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ORIGINAL ARTICLE

# Atropine Slows Myopia Progression More in Asian than White Children by Meta-analysis

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## ABSTRACT

***Purpose.*** To conduct a meta-analysis on the effects of atropine in slowing myopia progression and to compare Asian and white children and randomized controlled trials (RCTs) and observational studies.

***Methods.*** Randomized controlled trials and observational studies that assessed the effects of all concentrations of atropine in slowing myopia progression in children were searched from MEDLINE, EMBASE, and the Cochrane Library up to April 2013. Jadad scoring was used to evaluate the quality of RCTs, and the Newcastle-Ottawa Scale was used for observational studies.

***Results.*** Four RCTs and seven cohort studies (a kind of observational study) with 1815 children aged 5 to 15 years were included. The children had a baseline refraction of −0.50 to −9.75 diopters (D) and were followed up for 22.0 months (range, 12.0 to 36.5 months). The weighted mean differences in myopia progression in RCTs and cohort studies of Asian children were 0.55 D per year ($p < 0.01$) and 0.54 D per year ($p < 0.001$), respectively, and 0.35 D per year ($p = 0.01$) in cohort studies of white children. Compared with placebo, the risk of fast myopia progression (>1.0 D per year) using atropine was significantly decreased in both RCTs (odds ratio [OR], 0.14; $p < 0.01$) and cohort studies (OR, 0.08; $p < 0.01$), and the benefit of slow myopia progression (<0.50 D per year) using atropine was significantly increased in both RCTs (OR, 6.73; $p < 0.01$) and cohort studies (OR, 22.10; $p < 0.01$).

***Conclusions.*** Atropine could significantly slow myopia progression in children, with greater effects in Asian than in white children. Randomized controlled trials and cohort studies provided comparable effects.
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Key Words: myopia, myopia progression, atropine, meta-analysis, RCTs, cohort studies

During the past two decades, myopia has risen to epidemic levels worldwide.[1] In the United States and Europe, the prevalence of myopia is greater than 25% among adults,[2] whereas in some Asian areas, the prevalence is 80% or higher.[3–6] Myopia has become a global health issue leading to visual impairment.[7] In some epidemiological studies conducted in Asian areas,[8–11] retinopathy caused by high myopia has become the second most frequent cause of low vision and blindness among adults. In children, the prevalence of myopia is still increasing and the proportion of high myopia, possibly pathological myopia, also seems to be rising in Asia[3–6] as well as in other parts of the world.[12] Therefore, slowing or even stopping the progression of myopia in the population of school-aged children is of great social concern.

Numerous studies[13–22] have demonstrated that atropine is effective in slowing myopia progression in children, although its side effects such as photophobia, blurred near vision, and systematic adverse effects are still sources of concern.[23,24] In one study with 0.1 and 0.5% atropine, 0.01% atropine produced comparable efficacy in controlling myopia progression and minimal side effects.[20] Compared with placebo, the effects of mixed concentrations of atropine on slowing myopia progression in children varied between studies, with a mean difference of about 0.80 diopters (D), as shown in recent reviews.[25,26] However, these reviews did not evaluate the effects of confounding factors such as variable dose of atropine, duration of follow-up, and ethnicity, and thus their conclusions might be biased. For example, Walline et al.[25] pooled the results of two studies at 1 year[19] and 18 months,[21] respectively. They included the results of the latter study with subtracting the regular single-vision lenses group from atropine

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with the multifocal lenses group and not the multifocal lenses group from atropine with the multifocal lenses group.[21] Song et al.[26] synthesized the data of randomized controlled trials (RCTs)[16,19,21] and of one prospective observational study[13] together and only in Asian children.

However, many well-conducted prospective observational studies on atropine, which have a control group that was not randomized,[13–15,27–29] have not been evaluated yet. Whether there is a difference in the effect of atropine in slowing myopia progression between RCTs and prospective observational studies remains unclear. Systematic review and meta-analysis on the same topic provide an opportunity to test the difference between RCTs and observational studies and to contribute new knowledge on the robustness of atropine in diverse conditions and in more patient-centered outcomes,[30] such as how many children will benefit from using atropine with myopia progression less than 0.50 D and how many children will benefit from using atropine with myopia progression greater than 1.00 D during the treatment period.

In our previous review, multifocal lenses were found to have greater average effect (0.25 D) on slowing myopia progression compared with single-vision lenses in children older than 6 to 36 months,[31] and Asian children with low myopia (0.19 D) seemed to benefit more from multifocal lenses than white children with low myopia (0.09 D) during 24 months because of a higher level of myopia at baseline and more rapid myopia progression. To date, all RCTs of atropine in slowing myopia progression in children were conducted in Asian children.[16,17,19,21] A few observational studies of atropine have been conducted in white children,[29,32] and the effect seemed smaller. However, the difference in the effect of atropine as a function of ethnicity cannot be determined until the difference between RCTs and observational studies has been evaluated or performed with the same study design.

Thus, the aim of this meta-analysis was to evaluate the overall effect of atropine based on RCTs and prospective observational studies in slowing myopia progression in Asian and white children and to determine whether there was a difference in the outcome of RCTs and observational cohort studies. To increase the power of analysis, studies with different concentrations of atropine will be combined if there are fewer studies available.

## METHODS

### Data Sources and Searches

We conducted a search of MEDLINE, EMBASE, and the Cochrane library for English-language RCTs and observational studies on humans up to April 6, 2013. We used the following as key words: myopia, refractive errors, muscarinic antagonists, cholinergic antagonists, mydriatics, atropine, cyclopentolate, tropicamide, Mydrin P, clinical trial, phenylephrine, placebo, and humans, as well as some relevant free terms. Boolean operator "AND," "OR," "NOT" were used to combine all search sets. References within the retrieved studies were searched for additional trials. We also searched in World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov to retrieve ongoing trials. We used a protocol for the present review that was used in our previous study.[31]

### Study Selection

Randomized controlled trials and cohort studies on the relevant topic were selected according to the following criteria: (1) participants were school-aged children (5 to 15 years) with myopia; (2) atropine was used in at least one treatment arm and placebo or nonatropine treatment in another as control; (3) primary outcomes were mean myopia progression per year (D per year), and secondary outcomes were the number of children with fast (>1.0 D per year) or slow (<0.50 D per year) myopia progression from baseline to the end of the intervention period.

### Data Extraction and Quality Assessment

Two reviewers (Shi-Ming Li and Shan-Shan Wu) independently and jointly determined eligibility and extracted information from the studies with Epidata Version 3.02, including author, publication year, country or area, sample size, study duration, intervention and control, mean change in cycloplegic spherical equivalent, proportions of children with fast or slow myopia progression, and information on methodology. Excel version 2007 was used to sort the data. Any discrepancies were resolved by consensus between the two independent assessors.

Quality of selected trials was determined according to Jadad scoring for RCTs,[33] which includes adequate method for randomization, appropriate blinding procedures, and detailed report of withdrawals and dropouts. Newcastle-Ottawa Quality Assessment Scale items were used to assess the quality of selected cohort studies, which includes eight items within three domains: selection (representativeness), comparability (because of design or analysis), and outcomes (assessment and follow-up). A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.[34]

### Statistical Analysis

Data pooling was performed using Review Manager, Version 5.1 (The Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, 2008). Differences in refractive changes between the two groups were expressed as weighted mean differences ([WMD] mean changes in the atropine group minus that in the control group), together with 95% confidence intervals (95% CIs). Odds ratio (OR) with 95% CI of proportions with fast/slow myopia progression was also calculated. Heterogeneity among studies was evaluated using $\chi^2$ test and $I^2$ statistics.[35] A value of $p < 0.1$ was considered significant for the test of heterogeneity. A fixed-effect model was used to calculate estimates unless there was significant heterogeneity, in which case a random-effects model was used. In addition, the effects of treatment on principal outcomes in cohort studies and RCTs were combined and analyzed separately for heterogeneity between different study designs.

## RESULTS

### Study Characteristics

A total of 366 studies were retrieved initially. After excluding 57 duplicate reports of the same studies, 283 unrelated studies

and review articles, and 15 studies that were editorial or comments or assessed other optical interventions, 11 studies met our inclusion criteria and were included in this meta-analysis, of which there were four RCTs[16,17,19,21] and seven cohort studies (a kind of observational study)[13–15,27–29,32] (Fig. 1). One thousand eight hundred fifteen children aged 5 to 15 years were included in this meta-analysis: 1038 children in cohort studies and 777 in RCTs. Of all children, 1061 were treated with atropine eyedrops, the others served as controls. The children had a baseline cycloplegic refraction ranging from −0.50 to −9.75D and a median follow-up period of 22.0 months (interquartile range, 12.0 to 36.5 months). In addition, there were five groups of children (younger than 8 years, 8 to 12 years, 12 to 15 years, 15 to 18 years, 18 years or older) in one cohort study by Brodstein et al.[32] We only included two groups eligible for our criteria (aged 8 to 12 years and 12 to 15 years). Study characteristics are listed in Table 1.

## Quality Assessment

The quality of the included RCTs was generally moderate (Table 2). Most of the RCTs reported the number of participants who were lost to follow-up, whereas the randomization and allocation concealment were unclear. The quality of the included cohort studies was generally high (Table 3). All of the seven cohort studies met the criteria for representativeness of the exposed group and for selection of the nonexposed group for exposure ascertainment and for the outcome not being present at study start. Five cohort studies[13–15,27,29] were adjusted for age, sex, initial spherical equivalent refraction, and other important potential confounders. One study[28] did not adjust for potential confounders. All studies had an independent outcome assessment or recorded linkage for the outcome. The follow-up of all studies was assessed adequately.

## Mean Change in Refraction (D per year)

### *Results of RCTs in Asian Children*

A random-effects model was used because there was statistically significant heterogeneity between the RCTs ($p = 0.04$, $I^2 = 58\%$). The pooled mean difference in effects of mixed concentrations of atropine versus placebo was 0.55 D per year (95% CI, 0.46 to

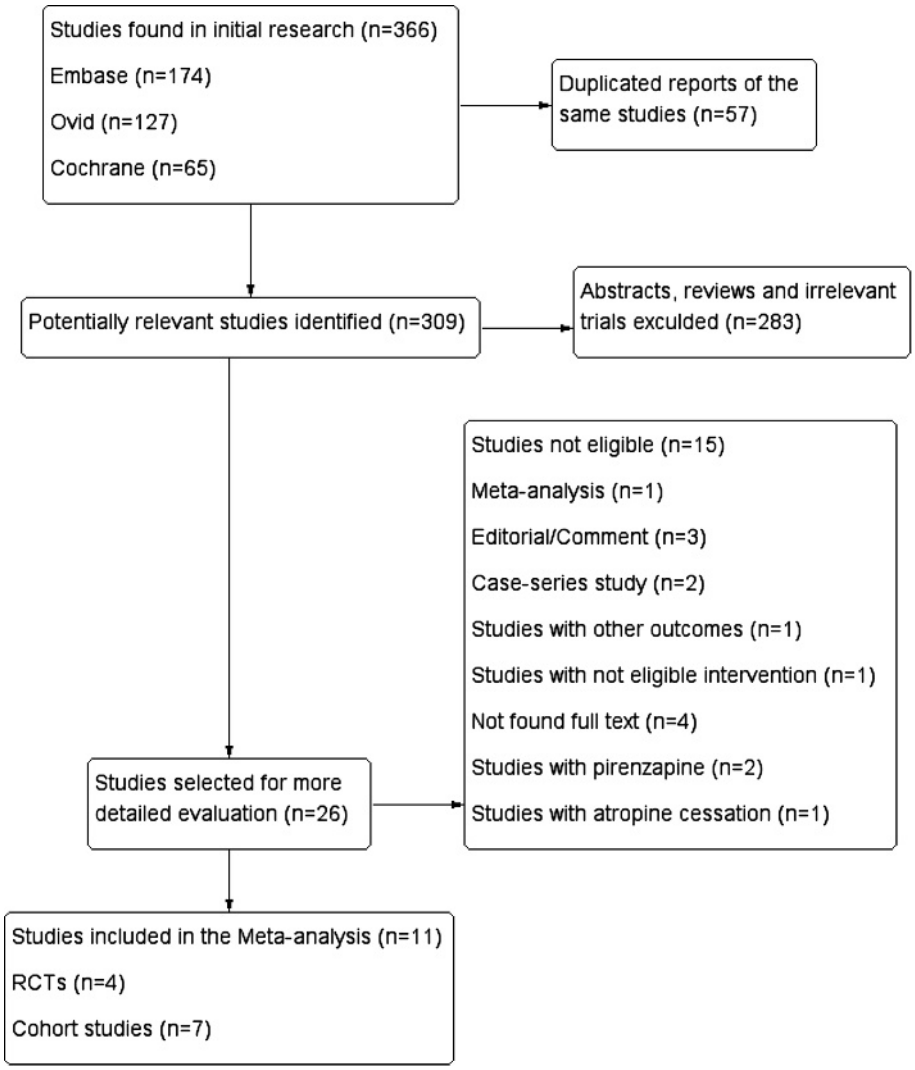


**FIGURE 1.**
Flowchart of studies included. RCTs, randomized controlled trials.

**TABLE 1.**
Characteristics of the studies included in the meta-analysis

| Study | Country or area | Design | Follow-up, mo | Age, y | Baseline refraction, D | Intervention |
|---|---|---|---|---|---|---|
| Yen et al.[17] | Taiwan | RCT | 12 | 6–14 | −1.523 ± 0.915 | 1% Atropine |
| Shih et al.[16] | Taiwan | RCT | 24 | 6–13 | −4.41 ± 1.47 | 0.5%, 0.25%, and 0.1% Atropine |
| Shih et al.[21] | Taiwan | RCT | 18 | 6–13 | −3.28 ± 0.13 | 0.5% Atropine |
| Chua et al.[19] | Singapore | RCT | 24 | 6–12 | −3.36 ± 1.38 | 1% Atropine |
| Brodstein et al.[32] | United States | Cohort study | 33 | 8–15 | Not available | 1% Atropine |
| Chou et al.[28] | Taiwan | Cohort study | 38 | 7–14 | ≤−6.0 | 0.5% Atropine |
| Kennedy et al.[29] | United States | Cohort study | 144 | 6–15 | −1.49 | 1% Atropine |
| Lee et al.[14] | Taiwan | Cohort study | 20 | 6–12 | −1.58 (−0.50 to −5.50) | 0.05% Atropine |
| Fan et al.[13] | Hong Kong | Cohort study | 12 | 5–10 | −5.18 (−3.00 to −9.75) | 1% Atropine |
| Fang et al.[15] | Taiwan | Cohort study | 18 | 6–12 | −0.31 ± 0.45 | 0.025% Atropine |
| Wu et al.[27] | Taiwan | Cohort study | 54 | 6–12 | −2.45 ± 1.63 | 0.05% Atropine |

0.64; $p < 0.01$) (Fig. 2, upper). When the study by Shih et al.[16] was excluded because of using tropicamide as control, the mean difference was 0.50 D per year (95% CI, 0.45 to 0.55; $p < 0.01$, not shown in Figure).

### *Results of Cohort Studies in Asian Children*

We used a random-effects model to achieve conservative results. The mean difference in the effects of mixed concentrations of atropine in slowing myopia progression was 0.54 D per year (95% CI, 0.40 to 0.67; $p < 0001$) compared with controls (Fig. 2, center).

### *Results of Cohort Studies in White Children*

We used a random-effects model because there was significant heterogeneity between the three cohort studies ($p = 0.002$, $I^2 = 84\%$). The mean difference in the effects of atropine versus control in slowing myopia progression was 0.35 D per year (95% CI, 0.08 to 0.63; $p = 0.01$) (Fig. 2, bottom).

## Fast Myopia Progression (>1.0 D per year)

### *Results of RCTs*

All four RCTs reported the number of children with fast myopia progression, and there was statistically significant heterogeneity between these RCTs ($p = 0.03$, $I^2 = 59\%$). We used a random-effects model to pool the data and found that the risk of fast myopia progression was significantly decreased in the atropine group (OR, 0.14; 95% CI, 0.07 to 0.28; $p < 0.01$) (Fig. 3, upper). When the study by Shih et al.[16] was excluded because of using tropicamide as control, the OR was 0.09 (95% CI, 0.06 to 0.14; $p < 0.01$, not shown in Figure).

### *Results of Cohort Studies*

Of the seven cohort studies, only four of them reported the number of children with fast myopia progression.[13,15,27,28] There was no statistically significant heterogeneity between four cohort studies ($p = 0.23$, $I^2 = 30\%$). We used a random-effects model for conservative results and found that the risk of fast myopia progression was also significantly decreased in the atropine group (OR, 0.08; 95% CI, 0.03 to 0.25; $p < 0.01$) (Fig. 3, bottom).

## Slow Myopia Progression (<0.5 D per year)

### *Results of RCTs*

There was a statistically significant heterogeneity between four RCTs ($p < 0.01$, $I^2 = 78\%$). A random-effects model was used, and it was found that the benefit of slowing myopia progression was significantly increased in the group treated with atropine (OR, 6.73; 95% CI, 2.45 to 18.50; $p < 0.01$) (Fig. 4, upper). When the study by Shih et al.[16] was excluded because of using tropicamide as control (Table 4), the OR was 4.47 (95% CI, 0.91 to 21.93; $p < 0.01$, not shown in Figure).

### *Results of Cohort Studies*

Only three cohort studies[13,14,27] reported this outcome with no significant heterogeneity ($p = 0.26$, $I^2 = 26\%$). The pooled data showed that the benefit of slowing myopia progression was

**TABLE 2.**
Quality assessment of RCTs included in the meta-analysis

| Study | Randomization | Blinding | Lost to follow-up | Allocation concealment | Analysis method | Jadad scoring |
|---|---|---|---|---|---|---|
| Yen et al.[17] | Unclear | No | Not adequate | Unclear | PP | 0 |
| Shih et al.[16] | Unclear | No | Adequate | No | PP | 2 |
| Shih et al.[21] | Unclear | SB | Adequate | Unclear | PP | 3 |
| Chua et al.[19] | Adequate | DB | Adequate | Adequate | ITT | 5 |

DB, double blinding; ITT, intention-to-treat analysis; No, no blinding or no allocation concealment; PP, per-protocol analysis; SB, single blinding.

**TABLE 3.**

Quality assessment of cohort studies included in the meta-analysis using Newcastle-Ottawa Quality Assessment Scale

| | Selection | | | | | Outcome | | |
|---|---|---|---|---|---|---|---|---|
| Study | Exposed cohort representative | Nonexposed cohort selection | Exposure ascertainment | Outcome not present at start | Comparability | Assessment | Follow-up length | Follow-up adequacy |
| Brodstein et al.[32] | * | * | * | * | * | * | * | * |
| Chou et al.[28] | * | * | * | * | — | * | * | * |
| Kennedy et al.[29] | * | * | * | * | ** | * | * | * |
| Lee et al.[14] | * | * | * | * | ** | * | * | * |
| Fan et al.[13] | * | * | * | * | ** | * | * | * |
| Fang et al.[15] | * | * | * | * | ** | * | * | * |
| Wu et al.[27] | * | * | * | * | ** | * | * | * |

* indicates score. A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

significantly increased in the group treated with atropine (OR, 22.10; 95% CI, 7.09~68.81; $p < 0.01$) using a random-effects model (Fig. 4, bottom).

### *Atropine Concentration*

Although the number of studies with the same concentration in either the RCT or cohort groups was too small to evaluate the effect of atropine concentration fairly, we attempted to estimate this effect by combining RCT and cohort studies, thus providing larger samples. Combining the types of studies with Asian children, at least, was reasonable because they yielded similar effects. We thus compared low and high concentration using the sets of data listed in Fig. 2 in two separate analyses. The first was a comparison between the set of data for concentrations of 0.25% or less (n = 5) versus concentrations of 0.5% or more (n = 9) and the second a comparison between 0.5% or less (n = 8) versus 1% (n = 6). Using the nonparametric Mann-Whitney *U* test, the results yielded no significant difference for either comparison of

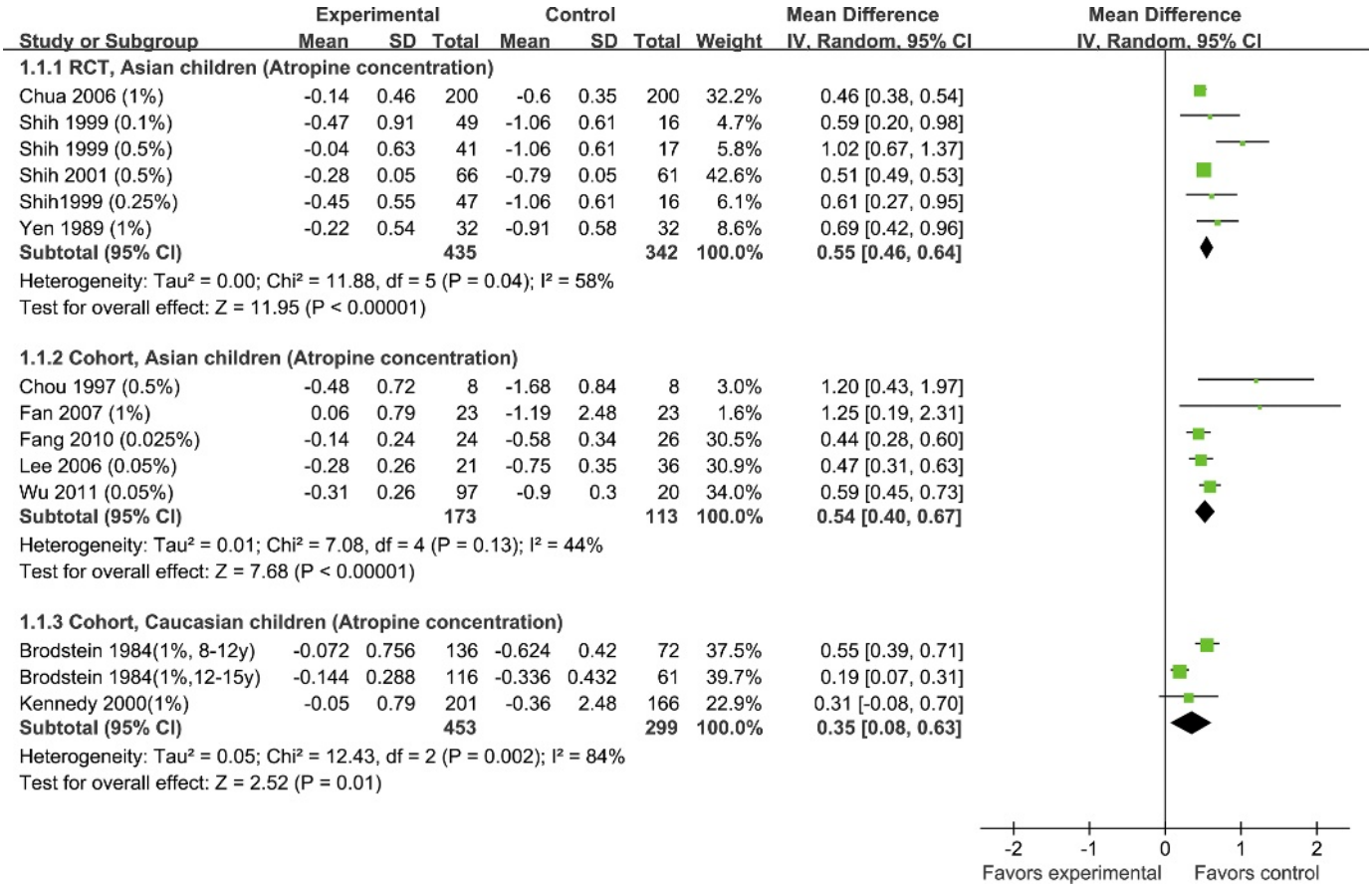


**FIGURE 2.**

Forest graph of the effect of atropine on myopia progression per year in Asian children and white children from both RCTs (n = 4) and cohort studies (n = 7). A color version of this figure is available online at www.optvissci.com.

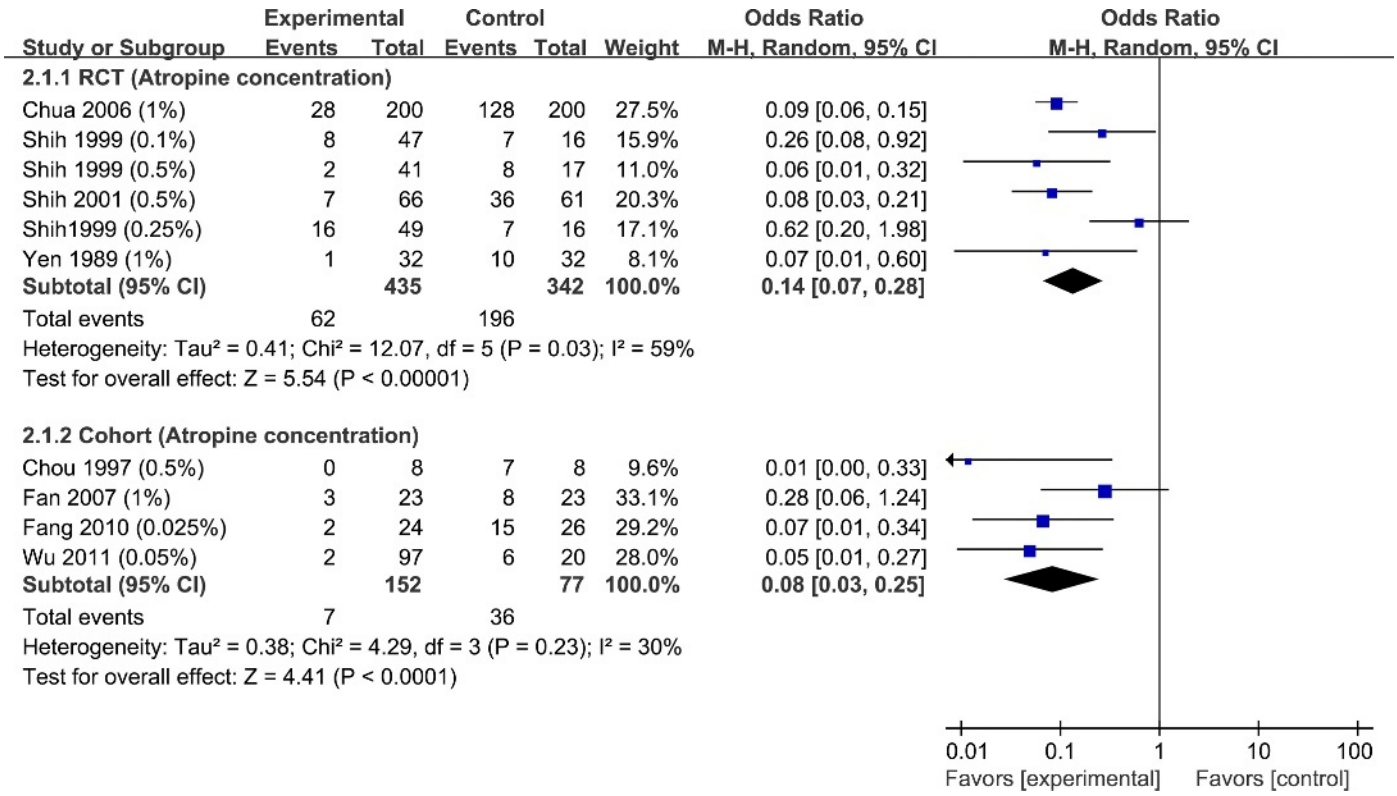


**FIGURE 3.**

Forest graph of the effect of atropine on proportions of children with fast myopia progression (>1.0 D) in RCTs (n = 4) and cohort studies (n = 4). A color version of this figure is available online at www.optvissci.com.

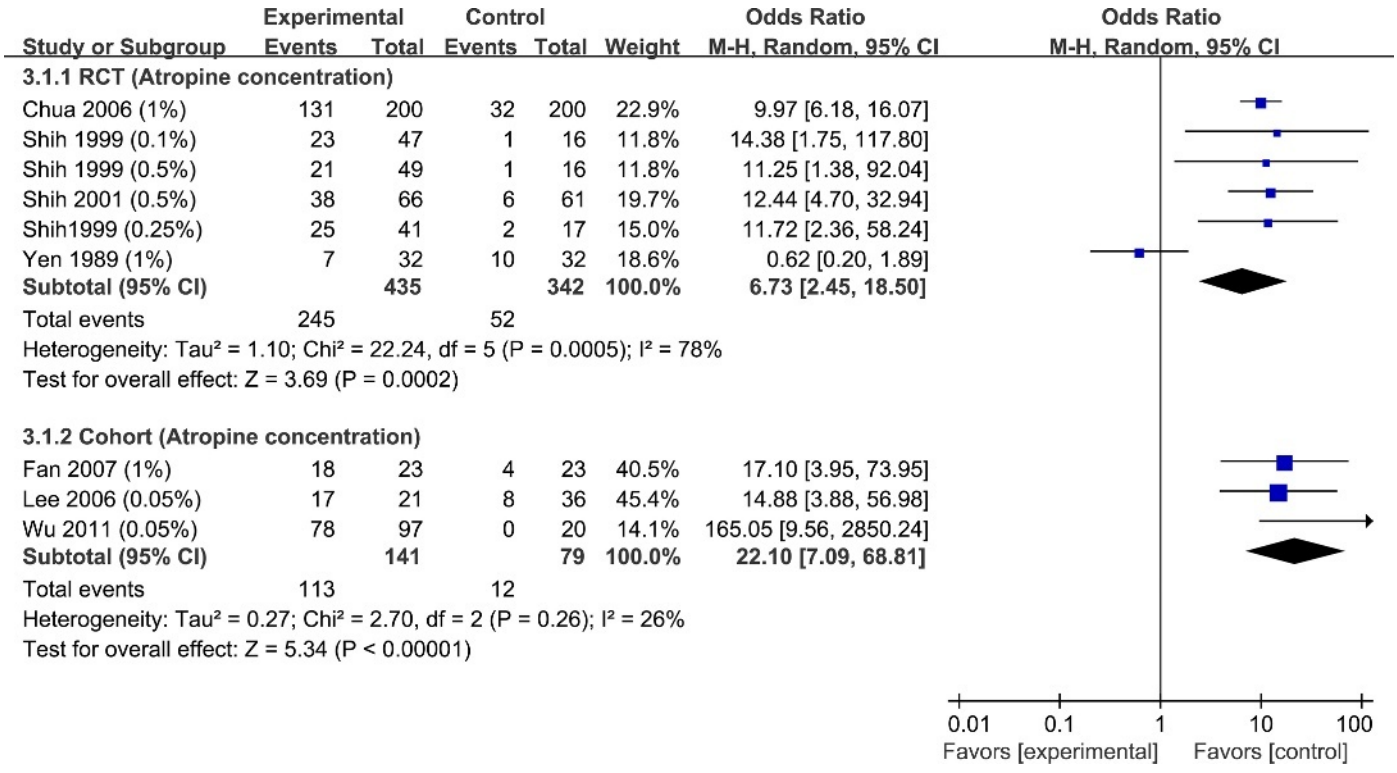


**FIGURE 4.**

Forest graph of the effect of atropine on proportions of children with slow myopia progression (<0.5 D) in RCTs (n = 4) and cohort studies (n = 3). A color version of this figure is available online at www.optvissci.com.

**TABLE 4.**
Mean changes of myopia progression in the studies included

| | Intervention group | | | Control group | | |
|---|---|---|---|---|---|---|
| Study | Intervention | No. patients | Mean change ± SD, D per year | Control | No. patients | Mean change ± SD, D per year |
| Yen et al.[17] | 1% Atropine | 32 | −0.22 ± 0.54 | Saline | 32 | −0.91 ± 0.58 |
| Shih et al.[16] | 0.5% Atropine | 41 | −0.04 ± 0.63 | Tropicamide | 17 | −1.06 ± 0.61 |
| | 0.25% Atropine | 47 | −0.45 ± 0.55 | Tropicamide | 16 | −1.06 ± 0.61 |
| | 0.1% Atropine | 49 | −0.47 ± 0.91 | Tropicamide | 16 | −1.06 ± 0.61 |
| Shih et al.[21] | 0.5% Atropine | 66 | −0.28 ± 0.05 | Placebo | 61 | −0.79 ± 0.05 |
| Chua et al.[19] | 1% Atropine | 200 | −0.14 ± 0.46 | Placebo | 200 | −0.60 ± 0.35 |
| Brodstein et al.[32] | 1% Atropine | 136 (8~12 y) | −0.072 ± 0.756 | Blank | 72 | −0.624 ± 0.42 |
| Brodstein et al.[32] | 1% Atropine | 116 (12~15 y) | −0.144 ± 0.288 | Blank | 61 | −0.336 ± 0.432 |
| Chou et al.[28] | 0.5% Atropine | 8 | −0.48 ± 0.72 | Blank | 8 | −1.68 ± 0.84 |
| Kennedy et al.[29]* | 1% Atropine | 201 | −0.05 ± 0.79 | Blank | 166 | −0.36 ± 2.48 |
| Lee et al.[14] | 0.05% Atropine | 21 | −0.28 ± 0.26 | Blank | 36 | −0.75 ± 0.35 |
| Fan et al.[13] | 1% Atropine | 23 | 0.06 ± 0.79 | Blank | 23 | −1.91 ± 2.48 |
| Fang et al.[15] | 0.025% Atropine | 24 | −0.14 ± 0.24 | Blank | 26 | −0.58 ± 0.34 |
| Wu et al.[27] | 0.05% Atropine | 97 | −0.31 ± 0.26 | Blank | 20 | −0.90 ± 0.30 |

*SDs were not reported in this study, and it was replaced by the SD of Fan et al.,[13] the maximum SD of the seven cohort studies.

atropine concentration, being $U = 25$, $p = 0.79$ and $U = 18$, $p = 0.49$, respectively.

## DISCUSSION

In this meta-analysis, we compared the results from four RCTs and seven well-conducted cohort studies on the same topic, that is, the effect of atropine in slowing myopia progression in children. The findings showed that mixed concentrations of atropine compared with control could significantly slow myopia progression in Asian children, with differences of 0.55 D per year and 0.54 D per year in RCTs and cohort studies, respectively, and to a smaller effect (0.35 D per year) in cohort studies of white children. Moreover, it would seem that atropine concentration did not affect the results. In RCTs, atropine achieved significantly lower risk in children with fast myopia progression (OR, 0.14) and significantly higher benefit in children with slow myopia progression (OR, 6.73). The cohort studies provided comparable outcomes (OR, 0.08 and 22.10) to those obtained with RCTs.

The effect of atropine compared with placebo from RCTs in the present study (0.55 D per year) was similar to that reported in two previous RCTs of high quality (0.46 D per year).[19,20] This result was smaller than those of previous reviews (0.80 D and 0.773 D per year).[25,26] It should be noted, though, that we considered myopia progression per year as primary outcome so that the confounding factor of different follow-up periods was adjusted. In addition, we evaluated the effects of atropine from RCTs and cohort studies separately. The pooled results from cohort studies in the present study provided comparable estimate (0.54 D per year), which further proved that atropine could slow myopia progression in children at a rate of about 0.50 D per year compared with controls.

As for ethnicity, atropine demonstrated a slight difference (0.19 D per year) in slowing myopia progression in Asian children and white children (Fig. 2), although the studies with Asians include various concentrations and the white studies include only higher concentrations. However, this difference was comparable to that found with multifocal lenses in our previous meta-analysis study (0.22 D).[31] Myopia progression rate was the main reason to account for the difference because Asian children have been reported to have more rapid myopia progression than white children.[36] Baseline refraction of children, which was related to myopia progression, might be another reason for the ethnic difference because previous studies have reported that Asian children had higher degrees of myopia than white children (Table 1).[37]

In the present study, it was interesting to find that cohort studies did not overestimate the effect of atropine but yielded similar effects to those of RCTs. Therefore, both RCTs and cohort studies could provide data on the effects of interventions.[30] Observational studies have some advantages over RCTs because of their feasibility, lower cost, and better compliance for long-term observation. Atropine has been clinically used since the early 1900s,[38] and few studies have reported its long-term adverse effects. Long-term observational studies, especially well-designed cohort studies,[29] or registry for evaluating outcomes, with participants with good compliance would help detect long-term adverse effects and may under these circumstances be as beneficial as RCTs. In a recent trial by Chia et al.,[20] it was reported that 0.01% atropine compared with higher concentrations had minimal side effects and comparable efficacy in controlling myopia progression. A second phase with children taking 0.01% atropine is expected to be performed on a long-term basis. Observational studies might be a good alternative for observing the long-term effects of low-concentration atropine.

In addition, myopic children in the real world are more likely to receive multiple interventions such as bifocal or progressive addition lenses,[31] eyedrops, traditional Chinese medicine like acupuncture, and so on. On one hand, it is hard to persuade children and their parents to participate in an RCT with a single intervention without receiving any other. On the other hand, myopia is an ocular abnormality that occurs and develops involving many different mechanisms.[39] Combined therapy may provide promising

effectiveness and reduce worrying adverse effects for controlling myopia progression in children.[22] Observational studies might be a good design to mitigate these concerns.

However, RCTs were performed on patients under well-controlled conditions, as for example, restrictive inclusion and exclusion criteria, monitoring for good compliance with interventions, no other coexisting diseases, or therapeutic methods for the target diseases. These factors made the results from RCTs more convincing, although they were really the effect prevailing in an ideal world and not in the real world. Therefore, it is still important to perform good RCTs to compare the effects of atropine in the future.

There are some limitations in the present study. First, both RCTs and observational studies in this meta-analysis investigated the overall effects of different concentrations of atropine because there are not enough studies for each concentration. This might be a source of heterogeneity. However, atropine concentration did not seem to influence the results because, when we compared different concentrations, irrespective of whether they came from RCT or cohort studies, there was no significant difference. Shih et al.[16] experimentally demonstrated that the ability to slow myopia was related to the concentration of atropine. In a subsequent retrospective review of studies of atropine, Cooper et al.[23] also reported that the ability to control myopia was related to concentration. Our findings using weighted meta-analysis, agrees with findings of Chia et al.,[20] whereby the ability to slow the progression of myopia is independent of the concentration of atropine. If our findings are substantiated by further research, then use of low-concentration atropine might become a powerful agent in controlling the progression of myopia. Second, the study by Shih et al.[16] was included in this meta-analysis although tropicamide was used as control. Third, only trials in English were included, which may lead to a potential publication bias. Last, most trials in the present meta-analysis were performed on Asian children. Only two trials with a high concentration of atropine (1%) were conducted in the United States[29,32] and reported a slight change in refraction. The data might be biased because there are no studies on low-concentration atropine in whites. The generalization of the results to other ethnicities was limited.

In summary, the present meta-analysis found that both RCTs and cohort studies demonstrated significant and similar effects of atropine, compared with controls, in slowing myopia progression in children. Asian children were more likely to benefit from atropine treatment than white children. Remaining questions that need to be clarified in future studies are "what is the specific mechanism for the ethnic difference of atropine?" and "how long the effect can last after the intervention stops?"

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