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ORIGINAL ARTICLE

Myopia control and prevention: From lifestyle to low-concentration atropine. The 2022 Josh Wallman Memorial Lecture

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Abstract

The purpose of this study was to explore the findings from the Hong Kong Children Eye Study and the Low Concentration Atropine for Myopia Progression (LAMP-1) Study. The incidence of myopia among schoolchildren in Hong Kong more than doubled during the COVID-19 pandemic, with outdoor time decreased significantly and screen time increased. The change in lifestyle during the COVID-19 pandemic aggravated myopia development. Low-concentration atropine (0.05%, 0.025% and 0.01%) is effective in reducing myopia progression with a concentration-related response. This concentration-dependent response was maintained throughout a 3-year follow-up period, and all low concentrations were well tolerated. An age-dependent effect was observed in each treatment group with 0.05%, 0.025% and 0.01% atropine. Younger age was associated with a poor treatment response to low-concentration atropine. Additionally, low-concentration atropine induced choroidal thickening along a concentration-dependent response throughout the treatment period. During the third year, continued atropine treatment achieved a better effect across all concentrations compared with the washout regimen. Stopping treatment at an older age and receiving lower concentration were associated with a smaller rebound effect. However, differences in the rebound effect were clinically small across all the three concentrations studied.

KEYWORDS
lifestyle, low-concentration atropine, myopia

BACKGROUND

Myopia is a worldwide public health threat with many regions showing increasing prevalence over the past decades, especially in East Asia.[1–3] By 2050, it is predicted that around half of the global population will become myopic, and one-tenth will be highly myopic (≤−6.00 D).[4] Myopia prevalence varies significantly among children of different races, regions and ages, and it is much higher in East and Southeast Asian countries than in non-Asian areas.[1]

Myopic individuals have excessive elongation of the globe and a higher risk of sight-threatening complications that lead to poor vision and even blindness.[5–7] Although high myopia carries a greater risk of complications and visual impairment, low and moderate myopia also have considerable risk. A meta-analysis revealed that low, moderate and high myopia significantly increased the risk of myopic macular degeneration (odds ratios [OR] = 13.57, 72.74 and 845.08, respectively), retinal detachment (OR = 3.15, 8.74 and 12.62, respectively), posterior subcapsular cataract (OR = 1.56, 2.55 and 4.55, respectively) and open-angle glaucoma (OR = 1.59 for low myopia and 2.92 in moderate and high myopia).[5] The prevalence of visual impairment attributable to myopia ranges from 0.1% to 0.5% in the European population and 0.2% to 1.4% in the Asian population.[8] Thus, this high prevalence of myopia poses a major public health challenge. It was estimated that the potential global productivity loss associated with visual impairment from uncorrected myopia was US$244 billion in 2015.[9]

This article summarises the 2022 Josh Wallman Memorial Lecture given at the International Myopia Conference (IMC) in Rotterdam, the Netherlands. Based on findings from the Hong Kong Children Eye study and the Low Concentration Atropine for Myopia Progression (LAMP-1) study, we will discuss the prevalence of myopia in Hong Kong, the surge in incidence during the COVID-19 pandemic and its associated risk factors of progression and intervention using low-concentration atropine.

Key points

- There is a high prevalence of childhood myopia in Hong Kong with a more than doubled incidence during the COVID-19 pandemic due to significantly decreased outdoor time and increased screen time.
- This study has established the efficacy of low-concentration atropine eye drops compared with a placebo group along a concentration-dependent effect, with the higher concentration exhibiting better efficacy.
- We observed an age-dependent effect. Younger age was associated with a poor treatment response to low-concentration atropine and these individuals should receive a higher concentration for improved efficacy.

PREVALENCE AND RISK FACTORS OF MYOPIA IN HONG KONG

The Hong Kong Children Eye Study

The Hong Kong Children Eye Study is an ongoing, prospective, population-based longitudinal examination of eye conditions among primary school children, 6–8 years of age. Recruitment for baseline data has been ongoing every week since 2015 to date, based on a stratified and clustered randomised sampling frame.[2,10–21] In brief, all Education Bureau-registered primary schools were stratified into seven cluster regions for the use of the Hospital Authority services in Hong Kong. This division into seven clusters was determined by the Hong Kong government according to an even distribution of population density in each cluster. The schools in each cluster region were then randomly assigned an invitation priority based on the ranking numbers generated by a computer. Invitations to participate in the cohort were sent according to the ranking numbers until the required sample was achieved in each cluster region. In March 2018, we began a 3-year longitudinal follow-up for subjects of the Hong Kong Children Eye Study who had been recruited at baseline since 2015. Cycloplegic autorefraction was measured for children and non-cycloplegic autorefraction for their parents. Parental educational level, children's outdoor time and near work were collected by validated questionnaires.

Prevalence of myopia in Hong Kong in 2020 (before COVID-19)

In the Hong Kong Children Eye Study, 4257 children between 6 and 8 years of age and 5880 parents were recruited from 2015 to 2018. 25.0% of the 6- to 8-year-old children were myopic, and the prevalence for the 6-, 7- and 8-year-olds was 12.7%, 24.4% and 36.1%, respectively.[2] Among the parents, 72.2% were myopic (73.2% of the mothers and 70.7% of the fathers), and 13.5% were highly myopic (12.8% of the mothers and 14.5% of the fathers).[2] Myopia prevalence decreased with age and increased with education level.

There is a strikingly high prevalence of myopia in Hong Kong children aged 6–8 years, much higher than that found in other regions of China. The crowded living environment in Hong Kong may promote near-work activities and less outdoor time compared with other regions. Furthermore, the prevalence of myopia among Hong Kong parents is also high, and an increased incidence has been seen in working age groups of this generation. Thus, the prevention of childhood myopia, as well as the control and treatment of visual complications resulting from high myopia in adults is crucial for good public health.

Myopia incidence and lifestyle changes among schoolchildren during the COVID-19 pandemic

During the COVID-19 pandemic, measures devised to contain and mitigate the spread of the virus have particularly affected school-age children and students in general. Consequently, increased near-work time and decreased outdoor time have been implicated in the development of myopia.[22] The household quarantining and the rounds of school closures against the virus, resulting in lifestyle changes, may have a long-lasting impact on myopia progression in children. Thus, we evaluated myopia incidence and progression, in addition to the changes in lifestyle habits, among school-age children during the COVID-19 pandemic in Hong Kong.[23]

Two separate longitudinal cohorts of children aged 6–8 years from the Hong Kong Children Eye Study were examined. The COVID-19 cohort was recruited at the beginning of the outbreak (from 1 December 2019 to 24 January 2020), while the pre-COVID-19 cohort had completed follow-up before the onset in January 2020. A total of 1793 subjects were recruited, of whom 709 children comprised the COVID-19 cohort with 7.89 ± 2.30 months of follow-up and 1084 children comprised the pre-COVID-19 cohort with 37.54 ± 3.12 months of follow-up. The overall incidence of myopia was 19.44% (estimated annual incidence = 29.57%) and 36.57% (estimated annual incidence = 11.69%) in the COVID-19 and pre-COVID-19 cohort, respectively. During the COVID-19 pandemic, the change in spherical equivalent (SE) and axial length (AL) was −0.50 ± 0.51 D and 0.29 ± 0.35 mm, respectively. The time spent on outdoor activities decreased from 1.27 ± 1.12 to 0.41 ± 0.90 h/day ($p < 0.001$), while screen time increased from 2.45 ± 2.32 to 6.89 ± 4.42 h/day ($p < 0.001$).

This study demonstrated an increase in myopia incidence, a significant decrease in outdoor time and an increase in screen use among schoolchildren in Hong Kong during the COVID-19 pandemic. These results serve to warn not only eye care professionals but also policymakers, educators and parents. It is important to minimise the long-term collateral impact of COVID-19-related policies on a range of health outcomes such as myopia. Either due to the wide use of vaccines or the epidemic having been brought under control, lockdown measures have been eased in many regions of the world. However, lifestyle changes, such as the increasing adoption of and reliance upon digital devices, as well as reduced time outdoors, may persist beyond the period of the pandemic and have a long-lasting impact on myopia progression. Therefore, an ophthalmological surveillance programme for children with myopia should be considered, both during and after the pandemic is over. Collective efforts are needed to gain better control of the potential public health crisis and reduce the global burden of myopia as a result of COVID-19.

Parental myopia

Parental myopia is a known risk factor for childhood myopia development, indicating a genetic contribution.[24,25] However, the genetic contribution may not be the only risk, since environmental factors could also be linked to parental myopia, which itself affects children's vision.[26,27] Myopic parents may create a myogenic environment, including developed habits of intensive near-work and limited time outdoors.[26] We recruited 6155 subjects in 2055 family trios (one child and both parents) from the Hong Kong Children Eye Study, to investigate whether the severity of parental myopia influences childhood myopia. We also explored whether this effect is independent of such environmental factors as children's outdoor time and near work.[15]

Mild parental myopia did not increase the risk of childhood myopia, but the risk was 11.22-fold when both parents were highly myopic. Higher parental education (father: OR = 1.08, $p < 0.05$; mother: OR = 1.11, $p = 0.001$) and more reading time for the children were risk factors (OR = 1.21, $p = 0.04$). Reduced odds of myopia were associated with more time spent on outdoor activities (OR = 0.78, $p = 0.02$) and less on electronic devices (OR = 0.80, $p = 0.005$). Notably, all these factors became insignificant after adjustment, except for parental myopia. Children whose parents had more severe myopia spent more time reading but less on electronic devices. Parental myopic status alone accounted for 11.82% of the myopia variation in children. With age and parental myopia, the area under the receiving-operating characteristic curve for myopia was 0.73.

Parental myopia confers, in a dose-related manner, the strongest independent effect on childhood myopia. Therefore, based on parental myopia data, those children at high risk of myopia can be identified for early prevention strategies.

LOW-CONCENTRATION ATROPINE FOR MYOPIA PROGRESSION STUDY

Low-concentration atropine and questions remaining to be answered

Results from the Atropine for the Treatment of Myopia (ATOM)-2 studies brought about a paradigm shift in myopia control using low-concentration atropine eye drops, which are well tolerated and have less rebound effect following the cessation of treatment.[28] However, some questions remain to be answered, including the following: (1) Does low-concentration atropine prevent myopia progression in children compared with the placebo group? (2) Does the effect of low-concentration atropine vary with the concentration? (3) What is the optimal concentration with the best efficacy and safety treatment profile? (4) Is the longer term efficacy better in the second year than in the first year? (5) Is there any effect on corneal and crystalline lens power? (6) Are there any other factors associated with the treatment response? (7) Are there any biomarkers

for treatment efficacy? (8) Should treatment be continued or stopped after 2 years? (9) Does the rebound effect vary with drug concentration? (10) What are the long-term effects of low concentrations of atropine?

Low-concentration Atropine for Myopia Progression (LAMP-1) study

The LAMP-1 study was the first double-blind, randomised, placebo-controlled trial of low-concentration atropine for myopia progression (Figure 1). Children of 4–12 years with a myopic refraction of ≤–1.0 D in both eyes, astigmatism of <2.5 D and documented myopic progression of at least 0.5 D in the previous year were enrolled.[29–35] In Phase 1, the children were randomly assigned to four treatment groups (0.05%, 0.025%, 0.01% atropine and placebo), with follow-up at 4-month intervals after the initial treatment. In Phase 2, all children in the placebo group during Phase 1 were switched to receiving 0.05% atropine at the beginning of the second year until the end of the phase due to ethical consideration, after we had proved the efficacy of low-concentration atropine for myopia control compared with placebo at the end of the first year. Children in the original atropine treatment groups received the same concentrations throughout this second year. In Phase 3, the children in each of the three original treatment groups for Phase 1 (0.05%, 0.025% and 0.01% atropine) were randomised in a 1:1 ratio into a continued treatment subgroup and a treatment cessation or 'washout' subgroup, stratified further by sex and age. For the continued treatment subgroups, subjects continued to receive eye drops of the same concentration once nightly in both eyes throughout the third year. For the washout subgroups, subjects stopped receiving eye drops. Children in the switchover group for Phase 2 continued treatment with 0.05% atropine in the third year (Figure 1).

LAMP-1 study phase 1

This study aimed at evaluating the safety and efficacy of 0.05%, 0.025% and 0.01% atropine, in comparison with the placebo over a 1-year period.[29] A total of 438 children were

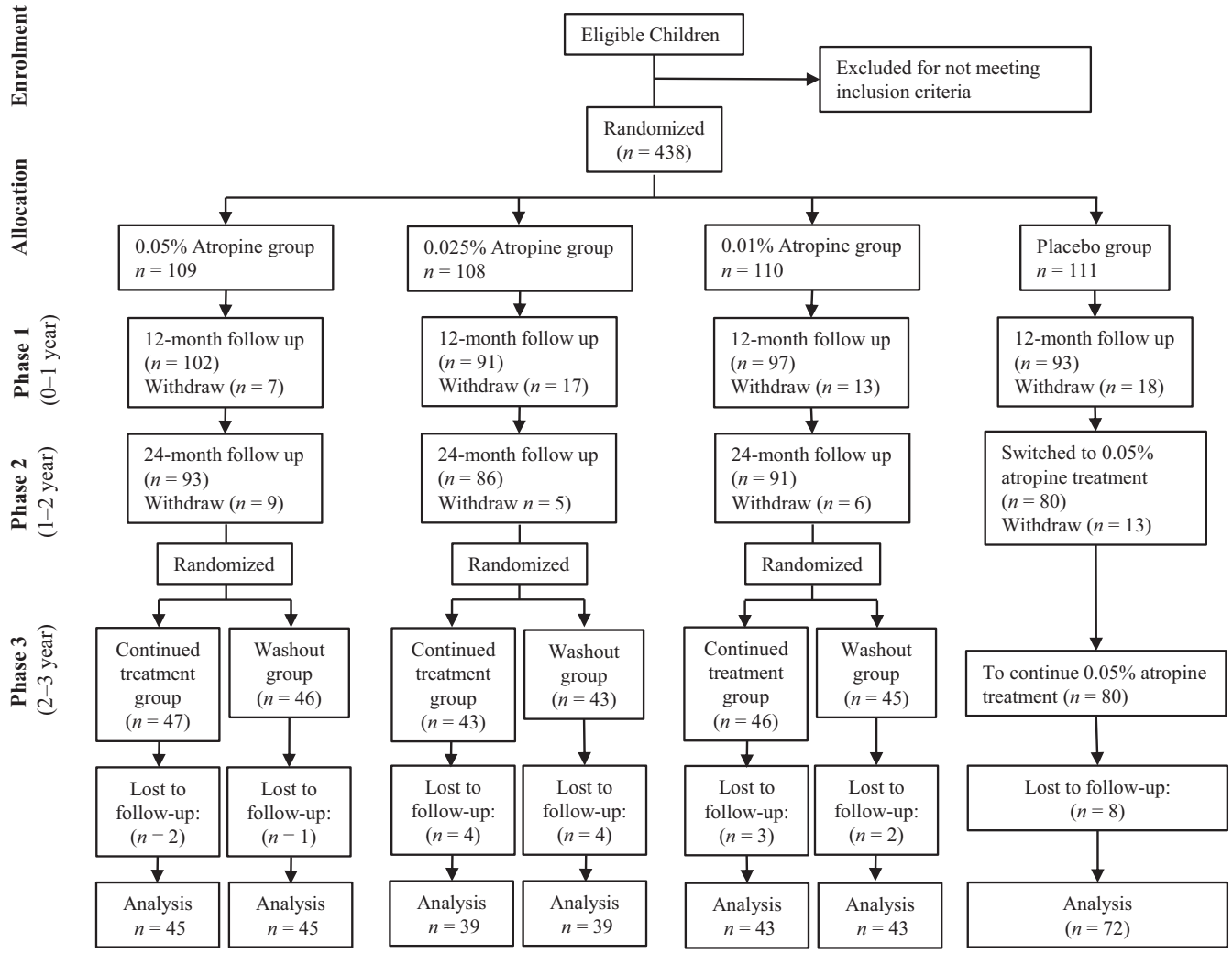

FIGURE 1 Flow chart for subject recruitment and follow-up in the low-concentration atropine for myopia progression study.[29–35]

recruited. After 1 year, the mean SE change was −0.27 ± 0.61, −0.46 ± 0.45, −0.59 ± 0.61 and −0.81 ± 0.53 D, in the 0.05%, 0.025%, 0.01% and placebo groups, respectively ($p < 0.001$), with respective mean increases in AL of 0.20 ± 0.25, 0.29 ± 0.20, 0.36 ± 0.29 and 0.41 ± 0.22 mm ($p < 0.001$) (Figure 2). The comparison of AL change between the 0.01% atropine and placebo groups was not statistically significant ($p = 0.18$). The accommodation amplitude was reduced by 1.98 ± 2.82, 1.61 ± 2.61, 0.26 ± 3.04 and 0.32 ± 2.91 D, respectively ($p < 0.001$). The pupil sizes under photopic and mesopic conditions were increased, respectively, by 1.03 ± 1.02 and 0.58 ± 0.63 mm for 0.05% atropine, 0.76 ± 0.90 and 0.43 ± 0.61 mm for 0.025% atropine, 0.49 ± 0.80 and 0.23 ± 0.46 mm for 0.01% atropine and 0.13 ± 1.07 and 0.02 ± 0.55 mm in the placebo group ($p < 0.001$). Visual acuity and the vision-related quality of life were not affected in any group.

We confirmed that 0.05%, 0.025% and 0.01% atropine eye drops can reduce myopia progression along a concentration-dependent response. All concentrations were well tolerated without any adverse effect on the vision-related quality of life. Of the three concentrations tested, 0.05% atropine was most effective in controlling SE progression and AL elongation over a 1-year period.

LAMP-1 study phase 2

A total of 383 subjects continued into Phase 2.[30] Over a 2-year period, the mean SE progression was 0.55 ± 0.86, 0.85 ± 0.73 and 1.12 ± 0.85 D for the 0.05%, 0.025% and 0.01% atropine groups, respectively ($p = 0.02$, $p < 0.001$ and $p = 0.02$ for pairwise comparisons) (Figure 3a), with respective mean AL changes over 2 years of 0.39 ± 0.35, 0.50 ± 0.33 and 0.59 ± 0.38 mm ($p = 0.04$, $p < 0.001$ and $p = 0.10$) (Figure 3b). Compared with the first year, the second-year efficacy of the 0.05% and 0.025% concentrations remained similar ($p = 0.45$ and $p = 0.31$) but mildly improved in the 0.01% atropine group ($p = 0.04$). For the phase 1 placebo group, myopia progression was significantly reduced after switching to 0.05% atropine (SE change was 0.18 D in the second year vs. 0.82 D in the first year, $p < 0.001$; additionally, AL elongated by 0.15 mm in the second year vs. 0.43 mm in the first year, $p < 0.001$).

Thus, over 2 years, the concentration-dependent response remained. The observed efficacy of 0.05% atropine was twice that of 0.01% atropine, and it remained the optimal concentration among those studied for slowing myopia progression. All concentrations of atropine were well tolerated without any apparent adverse effects on the quality of life in the second year.

Atropine differential effects on ocular biometry with 0.05%, 0.025% and 0.01% atropine

Both the ATOM-2 and LAMP-1 studies demonstrated a better anti-myopic effect in terms of SE progression than AL elongation.[28–30,36] The question remains whether the anti-myopic effect of low-concentration atropine is mediated via the reduction in axial elongation or other associated biometric changes. We evaluated the changes in ocular biometrics and their respective contributions to SE progression in 0.05%, 0.025% and 0.01% atropine, compared with placebo over 1 year in the LAMP-1 study.[34]

A total of 383 children who completed the first year of the LAMP-1 study were included. Over the first year, changes in AL were 0.20 ± 0.25, 0.29 ± 0.20, 0.36 ± 0.29 and 0.41 ± 0.22 mm for the 0.05% atropine, 0.025% atropine, 0.01% atropine and placebo groups, respectively ($p < 0.001$), with a concentration-dependent response. Corneal power remained stable, and changes were similar across all atropine concentrations: −0.02 ± 0.14, −0.01 ± 0.14, −0.01 ± 0.12 and 0.01 ± 0.14 D in the 0.05% atropine, 0.025% atropine, 0.01% atropine and placebo groups, respectively ($p = 0.10$). Crystalline lens power decreased over time for each concentration, but changes were also similar across concentrations: −0.31 ± 0.43, −0.38 ± 0.47, −0.40 ± 0.43 and −0.41 ± 0.43 D in the 0.05% atropine, 0.025% atropine, 0.01% atropine and placebo groups, respectively ($p = 0.24$). Changes in anterior chamber depth were also similar across concentrations ($p = 0.41$). Thus, the contributions of the ocular biometric changes to SE progression after adjusting for age and gender in each concentration were similar across all groups ($p > 0.05$).

Excessive axial elongation can cause mechanical stretching and thinning of the retina, choroid and sclera, leading to degenerative effects and subsequent complications such as myopic choroidal neovascularisation. Therefore, an effective myopia intervention should prioritise the reduction in axial elongation. Although other ocular biometric changes were thought to contribute to the anti-myopia effects of low-concentration atropine,[37,38] this study demonstrates that the reduction in AL elongation accounted for most of the effects. The largest reduction in AL elongation was observed with 0.05% atropine, followed by 0.025% and 0.01% atropine as compared with the placebo in a concentration-dependent response. Low concentrations of atropine (0.05%, 0.025% and 0.01%) have no clinical effect on corneal or lens power. The anti-myopic effects of low-concentration atropine act mainly by reducing AL elongation, and, therefore, could reduce the risk of subsequent myopia complications.

Treatment effect factors

The treatment responses of low-concentration atropine vary widely, as a proportion of children still progress quickly despite receiving treatment.[29,39] Associated factors are important for serving as a reference for concentration adjustment; otherwise, switching to alternative or combined therapies may be necessary. We assessed the effect of age at treatment and other factors – including gender, baseline refraction, parental myopia, outdoor time, near

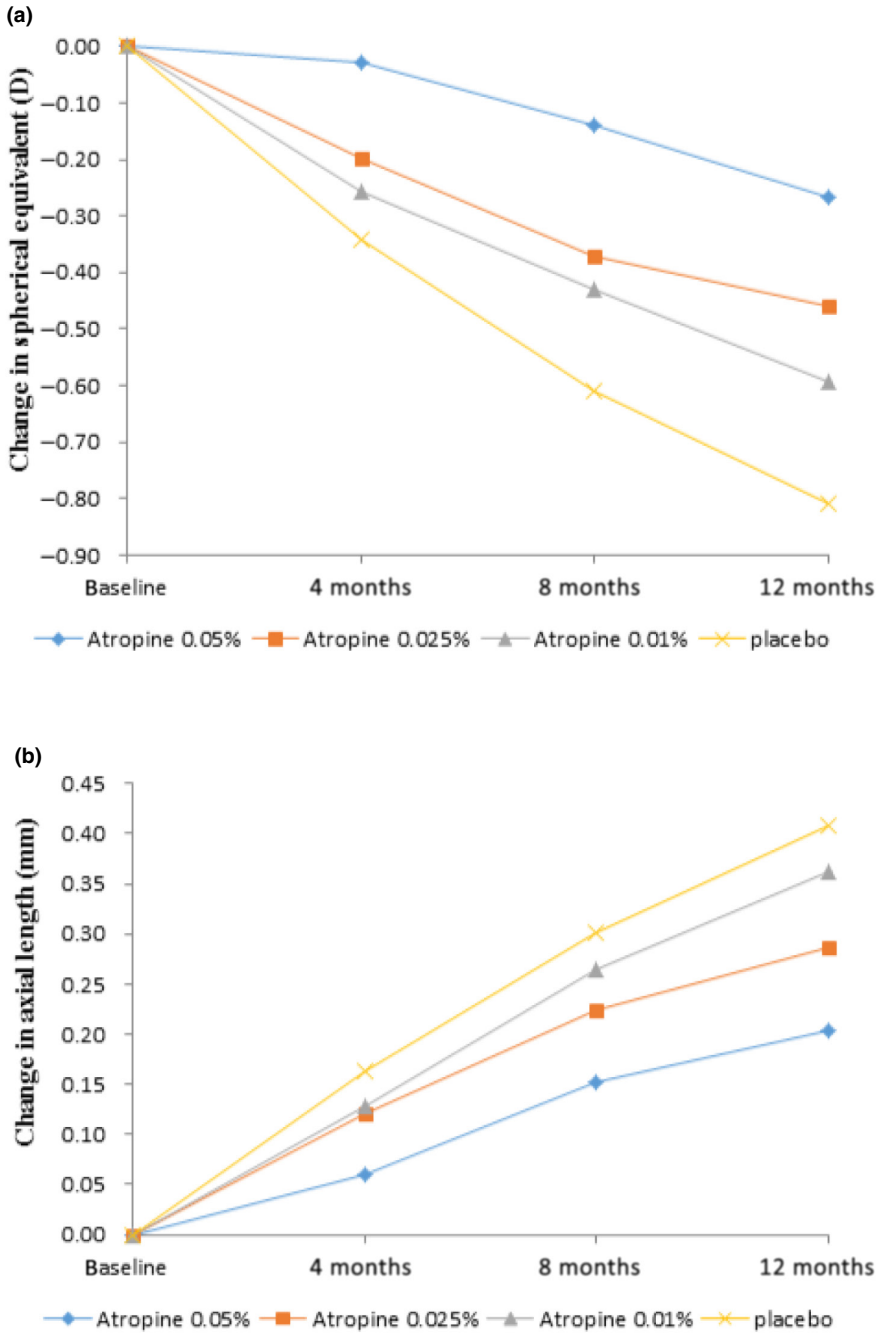

FIGURE 2 Changes in spherical equivalent (a), and axial length (b) for 0.05%, 0.025%, 0.01% atropine and placebo groups over 1 year.

work and treatment compliance – on treatment responses to 0.05%, 0.025% and 0.01% atropine in the 2-year LAMP-1 study.[32]

A total of 350 children who completed 2 years of the LAMP-1 study were included. Potential predictive factors for the change in SE and AL over 2 years were evaluated by generalised estimating equations in each treatment group. Evaluated factors included age at treatment, gender, baseline refraction, parental myopia, time outdoors, dioptre hours of near work and treatment compliance. In the 0.05%, 0.025% and 0.01% atropine groups, younger age was the only factor associated with SE progression (linear correlation coefficients of 0.14, 0.15 and 0.20, respectively) and AL elongation (linear correlation coefficient of −0.10, −0.11 and −0.12, respectively) over 2 years; the younger the age, the poorer the response (Figure 4). At each year of age from 4 to 12 across the treatment groups, higher concentrations showed a better treatment response, following a concentration-dependent effect ($p_{trend} < 0.05$ for each age group).

We showed a clear age-dependent effect of treatment responses to low-concentration atropine. Younger age was associated with poorer treatment response to low-concentration atropine. Among the

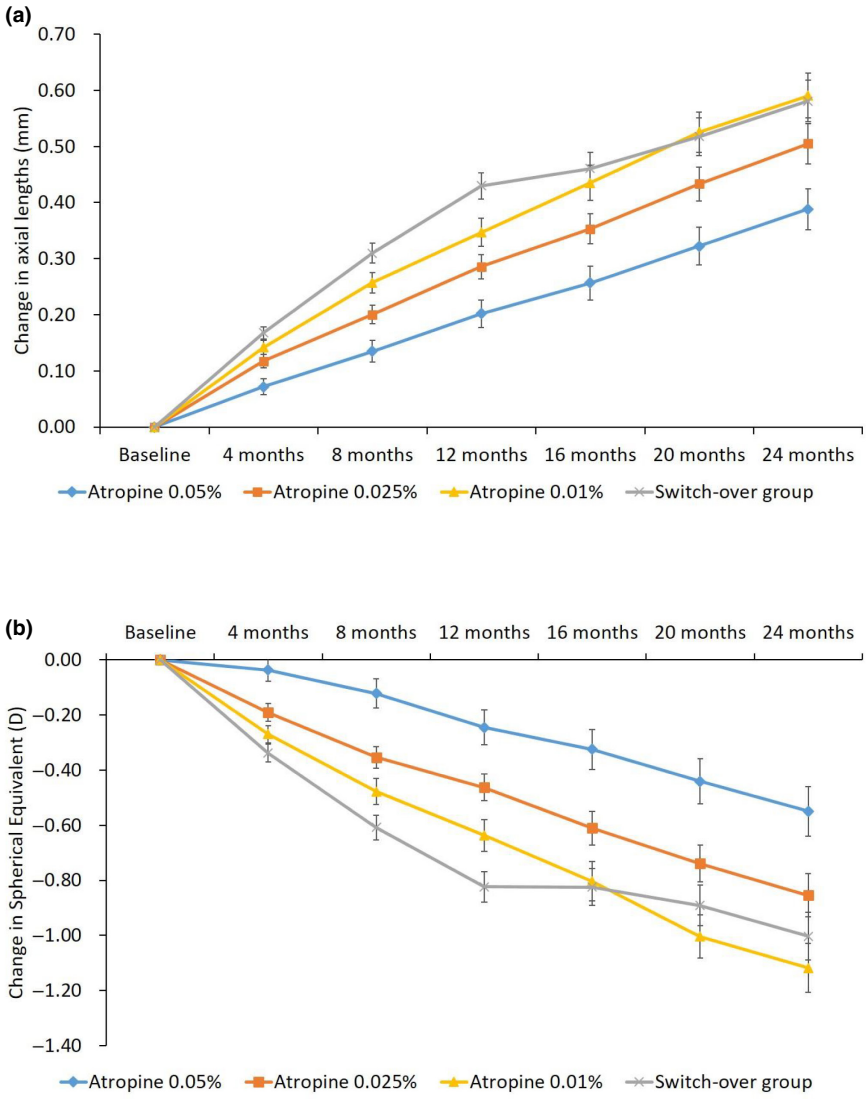

FIGURE 3 Changes in spherical equivalent (a) and axial length (b) for 0.05%, 0.025%, 0.01% and placebo groups over 2 years.

concentrations studied, younger children required the highest (0.05%) concentration to achieve a similar reduction in myopic progression compared with older children receiving lower concentrations. Younger age of onset is associated with high myopia development.[40] Given that younger children have the most years of myopic progression ahead of them to drive them into the highly myopic group, treatment of these children should be more aggressive to reduce the general burden of high myopia.

Biomarkers for treatment effect

In addition to the risk factors for treatment effects, there is a suggestion for using biomarkers to guide concentration titrations through the assessment of long-term treatment responses. In animal studies, the choroid has been found to play a role in the regulation of eye growth and refractive error development. We evaluated longitudinal changes in subfoveal choroidal thickness (SFChT) among children receiving 0.05%, 0.025% and 0.01% atropine.[33]

A total of 314 children with qualified choroidal data who completed 2 years of the LAMP-1 study were included. SFChT was measured at 4-monthly intervals using spectral domain optical coherence tomography. The 2-year changes in SFChT from baseline were 21.15 ± 32.99, 3.34 ± 25.30 and -0.30 ± 27.15 μm for the 0.05%, 0.025% and 0.01% atropine groups, respectively ($p < 0.001$). A concentration-dependent response was observed, with thicker choroids at higher atropine concentrations ($\beta = 0.89$, $p < 0.001$). Mean SFChT thickness increased significantly at 4 months in the 0.025% ($p = 0.001$) and 0.05% groups ($p < 0.001$) and then remained stable until the end of the second year ($p > 0.05$ for all groups) (Figure 5a). Over 2 years, an increase in SFChT was associated with slower SE progression ($\beta = 0.07$, $p < 0.001$) and reduced AL elongation ($\beta = -0.05$, $p < 0.001$).

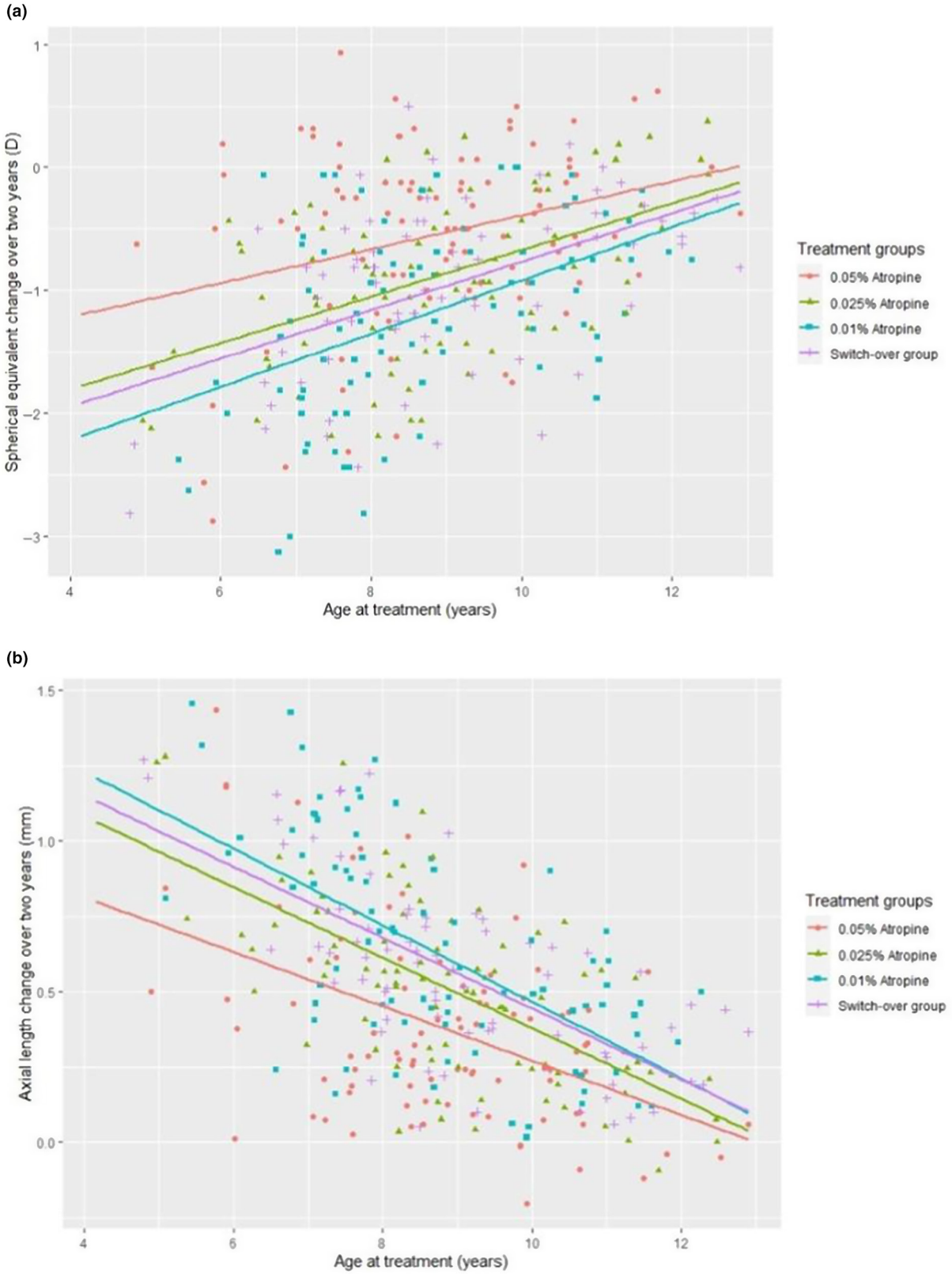

FIGURE 4 The association between age and changes in spherical equivalent (a) and axial length (b) with 0.05%, 0.025% and 0.01% atropine and placebo groups over 2 years.

In the mediation analysis, 18.5% of the effect on SE progression from 0.05% atropine was mediated via choroidal thickening (Figure 5b).

We revealed that low-concentration atropine induced choroidal thickening along a concentration-dependent response throughout the treatment period. Choroidal

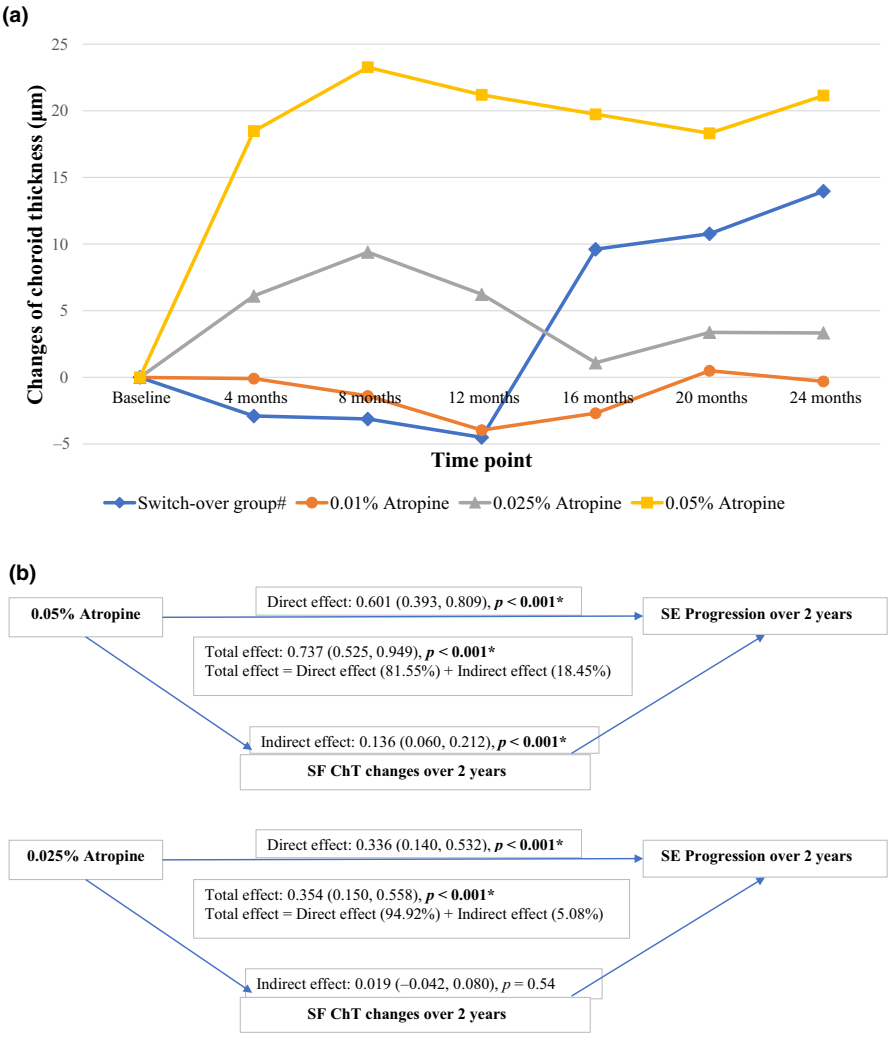

FIGURE 5 Changes in subfoveal choroidal thickness over 2 years. #Switch-over group: placebo in the first year and switched over to 0.05% atropine group in the second year (a) and mediation analysis regarding SE progression and choroidal thickening. The numbers in brackets represent the point estimates and confidence intervals of a mediation effect. *Significance level set at $p < 0.05$ (b). SE, spherical equivalent; SFChT, subfoveal choroidal thickness.

thickening was associated with slower SE progression and AL elongation among all the treatment groups. The anti-myopia effect of 0.05% atropine was partly mediated via choroidal thickening. Thus, the choroidal response can be used for the assessment of long-term treatment outcomes and as a guide for titrations of atropine concentration.

LAMP-1 study phase 3

In the third phase of the LAMP-1 study, we aimed to evaluate: (1) whether the efficacy of continued treatment (0.05%, 0.025%, 0.01% atropine) is better than stopping treatment during the third year, (2) the long-term efficacy of continued treatment of low-concentration atropine over 3 years and (3) the rebound effect and its associations with low-concentration atropine following treatment cessation.[30]

A total of 326 children completed 3 years of follow-up. During the third year, SE progression and AL elongation were faster in the washout subgroups than in the continued treatment groups across all concentrations: −0.68 ± 0.49 D versus −0.28 ± 0.42 D ($p < 0.001$) and 0.33 ± 0.17 mm versus 0.17 ± 0.14 mm ($p < 0.001$) for 0.05% atropine; −0.57 ± 0.38 D versus −0.35 ± 0.37 D ($p = 0.004$) and 0.29 ± 0.14 mm versus 0.20 ± 0.15 mm ($p = 0.001$) for 0.025% atropine and−0.56 ± 0.40 D versus −0.38 ± 0.49 D ($p = 0.04$) and 0.29 ± 0.15 mm versus 0.24 ± 0.18 mm ($p = 0.13$) for 0.01% atropine. Over the 3-year period, SE progressions were −0.73 ± 1.04, −1.31 ± 0.92 and −1.60 ± 1.32 D ($p = 0.001$) for the 0.05%, 0.025% and 0.01% groups in the continued treatment subgroups, respectively, and −1.15 ± 1.13, −1.47 ± 0.77 and −1.81 ± 1.10 ($p = 0.03$), respectively, in the washout subgroup (Figure 6a). The respective AL elongations were 0.50 ± 0.40, 0.74 ± 0.41 and 0.89 ± 0.53 mm ($p < 0.001$) for the continued treatment subgroups and 0.70 ± 0.47, 0.82 ± 0.37 and 0.98 ± 0.48 mm ($p = 0.04$) for the washout subgroup (Figure 6b). The rebound SE progressions during washout were concentration dependent, but their differences were

FIGURE 6 Changes in spherical equivalent (SE) (a) and axial length (AL) (b) in 0.05%, 0.025%, 0.01% and placebo groups over 3 years.

clinically small ($p = 0.15$). Older age was associated with smaller rebound effects in both SE progression (linear correlation coefficient = 0.08, $p < 0.001$) and AL elongation (linear correlation coefficient = −0.05, $p < 0.001$).

During the third year, continued atropine treatment achieved a better effect across all concentrations compared with the washout regimen. In our study, the mean age of the subjects was 8.34 and 10.89 years at the start of the first and third year, respectively. Therefore, we suggest continuation of atropine treatment at any concentration during the third year. The 0.05% solution remained the optimal concentration over 3 years in Chinese children. The differences in rebound effects were clinically small across all the three studied concentrations. Stopping treatment at an older age and receiving lower concentration were associated with a smaller rebound. Thus, both myopia progression rate and age factors should be considered when determining the cessation of atropine treatment. We suggest that low-concentration atropine treatment in children should be ended at an older age, when both the natural myopic progression rate and the rebound effect become smaller. In addition, we suggest a weaning-off strategy for stopping treatment, from higher to lower concentration and at an older age, when myopia progression becomes minimal.

CONCLUSIONS

During the COVID-19 pandemic, the incidence of myopia in Hong Kong has more than doubled, while outdoor time has decreased significantly and screen time increased among schoolchildren. Myopia development is expected to remain affected by the change in the children's lifestyle even beyond the COVID-19 pandemic. Parental myopia is a strong and independent factor associated with the child's myopia development, and the risk is 12 times higher for children whose parents are both highly myopic. Low-concentration atropine (0.05%, 0.025% and 0.01%) effectively reduces myopia progression with a concentration-related response. Furthermore, this concentration-dependent response was maintained, and all low concentrations were well tolerated throughout a 3-year follow-up period. Low-concentration atropine had no effect on corneal or crystalline lens power. An age-dependent effect was observed in each treatment group at all concentrations tested, although younger age was associated with a poor treatment response to low-concentration atropine. Low-concentration atropine induced choroidal thickening with a concentration-dependent response throughout the treatment period. During the third year of the trial, continued treatment achieved a better effect across all concentrations compared with the washout regimen. Stopping treatment at an older age and lower concentrations are associated with a smaller rebound effect, although the difference in rebound was clinically small across all the three atropine concentrations studied.

AUTHOR CONTRIBUTIONS

Jason C. Yam: Conceptualization (lead); funding acquisition (equal); investigation (equal); methodology (equal); writing – original draft (equal). **Xiu Juan Zhang:** Funding acquisition (equal); investigation (equal); writing – original draft (equal). **Ka Wai Kam:** Investigation (equal); writing – review and editing (equal). **Li Jia Chen:** Funding acquisition (equal); investigation (equal); writing – review and editing (equal). **Clement C. Tham:** Supervision (equal); writing – review and editing (equal). **Chi Pui Pang:** Conceptualization (equal); supervision (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest exist for any of the authors.

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