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INTEGRATED STUDY MASTER'S THESIS

The Impact of Lifestyle Habits on Ocular Biometric Changes and Refractive Error Progression Among University Students

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TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS

SE – Spherical equivalent

D – Diopter

AL – Axial length

OCT – Optical coherence tomography

CCT – Central corneal thickness

BMO – Bruch's membrane opening

BM – Bruch's membrane

ONH – Optic nerve head

RPE – Retinal pigment epithelium

ECM – Extracellular matrix

POAG – Primary open-angle glaucoma

CUVAF – Conjunctional ultraviolet autofluorescence

D1R – D1 receptor

EGR-1 – Early growth response factor-1

DLMO – Dim light melatonin onset

ipRGCs – Intrinsically photosensitive retinal ganglion cells

ChBP – Choroidal blood perfusion

2 SUMMARY

Aim and Objectives: Myopia, the most common vision disorder, is an increasing public health concern. Several lifestyle factors, including excessive near work, reduced exposure to natural outdoor light, and physical inactivity, have been linked to myopia onset and progression in children. However, there is still a lack of research on the impact of lifestyle factors on myopia progression among young adults. Therefore, this study aimed to assess the prevalence and progression of myopia among second-year medical students in Lithuania, France, and Germany, while investigating potential lifestyle-related risk factors.

Research methods: A questionnaire was administered to assess the prevalence of myopia, myopia progression and factors possibly affecting myopia onset and progression, such as near work, outdoor time, physical activity, sleep duration, screen time, screen breaks, smoking and dietary habits. Myopia was defined as a spherical equivalent of the worse eye of -0.5 diopters or less, with categories for mild, moderate and high myopia. Myopia progression was based on self-reported worsening or new need for vision correction during medical school.

Results: 81 students participated, two were excluded for incompleteness of the questionnaire, leaving 79 students. The sample included 71% females and 29% males, with a mean age of 21.2 years. The prevalence of myopia after two years of study was 40.5%, with 84.4% of affected students already myopic before university enrollment. Myopia progression occurred in 11.1% of students with preexisting myopia, while five students developed new-onset myopia during their time at university. There was no significant association between near work, screen time, screen breaks, diet, or device usage in the dark and myopia progression. However, time spent outdoors showed a statistically significant association with myopia prevalence (p=0.048), although not with progression of myopia. The place of origin of the students and physical activity had a significant effect on the progression of myopia (p=0.0038, p=0.0349). Surprisingly, a higher level of physical activity (3-4 hours daily) was linked to increased myopia progression (p=0.0033), contradicting previous findings suggesting a protective effect. Sleep duration showed a weak negative correlation with myopia progression, though statistical significance was not reached. Smoking was significantly associated with subjective vision worsening (p=0.039). Although females had a slightly higher rate of myopia progression compared to males, the difference did not reach statistical significance.

Conclusions: This study highlights the complex interaction of lifestyle factors and myopia development and progression. The data suggests that while increased outdoor exposure may reduce the prevalence of myopia, other variables, such as the amount of near work and physical activity, require further investigation. Future research with larger sample sizes and objective refractive measurements is needed to clarify these relationships.

Keywords: Myopia, myopia progression, lifestyle, near work, university students, refractive error

3 INTRODUCTION

The global prevalence of axial myopia has significantly risen over the past 30 years, particularly among the younger population. In a 2019 report on vision, the World Health Organization (WHO) predicted that the number of individuals with myopia will rise to 3.36 billion in 2030 worldwide (1). *Holden et al.* estimated that by the year 2050, almost 50% of the global population will be affected by myopia, with about 10% expected to develop high myopia (2). In 2015, around 312 million people with myopia were younger than 19 years (1). A tendency that can be observed particularly in East and Southeast Asia, where the prevalence of myopia reaches as high as 80% to 90% among senior high school students (3). In contrast, the prevalence among school children in Africa remains lower, at 4.7% (4).

Since axial elongation is a major risk factor for developing pathological myopia later in life, a significant proportion of these currently young myopic individuals may be at increased risk of future

vision-threatening complications. On top of that, individuals with myopia have an increased risk of complications like retinal detachment, glaucoma, cataract, and myopic maculopathy (5). According to the WHO, uncorrected or under-corrected myopia is a leading cause of visual impairment (1).

In contrast to previous assumptions that myopia is primarily linked to genetic factors, the importance of environmental factors like increased near work and decreased time spent outdoors on myopia development and its progression is now widely known (5)(6). Due to the high academic workload and decreased time spent outdoors, university students are at an increased risk of myopia (5). Yet, the research regarding the development and progression of myopia in university students is sparse.

The aim of this observational cross-sectional study is to investigate the impact of different lifestyle habits on ocular biometric changes and refractive error progression among university students. The objectives of this study are:

1. To emphasize the importance of preventing myopia progression.
2. To evaluate the significance of the following lifestyle factors on myopia progression among university students:
    a) Outdoor sunlight exposure
    b) Physical activity
    c) Near work
    d) Sleep
    e) Diet
    f) Smoking
3. To compare the findings with existing literature regarding myopia progression in university students.
4. To provide recommendations for preventing myopia progression in young adults based on the questionnaire results and literature review.

4 RESEARCH SUBJECTS AND METHODS

Based on a literature review of international research (7)(8), a questionnaire was designed to evaluate lifestyle factors possibly associated with myopia and myopia progression (Annex 1). Given the literature linking lifestyle factors associated with studying, such as an increased time spent indoors, poor quality of sleep, and increased near work, the questionnaire included various risk factors (1)(5). The questionnaire was distributed among second-year medical students from Lithuania (Vilnius), France (Guadeloupe), and Germany (Freiburg im Breisgau) between June to December 2024 via WhatsApp (a messaging platform) student groups.

The questionnaire consisted of 28 questions and was designed to evaluate the prevalence of myopia, myopia progression, subjective vision worsening, and possible risk factors. Firstly, demographic information and ophthalmic history were collected.

Secondly, details regarding the research participants' refractive error, subjective feeling of vision worsening, and new need for vision aid (glasses or contact lenses) were gathered. The students could specify if their onset of myopia occurred before or after starting medical studies at the university. Myopia was defined as the spherical equivalent (SE) of ≤ -0.5 D, emmetropia as >-0.5 and <+0.5 D, and hyperopia as >+0.5 D. Myopia was further classified into mild myopia, ranging between -0.25 and -2.75 D. Moderate myopia was defined as SE ranging from -3.0 to -5.75 D, and severe myopia was defined as SE -6.0 D and greater. Similarly, hyperopia was considered mild with a SE between +0.25 and +2.0 D, and moderate with a SE ranging from +2.25 to +4.75 D. Severe hyperopia was defined as +5.0 D and more.

Lastly, questions regarding students' lifestyle habits included the amount of time spent outdoors, physical activity, sleep, and near-work activities, including screen time and frequency of breaks, as well as diet and smoking habits were asked. Hours spent outdoors, performing near work, and daily screen time were categorized into these groups: <1 h, 1-2 h, 3-4 h, >4 h. Break frequency (30 min, 1 h, 2 h, ≤3 h), hours of sleep per night (<6, 6 h, 7 h, 8 h, ≥9 h), and technical device usage in the dark were also categorized. The study participants were also asked about smoking, its frequency and type (if applicable). Furthermore, participants were asked about their dietary habits, including daily consumption of fruit and vegetables. All these lifestyle factors were combined and tested for their statistically significant effect on myopia progression, the development of myopia, and subjective worsening of vision.

The answers were collected by Google documents and later analyzed using the statistical package R (version 4.4.2). A descriptive analysis was conducted to examine participant demographics and behavioral patterns. Categorical variables were analyzed using grouped frequency distributions. To assess the association between potential risk factors and myopia as well as myopia progression, statistical tests were performed. Fisher's exact test was used to determine whether categorical variables such as gender, time spent outdoors, near work, physical activity, and hours of sleep were significantly associated with myopia or myopia progression. For the analysis of myopia progression, participants were categorized into those who had myopia at the beginning of university and experienced further progression, as well as those who developed myopia during their studies. The association between myopia progression and different lifestyle factors was assessed by comparing the proportion of students in different groups. A p-value of less than 0.05 was considered statistically significant.

After analyzing the results, a literature review regarding the impact of lifestyle habits on ocular biometric changes and refractive error progression was conducted and the results of the questionnaire were compared to the available research. The literature search included literature and publications from books, research articles, and ophthalmological journals. Most of the literature used was published within the last ten years to ensure the inclusion of the most relevant data. Studies were mainly found from online publication websites, including PubMed, Google Scholar, Elsevier, ClinicalKey, ScienceDirect, and Research Gate. To ensure the quality of this work, specific inclusion and exclusion criteria were applied. Inclusion criteria were articles published in English and German, and literature with a clear definition of myopia. To ensure that the selected literature is from primary resources, the selection criteria include systematic reviews, meta-analyses, cross-sectional studies, cohort studies, and retrospective studies.

Exclusion criteria included case reports and case series, as well as studies without a clear definition or classification of myopia. Furthermore, literature focusing primarily on non-refractive pathologies was excluded.

Myopia progression was characterized as the difference between SE before starting university and after two years of studying. Therefore, myopia progression included students with a new onset of myopia during the first two years of university. The SE from the worse eye was chosen for the analysis.

5 RESULTS

A total of 81 students were enrolled in the study. Two participants were excluded due to incomplete questionnaire survey data. The demographic characteristics of the remaining 79 participants are reported in Table 1. 71% (n=56) were female and 29 % (n=23) were male. The mean age of the students was 21.2 years (range 17-32 years). Most of the students came from a town, accounting for 42.3% of all participants, while 38.5% came from a city and 19.2% from a village. A high prevalence of myopia among parents was observed, with 57% of students indicating that one or both parents had myopia. 48.9 % of those with a parental history of myopia were myopic at the beginning of medical school, while only 29.4% of the students without myopic parents had myopia. For most students, it was the first time they enrolled in a university (69.6%). Among the participants in this study, 46.84% (n=37) were studying in Lithuania, 25.32% (n=20) in France, and another 27.85% (n=22) were enrolled at a university in Germany.

Table 1: Demographic characteristics of study participants

Variables	N	%
Age, years (median)	21.2	
Sex		
Female	56	71.0
Male	23	29.0
Place of origin		
Village (100-2000 citizens)	15	19.2
Town (2001-100,000 citizens)	33	42.3
City (>100,000 citizens)	30	38.5
First time enrolled in university		
Yes	55	69.6
No	24	30.4
Parental history of myopia		
Both parents myopic	15	19
One parent myopic	30	38
Neither myopic	34	43

Among the 79 students, 32 (40.5%) were myopic after two years of medical school. 27 (84.4%) of the myopic students developed myopia before starting university, out of which 55.56% (n=15) had mild myopia, 37,04% (n=10) were moderately myopic and 2.53% (n=2) had high myopia. Of the students who were already myopic at the start of medical school, myopia progressed in 11.11% (n=3) of students. Additionally, 5 students developed myopia during the first two years of university. In these cases, only mild myopia was detected. No students developed high myopia during their first two years of studies.

After two years of medical school, the prevalence of myopia was comparable between female and male students (39.3% and 43.5%, respectively; Table 2). Yet, a greater proportion of female students developed myopia during university (18.2% vs. 10%) and experienced progression while studying medicine (12.5% versus 4.4%). However, these observed differences between genders were not statistically significant either before the beginning of university (Fisher test, p=0.449) or after two years of studying (Fisher test, p= 0.8031).

5.06% (n=4) of the students reported being hyperopic before starting university and additionally, 2.03% (n=2) reported being diagnosed with hyperopia after two years. The place of origin had a significant effect on the progression of myopia (Fisher test, p= 0.0038). It showed that 23.3% (n=7)

originating from a city had a myopia progression, while myopia progressed in only 6.7% (n=1) of the students from a village and in no student originating from a town.

The mean of the prescription before starting university was -1.419 D with a standard deviation of 2.377. After two years of medical school, the mean was -1.548 D with a standard deviation of 2.406.

58.23% (n=46) of study participants stated that their vision worsened subjectively since starting university.

When comparing the different study places, students who studied in Germany had the highest prevalence of myopia with 54.55% (n=12), and France had the smallest proportion of students with myopia with 30% (n=6). The prevalence of myopic students studying in Lithuania was 37.84% (n=14). However, this result did not reach statistical significance (Fisher's exact test, p=0.2478).

When looking at the progression of myopia in students studying in different countries, myopia progressed most frequently in students studying in Lithuania with 42.86% (n=6), then in students in France with 33.33% (n=2) and lastly in students in Germany, where none of the students in this study experienced myopia progression. This study found no association between the country of studies and myopia progression (Fisher's exact test, p=0.1275).

Table 2: Distribution of Refractive Errors and Myopia Progression among Students (n=79)

	Number of Females (%)	Number of Males (%)	Total (%)
Refractive status after two years of medical school			
Myopic	22 (39.3)	10 (43.5)	32 (40.5)
Nonmyopic	34 (60.7)	13 (56.5)	47 (59.5)
Time of myopia onset			
Before university	18 (81.8)	9 (90)	27 (84.4)
During university	4 (18.2)	1 (10)	5 (15.6)
Myopia progression during medical school*			
Yes	7 (12.5)	1 (4.4)	8 (10.1)
No	49 (87.5)	22 (95.7)	71 (89.9)

*Among all students

A majority of 75.9% stated that they spend more than four hours of near work per day. The second largest proportion with 17.7%, reported spending between three and four hours daily. A further 5.1% indicated a near work duration between one and two hours and 1.3% of students stated spending less than one hour of daily near work. Near-work was not significantly linked with myopia

progression (Fisher's exact test, p=0.413). No significant association between excessive near-work and subjective vision worsening (Fisher's exact test, p= 0.6437) could be observed.

More than four hours of daily screen time were reported by 70.9% of the students. Additionally, 15.2% stated to have a daily screen time of three to four hours, while 13.9% reported spending one to two hours per day. There was a moderate positive correlation between screen time and myopia progression, however, it was not statistically significant (Fisher's exact test, p=0.223). No significant association with screen time could be found among students who presented with a new onset of myopia during the first two years of studying (Fisher's exact tests, p= 0.4557). On top of that, no significant association between prolonged screen time and subjective vision worsening was found. (Fisher's exact test, p= 0.7725).

Excessive near work in combination with prolonged screen time (3-4h + >4h daily) has not been associated with a higher myopia progression when compared to those with less near work and shorter screen time (Fisher's exact test, p=1). Furthermore, no significant association between excessive near work in combination with prolonged screen time (3-4h + >4h daily) and new onset of myopia (Fisher's exact test, p=1) was observed.

The groups of students taking a break every hour and every two hours when working on a screen were almost identically large with 36.7% and 38%, respectively. Furthermore, 13.9% of students reported taking screen breaks every three hours or less frequently and 11.4% stated taking a break every 30 minutes or more frequently. The frequency of screen breaks showed no significant association with myopia progression (Fisher's exact test, p=0.296). Additionally, no significant association was observed between the subjective worsening of vision and the frequency of breaks during screen time (Fisher's exact test, p=1). Similarly, there was no significant association between the frequency of screen breaks and new-onset myopia (Fisher's exact test, p=0.41).

With 50.6%, more than half of the students in this study stated to use technical devices in the dark every night. 25.3% reported to frequently use technical devices in the dark. Additionally, 12.7% indicated using devices in the dark weekly. A minority of participants reported monthly (2.5%) or no nightly usage at all (8.9%). However, no significant association between frequent usage of devices in the dark and myopia progression (Fisher's exact test, p=0.212) was observed, nor was a significant association between subjective vision worsening and frequent usage of technical devices in the dark (Fisher's exact test, p= 0.3572). In addition, no significant association between frequent usage of devices in the dark and new myopia onset (Fisher's exact test, p= 1) was established.

The largest group of students (51.9%) spent around 1 to 2 hours outside daily. Here, 48.78% (n=20) stated that their vision stayed constant, and 51.22% stated that their vision worsened, making the two groups almost identical. There was a statistically significant association between time spent outdoors daily and the prevalence of myopia (Fisher's exact test, p= 0.048). Yet, there was no

significant association detected between time spent outdoors and myopia progression (Fisher's exact test, p=0.936). The new onset of myopia and a low amount of time spent outdoors is not significantly associated in the study (Fisher's exact test, p=1). No significant association was found between time spent outdoors and subjective vision worsening (Fisher's exact test, p=0.075).

Most students (51.9%) reported to be physically active between one and two hours per day. Another 27.8% stated to be physically active less than one hour daily. Meanwhile, 19% of participants claimed to be physically active between three and four hours and only 1.3% of students performed over four hours of physical activity per day. When comparing the amount of time of physical activity between students with and without myopia progression a significant difference could be observed between those spending one to two hours of physical activity daily and those who spend between three to four hours with physical activity on average (Dunn Kruskal-Wallis multiple comparison p-values adjusted with the Bonferroni method, p= 0.0033). However, no significant association could be established when analyzing the new onset of myopia separately (Fisher's exact test, p=1) and subjective vision worsening with time of daily average physical activity (Fisher's exact test, p= 0.1362).

When combining the time spent outdoors and physical activity, no significant association could be found between myopia progression and a high outdoor time combined with a high amount of time spent doing physical activity (Fisher's exact test, p= 0.9263). Outdoor time plus physical activity could not be shown to be a protective factor for subjective worsening of vision (Fisher's exact test, p=0.876). In fact, all students with a high outdoor time and high physical activity (n=8) noticed a subjective decrease in vision. High amounts of time spent outdoors, combined with physical activity did not show to be a significant protective factor against the new onset of myopia in this study (Fisher's exact test, p=0.743).

The biggest group of participants with 38%, reported sleeping eight hours per night on average. 34.2% claimed to sleep seven hours per night, while 20.3% stated to sleep six hours on average. A small percentage of students reported sleeping less than six hours (5.1%) or nine hours or more (2.5%) per night. In this study, a weak correlation between a low amount of sleep and myopia progression could be established using the Spearman Correlation Test (rho=-0.30). However, the result was not statistically significant (Fisher's exact test, p=0.945). Furthermore, the subjective vision worsening was shown to be not significantly connected to the amount of sleep (Fisher's exact test, p= 0.6597). No significant association was found between the amount of sleep and the new onset of myopia (Fisher's exact test, p=1).

Moreover, a majority of 87.3% of participants did not smoke. Only a small proportion stated that they smoked, with 6.3% indicating occasional smoking and another 6.3% reporting regular smoking habits. Students who smoked reported worsening of their vision significantly more often

compared to non-smokers (Fisher's exact test, p=0.03934). The number of cigarettes smoked per day did not influence that (Fisher's exact test, p=1). Also, there was no significant association between smoking and myopia progression (Fisher's exact test, p=266), nor between smoking and the new onset of myopia (Fisher's exact test, p=1).

Almost two-thirds of the students (65.8%) reported following an omnivorous diet, whereas 27.8% identified as vegetarians, 1.3% as vegans and another 5.1% claimed to follow another diet that was not further specified. Omnivore, vegetarian or vegan diets showed no significant effect on myopia progression (Fisher's exact test, p=0.554), subjective vision worsening (Fisher's exact test, p= 0.2373), and new onset of myopia (Fisher's exact test, p=1). Similarly, no significant association between myopia progression (Fisher's exact test, p=1), new onset of myopia (Fisher's exact test, p= 0.7143) and subjective vision worsening (Fisher's exact test, p= 1), and the amount of vegetables and fruits consumed was shown.

The baseline distribution of myopia and its progression across different groups categorized by potential risk factors are shown in Table 3.

Table 3: Occurrence of Myopia and Myopia Progression among different Lifestyle groups

Variables	Myopia (n = 79)			Myopia Progression (n = 79)		
	Total	With Myopia (%)	P-value	Total	With Progression (%)	P-value
Gender						
Female	56	22 (39.3)	0.888	56	7 (12.5)	0.426
Male	23	10 (43.5)		23	1 (4.4)	
Place of origin						
Village	15	5 (33.3)	0.636	15	1 (6.7)	**0.004**
Town	33	14 (42.4)		33	0 (0)	
City	30	12 (40)		30	7 (23.3)	
Parental history of myopia						
Yes	45	22 (48.9)	1	45	4 (8.9)	0.719
No	34	10 (29.4)		34	4 (11.8)	
Hours of time spent outdoors/day						
<1	13	6 (46.2)	**0.048**	13	1 (7.7)	0.936
1-2	41	19 (46.2)		41	4 (9.8)	
3-4	19	6 (31.6)		19	2 (10.5)	
>4	6	1 (16.7)		6	1 (16.7)	
Hours of physical activity/day						
<1	22	7 (31.8)	0.198	22	2 (9.1)	**0.035**
1-2	41	20 (48.8)		41	2 (4.9)	
3-4	15	4 (26.7)		15	3 (20)	
>4	1	1 (100)		1	1 (100)	
Hours of near work/day						
<1	1	0 (0)	1	1	0 (0)	0.413
1-2	4	1 (25)		4	0 (0)	
3-4	14	5 (35.7)		14	3 (21.4)	
>4	60	26 (43.3)		60	5 (8.3)	
Hours of screen time/day						
<1	0	0 (0)	0.374	0	0 (0)	0.223
1-2	11	2 (18.2)		11	2 (18.2)	
3-4	12	4 (33.3)		12	2 (16.7)	
>4	56	26 (46.4)		56	4 (7.1)	
Frequency of using technical devices in the dark						
Every night	40	15 (37.5)	1	40	3 (7.5)	0.212
>3 times/week	20	9 (45)		20	2 (10)	
Weekly	10	3 (30)		10	2 (20)	
Once a month	2	2 (100)		2	1 (50)	
Never	7	3 (42.9)		7	0 (0)	

Table 3: Occurrence of Myopia and Myopia Progression among different Lifestyle groups (*continued*)

Frequency of screen breaks						
≥30 min	9	2 (22.2)	0.41	9	1 (11.1)	0.296
Every hour	29	11 (37.9)		29	5 (17.2)	
Every two hours	30	12 (40)		30	1 (3.3)	
≤ 3	11	7 (63.6)		11	1 (9.1)	
Hours of sleep/day						
<6	4	1 (25)	0.745	4	0 (0)	0.945
6	16	7 (43.8)		16	1 (6.25)	
7	27	11 (40.7)		27	3 (11.1)	
8	30	12 (40)		30	4 (13.3)	
≥9	2	1 (50)		2	0 (0)	
Smoking						
Yes	5	1 (20)	1	5	1 (20)	0.266
No	69	30 (43.5)		69	6 (8.8)	
Rarely	5	1 (20)		5	1 (20)	
Diet						
Omnivore	52	21 (40.4)	1	52	5 (9.6)	0.554
Vegetarian	22	9 (40.9)		22	2 (9.1)	
Vegan	1	0 (0)		1	0 (0)	
Other	4	2 (50)		4	1 (25)	

P-values determined using Fisher's exact test.

6 DISCUSSION

6.1 Anatomy of the Eye

Myopia can affect multiple eye structures and contribute to the development of various ocular pathologies (5). Therefore, it is essential to have a solid understanding of the anatomy of the eye.

The eye can be anatomically divided into three tunics or layers, three chambers and the lens (Figure 1).

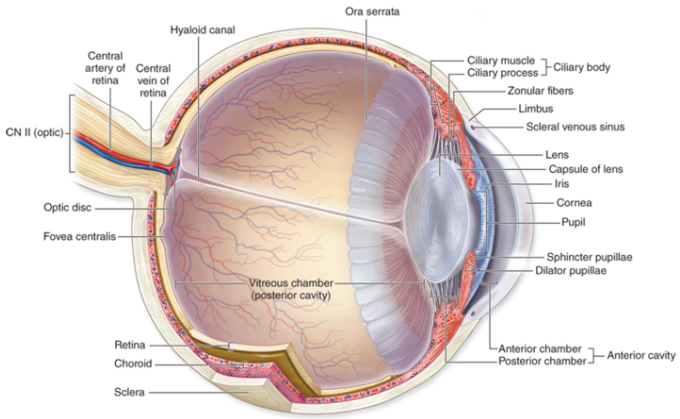

Figure 1: Anatomy of the eye (9)

The outer fibrous tunic includes the posterior sclera and the anterior transparent cornea, which are connected at the limbus (9). An ocular structure, which plays a significant role in myopia, is the sclera. The sclera is a dense, avascular, tough elastic tissue below the conjunctiva and continuous with the cornea. The thickness of the sclera varies depending on its anatomical location. During myopia progression, the sclera can undergo various changes, such as thinning and bulging at the posterior pole (10). The anterior exposed portion of the sclera is covered by the conjunctive – a thin mucosa. Conjunctival cells secrete mucous which is added to the tear film coating the anterior surface of the eye (9).

The cornea is a thin, transparent, smooth, avascular, and highly innervated tissue, making it the most sensitive tissue in the human body. It has a convex, aspherical shape and is directly exposed

to the external environment. Histologically, the cornea consists of five layers: the external stratified squamous non-keratinized epithelium, a thick anterior limiting membrane or Bowman's membrane, a thick stroma, a posterior limiting membrane, also known as Descemet's membrane, and an inner, simple squamous epithelium, also known as endothelium (9). Myopic eyes have been shown to have steeper corneas in comparison with hyperopic eyes. (10)

The eye's more vascular tunic is composed of the choroid, the ciliary body, and the iris. The choroid is a highly vascularized tissue, containing melanocytes and loose connective tissue. It is composed of two main layers: the inner choroidocapillary lamina and the Bruch's membrane (9). In myopic eyes, choroidal thinning and reduced blood supply to the retina can be observed (11).

The ciliary body is located posterior to the iris and plays a key role in several different functions of the eye, such as accommodation and the production of aqueous humor. The iris is positioned behind the cornea, separated from it by the anterior chamber. Histologically, the iris consists of three distinct layers: a layer of fibroblasts and melanocytes, stroma, and epithelium on the posterior surface. It forms a small circular opening, known as the pupil, in front of the lens, which regulates the amount of light reaching the retina (9).

Furthermore, there is an inner sensory tunic, called the retina, which communicates with the cerebrum through the optic nerve. The retina is one of the most important ocular tissues affected by myopia progression. It is located between the vitreous body and the choroid and consists of nine neural layers (Figure 2) – from inner to outer layers: inner limiting membrane, nerve fiber layer, ganglion cell layer, inner plexiform layer, inner nuclear layer, outer plexiform layer, outer nuclear layer, outer limiting membrane, and rod and cone layer (9).

The neural retina is attached to the retinal pigment epithelium (9). The inner limiting membrane is formed by expanded basal cytoplasmic processes of Müller cells. The nerve fiber layer contains the axons of ganglion cells, which assemble at the optic disc to form the optic nerve. The ganglion cell layer includes the cell bodies of ganglion cells and is thicker centrally than in the retinal periphery. The inner plexiform layer contains the synapses between ganglion cells and bipolar, amacrine, and horizontal neurons. The inner nuclear layer includes the cell bodies of bipolar, amacrine, and horizontal cells, which integrate signals from photoreceptors. The outer plexiform layer contains the synapses between bipolar, amacrine, and horizontal cells and the photoreceptors. The outer nuclear layer holds the cell bodies and nuclei of rods and cones. Furthermore, the outer limiting membrane is formed by junctional complexes between the apical processes of Müller cells and photoreceptors, providing structural support. The rod and cone layer consists of the outer segments of photoreceptors where light detection occurs. Finally, the retinal pigment epithelium lies adjacent to the choroid and performs essential supportive functions for the maintenance and function of the neural retina. Topographically, the retina is divided into the macula, fovea, optic disc, and peripheral

retina. The center of the macula, known as the fovea, is a crucial area for visual acuity. The fovea contains the highest concentration of narrow, elongated cone receptors to optimize light detection (9). During myopia progression the retina elongates (9). With axial elongation the retina gets thinner and the risk for retinal detachment increases (10).

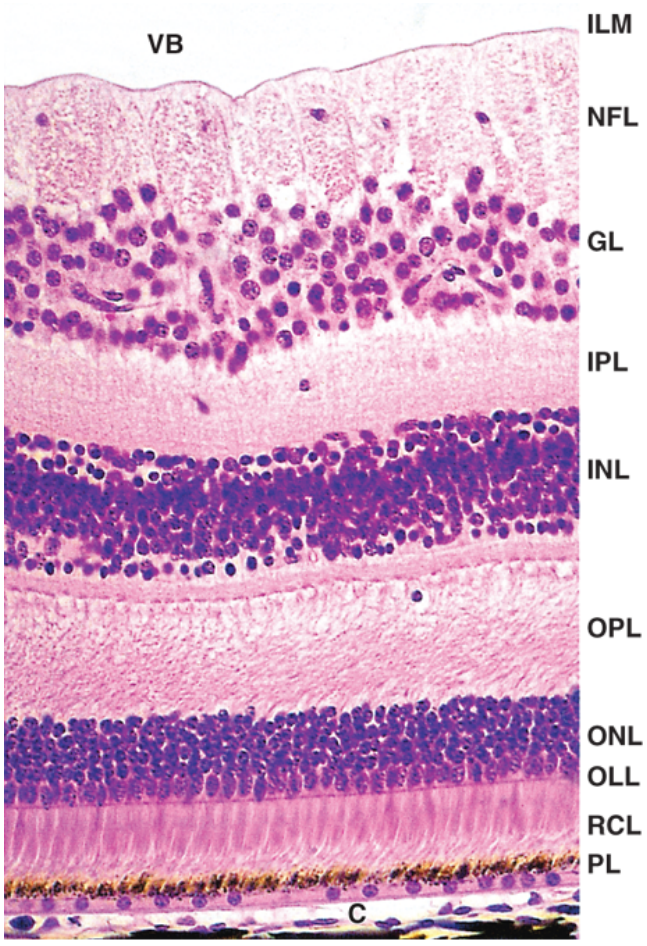

Figure 2: Histological section of the retinal layers. From outer to inner layers: Rod and cone layer (RCL), outer limiting layer (OLL), outer nuclear layer (ONL), outer plexiform layer (OPL), inner nuclear layer (INL), inner plexiform layer (IPL), ganglion cell layer (GL), nerve fiber layer (NFL), inner limiting membrane (ILM); Vitreous body (VB) (9).

The lens is a transparent, avascular, non-innervated, and biconvex structure, located behind the pupil and iris. It assists in refracting incoming light and focusing it onto the retina (9). Studies have shown that in moderately myopic eyes the thickness of the lens decreases with axial elongation (11). On top of that, refractive myopia is associated with an increased lens curvature, which increases the optical power of the eye (12). The microfibril of the lens capsule attach the lens centrally within the ciliary zonule. Together with the ciliary muscle, they enable visual accommodation by adjusting the lens curvature to focus on objects at varying distances. When viewing distant objects, the ciliary muscle relaxes, putting tension on the zonules and flattening the lens. To focus on near objects, the ciliary muscle contracts, shifting the ciliary body forward, reducing zonular tension, and allowing the

lens to adopt a more rounded shape for near vision (9). In myopic eyes the ciliary muscle is rarely utilized and undergoes atrophy (10).

The anterior chamber is the space between the cornea and the iris, while the posterior chamber is located between the posterior surface of the iris and the lens. Both of these chambers are filled with clear aqueous humor. Aqueous humor circulates through the pupil, which connects the anterior and posterior chambers of the eye (9).

Aqueous humor is a clear, slightly alkaline fluid produced continuously from plasma by the epithelial cells of the ciliary body. It supplies the avascular tissues of the eye with nutrients and oxygen, while also removing waste products, macrophages, blood, and cellular debris from the posterior cornea and the anterior surface of the lens. Additionally, it is crucial for maintaining the shape of the eyeball and regulating intraocular pressure. (9)

Posterior to the lens and its zonular fibers lies the vitreous chamber, enclosed by the retina, and filled with the vitreous body, which is a large, gelatinous, transparent mass of connective tissue. The vitreous body plays a crucial role in maintaining the structure of the globe (13). In myopic eyes, the vitreous body gets too small for the enlarged eye and collapses prematurely. This process leads to vitreous condensations, which patients perceive as floaters (10).

6.2 Biometric parameters of the eye

The most widely used ocular biometric parameters in clinical practice are axial length, the curvature of the anterior corneal surface, central corneal thickness, anterior chamber depth and lens thickness.

Axial length (AL) is defined as the distance between the cornea and the retinal pigment epithelium or the internal retinal membrane, depending on which technique is used (14). Currently, AL can be assessed through ultrasound biometry, optical biometry, or optical coherence tomography (OCT) techniques (15)(16). However, refractive error is clinically more meaningful compared to AL. Although the use of AL measurements has become more common in clinical practice over the past decade, standardized thresholds for distinguishing between physiological and accelerated axial elongation have not been established. It is widely recognized that, during the process of emmetropization, axial growth occurs more rapidly in younger children from 6 to 10 years compared to older children aged 12 to 16 (5). Nevertheless, axial length varies considerably, with emmetropic eyes usually measuring between 22 and 24.5 mm. Myopia is frequently associated with axial lengths exceeding 25 mm. In normal eyes AL increases approximately 0.1 mm per year, while 0.2 to 0.3 mm per year is linked to increasing myopia (17).

The curvature of the anterior corneal surface can be determined by keratometry. Typically, the steepest and flattest meridians are measured. It can be expressed in diopters or millimeters of radius

of curvature. Keratometry is frequently carried out by an interferometry apparatus, also used to measure AL. Alternatively, if the interferometry apparatus is unsuitable, manual keratometry or corneal topography can be used (16).

Central corneal thickness (CCT) can be measured using Orbscan or by pachymetry. The normal distribution of CCT is 540±30 microns (16).

Anterior chamber depth can be assessed by various imaging modalities, including OCT, ultrasound biometry, and optical interferometry techniques, for example the Zeiss IOLMaster (16).

Lens thickness refers to the distance between the anterior and posterior surfaces of the lens. It can be determined using ultrasound biometry, OCT, or Scheimpflug Imaging (18).

Refractive error is closely related to ocular biometric parameters. It occurs from a disproportion between the axial length of the eye and the refractive power of the lens and cornea. The most frequent refractive errors are myopia (nearsightedness), hyperopia (farsightedness), and astigmatism (10). Refractive error can be measured using subjective or objective measuring techniques. However, most of the time, both methods are combined. During subjective refraction measurement, different lens options are held in front of the eyes of the patient until the best corrected visual acuity is achieved. Objective measurement of the refractive error can be performed using refractometry, autorefractometry, or retinoscopy. The principle of refractometry is based on the ophthalmoscopic observation of a test figure imaged on the patient's retina. It involves adjusting the position of the test image relative to the eye until it appears clearly focused on the retina. Based on this adjustment, the refractive error can then be determined. Alternatively, instead of varying the distance, different lenses can also be held in the beam path. Similarly, in autorefractometry, the refraction is determined automatically using light-sensitive sensors and a computer-controlled system, which continues adjusting until a sharp retinal image is obtained. These devices work in the infrared range. Lastly, retinoscopy may be used to measure refractive error. In this method, light is projected onto the retina through the pupil. The examiner observes the reflex movements within the pupil while moving the light. Retinoscopy is performed with the help of a trial lens (10).

6.3 Pathogenesis of myopia

Myopia, also known as nearsightedness, is a refractive error in which light rays entering the eye parallel to the optic axis focus in front of the retina when accommodation is relaxed (19). This leads to the blurred vision of distant objects (20). There are two main categories of myopia based on its pathogenesis – axial and refractive myopia (Figure 3). Axial myopia, the more common type, typically develops when the eye becomes too long, especially through an elongation of the vitreal chamber (19). Axial length has the highest correlation with refractive status and shows the greatest

variability during growth. Thus, regulation of axial elongation is essential for emmetropization and represents a key target for interventions aiming to limit the progression of myopia (21).

On the other hand, refractive myopia is caused by a steep cornea, an increased optical power of the lens, or a combination of both (19).

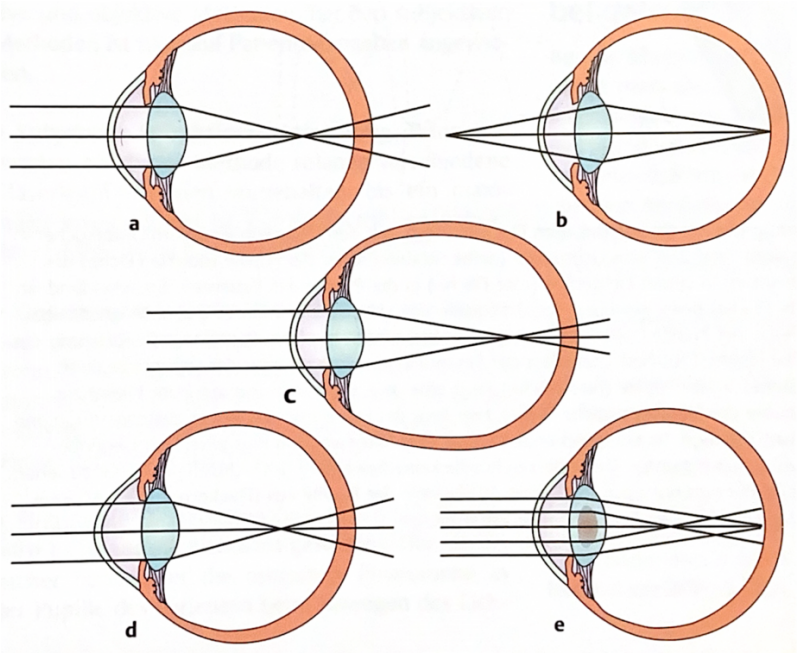

Figure 3: Refractive Conditions in Myopia. (a) The focal point of parallel incoming light rays lies in front of the retina. (b) Only nearby objects, which present a diverging path of light rays toward the eye, are focused onto the retina and perceived sharply. The far point lies at a finite distance. (c) Axial myopia: normal refractive power with an eye that is too long. (d) Refractive myopia: excessive refractive power with a normal sized eye. (e) Nuclear cataract with an additional focal point. (10)

As mentioned above, although axial length is biologically important, refractive error is clinically more meaningful. Refractive error is typically measured as the spherical equivalent (SE) in diopters, calculated by adding the spherical refraction and half of the negative cylinder. Myopia is generally defined as an SE of -0.5 D or less when ocular accommodation is relaxed, while high myopia is defined as an SE of -6.00 D or less when ocular accommodation is relaxed (19)(20).

Most children are born hyperopic, with refractive errors typically following a normal distribution. In 1-year-old to 2-year-old children, this distribution becomes narrower, with a mean in hyperopic range of +1-2 D. This change shows that there is an active mechanism that regulates the development of refraction, which is called emmetropization (20).

Emmetropization is a vision-dependent developmental mechanism that begins at birth and guides the axial growth of the eye to ensure alignment between its length and refractive capabilities. Disruptions in this process, or the failure to sustain its results, are considered key contributors to the onset of myopia. Emmetropization can be generally divided into two main phases: an early, rapid

infantile stage and a later, slower juvenile stage. The infantile phase, occurring within the first year of life, is characterized by significant axial elongation alongside reductions in the refractive power of the cornea and lens to achieve near-emmetropic vision.

This results in a refractive shift from approximately +2.00 D at three months to +0.75 D by three and a half years (12).

Starting around age three, the juvenile phase involves continued but slower axial growth, accompanied by more gradual refractive adjustments. Myopia commonly begins during this phase, particularly between ages six and nine, and tends to progress quickly before stabilizing in early adulthood. When myopia arises after the emmetropization period, it is usually due to the inability to maintain emmetropic balance rather than a failure of the initial emmetropization process (12).

6.4 Ocular biometric and structural changes associated with myopia

It is important to highlight the ocular changes in myopic eyes to improve the understanding of the process of axial elongation in myopia, associated structural changes and the consequences of myopia on visual performance. In patients with myopia, the anatomy of the eye changes in several areas, particularly due to the lengthening of the eyeball, as seen in axial myopia. This leads to several structural changes regarding the orbit and ocular shape, optic nerve, retina, choroid, sclera, and vitreous (11). In the following, the most important ocular biometric changes and structural alterations seen in myopic eyes will be discussed.

Emmetropic eyes commonly have a slightly spherical or prolate shape. Yet, in case of myopic axial elongation, it becomes more elongated and resembles a prolate ellipsoid. This modification mainly occurs in the area between the equator and the posterior pole (retro-equatorial region) (22). However, not only the axial elongation alone is causing the enlargement of the eye wall in myopic eyes. In addition to axial elongation, the eye undergoes slight increases in both horizontal and vertical dimensions, along with a modest thickening of the eye wall in the region anterior to the equator (11). This discovery helps explain why the Bruch's membrane opening (BMO) is also enlarged in myopic eyes. The strain on Bruch's membrane (BM) caused by the enlargement of the eyeball can induce an expansion of the BMO and may further lead to secondary structural alterations in the macular region (11). Myopic enlargement of the eye wall

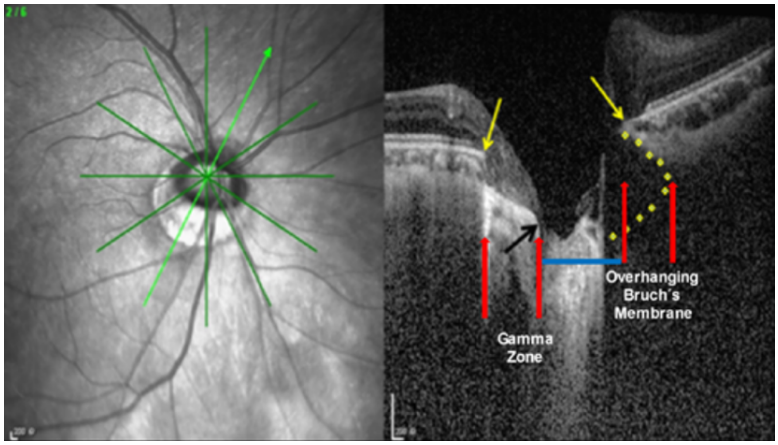

Figure 4: Visualization of intrapapillary overhanging of BM in nasal region in moderately myopic eye (11)

presents especially in the retro-equatorial and equatorial region, suggesting a feedback mechanism to regulate axial elongation in the mid-peripheral region of the eyeball. This enlargement is consistent with clinical findings indicating a shift of the BMO towards the fovea (11). It furthermore illustrates other features observed in axial myopia, such as BM overhanging into the intrapapillary compartment at the nasal optic disc border, a vertically ovalized optic disc shape, and lastly the lack of Bruch's membrane in the temporal parapapillary area, known as the gamma zone (Figure 4) (11)(23).

Furthermore, changes of the optic nerve can be observed in myopic eyes. Here, the extent of change depends on the degree of myopia. In moderately myopic eyes, the optic disc transforms from a primarily circular to oval shape, typically vertically oval, while highly myopic eyes frequently present with an increased size of the optic disc (24). On top of that, highly myopic eyes frequently present with an enlarged optic nerve head (ONH) canal compared to emmetropic or moderately myopic eyes (25). Moreover, a significantly thinner lamina cribrosa can be observed in highly myopic eyes, compared to non-highly myopic eyes (26).

The optic disc shape in highly myopic eyes shows great individual variability in its shape, with the longest axis being vertically, obliquely, or occasionally horizontally oriented. In extremely myopic eyes, backward traction of the optic nerve, possibly due to the dura mater of the optic nerve, can affect the shape of the optic disc, resulting in a vertical oval shape, rotation of the ONH, and even sagittal rotation toward the fovea (27).

In addition, retinal alterations are commonly observed in myopic eyes. This is because axial elongation results in an increase in ocular circumference, which is associated with retinal stretching, seen by an increased distance between the ora serrata and both the optic disc and macula. For every millimeter of axial elongation, the retinal length (from the ora serrata to the optic disc) extends by 0,73 mm, while the ciliary body length (from the scleral spur to the ora serrata) increases by 0,16 mm. A direct correlation between retinal and ciliary body lengths has been observed, with each millimeter increase in retinal length corresponding to a 0,12 mm increase in ciliary body length (28). Studies have shown that the density of the photoreceptors and the cells of the retinal pigment epithelium (RPE), along with the thickness of the retina decrease with increasing axial length, especially in the retro-equatorial region (29). On top of that, the occurrence of lattice degeneration as well as cobblestone degeneration typically increases with axial elongation (30). This is especially important, as lattice degenerations are linked with an increased prevalence of retinal tears and detachment. While the lifetime risk of a retinal detachment in individuals with lattice degeneration is only about 1%, it is important to mention that lattice degeneration can be found in approximately 40% of eyes with retinal detachment (16).

Studies have shown that, with axial elongation, there is a decrease in choroid thickness, especially in the subfoveal region (31). Choroidal thinning primarily involves the medium and large

vessel layers of the choroid, while the thickness of the choriocapillaris remains largely unaffected or is only minimally reduced. Thus, the proportion of the large and medium choroidal vessel layers relative to total choroidal thickness decreases with increasing axial length, whereas the proportion of the choriocapillaris increases (32).

The sclera is also considerably affected by axial elongation. With a longer axial length the sclera gets thinner, especially at the posterior pole. In contrast, the scleral thinning is least noticeable near and anterior to the ora serrata (33). Scleral remodeling is strongly associated with modifications in the composition of the extracellular matrix (ECM) and the behavior of scleral fibroblasts. These fibroblasts are responsible for producing collagen and other ECM components. Research has suggested that axial elongation in myopic eyes might be related to ongoing remodeling activity that weakens scleral structure (34). Electron microscopy studies have revealed that myopic sclera typically presents with a lamellar arrangement of collagen fiber bundles, a reduction of collagen fibril diameter, a broader distribution of fibril sizes and an increased presence of atypical, star-shaped fibrils in cross-section. Additionally, myopic sclera contains more groups of uniform, fine fibrils than those seen in non-myopic eyes (11)(35).

The vitreous may also change with axial elongation. Here, with an axial elongation structural macromolecules such as collagen and hyaluronan undergo modification (11). A study published in 2017 concluded that the volume of liquid vitreous fraction notably increased in myopic eyes, whereas potassium, sodium, and chloride concentrations significantly decreased (36). Due to the myopia-related collagen and hyaluronan association alteration a decrease in vitreous viscosity and fibrous degeneration can be observed. As a result, the likelihood of posterior vitreous detachment increases (Figure 5). This detachment process is frequently accompanied by vitreous opacities and collapse of the vitreous body, which are primary causes of vitreous floaters (11)(37).

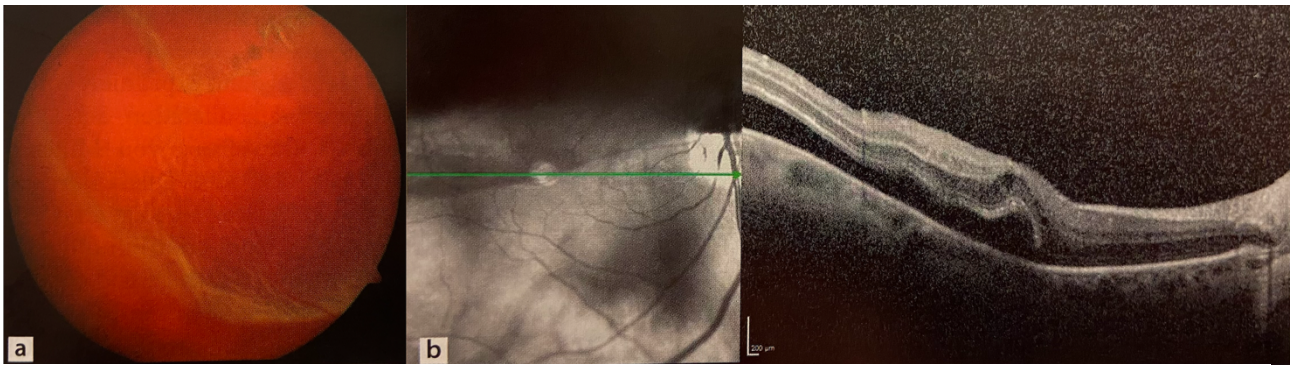

Figure 5: Retinal detachment: Horseshoe tear at the edge of lattice degeneration in pathological myopia. (a) Fundus photograph. (b) SD-OCT image showing macular detachment. (21)

Lastly, the anterior chamber becomes deeper, and the anterior chamber angle widens with increased axial length. Thus, it reduces the risk of primary angle-closure glaucoma. However, myopia

is associated with an increased incidence of primary open-angle glaucoma (POAG) and myopic eyes may be more susceptible to damage caused by glaucoma (16). While the definite mechanism is not yet fully understood, there are some hypotheses. The increased risk of POAG seen in myopic individuals could be related to the increased AL and thinner sclera in myopic eyes. This leads to a deformation of the lamina cribrosa, potentially associated with stress-induced mechanical alterations resulting from increased scleral tension across the lamina cribrosa. Such changes may contribute to an increased susceptibility to glaucomatous optic neuropathy. Furthermore, the increased susceptibility for glaucomatous optic neuropathy could be caused by peripapillary anatomical changes seen in highly myopic eyes. Additionally, to the anatomical basis, diagnostic challenges in the differentiation of normal tension glaucoma and myopia-related optic neuropathy may increase the occurrence of complications in POAG (38). Moreover, reduced scleral rigidity of myopic eyes leads to wrong low intraocular pressure values when measured with a Schiötz Tonometer. On top of that, the assessment of the optic disc excavation is difficult to evaluate in myopic patients, due to the oblique entry of the optic nerve (10).

The thickness and diameter of the cornea appear to be independent of axial length, although a mild decrease in anterior corneal curvature may be observed with increasing axial length in moderately myopic eyes. With increased AL in moderately myopic eyes, the thickness of the lens decreases. However, lens thickness is not related to AL in highly myopic eyes. Overall, changes in the anterior segment are less marked in comparison to the posterior segment (11).

6.5 Lifestyle factors contributing to myopia progression

While in the 1950s, myopia was mainly believed to have a genetic etiology with only little environmental influences, experimental studies nowadays have shown the impact of environmental factors on the development of myopia (20).

In the following, risk factors for myopia associated with the lifestyle of university students, including light environment, time spent outdoors, physical activity, near work, sleep, diet and smoking will be discussed.

In this study, an association between myopia and the following factors among second-year medical students from Lithuania, France, and Germany has been found: time spent outdoors, performing 1 to 2 hours of physical activity per day, and smoking.

6.5.1 Time spent outdoors

In this study, time spent outdoors was found to have a significant association with the prevalence of myopia. Similarly, both longitudinal and cross-sectional studies have shown a strong

association between more time spent outdoors and a decreased prevalence of myopia. This protective effect has been linked to objective measures of both the duration of outdoor exposure and the intensity of light (39).

Research regarding the effect of time spent outdoors on university students is limited. However, there are multiple studies on school children such as the Sydney Myopia Study. This study is a cross-sectional study where 1,765 6-year-olds and 2367 12-year-olds had an eye examination including cycloplegic refraction. On top of that, the parents and children were asked to fill out detailed questionnaires on the children's activities. It showed that children who spent more than two hours outdoors each day had a lower risk of developing myopia, even when they engaged in a lot of near-work activities. Students with low levels of near work and high levels of outdoor activity had the lowest myopia rates (40). Subsequent intervention studies confirmed these findings, showing that increasing outdoor time reduced the incidence of myopia in children (41). A meta-analysis that was published in 2012 reported that the prevalence of developing myopia decreased by 2% per additional hour that was spent outdoors weekly (42). A meta-analysis conducted in 2017 agreed with that, estimating that children who spent more time outdoors had a reduced risk of developing myopia. The risk ratio ranged from 0.54 to 0.57 when comparing high versus low outdoor exposure. Cross-sectional studies reported an odds ratio of 0,96 per additional hour spent outdoors. However, while outdoor exposure appeared effective in lowering the initial onset of myopia, it did not significantly affect the rate of progression in children who were already myopic (43). Another review from 2019 further stated that more time spent outdoors was effective in slowing axial length changes and lowering the risk of developing myopia (44).

These findings are subsequent to a 2017 cluster-randomized intervention-controlled trial in Taiwan, where *Wu et al.* divided 693 grade 1 school children into an intervention group and a control group. This study evaluated a school-based intervention, which aimed to promote outdoor activities to prevent myopia. It furthermore aimed to identify protective light intensities by improving indoor lighting. Other measurements attempting to prevent myopia like adjusting table height, encouraging distance gazing, and eye exercises were performed. Furthermore, they implemented a 39-minute near-work period followed by a 10-minute break. However, these interventions did not lead to a decrease in the incidence or prevalence of myopia, which continued to rise annually. A significant decline in both the incidence and the degree of myopia was only observed after the implementation of an education policy mandating a minimum of 80 minutes of outdoor activity per day. Following this change, the incidence dropped from 17% to 8%, and the average myopic shift decreased from 0.38 to 0.25 diopters. This preventive approach proved especially effective in children prior to the onset of myopia (45). A cross-sectional study from 2019 on factors associated with myopia in Nanjing showed that spending more than 2 hours of outdoor activity daily was associated with a decreased prevalence

of myopia among university students (46). Similar to these findings, a cross-sectional observational study conducted on 208 university students in Navarra suggested that increased outdoor activity may lead to a reduction of the onset and progression of myopia. This study used conjunctional ultraviolet autofluorescence (CUVAF) measurements as a biomarker for the time spent outdoors (8).

The exact mechanisms linking increased outdoor time to a reduced incidence of myopia have not been fully clarified, but several factors have been proposed. These include exposure to higher light intensities, alterations in chromatic light composition, variations in dioptric topographies, reduced engagement in near-vision tasks, and a decrease in accommodative demand (47). The hypothesis of a protective effect from increased time spent outdoors is supported by evidence from animal studies, including those on primates, which showed that brighter light stimulates dopamine release from the retina. Dopamine and dopamine agonists have been shown to slow axial elongation, the structural cause of axial myopia. This theory has been validated in animal models of myopia, where higher light intensity was found to completely inhibit myopia development, without altering other parameters (48).

It is important to note that not only the total time spent outdoors but also the timing of outdoor exposure following sustained near work may play a key role in the prevention and progression of myopia. Evidence from animal studies indicates that brief periods of plus defocus or exposure to bright light immediately after a minus defocus treatment can effectively counteract the signals that promote myopia development (12)(49).

6.5.2 Light environment

Currently, there is limited research on the effects of light environment on myopia progression in adults. A study conducted by *Muralidharan et al.* has shown that different lighting characteristics may influence ocular growth and development. These characteristics include light intensity, spectral composition, duration, pattern, and timing (12)(50).

Reduced exposure to daylight, as recorded by light sensors worn on the wrist, has been associated with an increase in axial length and a higher risk of developing myopia (51). Also, lower light intensity levels in nursery environments (359 compared to 671 lux) for children aged 4 to 5 years may contribute to greater eye growth and the onset of myopia (12)(52). This is especially interesting when taking into consideration that indoor light levels typically range from 112 to 156 lux, while even on a cloudy day or in shaded areas, outdoor light levels can range from 11,080 to 18,176 lux (53). Consequentially, exposure to moderate illumination levels (500-1,000 lux) for long and short-term periods (30-120 minutes) has been shown to significantly reduce axial elongation. It furthermore showed a choroidal thickening in young individuals (12)(54). Similar findings were observed in a 1-

year randomized controlled trial involving 1,713 children aged 6 to 14 years, where higher ambient light levels at the desk (558 lux vs 98 lux) and blackboard (440 lux vs 76 lux) were found to protect against the onset and progression of myopia, as well as ocular axial elongation (55).

Simultaneously to the light intensity, the spectral composition of light may affect the process of emmetropization and the development of myopia. Natural sunlight provides a dynamic and broad spectrum of wavelengths that varies throughout the day. It includes ultraviolet, near infrared, and infrared light. In contrast, commonly used artificial indoor lighting (such as fluorescent lights, light-emitting diodes, or halogen lamps) usually has an adynamic wavelength. The role of different light wavelengths in the development of myopia remains incompletely understood, particularly in human subjects. A study by *Torii et al.* stated that UVA light (360–400 nm), which is typically missing from standard indoor lighting, may help to slow down the progression of myopia and limit axial eye growth by increasing the expression of the early growth response factor-1 (EGR-1) (56). However, further studies are necessary to determine the potential effectiveness and safety of UVA light exposure in controlling myopia (12)(39).

Bright light exposure has been shown to inhibit the progression of myopia, due to an increased concentration of dopamine in the retina. Animal studies where dopamine was injected intravitreally even achieved an inhibition of myopia development (21). The release of dopamine, a neuromodulator and most widely studied neurotransmitter, plays a significant role in the regulation of eye growth. Its release is influenced by visual factors such as ambient light levels and image contrast, both of which are detected by retinal photoreceptors and have been linked to the onset of myopia. Therefore, increasing exposure to bright light has been proposed as a potential environmental strategy for managing myopic development. On top of that, apomorphine, a non-selective dopamine receptor agonist, and the D2 receptor agonist quinpirole inhibited ocular growth that was induced by a negative lens with increases in the thickness of the choroid, like brief daily periods of unrestricted vision. These findings imply that dopamine may act as a mediator for the protective effects of visual stimuli, including high-intensity light exposure and short periods of unrestricted vision on myopia. Furthermore, dopamine is known to induce thickening of the choroid and inhibition of axial elongation by stimulating the release of other transmitters, such as nitric oxide (57).

There are two possible mechanisms through which dopamine activity could influence the visual system to alter visually guided eye growth. Either dopamine directly modulates specific visual pathways via its receptors, thereby affecting their function, or the activity of these visual pathways alters dopamine release and signaling, and therefore impacting myopia progression (57).

To study these mechanisms, genetic labeling of dopamine receptor-expressing cells has been used (Figure 6). Here, BAC-Drd1a-tdTomato mice were used in combination with c-fos immunohistochemistry to identify subpopulations of D1R-expressing retinal cells activated by light.

Bright light exposure (2500-5000 lux) significantly increased the expression of c-fos, especially in D1R+ horizontal and bipolar cells, compared to normal light conditions (100-200 lux) (57).

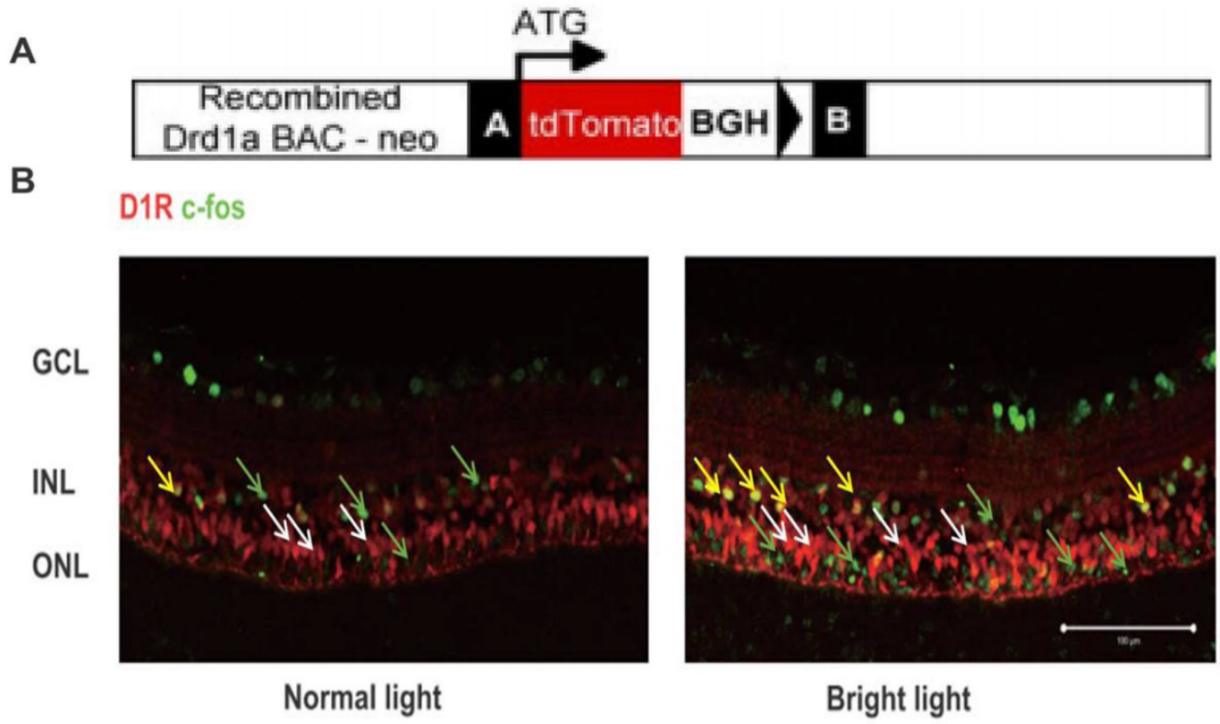

Figure 6: Light-induced activation of D1R-expressing retinal cells in BAC-Drd1a-tdTomato transgenic mice. White arrows indicate D1R+ cells. Green arrows show c-fos expression. Yellow arrows indicate activated D1R+ neurons. (57)

While some cross-sectional studies have identified lower vitamin D levels in individuals with myopia compared to those without (58)(59), later research failed to confirm a consistent link between vitamin D deficiency and myopia (60)(61). Given that myopia is not typically associated with conditions caused by vitamin D deficiency, it is more likely that vitamin D levels reflect the amount of time spent outdoors rather than having a direct protective effect (12)(17)(60).

6.5.3 Physical activity

This study showed that being physically active between 1 and 2 hours per day has a significant protective effect on myopia progression. Surprisingly, students performing between 1 and 2 hours of physical activity per day had significantly lower myopia progression compared to the students who were active for around 3 to 4 hours per day. However, here the small sample size and therefore low statistical power should be taken into consideration.

In 2008, a study of the University of Copenhagen, involving 156 first-year medical students was conducted to investigate how physical activity influences the progression and development of myopia in medical students. It was found that there is an inverse relationship between time spent on physical activity and refractive changes toward myopia. Here, the results of the multiple regression analysis indicate that one hour of daily physical activity has a protective effect on eye health that is

comparable in size to the negative impact of three hours of daily study. These findings support the hypothesis that regular physical activity may help reduce both the development and worsening of myopia in medical students (62). Another study on 3,600 university students in China compared myopia occurrence and progression between students participating in sports clubs at least 3 times per week for at least two hours and another group of students who were physically inactive. The study showed a statistically significant preventive effect of physical activity on myopia occurrence (63). A study published in 2022 conducted on 759 university students in China during the COVID-19 pandemic using a multiple-mediator SEM model also concluded that sedentary behavior significantly predicted an increase in myopia among university students, while physical activity achieved a decrease in myopia (64).

However, recent reviews have emphasized the importance of high outdoor time, rather than physical activity alone, in preventing the progression of myopia. These findings suggest that exposure to natural light and outdoor environments may be more influential in managing myopia development than physical exercise alone (62).

6.5.4 Near work

Different levels of near work showed no significant effect on myopia development and progression in this study. Similarly, a study conducted by *Onal et al.* to determine the change in refractive status of medical students within one year showed no significant difference between the time spent doing near work between myopic and non-myopic individuals (65). A study on 177 third-year law students by *Loman et al.* showed no association between near work and myopia progression (7).

Likewise, a cross-sectional study on 968 first-year university students in Nanjing showed no significant association between near work and the use of technical devices and myopia. Yet, incorporating breaks following every 30 minutes of uninterrupted reading has been linked to a decreased risk of developing myopia (46). However, this study found no association between different break frequencies while using technical devices on myopia.

Literature regarding the effect of screen time on myopia is conflicted. On one hand, there are frequent associations between screen time and myopia (17). Multiple researchers from China and the United States stated that increased screen time has been linked to the development and progression of myopia, which was especially noticed during and after the COVID-19 pandemic (66)(67).

On the other hand, myopia epidemics occurred long before the widespread usage of technical devices (17). A study by *Xie et al*., published in 2022 on 759 Chinese college students using a serial multiple

mediator SEM analysis found no correlation between screen time and myopia (64). It is still uncertain if technical device usage is just a new form of near work (17).

Self-reported usage of frequent technical device usage in the dark in this study is high, with 76 percent of medical students claiming to use technical devices in the dark frequently (3 nights per week or more). However, this study found no association between technical device usage in the dark or screen time and myopia prevalence. Literature on the effect of using technical devices in the dark on myopia in university students is sparse.

Due to the linkage of myopia and educational performance, as well as close-work activities, near work has been widely acknowledged as an environmental risk factor for the onset of myopia in children. One mechanism, how this could develop is due to increased ocular accommodation.

As an object moves closer to the eye, ocular accommodation increases, primarily through a change in the shape of the lens, which becomes more convex. This mechanism, part of the accommodation reflex, also involves pupil constriction and convergence of the eyes, all of which contribute to enhancing the eye's focusing ability (68). Even during routine visual tasks such as reading or using digital screens, the eye experiences noticeable shifts in refractive power across the retina, from the fovea to the peripheral retina. In comparison to indoor settings, where these variations often result in greater peripheral defocus, outdoor environments tend to provide a more consistent retinal image focus (12). Furthermore, the accommodative lag is seen to be higher in indoor environments. For near work like reading the accommodative lag can be 2,88 D and between 0,14 to 1,77 D for the use of a computer, while for outdoor tasks it ranges around 0,05 D. Overall, accommodation demand is much more prominent indoors, due to shorter viewing distances, greater dioptric variability, and less uniform retinal focus, whereas outdoor environments are associated with more relaxed accommodation due to longer viewing distances, a more stable accommodative demand, and a more consistent retinal focus (69).

However, the role of accommodation in myopia development and progression remains unclear. Studies on the association between myopia and accommodative lag have shown conflicting results, with some reporting reduced accommodative amplitude in myopes and others finding no correlation. Similarly, bifocal and progressive addition lenses, prescribed to reduce accommodative lag, found alternating results on myopia progression (12). These lenses induce relative peripheral myopia, making it uncertain whether their impact is due to altered peripheral refraction or changes in accommodation (12)(70).

The effect of near work on myopia has been explored especially in school children. It has been observed that myopic children tend to spend more time engaging in near-work activities such as studying, reading, and writing in comparison to non-myopic children. A comparable pattern of increased hours performing near-work tasks has been observed in urban populations, where children

showed an increased prevalence of myopia compared to rural children (71). Additionally, children who read two or more books weekly were reported to have a threefold risk of developing myopia compared to those with lower reading frequency (72). The Sydney Myopia Study concluded that specific factors of near-work activities, including prolonged, uninterrupted reading sessions exceeding 30 minutes and maintaining a working distance of less than 30 centimeters, were significantly associated with an increased risk of myopia onset (69).

6.5.5 Sleep

A weak correlation between a low amount of sleep and myopia progression was established using the Spearman Correlation Test in this study. However, the association was not significant. Furthermore, this study showed no association between the development of myopia and sleep duration. While research on the influence of sufficient sleep on myopia progression is conflicted, a recent systematic review and meta-analysis by *Zhao et al.* suggested a significant effect of insufficient sleep on the prevalence of myopia and high myopia in children and adolescents. Insufficient sleep was defined, according to the American Academy of Sleep Medicine (AASM), as less than 10 hours for 3 to 5-year-olds, less than 9 hours for 6 to 12-year-olds, and less than 8 hours for 13 to 17-year-olds. The study showed a correlation between short sleep duration and more rapid change in axial length. However, follow-up studies failed to establish a link between insufficient sleep and myopia onset and progression (73).

The involvement of circadian rhythm in myopia has been investigated through studies evaluating the relationship between melatonin and myopia. Melatonin is a neurohormone that is released in low-light or dark conditions, promotes sleep, and helps regulate the circadian rhythm. Dim light melatonin onset (DLMO) is generally identified as an important marker of the circadian phase. The suppression of melatonin release by light is mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs) in the human retina (74). A study conducted by *Chakraborty et al.* suggested a potential association between circadian rhythms and myopia in young adults using DLMO measurements. Myopic individuals exhibited a phase delay in DLMO of over one hour compared to non-myopic participants and reduced overnight urinary melatonin levels. Furthermore, the myopic children showed significantly later sleep onset and wake-up times, as well as a reduced overall sleep quality compared to emmetropes (12)(75).

Another 2020 2-year school-based, prospective trial by *Liu et al.* suggested delayed sleep onset as a risk factor for the development and progression of myopia (76). Subsequently, a population-based cross-sectional study conducted by *Jee et al.* showed an inverse relationship between sleep duration and myopia, stating that the adjusted odds ratio for myopia was decreased in those with more

than 9 hours of sleep, compared to those sleeping less than 5 hours every night (77). In contrast, a study on 177 third-year law students from Pennsylvania reported no significant association between the amount of sleep and the occurrence of myopia, as well as myopia progression (7). Similarly, a cross-sectional study published in 2019, which was conducted on 1200 first-year university students in Nanjing found no association between sleep duration and myopia (46).

Possible mechanisms are still under debate. It has been presumed that lower amounts of sleep could lead to an increased time available for near work in children and therefore increase the risk of myopia (76).

Current findings are conflicting and more research to clarify potential links between sleep patterns, circadian rhythms, and the development of myopia is needed (12)(76).

6.5.6 Diet

This study found no association between diet and myopia. The association between dietary habits and myopia remains a subject of debate. A study conducted in 2021 showed partial alleviation of the decrease in choroidal blood perfusion (ChBP) induced by near work in first-year medical students by oral intake of omega-3 polyunsaturated fatty acids (ω-3 PUFAs) (78). A study analyzing 6855 Americans between the ages of 12 and 25 showed no link between nutritional factors, such as serum vitamin D, glucose levels and caffeine intake and refractive or myopia status. Although, an increase in insulin levels was related to an increased likelihood of myopia (79). A Korean study collecting data from 18,077 adolescents concluded that elevated intake of carbohydrates, cholesterol, sodium, protein, and vitamin B2 was positively linked with a higher likelihood of developing myopia. In contrast, increased consumption of vitamin C seemed to reduce the occurrence of myopia (80).

The exact mechanism of a possible dietary influence on myopia is not yet fully understood, however, there are a few theories. A theory is that diets high in glycemic index lead to increased blood insulin levels, which then promote the secretion of insulin-like growth factor 1 (IGF-1). IGF-1 regulates cell growth and differentiation and therefore may contribute to axial elongation and myopia development (81).

A study by *Tang et al.* aiming to evaluate the impact of IGF-2 on myopia development using an animal model observed a myopic shift and axial elongation, along with an upregulation of retinal IGF-2. In an experiment on guinea pigs, form-deprived (FD) eyes that received an intravitreal injection of IGF-2 antisense oligonucleotide (ASON), an inhibitor of retinal IGF-2 expression, showed a reduction in myopia and a shortening of axial length. The authors suggested that FD-induced upregulation of retinal IGF-2 contributes to increased myopic diopters and ocular growth, while IGF-2 ASON effectively blocked its expression and inhibited myopia progression (82).
However, further studies are needed to determine the influence of diet and nutrition on myopia.

6.5.7 Smoking

This study found no association between smoking and myopia. Yet, the study showed a statistically significant effect of subjective vision worsening in smoking individuals compared to non-smokers.

At present, only a sparse amount of research on the effect of smoking on refractive error in adolescents and adults is available. However, there are a few studies on second-hand smoking in children and myopia.

Previous studies investigating the relationship between second-hand smoke exposure and myopia showed inconsistent findings, primarily due to the presence of uncontrollable variables such as age, socioeconomic background, parental education level, and housing conditions. The STARS study including 3009 6 to 72-month-old children showed that parental smoking is associated with a decreased odds ratio of childhood myopia (83). Conversely, a more recent large-scale cross-sectional study in Hong Kong on children between 6 and 8 years of age revealed an association between passive smoke exposure and both the onset and progression of myopia. Furthermore, the study also reported a slight but dose-dependent shift of 0.07 D in refractive error or 0.04 mm in axial length per 10 cigarettes smoked daily by a parent. However, due to the cross-sectional nature of the study, a causal relationship could not be definitively established (84).

A recent Mendelian randomized study intending to examine a potential causal link between smoking and the development of myopia or astigmatism showed no association between smoking and the development of myopia (85). A cross-sectional study conducted in 2020 on the prevalence and risk factors of myopia in China stated that a history of smoking was found to be negatively associated with myopia. Here, 3,845 participants between the ages of 40 and 80 of the Han and Yugur populations were included. However, it should be taken into consideration that while in this study the Yugur population presented with lower myopia and higher smoking rates, higher physical activity and increased outdoor time were also more prominent, and educational levels were lower in that population. Therefore, socioeconomic status should be taken into consideration (86).

Further research is needed to evaluate the effect of smoking on ocular biometric changes in university students.

Some limitations of this study were that both myopia status and behavioral factors were based on self-reported data. The absence of clinical confirmation of myopia could result in an underestimation of myopia prevalence, as students with only slight myopic symptoms might not experience noticeable difficulties with distant vision, and therefore may not report themselves as myopic.

Also, it is important to mention that a high number of students stated that their vision deteriorated subjectively. Medical students might not prioritize regular ophthalmologic consultations to confirm myopia due to the high workload.

Furthermore, behavioral data is subject to recall bias, as there is no objective data on the lifestyle habits of the students. An idea for future research could be the use of devices to measure physical activity, like a smartwatch to gather more detailed information. On top of that, the small sample size is a limitation of this study. Also, the severity of myopia was classified into categories and was only divided into mild, moderate, and high myopia. Therefore, possible smaller changes in refractive error might have remained undetected.

Further research would benefit from larger and more diverse sample groups, as well as objective measurements of refractive error and lifestyle habits of university students.

7 CONCLUSIONS AND RECOMMENDATIONS

The prevalence of myopia among university students highlights the importance of research in this field and focus on preventative measures. This study highlights the complex interaction of genetic predisposition and environmental influences on myopia development and progression among university students. A hereditary component was observed, as students with myopic parents showed a higher prevalence of myopia at the beginning of university. While a significant number of students reported subjective visual deterioration during their studies, objective myopia progression was limited and less pronounced than anticipated based on research. However, this study shows that myopia can progress in university students and certain lifestyle factors influence the progression and prevalence of myopia.

Near work and screen time were not significantly associated with myopia onset or progression. In contrast, time spent outdoors was shown to be a protective factor against myopia prevalence. Yet, the effect of time spent outdoors on myopia progression remained inconclusive. Interestingly, physical activity showed an unexpected association with myopia progression, particularly in students with high levels of physical activity, suggesting the need for further investigations. On top of that, originating from a village or town showed to be a protective factor against myopia progression, while the prevalence of myopia progression in students originating from a city was high. Furthermore, smoking was significantly associated with subjective vision deterioration, while dietary habits, sleep, and screen break frequency showed no notable influence on myopia outcomes.

Based on the findings of this study and the literature review, increasing time spent outdoors and physical activity should be promoted among university students as a preventive measure. Based on this study, physical activity of between one and two hours a day is recommended to prevent myopia progression.

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9 ANNEXES

Annex 1. Questionnaire.

Demographic details and ophthalmic medical history

1. What is your gender?
   - ☐ Female
   - ☐ Male
   - ☐ Other

2. How old are you?

   _____

3. Are you from a rural or urban area?
   - ☐ Village (100-2000 citizens)
   - ☐ Town (2001- 100,000 citizens)
   - ☐ City (>100,000 citizens)

4. Is this the first time you are enrolled in university?
   - ☐ Yes
   - ☐ No

5. Did you need glasses or contact lenses to see clearly before starting university?
   - ☐ Yes, I wore glasses
   - ☐ Yes, I wore contact lenses
   - ☐ Yes, I wore both
   - ☐ No

   a. If **yes**, what was your glasses or contact lenses prescription before enrolling in university?
      - ☐ Mild myopia (nearsighted): -0,25 D to -2,75 D
      - ☐ Moderate myopia: -3,0 D to -5,75 D
      - ☐ Severe myopia: ≥ -6,0 D

      - ☐ Mild Hyperopia (farsighted): + 0,25 D to +2,0 D
      - ☐ Moderate Hyperopia: +2,25 D to +4,75 D
      - ☐ Severe hyperopia: ≥ +5,0 D

      - ☐ Astigmatism (imperfections of curvature of cornea): 0,25 D -1,0 D
      - ☐ Astigmatism: 1,0 - 1,75 D
      - ☐ Astigmatism: ≥ 2.0 D

      - ☐ I don't know

   b. If **yes** in question e, what is your **current** glasses or contact lenses prescription?

      - ☐ Mild myopia (nearsighted): -0,25 D to -2,75 D
      - ☐ Moderate myopia: -3,0 D to -5,75 D
      - ☐ Severe myopia: ≥ -6,0 D

☐ Mild Hyperopia (farsighted): + 0,25 D to +2,0 D
☐ Moderate Hyperopia: +2,25 D to +4,75 D
☐ Severe hyperopia: ≥ +5,0 D

☐ Astigmatism (imperfections of curvature of cornea): 0,25 D -1,0 D
☐ Astigmatism: 1,0 - 1,75 D
☐ Astigmatism: ≥ 2.0 D

☐ I don't know

c. If you didn't need glasses or lenses to see clearly **before** starting university, did you get a prescription for visual aid **since starting** your studies? (If no go to question 6)
☐ Yes
☐ No

i. If yes, what is your current prescription?
1. ☐ Mild myopia (nearsighted): -0,25 D to -2,75 D
2. ☐ Moderate myopia: -3,0 D to -5,75 D
3. ☐ Severe myopia: ≥ -6,0 D
4.
5. ☐ Mild Hyperopia (farsighted): + 0,25 D to +2,0 D
6. ☐ Moderate Hyperopia: +2,25 D to +4,75 D
7. ☐ Severe hyperopia: ≥ +5,0 D
8.
9. ☐ Astigmatism (imperfections of curvature of cornea): 0,25 D -1,0 D
10. ☐ Astigmatism: 1,0 - 1,75 D
11. ☐ Astigmatism: ≥ 2.0 D

6. Do you feel that your vision has worsened since you started studying at university?
☐ Yes
☐ No

7. Do you have a history of any of the following eye diseases?
☐ Glaucoma
☐ Amblyopia
☐ Strabismus
☐ Keratitis
☐ Uveitis
☐ Retinal detachment
☐ Eye trauma
☐ Ocular surgery

8. Do you have a history of other means to prevent myopia in childhood/early teenage years?
☐ Atropine drops
☐ Pirenzepine gel
☐ Orthokeratology
☐ Myopia management glasses
☐ Defocus incorporated soft contact (DISC) lenses/ Bifocal contact lenses
☐ Eye exercises

9. Does your mother have myopia, hyperopia or astigmatism?
☐ Myopia

- ☐ Hyperopia
- ☐ Astigmatism
- ☐ None of these

10. Does your father have myopia, hyperopia or astigmatism?
    - ☐ Myopia
    - ☐ Hyperopia
    - ☐ Astigmatism
    - ☐ None of these

Lifestyle

11. What is your average time spent outside daily?
    - ☐ <1 hour
    - ☐ 1-2 hours
    - ☐ 3-4 hours
    - ☐ >4 hours

12. How many hours are you physically active per day on average?
    - ☐ <1 hour
    - ☐ 1-2 hours
    - ☐ 3-4 hours
    - ☐ >4 hours

13. What kind of physical activity are you doing? (Please mark all options that are applicable)
    - ☐ Running
    - ☐ Walking
    - ☐ Cycling
    - ☐ Weightlifting
    - ☐ Soccer
    - ☐ Tennis
    - ☐ Other, if so please specify _____

14. How many hours do you sleep per night on average?
    - ☐ <6 hours
    - ☐ 6 hours
    - ☐ 7 hours
    - ☐ 8 hours
    - ☐ 9 hours or more

15. How many hours do you generally spend doing near work per day? (e.g. reading, writing, working on tablet/computer)
    - ☐ <1 hour
    - ☐ 1-2 hours
    - ☐ 3-4 hours
    - ☐ >4 hours

16. How much screen time (including social media, etc.) do you have per day?
    - ☐ <1 hour
    - ☐ 1-2 hours
    - ☐ 3-4 hours
    - ☐ >4 hours

17. How often do you take breaks when working on the screen?
- ☐ Every 30 min or more
- ☐ Every hour
- ☐ Every 2 hours
- ☐ Every 3 hours or less

18. What do you do during these breaks?
- ☐ Physical activity
- ☐ Scrolling through the phone
- ☐ Reading
- ☐ Outdoor activities
- ☐ Other, if so please specify _____

19. How often do you use technical devices in the dark?
- ☐ Every night
- ☐ Frequently (>3 times a week)
- ☐ Weekly
- ☐ Once a month
- ☐ Never

20. Do you smoke?
- ☐ Yes
- ☐ No
- ☐ Rarely/sometimes

    a. If yes, what are you smoking?
    - ☐ Cigarettes
    - ☐ ICOS
    - ☐ E-cigarettes/ Vapes
    - ☐ Shisha/ Hookah
    - ☐ Other

    b. If yes, how often do you smoke?
    - ☐ > 20 (cigarettes) a day
    - ☐ 10-20 (cigarettes) a day
    - ☐ 9 (cigarettes) per day or less

21. What diet are you mostly following?
- ☐ Omnivore
- ☐ Vegetarian
- ☐ Vegan
- ☐ Other

22. How many portions of vegetables or fruits do you eat daily? (1 portion - ~75 gr)
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ >3