/60 participants in the type II group, 5/50 participants in the type III group and 1/50 participants in the SVL group reported noticing blurred side vision. Three participants reported visual distortion, one in the type I group and two in the SVL group. Two participants in the type II group experienced dizziness; for one participant the dizziness resolved after one month, for the other, the dizziness was accompanied by headaches causing the participant to withdraw from the study. Two falls were reported during the study period, both occurred in the type II lens group during the first weeks of the study.

**Bifocal soft contact lenses versus single vision soft contact lenses—**One study compared bifocal soft contact lenses (BSCLs) with single vision soft contact lenses (SVSCLs) (Aller 2006). There were 38 participants in the BSCL group and 40 in the SVSCL group.

**Change in refractive error (Analysis 4.1):** At one year, myopia in the BSCL group progressed significantly slower than in the SVSCL group (MD 0.56 D, 95% CI 0.38 to 0.74). Refractive error was measured by cycloplegic autorefraction.

**Change in axial length (Analysis 4.2):** At one year, axial elongation in the BSCL group was significantly less than in the SVSCL group (MD -0.19 mm, 95% CI -0.26 to -0.12).

**Change in corneal radius of curvature:** Corneal radius of curvature was not assessed by Aller 2006.

**Rigid gas permeable contact lenses versus spectacles or soft contact lenses**—Two studies investigated the use of rigid gas permeable contact lenses (RGPCs) in slowing the progression of myopia in children. RGPCs were compared with soft contact lenses (SCLs) in one study (CLAMP Study) and with SVLs in the other (Katz 2003). The CLAMP Study followed up participants for three years and the Katz 2003 study followed up participants for two years.

**Change in refractive error (Analysis 5.1):** Data from the CLAMP Study suggest the use of RGPs to slow the progression of myopia in children compared with SCLs. At one (MD 0.40 D, 95% CI 0.19 to 0.61), two (MD 0.54 D, 95% CI 0.27 to 0.81) and three (MD 0.63 D, 95% CI 0.30 to 0.96) years follow-up, participants wearing RGPs had significantly less progression of myopia compared with participants wearing SCLs (Figure 5). After one and two years of follow-up, no difference in myopia progression was observed between RGP wearers and SVL wearers in the Katz 2003 study (MD -0.02, 95% CI -0.14 to 0.10 and MD -0.05 D, 95% CI -0.25 to 0.15, respectively). Data were not pooled for these studies due to statistical heterogeneity ( $I^2 = 91%$  at one year and 92% at two years).

**Change in axial length (Analysis 5.2):** At one year, meta-analysis of the two studies showed that axial elongation was 0.02 mm (95% CI -0.05 to 0.10) greater for the 176 RGP wearers than the 239 control participants. After two years, it was 0.03 mm greater (95% CI -0.05 to 0.12) for the 154 RGP wearers than the 240 control participants who were followed-up by the two studies. After three years, it was 0.05 mm greater (95% CI -0.12 to 0.22) for the 59 RGP wearers than the 57 SCL participants in the CLAMP Study.

**Change in corneal radius of curvature (Analysis 5.3):** Data from the CLAMP Study suggest that the use of RGPs may prevent increases in the corneal radius of curvature compared with SCLs. At one, two and three years follow-up, the MD between participants wearing RGPs and participants wearing SCLs was -0.24 D (95% CI -0.43 to -0.05), -0.38 D (95% CI -0.56 to -0.20) and -0.26 D (95% CI -0.48 to -0.04), respectively. After one year follow-up, the Katz 2003 study also suggested that RGPs may be beneficial compared with SCLs (MD -0.08 D, 95% CI -0.14 to -0.01); however, these results were not statistically significant at two years follow-up (MD -0.06 D, 95% CI -0.14 to 0.02). Data were not pooled for these studies due to statistical heterogeneity ( $I^2 = 60%$  for year one results and 90% for year two results).

**Anti-muscarinic agents versus placebo—**Five studies compared topical anti-muscarinic agents with placebo for slowing the progression of myopia in children. Two studies evaluated 2% pirenzepine gel (PIR-205 Study; Tan 2005); two studies evaluated an atropine ophthalmic solution, one at 0.5% (MIT study) and one at 1% (ATOM study); and one study evaluated 1% cyclopentolate ophthalmic solution (Yen 1989). Study groups included in these analyses from the MIT study were also provided with PALs. With the exception of Yen 1989, which measured refractive error by subjective cycloplegic refraction, the studies included in the analysis used cycloplegic autorefractometry for refraction measurements.

**Change in refractive error (Analysis 6.1; Analysis 6.2):** Due to statistical heterogeneity ( $I^2 = 90%$ ), we did not combine results for all anti-muscarinic agents and instead pooled the subgroups separately. At one year follow-up, the average progression was 0.31 D slower (95% CI 0.17 to 0.44) for participants treated with pirenzepine, 0.80 D slower (95% CI 0.70 to 0.90) for participants treated with atropine and 0.34 D slower (95% CI 0.08 to 0.60) for participants treated with cyclopentolate (Figure 6). The difference in progression between groups continued among participants in the two studies with two years of follow-up: MD

0.41 D (95% CI 0.13 to 0.69) for pirenzepine (PIR-205 Study) and MD 0.92 D (95% CI 0.75 to 1.09) for atropine (ATOM study).

**Change in axial length (Analysis 6.3; Analysis 6.4):** Three studies reported axial length outcomes; however we did not pool results due to statistical heterogeneity ( $I^2 = 96\%$ ). At one year follow-up the ATOM study reported significantly less axial elongation for participants assigned to atropine compared with participants assigned to placebo (MD  $-0.34$  mm, 95% CI  $-0.40$  to  $-0.28$ ). This effect persisted at the end of two years (MD  $-0.40$  mm, 95% CI  $-0.48$  to  $-0.32$ ). Tan 2005 reported that after one year, the mean increase in axial length was greatest in the placebo/placebo treated group (0.33 mm) compared with the placebo/gel (0.30 mm) and gel/gel (0.20 mm) groups. Although the standard deviations (DSs) for mean changes in axial length were only shown in a graph, the paper reported that there was a statistically significant treatment effect at one year (repeated-measures analysis of variance,  $P = 0.008$ ). No significant changes in axial length were observed at one year in the PIR-205 Study (MD  $-0.04$  mm, 95% CI  $-0.15$  to 0.07).

**Change in corneal radius of curvature:** Corneal radius of curvature outcomes were not assessed by studies comparing topical anti-muscarinic agents with placebo.

**Adverse effects:** Both of the studies evaluating pirenzepine documented ocular and systemic adverse events during the trials (Table 6). Both studies used a significance level of  $P < 0.15$  for reporting adverse events. The three most frequent systemic adverse events reported were headache, common cold and flu syndrome in the PIR-205 Study and increased cough, respiratory infection and rhinitis in Tan 2005. In the PIR-205 Study, events of common cold, rhinitis and sinusitis differed statistically between groups ( $P < 0.15$ ) and occurred more frequently in the placebo group than the pirenzepine group. In the Tan 2005 study, there were more complaints of abdominal pain in the gel/gel group than the placebo/placebo group ( $P = 0.065$ ) and more incidents of rash in the placebo/gel group than the placebo/placebo group ( $P = 0.104$ ). The three most frequent ocular adverse events reported by both studies were symptoms of decreased accommodation, papillae/follicles and medication residue on the eyelids or eyelashes. Six ocular adverse events differed significantly ( $P < 0.15$ ) between groups in the PIR-205 Study: symptoms of decreased accommodation, papillae/follicles, decreases in visual acuity, eye discomfort and mydriasis occurred more frequently in the pirenzepine treated group and medication residue on the eyelids or eyelashes occurred more frequently in the placebo group. Four ocular adverse events differed significantly ( $P < 0.15$ ) between groups in Tan 2005: symptoms of decreased accommodation, papillae/follicles and decreases in visual acuity occurred more frequently in the gel/gel and placebo/gel groups, and itchy eyes occurred more frequently in the placebo/gel group compared with the placebo group.

Four studies included in this review evaluated atropine in at least one study arm (ATOM study; MIT study; Shih 1999; Yen 1989); however, only two studies compared atropine with placebo directly (ATOM study; MIT study) and three studies reported adverse effects. In the ATOM study, no serious adverse events were reported, although the four most common reasons for study withdrawal in the atropine group were allergic or hypersensitivity reactions or discomfort (4.5%), logistical difficulties (3.5%), glare (1.5%) and blurred near

vision (1%). There were no instances of decreased visual acuity, intraocular pressure changes over 5.5 mmHg, or lenticular, optic disc, or macular changes reported. Yen 1989 reported that all patients in the atropine (plus bifocal lenses) group had photophobia, which was not reported in the cyclopentolate (plus SVLs) or placebo (plus SVLs) groups. Shih 1999 reported three adverse events, all of which occurred in the highest dose atropine group (0.5%): two participants complained of photophobia and one participant had allergic blepharitis.

**Timolol drops versus no drops**—One study compared 0.25% timolol drops with no drops for slowing the progression of myopia in children (Jensen 1991). Participants in both groups wore SVLs. Refractive error was measured by cycloplegic autorefraction.

**Change in refractive error (Analysis 7.1):** There were no statistically significant differences in myopia progression for 46 participants who used timolol compared with 49 participants who did not, at one year (MD  $-0.05$  D, 95% CI  $-0.21$  to  $0.11$ ) and at two years (MD  $-0.04$  D, 95% CI  $-0.30$  to  $0.22$ ).

**Change in axial length:** Axial length was not measured by Jensen 1991.

**Change in corneal radius of curvature:** Corneal radius of curvature was not measured by Jensen 1991.

#### **Other comparisons of interventions**

**Bifocal spectacles versus SVLs with timolol drops (Analysis 8.1):** In a three-arm trial of +2.00 bifocal lenses, 0.25% timolol drops plus SVLs, and SVLs (Jensen 1991), a pair-wise comparison of bifocal and SVL plus timolol groups suggested use of bifocals slowed the progression of myopia more effectively than SVLs plus timolol drops at one year (MD  $0.19$  D, 95% CI  $0.06$  to  $0.32$ ) and two years (MD  $0.23$  D, 95% CI  $0.00$  to  $0.46$ ). Neither intervention when compared with the SVL only group were statistically significant for this study (see Analysis 2.1; Analysis 2.2; Analysis 7.1).

**Tropicamide plus bifocal spectacles versus SVLs:** In a co-twin study, one twin from each twin pair was randomized to receive either 1% tropicamide once per day and +1.25 bifocals or SVLs. Follow-up was for 3.5 years (Schwartz 1981). No numerical results were presented in the paper. The study authors stated that control twins showed more progression in myopia than their co-twins who received tropicamide and bifocals, but that this difference was not statistically significant.

**Atropine plus multifocal spectacles versus placebo plus SVLs (Analysis 9.1; Analysis 9.2):** Two studies compared atropine drops plus multifocal lenses with placebo drops plus SVLs to slow the progression of myopia in children. The MIT study used 0.5% atropine plus PALs and Yen 1989 used 1% atropine plus bifocal lenses. At one year, both studies showed less progression among atropine plus multifocal lens users compared to placebo plus SVL users (summary MD  $0.78$  D, 95% CI  $0.54$  to  $1.02$ ). At the end of the 18-month MIT study, participants in the atropine plus multifocal lens group had significantly less axial elongation

compared with participants in the placebo plus SVL group (MD  $-0.37$  mm, 95% CI  $-0.47$  to  $-0.27$ ).

**Atropine plus bifocal spectacles versus cyclopentolate plus SVLs (Analysis 10.1):** One study compared 1% atropine drops plus bifocal lenses with 1% cyclopentolate drops plus SVLs (Yen 1989). At one year, participants in the atropine plus bifocal lens group had significantly less myopia progression compared with participants in the cyclopentolate plus SVL group (MD 0.36 D, 95% CI 0.11 to 0.61).

**Atropine versus tropicamide (Analysis 11.1; Analysis 11.2):** One study compared three doses of atropine with tropicamide (Shih 1999). In the four-arm trial participants were assigned to receive 0.5% atropine drops plus bifocals, 0.25% atropine drops plus slightly undercorrected lenses, 0.1% atropine drops plus fully corrected SVLs, or 0.5% tropicamide drops (control group). At one year follow-up, myopia progression was significantly slowed for each atropine group compared with the tropicamide group, with the highest atropine dose showing the least progression (MD 0.78, 95% CI 0.49 to 1.07 for 0.1% atropine; MD 0.81, 95% CI 0.57 to 1.05 for 0.25% atropine; and MD 1.01, 95% CI 0.74 to 1.28 for 0.5% atropine). This effect was also observed at two years follow-up for each atropine group compared with the tropicamide group (MD 1.95, 95% CI 1.60 to 2.30 for 0.1% atropine; MD 1.98, 95% CI 1.68 to 2.28 for 0.25% atropine; and MD 2.42, 95% CI 2.16 to 2.68 for 0.5% atropine).

## DISCUSSION

### Summary of main results

Our findings suggest that there is limited evidence favoring full correction of myopia compared with undercorrection. Trials have shown a clinically insignificant benefit with progressive addition lenses (PALs) compared with single vision lenses (SVLs). The effects for axial length and corneal curvature did not support this small beneficial effect for refractive error comparing PALs with SVLs. Evidence supporting the benefit of bifocal lenses compared with SVLs is limited and inconsistent across heterogeneous trials. A single study, at high risk of bias, provided evidence of slower progression of refractive error when using bifocal soft contact lenses (BSCLs) compared with single vision soft contact lenses (SVSCLs). The evidence from this single trial should not be considered conclusive. The evidence regarding the beneficial effect of rigid gas permeable contact lenses (RGPCs) is conflicting and may be related to the ethnicity of participants and/or the comparator intervention in the included trials. For example, Asian children are more likely to be myopic and their myopia progresses faster than Caucasian children (Lin 1999; Zhan 2000), so any myopia control agent may be more or less effective for Asian children than Caucasian children because the cause of their myopia may be different. A statistically significant effect of 0.63 D (95% CI 0.30 to 0.96) favoring RGPCs was observed in a trial conducted among children comprised predominantly of Caucasian ethnicity. The comparator was soft contact lenses (SCLs). In a trial of children with Chinese ethnicity, compared with SVLs, we observed a very small, statistically non-significant beneficial effect.

We found consistent evidence favoring anti-muscarinic drugs compared with placebo for reducing the progression of myopia and elongation of the axial length in children with myopia. Atropine resulted in an effect with larger magnitude than pirenzepine or cyclopentolate. There was no trial directly comparing the three different anti-muscarinic drugs. These drugs also were associated with frequent side effects, such as sensitivity to light and blur while reading, which may lead to approximately 15% of children quitting the therapy (ATOM study). One study directly compared atropine versus tropicamide, although the concentration of atropine (0.1% and 0.25%) was much lower than that used in other trials, and found a statistically significant beneficial effect with atropine. Evidence from one trial each suggests that using atropine in addition to either bifocal (at 1% concentration) or PALs (at 0.05% concentration) resulted in slower progression of myopia and lesser elongation of axial length compared with SVLs without the use of atropine.

In summary, we found consistent evidence of a meaningful benefit with using anti-muscarinic drugs for slowing progression of myopia in children. Neither the optimal dose of anti-muscarinic drugs nor the additional value of using anti-muscarinic drugs along with spectacles or contact lenses has been adequately answered by available evidence. The evidence regarding beneficial effects of the other interventions included in this review is neither consistent nor confirmatory.

### **Overall completeness and applicability of evidence**

Several interventions have been investigated by more than one reporting source (journal publication, conference abstract, trial registry, etc.) and they provided sufficient evidence to determine the applicability of the treatment for slowing myopia progression. However, reporting of results was inconsistent among studies, so grouping of findings was difficult. Anti-muscarinic pharmaceutical agents hold the most promise for slowing myopia progression in children, but most investigations reported in the literature lacked complete data to include in the analysis.

The included trials have been conducted across populations of diverse ethnic and geographic locations. The effects that we observed for anti-muscarinic drugs was consistent across studies conducted in Caucasian populations as well as Asian populations.

### **Quality of the evidence**

This review was limited to RCTs, eliminating the chance of treatment selection bias based on participants' desires for a specific correction. However, not all biases were completely eliminated. For example, participants could not be masked with regard to treatment when they were assigned randomly to spectacles versus contact lenses or to one of two types of contact lenses. Although it is unlikely the participants could influence the outcome of myopic eye growth, they may have been more likely to end participation in a study if they received a treatment that did not interest them, which could potentially increase the risk of bias.

The primary outcome for myopia progression studies typically has been change in refractive error over time; however, as new methods of assessing myopia have become available, the primary outcome has switched to axial growth of the eye. During this transition, both



methods have been measured and reported, which may add confusion if the two methods provide differing information. For example, the RGPCL trial by Walline and colleagues found that RGPCLs significantly slowed myopia progression, but they did not slow axial eye growth (CLAMP Study). The change in the primary outcome of myopia control studies therefore could lead to a reporting bias, depending on how the study authors reported the data.

Although most studies used masked examiners to measure primary outcomes, several trials lacked masked examiners or did not report masking in the study, so the risk of examiner bias still exists. The vast majority of studies either did not mask the person analyzing the study data or they did not report whether or not the data were masked. It is important for statisticians to make decisions based solely on available data that should not include treatment allocation in order to reduce or eliminate the potential for reporting bias.

Overall, with the improvement of trials following the CONSORT Statement for RCTs (Schulz 2010), the potential for bias has been largely addressed, but many studies still lack the required rigor of reporting that is necessary to allow the reader to assess the risk of bias in individual trials.

### **Potential biases in the review process**

We reduced the risk of bias during the review process by utilizing a thorough literature search and by not limiting studies that were reviewed based on language or dates. Two review authors, including at least one clinician (JJW, DOM, SAC, JDT) and one methodologist (SSV, KL), independently assessed the search results for eligibility and extracted data. There is little reason to believe that investigations would have been missed by the search methods unless the results of the study were never reported.

### **Agreements and disagreements with other studies or reviews**

Saw 2002a, Saw 2002b and Gwiazda 2009 did not include a systematic and comprehensive literature search and any meta-analyses. The conclusions in these three reviews are consistent with our observations in this systematic review. Other treatments, such as undercorrection of myopia, multifocal spectacles and RGPCLs do not slow the growth of the eye in a clinically meaningful manner (slowing the growth of the eye by 50% or more).

## **AUTHORS' CONCLUSIONS**

### **Implications for practice**

Based on available evidence, the most effective method of slowing myopia progression is with anti-muscarinic topical medications, but the side effects and limited availability make them a little-used option for myopia control. Further investigations of myopia control must be conducted in order to find a treatment that is clinically meaningful and beneficial and with few adverse effects. The leading potential candidates at this time are corneal reshaping and BSCLs, but much more evidence must be presented in order to determine their abilities to slow myopia progression.



None of the interventions studied have slowed myopia progression in a clinically meaningful manner, with the exception of anti-muscarinic pharmaceutical agents. However, anti-muscarinic pharmaceutical agents either have significant side effects, such as mydriasis and cycloplegia, or they are not commercially available at this time.

### Implications for research

Until recently, there have been few RCTs conducted to investigate myopia control. The reporting of results from RCTs was extremely variable. Investigators must compare results to previous investigations and report findings according to the CONSORT statement in order to maximize the potential for combining results of a variety of studies. Future investigators should consider findings from this systematic review in determining the comparisons that should be examined and the patient populations to be studied. We have not found conclusive evidence of the effects of most interventions included in this review, despite our consistent findings for the effects of anti-muscarinic drugs. For example, there is limited evidence on an optimal dose of anti-muscarinic drugs for use in children. The evidence that we examined was limited in several ways including the potential for bias. Future trials should be designed and reported considering the potential for application of novel analytical methods such as multiple treatment meta-analyses. The added value of using anti-muscarinic drugs along with spectacles or contact lenses and the effects of other combinations of interventions in slowing the progression of myopia in children need to be clarified. If future investigators find a clinically and statistically significant treatment effect, they should determine whether the effect continues to be sustained after the treatment is discontinued and attempt to determine the true mechanism of the treatment effect.

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## APPENDICES

### Appendix 1. CENTRAL search strategy

- #1 MeSH descriptor Myopia
- #2 myop\*
- #3 short near sight\*
- #4 (#1 OR #2 OR #3)
- #5 MeSH descriptor Eyeglasses
- #6 spectacles or glasses
- #7 MeSH descriptor Contact Lenses
- #8 contact next lens\*
- #9 MeSH descriptor Mydriatics
- #10 mydriat\*
- #11 MeSH descriptor Muscarinic Antagonists
- #12 muscarinic next antagonist\*
- #13 anti next muscarinic
- #14 MeSH descriptor Cholinergic Antagonists
- #15 cholinergic next antagonist\*
- #16 anti next cholinergic
- #17 MeSH descriptor Timolol
- #18 timolol\*
- #19 MeSH descriptor Atropine
- #20 atropine\*
- #21 MeSH descriptor Cyclopentolate
- #22 cyclopentolate\*
- #23 MeSH descriptor Phenylephrine
- #24 phenylephrine\*
- #25 MeSH descriptor Pirenzepine
- #26 pirenzepine\*
- #27 MeSH descriptor Tropicamide

#28 tropicamide\*

#29 (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15  
OR #16 OR #17 OR #18 OR #19 OR # 20 OR #21 OR #22 OR #23 OR #24 OR #25  
OR #26 OR #27 OR #28)

#30 MeSH descriptor Refractive Errors

#31 refract\*

#32 MeSH descriptor Accommodation, Ocular

#33 MeSH descriptor Visual Acuity

#34 accommodat\* or acuity

#35 progress\* or slow\* or retard\* or funct\*

#36 (#30 OR #31 OR #32 OR #33 OR #34 OR #35)

#37 (#4 AND #29 AND #36)

## Appendix 2. MEDLINE (OVID) 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 myopia/
14. myop\$.tw.
15. ((short or near) adj3 sight\$).tw.
16. or/13-15
17. exp eyeglasses/
18. (spectacles or glasses).tw.
19. exp contact lenses/

20. (contact adj2 lens\$.tw.
21. exp mydriatics/
22. mydriat\$.tw.
23. exp muscarinic antagonists/
24. (muscarinic adj2 antagonist\$.tw.
25. (anti adj1 muscarinic).tw.
26. exp cholinergic antagonists/
27. (cholinergic adj2 antagonist\$.tw.
28. (anti adj1 cholinergic).tw.
29. exp timolol/
30. timolol\$.tw.
31. exp atropine/
32. atropine\$.tw.
33. exp cyclopentolate/
34. cyclopentolate\$.tw.
35. exp phenylephrine/
36. phenylephrine\$.tw.
37. exp pirenzepine/
38. pirenzepine\$.tw.
39. exp tropicamide/
40. tropicamide\$.tw.
41. or/17–40
42. exp refractive errors/
43. refract\$.tw.
44. exp accommodation, ocular/
45. exp visual acuity/
46. (accommodat\$ or acuity).tw.
47. (progress\$ or slow\$ or retard\$ or funct\$.tw.
48. or/42–47
49. 16 and 41 and 48
50. 12 and 49

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

### Appendix 3. EMBASE (OVID) search strategy

1. exp randomized controlled trial/
2. exp randomisation/
3. exp double blind procedure/
4. exp single blind procedure/
5. random\$.tw.
6. or/1–5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin\$ adj3 trial\$).tw.
14. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
15. exp placebo/
16. placebo\$.tw.
17. random\$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12–21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control\$ or prospectiv\$ or volunteer\$).tw.

29. or/25–28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp myopia/
34. myop\$.tw.
35. ((short or near) adj3 sight\$.tw.
36. or/33–35
37. exp spectacles/
38. (spectacles or glasses).tw.
39. exp contact lens/
40. (contact adj2 lens\$.tw.
41. exp mydriatic agent/
42. mydriat\$.tw.
43. exp Muscarinic Receptor Blocking Agent/
44. (muscarinic adj2 antagonist\$.tw.
45. (anti adj1 muscarinic).tw.
46. exp Cholinergic Receptor Blocking Agent/
47. (cholinergic adj2 antagonist\$.tw.
48. (anti adj1 cholinergic).tw.
49. exp timolol/
50. timolol\$.tw.
51. exp atropine/
52. atropine\$.tw.
53. exp cyclopentolate/
54. cyclopentolate\$.tw.
55. exp phenylephrine/
56. phenylephrine\$.tw.
57. exp pirenzepine/
58. pirenzepine\$.tw.
59. exp tropicamide/
60. tropicamide\$.tw.



61. or/37–60
62. exp refraction error/
63. refract\$.tw.
64. exp accommodation/
65. exp visual acuity/
66. (accommodat\$ or acuity).tw.
67. (progress\$ or slow\$ or retard\$ or funct\$).tw.
68. or/32–67
69. 36 and 61 and 68
70. 32 and 69

#### Appendix 4. LILACS search terms

myop\$ and spectacle\$ or glasses or lens\$ or mydriatic\$ or muscarin\$ or cholinergic and refract\$ or accommodat\$ or acuity or progress\$ or slow\$ or retard\$ or funct\$

#### Appendix 5. metaRegister of Controlled Trials search strategy

(progress or slow or retard) and myopia

#### Appendix 6. ClinicalTrials.gov search strategy

(Progress OR Slow OR Retard OR Function) AND Myopia

### DATA AND ANALYSES

#### Comparison 1. Undercorrection vs. Full correction spectacles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in refractive error from baseline	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 At one year	2	142	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.29, -0.00]
1.2 At two years	1	94	Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.50, 0.04]
2 Change in axial length from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 At one year	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 At two years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

## Comparison 2. Multifocal lenses vs. Single vision lenses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in refractive error from baseline (1 year)	7	1266	Mean Difference (Random, 95% CI)	0.16 [0.07, 0.25]
1.1 Bifocal lenses	4	421	Mean Difference (Random, 95% CI)	0.16 [0.01, 0.32]
1.2 Progressive addition lenses	3	845	Mean Difference (Random, 95% CI)	0.17 [0.10, 0.24]
2 Change in refractive error from baseline (2 years)	7		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Bifocal lenses	4		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Progressive addition lenses	3		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Change in refractive error from baseline (3 years)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Bifocal lenses	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Progressive addition lenses	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Change in axial length from baseline (1 year)	3	812	Mean Difference (Random, 95% CI)	-0.07 [-0.09, -0.04]
5 Change in axial length from baseline (2 years)	2	723	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.10, -0.01]
6 Change in axial length from baseline (3 years)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Change in corneal radius of curvature from baseline-Horizontal (3 years)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 At three years, horizontal	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 At three years, vertical	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

## Comparison 3. Novel lens spectacles vs. Single vision lenses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in refractive error from baseline (1 year)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Type I	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Type II	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Type III	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in axial length from baseline (1 year)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Type I	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Type II	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Type III	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

#### Comparison 4. Bifocal soft contact lenses vs. Single vision soft contact lenses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in refractive error from baseline (1 year)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Change in axial length from baseline (1 year)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

#### Comparison 5. Rigid gas permeable contact lenses vs. Control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in refractive error from baseline	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 At one year	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 At two years	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 At three years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in axial length from baseline	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 At one year	2	415	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.05, 0.10]
2.2 At two years	2	394	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.05, 0.12]
2.3 At three years	1	116	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.12, 0.22]
3 Change in corneal radius of curvature from baseline	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 At one year	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 At two years	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 At three years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

**Comparison 6. Anti-muscarinic agents vs. Placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in refractive error from baseline (1 year)	5		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 Pirenzepine 2% gel	2	326	Mean Difference (Fixed, 95% CI)	0.31 [0.17, 0.44]
1.2 Atropine eye drops	2	497	Mean Difference (Fixed, 95% CI)	0.80 [0.70, 0.90]
1.3 Cyclopentolate eye drops	1	64	Mean Difference (Fixed, 95% CI)	0.34 [0.08, 0.60]
2 Change in refractive error from baseline (2 years)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Pirenzepine 2% gel	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Atropine eye drops	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Change in axial length from baseline (1 year)	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Pirenzepine 2% gel	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Atropine eye drops	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Change in axial length from baseline (2 years)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

**Comparison 7. Timolol 0.25% eye drops vs. No eye drops**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in refractive error from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 At one year	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 At two years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

**Comparison 8. Bifocal spectacles vs. Single vision lenses + Timolol**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in refractive error from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 At one year	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 At two years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

**Comparison 9. Atropine + Multifocal lenses vs. Placebo + Single vision lenses**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in refractive error from baseline (1 year)	2	191	Mean Difference (Fixed, 95% CI)	0.78 [0.54, 1.02]
2 Change in axial length from baseline (1 year)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

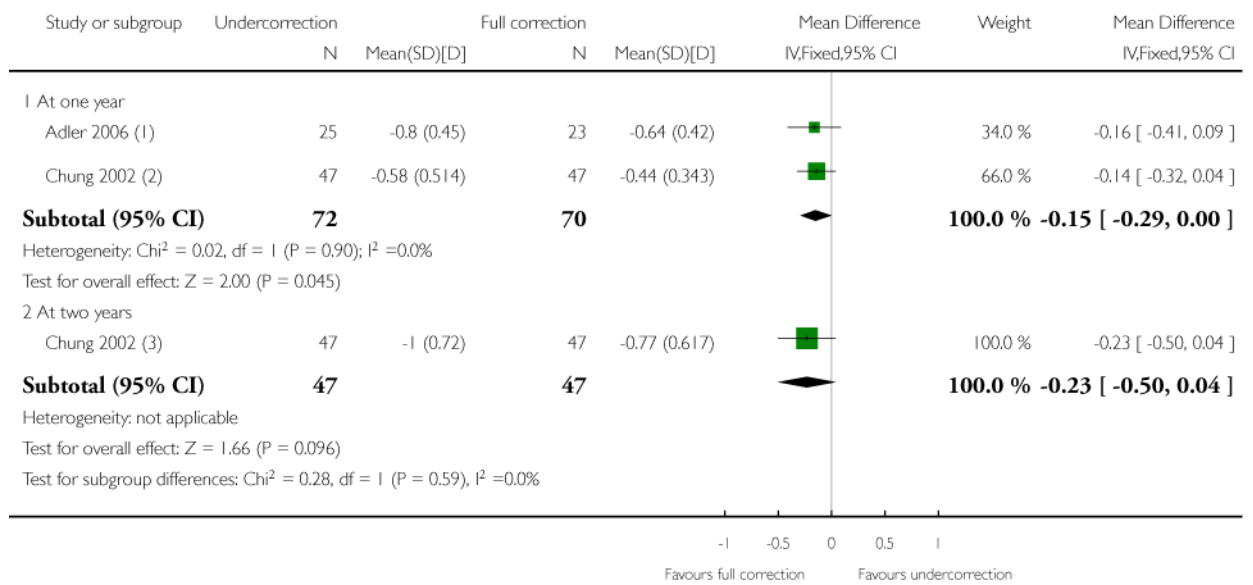
**Comparison 10. Atropine + Multifocal lenses vs. Cyclopentolate + Single vision lenses**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in refractive error from baseline (1 year)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

**Comparison 11. Atropine vs. Tropicamide**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in refractive error from baseline (1 year)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Atropine 0.5%	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Atropine 0.25%	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Atropine 0.1%	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in refractive error from baseline (2 years)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Atropine 0.5%	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Atropine 0.25%	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Atropine 0.1%	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Review: Interventions to slow progression of myopia in children  
 Comparison: 1 Undercorrection vs. Full correction spectacles  
 Outcome: 1 Change in refractive error from baseline

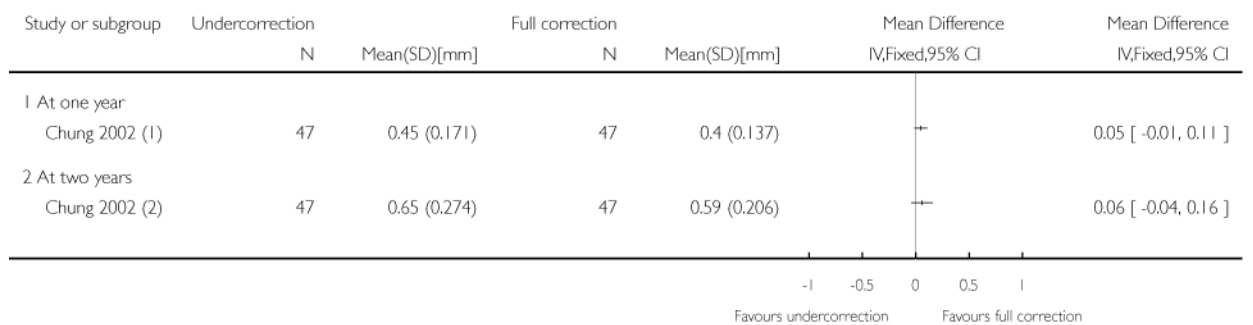


(1) Data provided by study author.  
 (2) Data estimated from graph.  
 (3) Data estimated from graph (although reported as statistically significant in the article).

**Analysis 1.1.**

**Comparison 1 Undercorrection vs. Full correction spectacles, Outcome 1 Change in refractive error from baseline.**

Review: Interventions to slow progression of myopia in children  
 Comparison: 1 Undercorrection vs. Full correction spectacles  
 Outcome: 2 Change in axial length from baseline



(1) Data estimated from graph.  
 (2) Data estimated from graph (reported as significant in text).

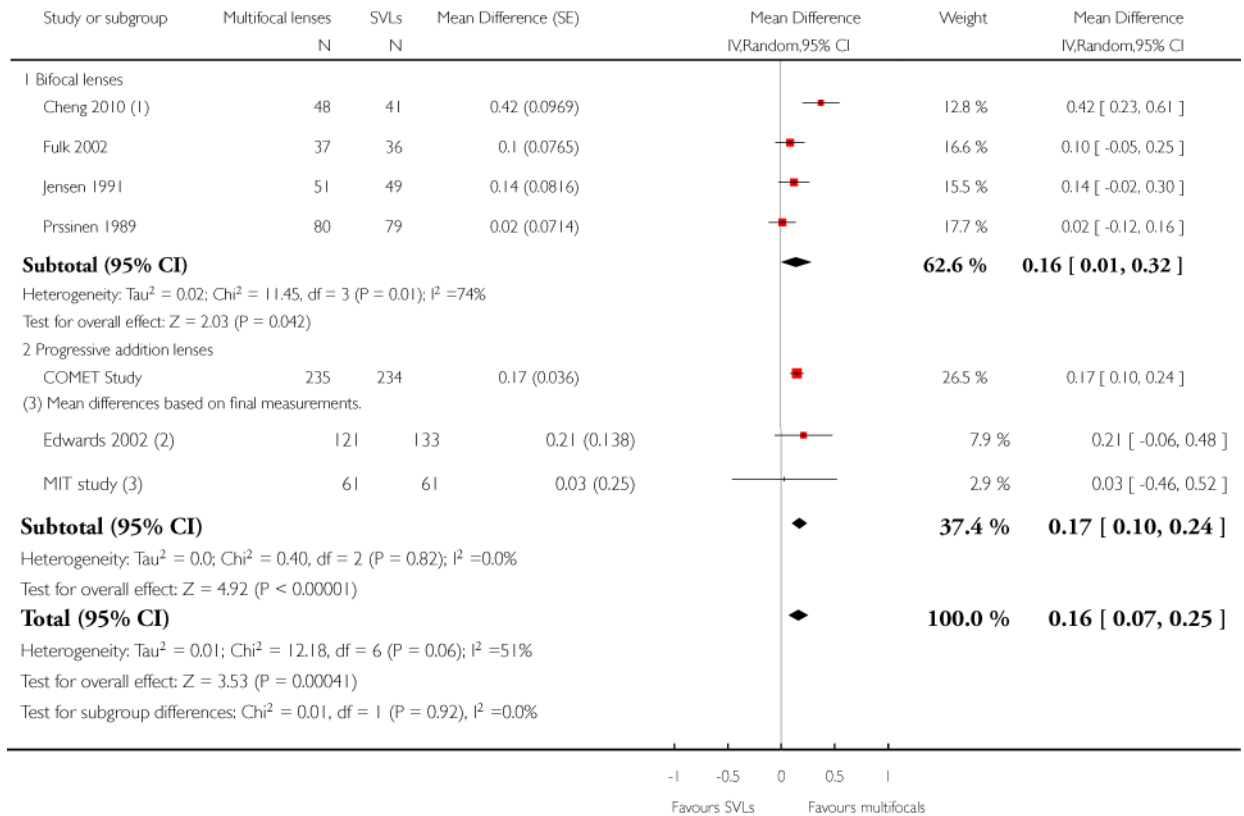
**Analysis 1.2.**

**Comparison 1 Undercorrection vs. Full correction spectacles, Outcome 2 Change in axial length from baseline.**

Review: Interventions to slow progression of myopia in children

Comparison: 2 Multifocal lenses vs. Single vision lenses

Outcome: 1 Change in refractive error from baseline (1 year)



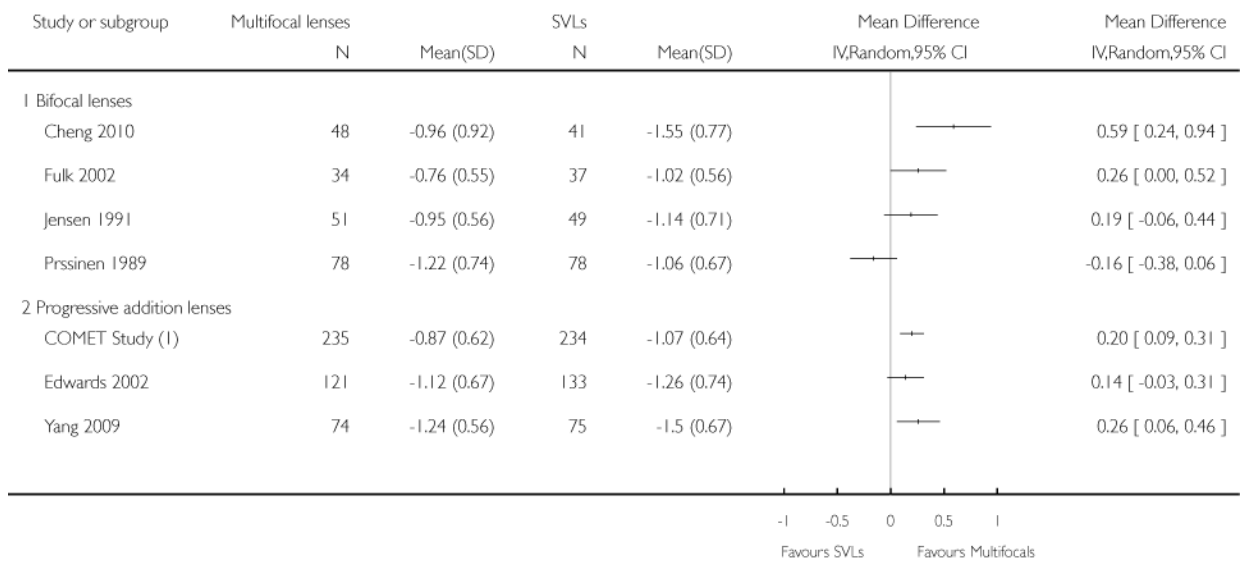
- (1) Data provided by study author.
- (2) Mean differences based on final measurements.
- (3) Mean differences based on final measurements.

**Analysis 2.1.**

Comparison 2 Multifocal lenses vs. Single vision lenses, Outcome 1 Change in refractive error from baseline (1 year).



Review: Interventions to slow progression of myopia in children  
 Comparison: 2 Multifocal lenses vs. Single vision lenses  
 Outcome: 2 Change in refractive error from baseline (2 years)

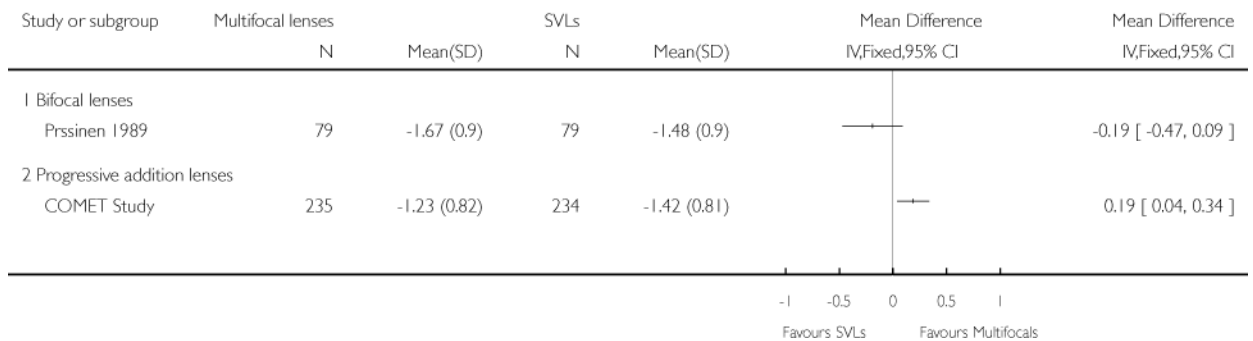


(1) Data provided by study authors.

**Analysis 2.2.**

Comparison 2 Multifocal lenses vs. Single vision lenses, Outcome 2 Change in refractive error from baseline (2 years).

Review: Interventions to slow progression of myopia in children  
 Comparison: 2 Multifocal lenses vs. Single vision lenses  
 Outcome: 3 Change in refractive error from baseline (3 years)



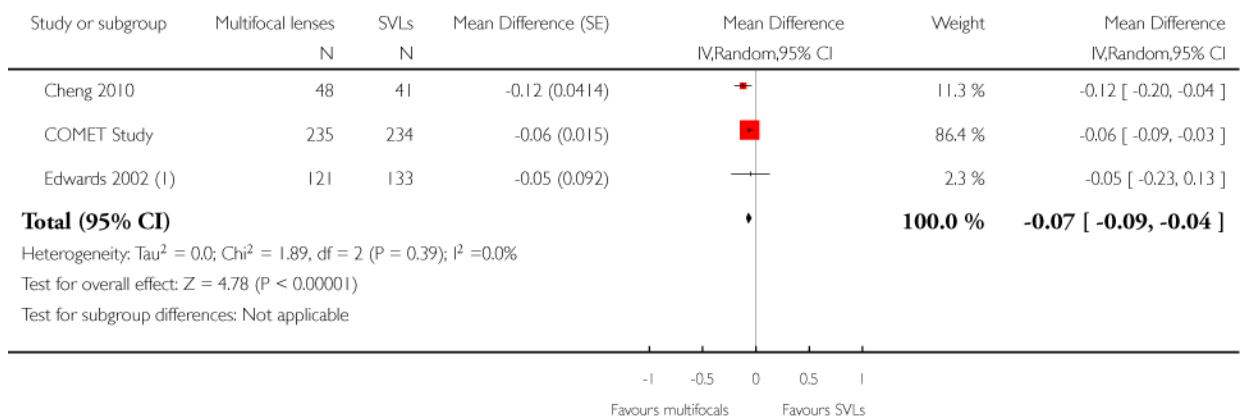
**Analysis 2.3.**

Comparison 2 Multifocal lenses vs. Single vision lenses, Outcome 3 Change in refractive error from baseline (3 years).

Review: Interventions to slow progression of myopia in children

Comparison: 2 Multifocal lenses vs. Single vision lenses

Outcome: 4 Change in axial length from baseline (1 year)



(1) Mean differences based on final measurements.

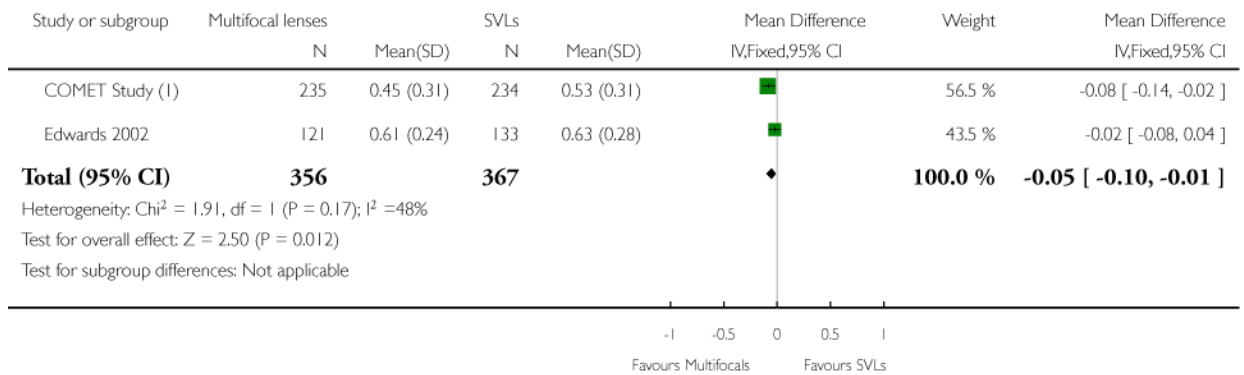
**Analysis 2.4.**

**Comparison 2 Multifocal lenses vs. Single vision lenses, Outcome 4 Change in axial length from baseline (1 year).**

Review: Interventions to slow progression of myopia in children

Comparison: 2 Multifocal lenses vs. Single vision lenses

Outcome: 5 Change in axial length from baseline (2 years)



(1) Data estimated from graph.

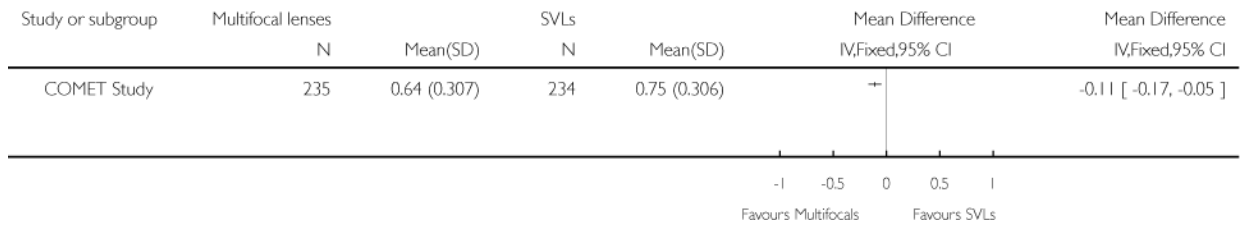
**Analysis 2.5.**

**Comparison 2 Multifocal lenses vs. Single vision lenses, Outcome 5 Change in axial length from baseline (2 years).**

Review: Interventions to slow progression of myopia in children

Comparison: 2 Multifocal lenses vs. Single vision lenses

Outcome: 6 Change in axial length from baseline (3 years)



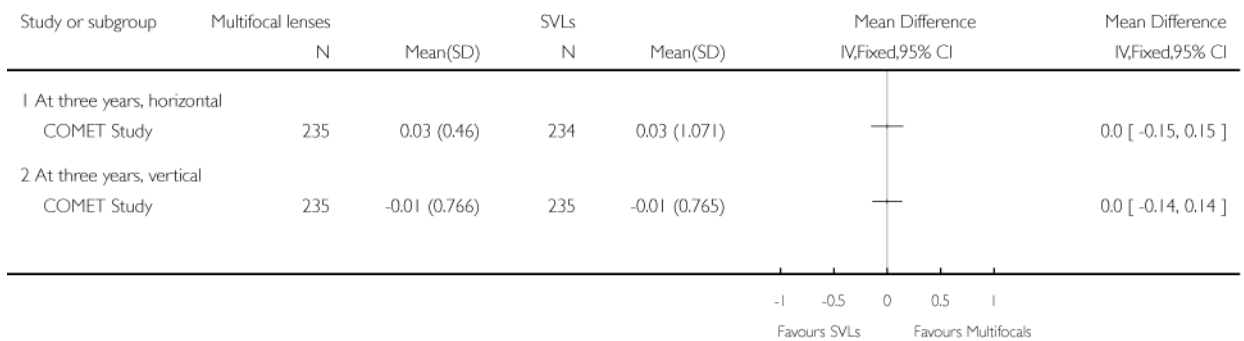
**Analysis 2.6.**

Comparison 2 Multifocal lenses vs. Single vision lenses, Outcome 6 Change in axial length from baseline (3 years).

Review: Interventions to slow progression of myopia in children

Comparison: 2 Multifocal lenses vs. Single vision lenses

Outcome: 7 Change in corneal radius of curvature from baseline-Horizontal (3 years)



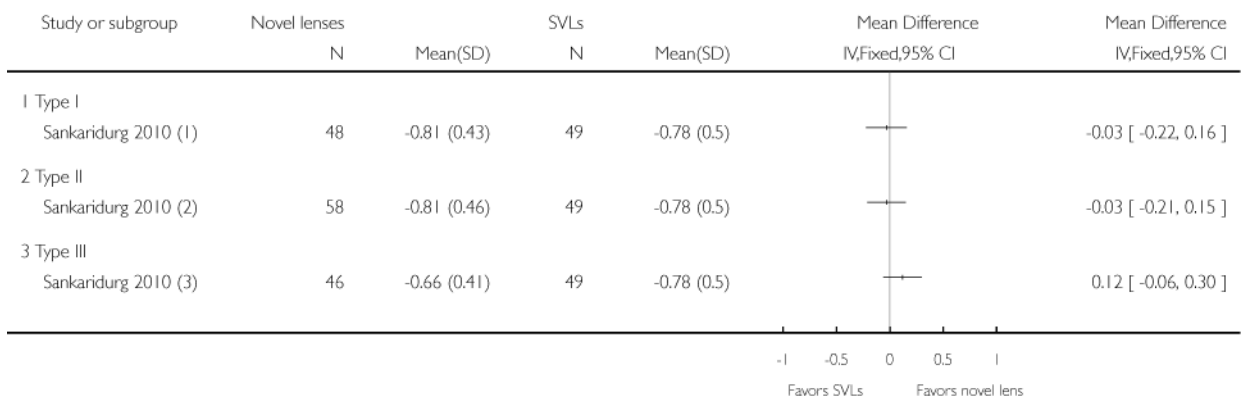
**Analysis 2.7.**

Comparison 2 Multifocal lenses vs. Single vision lenses, Outcome 7 Change in corneal radius of curvature from baseline-Horizontal (3 years).

Review: Interventions to slow progression of myopia in children

Comparison: 3 Novel lens spectacles vs. Single vision lenses

Outcome: 1 Change in refractive error from baseline (1 year)



- (1) SD for novel lens estimated from graph.
- (2) SD for novel lens estimated from graph.
- (3) SD for novel lens estimated from graph.

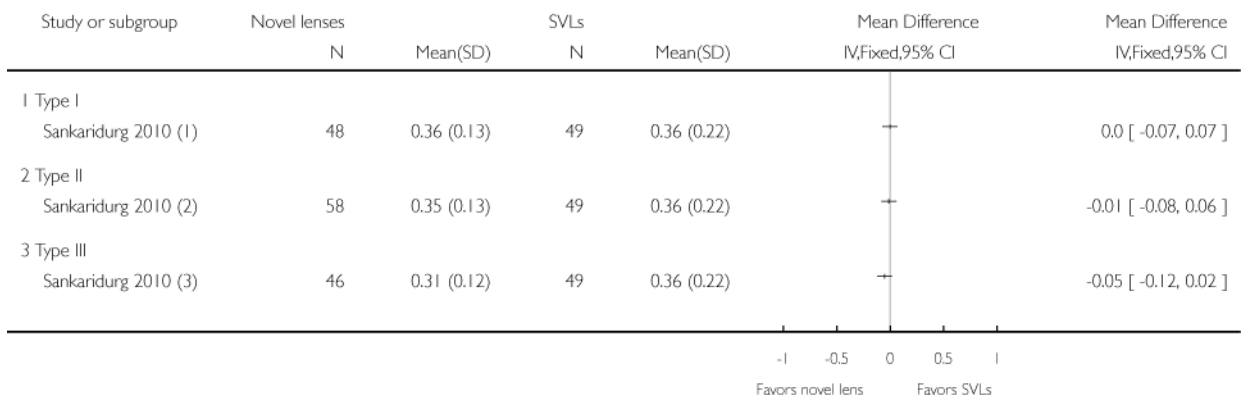
**Analysis 3.1.**

**Comparison 3 Novel lens spectacles vs. Single vision lenses, Outcome 1 Change in refractive error from baseline (1 year).**

Review: Interventions to slow progression of myopia in children

Comparison: 3 Novel lens spectacles vs. Single vision lenses

Outcome: 2 Change in axial length from baseline (1 year)



- (1) SD for novel lens estimated from graph.
- (2) SD for novel lens estimated from graph.
- (3) SD for novel lens estimated from graph.

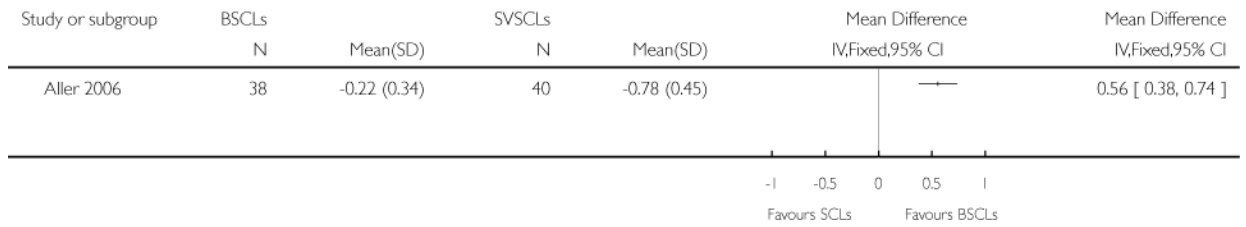
**Analysis 3.2.**

**Comparison 3 Novel lens spectacles vs. Single vision lenses, Outcome 2 Change in axial length from baseline (1 year).**

Review: Interventions to slow progression of myopia in children

Comparison: 4 Bifocal soft contact lenses vs. Single vision soft contact lenses

Outcome: 1 Change in refractive error from baseline (1 year)



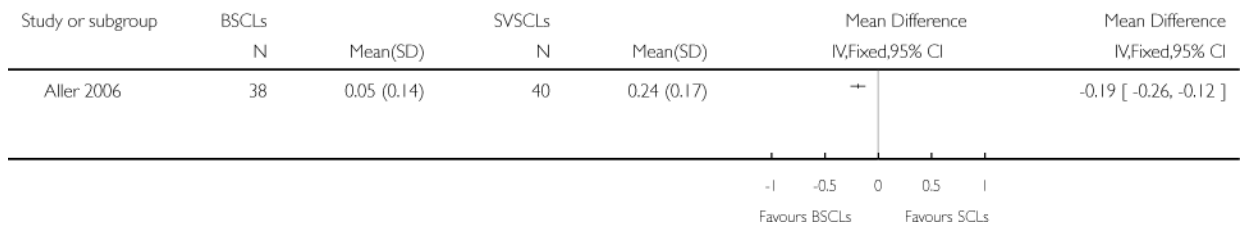
**Analysis 4.1.**

Comparison 4 Bifocal soft contact lenses vs. Single vision soft contact lenses, Outcome 1  
Change in refractive error from baseline (1 year).

Review: Interventions to slow progression of myopia in children

Comparison: 4 Bifocal soft contact lenses vs. Single vision soft contact lenses

Outcome: 2 Change in axial length from baseline (1 year)



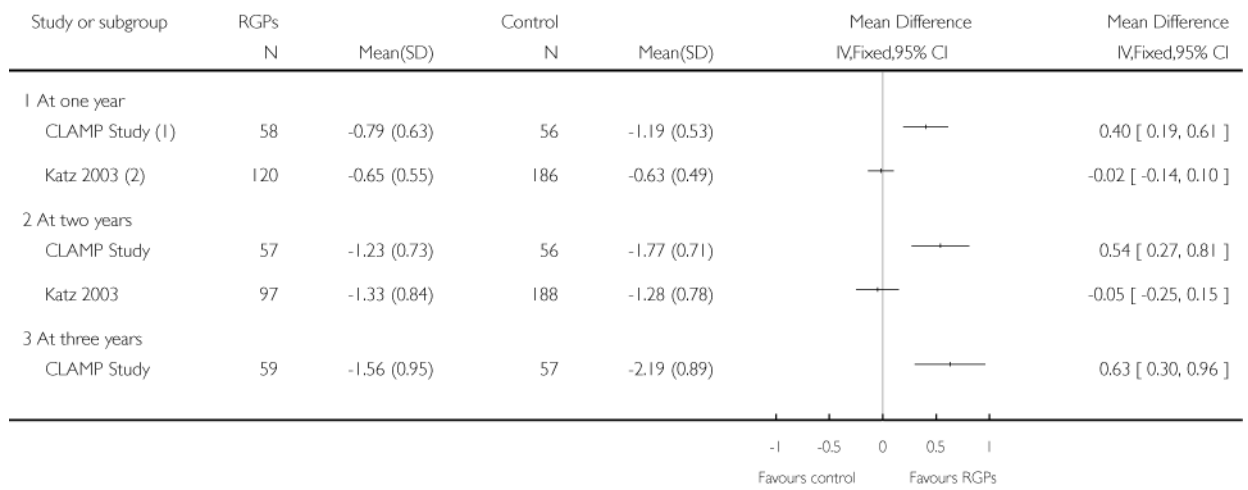
**Analysis 4.2.**

Comparison 4 Bifocal soft contact lenses vs. Single vision soft contact lenses, Outcome 2  
Change in axial length from baseline (1 year).

Review: Interventions to slow progression of myopia in children

Comparison: 5 Rigid gas permeable contact lenses vs. Control

Outcome: 1 Change in refractive error from baseline



(1) Control group wore soft contact lenses.

(2) Control group wore single vision spectacles.

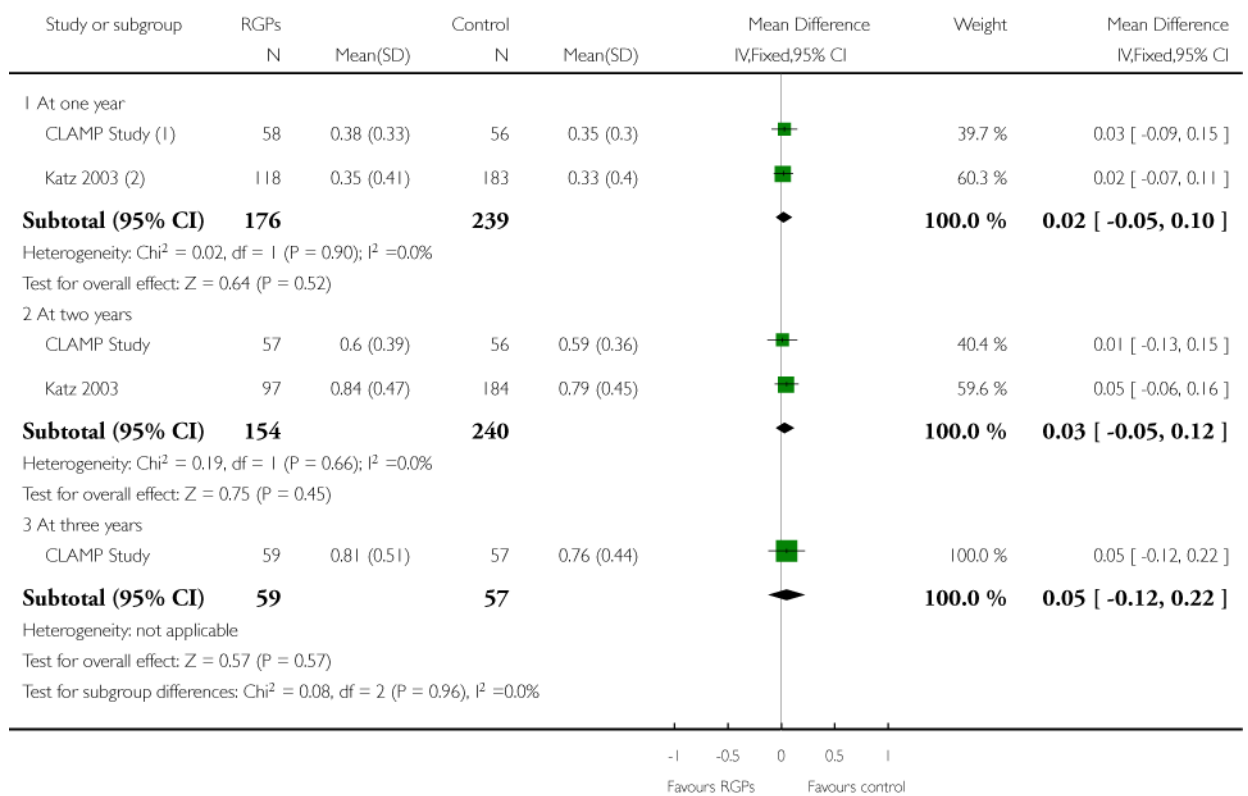
**Analysis 5.1.**

Comparison 5 Rigid gas permeable contact lenses vs. Control, Outcome 1 Change in refractive error from baseline.

Review: Interventions to slow progression of myopia in children

Comparison: 5 Rigid gas permeable contact lenses vs. Control

Outcome: 2 Change in axial length from baseline



(1) Control group wore soft contact lenses.  
 (2) Control group wore single vision spectacles.

**Analysis 5.2.**

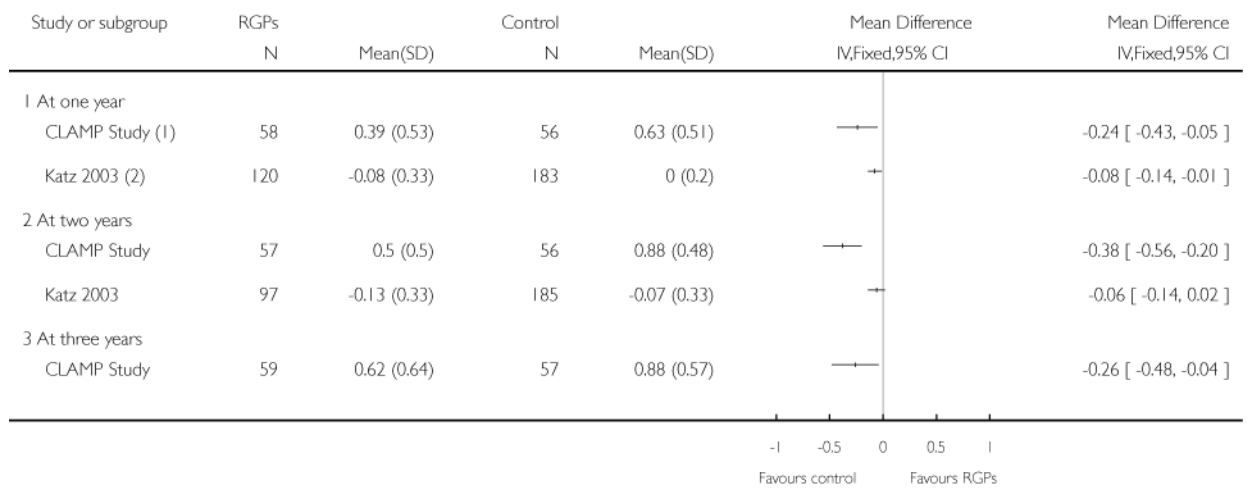
Comparison 5 Rigid gas permeable contact lenses vs. Control, Outcome 2 Change in axial length from baseline.



Review: Interventions to slow progression of myopia in children

Comparison: 5 Rigid gas permeable contact lenses vs. Control

Outcome: 3 Change in corneal radius of curvature from baseline



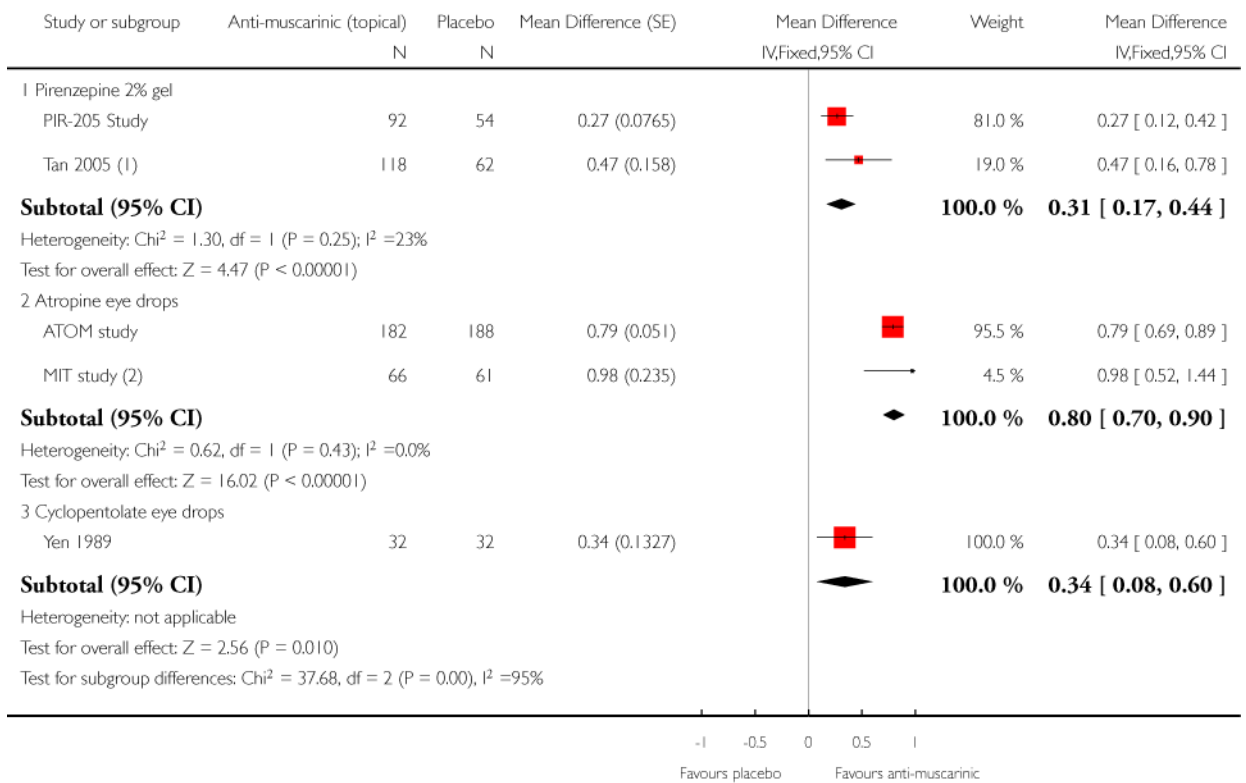
(1) Control group wore soft contact lenses.

(2) Control group wore single vision spectacles.

**Analysis 5.3.**

Comparison 5 Rigid gas permeable contact lenses vs. Control, Outcome 3 Change in corneal radius of curvature from baseline.

Review: Interventions to slow progression of myopia in children  
 Comparison: 6 Anti-muscarinic agents vs. Placebo  
 Outcome: 1 Change in refractive error from baseline (1 year)

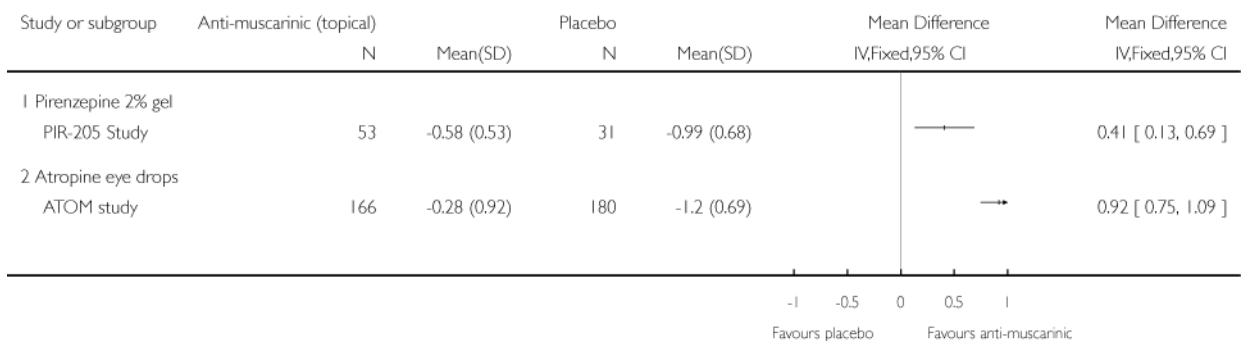


(1) Mean differences based on final measurements.  
 (2) Mean differences based on final measurements.

**Analysis 6.1.**

**Comparison 6 Anti-muscarinic agents vs. Placebo, Outcome 1 Change in refractive error from baseline (1 year).**

Review: Interventions to slow progression of myopia in children  
 Comparison: 6 Anti-muscarinic agents vs. Placebo  
 Outcome: 2 Change in refractive error from baseline (2 years)



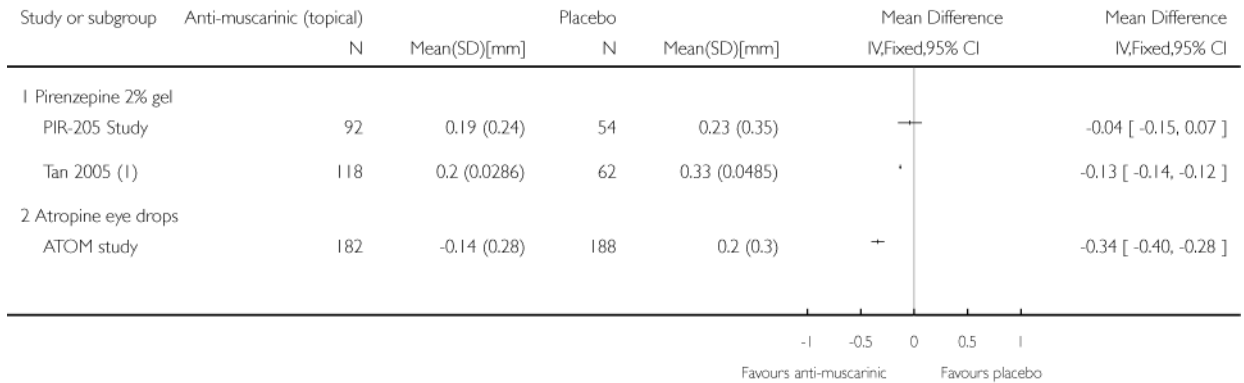
**Analysis 6.2.**

Comparison 6 Anti-muscarinic agents vs. Placebo, Outcome 2 Change in refractive error from baseline (2 years).

Review: Interventions to slow progression of myopia in children

Comparison: 6 Anti-muscarinic agents vs. Placebo

Outcome: 3 Change in axial length from baseline (1 year)



(1) Standard deviations estimated from graph.

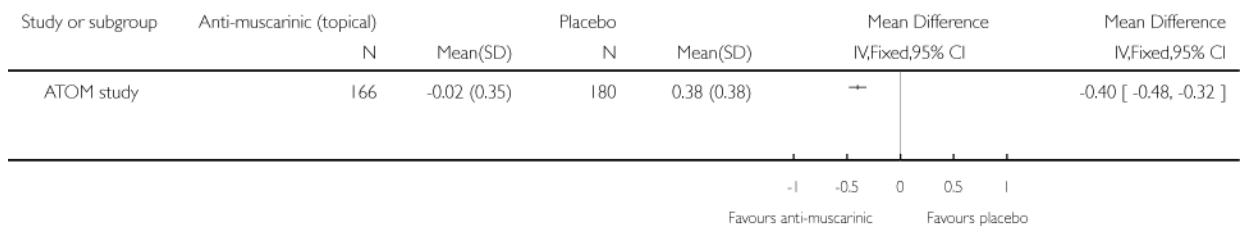
**Analysis 6.3.**

Comparison 6 Anti-muscarinic agents vs. Placebo, Outcome 3 Change in axial length from baseline (1 year).

Review: Interventions to slow progression of myopia in children

Comparison: 6 Anti-muscarinic agents vs. Placebo

Outcome: 4 Change in axial length from baseline (2 years)

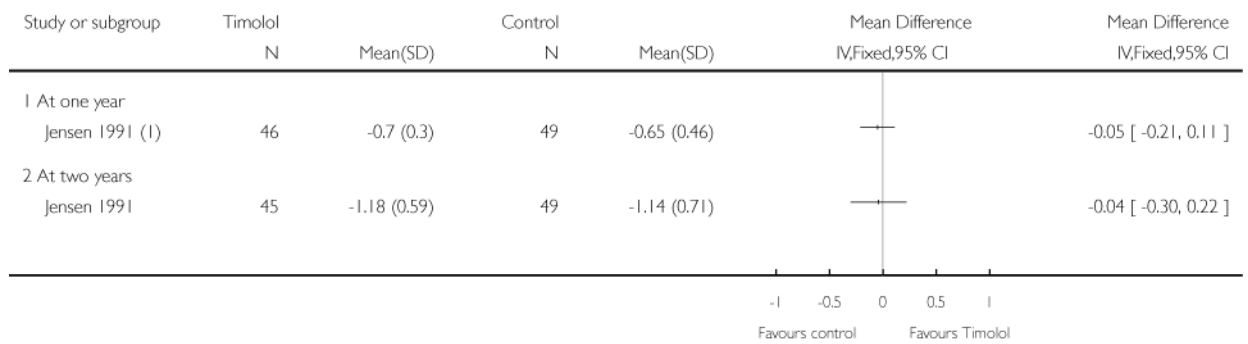
**Analysis 6.4.**

Comparison 6 Anti-muscarinic agents vs. Placebo, Outcome 4 Change in axial length from baseline (2 years).

Review: Interventions to slow progression of myopia in children

Comparison: 7 Timolol 0.25% eye drops vs. No eye drops

Outcome: 1 Change in refractive error from baseline



(1) Timolol 0.25% twice daily; all children wore SVLs.

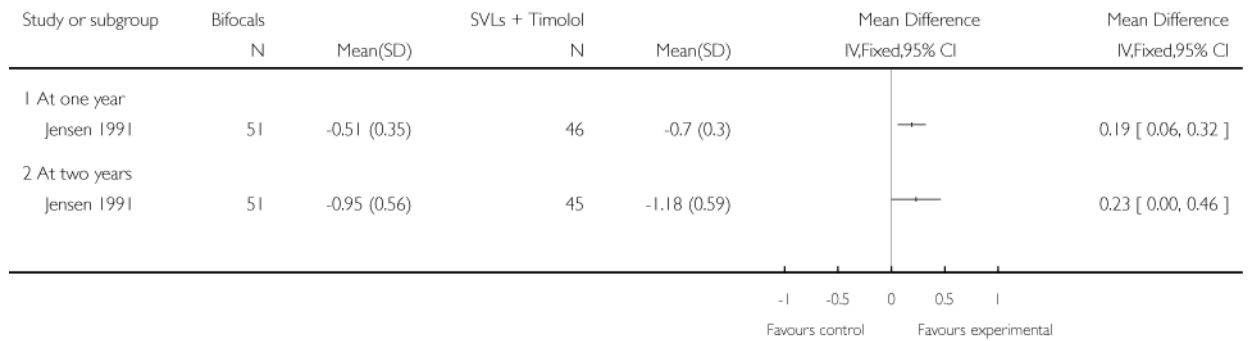
**Analysis 7.1.**

Comparison 7 Timolol 0.25% eye drops vs. No eye drops, Outcome 1 Change in refractive error from baseline.

Review: Interventions to slow progression of myopia in children

Comparison: 8 Bifocal spectacles vs. Single vision lenses + Timolol

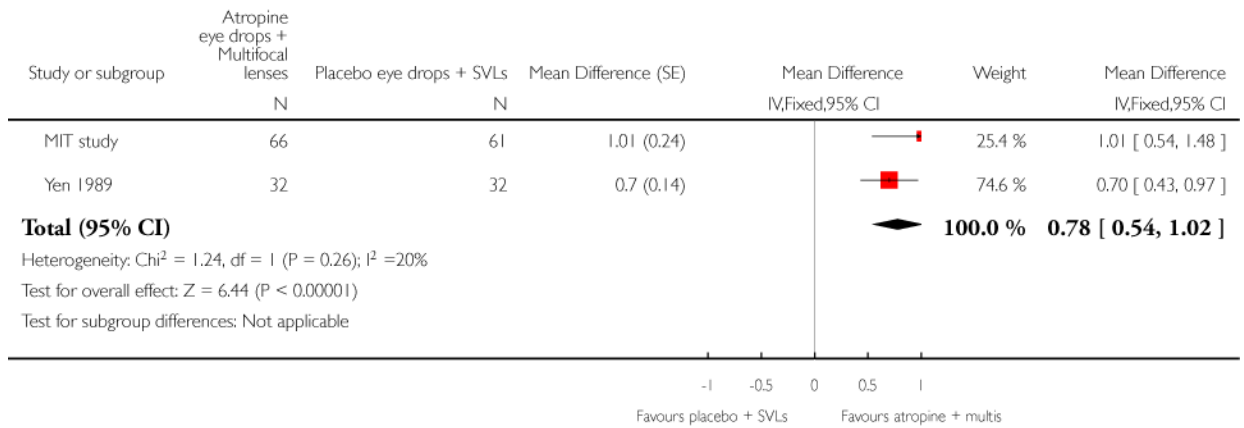
Outcome: 1 Change in refractive error from baseline



**Analysis 8.1.**

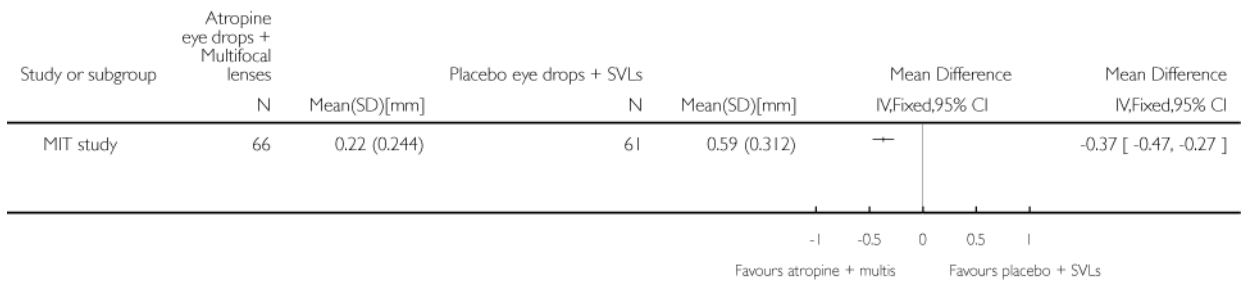
Comparison 8 Bifocal spectacles vs. Single vision lenses + Timolol, Outcome 1 Change in refractive error from baseline.

Review: Interventions to slow progression of myopia in children  
 Comparison: 9 Atropine + Multifocal lenses vs. Placebo + Single vision lenses  
 Outcome: 1 Change in refractive error from baseline (1 year)



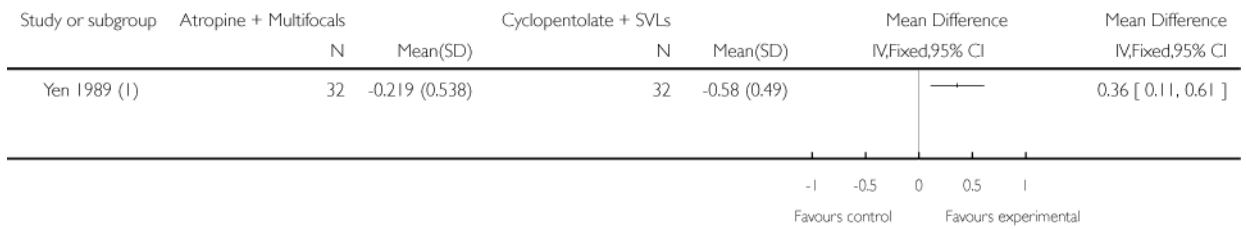
**Analysis 9.1.**  
 Comparison 9 Atropine + Multifocal lenses vs. Placebo + Single vision lenses, Outcome 1  
 Change in refractive error from baseline (1 year).

Review: Interventions to slow progression of myopia in children  
 Comparison: 9 Atropine + Multifocal lenses vs. Placebo + Single vision lenses  
 Outcome: 2 Change in axial length from baseline (1 year)



**Analysis 9.2.**  
 Comparison 9 Atropine + Multifocal lenses vs. Placebo + Single vision lenses, Outcome 2  
 Change in axial length from baseline (1 year).

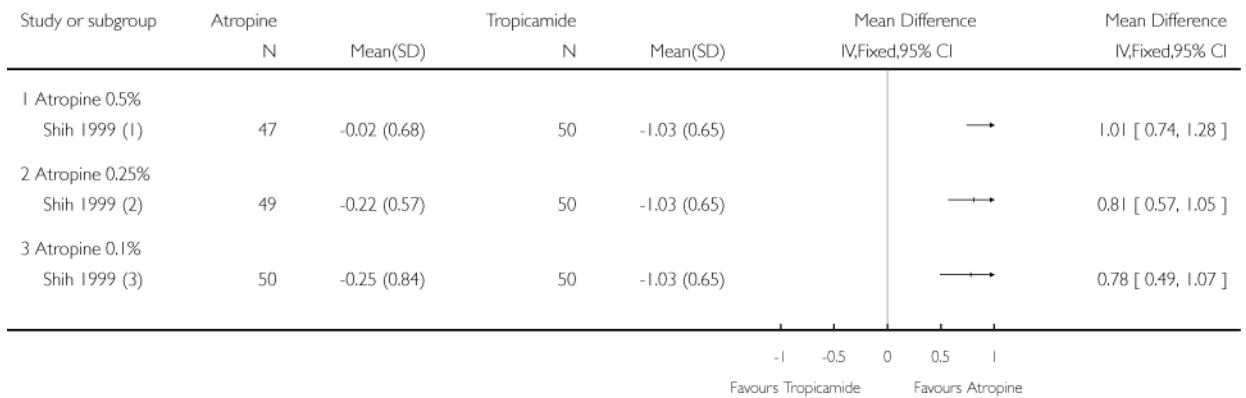
Review: Interventions to slow progression of myopia in children  
 Comparison: 10 Atropine + Multifocal lenses vs. Cyclopentolate + Single vision lenses  
 Outcome: 1 Change in refractive error from baseline (1 year)



(1) 1% Atropine every other day + Bifocal spectacles; 1% Cyclopentolate every day + SVLs

**Analysis 10.1.**  
**Comparison 10 Atropine + Multifocal lenses vs. Cyclopentolate + Single vision lenses,**  
**Outcome 1 Change in refractive error from baseline (1 year).**

Review: Interventions to slow progression of myopia in children  
 Comparison: 11 Atropine vs. Tropicamide  
 Outcome: 1 Change in refractive error from baseline (1 year)



(1) Atropine 0.5% instilled daily, advised to wear bifocals; tropicamide 0.5% instilled daily  
 (2) Atropine 0.25% instilled daily, advised to wear slightly undercorrected lenses; tropicamide 0.5% instilled daily  
 (3) Atropine 0.1% instilled daily, advised to wear fully corrected lenses; tropicamide 0.5% instilled daily

**Analysis 11.1.**  
**Comparison 11 Atropine vs. Tropicamide, Outcome 1 Change in refractive error from**  
**baseline (1 year).**

Review: Interventions to slow progression of myopia in children

Comparison: 11 Atropine vs. Tropicamide

Outcome: 2 Change in refractive error from baseline (2 years)

Study or subgroup	Atropine		Tropicamide		Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
	N	Mean(SD)	N	Mean(SD)		
1 Atropine 0.5% Shih 1999 (1)	41	-0.09 (0.56)	49	-2.51 (0.69)		2.42 [ 2.16, 2.68 ]
2 Atropine 0.25% Shih 1999 (2)	47	-0.53 (0.82)	49	-2.51 (0.69)		1.98 [ 1.68, 2.28 ]
3 Atropine 0.1% Shih 1999 (3)	49	-0.56 (1.04)	49	-2.51 (0.69)		1.95 [ 1.60, 2.30 ]

(1) Atropine 0.5% instilled daily, advised to wear bifocals; tropicamide 0.5% instilled daily

(2) Atropine 0.25% instilled daily, advised to wear slightly undercorrected lenses; tropicamide 0.5% instilled daily

(3) Atropine 0.1% instilled daily, advised to wear fully corrected lenses; tropicamide 0.5% instilled daily

**Analysis 11.2.**

Comparison 11 Atropine vs. Tropicamide, Outcome 2 Change in refractive error from baseline (2 years).

**References to studies included in this review**

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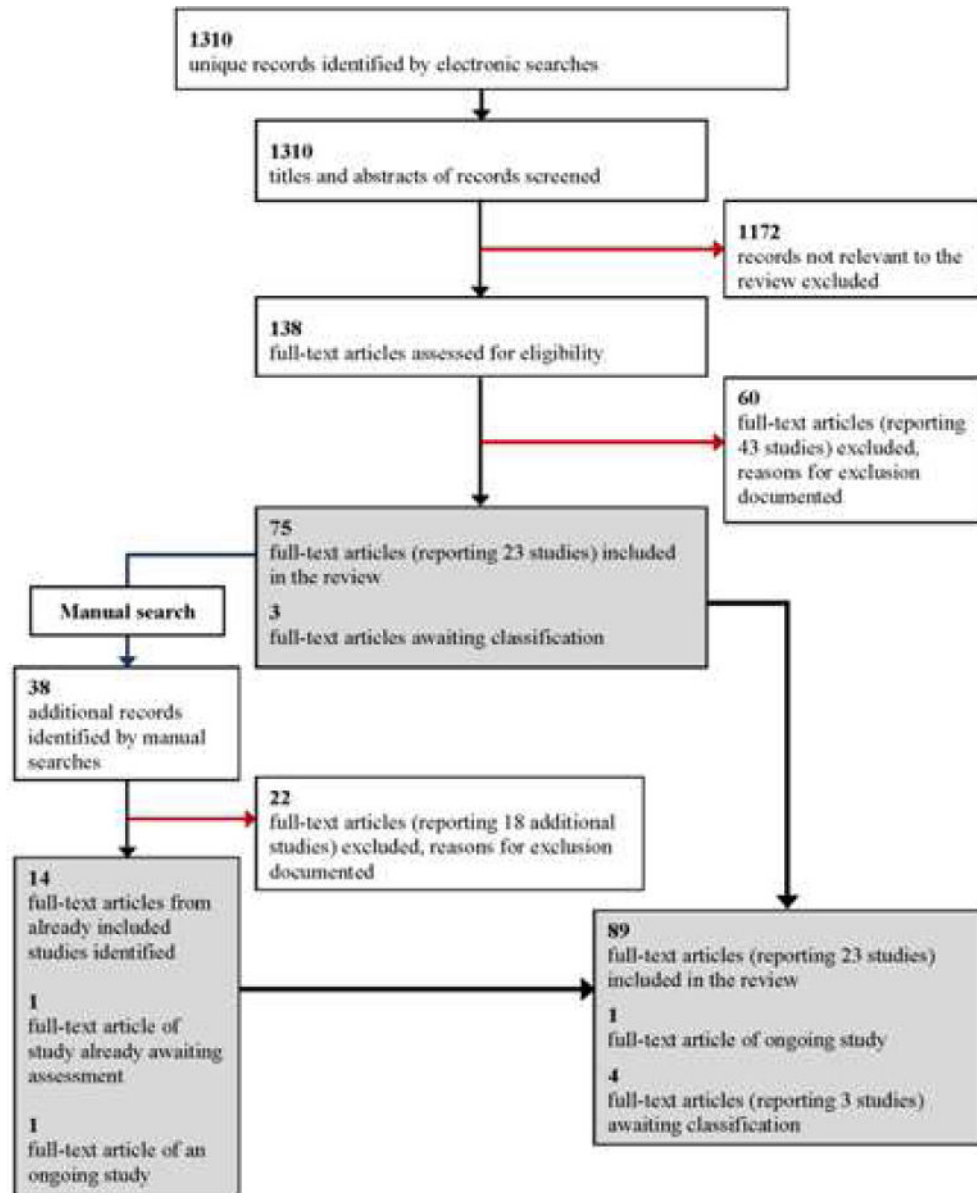
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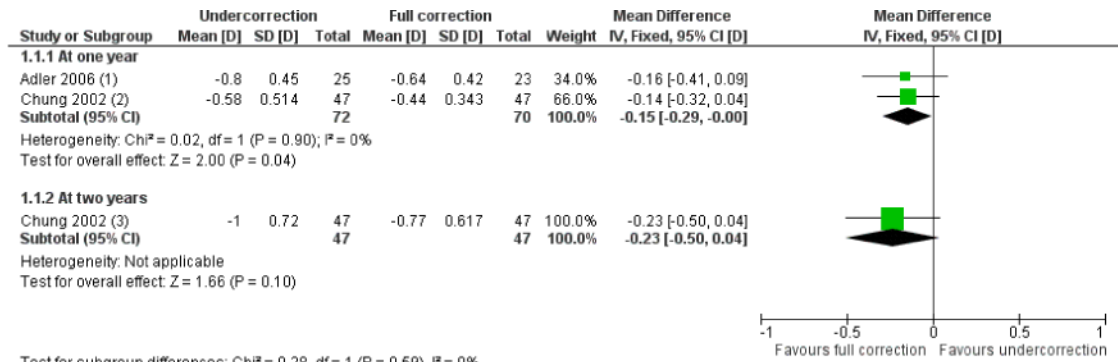


**Figure 1.**  
Results from searching for studies for inclusion in review.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Masking of participants (performance bias)	Masking of outcome assessors (detection bias): Primary outcome	Masking of outcome assessors (detection bias): Secondary outcomes	Masking of data analyzers	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Adler 2006	+	+	-	+	?	?	-	+	+
Aller 2006	?	?	?	+	+	?	?	-	-
ATOM study	+	+	+	+	+	?	?	+	?
Cheng 2010	-	-	-	-	-	+	-	+	?
Chung 2002	+	+	-	+	+	?	+	+	+
CLAMP Study	+	+	-	+	+	?	+	+	?
COMET Study	+	+	-	+	+	?	+	+	?
Edwards 2002	+	+	-	+	+	+	+	+	+
Fulk 1996	+	+	-	+	+	?	+	?	+
Fulk 2002	+	+	-	+	+	?	+	+	+
Hasebe 2008	+	+	-	+	+	+	+	+	?
Houston Study	+	+	-	-	+	?	-	-	-
Jensen 1991	+	+	-	-	-	?	-	-	+
Katz 2003	+	+	-	-	-	?	?	-	-
MIT study	+	+	-	+	+	+	-	+	+
PIR-205 Study	+	+	+	+	+	?	-	+	?
Pärssinen 1989	+	+	-	-	-	?	+	+	+
Sankaridurg 2010	+	+	?	+	+	?	-	+	?
Schwartz 1981	+	+	-	+	?	?	-	+	?
Shih 1999	+	+	-	+	?	+	-	+	-
Tan 2005	+	+	+	+	+	?	-	+	?
Yang 2009	?	?	-	+	+	?	?	+	?
Yen 1989	+	?	-	?	?	?	-	-	-

**Figure 2.** Risk of bias summary: review authors' judgements about each risk of bias item for each included study.





Test for subgroup differences: Chi<sup>2</sup> = 0.28, df = 1 (P = 0.59), I<sup>2</sup> = 0%

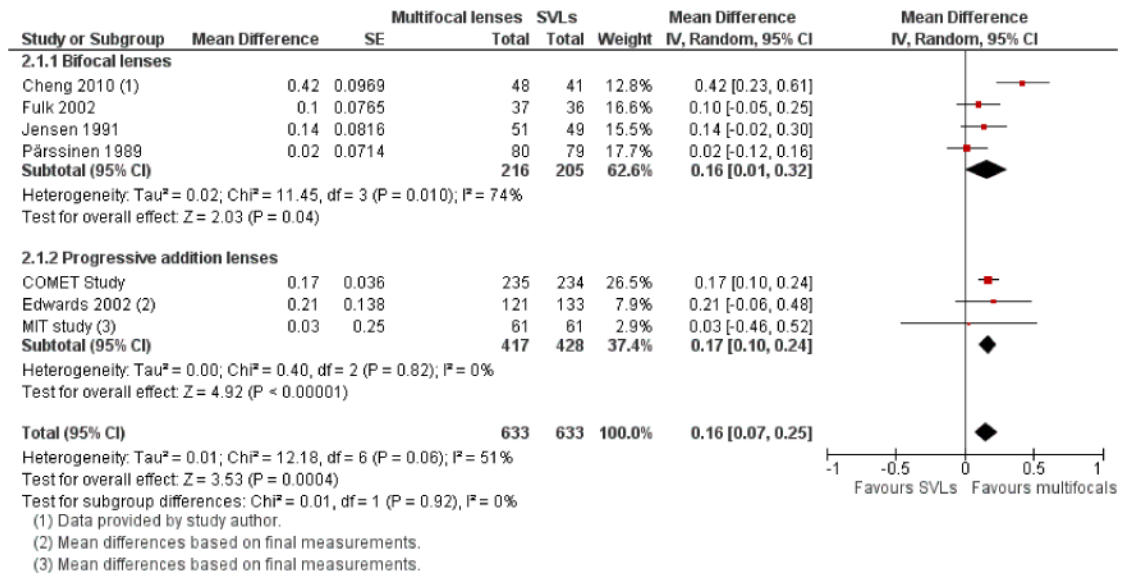
(1) Data provided by study author.

(2) Data estimated from graph.

(3) Data estimated from graph (although reported as statistically significant in the article).

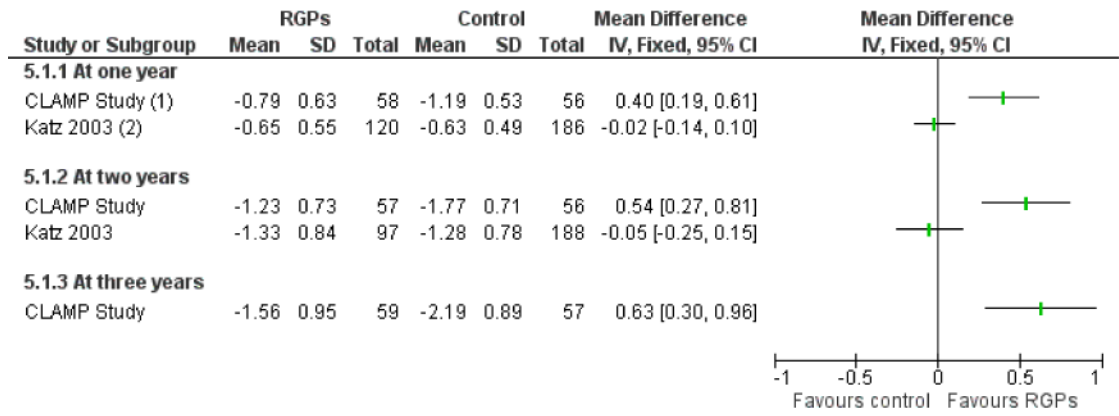
**Figure 3.**

Forest plot of comparison: 1 Undercorrection vs. Full correction spectacles, outcome: 1.2 Change in refractive error from baseline (1 year).



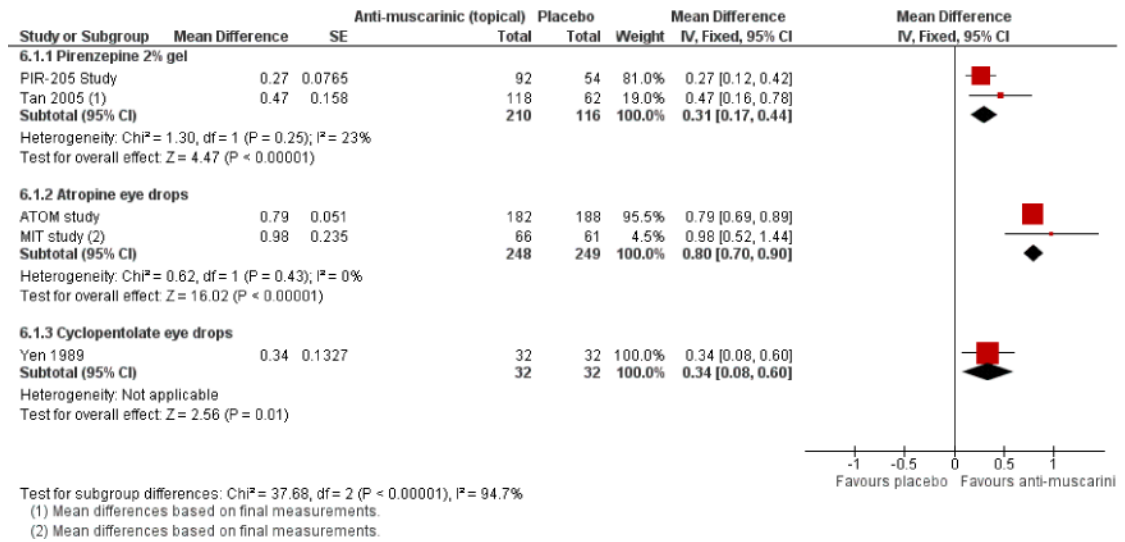
**Figure 4.** Forest plot of comparison: 2 Multifocal lenses vs. Single vision lenses, outcome: 2.1 Change in refractive error from baseline (1 year).





- (1) Control group wore soft contact lenses.
- (2) Control group wore single vision spectacles.

**Figure 5.** Forest plot of comparison: 5 Rigid gas permeable contact lenses vs. Control, outcome: 5.1 Change in refractive error from baseline.



**Figure 6.** Forest plot of comparison: 6 Anti-muscarinic agents vs. Placebo, outcome: 6.1 Change in refractive error from baseline (1 year).

Table 1

## Interventions of included studies

STUDY	Spectacles				Contact lenses			Pharmaceutical agents				Combination of interventions		
	Uncorrected SVLs <i>a</i>	Multi-focal lenses		Fully-corrected SVLs	RGP <i>c</i>	Soft bifocal lenses	SVS <sup>d</sup>	Atropine			Pirenzepine		Reference group	
		Bi-focal lenses <i>1</i>	Bi-focal lenses <i>2</i>					PALs <i>b</i>	Distance use only	Continuous use				1
Adler 2006; 2 study arms	X													
Chung 2002; 2 study arms	X													
Fulk 1996; 2 study arms		+1.25												
Fulk 2002; 2 study arms		+1.50												
Jensen 1991; 3 study arms		+2.00												
Houston Study; 3 study arms		+1.00	+2.00											Timolol + SVLs
Cheng 2010; 3 study arms		+1.50	+1.50 prism											
Pärssin, 1989; 3 study arms		+1.75		X										
COMET Study; 2 study arms			+2.00											
Edwards 2002; 2 study arms			+1.50											
Yang 2009; 2 study arms			+1.50											
Hasebe 2008; 2 study arms <sup>e</sup>			+1.50											
Sankari 2010; 4 study arms				X*										
Katz 2003; 2 study arms					X									
CLAMP Study; 2 study arms					X			X						
Aller 2006; 2 study arms						X		X						
MIT study; 3 study arms			Plus placebo drops											Atropine + PALs
ATOM study; 2 study arms									1%					Placebo drops
Shih 1999; 4 study arms									0.1%	0.25%	0.5%			0.5% tropicamide
Yen 1989; 3 study arms									1% + bifocals					Saline + SVLs
PIR-205 Study; 2 study arms														Placebo gel
Tan 2005; 3 study arms														Placebo gelx2

STUDY	Spectacles				Contact lenses			Pharmaceutical agents			Combination of interventions	
	Uncorrected SVLs <sup>a</sup>	Multi-focal lenses		Fully-corrected SVLs		RGP <sup>c</sup>	Soft bifocal lenses	SYS <sup>d</sup>	Atropine			Reference group
		Bi-focal lenses 1	Bi-focal lenses 2	PALs <sup>b</sup>	Distance use only				Continuous use	1		
Schwar 1981; 2 study arms												Tropicamide + bifocals

<sup>a</sup>SVLs: single vision lenses.

<sup>b</sup>PALs: progressive addition lenses.

<sup>c</sup>RGP: rigid gas permeable.

<sup>d</sup>SVS: single vision soft lenses.

<sup>e</sup>cross-over trial.

\* study included four groups; three groups received spectacles with novel lens designs and the fourth group received SVLs. The novel lenses were designed to reduce peripheral hyperopic defocus.

**Table 2**

Outcomes reported by studies of spectacle interventions \*

Outcomes	Interventions studied			
	Undercorrected lenses: 2 studies	Bifocal lenses: 6 studies	Progressive addition lenses: 5 studies	Novel lenses to minimize peripheral hyper-opic defocus: 1 study
Primary outcome: change in refractive error	Analysis 1.1	Analysis 2.1; Analysis 2.2; Analysis 2.3	Analysis 2.1; Analysis 2.2; Analysis 2.3	Analysis 3.1
Secondary outcome: change in axial length	Analysis 1.2	Analysis 2.4; Analysis 2.5; Analysis 2.6	Analysis 2.4; Analysis 2.5; Analysis 2.6	Analysis 3.2
Secondary outcome: change in corneal radius of curvature	Not measured by Adler 2006 and reported as non-significant by Chung 2002	Not reported	Analysis 2.7	Not reported
Adverse effects	Two participants who were under-corrected complained of blurred vision (Adler 2006)	None reported	None reported	Participants reported blurred side vision, visual distortion, dizziness, headaches and falls (Sankaridurg 2010)

\* Compared with fully-corrected single vision lenses.

**Table 3**

Outcomes reported by studies of contact lens interventions\*

Outcomes	Interventions studied	
	Soft bifocal contact lenses: 1 study	Rigid gas permeable contact lenses: 2 studies
Primary outcome: change in refractive error	Analysis 4.1	Analysis 5.1
Secondary outcome: change in axial length	Analysis 4.2	Analysis 5.2
Secondary outcome: change in corneal radius of curvature	Not reported	Analysis 5.3
Adverse effects	Not reported	Not reported

\* Compared with fully-corrected single vision lenses or soft contact lenses.

**Table 4**

Outcomes reported by studies of pharmaceutical interventions\*

Outcomes	Interventions studied				
	Pirenzepine: 2 studies	Atropine: 2 studies	Cyclopentolate: 1 study	Timolol: 1 study	Tropicamide (plus bifocals): 1 study
Primary outcome: change in refractive error	Analysis 6.1; Analysis 6.2	Analysis 6.1; Analysis 6.2	Analysis 6.1	Analysis 7.1	Control twins showed more progression in myopia than their cotwins who received tropicamide and bifocals, but this difference was not statistically significant (Schwartz 1981)
Secondary outcome: change in axial length	Analysis 6.3	Analysis 6.3; Analysis 6.4	Not reported	Not reported	Not reported
Secondary outcome: change in corneal radius of curvature	Not reported	Not reported	Not reported	Not reported	Not reported

\* Compared with placebo or no drops.



**Table 5**

## Unit of analysis for included studies

Unit of analysis	Studies reporting each type of unit of analysis
The average of both eyes	10 studies: Adler 2006; Aller 2006; Chung 2002; Fulk 1996; Fulk 2002; PIR-205 Study; Sankaridurg 2010; Schwartz 1981; Shih 1999; Tan 2005
Right eye only	7 studies: Cheng 2010; CLAMP Study; Edwards 2002; Houston Study; Katz 2003; MIT study; Yen 1989
The average of both eyes or one eye only *	2 studies: COMET Study; Hasebe 2008
Right and left eyes reported separately	2 studies: Jensen 1991; Pärssinen 1989
Eye randomized and treated	1 study: ATOM study
Not reported	1 study: Yang 2009

\* The average values of both eyes were used if the correlation coefficient was  $> 0.85$  between eyes and the mean difference (MD) was not statistically significant; otherwise the eye with more myopic change was used for each child (COMET Study). The mean of both eyes or right eye only (Hasebe 2008).

**Table 6**

Adverse effects reported by studies of pharmaceutical interventions

Study	Interventions Studied	Details
PIR-205 Study	Pirenzepine gel vs. placebo gel	Reported 6 ocular adverse events with P = 0.15 <ol style="list-style-type: none"> <li>1 Accommodation abnormality symptoms: 40% vs. 7%</li> <li>2 Papillae and follicles: 40% vs. 18%</li> <li>3 Medication residue: 38% vs. 53%</li> <li>4 Visual acuity decreased: 15% vs. 2%</li> <li>5 Eye discomfort: 10% vs. 4%</li> <li>6 Mydriasis: 9% vs. 2%</li> </ol>
Tan 2005	Pirenzepine gel and placebo gel <ol style="list-style-type: none"> <li>1 PIR/PIR</li> <li>2 PLC/PIR</li> <li>3 PLC/PLC</li> </ol>	Reported 4 ocular adverse events with P = 0.15 (compared to PLC/PLC) <ol style="list-style-type: none"> <li>1 Papillae and follicles: 1 = 58.5%; 2 = 51.4%; 3 = 14.1%</li> <li>2 Abnormality of accommodation: 1 = 44.4%; 2 = 22.1%; 3 = 2.8%</li> <li>3 Eye itching: 2 = 10.0%; 3 = 18.3%</li> <li>4 Visual acuity decreased: 1 = 16.9%; 2 = 14.3%; 3 = 1.4%</li> </ol>
ATOM study	Atropine 1% vs. placebo eye drops	No serious adverse events reported, but reasons for withdrawal among atropine users included: allergic or hypersensitivity reactions or discomfort (4.5%), glare (1.5%), blurred near vision (1%) and logistical difficulties (3.5%)
Yen 1989	Atropine 1% + bifocals vs. cyclopentolate + SVLs vs. placebo + SVLs	All atropine users reported photophobia; most reported that they stopped gym classes and did not like going outdoors. No other systemic or ocular complications were observed
Shih 1999	Atropine 0.5%, 0.25%, 0.1% and tropicamide 0.5%	Three events reported in the atropine 0.5% group: two patients complained of photophobia, one with allergic blepharitis

PIR: Pirenzepine gel

PLC: Placebo gel

SVLs: single vision lenses

vs: versus

## Characteristics of included studies [ordered by study ID]

Adler 2006	
Methods	Study design: RCT Study center: urban private optometric practice in Jerusalem, Israel Number randomized: 62 children Study follow-up: 18 months Exclusions and losses to follow-up: 5 (8%) children who were randomized were excluded from the analyses; 9 (14.5%) were lost to follow-up
Participants	Age: mean = 10.08 years (range 6 to 15 years) Gender: 34 boys, 14 girls Culture: most children were orthodox Jews who attended school year round and performed a study method of swaying back and forth while learning and reading Inclusion criteria: pediatric patients from study center with early-onset myopia aged 6 to 15 years Exclusion criteria: 1) strabismus; 2) amblyopia; 3) VA < 6/9; 4) spherical equivalent > -6.00 D or < -0.50 D in either eye; 5) astigmatism over 1.50 D in either eye; 6) anisometropia over 1.50 D; 7) a difference between objective and subjective refraction findings of 0.75 D or more; 8) any ocular pathological manifestations; and 9) born prematurely
Interventions	Undercorrected group (n = 25): blurred by +0.50 D; glasses were to be worn continuously Fully-corrected group (n = 23): glasses were to be worn continuously Note: changes in prescription were made if the subjective refraction had changed by at least 0.50 D for one or both eyes
Outcomes	<u>Progression of early-onset myopia</u>  1 Objective refractions without cycloplegia: static retinoscopy (spherical equivalent) 2 Subjective refractions without cycloplegia: endpoint of maximum plus for best acuity 3 Near lateral phoria: alternating cover test using 6/9 size picture target held at 40 cm from eye  Measurements taken at baseline, 6 months, 12 months and 18 months Unit of analysis: the average values of both eyes were used for all results
Notes	Study dates: enrolment was over an eight-month period Materials: free spectacle lenses were supplied by Einit Optical Clinic Additional data: study author provided unpublished data via email correspondence

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A coin was tossed to determine the group assignment
Allocation concealment (selection bias)	Low risk	The assignment for each participant was determined after enrolment by tossing a coin
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to performance differences between the interventions studied
Masking of outcome assessors (detection bias) Primary outcome	Low risk	The optometrist conducting the examination was masked to the treatment group and previous results for each participant
Masking of outcome assessors (detection bias) Secondary outcomes	Unclear risk	N/A (study did not measure secondary outcomes of this review)
Masking of data analyzers	Unclear risk	The analysis of the results was carried out by the other member of the team only after all the data had been collected
Incomplete outcome data (attrition bias)	High risk	Of the 62 children recruited, 48 are included in the analysis; 5 were excluded (3 did not wear their glasses continually, 2 were twins born prematurely) and 9 were lost to follow-up

Incomplete outcome(s) data		
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	Low risk	
Aller 2006		
Methods	Study design: RCT Study center: 1 Number randomized: 78 children Study follow-up: 1 year Exclusions and losses to follow-up: not reported	
Participants	Age: range 8 to 18 years Gender: included boys and girls Culture: California, US Inclusion criteria: 1) myopia between -0.50 D and -6.00 D; 2) esofixation disparity at 33 cm with distance correction; 3) astigmatism 1.00 D or less; 4) ability to wear SCLs Exclusion criteria: 1) presence of ocular disease preventing wear of contacts; 2) pregnancy or nursing; 3) use of certain medications	
Interventions	(n = 38): wore BSCLs with simultaneous vision design (n = 40): wore SVSCLs	
Outcomes	<p><u>Primary outcomes:</u></p> <ol style="list-style-type: none"> <li>1 Changes in cycloplegic autorefraction in one year</li> <li>2 Changes in cycloplegic subjective refraction in one year</li> <li>3 Changes in axial length at one year</li> </ol> <p><u>Secondary outcomes:</u></p> <ol style="list-style-type: none"> <li>1 Keratometric changes at one year</li> <li>2 Changes in manifest refraction at one year</li> <li>3 Relationship between residual fixation disparity and myopia progression</li> </ol> <p>Measurements taken at baseline, 6 months and 12 months Unit of analysis: the average values of both eyes</p>	
Notes	Study dates: start date was October 2003; completed in 2006 Funding source: Vistakon Notes: study was also known as the CONTROL study; trial was registered at <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a> (NCT00214487), but has not been published as a full length, peer reviewed article Additional information: study author provided unpublished information via email correspondence	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Participants were coded and randomly assigned to either single vision or bifocal contact lens groups. A matrix was used to help ensure that each group contained roughly equal mixes of sexes, ages, prescription strengths, ethnicities and degrees of esofixation disparity (via email communication with author)
Allocation concealment (selection bias)	Unclear risk	Contact lens prescriptions for eligible participants were transmitted to an off-site research assistant for allocation (via email communication with author)
Masking of participants (performance bias)	Unclear risk	The packages containing contact lenses were masked so that the participant did not know from the label what he/she was wearing; however, it was not clear whether the two types of contact lenses were different functionally. Information about whether or not the masking worked was not reported
Masking of outcome assessors (detection bias) Primary outcome	Low risk	"Masking was aided by the choice of lenses; both were 58% water, two-week disposable lenses, identical in appearance and supplied in masked packaging"

Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Unclear risk	Final sample size was reported, but it was unclear whether the same number of participants were enrolled; exclusion and loss to follow-up data were not reported
Selective reporting (reporting bias)	High risk	The complete results for this study are not yet available. Primary investigator's website cited: 'Full disclosure of the results is awaiting approval by the sponsor, but some results have already been published in abstract form' (Aller 2010)
Other bias	High risk	A detailed description of the methods was lacking as the study has only been reported in abstract form. Full publications are awaiting approval by the study sponsor

## ATOM study

Methods	Study design: RCT, with 2 week run-in period Study center: 1 Number randomized: 400 children Study follow-up: 2 years Exclusions and losses to follow-up: no exclusions; 54 (13.5%) were lost to follow-up	
Participants	Age: mean = 9.2 years (range 6 to 12 years) Gender: 220 boys, 180 girls Culture: Chinese (94%) and Indian children (4%) in Singapore Inclusion criteria: 1) age 6 to 12 years old; 2) myopia with spherical equivalent refractive error between -1.00 D and -6.00 D in each eye as measured by cycloplegic autorefractometry; 3) distance vision correctable to logMAR 0.2 or better in both eyes; 4) normal ocular health; 5) good general health with no history of cardiac or significant respiratory diseases; 6) normal binocular function and stereopsis; 7) willingness and ability to tolerate monocular cycloplegia and mydriasis Exclusion criteria: 1) astigmatism greater than -1.50 D by cycloplegic autorefractometry; 2) IOP of 21 mmHg or greater; 3) allergies to atropine, cyclopentolate, proparacaine or benzalkonium chloride; 4) previous or current use of contact lenses, bifocals, PALs or other forms of myopia treatment; and 5) amblyopia or manifest strabismus, including intermittent tropia	
Interventions	Atropine (n = 200): one eye randomized to one drop of 1% atropine sulfate nightly; the other eye received nothing Placebo-control (n = 200): one eye randomized to one drop of vehicle nightly; the other eye received nothing Note: all children received single vision photochromatic lenses for the correction of refractive errors	
Outcomes	<u>Primary efficacy outcome</u> : progression of myopia defined as the change in spherical equivalent refractive error from baseline and measured by cycloplegic autorefractometry <u>Secondary efficacy outcome</u> : change in axial length from baseline and measured by A-scan ultrasonography <u>Primary safety outcome</u> : occurrence of adverse events <u>Secondary safety outcomes</u> : best-corrected VA, IOP, slit-lamp biomicroscopy and fundus examination Measurements taken at baseline and annually for 2 years Note: baseline measurements were recorded 2 weeks after treatment began to allow for stabilization of the cycloplegic effect of atropine Unit of analysis: only one eye per patient was randomized to receive treatment (fellow eyes were controls)	
Notes	Study dates: enrolment between April 1999 to September 2000 Materials: vehicle drops prepared by Acon Laboratories; spectacles were SOLA Transitions SVLs Funding source: National Medical Research Council, Singapore Additional data: study author provided unpublished data via email correspondence	

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Children were allocated to groups based on a computer-generated randomization list
Allocation concealment (selection bias)	Low risk	Methods section stated "allocated with concealment"

Masking of participants (performance bias)	Low risk	Study was placebo-controlled and identical appearing bottles with coded labels were distributed
Masking of outcome assessors (detection bias) Primary outcome	Low risk	Use of identical appearing bottles with coded labels, dilation of both pupils before examination
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Unclear risk	“All statistical analyses were based on the intention-to-treat principle” Study authors noted (via personal communication) that there was a typographical error in the publication (54 were lost to follow-up, 34 from the atropine group and 20 from the placebo group), the paper reports that those who did not complete the study were characteristically similar to those that completed the study for each group
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	Unclear risk	There was pre-randomization administration of the intervention that may have enhanced or diminished the effect of the intervention during the subsequent, randomized evaluation period
Cheng 2010		
Methods	Study design: RCT Study center: 1 (optometric practice in Mississauga, Ontario, Canada) Number randomized: 150 children Study follow-up: 2 years Exclusions and losses to follow-up: 15 (10%) children who were randomized were excluded from the analyses; 4 (3%) were lost to follow-up	
Participants	Age: mean = 10 years (range 8 to 13 years) Gender: 62 boys and 73 girls received treatment Culture: Chinese Canadian children were recruited by reviewing clinical records and mailing invitation letters addressed to their parents, by responding to poster in the practice, or during regular eye examinations Inclusion criteria: 1) Chinese Canadian children who were seen at the practice in the last 9 to 18 months; 2) age 8 to 13 years old; 3) myopia between -1.00 D to -5.50 D; 4) myopia progression equal to or greater than 0.50 D in the preceding year; 5) distance monocular visual acuity of 6/6 or better; 6) near monocular visual acuity of 6/6 or better; 7) stereoacuity of 40 s of arc at 40 cm; 8) single-vision distance lens wear; and 9) consent of child and parent for study participation Exclusion criteria: 1) astigmatism > 1.50 D; 2) anisometropia > 1.50 D; 3) strabismus; 4) unable to respond to subjective testing; 5) history of systemic or ocular diseases; and 6) history of bifocal lens wear and/or contact lens use	
Interventions	SVLs (n = 50): single-vision distance lenses Bifocal lenses (n = 50): bifocal lenses with +1.50 D near addition Prismatic bifocal lenses (n = 50): prismatic bifocal lenses with +1.50 D addition and a 3-prism diopters base-in prism in the near segment Note: distance prescription changes were made if subjective refraction changed by 0.50 D or more in either eye	
Outcomes	<u>Primary outcome</u> : myopic progression defined as the difference between the mean cycloplegic spherical equivalent measured by an automated refractor at the baseline visit and subsequent 6-month visits for 24 months <u>Secondary outcome</u> : eye growth defined as the difference between mean axial lengths measured by ultrasonography at the baseline visit and subsequent 6-month visits for 24 months Measurements taken at baseline and every 6-months for two years Unit of analysis: only data from right eyes were used	
Notes	Study dates: April 2003 to April 2008 Funding source: Essilor International of France Auxiliary data: Parents and/or guardians completed questionnaires relating to vision habits of the enrolled child and the child's birth parents' refractive errors. The number of years the children were myopic prior to entering the study were estimated from clinical records. Auxiliary data were used as covariates for regression statistics and to test the hypothesis	

that bifocal treatment is more effective with a shorter duration of myopia Additional data: study author provided unpublished data via email correspondence

<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	High risk	"Randomization was implemented by putting the subjects' file numbers on slips of paper and drawing them from a container at random...The first 50 subjects drawn were assigned to the control group; the second 50 were assigned to the bifocal group, and so forth"
Allocation concealment (selection bias)	High risk	"The first 50 subjects drawn were assigned to the control group; the second 50 were assigned to the bifocal group, and so forth"
Masking of participants (performance bias)	High risk	"The subjects and the investigator were aware of the treatment assignments." Masking was not applicable due to visual and functional differences between the interventions studied
Masking of outcome assessors (detection bias) Primary outcome	High risk	"The subjects and the investigator were aware of the treatment assignments. Masking was difficult to achieve in a practice-based intervention, particularly when the lens treatments were visually very different." The primary study investigator dispensed lenses and performed examinations
Masking of outcome assessors (detection bias) Secondary outcomes	High risk	"...the primary and secondary outcome variables were measured by objective methods to minimize possible bias of the unmasked investigator"
Masking of data analyzers	Low risk	"The data analyst discerned the study investigated the effect of three types of lenses on ocular refraction, but he was masked to the possible effect of bifocal or prismatic bifocal lens on myopia control" (via email communication with study author)
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	"The analysis of the data followed the intention-to-treat approach, and we used the last progression information (i.e. carry forward) method for subjects lost to follow-up" Although study authors stated that they used intention-to-treat analysis, 15 of the 150 children randomized were not included in the analysis: 9 children randomized to single vision lenses dropped out because their parents wanted them to receive bifocals; and 2 children in the bifocals group and 4 in the prismatic bifocals group were excluded due to adverse reactions following cycloplegia
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	Unclear risk	This study was funded by a company that produces the types of lenses being investigated
Chung 2002		
Methods	Study design: RCT Study center: patient care unit at the Department of Optometry, Faculty of Allied Health Science, National University of Malaysia Number randomized: 106 children Study follow-up: 2 years Exclusions and losses to follow-up: no exclusions; 12 (11%) were lost to follow-up	
Participants	Age: mean =11.56 years (range 9 to 14 years) Gender: 39 boys, 55 girls Culture: Malay and Chinese ethnic origin Inclusion criteria: 1) age 9 to 14 years old; 2) myopia with spherical equivalent refractive error of $-0.50$ D or more in both eyes, with no principle meridian being plano or having any amount of plus power; 3) corrected VA of 6/6 or better in each eye; 4) normal ocular health; and 5) willingness to give written consent Exclusion criteria: 1) more than two diopters of astigmatism in each eye; 2) binocular vision problems, including anisometropia over 2.00 D, problems requiring refractive therapy, strabismus and amblyopia; 3) previous contact lens wear; 4) family was planning to leave the area before the end of the study period	
Interventions	Undercorrected group (n = 47): monocular VA blurred to 6/12 (approximately +0.75 D) in each eye with spectacles Fully-corrected group (n = 47): monocular VA maintained at 6/6 or better in each eye with spectacles	



	Note: In the fully-corrected group, changes in prescription were made if the subjective refraction had changed by at least 0.50 D for one or both eyes. For the undercorrected group, changes in prescription were made to maintain a vision of 6/12 in each eye
Outcomes	<p><u>Progression of early-onset myopia</u></p> <ol style="list-style-type: none"> <li>1 Static retinoscopy without cycloplegia</li> <li>2 Keratometry</li> <li>3 Subjective cycloplegic refractions using the endpoint of maximum plus or minimum plus for best acuity</li> <li>4 Ocular components measurements by means of A-scan ultrasonography</li> </ol> <p>Measurements taken at baseline and every 6 months for two years Unit of analysis: the average values of both eyes were used for all results</p>
Notes	<p>Study dates: not reported Funding source: IRPA grant Compliance in wearing glasses was monitored with questionnaires. Compliance was defined as wearing glasses for at least 8 hours a day (40 patients in the undercorrected group versus 41 in the fully-corrected group). Partial compliance was defined as wearing glasses 6 to 8 hours a day (7 patients in the undercorrected group versus 6 in the fully-corrected group)</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization based on age, sex, race and refractive error. Treatment and control pairings were made to complete cells based on 3 age categories, 4 refractive error categories, 2 racial groups and 2 gender groups ( $3 \times 4 \times 2 \times 2 = 48$ cells) Patients were designated as subject 1 or subject 2 for each cell based on a predetermined randomization procedure
Allocation concealment (selection bias)	Low risk	Once the patients were paired, a coin toss determined which patient was assigned to the treatment or control group. Heads meant subject 1 was allocated to undercorrection and subject 2 received full correction. Tails meant subject 1 was allocated to full correction and subject 2 received undercorrection. A coin toss was performed for each pair
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to performance differences between the interventions studied
Masking of outcome assessors (detection bias) Primary outcome	Low risk	During all evaluations, the examining optometrist was not aware of the group assignment
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	Results were only analyzed after the last reading of the last patient was collected
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	Of the 106 children recruited, 94 completed the study and were included in the analyses; 12 (11.3%) dropped out and were excluded from the analyses
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	Low risk	

**CLAMP Study**

Methods	<p>Study design: RCT, with run-in period Study center: 1 (The Ohio State University College of Optometry) Number randomized: 116 children</p>
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	Study follow-up: 3 years Exclusions and losses to follow-up: none
Participants	Age: mean = 10.7 years (range 8 to 12 years) Gender: 47 boys, 69 girls Culture: Columbus, Ohio, US; 84.5% white (not of Hispanic origin), 8.6% Asian or Pacific Islander, 4.3% Black (not of Hispanic origin) Inclusion criteria: 1) age 8 to 11 years old at time of randomization; 2) myopia with spherical equivalent refractive error between -0.75 D and -4.00 D in each eye, as measured by cycloplegic refraction; 3) corrected VA of 20/20 or better in each eye Exclusion criteria: 1) astigmatism > 1.50 DC in each eye by cycloplegic refraction or > 1.00 DC on manifest refraction; 2) previous or attempted history of contact lens wear; 3) anisometropia > 1.00 D between eyes; 4) eye disease and binocular vision problems; 5) systemic disease that may affect vision or vision development Note: All participants had to successfully complete a run-in period before enrolment into the study in order to exclude those who could not adapt to rigid contact lenses; 32 children did not complete the run-in period and were excluded. Success for the run-in period was defined as wearing the lenses at least 40 hours/week and stating that the lenses were "always comfortable" or "usually comfortable"
Interventions	(n = 59): RGPCLs worn during waking hours for 3 years (n = 57): SCLs worn during waking hours for 3 years Note: prescription changes were made by an unmasked examiner based on participant complaints and improvement in visual acuity
Outcomes	<b>Primary outcome:</b> change in cycloplegic autorefraction during 3 years (spherical equivalent) <b>Secondary outcomes:</b> <ol style="list-style-type: none"> <li>1 Change in axial length</li> <li>2 Change in peripheral autorefraction</li> <li>3 Change in crystalline lens curvatures</li> <li>4 Change in corneal curvature and thickness</li> <li>5 Change in accommodation</li> <li>6 Change in IOP</li> </ol> <p>Measurements taken at baseline and every 6 months for three years Unit of analysis: data analyzed for right eye only</p>
Notes	Study dates: enrolment 8 July 1998 to 26 February 2000 Funding source: National Eye Institute, National Institutes of Health; Menicon Co, Ltd.; CIBA Vision Corporation; SOLA Optical; and Essilor

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized participants stratified by gender and in treatment blocks of 3. A list of randomized treatment assignments was prepared by an independent person before the beginning of the study
Allocation concealment (selection bias)	Low risk	Individual treatment assignments from the list were placed in sequentially numbered envelopes that were sealed. Envelopes were drawn from the pool in sequential order according to the participant's gender
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to material differences between the interventions studied
Masking of outcome assessors (detection bias) Primary outcome	Low risk	Masked examiners conducted the primary outcome procedure and all secondary outcomes except visual acuity. When the masked examiner was in the room, the participants wore only spectacle correction or no correction and was told not to mention any contact lens wear to the masked examiner. No assessment of masking was reported
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	The outcome measures were performed by examiners masked to the mode of correction worn by the participant with the exception of the visual acuity measurements

Masking of data analyzers	Unclear risk	Not reported in the paper, but the persons conducting the analyses were not masked to treatment group allocation (JW). Outcome measures were not presented by treatment group until the conclusion of the trial. Data was managed using a dual-entry format
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	All data were analyzed according to the original result of the random assignment and there were no missing data. "We analyzed all data using intention-to-treat methods"
Selective reporting (reporting bias)	Low risk	All outcomes outlined in the study protocol were reported
Other bias	Unclear risk	There was pre-randomization administration of the intervention that may have enhanced or diminished the effect of the intervention during the subsequent, randomized evaluation period The study was partially funded by companies that produce the interventions being investigated
COMET Study		
Methods	Study design: RCT Study center: multicenter, including (1) a study chair, (2) a coordinating center, (3) four clinical centers and (4) the National Eye Institute, US Number randomized: 469 children Study follow-up: 3 years Exclusions and losses to follow-up: no exclusions; 7 (1.5%) were lost to follow-up	
Participants	Age: mean = 9.3 years (range 6 to 11 years) Gender: 223 boys, 246 girls Culture: four major cities in the US (Birmingham, Alabama: n = 133; Boston, Massachusetts: n = 110; Philadelphia, Pennsylvania: n = 108; and Houston, Texas: n = 118) Inclusion criteria: 1) age 6 to 11 years old; 2) myopia with spherical equivalent refractive error between -1.25 D and -4.50 D in both eyes, as measured by cycloplegic autorefraction; 3) astigmatism < 1.50 D; 4) no anisometropia (difference in spherical equivalent < 1.00 D between eyes); 5) best corrected VA of 20/32 or better; 6) no strabismus by cover test for far (4.0 m) and/or near (0.33 m) fixation; 7) willingness to not wear contact lenses for study duration Exclusion criteria: 1) strabismus detected by cover test; 2) any ocular, systemic, or neurodevelopmental conditions that could influence refractive development; 3) chronic medication use that might affect myopia progression or visual acuity; 4) birthweight < 1250g; 5) previous use of bifocals, PALs, or contact lenses; 6) problems with adherence to the protocol or follow-up period	
Interventions	PAL group (n = 235): multifocal lenses (no-line bifocals) with gradual and progressive change toward less negative or more positive power from the distance portion to the near portion of the lens (power +2.00 D); worn during waking hours for 3 years SVL (n = 234): single vision lenses with same focal power throughout the lens area; worn during waking hours for 3 years Note: Prescription changes were made if the subjective refraction had changed by at least 0.50 D for one or both eyes. Smaller prescription changes were made if clinically indicated. Both groups were offered single vision sports glasses to use while participating in sports activities	
Outcomes	<b>Primary outcome:</b> change in refractive error Magnitude of change in spherical equivalent refractive error relative to baseline measured by cycloplegic autorefraction with 2 drops of 1% tropicamide <b>Secondary outcomes:</b> <ol style="list-style-type: none"><li>1 Axial length (magnitude of change in axial length relative to baseline using the average 3–5 measurements using the Sonomed A-scan)</li><li>2 Changes in ocular components, including lens thickness, anterior chamber depth, vitreous chamber depth</li><li>3 Accomodation and phoria by Maddox rod</li><li>4 Corneal curvature based on keratometry measured with the autorefractor</li><li>5 Normal reading distance for standardized age-appropriate text</li></ol> Measurements taken at baseline and every 6 months for three years <b>Unit of analysis:</b> child-based The average values of both eyes were used if the correlation coefficient was > 0.85 between eyes and the mean difference was not statistically significant; otherwise the eye with more myopic change was used for each child	
Notes	Study dates: enrolment was from September 1997 to September 1998; follow-up was designed for 3 years, but continued for 7 years, including 5 years wearing original lens assignments and 2 years wearing either glasses or contact lenses Funding source: NEI grants, Essilor of America, Marchon Eyewear, Marco Technologies and Welch Allyn Sample of 150 children were followed up at 1 month to evaluate possible lens-induced phoria changes; no problems were detected in either group	

Compliance in wearing glasses was monitored with separate questionnaires for children and parents (93% compliance in PAL group, 96% compliance in SVL group). Attitude towards wearing glasses and self-esteem were also measured  
Additional data: study author provided unpublished data via email correspondence

<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Randomization derived by permuted block design with preset block size and stratified by clinical center by the coordinating center
Allocation concealment (selection bias)	Low risk	Randomization assignments were allocated by the coordinating center after the eligibility of each participant was verified
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to functional differences between the interventions studied
Masking of outcome assessors (detection bias) Primary outcome	Low risk	Optometrists responsible for assessing study outcomes were unaware of the lens assignments
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	"The data analysts were not masked to treatment assignment when analyzing the data" (via email communication with study author)
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	"Follow-up data were analyzed by applying an intention-to-treat principle according to the child's original lens assignment and the last known value of the outcome measures. For the seven children lost to follow-up and thus without data at the third annual visit, progression information from the latest follow-up visit was used"
Selective reporting (reporting bias)	Low risk	All outcomes published a priori in the design paper (Hyman 2001) were reported in results papers
Other bias	Unclear risk	The study was partially funded by companies that produce the interventions being investigated
Edwards 2002		
Methods	Study design: RCT Study center: 1 (Centre for Myopia Research) Number randomized: 298 children Study follow-up: 2 years Exclusions and losses to follow-up: no exclusions; 44 (15%) were lost to follow-up	
Participants	Age: mean = 9.09 years (range 7 to 10.5 years) Gender: 122 boys, 132 girls Culture: Hong Kong children, recruited through newspaper advertisements Inclusion criteria: 1) age 7 to 10.5 years old; 2) spherical equivalent refractive error between -1.25 D and -4.50 D, as measured under cycloplegia; 3) best corrected VA of 0.00 logMAR or better; 4) no previous use of contact lenses and willingness to not wear contact lenses; 5) willingness to wear glasses constantly; 6) parents acceptance of randomization Exclusion criteria: 1) astigmatism > 1.50 D; 2) anisometropia > 1.50 D in spherical or cylindrical error; 3) any ocular or systemic condition that might affect refractive development; 4) previous use of bifocals or PALs; 5) problems with adherence to the protocol or follow-up period	
Interventions	PAL group (n =138): SOLA MC progressive lenses (add +1.50 D); worn constantly for 2 years SVL (n = 160): SOLA single vision lenses; worn constantly for 2 years Note: prescription changes were made if there was a reduction in aided vision of 0.10 logMAR units	
Outcomes	<u>Primary outcomes</u> <b>1</b> Refractive error measured under cycloplegia (by autorefractometry for data analysis and by subjective refraction for spectacle prescription)	

	<p>2 Axial length measured under cycloplegia</p> <p><u>Secondary outcomes:</u></p> <p>1 Aided visual acuity in each eye</p> <p>2 Mean monocular and binocular distance and near PD</p> <p>3 Noncycloplegic refraction</p> <p>4 Horizontal and vertical heterophoria</p> <p>5 Normal reading distance for standardized age-appropriate text</p> <p>Measurements taken at baseline and every 6 months for two years Unit of analysis: only data from the right eyes are reported</p>	
Notes	Materials: Lenses provided by Sola (Hong Kong) Ltd Funding source: Centre for Myopia Research (Area of Strategic Development), The Hong Kong Polytechnic University	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Predetermined random sequence
Allocation concealment (selection bias)	Low risk	The investigator was not aware of group allocation until child was enrolled in study
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to functional differences between the interventions studied
Masking of outcome assessors (detection bias) Primary outcome	Low risk	The investigator measuring refractive error was masked to treatment assignment
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	The investigator measuring axial length was masked to treatment assignment
Masking of data analyzers	Low risk	The masked and unmasked investigators independently analyzed the data
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	There were no exclusions after randomization. There were 44 patients lost to follow-up: n = 17 in PAL group; n = 27 in SVL group. It was reported that whether or not a patient was retained in the study was not statistically associated with treatment allocation
Selective reporting (reporting bias)	Low risk	The results for study outcomes were reported at 2-year follow-up
Other bias	Low risk	
Fulk 1996		
Methods	Study design: RCT Study center: 1 (Indian Health Service Hospital, Optometry Department, Tahlequah, Oklahoma, USA) Number randomized: 32 children Study follow-up: 18 months Exclusions and losses to follow-up: no exclusions; 4 (12.5%) were lost to follow-up	
Participants	Age: range 6 to 13 years Gender: included boys and girls (numbers not reported) Culture: children with myopia and nearpoint esophoria identified from medical records and referred by local optometrists	

	<p>Inclusion criteria: 1) at least 0.50 D of myopia in both principal meridians of both eyes; 2) ages 6 to 13.99 years for boys and 6 to 12.99 years for girls; 3) nearpoint esophoria; 4) corrected acuity of at least 20/25 in each eye, distance and near, with SVLs; 5) ability to respond to subjective tests</p> <p>Exclusion criteria: 1) strabismus; 2) astigmatism greater than 2.00 D in either eye; 3) anisometropia greater than 2 D; 4) convergence insufficiency accompanied by symptoms; 5) diabetes or other systemic disease with potential effects on refractive error; 6) ocular disease other than mild inflammation of the adnexa</p>
Interventions	<p>Bifocals (n = 16): bifocal lenses with +1.25 D addition</p> <p>SVLs (n= 16): single vision lenses</p> <p>Note: prescription changes were made if the spherical equivalent in either eye had changed by 0.50 D</p>
Outcomes	<p><u>Primary outcomes:</u></p> <p>1 Change in refractive error (spherical equivalent) measured by cycloplegic autorefraction</p> <p>2 Change in axial length measured by Humphrey A/B Scan under cycloplegia</p> <p>Measurements taken at baseline and every 6 months for 18 months</p> <p>Unit of analysis: the average values of both eyes</p>
Notes	Funding source: Northeastern State University Faculty Research Committee (Tahlequah, Oklahoma, USA)

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization process was used with reference to Zelen
Allocation concealment (selection bias)	Low risk	"The optician kept envelopes containing the assignment and fitted the appropriate glasses at the end of the base-line examination"
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to visual and functional differences between the interventions studied
Masking of outcome assessors (detection bias) Primary outcome	Low risk	"A research assistant who did not know what type of glasses the child wore, measured..." However, the success of masking of examiner was not addressed in paper
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	32 participants enrolled; 4 dropped out; 2 from each treatment group; does not address reason for drop-outs. Analysis is for the 28 remaining participants, so not "intention to treat" in terms of including all enrolled participants for analysis at end; however, equal drop-outs in each arm and patients were analyzed by group they were randomized. It was not stated whether all 28 participants completed all 3 follow-up visits, although it was stated that they completed the study
Selective reporting (reporting bias)	Unclear risk	Refractive error outcome was reported. Axial length outcome (in mm) was plotted against myopia progression in D, but mean values by treatment groups were not given
Other bias	Low risk	

## Fulk 2002

Methods	<p>Study design: RCT and study of variables that may influence myopia progression in children</p> <p>Study centers: 2 (Tahlequah and Tulsa, Oklahoma, USA)</p> <p>Number randomized: 82 children</p> <p>Study follow-up: 30 months</p> <p>Exclusions and losses to follow-up: no exclusions; 7 (8.5%) were lost to follow-up</p>
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Participants	<p>Age: mean = 10.7 years (range 6 to 12 years)</p> <p>Gender: 43 boys and 39 girls</p> <p>Culture: children with myopia and nearpoint esophoria recruited locally and through clinics operated by the Cherokee Nation: 58% Caucasian, 29% American Indian, 5% Hispanic, 4% African-American, 3% other and 1% Asian/Pacific Islander</p> <p>Inclusion criteria: 1) at least 0.50 D of myopia in both principal meridians of both eyes; 2) ages 6 to 12.99 years for boys and 6 to 11.99 years for girls; 3) nearpoint esophoria; 4) corrected VA of at least 20/25 in each eye at distance and binocularly with SVLs; 5) corrected stereoacuity of at least 40 sec arc with SVLs at 40 cm; 6) assent of child and consent to participate</p> <p>Exclusion criteria: 1) strabismus; 2) astigmatism or anisometropia greater than 2.00 D; 3) diabetes or other systemic disease with potential effects on refractive error; 4) ocular disease other than mild inflammation of the adnexa; 5) known history of allergic reaction to proparacaine or tropicamide; 6) history of use of RGPs; 7) current use of bifocals or use within the last year; 8) high myopia of <math>-6.00</math> D or more for children younger than 9 year or <math>-8.00</math> D or more for children 9 years or older; 9) inability to respond to subjective testing or hold fixation sufficiently to allow for study measurements</p>
Interventions	<p>Bifocals (n = 42): bifocal lenses with +1.50 D add</p> <p>SVLs (n = 40): single vision lenses</p> <p>Note: prescription changes were made if 1) the spherical equivalent in either eye had changed by 0.50 D or 2) any combination of sphere or cylinder change could improve the distance acuity by three letters or more in either eye</p>
Outcomes	<p><b>Primary outcome:</b> change in refractive error (spherical equivalent) (cycloplegic autorefraction)</p> <p><b>Secondary outcomes:</b></p> <ol style="list-style-type: none"> <li>1 Change in axial length (A-scan ultrasonography)</li> <li>2 Change in vitreous chamber depth (A-scan ultrasonography)</li> <li>3 Changes in the cylinder component (<math>J_0</math> and <math>J_{45}</math>)</li> <li>4 Variables associated with myopia progression: parental myopia, season, nearpoint habits and academic achievement</li> </ol> <p>Measurements taken at baseline and every 6 months for 30 months</p> <p>Unit of analysis: the average values of both eyes</p>
Notes	<p>Study dates: enrolment between August 20 and October 15, 1996; original follow-up was for 30 months, some children remained for 54 months</p> <p>Funding source: National Eye Institute, National Institutes of Health</p> <p>Notes: study was also know as the Myopia Progression Study</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized permuted block design, with separate number sequences for each of the 2 sites stratified by gender to assign participants in approximately equal allocation to the 2 treatments
Allocation concealment (selection bias)	Low risk	"Sealed envelopes containing the treatment assignments were maintained at each site and opened by the optician after a subject was enrolled"
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to visual and functional differences between the interventions studied
Masking of outcome assessors (detection bias) Primary outcome	Low risk	"A research assistant who did not know what type of glasses the child wore, measured..." However, the success of masking of examiner was not addressed in paper
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	"This is an intention-to-treat analysis, with all subjects being classified according to their original treatment assignment — disregarding the fact that many discontinued that mode of correction during the last year"

Incomplete outcome(s) data		Seven participants did not complete the study: 6 of 42 randomized to bifocals (2 died, 1 drowned and 1 died in auto accident; 4 were “unwilling”) and 1 of 40 randomized to SVL (participant moved). “In a secondary analysis, estimates of myopia progression were imputed for children who did not complete the study; each subject who left the study prematurely was assumed to have myopia progression equal to that of mean progression observed in the SVL group for the time period for which their data were missing.” This weakened the treatment effect
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were reported a priori
Other bias	Low risk	
Hasebe 2008		
Methods	Study design: randomized cross-over trial Study center: 1 (Okayama University Medical School) Number randomized: 92 children Study follow-up: 3 years Exclusions and losses to follow-up: no exclusions; 6 (6.5%) were lost to follow-up	
Participants	Age: mean = 9.85 years (range 6 to 12 years) Gender: 47 boys, 45 girls Culture: Okayama, Japan Inclusion criteria: 1) age 6 to 12 years old; 2) spherical equivalent refractive error between -1.25 D and -6.00 D in both eyes, as measured by noncycloplegic autorefractometry; 3) best corrected VA of 20/20 or better in each eye; 4) no other eye disease; 5) experience wearing spectacles; 6) willingness to wear glasses constantly and attend follow-up visits; 7) acceptance of randomization Exclusion criteria: 1) astigmatism > 1.50 D in both eyes; 2) anisometropia > 1.50 D; 3) manifest strabismus; 4) birthweight < 1250 g; 5) heterotropia or severe ophthalmic disease that may affect refractive development; 6) previous use of PALs or contact lenses	
Interventions	PALs (n = 46): 18 months wearing PALs (add +1.50 D), followed by 18 months wearing SVLs SVLs (n = 46): 18 months wearing SVLs, followed by 18 months wearing PALs (addition + 1.50 D) Note: prescription changes were made if corrected distance visual acuity was less than 20/30 in at least one eye	
Outcomes	<p><u>Primary outcome</u>: progression of myopia measured by cycloplegic autorefractometry</p> <p><u>Secondary outcomes</u>:</p> <ol style="list-style-type: none"> <li>1 Noncycloplegic autorefractometry</li> <li>2 Noncycloplegic subjective refraction</li> <li>3 Cycloplegic subjective refraction</li> <li>4 Distant vision and myopia place</li> <li>5 Corrected distant vision</li> <li>6 Lags of accommodation measured by noncycloplegic, open-field autorefractometry</li> <li>7 Near-point of accommodation</li> <li>8 Reaction of accommodation by open-field autorefractometry</li> </ol> <p>Measurements taken at baseline and every 6 months for three years Unit of analysis: child-based (mean of both eyes or right eye only)</p>	
Notes	Study dates: enrolled July 2002 to June 2003 Funding source: Japanese Ministry of Education, Culture, Sports, Science and Technology and Megane Tanaka Chain, Ltd	

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly allocated to Group 1 or Group 2 by drawing lots. “Participants drew lots (number of 1–80 was described in each card) at initial inspection and participant number was randomly decided” (Hasebe 2002)
Allocation concealment (selection bias)	Low risk	Physicians conducting examinations did not know the allocation. Participants drew lots from numbered cards, then the principal investigator and three opticians determined allocation based on the number drawn (Hasebe 2002)
Masking of participants	High risk	Masking of participants was not applicable due to visual and functional differences between the interventions studied



(performance bias)		
Masking of outcome assessors (detection bias) Primary outcome	Low risk	The examiners collecting data or prescribing spectacles were masked to lens assignment
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Low risk	Methods paper stated that the statistician was masked to the lens assignments (Hasebe 2002)
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	“Only six children, two in group 1 and four in group 2, failed to return for the final visit. The reasons for being lost to follow-up or excluded from the analysis included a problem in using cycloplegic eye drops (two children), moving to another prefecture (two children), desire to wear contact lenses (one child), or the occurrence of exotropia (one child)”
Selective reporting (reporting bias)	Low risk	All outcomes published a priori in the design paper were reported in results papers
Other bias	Unclear risk	Design-specific risk of bias: cross-over trial. Four children dropped out during the second study period The study was partially funded by a company that produces the type of lenses being investigated
Houston Study		
Methods	Study design: RCT Study center: 1 (University of Houston, Texas, USA) Number randomized: 207 children Study follow-up: 3 years Exclusions and losses to follow-up: 83 (40%) children were excluded from or dropped out of the study	
Participants	Age: range 6 to 15 years Gender: 58 boys and 66 girls completed the study Culture: children were recruited from patients, from family members of faculty and staff and from the racially diverse Houston community Inclusion criteria: 1) myopia of $-0.25$ D in one or both eyes; 2) ages 6 to 15 years; 3) best corrected VA of 20/20 or 20/15; 4) normal ocular health; and 5) able to provide informed consent Exclusion criteria: 1) strabismus or amblyopia; 2) contact lens wearers; 3) astigmatism of 2.00 D or more; and 4) particularly high or low gradient AC/A ratios	
Interventions	Bifocals 1: bifocal lenses with +1.00 D addition Bifocals 2: bifocal lenses with +2.00 D addition SVLs Note: prescription changes were made if 1) there was a change of spherical power of 0.50 D or more in one or both eyes or 2) there was an improvement of one line of visual acuity	

Outcomes	<p><u>Patient care team outcomes (unmasked):</u></p> <ol style="list-style-type: none"> <li>1 Change in refractive error (spherical equivalent, noncycloplegic subjective refraction)</li> <li>2 Characteristics of patients for whom bifocals were the most effective in reducing the progression of myopia</li> </ol> <p><u>Evaluation team outcomes (masked):</u></p> <ol style="list-style-type: none"> <li>1 Change in refractive error (cycloplegic retinoscopy, noncycloplegic autorefraction and cycloplegic autorefraction)</li> <li>2 Change in corneal refracting power</li> <li>3 Change in anterior chamber depth</li> <li>4 Change in lens radii of curvature and thickness</li> <li>5 Change in vitreous chamber depth</li> <li>6 Change in axial length of the eye</li> </ol> <p>Measurements taken at baseline and every 6 months for 3 years Unit of analysis: data from the right eyes</p>
Notes	<p>Study dates: "Subjects were admitted to the study over a period of 20 months, in five 'accrual groups.' The first group of subjects entered the study in February, 1981 and completed the study in February, 1984, whereas the last group of subjects entered the study in October, 1982," and completed the study in October, 1985 Materials: bifocals were executive one-piece lenses in CR-39 plastic (American Optical Corporation); SVLs were polycarbonate lenses (Gentex Corporation)</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Placed in treatment group "on basis of a table of random numbers" using block randomization technique
Allocation concealment (selection bias)	Low risk	"Neither the investigator nor the subject know the treatment to be assigned at the time the subject is registered for the study"
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to visual and functional differences between the interventions studied
Masking of outcome assessors (detection bias) Primary outcome	High risk	This study involved a team of masked observers (Evaluation team) and a team of unmasked observers (Patient care team) The results presented in the final analysis are from the unmasked group
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Evaluation team members collecting this data were masked
Masking of data analyzers	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	Patients were dismissed for "noncompliance" and some were fitted with contact lenses without letting study personnel know, so they were also dropped. Also, participants who did not return and those who moved were dropped. Out of 207 enrolled 83 (40% dropped out). It was not clear from which treatment groups the drops-outs came. Incomplete data as only 60% remained in study
Selective reporting (reporting bias)	High risk	Results were not reported for the evaluation team measurements or for other secondary outcomes outlined in the design paper. The methods paper stated that an evaluation team report would be based on 1) cycloplegic retinoscopy, 2) non-cycloplegic autorefraction and 3) cycloplegic autorefraction performed by masked examiners. However, these were never reported in outcome paper. Also secondary outcomes, including axial length, were never reported in outcome paper

Other bias	High risk	One participant was allowed to wear contact lenses when playing basketball Primary outcome measure was not under cycloplegic conditions, was an unmasked subjective refraction, and sometimes student examiners were used
Jensen 1991		
Methods	Study design: RCT Study center: 1 (Odense University Hospital, Denmark) Number randomized: 159 children Study follow-up: 2 years Exclusions and losses to follow-up: 4 (2.5%) children who were randomized were excluded from the analyses; 16 (10%) were lost to follow-up	
Participants	Age: mean = 10.9 years Gender: 87 boys, 72 girls Culture: Medical records of children from schools in Odense, Denmark were screened for myopia; n = 8769. Possible cases of myopia underwent a primary examination; n = 1216. Myopic children with at least -1.0 D in either eye, and in 2nd to 5th grades were examined at the eye clinic; n = 361. Children meeting inclusion/exclusion criteria at the eye exam were mailed invitations to participate in the trial; n = 227 Inclusion criteria: 1) in 2nd to 5th grades at screening; 2) myopia with spherical equivalent refractive error between -1.25 D and -6.00 D in both eyes; 3) normal corrected vision; 4) Danish parents; and 5) affirmative response to mailed invitation for study Exclusion criteria: 1) unilateral myopia; 2) eye disease or general illness, especially heart/lung disease; and 3) experience in pilot study	
Interventions	Bifocals (n = 57): constant wear of bifocals with +2.0 D addition to upper edge of reading segment Timolol (n = 51): one drop of 0.25% timolol maleate in each eye twice daily and constant wear of SVLs for corrected visual acuity 0.8 Control (n = 51): constant wear of SVLs for corrected visual acuity 0.8 Note: participants were permitted to wear their own SVLs if corrected visual acuity was >0.8	
Outcomes	<p><b>Primary outcomes:</b></p> <ol style="list-style-type: none"> <li>1 Rate of myopia progression and changes in refractive components (spherical equivalent measured by cycloplegic autorefraction)</li> <li>2 Prevention or delay of myopia with bifocals</li> <li>3 Prevention or delay of myopia with pressure lowering eye drops</li> </ol> <p><b>Secondary outcomes:</b></p> <ol style="list-style-type: none"> <li>1 Changes in the fundus</li> <li>2 Intraocular pressure</li> <li>3 Phoria-status</li> <li>4 Accommodation</li> <li>5 Close work</li> <li>6 Body growth</li> </ol> <p>Measurements taken at baseline and every 6 months for two years Unit of analysis: right eyes and left eyes analyzed separately</p>	
Notes	Study dates: screening January to April 1983; eye clinic exams October 1984 to April 1985 Notes: the children who chose not to participate in the study (n = 44) did not statistically differ from those examined with regard to age and degree of myopia	

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization based on age, sex and refractive error. Intervention and control groups were made by completing cells based on 3 age categories, 3 refractive error categories and 2 gender groups (3 × 3 × 2 = 18 cells). Participants were assigned to each cell after baseline examinations
Allocation concealment (selection bias)	Low risk	For each cell the children in groups of 3 were allocated to study groups by drawing numbers 1 to 6 for the first assignment The second and third assignments were dependent on the first assignment
Masking of participants	High risk	Masking of participants was not applicable due to visual and functional differences between the interventions studied

(performance bias)		
Masking of outcome assessors (detection bias) Primary outcome	High risk	Masking was not reported, but there was only one study investigator
Masking of outcome assessors (detection bias) Secondary outcomes	High risk	Primary and secondary outcomes were assessed by the same examiner
Masking of data analyzers	Unclear risk	Data were analyzed by the study investigator
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	There were 159 children enrolled: 51 SVLs, 57 bifocals, 51 timolol. At the first year visit 13 (8%) children were excluded or lost to follow-up: one patient given contact lenses was excluded and one patient dropped out from the control group; six patients dropped out from the bifocal group (3 because they could not adapt to the bifocals); and two patients were excluded and three dropped out from the timolol group. At the second year visit an additional seven (4.5%) children were excluded or lost to follow-up: one patient given contact lenses was excluded from the control group; three patients dropped out from the bifocal group because they could not adapt to the bifocals; and three dropped out from the timolol group
Selective reporting (reporting bias)	High risk	The methods section of the article described that results would be discussed only if exceptional
Other bias	Low risk	
Katz 2003		
Methods	Study design: RCT, with 3 month adaptation period Study center: 1 (Myopia Clinic of the Singapore Eye Research Institute) Number randomized: 564 children (428 children attended initial visit; 383 children completed the adaptation period) Study follow-up: 2 years Exclusions and losses to follow-up: 136 (24%) children who were randomized did not attend the initial visit and 45 (8%) more did not complete the adaptation period; 86 (22%) of the 383 children who completed the adaptation period were lost to follow-up	
Participants	Age: mean = 8.3 years (range 6 to 12 years) Gender: 204 boys, 179 girls Culture: Singaporean children with Chinese ethnicity Inclusion criteria: 1) age 6 to 12 years old; 2) myopia with spherical equivalent refractive error between -1.0 D and -4.0 D; 3) Chinese ethnicity; and 4) provided informed consent Exclusion criteria: 1) astigmatism > 2.0 D; 2) previous contact lens wear; 3) other ocular pathologies Note: all participants were provided a three-month period to adapt to assigned intervention	
Interventions	Contact lenses (n = 158): RGPCLs worn daily for at least 8 hours per day Spectacles (n = 225): SVLs worn daily for at least 8 hours per day Note: prescription changes were made if corrected visual acuity fell below 20/40	
Outcomes	<u>Primary outcome:</u> change in refractive error (spherical equivalent) Measured by subjective cycloplegic refraction from post-adaption through 2 years of follow-up <u>Secondary outcomes:</u>  1 Change in keratometry (autokeratometry) 2 Change in axial length (A-Scan ultrasonography)  Measurements taken at baseline and every 3 months over a 24 month period Unit of analysis: only data from the right eyes are reported	
Notes	Materials: Asian Design Lens, Baush and Lomb, Rochester, New York, USA Adherence to treatment was measured from children and parents (agreement was almost 100%) and defined as use of contact lenses or spectacle use for at least 8 hours per day, 7 days per week Additional data: study author provided unpublished data via email correspondence	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>

Random sequence generation (selection bias)	Low risk	Randomization schedule of block size 6, generated from random number tables in Baltimore, US
Allocation concealment (selection bias)	Low risk	Assignments were placed in sealed envelopes with sequential patient numbers
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to visual and functional differences between the interventions studied
Masking of outcome assessors (detection bias) Primary outcome	High risk	Clinical observers were not masked to treatment group
Masking of outcome assessors (detection bias) Secondary outcomes	High risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	The data analyst was not masked (via email communication with study author)
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Unclear risk	Of the 564 children randomized, 297 (53%) completed the study. There were 86 (22%) children who completed the adaptation period who were lost to follow-up or censored from the study for not attending the final study visit. Statistical comparisons between those lost to follow-up and those who completed the study showed "a higher proportion of girls in the contact lens (59%) than spectacle group (42%) completed the study ( $P = 0.004$ )". It was also reported that "axial length and astigmatism were similar between the treatment groups that completed the study, but the contact lens group that completed the study had 0.3 diopters more myopia at baseline than did those in the spectacle group that completed the study ( $P = 0.003$ )"
Selective reporting (reporting bias)	High risk	Although all outcomes identified in the study methods were reported, it is unclear why some participants were not included in the analyses. There should be 105 RGPCL and 192 SVL wearers examined over 2 years, but only 97 RGPCL and 188 SVL wearers were included in the analyses
Other bias	High risk	Unequal loss to follow-up; imbalance in gender, corneal curvature and refractive error at baseline visit (controlled for in analyses); many participants lost from study before being examined for outcomes
MIT study		
Methods	Study design: RCT Study center: 1 (National Taiwan University Hospital vision care center) Number randomized: 227 children Study follow-up: 18 months Exclusions and losses to follow-up: 39 (17%) children were excluded or lost to follow-up	
Participants	Age: range 6 to 13 years Gender: 105 boys, 122 girls Culture: school children in Taiwan with an average myopia of $-3.27$ D Inclusion criteria: 1) age 6 to 13 years old; 2) provided informed consent; 3) willing to wear glasses; and 4) available for follow-up period Exclusion criteria: 1) tropia or amblyopia; and 2) increase of more than 2 D in any eye during the treatment period	
Interventions	SVLs (n = 76): regular SVLs worn all the time and placebo drops PALs (n = 75): multi-focal lenses with the near addition part for reading and placebo drops PALs plus atropine (n = 76): 0.5% atropine instilled once a day at bedtime, in addition to PALs Note: An intervention group of atropine and SVLs was omitted from the study design since difficulty while reading due to the intervention would have induced poor compliance. Prescription changes were made for any child whose refractive error increased more than 0.75 D	
Outcomes	Primary outcome: myopic progression measured by cycloplegic autorefraction (spherical equivalent)	

	<p>Secondary outcomes:</p> <ol style="list-style-type: none"> <li>1 Change in IOP (tonopen)</li> <li>2 Change in biometric axial length (A-Scan ultrasonography)</li> <li>3 Change in corneal radius (autorefracton)</li> </ol> <p>Measurements taken at baseline and every 3 months over an 18 month period Unit of analysis: data from the right eyes were analyzed</p>
Notes	<p>Study dates: 1997 to 2000 Materials: HOYALUX3 plastic lenses were used for PALs; polycarbonate plastic lenses were used for SVLs Additional data: study author provided unpublished data via email correspondence</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratification was based on age (younger than 9.5 years or not), sex (boy or girl) and myopic severity (more than -4.0 D for both eyes or not) at the baseline visit. This resulted in the total of 8 strata. Each participant was categorized into one of the strata and then randomized to receive one of the three treatments. A block size of 9 was used to balance the number of patients in the three treatment categories for each stratum (via email communication with study author)
Allocation concealment (selection bias)	Low risk	Group assignments were unknown to study personnel when participants were being enrolled by using coded bottles with sealed envelopes (via email communication with study author)
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to functional differences between the interventions studied
Masking of outcome assessors (detection bias) Primary outcome	Low risk	Ophthalmologists were masked and it would be improbable to guess the patients' treatment by examination of the pupils because the ocular examination was performed only after giving the cycloplegic agent in each patient at each visit (via email communication with study author)
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Ophthalmologists (outcome assessors) were masked (via email communication with study author)
Masking of data analyzers	Low risk	Data analysts were masked (via email communication with study author)
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	Attritions were reported by group: atropine, n = 10 (13%); PALs, n = 14 (19%); SVLs, n = 15 (20%). Reasons for attrition were poor follow-up, switching to contact lenses, poor compliance, myopic progression greater than 2.00 D per year (one patient from the PAL group and one from the SVL group) or loss to follow-up without any specified reason
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	Low risk	

## PIR-205 Study

Methods	<p>Study design: RCT Study centers: 13 (US academic clinics and private practices) Number randomized: 174 children Study follow-up: 1 year (planned), plus 1 year extension Exclusions and losses to follow-up: 27 (15.5%) children who were randomized were excluded from the analyses; 2 (1%) were lost to follow-up</p>
Participants	<p>Age: mean = 9.9 ± 1.3 years (range 8 to 12 years) Gender: 71 boys, 103 girls Culture: children from US cities of study centers: 73% white, 7% black, 4% Asian, 12% Hispanic, 4% other Inclusion criteria: 1) age 8 to 12 years old; 2) myopia of -0.75 D to -4.00 D; 3) best</p>

	corrected VA of 20/25 or better; 4) normal pupils; and 5) good general health Exclusion criteria: 1) anisometropia or astigmatism greater than 1.00 D; 2) any manifest tropia; 3) current use of either contact lenses or bifocals; 4) history of ocular surgery, trauma, or chronic ocular disease, including allergic conjunctivitis; 5) diseases requiring long-term or regular intermittent medication; 6) behavioral or neurological disorders that would interfere with the study; 7) participation in any study that involved an investigational drug within one month of enrolment; 8) intolerance or hypersensitivity to topical anesthetics, mydriatics, or components of the formulations; 9) contraindications to antimuscarinic agents; and 10) pregnancy or planned pregnancy
Interventions	Pirenzepine (n =117): 2% pirenzepine ophthalmic gel applied twice a day Control (n = 57): vehicle-placebo gel applied twice a day
Outcomes	<u>Primary outcome</u> : change in refractive error measured by cycloplegic autorefraction (spherical equivalent) <u>Secondary outcome</u> : change in axial length measured by A-scan ultrasonography Measurements taken at baseline and every 3 months for 1 year Unit of analysis: the average of both eyes
Notes	Study dates: March 1, 2000 to February 28, 2002 Funding source: Valley Forge Pharmaceuticals, Inc Notes: study also known as the Collaborative Assessment of Myopia Progression with Pirenzepine (CAMPP) study

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible patients were randomized using a sponsor-prepared, computer-generated list stratified by site. Randomization was in a 2:1 ratio of pirenzepine to placebo
Allocation concealment (selection bias)	Low risk	"Study sites used coded lists to determine which tube of medication to administer to the next enrolled subject. The pirenzepine gels and placebo gels were packaged in identical tubes and the gels themselves appeared identical. Thus study personnel had no way of knowing which tubes had which medications, same for patients" (SC)
Masking of participants (performance bias)	Low risk	Study was placebo-controlled and identical bottles with coded labels were distributed
Masking of outcome assessors (detection bias) Primary outcome	Low risk	"Since the pirenzepine gels and placebo gels were packaged in identical tubes and the gels themselves appeared identical, the study personnel had no way of knowing which tubes had which medications" (SC)
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	Data analyzers were not masked (personal communication with biostatistician)
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	Screened 277 patients and enrolled 174. Attrition was reported: 145 of 174 patients completed the trial. There were significantly more dropouts in pirenzepine arm: 26/117 (26%), compared with placebo arm: 3/57 (5%). Reasons for dropout included occurrence of adverse events, non-adherence and loss to follow-up "Additional methods were used to impute missing values due to patients who discontinued the study. In all 3 methods used (last observation carried forward, visit-to-visit extrapolation using median of respective treatment, and visit-to-visit extrapolation using median of placebo group), the treatment effect was similar to or greater than in the primary analysis method"
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were chosen a priori and all were reported
Other bias	Unclear risk	Some study authors were employed by the pharmaceutical company funding the study

Pärssinen 1989

Methods	Study design: RCT Study center: 1 (outpatient clinic of the Central Hospital of Central Finland) Number randomized: 240 children Study follow-up: 3 years Exclusions and losses to follow-up: 1 (0.4%) child who was randomized was excluded from the analyses; and 2 (0.8%) were lost to follow-up
Participants	Age: mean = 10.9 years (range 8.8 to 12.8 years) Gender: 119 boys, 121 girls Culture: school children with suspected myopia were referred by school nurses and doctors after routine vision check-ups Inclusion criteria: 1) in 3rd to 5th grades; 2) myopia with spherical equivalent refractive error between $-0.25$ D and $-3.0$ D in both eyes and $-0.50$ D in the worst eye; and 3) corrected VA of 6/6 or better in both eyes Exclusion criteria: 1) astigmatism $> 2.0$ D; 2) anisometropia $> 2.0$ D; 3) manifest strabismus; 4) horizontal phorias more than $-10$ or $+9$ or vertical more than $1$ ; 5) previous use of spectacles for myopia; 6) eye disease or serious general disease; and 7) plans to move out of the area in the near future or the child not wanting to have spectacles
Interventions	Distant use (n = 80): minus lenses with full correction to be used for distant vision only; advised to read at greatest distance possible Bifocals (n = 80): clear plastic bifocal lenses with $+1.75$ D addition for continuous use Continuous use (n = 79): minus lenses with full correction for continuous use; advised to only remove spectacles if there was a danger of breaking them Note: prescription changes were made if corrected visual acuity fell below 20/40
Outcomes	<b>Primary outcome:</b> change in spherical equivalent (subjective cycloplegic refraction) <b>Secondary outcomes:</b> <ol style="list-style-type: none"><li>1 Change in spherical refraction</li><li>2 Change in visual acuity</li><li>3 Change in astigmatism</li><li>4 Change in reading distance</li></ol> Measurements taken at baseline and annually for three years Unit of analysis: right eyes and left eyes analyzed separately
Notes	Study dates: enrolment March 1983 to April 1985 Funding source: Academy of Finland Compliance was measured by questionnaires and classified as compliant, partly compliant or noncompliant

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random, sex-stratified codes
Allocation concealment (selection bias)	Low risk	Treatment assignments were sealed in envelopes
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to visual and functional differences between the interventions studied
Masking of outcome assessors (detection bias) Primary outcome	High risk	The ophthalmologist did not look at the group assignment before the examination, but often, for different reasons, the group was revealed. The 3-year examinations were conducted by two different ophthalmologists, one of whom did not know the group assignments
Masking of outcome assessors (detection bias) Secondary outcomes	High risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	"After allocation one of the boys in the continuous use group was excluded from comparison with the other treatment groups when we found that his sister has been included previously in a different



Incomplete outcome(s) data		group. Two children moved from the area, and their refraction values could not be obtained" The remaining participants were analyzed by their original treatment assignments
Selective reporting (reporting bias)	Low risk	Results reported for outcomes described in a study design paper
Other bias	Low risk	
Sankaridurg 2010		
Methods	Study design: RCT Study center: 1 (Zhongshan Ophthalmic Center, Sun Yet Sen University China) Number randomized: 210 children Study follow-up: 12 months (the study was originally planned to be two years in duration) Exclusions and losses to follow-up at 12-month visit: two children who were randomized were excluded from the analyses; 7 (3.3%) were lost to follow-up	
Participants	Age: mean = 11 years (range 6 to 16 years) Gender: 110 boys, 100 girls Culture: Chinese children in Guangzhou, China Inclusion criteria: 1) age 6 to 16 years; 2) bilaterally myopic (spherical component range from -0.75 D to -3.50 D inclusive) with astigmatism not exceeding -1.50 D and a maximum of 1.00 D of anisometropia; 3) vision correctable to 6/9.5 or better in each eye; 4) ocular findings considered to be normal; 5) willing to wear the study spectacles and adhere to the protocol schedule	
Interventions	Novel spectacle lens type I (n = 50): a rotationally symmetrical design, featured a clear central aperture of 20 mm diameter, a maximum spherical equivalent of +1.0 D relative peripheral power achieved 25 mm from its axis Novel spectacle lens type II (n = 60): a rotationally symmetrical design, featured a clear central aperture of 14 mm diameter, a maximum spherical equivalent of +2.00 D relative peripheral power achieved 25mm from its axis Novel spectacle lens type III (n = 50): an asymmetric design, a clear central aperture extended approximately 10 mm either side of center along the horizontal meridian and a similar distance inferiorly, a positive additional peripheral power of 1.9 D 25 mm from the axis in that meridian SVLs (n = 50): a conventional, single-vision design Note: lenses were fitted to spectacle frames that ranged in eye-size from 45 mm to 55 mm with depths from 27 mm to 33 mm	
Outcomes	<u>Primary outcome</u> : cycloplegic autorefraction assessed with an open-field autorefractor <u>Secondary outcomes</u> : axial length Measurements taken at baseline, 6 months and 12 months Unit of analysis: the average of both eyes	
Notes	Study dates: recruitment October 2007 to January 2009 Funding source: Australian Federal Government; Institute for Eye Research, Sydney, Australia; Vision CRC, Australia Lenses were provided by industry	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	"Subjects were randomized to a single treatment using the method of randomly permuted blocks of a constant size of 20" The website randomization.com was used
Allocation concealment (selection bias)	Low risk	Central allocation by web-based randomization was performed: "The four designs (3 novel and one standard) were coded A, B, C, and D and the randomization scheme generated using the website randomization.com ( <a href="http://www.randomization.com">http://www.randomization.com</a> )."
Masking of participants (performance bias)	Unclear risk	Although masking was reported for the participants, the study authors noted that the novel lenses were substantially different from SVLs. For this reason, 10 additional participants were enrolled for group allocated to lens type II
Masking of outcome assessors (detection bias) Primary outcome	Low risk	"Access to the study randomization table was restricted to the study optical dispenser who allocated the randomization and coordinated with the laboratory for the delivery of the spectacles. The dispenser was masked to the lens design. Also, the participants and investigators were masked to the spectacle lenses used in the study"
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	"Access to the study randomization table was restricted to the study optical dispenser who allocated the randomization and coordinated with the laboratory for the delivery of the spectacles. The dispenser was masked to the lens design. Also, the participants and investigators were masked to the spectacle lenses used in the study"

Masking of data analyzers	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	Two children who were randomized were excluded from the analyses, and 7 (3.3 %) were lost to follow-up at 12 months (two in type I, one each in type II and control and three in type III). One child in type II withdrew due to adverse event, and one in type III lenses withdrew consent. They were not included in the analysis, and there was no re-inclusion
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	Unclear risk	Study originally was planned for two years, but stopped early at one year Lenses being investigated were provided by industry

## Schwartz 1981

Methods	Study design: randomized twin study Study center: 1 Number randomized: 52 children (26 twin pairs) Study follow-up: 3 years (planned), extended 6 months Exclusions and losses to follow-up: 2 (4%) children (1 twin pair) who were randomized were excluded from the study; none were lost to follow-up	
Participants	Age: mean = 11.2 years (range 7 to 14 years) Gender: 26 boys (13 twin pairs) and 24 girls (12 twin pairs) completed the study Culture: pairs of monozygotic (MZ) twins identified from the Twin Registry of Eye Examinations from the Washington, D.C. area; all were Caucasian Inclusion criteria: 1) MZ twins with bilateral myopia; 2) ages 7 to 13 years; 3) shared domicile in local area; 4) good general health; 5) vision correctable to 20/20 or better; 6) third degree fusion; 7) no other significant abnormality Exclusion criteria: 1) astigmatism or anisometropia greater than 1.00 D; 2) difference in refraction between co-twins of 1.50 D or more in the more advanced eye	
Interventions	Treatment group (n = 26): combined treatment of bifocal spectacles with 1.25 D addition and two drops of 1% tropicamide ophthalmic solution instilled to each eye nightly Control group (n = 26): standard spectacle correction (SVLs) Note: full cycloplegic correction in the treatment group was sometimes reduced up to 0.50 D when it did not impair vision below 20/20	
Outcomes	<u>Primary outcome</u> : change in refractive error (spherical equivalent) (cycloplegic refraction) <u>Secondary outcome</u> : compliance to treatment regimen (child and parent interviews) Measurements taken at baseline and every 6 months for 3 years Unit of analysis: the average values of both eyes	
Notes	Materials: 1% tropicamide (Mydracyl) ophthalmic solution supplied by Alcon Laboratories Inc	

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The assignment of special treatment or control status to members of each twinship was based on a strict randomization protocol"
Allocation concealment (selection bias)	Low risk	"Treatment or control status was randomly assigned only after the twin pair and the parents expressed willingness to accept the rigorous requirements and the desire to participate"
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to visual and functional differences between the interventions studied
Masking of outcome assessors (detection bias) Primary outcome	Low risk	"All refractions were performed by the author, who was unaware of the treatment or control status of examinees"

Masking of outcome assessors (detection bias) Secondary outcomes	Unclear risk	N/A (study did not measure secondary outcomes of this review)
Masking of data analyzers	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	Of 26 twin pairs enrolled, 25 pairs completed the study and one pair was excluded due to non-compliance after one year
Selective reporting (reporting bias)	Low risk	Outcomes chosen a priori and presented in methods and design paper
Other bias	Unclear risk	Unclear who reviewed the participants' activities when they came in for follow-up and how the examiner remained masked at follow-up visits

## Shih 1999

Methods	Study design: RCT Study center: 1 (National Taiwan University Hospital) Number randomized: 200 children Study follow-up: 2 years Exclusions and losses to follow-up: 14 (7%) children who were randomized were excluded from the study; none were lost to follow-up	
Participants	Age: mean = 9.2 years (range 6 to 13 years) Gender: included boys and girls Culture: children recruited from the vision care center at National Taiwan University Hospital Inclusion criteria: 1) age 6 to 13 years old; 2) myopia with refractive error between -0.50 D and -6.75 D Exclusion criteria: 1) amblyopia or tropia; 2) astigmatism -2.00 D or greater; and 3) anisometropia -2.00 D or greater	
Interventions	Atropine 0.5% (n = 50): one drop of 0.5% atropine nightly; advised to wear bifocal spectacles Atropine 0.25% (n = 50): one drop of 0.25% atropine nightly; advised to wear slightly undercorrected spectacles Atropine 0.1% (n = 50): one drop of 0.1% atropine nightly; advised to wear fully corrective spectacles Control (n = 50): one drop of 0.5% tropicamide nightly Note: all children were advised to wear sunglasses with UV protection in bright light	
Outcomes	<u>Primary outcome</u> : change in refractive error measured by cycloplegic autorefraction (spherical equivalent) Measurements taken at baseline and every 3 months for 2 years Unit of analysis: the average values of both eyes	
Notes	Study dates: 1994 Funding source: Department of Health grant (Taiwan) Additional data: study author provided unpublished data via email correspondence	

*Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization: each participant was categorized into one of the strata and then randomized to receive one of the four treatments. A block size of 12 was used to balance the number of patients in the four treatment categories for each stratum (via email communication with study author)
Allocation concealment (selection bias)	Low risk	Group assignments were unknown to study personnel when participants were being enrolled by using coded bottles with sealed envelopes (via email communication with study author)
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to visual and functional differences between the interventions studied
Masking of outcome assessors (detection bias) Primary outcome	Low risk	For all study personnel, physicians, examiner and data analysts were all masked to treatment assignment (via email communication with study author)

Masking of outcome assessors (detection bias) Secondary outcomes	Unclear risk	N/A (study did not measure secondary outcomes of this review)
Masking of data analyzers	Low risk	For all study personnel, physicians, examiner and data analysts were all masked to treatment assignment (via email communication with study author)
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	There were 14 (7%) children excluded from the study: 9 from the 0.5% atropine group (4 had no patience for eye drops, 2 for photophobia, 2 from fear of drops, 1 for allergic blepharitis); 3 from the 0.25% atropine group (no patience for eye drops); 1 from the 0.1% atropine group (no patience for eye drops); and 1 from the 0.5% tropicamide group (no patience for eye drops)
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	High risk	Children were advised to wear differing types of spectacle lenses depending on the concentration of atropine received

Tan 2005

Methods	Study design: RCT Study centers: 7 (academic centers and clinical practices in Singapore, Hong Kong, and Thailand) Number randomized: 353 children Study follow-up: 1 year Exclusions and losses to follow-up: 55 (16%) children who were randomized were dropped from the analyses	
Participants	Age: mean = 8.7 years (range 6 to 13 years) Gender: 177 boys, 176 girls Culture: 99.4% Asian Inclusion criteria: 1) age 6 to 12 years old; 2) myopia of $-0.75$ D and $-4.00$ D; 3) good general health; 4) round pupils; 5) refractive to light; and 6) best corrected VA of 20/25 or better in each eye Exclusion criteria: 1) astigmatism greater than 1.00 D; 2) anisometropia greater than 1.00 D; 3) strabismus; 4) current use of either contact lenses or bifocals; 5) history of ocular surgery, trauma, or chronic ocular disease, including allergic conjunctivitis; 6) previous use of atropine for myopia; 7) diseases requiring long-term or regular intermittent medication; 8) behavioral or neurological disorders that would interfere with the study; 9) participation in any study that involved an investigational drug within one month of enrolment; 10) intolerance or hypersensitivity to topical anesthetics, mydriatics, or components of the formulations; 11) contraindications to antimuscarinic agents; 12) and pregnancy or planned pregnancy	
Interventions	Gel/gel (n = 142): 2% pirenzepine ophthalmic gel applied twice a day Placebo/gel (n = 140): 2% pirenzepine ophthalmic gel applied once a day and placebo gel applied once a day Placebo/placebo (n = 71): vehicle-placebo gel applied twice a day	
Outcomes	<b>Primary outcome:</b> change in refractive error measured by cycloplegic autorefraction (spherical equivalent) <b>Secondary outcome:</b> change in axial length measured by A-scan ultrasonography Measurements taken at baseline and every 3 months for 1 year Unit of analysis: the average of both eyes	
Notes	Study dates: November 2000 to July 2002 Funding source: Valley Forge Pharmaceuticals, Inc. and Novartis Ophthalmics AG	

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible patients were randomized using a sponsor-prepared, computer-generated list stratified by site. Randomisation was in a 2:2:1 ratio of pirenzepine twice daily, pirenzepine once daily, and placebo
Allocation concealment (selection bias)	Low risk	Study sites used coded lists to determine which tubes of medication to administer to the next enrolled participant. The pirenzepine gels and placebo gels were packaged in identical tubes for morning and night applications and the gels themselves appeared identical. All morning tubes had yellow labels and all evening tubes had blue labels. Thus study personnel had no way of knowing which tubes had which medications, same for patients
Masking of participants	Low risk	Study was placebo-controlled and identical appearing bottles with coded labels were distributed

(performance bias)		
Masking of outcome assessors (detection bias) Primary outcome	Low risk	Since the pirenzepine gels and placebo gels were packaged in identical tubes and the gels themselves appeared identical, the study personnel had no way of knowing which tubes had which medications. The study reported that "no treatment code was unmasked for any subject during the study"
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	Data analyzers were not masked (personal communication with biostatistician)
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	There were 55 (16%) children who were dropped from the study after randomization: 25 (18%) were gel/gel, 21 (15%) were placebo/gel, and 9 (13%) were placebo/placebo (this difference was not statistically different). Of these 55 patients, 31 discontinued the study because of adverse events (20 gel/gel and 11 placebo/gel, none in placebo); 5 were not adherent to study medication regimen; and 1 was dropped for inadequate efficacy (progression of myopia) "We considered statistical methods to impute missing values due to patients who discontinued treatment. However, as the proportion of patients not completing the study was similar across treatment groups, any correction would apply similarly to all groups, and thus we did not conduct these analyses"
Selective reporting (reporting bias)	Low risk	The primary and secondary outcomes were chosen a priori
Other bias	Unclear risk	Some study authors were employed by the pharmaceutical company funding the study

Yang 2009

Methods	Study design: RCT Study center: 1 (Guangzhou city, China) Number randomized: 178 children Study follow-up: 2 years Exclusions and losses to follow-up: no exclusions; 29 (16%) were lost to follow-up
Participants	Age: range 7 to 13 years Gender: 94 boys, 84 girls Culture: urban children from Guangzhou city, China Inclusion criteria: 1) age 7 to 13 years old; 2) myopia with spherical equivalent refractive error between -0.50 D and -3.00 D in both eyes, as measured under cycloplegia; 3) astigmatism < 1.50 D; 4) no anisometropia (difference in spherical equivalent < 1.00 D between eyes); 5) best corrected VA of 6/6 or better; 6) no strabismus; 7) normal IOP; 8) willingness to wear glasses constantly for study duration; 9) and understanding of random assignment and willingness to not use other medications Exclusion criteria: 1) any ocular or systemic conditions known to influence refractive development; 2) use of medications that might affect refractive development; 3) moderately or highly myopic (< -3.00 D) parents; 4) birthweight < 1250 g; and 5) previous use of bifocals, PALs or contact lenses
Interventions	PAL group (n = 89): multifocal lenses with +1.50 D near addition worn constantly SVL group (n = 89): single vision lenses worn constantly Note: prescription changes were made if the subjective refraction had changed by at least 0.50 D for one or both eyes or if clinically indicated
Outcomes	<u>Primary outcome</u> : progression of myopia Change in spherical equivalent refractive error relative to baseline measured by cycloplegic autorefractometry with 0.5% tropicamide + 0.5% phenylephrine hydrochloride <u>Secondary outcomes</u> : <ol style="list-style-type: none"><li>1 Change in vitreous chamber depth by A-scan ultrasonography</li><li>2 Distance (5 m) and near (33 cm) horizontal heterophoria by cover test</li><li>3 Accommodative response by open-field autorefractor</li><li>4 Near workload, compliance and adherence assessed by questionnaire</li></ol> Measurements taken at baseline and every 6 months for two years

	Unit of analysis: not reported
Notes	Study dates: enrolment was from July 2004 to March 2005 Funding source: National Natural Science Grant, China Materials: lenses provided by Sola (China) Ltd Compliance in wearing glasses was monitored with separate questionnaires for children and parents (87% overall compliance)

<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	"Enrolled subjects were assigned randomly to either the SV group or PAL group"
Allocation concealment (selection bias)	Unclear risk	No details given
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to functional differences between the interventions studied
Masking of outcome assessors (detection bias) Primary outcome	Low risk	Masked investigators were unaware of allocation groups during evaluations; although an unmasked investigator was available if clinical consultations were needed
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	"All statistical analysis was carried out independently"
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Unclear risk	29 (16%) patients dropped out of the study: 15 in the PAL group and 14 in the SVL group. Statistical analyses comparing the retained participants to those lost to follow-up showed that drop outs had significantly worse myopia than those who remained in the study at baseline ( $P = 0.01$ )
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	Unclear risk	Unit of analysis (i.e. average value of both eyes or right eye only) was not reported

Yen 1989	
Methods	Study design: RCT Study center: 1 (Refraction Clinic, Veterans General Hospital, Taipei, Taiwan) Number randomized: 247 children Study follow-up: 1 year Exclusions and losses to follow-up: 151 (61%) children were excluded or lost to follow-up
Participants	Age: mean = 9 years (range 6 to 14 years) Gender: 118 boys, 129 girls Culture: children with simple myopia randomly selected from clinic records Inclusion criteria: 1) age 6 to 14 years old; and 2) myopia with refractive error between -0.5 D and -4.0 D Exclusion criteria: 1) amblyopia or tropia; and 2) cylinder refraction greater than 1.0 D
Interventions	Atropine: 1% atropine drops every other night; bifocal spectacles prescribed 2 weeks after treatment began Cyclopentolate: 1% cyclopentolate drops every night; single vision spectacles prescribed if necessary Saline control: normal saline eye drops every night; single vision spectacles prescribed if necessary

Outcomes	<p><b>Primary outcome:</b> change in refractive error measured by cycloplegic refraction (spherical equivalent)</p> <p><b>Secondary outcomes:</b> changes in vision, funduscopy, and IOP</p> <p>Measurements taken at baseline and every 3 months for 1 year</p> <p>Note: baseline for atropine group was measured 2 weeks after treatment began</p> <p>Unit of analysis: right eyes only</p>
Notes	<p>Study dates: enrolment from July 1, 1985 to October 31, 1986</p> <p>Additional data: study author provided unpublished data via email correspondence</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The ophthalmic examinations were done by 3 doctors. Each doctor got a random table. The patients were assigned to three groups according to the sequence on the random table (via email communication with study author)
Allocation concealment (selection bias)	Unclear risk	Allocation was done using a random numbers table, but it was not clear whether or not the allocation sequence was concealed
Masking of participants (performance bias)	High risk	Masking of participants was not reported for the pharmaceutical agents; however, one group received bifocal spectacles rather than single vision spectacles which therefore was not masked
Masking of outcome assessors (detection bias) Primary outcome	Unclear risk	No details given
Masking of outcome assessors (detection bias) Secondary outcomes	Unclear risk	"To avoid deviation during retinoscopy all examinations were done by three doctors"
Masking of data analyzers	Unclear risk	No details given
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	"Patients who used the eye drops continuously for one year received another complete ophthalmologic examination...96 such patients were collected for evaluation, 32 in each group". Patients who discontinued using the eye drops or did not use them consistently were excluded from the study. Of the 247 children randomized in the study 151 (61%) were not included in the analyses. The 96 patients analyzed included the first subset of children who followed the treatment protocol and were examined at one year (via email communication with study author)
Selective reporting (reporting bias)	High risk	Not all outcomes described in the methods section were reported (changes in vision, funduscopy and IOP)
Other bias	High risk	"For statistical significance, each group should include at least 30 samples. Our aim was to evaluate the results after using the medication for 1 year. So, when we felt we had enough numbers of patients who had continuously used the eye drops for 1 year, we decided to analyze the data. It happened to be 32 in each group" (via email communication with study author)

AC/A: accommodative convergence (in prism diopters) to the stimulus/accommodation ratio

BSCL: bifocal soft contact lens

cm: centimeters

D: diopters

DC: diopter cylinder

IOP: intraocular pressure

logMAR: logarithm of the Minimum Angle of Resolution

mmHg: millimeters of Mercury

N/A: not applicable

PAL: progressive addition lens

RCT: randomized controlled trial  
RGPCl: rigid gas permeable contact lens  
SCL: soft contact lens  
SVL: single vision lens  
SVSCL: single vision soft contact lens  
VA: visual acuity



## Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abraham 1966	Not randomized: case report
ACHIEVE study	Not intended to control progression of myopia: glasses vs. contacts for self-esteem in school children
Aller 2008	Interventional twin case series: included only one pair of twins, one randomized to wear bifocal SCLs and the other to wear SVSCLs for one year Both wore BSCLs for the second year
Andreo 1990	Not randomized; not intended to control progression of myopia; participants older than 18 included
Baldwin 1969	Not randomized: patients selected treatment assignment
Baltimore myopia project	Not intervention of interest: vision training for myopia
Baronet 1979	Not randomized: retrospective review of patients treated with atropine at a medical practice with no comparison group
Bedrossian 1979	Not randomized: method of allocation is not specified. Cross-over study of atropine in one eye for one year, with the fellow eye serving as the control, then alternated treatment group after each year for four years
Berkeley OK Study	Not population of interest: participants were 21 to 28 years old
Bier 1988	Not randomized: sequential assignment to groups
Brodstein 1984	Not randomized: "The lack of randomization permits a possibility for bias"
Chou 1997	Not randomized: allocation by parental decision
Dumbleton 1999	Not an intervention pre-specified in protocol: lenses with different oxygen permeability
Dyer 1979	Not randomized: case-control study
Ebri 2007	Not intended to control progression of myopia: cycloplegic effect and pupillary dilation outcomes, as well as cost-effectiveness; follow-up was 3 days
Filip 2000	Not population of interest: myopia progression in adult myopes
Gimbel 1973	Not randomized: patients compared to historical cohort
Goss 1984	Not randomized: treatment group included patients with overcorrection; controls included random patients selected retrospectively
Grosvenor 1991	Not randomized: historical control group
Horner 1999	Not intended to control progression of myopia: compared soft spherical contact lenses to spectacles; SCLs are not expected to slow myopia progression. In fact, the study was conducted because they believed the SCLs may increase myopia progression
Hosaka 1982	Not randomized: interventional case series of children aged 6 to 14 years treated with labetalol ophthalmic solution
Hosaka 1988	Not randomized: interventional case series
Huffman 2002	Not intended to control progression of myopia: aspheric vs. spheric lenses; outcome was to decrease spherical aberration; included adults
Kao 1988	Not randomized: children were enrolled in two separate series of patients
Keller 1996	Not randomized: all children wore RGPCLs
Kennedy 1995	Not randomized: treatment was atropine; controls were patients matched using medical records
Khoo 1999	Allocation method not clear, randomization not specified; compared RGPs to spectacles over 3 years
Lakkis 2006	Not intended to control progression of myopia: two-week randomized cross-over trial to evaluate visual performance and satisfaction of clear and photochromic spectacle lenses in children aged 10 to 15 years wearing fully corrected spectacles
Leung 1999	Not randomized: quasi-randomized (odd & even case numbers to determine the two groups)
Li 2005	Not randomized: experimental group received progressive multifocal lenses, control group wore common glasses; participants were 6 to 23 years old
Liang 2008	Not intervention of interest: RCT comparing atropine eyedrops alone with a combined treatment of atropine and stimulation of the auricular acupoints in school-aged children with myopia

Study	Reason for exclusion
Lu 2010	Not randomized: case-control study comparing myopic children treated with seasonal doses of atropine with non-myopic children
Mandell 1959	Not randomized: historical cohort, included adults
Meythaler 1971	Not randomized: interventional cases series (70 eyes from 8–35 years of age persons were checked); 3 groups based on age, youngest group was 8 to 19 years old
Neetens 1985	Not randomized: control group consisted of participants that could not use bifocals
Nesterov 1990	Not randomized: compared a group using cycloplegics and ocular hypotensives to a reference group for progression of myopia
Oakley 1975	Not randomized: control group consisted of children (or parents) who refused bifocals
Parker 1958	Not randomized: compared author's practice to other practices
Perrigin 1990	Not randomized: treatment was silicone lenses; control was a historical cohort
Pirenzepine 2003	Not randomized: review of Pirenzepine studies and mechanism of action
Pritchard 1999	Not intended to control progression of myopia: extended wear for low Dk vs. high Dk lenses in adults
Rah 2002	Not randomized; overnight orthokeratology in adults (LOOK study)
Rainey 2000	Not an intervention pre-specified in protocol: vision therapy vs. control
Ritchey 2005	Not population of interest: included adults aged 18 and older (COLM study)
Sankaridurg 2003	Not intended to control progression of myopia: RCT to compare adverse events for SCLs vs. SVLs (spectacles); participants were 16 to 35 years old
Savoliuk 1968	Not randomized: compared groups using SVLs continuously or for distance-use only with no spectacles
Shimmyo 2003	Allocation method not clear, randomization not specified: Atropine vs. control for 2 years
Soni 2006	Not randomized; included adults
Stone 1976	Not intended to control progression of myopia: authors state that "the research team is not purposely attempting to flatten the cornea in order to arrest the myopia"
Sun 2007	Not randomized: case-control study of spectacle users vs. controls
Syniuta 2001	Not randomized: intervention group included patients whose parents requested treatment for myopic progression, control group comprised the next myopic child by alphabetical order after study child's record number
Takano 1964	Not randomized: cohort study comparing treatment with Mydrine (tropicamide + phenylephrine) eye drops with or without Neosynesis (phenylephrine) eye drops, included boys and girls with myopia ages 7 to 19 years, follow-up was 20 days
Toki 1960	Not randomized: cohort study of patients receiving 5% Neosynesis (phenylephrine) eye drops, included boys and girls with myopia ages 7 to 21 years, follow-up was 14 to 28 days
Tokoro 1964	Not randomized: non-randomized study of treatment with Mydrine (tropicamide + phenylephrine) eye drops + 5% Neosynesis (phenylephrine) eye drops + low frequency electro stimulus in children ages 7 to 15 years, included children with hyperopia
Tokoro 1965	Not randomized: retrospective cohort comparing full correction spectacles to under correction (< -1 D) spectacles or full correction in case of need in children ages 7 to 14 years, included children with hyperopia
Xiao 2009	Not randomized: observational study of two groups of children who wore RGPCLs or spectacles
Yamada 2004	Not randomized: review article with some cohort data on children with high myopia
Yamaji 1967	Not randomized: observation of children treated with Mydrine-M; no control group
Yi 2011	Not an intervention pre-specified in protocol: RCT of children, intervention was less than 30 hours of near- and middle-vision activities per week and more than 14 hours of outdoor activities per week compared with controls
Young 1992	Not intended to control progression of myopia: comparison of overnight lenses for 12 months in adults only
Zeng 2009	Not intended to control progression of myopia: RCT to evaluate visual performance and satisfaction of ready-made spectacles with custom spectacles in Chinese school-aged children with uncorrected refractive error

BSCL: Bifocal soft contact lens

COLM: Comparison of Overnight Lens Modalities

Dk: oxygen permeability

LOOK: Lenses and Overnight Orthokeratology

SCL: soft contact lens

SVL: single vision lens

RCT: randomized controlled trial

RGPCl: rigid gas permeable contact lens

## Characteristics of studies awaiting assessment [ordered by study ID]

Anstice 2011	
Methods	<p>Study name: Effect of Dual-Focus Soft Contact Lens Wear on Axial Myopia Progression in Children</p> <p>Study design: paired-eye RCT with cross-over</p> <p>Study center: 1</p> <p>Number randomized: 40 children</p> <p>Study follow-up: 20 months (10 months for each period)</p> <p>Exclusions and loss to follow-up: no exclusions; 5 (12.5%) and 6 (15.0%) were lost to follow-up in 10-month and 20-month visit, respectively</p>
Participants	<p>Country: New Zealand</p> <p>Age: mean 13.4 ± 0.85 years</p> <p>Gender: 11 boys, 29 girls</p> <p>Inclusion criteria: 1) 11 to 14 years old at recruitment; 2) spherical equivalent between -1.25 and -4.50 D in the least myopic eye as determined by non-cycloplegic subjective refraction; 3) myopia progression 0.50 D in the previous 12 months, established from previous records or estimated from the current spectacle prescription; 4) best corrected spectacle visual acuity of Snellen 6/6 or better in each eye; 5) prepared to wear contact lenses for at least 8 hours per day during the study</p> <p>Exclusion criteria: history of 1) astigmatism 1.25 D; 2) anisometropia 1.00 D; 3) strabismus at distance or near as assessed by cover test; 4) ocular or systemic pathology likely to affect refractive development or successful contact lens wear; 5) a birth weight of 1250 g</p>
Interventions	<p>Group 1 (n=21): 10 months wearing Dual-Focus (DF) lens in the dominant eye and single vision distance (SVD) lens in the contralateral eye, followed by 10 months wearing of the swapped lens assignment</p> <p>Group 2 (n= 19): 10 months wearing DF lens in the non-dominant eye and SVD lens in the contralateral eye, followed by 10 months wearing of the swapped lens assignment</p>
Outcomes	<p><u>Primary outcomes</u>: change in spherical equivalent refraction measured by cycloplegic autorefraction</p> <p><u>Secondary outcomes</u>: change in axial eye length measured by partial coherence interferometry Measurements taken at baseline and every 5 months for 20 months</p> <p><u>Unit of analysis</u>: the eye</p>
Notes	<p>Study dates: not reported</p> <p>Publication language: English</p> <p>Purpose of this study was to test the efficacy of an experimental Dual-Focus soft contact lens in reducing myopia progression</p>
ATOM 2	
Methods	<p>Study name: Atropine for the treatment of childhood myopia 2</p> <p>Study design: Phase I was an RCT; Phase II was an open-label study</p> <p>Study center: 1</p> <p>Number randomized: 400 children</p> <p>Study follow-up: 24 months for Phase I</p> <p>Exclusions and loss to follow-up: one participant in the 0.5% excluded due to missing second year visit; 21 (13%), 14 (9%) and 9 (11%) were lost to follow-up in the 0.5%, 0.1% and 0.01% groups respectively</p>
Participants	<p>Age: mean = 9 years (range 6 to 12 years)</p> <p>Gender: 211 boys, 189 girls</p> <p>Culture: ethnic Chinese origin</p> <p>Inclusion criteria: 1) age 6 to 12 years old; 2) refractive error of spherical equivalent -2.00 D or worse in each eye; 3) astigmatism of less than 1.50 D; 4) documented myopia progression of at least spherical equivalent -0.50 D over the last 12 months as determined or suggested by refractive records or change in lens power</p> <p>Exclusion criteria: 1) ocular pathology (e.g., amblyopia or strabismus); 2) previous use of atropine or pirenzepine; 3) allergy to atropine; 4) systemic ill health (e.g., cardiac or respiratory illness)</p>
Interventions	<p>Three concentrations of atropine eye drops to be applied once nightly in both eyes:</p> <ol style="list-style-type: none"> <li>1. 0.5% atropine (n=161);</li> <li>2. 0.1% atropine (n=155); or</li> <li>3. 0.01 % atropine (n=84)</li> </ol>
Outcomes	<p><u>Primary outcome</u>: myopia progression at two years (spherical equivalent refraction determined by cycloplegic autorefraction)</p> <p><u>Secondary outcomes</u>:</p> <ol style="list-style-type: none"> <li>1 Myopia progression at one year</li> <li>2 Change in axial length at one and two years</li> <li>3 Side effect parameters, such as changes in accommodation amplitude, mesopic and photopic pupil size, and distance and near BCVA</li> <li>4 Visual symptoms such as allergy, blurred near vision, glare, or visual loss, and if children had been ill or hospitalized since last visit</li> </ol> <p>Adverse events documented</p>

	Measurements taken at baseline, two weeks, and 4, 8, 12, 16, 20 and 24 months Note: baseline for myopia progression and axial length was measured 2 weeks after treatment began Unit of analysis: the individual (data for both eyes pooled for each person)
Notes	Study dates: not reported Funding source: National Medical Research Council and SingHealth (Singapore) Additional data: information assessed from Clinicaltrials.gov website on 10 April 2009 Purpose of this study was to find an optimal dose of atropine for preventing the rapid progression of myopia in children by comparing the efficacy, safety and functional impact of binocular treatment with 0.5%, 0.1% and 0.01% atropine and to develop a treatment regimen for the routine management of childhood myopia
COMET 2	
Methods	Study name: Progressive-Addition Lenses versus Single-Vision Lenses for Slowing Progression of Myopia in Children with High Accommodative Lag and Near Esophoria (also called the COMET 2 study) Study design: RCT Study centers: 8, including 7 optometry colleges and schools and 1 community-based ophthalmology practice Number randomized: 118 children Study follow-up: 3 years Exclusions and loss to follow-up: no exclusions; 8 (7%) were lost to follow-up
Participants	Country: USA Age: mean 10.1 ± 1.1 years Gender: 54 boys, 64 girls
	Inclusion criteria: 1) 8 to <12 years of age; 2) refractive error determined by cycloplegic autorefraction which meets all of the following: spherical equivalent -0.50 to -3.00 D in both eyes; astigmatism < 1.5 D in both eyes; anisometropia < 1.00 D difference between eyes in spherical equivalent; 3) visual acuity at least 20/20 with best subjective refraction in both eyes; 4) accommodative response at near (33 cm) is less than 2.0 D by non-cycloplegic autorefraction; 5) near esophoria (< 2.0 PD) present by alternate prism and cover test (APCT) at near using best refractive correction determined from non-cycloplegic subjective refraction
	Exclusion criteria: 1) history of strabismus; 2) current or prior use of PALs, bifocals, or contact lenses in either eye (prior or current use of SVLs was permitted)
Interventions	PAL group (n=59): Varilux Ellipse progressive addition lenses with a +2.00 D near addition; worn during all waking hours for three years
	SVL group (n=59): standard single vision lenses (spectacles); worn during all waking hours for three years Notes: the distance correction was changed if the endpoint of the noncycloplegic subjective refraction differed from the current prescription by 0.50 D or more in spherical equivalent. Prescription changes could be made for smaller differences at investigator discretion if the new prescription improved the subject's visual acuity by at least one line over that in their current correction
Outcomes	<u>Primary outcomes</u> : change in spherical equivalent refractive error in diopters from baseline to the three year visit measured by cycloplegic autorefraction <u>Secondary outcomes</u> : main axis astigmatism ( $J_0$ , dioptric power of a Jackson cross cylinder with axis at 0°) and oblique astigmatism ( $J_{45}$ , dioptric power of a Jackson cross cylinder with axis at 45°) by using the power vector approach Measurements taken at baseline and every six months for three years <u>Unit of analysis</u> : child-based (the median for each eye was averaged to obtain the spherical equivalent used for analysis)
Notes	Study dates: enrollment from April 2005 to March 2007 Publication language: English Purpose of this study was to determine whether progressive-addition lenses (PALs) relative to single-vision lenses (SVLs) slowed the progression of low myopia in children with high accommodative lag and near esophoria Study information also assessed from Clinicaltrials.gov website on 1 November 2011

BCVA: best corrected visual acuity

D: diopters

g: grams

PAL: progressive addition lens (spectacles)

RCT: randomized controlled trial

SVL: soft vision lens (spectacles)

## Characteristics of ongoing studies [ordered by study ID]

Berntsen 2011	
Trial name or title	Study of theories about myopia progression (STAMP)
Methods	Study design: randomized clinical trial Study center: 1 (The Ohio State University College of Optometry) Number randomized: 85 children Study follow-up: 24 months
Participants	Age: mean = 9.8 years (range 6 to 11 years) Gender: 41 boys, 44 girls Culture: Ohio, USA: 20% Black, 68% White, 7% Asian and 5% other Inclusion criteria: 1) 6 to 11 years of age; 2) 1.30 D accommodative lag (4 D stimulus) without correction for lens effectivity; 3) esophoria at near if more than -2.25 D spherical equivalent; 4) at least -0.75 D myopia in each meridian measured with cycloplegic autorefraction but not more than -4.50 D in each meridian in each eye; 5) astigmatism 2.00 DC in each eye; 6) anisometropia 2.00 D; 7) best-corrected VA of at least 20/32 logMAR equivalent; 8) birth weight 1250 g by parental report Exclusion criteria: 1) strabismus; 2) history of contact lens wear; 3) history of previous bifocal wear; and 4) diabetes mellitus
Interventions	PALs (n = 42): PALs with a + 2.00 D addition SVLs (n = 43) Note: children were randomly assigned to wear either PALs or SVLs for the first year of the study, and all children wore SVLs for the second year of the study
Outcomes	<u>Primary outcome:</u> Central spherical equivalent refractive error <u>Secondary outcomes:</u> <ol style="list-style-type: none"> <li>1 axial length</li> <li>2 peripheral ocular shape</li> <li>3 central and peripheral aberrations</li> <li>4 accommodative lag</li> <li>5 AC/A ratio</li> <li>6 corneal shape and thickness</li> <li>7 anterior chamber depth</li> <li>8 crystalline lens thickness and curvatures</li> <li>9 phoria</li> <li>10 intraocular pressure</li> </ol> Measurements taken at baseline and 6-month intervals for two years Unit of analysis: not specifically reported
Starting date	Study dates: enrolment December 2006 to May 2008
Contact information	David A. Berntsen, OD, PhD, FAAO University of Houston College of Optometry 505J Davis Armistead Bldg Houston, TX 77204-2020 e-mail: dberntsen@optometry.uh.edu
Notes	Design and baseline data were published Funding source: The Ohio State University and National Eye Institute

AC/A: accommodative convergence (in prism diopters) to the stimulus/accommodation ratio

D: diopters

DC: diopter cylinder

g: grams

logMAR: logarithm of the Minimum Angle of Resolution

PAL: progressive addition lens (spectacles)

SVL: soft vision lens (spectacles)

VA: visual acuity