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REVIEW ARTICLE

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Spatial frequency of environments and myopia: A systematic review on associated evidence and underlying mechanisms

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Abstract

Purpose: Previous animal studies have found a relationship between spatial frequency and myopia. New research in humans suggest that reduced high spatial content of the visual environment may be a contributing factor for myopia development. This study aims to review the literature and elucidate the potential biological mechanisms linking spatial frequency and myopia.
Methods: A systematic search was conducted across PubMed and Web of Science databases. The studies published from their inception to August 2024 that have explored the connection between spatial frequency and myopia. Only full-text articles in English were included. PRISMA was used for data validity.
Results: A total of 13 articles were included in this review, comprising seven animal model studies, four population-based studies, one pictorial analysis and one study on research design. Epidemiological evidence is comparatively limited and has only begun to emerge in recent years. Mid- to high spatial frequencies were found to play an important role in the emmetropization process of the eye. Low spatial frequencies can increase the risk of myopia incidence. Furthermore, the potential mechanisms of how spatial frequency affects myopia are summarized as visual information processing characteristics, eye accommodation function and eye movements, contrast sensitivity and relevant molecules involved in the pathway.
Conclusion: The evidence suggests that indoor spatial frequency may be related to the development of myopia. Further studies are warranted to understand if the incorporation of changes in indoor environments is helpful in the prevention and control of myopia.

KEYWORDS
myopia, spatial frequency, systematic review

1 | INTRODUCTION

Myopia, or nearsightedness, is one of the most common refractive errors among children and adolescents, representing a significant global public health concern (Dolgin, 2015; Jonas et al., 2021). Over the years, the global prevalence of myopia, particularly in East Asian countries and Singapore, has been on the rise (Morgan et al., 2018; Spillmann, 2020). By 2050, it is estimated that 5 billion people worldwide will be affected by myopia, with one in every 10 experiencing high myopia (Holden et al., 2016). Characterized by its high prevalence and a marked shift towards younger age groups, myopia poses an elevated risk for the development of high myopia, which in turn predisposes individuals to vision-threatening complications such as myopic macular degeneration and retinal detachment (Flitcroft et al., 2019; Sun et al., 2015). Furthermore, the economic burden of treating myopia is substantial. According to a study by Fricke et al. (Fricke et al., 2023), basic correction of myopia such as single-vision lenses are costly, amounting to US$7437 in Australia and US$8006 in China (lifetime). Treatments for myopia progression, including atropine eye drops, myopia control spectacles, myopia control multifocal soft contact lenses and orthokeratology, are significantly more expensive than corrective interventions (Ma et al., 2022). Consequently, the financial investment required to manage myopia represents a considerable expense for both society and individual families. Given the multifaceted aetiology of myopia, identifying and addressing its risk factors, particularly modifiable environmental and behavioural, are paramount for effective prevention and control strategies (Bullimore et al., 2021; Jonas et al., 2021).

Beyond the wavelength and illuminance of light, spatial frequency has emerged as a potential protective factor of outdoor activities against myopia (Flitcroft et al., 2020; Schaeffel, 2006). Spatial frequency is defined as the number of cycles per degree of visual angle of sinusoidal modulation of light and dark elements within an image or stimulus, measured in cycles per degree (cpd). (L & K, 1990). In everyday life, this pertains to the spatial arrangement, distribution of objects and contrast levels in the environment (Flitcroft et al., 2020). For the human eye, spatial frequency represents the number of alternations of a sinusoidal grating within a given visual angle, indicating the rate of change between light and dark stripes (Hess et al., 2006; Tolhurst et al., 1992). Lower spatial frequencies correspond to slower changes, while higher spatial frequencies signify more rapid alterations (Hess et al., 2006). Cells within the visual system exhibit distinct spatial frequency properties, and their concerted action contributes to the eye's differential sensitivity to various spatial frequencies (Chen et al., 2018). Scene recognition, a swift, automated and reliable process, relies heavily on the efficient encoding of complex natural scenes, where spatial frequency attributes play a pivotal role (Kauffmann et al., 2015; Kihara & Takeda, 2010). Visual analysis extracts features from different spatial frequencies, primarily following a 'coarse-to-fine' processing sequence (Bullier, 2001; Kauffmann et al., 2015). Research has indicated that responses to spatial frequency vary across different refractive states, suggesting a potential influence on myopia (Day et al., 2009; Maiello et al., 2017). However, although research on the characteristics of spatial frequency in the field of computer vision began over 40 years ago, studies linking it to myopia started slightly later, and currently, they mainly involve animal models and visual image studies (Kerber et al., 2016; McGonigle et al., 2016; Schmid & Wildsoet, 1997). Despite these efforts, a systematic understanding of how spatial frequency modulates myopia remains elusive, especially from a public health perspective, which limits its translation into health intervention measures and policies.

This review aims to describe the association between spatial frequency and myopia, combining the results from both animal models and human epidemiological studies. By examining the underlying biological mechanisms, we seek to uncover potential avenues for research in the prevention and management of myopia.

2 | MATERIALS AND METHODS

Literature regarding the association between myopia and spatial frequency was collected, using Medical Subject Headings (MeSH) and free words combined with [('spatial frequency' or 'space spectrum') and ('myopia' or 'nearsightedness' or 'refractive error' or 'ametropia')] from their inception to August 2024. The search was done on Web of Science and PubMed databases. All retrieved articles were imported into EndNote 21 for management and screening. This review was performed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analyses) statement (Page et al., 2021). We registered the protocol of our study in the International Prospective Register of Systematic Reviews (CRD42024585924).

The studies were selected according to the following criteria: (1) the research topic is related to spatial frequency and myopia or to indicators associated with myopia, including axial length, corneal radius, anterior chamber depth and so on; (2) the research is published in English; (3) the articles are full-text publications; (4) the study subjects are populations or animals, excluding reviews, case reports, conference abstracts and editorials. The selection process is independently conducted by two researchers, and in the event of a disagreement, a third person joins the judgement. The primary outcome was spherical equivalent, while the secondary outcomes included myopia-related indicators including axial length, corneal radius, anterior chamber depth and vitreous chamber depth. As the research object was the relationship between spatial frequency and myopia, underlying pathological mechanisms, illumination and spectrum were excluded from this overview. The retrieval identified 340 articles, and ultimately, 13 articles were included. The flow chart of the study was shown in Figure 1.

The quality of population studies was evaluated using the Newcastle-Ottawa Quality Scale (NOS). This scale evaluates research based on selection of study groups, comparability of groups and ascertainment of the outcome of interest. Studies scoring between 7 and 9 were classified as high quality, 4 to 6 as moderate quality, and 3 or less as low quality (Stang, 2010). For animal studies, the Stroke Therapy Academic Industry Roundtable (STAIR) was employed to assess the quality (Fisher et al., 2009). The STAIR has formulated 'Guidelines for Maintaining Rigorous Scientific Inquiry', which encompasses seven aspects including the calculation of sample size, criteria for participant inclusion and exclusion, the process of randomization, the concealment of allocation, the documentation of animals not included in the analysis, the blind assessment of outcomes and the disclosure of potential conflicts of interest along with details regarding study funding.

3 | LOW SPATIAL FREQUENCY CONTRIBUTES TO MYOPIA DEVELOPMENT

3.1 | Animal models

The process of emmetropization, fundamental to the attainment of clear vision, encompasses the adjustment of ocular growth to harmonize with its focal length (Logan et al., 2021). Animal models, notably chickens and guinea pigs, have served as invaluable tools in elucidating the influence of spatial frequency on this dynamic process (Bowrey et al., 2015; Diether

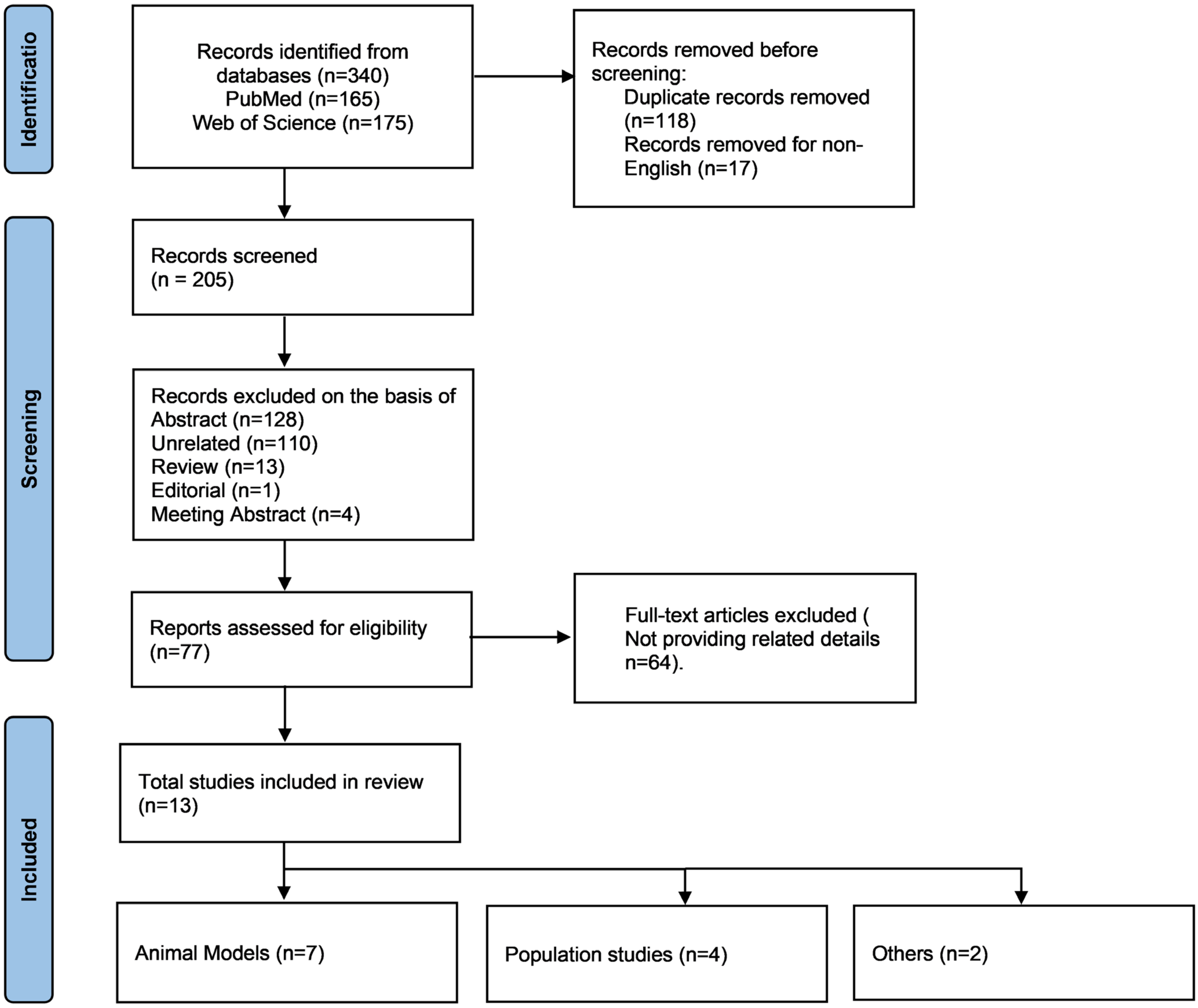

FIGURE 1 Flow chart of the study.

& Wildsoet, 2005; Hess et al., 2006; Schmid & Wildsoet, 1997; Zhi et al., 2013). Beyond mere observation, these models have facilitated a deeper understanding of the mechanisms underlying refractive development. The characteristics of seven studies are summarized in Table 1. The quality assessment of the literature is presented in Table S1, and it is evident that the quality of the literature is generally poor. Specifically, these studies did not report significant results in terms of sample size calculation, inclusion and exclusion criteria, randomization, allocation concealment, animal report exclusion analysis and outcome assessment blinding, which may limit our understanding and evaluation of these animal experimental studies.

The results from the included studies highlight the exquisite sensitivity of emmetropization to the spatial frequency content of the visual environment (Norton & Siegwart, 2013; Rucker, 2019; Zhang & Zhu, 2022). In addition, the threshold contrast required for effective compensation against refractive errors is intricately tied to the spatial frequency composition of the retinal image, emphasizing the importance of considering both factors concurrently in studying emmetropization (Marcos et al., 1999a). In Zhi's research, the variations in both contrast and spatial frequency were concurrently considered, highlighting the necessity for a comprehensive visual stimulation protocol (Zhi et al., 2013).

In constructing environments with diverse spatial frequencies, the majority of studies opted for images with varying stripe spatial frequencies, utilizing the physical size of spatial frequencies as a proxy for the perceived visual spatial frequency (Hess et al., 2006; Schmid & Wildsoet, 1997; Zhi et al., 2013). However, in specific scenarios, perceived grating frequency may differ due to the visual background and the distance of the animal from the stimulus, a factor considered only in selected studies (Zhi et al., 2013). It should be noted that the use of Bangerter foils with varying densities to simulate environments with distinct spatial frequencies is also a common approach (Bowrey et al., 2015; Smith & Hung, 2000; Tran et al., 2008). These foils produce a monotonic increase in the attenuation of higher spatial frequencies, with the cut-off varying in an approximately graded manner according to the strength of the foil.

The findings from animal models highlight the complex interactions among various visual factors and the genesis of refractive errors. They offer profound insights

TABLE 1 Characteristics of animal studies on the relationship between spatial frequency and refractive status.

Author and date	Animal	SF	Refractive status indicator	Main findings
Schmid & Wildsoet, 1997	Chick	High SF (4.3 c/d); mid SF (0.86 c/d); low SF (0.086 c/d); high–low SF (4.3 and 0.086 c/d); mixed SF (4.3 and 0.86 and 0.086 c/d)	SE; ACD	Mid and mixed spatial frequency environments significantly reduced the form deprivation response
Smith & Hung, 2000	Monkey	'LP' (strongest) bangerter diffuser, 0.1 (intermediate) bangerter diffuser, 0.4 (weakest) bangerter diffuser	SE, VCD	The chronic reductions in image contrast associated with optical diffusion caused axial myopia in young monkeys and the degree of myopia varied directly with the degree of image degradation
Diether & Wildsoet, 2005	Chicken	Standard and 'Maltese cross' stripes (higher SF)	SE, AL	Compensation of myopic defocus was strongly affected by the presence of middle and high spatial frequencies in the stimulus
Hess et al., 2006	Chick	High SF (2.17 c/d); mid SF (0.52 c/d); low SF (0.08 c/d)	SE, AL	The total activity in a subset of retinal cells responding in the higher spatial frequency range may be sufficient to drive the emmetropization process
Tran et al., 2008	Chick	Plano lens only; Plano lens +0.6 Bangerter filter; Plano lens +0.1 Bangerter filter; Plano lens + <0.1 Bangerter filter; Plano lens + Light Perception Bangerter filter	SE, AL	Middle spatial frequency plays an important role in eye growth regulation and thus emmetropization
Zhi et al., 2013	Guinea pigs	Grey, sine, square and normal control groups	SE, AL, VCD	Spatial visual stimuli are necessary to accomplish emmetropization and to maintain a stable refractive status after the emmetropization
Bowrey et al., 2015	Guinea pigs	Five Bangerter foils (0.8, 0.6, 0.4, 0.2, light perception only)	SE, AL	Lack of spatial frequency information in the eyes can lead to a long-term reduction in the modulation transfer function, resulting in myopia

Abbreviations: ACD, anterior chamber depth; AL, axial length; c/d, cyc/deg.; SE, Spherical equivalent; SF, spatial frequency; VCD, vitreous chamber depth.

into the environmental influences on myopia development, emphasizing the importance of varied contrast and spatial frequency. While its overall impact remains a topic of ongoing debate, the possibility of chromatic cues influencing refractive development underscores the need for further investigation into the role of colour vision in emmetropization (Chakraborty et al., 2019; Rucker, 2019). Future research should strive to integrate these findings into comprehensive strategies for myopia prevention and control, with a focus on promoting healthy visual environments and habits among children.

Animal models offer a controlled setting to manipulate visual inputs and monitor the consequent ocular reactions. These models are crucial for clarifying the potential biological mechanisms that regulate ocular growth, especially in response to varying spatial frequency content. Researchers can study the effects on ocular development and the progression of myopia by exposing animals to environments with adjustable spatial frequencies, providing insights that are challenging to achieve through human research alone. However, due to species differences and the complexity of human life, conclusions from animal experiments cannot be simply extrapolated to humans. Therefore, to fully understand the complex relationship between spatial frequency and myopia, epidemiological studies and animal models are essential to explore their interrelationship.

3.2 | Population studies

Compared to animal model experiments, there is a relative scarcity of population-based studies, the majority of which involve human trials. Epidemiology-based research initiated within the last few years, and the body of work in this area remains quite limited with studies having low sample sizes. The characteristics of these population-based studies are presented in Table 2. The results of the literature quality assessment are shown in Table S2. Three articles were rated as high quality, and one as medium, indicating a relatively reliable and complete set of findings.

Similar to animal experiments, controlled settings that manipulate visual input and monitor the resulting visual responses were also employed in human studies. Electroretinogram (ERG) analysis is commonly used to confirm the high sensitivity of the retina, particularly its peripheral regions, to defocused signals, mainly at lower spatial frequencies (Chin et al., 2015). This sensitivity underscores the retina's involvement in regulating ocular growth, a vital aspect in understanding and preventing

TABLE 2 Characteristics of epidemiological studies on the relationship between spatial frequency and refractive status.

Author and date	Subjects (age)	Sample size	Method to assess spatial frequency	Refractive status indicator	Main findings
Wei et al., 2021	Young adults (aged 22–26 years)	17	Phase-shifted gratings in a two-dimensional Gaussian window. Spatial frequencies: 0.6, 1.2, 2.4 and 4.0 c/d at 20° eccentricity and 0.6, 1.2, 2.0 and 3.2 c/d at 27° eccentricity	Peripheral motion perception	Lower motion detection thresholds were associated with higher level of myopia, especially for detection of low spatial frequency targets and at 20° of the visual field
Vera-Diaz et al., 2018	Young adults (aged 18–31 years, 24.6 ± 1.85 years)	33	Scaling the image on a monitor to peak spatial frequencies of 1, 2, 4 and 8 c/deg	Binocular visual function task	Compared with emmetropia group, myopia group showed greater degrees of binocular imbalance at mid- to high spatial frequencies
Chin et al., 2015	Young adults (aged 21–27 years, 22.5 ± 1.6 years)	46	Various spatial frequencies (0.24, 1.2, 2.4, 4.8 cycle per cpd)	Electroretinogram	The peripheral retina can differentiate positive and negative defocus more effectively for low spatial frequencies than can the central retina
Li et al., 2024	Children (aged 5–12 years; 8.04 ± 1.47 years)	566	Quantitative evaluation of participants' indoor and outdoor spatial frequencies through pictures	SE (cycloplegic refraction)	Lower indoor spatial frequency was associated with a higher level of myopia

Abbreviations: c/d, cyc/deg.; SE, Spherical equivalent.

myopia (Chin et al., 2015). Furthermore, Vera-Diaz FA's study on myopia's impact on binocular vision and temporal processing revealed that myopic individuals showed more binocular imbalance at medium to high spatial frequencies compared to hyperopic individuals. This indicates potential spatial frequency-dependent performance disparities in binocular tasks between emmetropic and myopic individuals, possibly linked to structural changes during emmetropization (Vera-Diaz et al., 2018). Peripheral motion perception, as an indicator related to refractive status, reveals a complex relationship between myopia severity and peripheral motion detection thresholds underscores the multifaceted nature of visual processing in this condition, highlighting the complexity and interdependence of various visual systems (Wei et al., 2021).

The growing research exploring the association between spatial frequency and myopia progression underscores the critical impact of environmental factors, particularly within urban and indoor environments (Tolhurst et al., 1992). Comparative studies between natural outdoor landscapes, which are abundant in high spatial frequencies, and their artificial indoor counterparts, often lacking such frequencies, have become a hotspot of inquiry. Flitcroft confirmed the difference in spatial frequency between indoor and outdoor environments by analysing the images, and pointed out that these indoor settings were similar to the myopic induction effect of Bangerter filter, suggesting that the disparity in visual stimuli between indoor and outdoor settings could be a potential risk factor for myopia development (Flitcroft et al., 2020). Following this, China's pioneering 'outdoor classroom' initiative serves as a testament to this understanding, showcasing encouraging preliminary outcomes in terms of user acceptance and hinting at a potential role in mitigating myopia progression (Yi et al., 2023). However, the initiative did not assess the environment, and the follow-up outcomes have yet to be reported. Li and colleagues assessed the spatial frequencies of images of indoor and outdoor environments and found that the spatial frequency slope of indoor environments was significantly lower than outdoors (Li et al., 2024). The reduced high spatial frequency content indoors was correlated with a higher level of myopia among children, providing epidemiological evidence for the influence of environmental spatial frequency on myopia.

In conclusion, a holistic approach combining human studies with animal models may to unlock new avenues in the prevention and management of myopia. By leveraging the strengths of both methodologies, we can gain a deeper understanding of the role of spatial frequency in ocular growth regulation and devise targeted interventions, such as enriching indoor environments to mimic natural outdoor spatial properties, improving indoor illumination, and ultimately reduce the burden of myopia worldwide.

3.3 | Potential underlying mechanisms

3.3.1 | Visual information processing characteristics

The retinal processing of spatial frequency can be elucidated through the distribution and neurophysiological characteristics of photoreceptors and ganglion cells within the retina. In the retina, two primary cell types, X-cells and Y-cells, play pivotal roles in visual information processing. X-cells, predominantly located near the fovea centralis, exhibit heightened sensitivity to visual details, colours and static shapes, demonstrating a robust response to visual signals with high spatial resolution (Chen et al., 2018). Conversely, Y-cells, mainly distributed in the retinal periphery, are more sensitive to the perception of motion, depth, and visual signals with low spatial frequencies (Ramanoel et al., 2018). Low-frequency spatial signals predominantly stimulate the Y-cell pathway in the retinal periphery, which results in blurred images. This may trigger axial elongation of the eye to achieve clearer imaging, thereby facilitating axial growth and the onset of myopia (Liou & Chiu, 2001).

Furthermore, studies suggested that the influence of spatial frequency on ocular growth regulation may be mediated by retinal dopamine (Feldkaemper et al., 1999; Souza et al., 2017). Activation of dopamine D1 receptors inhibits myopia, whereas D2 receptor activation promotes it. Retinal dopamine maintains normal refractive development through the homeostatic balance formed by activating both D1 and D2 receptors. During myopia induction, dopamine levels decrease. Some studies have speculated that dopamine's higher affinity for D2 receptors compared to D1 receptors may lead to a reduced activation of D1 receptors first, which disrupts the homeostatic balance and results in myopia (Zhou et al., 2017). Dopamine D2 receptors modulate the spatial frequency selectivity of neurons in the visual system. Genetic knockout of D2 receptors in mice has been shown to increase the sensitivity of the visual cortex V1 to spatial frequency (Souza et al., 2017). Additionally, decreased activation of dopamine D1 receptors leads to increased coupling of horizontal cells and a lowered spatial frequency threshold (Aung et al., 2022).

In this process, spatial frequency also influences the differential activation of ON–OFF visual pathways (Aung et al., 2022; Pan, 2019). As visual information travels from the retina through the lateral geniculate nucleus (LGN) to the visual cortex, the ON–OFF pathways within the LGN receptive fields are sensitive to luminance changes. Reducing visual stimulation of the ON pathway and disrupting the balance between ON and OFF pathways can facilitate myopia development (Morgan & Jan, 2022; Poudel et al., 2024). Animal models have confirmed that the dominance of ON–OFF activation is correlated with spatial frequency, with low spatial frequencies activating OFF-pathway-dominated neurons five times more than ON-dominated ones (Jansen et al., 2019; Kremkow et al., 2014).

The choroid, an essential conduit for retinal signals to the sclera, is also implicated in this process (Nickla & Wallman, 2010). Upon input of low-frequency visual signals, the resultant alterations in retinal visual signals not only impact the rod pathway but also reduce choroidal blood flow, ultimately inducing myopia, a phenomenon corroborated in animal models (Choi et al., 2022). These findings underscore the intricate interplay between spatial frequency, retinal physiology, and the development of myopia, offering insights into potential therapeutic targets for myopia prevention and management.

3.3.2 | Eye accommodation function and eye movements

The presence of accommodation cues is important for guiding appropriate growth adjustments, emphasizing the need for visual tasks that engage the accommodative system (Logan et al., 2021). This underscores the potential benefits of incorporating near-work activities with appropriate breaks and distance viewing into children's daily routines (Diether & Wildsoet, 2005; Logan et al., 2021). Studies have demonstrated that as spatial frequency increases, so does the accommodative response of the eye. During the onset and progression of myopia, accommodative lag emerges as a significant inducer. Consequently, low spatial frequencies prevalent in indoor environments are more likely to cause accommodative lag and reduced accommodative fluctuations, thereby facilitating the development and progression of myopia (Allen et al., 2010).

Groner et al. further investigated the impact of spatial frequency components on oculomotor parameters and found a correlation between spatial frequency content with mean fixation duration, with higher spatial frequencies resulting in longer fixation durations (Groner et al., 2008). Beyond fixation duration, spatial frequency also influences saccadic amplitude. Stimulation by low spatial frequency signals tends to increase saccadic amplitude, enabling the visual system to analyse information from more distant peripheral visual fields, thereby eliciting larger saccades. These findings suggest that spatial frequency exerts a modulating effect on both eye movements and accommodative function (Groner et al., 2008). Xu et al., in their analysis of spatial frequency characteristics of accommodative performance among children with different refractive states, further discovered that the instability of accommodative function in children is spatially frequency dependent. Specifically, compared to emmetropia children, myopic children were less sensitive to blur induced by low contrast at high spatial frequencies (Xu et al., 2019).

In the context of myopia incidence and development, understanding the complex interplay between spatial frequency, ocular accommodation, and eye movement may provide potential strategies to prevent and manage myopia. This can be achieved by manipulating the visual environment to optimize spatial frequency exposure and promote healthy visual development.

3.3.3 | Contrast sensitivity

The sensitivity of the human eye to spatial frequency, or the number of gratings, is inversely proportional to the contrast of those gratings. By examining the relationship between spatial frequency magnitude and contrast threshold across various ranges, one can construct the contrast sensitivity function (CSF) of the human eye

(Radhakrishnan et al., 2004; Tran et al., 2008). The CSF, a measure of visual responsiveness to specific narrow-band stimuli across various spatial frequencies, enables the identification and comprehension of fine details within real-world visual environments (Arden, 1978).

The absence of high-frequency visual information can lead to a decrease in contrast sensitivity, which in turn may contribute to the onset of myopia. Existing research has confirmed that the higher the degree of myopia, the lower the contrast sensitivity (Huang et al., 2007; Ye et al., 2023). As the spatial frequency of input visual signals increases, the degrading effect of defocus blur on retinal image contrast becomes more pronounced, indicating greater sensitivity of the eye to contrast variations in higher frequency signals (Marcos et al., 1999a).

Compared to individuals with normal vision, myopic individuals exhibit reduced sensitivity to defocus blur, possibly due to a reduced activation of the retina by low spatial frequencies (Taylor et al., 2009). These findings highlight the intricate relationship between contrast sensitivity, spatial frequency and myopia. They suggest that interventions targeting enhanced contrast sensitivity, particularly at high spatial frequencies, may be effective in mitigating the risk of myopia development and progression. Additionally, the observed differences in sensitivity to defocus blur between myopic and non-myopic individuals highlight the importance of considering individual visual characteristics when designing visual environments and corrective strategies.

3.3.4 | Relevant molecules involved in the pathway

In vertebrates, the Sonic hedgehog (Shh) gene plays a pivotal role in the differentiation of retinal ganglion cells, photoreceptors, and retinal pigment epithelium. It has been shown to induce myopia by enhancing the expression of matrix metalloproteinase (MMP) 2 (Amato et al., 2004; Chen et al., 2014). Qian et al. established a mouse model of form-deprivation myopia and found that reducing the spatial frequency of visual information through diffusers disrupted the Shh signalling pathway, leading to axial elongation and the onset of myopia (Qian et al., 2009). Beyond Shh expression, Brand et al. observed in their mouse model that the removal of high-frequency visual information reduced the mRNA and protein levels of Early growth response 1 (Egr-1) in the retina, resulting in refractive development abnormalities and the development of myopia (Brand et al., 2005, 2007).

Furthermore, research has emphasized the crucial role of visual connexins in visual functions such as contrast sensitivity, scotopic vision and regulating visual acuity under varying light intensities (Vaney, 2002). In a guinea pig model, it was discovered that visual connexins also participate in the process of myopia induced by spatial frequency deprivation. This deprivation affects myopia development by modulating the phosphorylation of retinal connexin 36 (Cx36), thereby influencing the rod signalling pathway and ultimately inducing myopia (Shi et al., 2020).

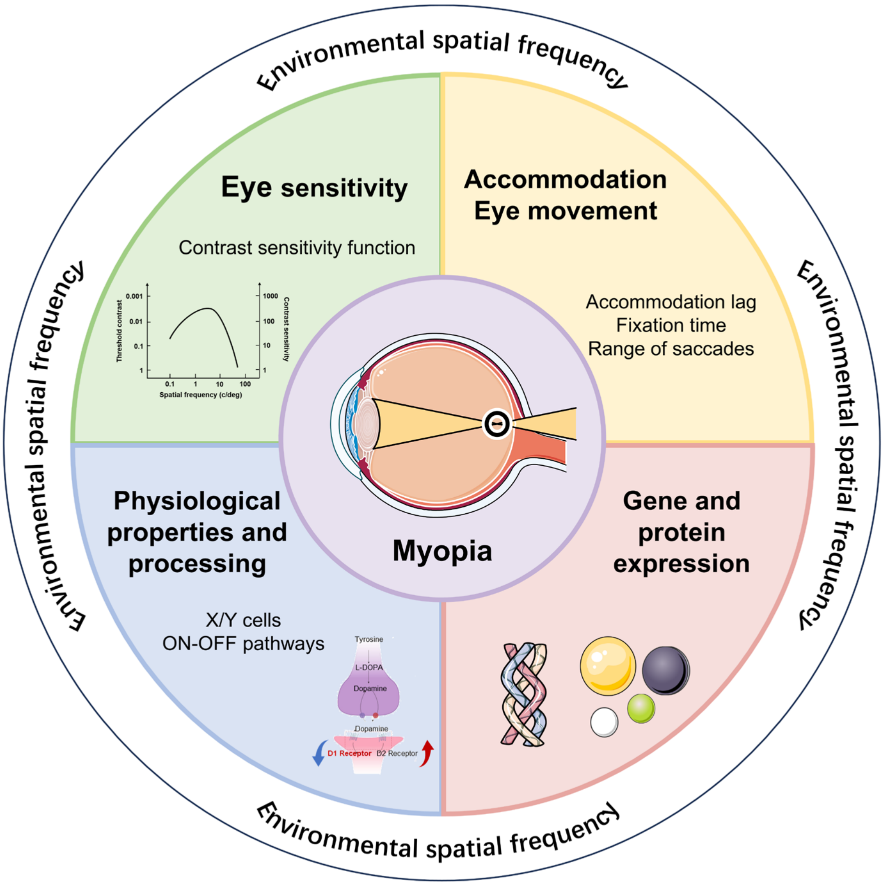

FIGURE 2 The underlying mechanisms of spatial frequency on myopia.

While the animal models demonstrate that reduced spatial frequency contributes to myopia, it is not the sole factor. Therefore, further research is necessary to investigate the specific genes and protein expressions that mediate the relationship between spatial frequency and myopia onset. Additionally, validation studies in human populations are essential to confirm these findings and gain a more comprehensive understanding of the underlying mechanisms.

In conclusion, the mechanisms of environment spatial frequency and the possible association with myopia are comprehensively summarized in Figure 2. Figure 2 summarizes four distinct yet interconnected pathways implicated in the incidence and development of myopia. The interplay among these factors is posited to underpin the complex dynamics of myopia's onset and progression.

4 | CONCLUSION AND FUTURE PERSPECTIVES

The environmental spatial frequency seems to play an important role in the development of myopia. Our understanding of the biological mechanisms underlying the modulation of myopia by spatial frequency, offers promising avenues for the development of innovative interventions, although further research is necessary. A multifaceted approach, integrating environmental modifications, behavioural changes and potentially genetic interventions, may hold the key to mitigate the burden of myopia.

From a public health perspective, promoting the design of visually rich environments, particularly for children and adolescents, may be a potential preventive strategy alongside with increasing outdoor time which is imperative. This involves incorporating elements that enhance the availability of high spatial frequencies in both indoor and outdoor settings, thereby mimicking the protective effects of natural outdoor scenes. Strategies such as introducing spatial frequency-modulated visual stimuli in schools, homes and workplaces could serve as effective measures to curb the escalating trend of myopia.

Moreover, the interaction of other visual factors such as illumination and spectrum with spatial frequency merits further investigation, as they may offer additional insights into the modulation of refractive development. Population-based intervention trials, designed to systematically evaluate the efficacy of these interventions, are needed to provide robust evidence for their implementation at a larger scale.

Ultimately, by leveraging the knowledge gained from animal models and human studies, we can devise tailored interventions that not only address the immediate challenges posed by myopia but also contribute to the long-term visual health and well-being of individuals worldwide. The significance of these endeavours extends beyond the realm of ophthalmology, underscoring the profound implications for public health and the overall quality of life. As we embark on this journey, the pursuit of comprehensive strategies for myopia prevention and control becomes paramount, with the potential to significantly alleviate the global burden of this pervasive ocular condition.

AUTHOR CONTRIBUTIONS

Conception and design: Chen-Wei Pan, Dan-Lin Li. Analysis and interpretation: Dan-Lin Li. Data collection: Dan-Lin Li. Drafting of the manuscript: Dan-Lin Li. Critical revision of the manuscript: Carla Lanca, Xiu-Juan Zhang, Andrzej Grzybowski, Xian-Gui He, Chen-Wei Pan. Overall responsibility: Chen-Wei Pan.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflicts of interest to disclose.

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REFERENCES

Allen, P.M., Hussain, A., Usherwood, C. & Wilkins, A.J. (2010) Pattern-related visual stress, chromaticity, and accommodation. *Investigative Ophthalmology & Visual Science*, 51, 6843–6849.

Amato, M.A., Boy, S. & Perron, M. (2004) Hedgehog signaling in vertebrate eye development: a growing puzzle. *Cellular and Molecular Life Sciences*, 61, 899–910.

Arden, G.B. (1978) The importance of measuring contrast sensitivity in cases of visual disturbance. *The British Journal of Ophthalmology*, 62, 198–209.

Aung, M.H., Hogan, K., Mazade, R.E., Park, H.N., Sidhu, C.S., Iuvone, P.M. et al. (2022) ON than OFF pathway disruption leads to greater deficits in visual function and retinal dopamine signaling. *Experimental Eye Research*, 220, 109091.

Bowrey, H.E., Metse, A.P., Leotta, A.J., Zeng, G. & McFadden, S.A. (2015) The relationship between image degradation and myopia in the mammalian eye. *Clinical & Experimental Optometry*, 98, 555–563.

Brand, C., Burkhardt, E., Schaeffel, F., Choi, J.W. & Feldkaemper, M.P. (2005) Regulation of Egr-1, VIP, and Shh mRNA and Egr-1 protein in the mouse retina by light and image quality. *Molecular Vision*, 11, 309–320.

Brand, C., Schaeffel, F. & Feldkaemper, M.P. (2007) A microarray analysis of retinal transcripts that are controlled by image contrast in mice. *Molecular Vision*, 13, 920–932.

Bullier, J. (2001) Integrated model of visual processing. *Brain Research. Brain Research Reviews*, 36, 96–107.

Bullimore, M.A., Ritchey, E.R., Shah, S., Leveziel, N., Bourne, R. & Flitcroft, D.I. (2021) The risks and benefits of myopia control. *Ophthalmology*, 128, 1561–1579.

Chakraborty, R., Yang, V., Park, H.N., Landis, E.G., Dhakal, S., Motz, C.T. et al. (2019) Lack of cone mediated retinal function increases susceptibility to form-deprivation myopia in mice. *Experimental Eye Research*, 180, 226–230.

Chen, C.Y., Sonnenberg, L., Weller, S., Witschel, T. & Hafed, Z.M. (2018) Spatial frequency sensitivity in macaque midbrain. *Nature Communications*, 9, 2852.

Chen, M., Qian, Y., Dai, J. & Chu, R. (2014) The sonic hedgehog signaling pathway induces myopic development by activating matrix metalloproteinase (MMP)-2 in Guinea pigs. *PLoS One*, 9, e96952.

Chin, M.P., Chu, P.H., Cheong, A.M. & Chan, H.H. (2015) Human electroretinal responses to grating patterns and defocus changes by global flash multifocal electroretinogram. *PLoS One*, 10, e0123480.

Choi, K.Y., Chan, S.S. & Chan, H.H. (2022) The effect of spatially-related environmental risk factors in visual scenes on myopia. *Clinical & Experimental Optometry*, 105, 353–361.

Day, M., Gray, L.S., Seidel, D. & Strang, N.C. (2009) The relationship between object spatial profile and accommodation microfluctuations in emmetropes and myopes. *Journal of Vision*, 9, 5.1–5.513.

Diether, S. & Wildsoet, C.F. (2005) Stimulus requirements for the decoding of myopic and hyperopic defocus under single and competing defocus conditions in the chicken. *Investigative Ophthalmology & Visual Science*, 46, 2242–2252.

Dolgin, E. (2015) The myopia boom. *Nature*, 519, 276–278.

Feldkaemper, M., Diether, S., Kleine, G. & Schaeffel, F. (1999) Interactions of spatial and luminance information in the retina of chickens during myopia development. *Experimental Eye Research*, 68, 105–115.

Fisher, M., Feuerstein, G., Howells, D.W., Hurn, P.D., Kent, T.A., Savitz, S.I. et al. (2009) Update of the stroke therapy academic industry roundtable preclinical recommendations. *Stroke*, 40, 2244–2250.

Flitcroft, D.I., Harb, E.N. & Wildsoet, C.F. (2020) The spatial frequency content of urban and indoor environments as a potential risk factor for myopia development. *Investigative Ophthalmology & Visual Science*, 61, 42.

Flitcroft, D.I., He, M., Jonas, J.B., Jong, M., Naidoo, K., Ohno-Matsui, K. et al. (2019) IMI - defining and classifying myopia: a proposed set of standards for clinical and epidemiologic studies. *Investigative Ophthalmology & Visual Science*, 60, M20–M30.

Fricke, T.R., Sankaridurg, P., Naduvilath, T., Resnikoff, S., Tahhan, N., He, M. et al. (2023) Establishing a method to estimate the effect of antimyopia management options on lifetime cost of myopia. *The British Journal of Ophthalmology*, 107, 1043–1050.

Groner, M.T., Groner, R. & von Muhlenen, A. (2008) The effect of spatial frequency content on parameters of eye movements. *Psychological Research*, 72, 601–608.

Hess, R.F., Schmid, K.L., Dumoulin, S.O., Field, D.J. & Brinkworth, D.R. (2006) What image properties regulate eye growth? *Current Biology*, 16, 687–691.

Holden, B.A., Fricke, T.R., Wilson, D.A., Jong, M., Naidoo, K.S., Sankaridurg, P. et al. (2016) Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology*, 123, 1036–1042.

Huang, C., Tao, L., Zhou, Y. & Lu, Z.L. (2007) Treated amblyopes remain deficient in spatial vision: a contrast sensitivity and external noise study. *Vision Research*, 47, 22–34.

Jansen, M., Jin, J., Li, X., Lashgari, R., Kremkow, J., Bereshpolova, Y. et al. (2019) Cortical balance between ON and OFF visual responses is modulated by the spatial properties of the visual stimulus. *Cerebral Cortex*, 29, 336–355.

Jonas, J.B., Ang, M., Cho, P., Guggenheim, J.A., He, M.G., Jong, M. et al. (2021) IMI prevention of myopia and its progression. *Investigative Ophthalmology & Visual Science*, 62, 6.

Kauffmann, L., Ramanoel, S., Guyader, N., Chauvin, A. & Peyrin, C. (2015) Spatial frequency processing in scene-selective cortical regions. *NeuroImage*, 112, 86–95.

Kerber, K.L., Thorn, F., Bex, P.J. & Vera-Diaz, F.A. (2016) Peripheral contrast sensitivity and attention in myopia. *Vision Research*, 125, 49–54.

Kihara, K. & Takeda, Y. (2010) Time course of the integration of spatial frequency-based information in natural scenes. *Vision Research*, 50, 2158–2162.

Kremkow, J., Jin, J., Komban, S.J., Wang, Y., Lashgari, R., Li, X. et al. (2014) Neuronal nonlinearity explains greater visual spatial resolution for darks than lights. *Proceedings of the National Academy of Sciences of the United States of America*, 111, 3170–3175.

L, R. & K, K. (1990) *Spatial Vision*. New York: Oxford University Press, pp. 87–96.

Li, D.L., Dong, X.X., Yang, J.L., Lanca, C., Grzybowski, A. & Pan, C.W. (2024) Lower indoor spatial frequency increases the risk of myopia in children. *The British Journal of Ophthalmology*, bjo-2024-325888.

Liou, S.W. & Chiu, C.J. (2001) Myopia and contrast sensitivity function. *Current Eye Research*, 22, 81–84.

Logan, N.S., Radhakrishnan, H., Cruickshank, F.E., Allen, P.M., Bandela, P.K., Davies, L.N. et al. (2021) IMI accommodation and binocular vision in myopia development and progression. *Investigative Ophthalmology & Visual Science*, 62, 4.

Ma, Y., Wen, Y., Zhong, H., Lin, S., Liang, L., Yang, Y. et al. (2022) Healthcare utilization and economic burden of myopia in urban China: a nationwide cost-of-illness study. *Journal of Global Health*, 12, 11003.

Maiello, G., Walker, L., Bex, P.J. & Vera-Diaz, F.A. (2017) Blur perception throughout the visual field in myopia and emmetropia. *Journal of Vision*, 17, 3.

Marcos, S., Moreno, E. & Navarro, R. (1999a) The depth-of-field of the human eye from objective and subjective measurements. *Vision Research*, 39, 2039–2049.

McGonigle, C., van der Linde, I., Pardhan, S., Engel, S.A., Mallen, E.A.H. & Allen, P.M. (2016) Myopes experience greater contrast adaptation during reading. *Vision Research*, 121, 1–9.

Morgan, I.G., French, A.N., Ashby, R.S., Guo, X., Ding, X., He, M. et al. (2018) The epidemics of myopia: Aetiology and prevention. *Progress in Retinal and Eye Research*, 62, 134–149.

Morgan, I.G. & Jan, C.L. (2022) China turns to school reform to control the myopia epidemic: a narrative review. *Asia Pac J Ophthalmol (Phila)*, 11, 27–35.

Nickla, D.L. & Wallman, J. (2010) The multifunctional choroid. *Progress in Retinal and Eye Research*, 29, 144–168.

Norton, T.T. & Siegwart, J.J. (2013) Light levels, refractive development, and myopia – a speculative review. *Experimental Eye Research*, 114, 48–57.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D. et al. (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, 372, n71.

Pan, F. (2019) Defocused image changes signaling of ganglion cells in the mouse retina. *Cells-Basel*, 8, 8.

Poudel, S., Jin, J., Rahimi-Nasrabadi, H., Dellostritto, S., Dul, M.W., Viswanathan, S. et al. (2024) Contrast sensitivity of ON and OFF human retinal pathways in myopia. *The Journal of Neuroscience*, 44, e1487232023.

Qian, Y.S., Chu, R.Y., Hu, M. & Hoffman, M.R. (2009) Sonic hedgehog expression and its role in form-deprivation myopia in mice. *Current Eye Research*, 34, 623–635.

Radhakrishnan, H., Pardhan, S., Calver, R.I. & O'Leary, D.J. (2004) Effect of positive and negative defocus on contrast sensitivity in myopes and non-myopes. *Vision Research*, 44, 1869–1878.

Ramanoel, S., Chokron, S., Hera, R., Kauffmann, L., Chiquet, C., Krainik, A. et al. (2018) Age-related macular degeneration changes the processing of visual scenes in the brain. *Visual Neuroscience*, 35, E006.

Rucker, F. (2019) Monochromatic and white light and the regulation of eye growth. *Experimental Eye Research*, 184, 172–182.

Schaeffel, F. (2006) Myopia: the importance of seeing fine detail. *Current Biology*, 16, R257–R259.

Schmid, K.L. & Wildsoet, C.F. (1997) Contrast and spatial-frequency requirements for emmetropization in chicks. *Vision Research*, 37, 2011–2021.

Shi, Q., Teves, M.M., Lillywhite, A., Pagtalunan, E.B. & Stell, W.K. (2020) Light adaptation in the chick retina: dopamine, nitric oxide, and gap-junction coupling modulate spatiotemporal contrast sensitivity. *Experimental Eye Research*, 195, 108026.

Smith, E.R. & Hung, L.F. (2000) Form-deprivation myopia in monkeys is a graded phenomenon. *Vision Research*, 40, 371–381.

Souza, B., Abou, R.M., Quintana, C., Beaulieu, J.M. & Casanova, C. (2017) Spatial frequency selectivity is impaired in dopamine D2 receptor knockout mice. *Frontiers in Integrative Neuroscience*, 11, 41.

Spillmann, L. (2020) Stopping the rise of myopia in Asia. *Graefe's Archive for Clinical and Experimental Ophthalmology*, 258, 943–959.

Stang, A. (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology*, 25, 603–605.

Sun, H.P., Li, A., Xu, Y. & Pan, C.W. (2015) Secular trends of reduced visual acuity from 1985 to 2010 and disease burden projection for 2020 and 2030 among primary and secondary school students in China. *Jama Ophthalmol*, 133, 262–268.

Taylor, J., Charman, W.N., O'Donnell, C. & Radhakrishnan, H. (2009) Effect of target spatial frequency on accommodative response in myopes and emmetropes. *Journal of Vision*, 9, 1–14.

Tolhurst, D.J., Tadmor, Y. & Chao, T. (1992) Amplitude spectra of natural images. *Ophthalmic & Physiological Optics*, 12, 229–232.

Tran, N., Chiu, S., Tian, Y. & Wildsoet, C.F. (2008) The significance of retinal image contrast and spatial frequency composition for eye growth modulation in young chicks. *Vision Research*, 48, 1655–1662.

Vaney, D.I. (2002) Retinal neurons: cell types and coupled networks. *Progress in Brain Research*, 136, 239–254.

Vera-Diaz, F.A., Bex, P.J., Ferreira, A. & Kosovicheva, A. (2018) Binocular temporal visual processing in myopia. *Journal of Vision*, 18, 17.

Wei, J., Kong, D., Yu, X., Wei, L., Xiong, Y., Yang, A. et al. (2021) Is peripheral motion detection affected by myopia? *Frontiers in Neuroscience*, 15, 683153.

Xu, J., Lu, X., Zheng, Z., Bao, J., Singh, N., Drobe, B. et al. (2019) The effects of spatial frequency on the accommodative responses of myopic and emmetropic Chinese children. *Translational Vision Science & Technology*, 8, 65.

Ye, Y., Xian, Y., Liu, F., Lu, Z.L., Zhou, X. & Zhao, J. (2023) Characteristics and related parameters of quick contrast sensitivity function in Chinese Ametropia children. *Eye & Contact Lens*, 49, 224–233.

Yi, X., Wen, L., Gong, Y., Zhe, Y., Luo, Z., Pan, W. et al. (2023) Outdoor scene classrooms to arrest myopia: design and baseline characteristics. *Optometry and Vision Science*, 100, 543–549.

Zhang, P. & Zhu, H. (2022) Light signaling and myopia development: a review. *Ophthalmology and therapy*, 11, 939–957.

Zhi, Z., Pan, M., Xie, R., Xiong, S., Zhou, X. & Qu, J. (2013) The effect of temporal and spatial stimuli on the refractive status of Guinea pigs following natural emmetropization. *Investigative Ophthalmology & Visual Science*, 54, 890–897.

Zhou, X., Pardue, M.T., Iuvone, P.M. & Qu, J. (2017) Dopamine signaling and myopia development: what are the key challenges. *Progress in Retinal and Eye Research*, 61, 60–71.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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