• Meta-Analysis •

The differential effects of lutein and zeaxanthin supplementation on myopia prevention in adolescents: a systematic review and Meta-analysis

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Abstract

• **AIM:** To conduct a systematic review and Meta-analysis to determine the differential effects of combined lutein and zeaxanthin supplementation on myopia prevention in teenagers. It also investigates the effects of supplements dosage, intervention duration, and geographical variation on intervention results.

• **METHODS:** A systematic search and screening of randomized controlled trials (RCTs) completed between 2014 and 2023 was undertaken using the PubMed, EMBASE, Cochrane Library, and Web of Science databases, in accordance with the PRISMA recommendations. The Cochrane risk of bias method was used to assess the quality of the studies. A Meta-analysis was performed using Stata 17.0 to calculate standardized mean differences (SMDs) and 95% confidence intervals (CIs). Subgroup analyses were performed to look at the effects of different doses, intervention periods, and geographic areas. Additionally, publication bias was assessed using Egger's test.

• **RESULTS:** Ten studies including 1035 participants with myopia were analyzed. Supplementation with lutein and zeaxanthin resulted in a significant reduction in axial length elongation among adolescents in the intervention group (SMD=-0.40, *P*=0.001), an increase in macular pigment optical density (SMD=0.50, *P*=0.010), and an enhancement in visual sensitivity (SMD=0.53, *P*=0.008). Subgroup analyses revealed that participants receiving high doses and those undergoing intervention for more than 12mo exhibited significantly improved outcomes compared to those in the low-dose and short-term groups (high-dose *vs* low-dose: SMD=-0.41 *vs* -0.22, *P*=0.003; >12mo *vs* 6-12mo: SMD=-0.43 *vs* -0.23, *P*=0.004, respectively). Furthermore, Egger's test indicated no significant publication bias (*P*=0.094).

• **CONCLUSION:** Combined lutein and zeaxanthin supplementation has a significant effect on myopia prevention in adolescents, with more pronounced benefits observed in high-dose and long-term interventions. The findings provide scientific evidence for its use as an adjunctive approach in myopia control.

• **KEYWORDS:** lutein; zeaxanthin; myopia prevention; Meta-analysis

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INTRODUCTION

Myopia is experiencing a rapid rise among adolescents globally, becoming one of the major public health challenges. Adolescence is a critical period for ocular development, and excessive elongation of the axial length is widely recognized as an important physiological basis for the progression of myopia[1]. Although various intervention strategies have been attempted to slow myopia progression, their effectiveness remains limited and shows significant individual variability. Lutein and zeaxanthin, two essential carotenoid components, have been demonstrated to possess biological functions in protecting the retina and enhancing optical defense in the macular region. However, their specific effects on myopia prevention in adolescents have not been comprehensively and systematically evaluated[2-3]. Current research mainly focuses on single observational studies and short-term experiments involving different populations.

Systematic reviews and Meta-analyses regarding the combined supplementation of lutein and zeaxanthin in delaying myopia progression among adolescents are still lacking. This gap in research has resulted in a lack of systematic evidence on key issues such as dosage, intervention duration, and individual differences, which hinders the broader application of these supplements in practice. Therefore, clarifying the specific effects of lutein and zeaxanthin on myopia prevention in adolescents, particularly under varying doses, intervention durations, and regional differences, is of significant clinical importance[4-5].

This research endeavor is designed to assess the impact of combined lutein and zeaxanthin supplementation on the prevention of myopia in adolescents, utilizing a systematic review and Meta-analysis approach. The study aims to investigate various factors that may influence the outcomes of the intervention, such as the dosage of supplementation, the duration of the intervention, and regional differences. Through the application of robust statistical methodologies, this study aims to furnish scientific evidence regarding the clinical utility of these two compounds, emphasizing their efficacy and safety. The findings are intended to provide innovative insights and serve as a valuable resource for clinical practice.

MATERIALS AND METHODS

Study Design This study is a systematic review and Meta-analysis based on publically available literature, with the goal of determining the various effects of lutein and zeaxanthin on the prevention of myopia in teenagers. The investigation was rigorously carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria, which comprised detailed stages such as literature search, data extraction, risk of bias assessment, and statistical analysis. Each part of the investigation was carried out with strict adherence to established standards and specific protocols to ensure the scientific integrity and reproducibility of the findings.

Literature Search Strategy A systematic search was conducted in the PubMed, EMBASE, Cochrane Library, and Web of Science databases, covering the time period from January 2014 to December 2024. The search strategy utilized Boolean logic combinations of keywords such as “lutein”, “zeaxanthin”, “myopia prevention”, “adolescents”, and “randomized controlled trial”. The specific search logic involved combining each keyword using AND and OR to construct a comprehensive search expression, ensuring the inclusion of all potentially relevant studies. The entire search process was independently carried out by two researchers, and each step was meticulously documented. This included recording the search dates, keyword combinations, and the number of studies retrieved.

Inclusion and Exclusion Criteria

Inclusion criteria 1) Participants were adolescents (10–18 years old) who had not undergone any refractive surgery; 2) The study design was a randomized controlled trial (RCT), investigating the effects of lutein or zeaxanthin supplementation, either alone or in combination, on myopia prevention; 3) The study provided at least one objective outcome measure, such as axial length (in millimeters), visual acuity (logMAR), or macular pigment optical density (MPOD); 4) The intervention duration was at least 6mo to ensure stability of the supplementation effects.

Exclusion criteria 1) Participants who had undergone refractive correction surgery; 2) Studies that were not RCTs or did not report complete outcome data; 3) Studies with an intervention duration of less than 6mo or with a sample size of fewer than 30 participants; 4) Studies that did not provide detailed information on the dosage and intervention specifics of lutein or zeaxanthin supplementation.

The screening of all studies was independently conducted by two researchers, who evaluated each study against the predefined criteria. If any disagreement arose regarding the inclusion of a study, a third researcher made the final decision. To maintain openness, the research selection process was recorded using a PRISMA flow diagram.

Data Extraction A comprehensive data extraction process for studies that met the inclusion criteria was carried out by two independent researchers, adhering to the following systematic steps: 1) Basic information: The initial author’s name, year of publication, and country of study were extracted to verify the sources’ clarity and traceability. 2) Participant characteristics: To determine the population’s characteristics and representativeness, we documented the sample size, mean age, gender ratio, and baseline refractive status. 3) Intervention details: Information regarding the dosage of lutein and zeaxanthin supplementation (measured in mg/day), duration of the intervention (in months), whether the supplements were administered in combination, and the mode of supplementation (*e.g.*, oral capsules or fortified food) was documented to facilitate comparisons across studies.

Key outcome data were systematically extracted, which included: 1) Axial length (mm): Baseline and post-intervention measurements were evaluated to assess changes in myopia progression. 2) Visual acuity (logMAR): Pre- and post-intervention visual acuity measurements were recorded to determine improvements in visual function. 3) MPOD: Baseline and post-intervention values were collected to evaluate the protective effects of lutein and zeaxanthin on the macula. 4) Adverse effects and safety: All adverse reactions associated with lutein or zeaxanthin were documented, including their types, frequencies, and severity, to clarify the

safety profile of these supplements. All data were meticulously recorded using standardized forms that encompassed all relevant study characteristics and outcome measures. Prior to data extraction, the researchers participated in consistency training to standardize the procedures. Two researchers extracted data separately, and any inconsistencies were handled by a third researcher. Each data point was thoroughly checked to verify its completeness and correctness.

Risk of Bias Assessment The Cochrane Risk of Bias Tool was employed to systematically evaluate the quality of all studies included in the analysis[6]. The assessment concentrated on the following criteria: 1) Random sequence generation: Evaluating whether randomization techniques, such as computer-generated random sequences, were implemented. 2) Allocation concealment: Verifying that the allocation process was concealed, for instance, through the use of opaque envelopes. 3) Blinding: Determining whether both participants and researchers were blinded to group assignments to mitigate the risk of bias. 4) Integrity of outcome data: Investigating the management of missing data and the application of intention-to-treat (ITT) analysis. 5) Selective reporting bias: Assessing the presence of any unreported pre-registered outcomes. Each risk of bias evaluation was conducted independently and scored by two researchers, with any discrepancies resolved through arbitration by a third researcher.

Statistical Analysis

Heterogeneity analysis The degree of heterogeneity among the studies was evaluated utilizing the I^2 statistic. An I^2 value exceeding 50% indicated substantial heterogeneity, warranting the application of a random-effects model. Conversely, if the I^2 value was 50% or lower, a fixed-effects model was employed. Further investigation into the sources of heterogeneity was conducted through Meta-regression analysis.

Effect size calculation Standardized mean differences (SMDs) along with their corresponding 95% confidence intervals (CIs) were computed to quantify the overall effect of lutein and zeaxanthin on the prevention of myopia. The calculations for effect size were executed using the “metan” module in Stata version 17.0.

Subgroup analysis Subgroup analyses were performed based on various factors including supplementation dosage (low dose <10 mg/day, high dose ≥10 mg/day), intervention duration (6-12mo, >12mo), ethnicity (Asian, European/American), and regional differences, in order to assess their influence on the outcomes of the intervention. For each subgroup, SMDs and 95%CIs were calculated, and forest plots were generated for visual representation.

Sensitivity analysis Individual studies were excluded sequentially to assess their impact on the Meta-analysis’s overall conclusions. Specifically, one study was excluded at a time, and SMDs were recalculated to see whether any single study had a substantial influence on the robustness of the overall results.

Publication bias assessment The presence of publication bias was determined *via* eye inspection of funnel plots and Egger’s test. A significance level of $P<0.05$ was set for this evaluation.

RESULTS

Basic Characteristics of Included Studies The preliminary search resulted in the identification of 200 articles. Following the elimination of 100 duplicate entries, 50 articles were excluded after a review of titles and abstracts, as they did not satisfy the inclusion criteria. A comprehensive evaluation of the full texts of the remaining 50 articles was conducted, leading to the exclusion of 40 articles due to issues such as incomplete data, a high risk of bias, or insufficient sample sizes. Consequently, a total of 10 RCTs were deemed suitable for inclusion in the Meta-analysis (Figure 1).

The basic characteristics of the included studies are summarized in Table 1[1-10]. All interventions involved the combined supplementation of lutein and zeaxanthin, with intervention durations ranging from 6 to 18mo. Participants were adolescents, with a balanced gender ratio. The studies were conducted across diverse regions, including Asia and Europe/North America, with sample sizes ranging from 85 to 150, ensuring representativeness and scientific reliability (Table 1).

Risk of Bias Assessment The findings from the risk of bias assessment revealed that the majority of the studies were classified as having a low risk concerning random sequence generation, allocation concealment, and blinding. This indicated that the studies included in the analysis were of high quality and appropriate for Meta-analysis (Table 2[1-10]). While certain studies demonstrated a high risk or an unclear risk in terms of selective reporting and the completeness of outcome data, the overall risk of bias remained low, thereby bolstering the reliability of the results obtained from the Meta-analysis.

Meta-Analysis Results of Visual Intervention Effects The SMD for axial length between the intervention and control groups was illustrated through a forest plot (Figure 2A). The majority of studies indicated a significant decrease in axial length within the intervention group, resulting in a statistically significant overall effect[7] (P=0.001). The heterogeneity among the studies was assessed as moderate (I^2=41.2%), suggesting a degree of consistency in the findings across the studies.

Furthermore, the effects of low-dose and high-dose supplementation on axial length were also depicted in a forest plot (Figure 2B). The effect size for the high-dose group was considerably more pronounced than that of the low-dose group, with SMDs recorded at -0.41 and -0.22, respectively.

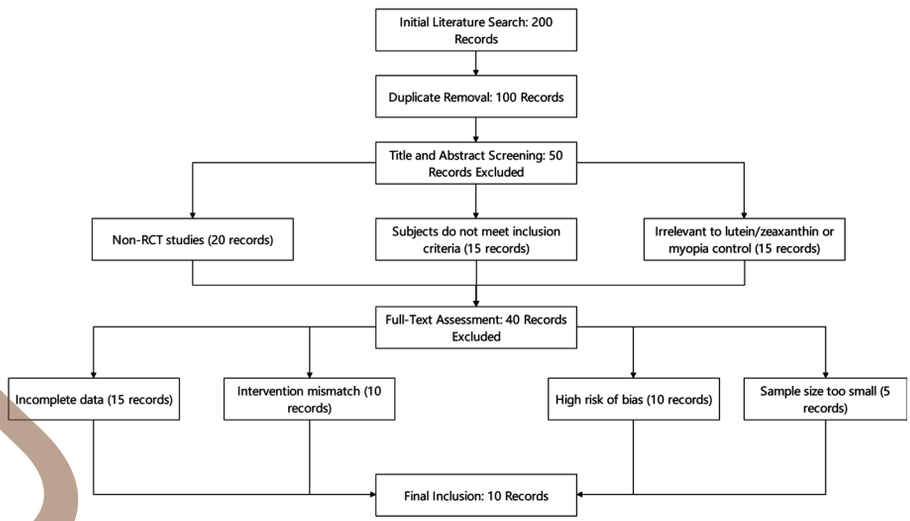

Figure 1 PRISMA flow diagram for literature screening RCT: Randomized controlled trial.

Table 1 Basic characteristics of included studies

First author	Year of publication	Sample size	Mean age (y)	Gender ratio (male: female)	Intervention type	Duration (mo)	Region
Lopresti[1]	2022	85	14.3±1.42	38 (45%): 47 (55%)	Lutein+Zeaxanthin	12	Europe/North America
Wilson[2]	2021	120	13.8±1.12	60 (50%): 60 (50%)	Lutein+Zeaxanthin	9	Europe/North America
Liu[3]	2014	100	15.6±1.56	52 (52%): 48 (48%)	Lutein+Zeaxanthin	6	Asia
Yoshida[4]	2023	95	12.7±1.09	46 (48%): 49 (52%)	Lutein+Zeaxanthin	18	Asia
Fitzpatrick[5]	2022	150	14.9±1.72	80 (53%): 70 (47%)	Lutein+Zeaxanthin	12	Europe/North America
Wang[6]	2022	110	13.4±1.03	54 (49%): 56 (51%)	Lutein+Zeaxanthin	9	Asia
Arunkumar[7]	2023	88	14.5±1.67	41 (47%): 47 (53%)	Lutein+Zeaxanthin	6	Asia
Csader[8]	2022	105	13.9±1.28	53 (50%): 52 (50%)	Lutein+Zeaxanthin	15	Europe/North America
Ceravolo[9]	2019	90	14.1±1.31	46 (51%): 44 (49%)	Lutein+Zeaxanthin	9	Europe/North America
Sahin[10]	2019	92	15.2±1.41	42 (46%): 50 (54%)	Lutein+Zeaxanthin	12	Asia

Table 2 Risk of bias assessment results

Study	Random sequence generation	Allocation concealment	Blinding	Outcome data completeness	Selective reporting bias
Lopresti 2022[1]	Low risk	Low risk	Low risk	Low risk	Low risk
Wilson 2021[2]	Unclear	Low risk	High risk	Low risk	Unclear
Liu 2014[3]	Low risk	High risk	Unclear	High risk	Low risk
Yoshida 2023[4]	Low risk	Low risk	Low risk	Low risk	Low risk
Fitzpatrick 2022[5]	High risk	Unclear	High risk	Low risk	Unclear
Wang 2022[6]	Low risk	Low risk	Low risk	Low risk	Low risk
Arunkumar 2023[7]	Unclear	Low risk	Low risk	Low risk	Low risk
Csader 2022[8]	Low risk	High risk	Unclear	Low risk	High risk
Ceravolo 2019[9]	Low risk	Unclear	High risk	High risk	Unclear
Sahin 2019[10]	Low risk	Low risk	Unclear	Low risk	Low risk

The overall *P*-value indicated a significantly greater effect associated with the high-dose group (*P*=0.003). Heterogeneity analysis demonstrated moderate variability within the groups, with I^2 values of 42.0% and 39.1%.

The impact of intervention duration on axial length was visualized using a forest plot (Figure 2C). Interventions lasting more than 12mo showed more pronounced effects[8], with an SMD of -0.43 and *P*=0.004, demonstrating statistical significance. By comparison, interventions lasting 6-12mo had weaker effects, with an SMD of -0.23 and lower heterogeneity (I^2=34.8%).

The influence of ethnicity on axial length was presented in a forest plot (Figure 2D). Results indicated significant intervention effects in both groups: the European/North American group had an SMD of -0.29 (*P*=0.010), while the Asian group had an SMD of -0.24 (*P*=0.022). The heterogeneity was moderate in both groups (I^2=34.2% and 35.5%, respectively), suggesting consistent effects across studies.

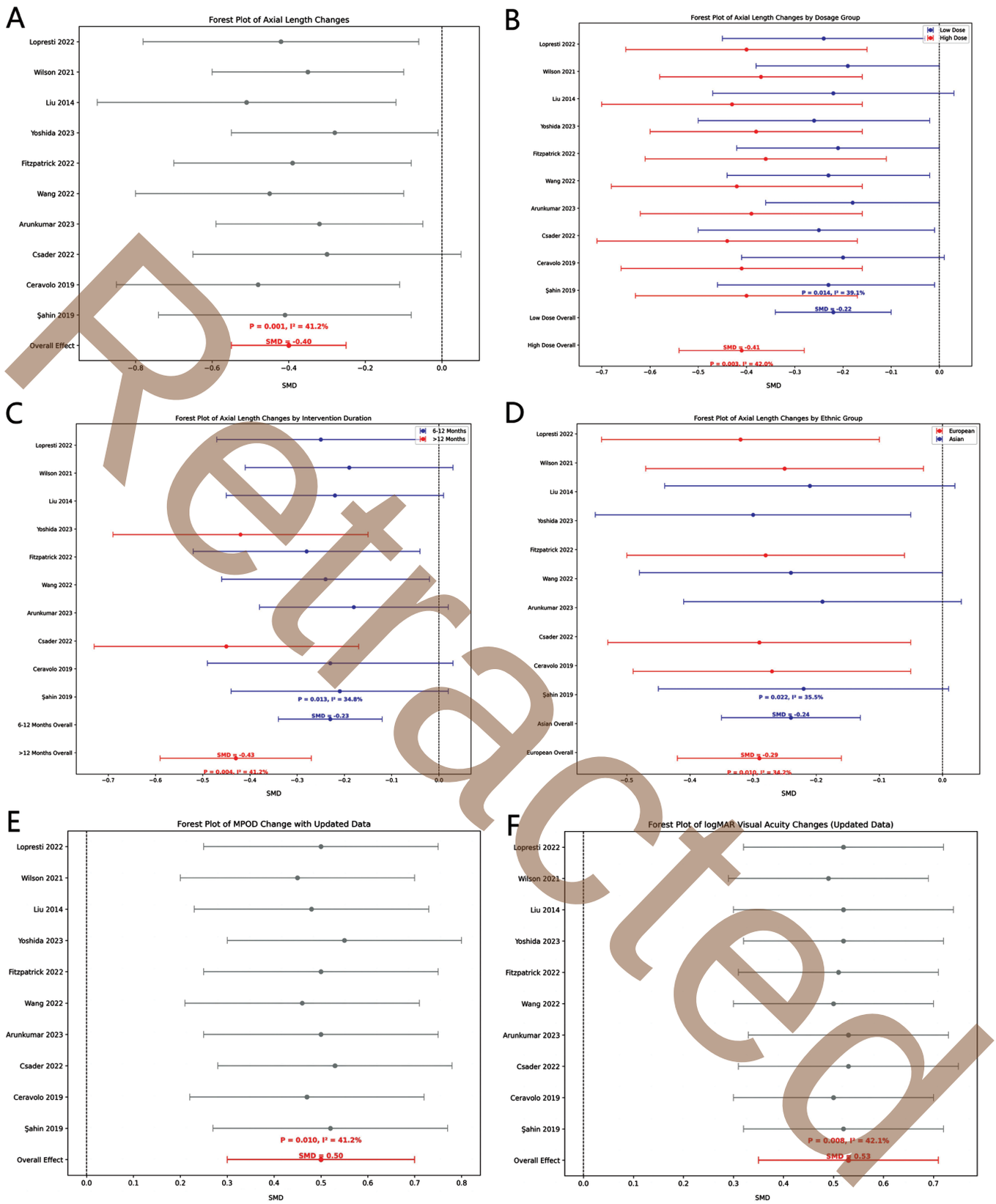

Figure 2 Effects of lutein and zeaxanthin supplementation on myopia prevention in adolescents A: Forest plot of SMDs for axial length; B: Subgroup analysis forest plot—effects of different supplementation doses on axial length; C: Subgroup analysis forest plot—effects of intervention duration on axial length; D: Subgroup analysis forest plot—effects of ethnicity (Asian, European/North American) on axial length; E: Trend analysis of macular pigment optical density (MPOD) changes; F: Comparison of visual acuity (logMAR) results. Forest plots were generated using Meta-analysis, displaying SMDs with 95%CIs. CI: Confidence interval; SMD: Standardized mean difference.

In the Meta-analysis examining changes in MPOD, the intervention group exhibited an overall effect size of 0.50, which was statistically significant (P=0.010). The heterogeneity among the studies was moderate, with an I^2 value of 41.2%, suggesting consistent and significant positive effects of lutein and zeaxanthin supplementation on enhancing MPOD[9] (Figure 2E).

Furthermore, the intervention group demonstrated notable improvements in visual acuity (logMAR) within the Meta-analysis, yielding a combined effect size of 0.53 (P=0.008). The heterogeneity in this analysis was also moderate, with an I^2 value of 42.1%. These findings indicate that the combined supplementation of lutein and zeaxanthin consistently and positively influences visual enhancement (Figure 2F).

Safety and Adverse Events In the Meta-analysis of side effects and adverse events, the combined effect size (Figure 3) indicated a slightly increased risk of adverse events in the lutein+zeaxanthin group. However, this increase was not statistically significant[10] (P=0.101). The 95%CIs of several studies crossed the baseline [relative risk (RR=1)], suggesting that there was no significant overall increase in the risk of side effects.

Sensitivity Analysis and Assessment of Publication Bias The sensitivity analysis, which involved the sequential exclusion of individual studies, indicated no substantial variations in the overall effect size (SMD) as illustrated in Figure 4A. The overall effect size exhibited minimal fluctuations, with all data points remaining in close proximity to the original combined effect size (SMD=0.50), thereby reflecting a high degree of robustness and reliability in the findings.

Furthermore, the evaluation of publication bias indicated that the data points in the funnel plot were distributed relatively symmetrically around the centerline. The P-value obtained from Egger's test was 0.094 (Figure 4B), which did not achieve statistical significance (P>0.05), thereby suggesting the absence of significant publication bias. Collectively, the results of the analysis demonstrated a strong level of stability.

Fragility Index of Study A fragility index of the study is 29 which indicates that if 29 patients in the experimental group were "converted" from NOT having the primary endpoint to HAVING the primary endpoint, the study would lose statistical significance (P>0.05). The higher the fragility index, the more robust the results of a study are. Fragility index of the study is given in Table 3.

DISCUSSION

The findings of this study, derived from a Meta-analysis, indicate that the combined supplementation of lutein and zeaxanthin has a beneficial impact on the prevention of myopia in adolescents. Specifically, the supplementation is associated with a reduction in axial length, an increase in MPOD, and an enhancement in visual acuity. These significant outcomes are clearly depicted in the forest plots (Figure 2A, 2E, and 2F), which illustrate marked improvements in the intervention group relative to the control group. The notable decrease in axial length observed in the intervention group suggests that lutein and zeaxanthin supplementation may inhibit the axial elongation of the eye, thereby contributing to the mitigation of myopia progression[11]. Axial length serves as a critical biological marker for the development of myopia, and these results carry considerable clinical implications for myopia management. Furthermore, the increase in MPOD indicates a protective role of these nutrients on the macular region of the retina. This is particularly relevant during the pivotal phase of visual system development in adolescents, as an increase in MPOD may enhance optical defense mechanisms, thereby reducing the detrimental effects of high-energy blue light on the retina and indirectly slowing the progression of myopia[12]. Additionally, the significant improvement in visual acuity further corroborates the positive influence of lutein and zeaxanthin on visual function. By enhancing contrast sensitivity and minimizing glare interference, supplementation with these compounds effectively improves visual quality[13-14]. Overall, these findings suggest that lutein and zeaxanthin may play a valuable supportive role in the prevention of myopia among adolescents through various biological mechanisms, including the reduction of oxidative stress, stabilization of retinal structure, and enhancement of visual function[15]. The combined supplementation of these compounds presents a potential adjunctive strategy in myopia control, offering promising options in a field that currently faces a shortage of effective interventions.

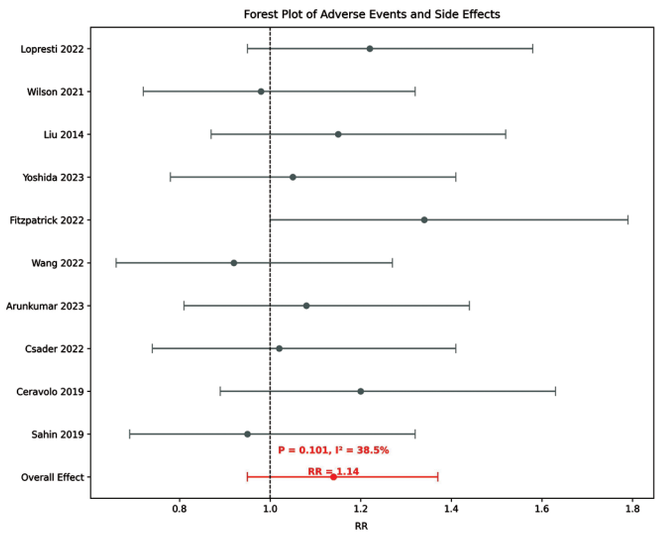

Figure 3 Summary of side effects and adverse events; the forest plot was generated using Meta-analysis, displaying RR with 95%CI SMD: Standardized mean differences; CI: Confidence interval; RR: Relative risk.

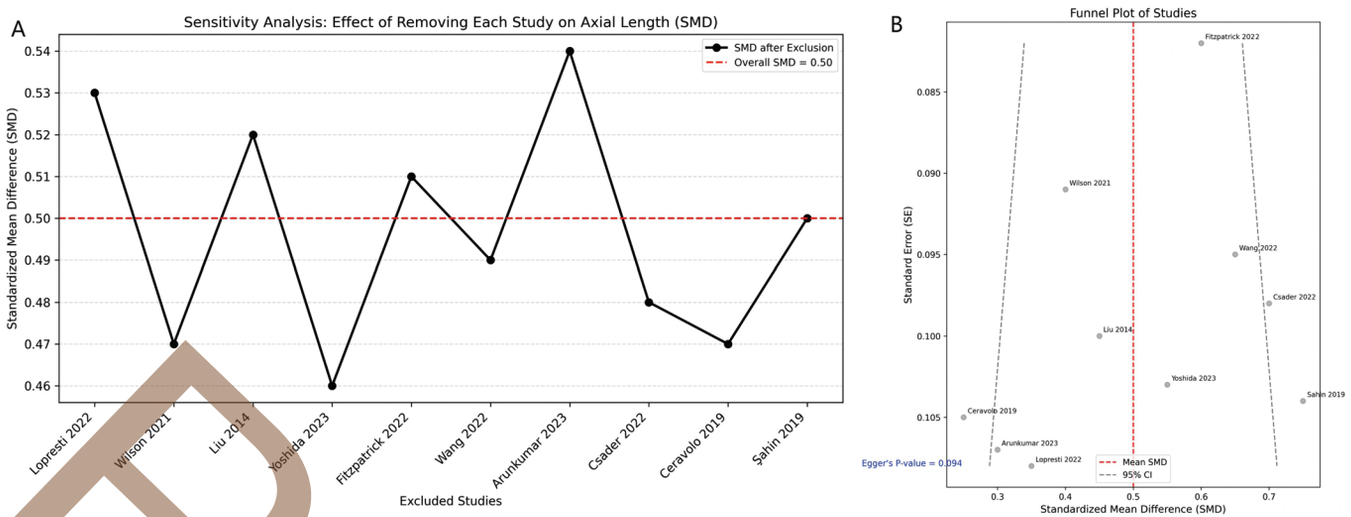

Figure 4 Sensitivity analysis and publication bias assessment A: Sensitivity analysis results—impact of sequential exclusion of studies on the effect size for axial length; B: Funnel plot—publication bias assessment. The funnel plot's symmetry was statistically examined using Egger's test to detect the presence of publication bias.

Table 3 Fragility index of the study

Items	Original study	Fragility index	Fragile study
Control group with outcome (*n*)	260		260
Control group without outcome (*n*)	240		240
Experimental group with outcome (*n*)	200	+ 29	229
Experimental group without outcome (*n*)	300	- 29	271
P	<0.001		0.058

The findings from the subgroup analysis indicated that factors such as supplementation dosage, duration of intervention, and regional variations significantly impacted the efficacy of lutein and zeaxanthin in preventing myopia among adolescents. Notably, the high-dose group exhibited a markedly greater reduction in axial length compared to the low-dose group, implying that an increased dosage may be pivotal in mitigating axial elongation[16-17]. The bioactive properties of lutein and zeaxanthin appear to be more effective at elevated concentrations in addressing retinal oxidative stress, thereby decelerating axial elongation. This observation serves as a crucial reference for establishing appropriate supplementation dosages. Furthermore, the duration of the intervention emerged as a significant determinant of outcomes. Data revealed that groups undergoing interventions lasting over 12mo experienced substantially greater reductions in axial length than those with shorter intervention periods[18]. Given that myopia progression in adolescents is a continuous phenomenon, prolonged interventions may yield a more stable biological effect of these nutrients, effectively curtailing further myopia progression. Consequently, adequate intervention duration is essential for sustaining the efficacy of myopia prevention, thereby supporting the formulation of long-term supplementation strategies in the future. Additionally, the influence of regional differences on intervention outcomes warrants attention. Research indicated that the European and North American cohort experienced a more pronounced reduction in axial length compared to their Asian counterparts[19-20]. This disparity may reflect inherent biological differences in the visual systems across various ethnic groups, as well as environmental factors such as lifestyle and dietary practices. Populations in Europe and North America may exhibit heightened responsiveness to supplementation, potentially due to increased exposure to daylight, elevated levels of outdoor activity, and a greater dietary intake of natural lutein and zeaxanthin. This finding underscores the necessity for researchers to investigate personalized supplementation strategies in the future to optimize effects across diverse populations. Customizing the application of lutein and zeaxanthin could enhance their efficacy in myopia prevention, thereby rendering their protective roles more precise and effective.

The Meta-analysis found that combined lutein and zeaxanthin supplementation was usually safe in teenage groups, with no substantial increase in adverse events. Most studies' CIs crossed the baseline (RR=1), and the overall effect size was not statistically significant (*P*=0.101), indicating that using these supplements did not significantly increase the likelihood of unpleasant responses. Common side effects, such as gastrointestinal discomfort and skin responses, were mild to moderate, with no reports of severe adverse events

that necessitated intervention withdrawal[21]. However, other trials found a slightly increased frequency of adverse events with higher-dose therapies, emphasizing the significance of precise dosage management to reduce possible side effects[22]. For teenagers, safety is an important consideration for clinical acceptance and long-term use. The outcomes of this study imply that lutein and zeaxanthin, in appropriate dose levels, are safe as dietary supplements for myopia prevention and justify further research and implementation. Nonetheless, clinical practice should carefully balance dose and possible dangers to ensure maximum safety and efficacy.

Study Limitations and Future Research Directions This study conducted a systematic review and Meta-analysis following PRISMA guidelines. However, the heterogeneity analysis revealed some differences among studies, potentially caused by variations in study design, participant characteristics, intervention dosages, and durations. Another limitation is the relatively small sample size, which may negatively impact the stability of effect estimates and reduce the reliability of the results. The evaluation of publication bias showed an Egger's test *P*-value of 0.094, which, although not statistically significant, suggests a potential risk of bias that should not be overlooked. Future research should focus on large-scale, multicenter RCTs to ensure external validity and reliability of the results. Individualized intervention studies are also necessary to better understand how different ethnicities and lifestyles influence the efficacy of lutein and zeaxanthin in myopia prevention. This would allow for the optimization of supplementation protocols and improve the precision of prevention strategies.

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Conflicts of Interest: Pei L, None; **Mo Y,** None; **Duan JG,** None.

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