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Fitting Soft Multifocal Customized Contact Lenses for Myopia Control: A Literature Review

by

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MASTER'S THESIS

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Abstract

The increasing prevalence of myopia throughout the industrialized world in recent decades has caused costs and problems for the eye health. Changed lifestyle and behavior are the main causes. For the pathogenesis of myopia, the amount of time spent outdoor and near activities play an important role. Various options for the treatment of myopia have been described as effective in the literature. Normal single vision glasses and contact lenses can only provide clear vision, but do not reduce myopia progression. Orthokeratology shows a slowing of axial growth, but has an increased risk of infectious keratitis. Low-dose atropine (0.01%) is currently the best pharmacological option. It proved safe, effective and showed the least rebound effect with negligible side effects. Other options for the treatment of myopia include special glasses, behavioral changes and prolonged outdoor exposure (to prevent the onset of myopia), as well as other methods. An increasingly important myopia management option is multifocal contact lenses, that provide a peripheral treatment zone producing myopic defocus. Such myopia control lenses are available as customized or as daily or monthly lenses. Children benefit from wearing contact lenses more than just having refractive error correction and myopia control, they have a better self-esteem and improved quality of life. The numerous findings on the safety and efficacy of soft multifocal distance center contact lenses in children to reduce the progression of myopia suggest that this modality should be considered as a main treatment option. Less, but similar to orthokeratology, when wearing soft lenses there is a risk of developing potentially serious complications such as microbial keratitis. The introduction of child-appropriate risk minimization strategies, and patient and parent education with regular monitoring is essential and leads to successful contact lens wear. This literature review summarized the actual knowledge about myopia management, prevalence, etiology and the visual and healthy consequences of myopia.

The three currently most important strategies for slowing the progression of myopia are soft multifocal distance center contact lenses, Orthokeratology and low-dose atropine ophthalmic drops.

Keywords: myopia; customized; soft multifocal contact lens; peripheral myopic defocus; myopia management; myopia control

Abstract in German

Die zunehmende Verbreitung von Kurzsichtigkeit in der gesamten industrialisierten Welt in den letzten Jahrzehnten hat Kosten und Probleme für die Augengesundheit verursacht. Veränderungen im Lebensstil und Verhalten sind die Hauptursachen. Für die Pathogenese der Myopie spielt die Zeit, die im Freien und mit Aktivitäten in der Nähe verbracht wird, eine wichtige Rolle. Verschiedene Möglichkeiten zur Behandlung von Myopie wurden in der Literatur als wirksam beschrieben. Normale Einstärkenbrillen und Kontaktlinsen bieten nur eine klare Sicht, verringern jedoch nicht das Fortschreiten der Myopie. Die Orthokeratologie zeigt eine Verlangsamung des axialen Wachstums, hat jedoch ein erhöhtes Risiko für eine infektiöse Keratitis. Niedrig dosiertes Atropin (0,01%) ist derzeit die beste pharmakologische Option. Diese erwies sich als sicher, wirksam und zeigte den geringsten Reboundeffekt mit vernachlässigbaren Nebenwirkungen. Andere Optionen für die Behandlung von Myopie umfassen spezielle Brillen, Verhaltensänderungen und längerer Aufenthalt im Freien (um das Einsetzen von Myopie zu verhindern) sowie andere Methoden. Eine zunehmend wichtige Option für das Myopiemanagement sind multifokale Kontaktlinsen, die eine periphere Behandlungszone bieten, die einen peripheren myopischen Defokus hervorruft. Solche Myopiekontrolllinsen sind als kundenspezifische oder als Tages- oder Monatslinsen erhältlich. Kinder profitieren vom Tragen von Kontaktlinsen nicht nur von der Korrektur von Brechungsfehlern und der Kontrolle Ihrer Kurzsichtigkeit, sondern auch von einem besseren Selbstwertgefühl und einer verbesserten Lebensqualität. Die zahlreichen Ergebnisse zur Sicherheit und Wirksamkeit von weichen, multifokalen Kontaktlinsen mit Fernsicht im Zentrum bei Kindern zur Verringerung des Fortschreitens der Myopie legen nahe, dass diese Modalität als Hauptbehandlungsoption in Betracht gezogen werden sollte. Weniger, aber ähnlich wie in der Orthokeratologie, besteht beim Tragen weicher Linsen das Risiko, dass potenziell schwerwiegende Komplikationen wie mikrobielle Keratitis auftreten. Die Einführung kindgerechter Risikominimierungsstrategien sowie eine regelmäßige Überwachung und Patienten- und Elternaufklärung sind unerlässlich, und führen zu einem erfolgreichen Tragen von Kontaktlinsen. Diese Literaturübersicht fasst das aktuelle Wissen über Myopiemanagement, Prävalenz, Ätiologie und die visuellen und gesundheitlichen Konsequenzen von Myopie zusammen.

Die drei derzeit wichtigsten Strategien zur Verlangsamung des Fortschreitens der Myopie sind weiche, multifokale Kontaktlinsen mit Fernsicht im Zentrum, Orthokeratologie und niedrig dosierte Atropin-Augentropfen.

Schlüsselwörter: Kurzsichtigkeit; kundenspezifisch; weiche multifokale Kontaktlinse; peripherer myopischer Defokus; Myopie-Management; Myopie-Kontrolle

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List of Abbreviations

AAO	American Academy of Optometry
AC/A	accommodative-convergence to accommodation ratio
ACD	anterior chamber depth
Add	Addition
AL	axial length
AMD	age-related macular degeneration
AOAMF	CIBA Vision Air Optix Aqua Multifocal
AOP	Vistakon Acuvue Oasys for Presbyopia
BC	Base curve
BCLA	British Contact Lens Association
BF	Bifocal
BMI	body mass index
CCL	Collagen Cross-linking
cd	candela
CI	Confidence interval
CIE	corneal infiltrative and inflammatory event
CL	Contact lens
CLARE	contact lens-induced acute red eye
CLPU	contact lens-associated peripheral ulcer
CREAM	Consortium for Refractive Error and Myopia
CS	Contrast sensitivity
CSP	corneo-scleral profile
D	Diopters
DIMS	Defocus Incorporated Multiple Segments Spectacle Lens
DoF	Depth of focus
Dpt	Diopters
e.g.	lat. “exempli gratia”, for example
E^3	European Eye Epidemiology
ECM	extracellular matrix
ECP	Eye care practicioner
Et al.	lat. “et alii, et alia, et aliae”, ‘and others’
Etc.	lat. “et cetera”, ‘and other similar things’, or ‘and so forth’
FDA	Food and Drug Administration
GP	Gas Permeable
GPC	Giant papillary conjunctivitis
HOA	Higher order aberration
i.e.	lat. “id est”, ‘that is’
IACLE	International Association of Contact Lens Educators
IOP	Intra-ocular pressure
LED	light-emitting diode
LT	lens thickness
lx	Lux
m	meter
Max	maximum
MeSH	Medical Subject Headings (vocabulary thesaurus used for PubMed)
MD	lat. “medicinae doctor”, doctor of medicine
MF	Multifocal or multi-focus

MFSCL	Multifocal soft contact lens
Min	minimum
mm	millimeter
MM	myopic maculopathy
MPS	multipurpose contact lens disinfection solution
MSC	mesenchymal stem cells
n.e.	numeric eccentricity
NECO	New England College of Optometry, Boston, USA
OCT	optical coherence tomography
OD	lat. “oculus dexter”, ‘right eye’
OR	Odds ratio
Ortho-K	orthokeratology
OS	lat. “oculus sinister”, ‘left eye’
OWT	ocular wavefront tomography
PAL	progressive addition spectacle lens
PL-NIBUT	pre-lens non-invasive break-up time
PSCC	posterior subcapsular cataract
PSR	Posterior Scleral Reinforcement
RCT	Randomized controlled trial
RD	retinal detachment
RGP	rigid gas permeable contact lens
ROP	retinopathy of prematurity
RPE	retinal pigment epithelium
RPR	Relative peripheral refraction
RS	Rotterdam study
Sag	sagittal (height)
SCL	Soft contact lens
sec	seconds
SE, SER	spherical equivalent, spherical equivalent refraction
SI	synergy index
SICS	solution induced corneal staining
SiH	silicone hydrogel
SNP	single nucleotide polymorphism
SR	Success rate
SSI	sclera strengthening injection
SV	Single Vision
SVSCL	Single vision soft CL
TV	television
US, USA	United States, United States of America
VA	Visual acuity
VCD	vitreous chamber depth
VL	violet light
vs.	Versus
WHO	World Health Organization
WMD	Weighted mean difference
WTW	white to white (corneal diameter)
µm	micrometer
Zoc	central optical zone for distance view

Acknowledgements

The days I finished my studies in Optometry at IFAO in Switzerland in 1997, I was twenty-four years old. I was sure, I had studied a very fulfilling job and got a nice title (Eidg. Dipl. Augenoptiker). After that, I was focused in earning and saving money to start an independent life, move away from home and build a family. I was still interested in optometry and spent my working life in an optometry practice. I was ready to study in this field.

Today, after more than twenty years, I am very proud of my family. There are many people whom I would like to thank and without whose help this work would not have been possible. First, I would like to express my special appreciation and thanks to my advisors Dr. Martin Lörtscher and Prof. Dr. Anna Nagl as well as Pascal Blaser from Swisslens. They supported me with a lot of information about myopia control contact lenses. Swisslens offered me to write a study for them, in this context I was able to get in direct contact with German speaking contact lens fitters in Europe. I would also like to thank the company I work for, Konstantin Tsiounis AG in Glarus, Switzerland, for the amount of time and paper they allowed me to use for my thesis. Sebastian Felgner and Andreas Tsiounis translated for me the questionnaires. Thank you!

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This thesis is dedicated to my father Rijk van der Heide. He died during my studies on June 20th 2017.

1 Introduction

1.1 Thesis Overview

This review has five chapters. The first chapter provides an overview of the current understanding of myopia development and interventions to slow down myopia progression. Chapter Two presents myopia facts and the principles behind the current therapies to inhibit myopia progression. Chapter Three describes the design of myopia control contact lens and presents knowledge about the safety of contact lens wear in children. While Chapter Four discusses conflicts of literature information and study results. Chapter Five concludes by summarizing the achievements of this thesis and points to future directions for research.

1.2 Aims

The aims of this literature review were:

1. To review and collect actual information about the myopia control options for optometrists in Switzerland.
2. To collect information about the safety of fitting soft (customized) myopia control lenses to children
3. To add own collected data to the findings

1.3 Introduction

Myopia, also called nearsightedness or shortsightedness, is the most usual refractive disorder of the eye (1) and is usually caused by an abnormal ocular elongation (2). For the World Health Organization (WHO) is myopia one of the five eye disorders with high-priority to control (3). The normal various methods for the correction of myopia, for example contact lenses (CLs), spectacles and LASIK, do not act on the underlying abnormal ocular elongation (4). In patients with higher myopia, over 6.5 diopters, an elevated number of diseases like myopic retinal degenerations, retinal detachment and glaucoma has been reported (5–7). Which factors contribute to the development of nearsightedness are part of ongoing research. It is likely that nearsightedness is multi-factorial in origin. Both genetic and environmental aspects seem to steer the amount and development of refractive differences. In some countries of South East Asia the prevalence of nearsightedness suddenly increased in the last century, this strongly suggests that environmental factors play an important role in myopia development (4,8,9).

After birth, the eye grows toward emmetropia. This process is called emmetropization and reduces the variability we usually see after birth, and leads normally the eye growth to produce a clear distance view. When children are older than six years, we see again an increasing variability. Flitcroft says, “the increased variability associated with ametropia points to a failure in homeostasis” (10).

Animal models of refractive development have increased our understanding of the likely environmental mechanisms that steer the refractive development and normal ocular growth in humans. Studies of developing animals, such as monkey (11) and chick (12,13) have shown that it is possible to influence and change the refractive development of the eye by adding positive and negative lenses. Edwards and Schmid were raising infant animals and let them wear a minus powered lens over one eye. This resulted in hyperopic retinal defocus, which caused axial eye growth and from this resulted myopia, if the minus lenses

were not worn any more. In contrast, a plus lens produced myopic retinal defocus and caused reduced eye length growth, and from this hyperopia (13,14).

The Results from animal studies give us a logical basis for optical treatments to control myopia progression in youngsters. Gwiazda et al. (15) have demonstrated that youngsters with nearsightedness have larger lags of accommodation with extended near work which leads to hyperopic retinal defocus. That might cause nearsightedness and axial eye growth (16,17). Bifocals and progressive addition lenses (PALs) and similar therapy forms planned to specifically reduce accommodative lag, have shown only limited effects in slowing myopia progression in young adults and children (18,19). A study of the effects of monovision spectacle lenses and myopia progression in New Zealand's schoolchildren (20) has shown that eyes that wore a fully distance corrected lens on one eye and on the other eye an under-corrected lens (monovision), the under-corrected eye experienced myopic defocus, and had remarkably less myopia progression compared with the fellow eye. This work showed that myopic retinal defocus could successfully reduce both the myopic refractive error and the abnormal growth of the eye length. But this monovision therapy is not a useful treatment in clinical practice, as myopia progression was reduced exclusively in one eye.

High dose atropine eye drops are an effective treatment available to inhibit the development of myopia or to slow its progression (21,22). But systemic and ocular effects are often reported, such as photophobia, blurred near vision, dermatitis and UV-related retinal damage. This has hindered the worldwide use of atropine 1.0% drops (23). Toxically effects of the accumulation of atropine over a long period of time may damage the neural retina, and the constant pupillary dilation, which increases the amount of light entering the eye, may lead to light-damage to the retina (24). These effects are a lot reduced, if low-dose atropine 0.01% is used. The side effects are mostly acceptable, the treatment effect is lower but still useful, combined with reduced rebound effects (25).

There is an urgent need to find good and acceptable methods to inhibit the development of nearsightedness in children. The complications of high myopia are on rank four of the leading causes of blindness (26). Myopia complications cause low vision, this often affect those in their most economically active years. This is leading to severe loss of earnings in many cases (27). Any therapy that successfully slowed the progression of myopia in school children would reduce the risk of developing myopia-associated complications as blindness or visual impairment and would have a major cost benefit to the health systems.

One of the most important things to start is defining myopia and myopia management (28). These topics need to be clearly understood by patients when considering myopia management options and to be compliant with the treatment (29). Nearsightedness or myopia can be defined as a "condition in which there is a mismatch in the eye's optical components. Because the image is in focus in front of the retina, that results in a blurred distance image. This mismatch most commonly results from the eye's axial length being too long" (30). Or, more simply put for patients, nearsightedness is an eye condition in which a patient can see objects in close distances clearly, but distant objects appear blurry without the aid of glasses or contacts.

When speaking to patients, it may be better to use the term "nearsightedness" because they can recognize it more often. In one study, only 66% of subjects defined myopia correctly when they received separate multiple-choice questions with three responses, while 89% of patients correctly defined nearsightedness (28).

Studies also showed that being able to correctly define myopia or nearsightedness was not associated with age, income, or education. So, it is to avoid jargon when speaking with even more sophisticated patients. Highly educated individuals actually prefer simple explanations with visual aids (29,31).

While practitioners have been treating myopia's visual limitations with glasses, contact lenses (CLs), or refractive surgery for many years, scientists and the vision community have developed promising methods for managing myopia progression (32). Myopia management or myopia control can be defined as "slowing the progression of myopia, a tactic that will hopefully result in a decrease in the treated patients' overall adult refractive error".

For whom is myopia control? The ideal patient is a patient getting his or her first pair of glasses (who is around –0.75 D). But myopia management options can be offered to every still progressing myopes. This group may include people in their late teens or early 20s. It is important to tell the patients that this age group has not been included in myopia control studies and that they may benefit probably less compared to someone younger. There are currently no data suggesting when patients should discontinue myopia control treatments (32,33).

With evidence of a dramatic rise in myopia prevalence in the last decades in many countries around the world (34), myopia is a growing problem (35). Significant increases in myopia prevalence have been observed in Europe (36), although the highest levels of myopia are typically seen in developed East Asian countries, and the United States (37). In 2014 reported the Gutenberg eye study a nearly equal prevalence in European Caucasian (50%) and Asian (53.4%) students in the United Kingdom (38). These increased levels of myopia are accompanied by elevated risks of numerous sight-threatening pathological complications such as myopic maculopathy, posterior subcapsular cataract and retinal detachment (39).

Because the impact of myopia on public health is growing, new studies in this area are in progress. An important recent trend in research examining the etiology and management of myopia is the use of high-resolution optical coherence tomography (OCT) imaging. This has provided important new insights understanding the mechanisms regulating eye growth and the development of myopia in the human eye. And we improved our understanding of a range of different myopia management options (34).

Not everywhere in the world use the eye care practitioners the same myopia control options (40,41). My work shall be a help for them to learn about the myopia management options, especially the soft customized myopia control contact lenses.

1.3.1 Fitting soft contact lenses

We have sound scientific basis for fitting gas permeable (hard) lenses, but not for soft lenses, which we typically fit based on corneal curvature. Fitting soft lenses based on predictable corneal shape factors may increase your fitting success. This is improving office efficiency and limiting the trial-and-error aspect of fitting soft lenses. It reduces costs and time for the clients (42).

Developing a unique, custom made soft contact lens design for each patient makes more sense than blindly choosing a manufacturer's lens, delivered just in one diameter and base curve. "One size fits all" is not true for fitting soft contact lenses. We need to have control over the specifications required to optimize comfort and vision for our patients. To follow the fitting guide of the lens producers helps, to have a first lens that suits the patient's eye well.

1.4 Background, rising prevalence of myopia

1.4.1 Animal Models of Refractive Development

Myopia is the most common ocular abnormality (39). But as a research topic in ophthalmology it does not play a key role. The old idea that most myopes have to be placed in the 'physiological myopia' category undoubtedly contributes to this position. But detailed analysis of 'physiological myopia' data in the 0 to -6 D range demonstrates statistically significant numbers of ocular pathologies from glaucoma to retinal detachment. In the case of myopic maculopathy and retinal detachment the risks are an order of magnitude greater than for hypertension, smoking and cardiovascular disease. This shows how important it is to find interventions that can limit or prevent myopia progression. We don't understand fully the regulatory processes that guide an eye to emmetropia. And why this mechanism sometimes fails and leads to refractive errors is unclear as well. For a few decades now, our knowledge of these processes is growing. We know now from observational clinical studies, animal studies, and more recently randomized clinical trials that the retinal image is influencing the growth of the eye. Recent animal studies, supported by clinical observational studies, have shown that the mechanisms of optically controlled eye growth are affected by the retinal image over a wide area of the retina and not just the fovea.

The multi-focal soft contact lens (MFSCL) designs employed in this thesis are based on the hypothesis that presenting myopic defocus to the peripheral retina acts to slow the axial elongation of the developing eye (4). The idea is to reduce juvenile myopia progression. The effects of myopic retinal defocus on the refractive development of animal eyes is briefly reviewed here:

Since the late 1980's we know that the refractive development of the eye can be altered with adding a positive or negative lens (12). When a negative lens is placed in front of the eye of a chick, the image plane is focused behind the retina, giving a hyperopic defocus. This increased axial growth, so the eye produces emmetropia in the lens-eye system. Conversely, when a plus lens is placed in front of one eye, the image plane is now focused in front of the retina, and reduced growth occurs to allow a sharp image (12,43). These alterations in axial growth can also be assessed locally in local selected areas of the visual field. This works as well even when accommodation and optic nerve are not intact. It seems that the retina controls the increase in eyeball length autonomically, by evaluating image sharpness itself (3,44). Irving et al. (43) showed that the induced refractive error difference between the eyes was equal to the power of the applied lens between -10 D and +15 D after one week of monocular lens wear in young chicks. Age had a significant effect: when lenses were applied nine days after hatching, approximately 80% of the power of the lens was compensated, compared with the full amount when lenses were applied the day after hatching. The developing chick eye was remarkably sensitive to retinal image defocus and it is able to accurately compensate for this defocus over a wide range of lens powers, the authors concluded. They also realized that the chick eye was able to respond to higher powers of plus lenses and with a more rapid response rate. From this asymmetrical response to plus and minus lenses they suggested that myopic retinal defocus was more 'powerful' than negative lens induced hyperopic defocus, in controlling eye growth.

It is not clear how the sign or direction of defocus is determined. But these experiments suggest that the eye is capable of sensing both the magnitude and the sign of the imposed retinal defocus and to compensate adequately. Different wavelengths have different focus points in the eye. This is a hypothetical trigger that eyes can respond to.

Lens compensation has also been shown to occur in chicks that were made unable to accommodate due to lesions in the Edinger Westphal nucleus (45,46) or ciliary nerve section (13,47). It could be argued that a "trial and error system" is employed which alters the growth of the eye to maximize the clarity. In this system the eye could not detect the sign of defocus, but would alter its growth pattern back and forth to maximize retinal clarity.

An experiment of Zhu et al. (48) showed that even a single 10 minute session of positive lens wear was enough to elicit significant choroidal thickening and reduced vitreous chamber depth, compared with the untreated fellow eye. Until now, no-one has identified the exact 'stop and grow' signals by which the eye correctly matches optical power with axial length. The chemical mediation of these signals is a topic under debate in contemporary myopia literature (49–51).

Different elements of biochemical signal cascades have been identified as being important in eye growth control (52). Dopamine, which is built and released in the retina according to image brightness, inhibits axial length growth of the eye (53). If a dopamine antagonist was given to the chicks, this blocked the slowing effect of bright light on myopia in chickens (54).

Nickla et al. (55) were asking whether the efficacy of the exposures to myopic defocus might also depend on the time of day that they are given. Animal models have shown that presenting this myopic defocus is a potent inhibitor of axial growth. Even short daily periods of defocus of one or two hours give the effect of much longer periods of hyperopic defocus or emmetropic vision. Nickla et al. tested half of the chicks wearing monocular +10 D lenses for 2 h per day for 5 days at one of 3 times of day: 5:30 a.m. (n = 11), 12 p.m. (n = 8) or 7:30 p.m. (n = 11). The other half wore monocular -10 D lenses continually for 7 days, except for a 2-hour period when lenses were taken away. The removal occurred at one of 2 times: 5:30 a.m. (n = 8) or 7:30 p.m. (n = 8). Both groups were tested for their axial length growth. In both paradigms, myopic defocus in the evening was significantly more effective at inhibiting eye growth than in the morning ($p < 0.01$ for both).

Typical schoolchildren are exposed to extended periods of hyperopic defocus during reading sessions, because the pages are so near. Nickla proposes by transmitting her findings to humans, such near-work might best be scheduled later in the day, along with frequent breaks for distance vision.

1.4.2 Recovery from induced refractive errors

Recovery from form deprivation myopia was first described by Wallman and Adams (56). After the restoration of normal unrestricted vision, the eyes recovered. This provides strong experimental evidence that a bi-directionally manipulation of the refractive state of the eye is possible (57). If the form deprivation myopia was optically corrected, the myopic refractive error tended to stabilize and was prevented from recovery (47). That the process of emmetropization was visually guided suggested that by correcting myopia the error signal that detected defocus was eliminated and thereby recovery inhibited.

In tree shrews and monkeys recovery from form deprivation and lens-induced myopic refractive errors have also been demonstrated (49,58–60). Recovery from form-deprivation myopia in higher primates is more variable than in the chick model, and the age of the monkey is a significant factor as the rate of recovery declines with increasing age (59).

1.4.3 Rising prevalence of myopia

The following figures are produced with data from a study of Matamoros et al. (61) about the prevalence of myopia in France: the individuals were 38.5 years old in average (±16.9, SD), with a gender ratio female/male of 1.39 (58'375 females /42'054 males, a total of 100'429 individuals). The refractive error was between −27.50 D to +20.25 D, with more myopes than hyperopes. The overall prevalence of nearsightedness was 39.1% (95% CI 38.8-39.4). The prevalence of mild, moderate, high and very high nearsightedness was respectively 25.1% (95% CI 25.4-24.9), 10.6% (95% CI 10.4-10.8), 3.4% (95% CI 3.3-3.5) and 0.5% (95% CI 0.48-0.57). In younger patients (20- to 39-year old) the prevalence of nearsightedness

and high nearsightedness were higher with a rate of 52.4% (P <0.0001). Prevalence of nearsightedness was slightly higher in females than in males.

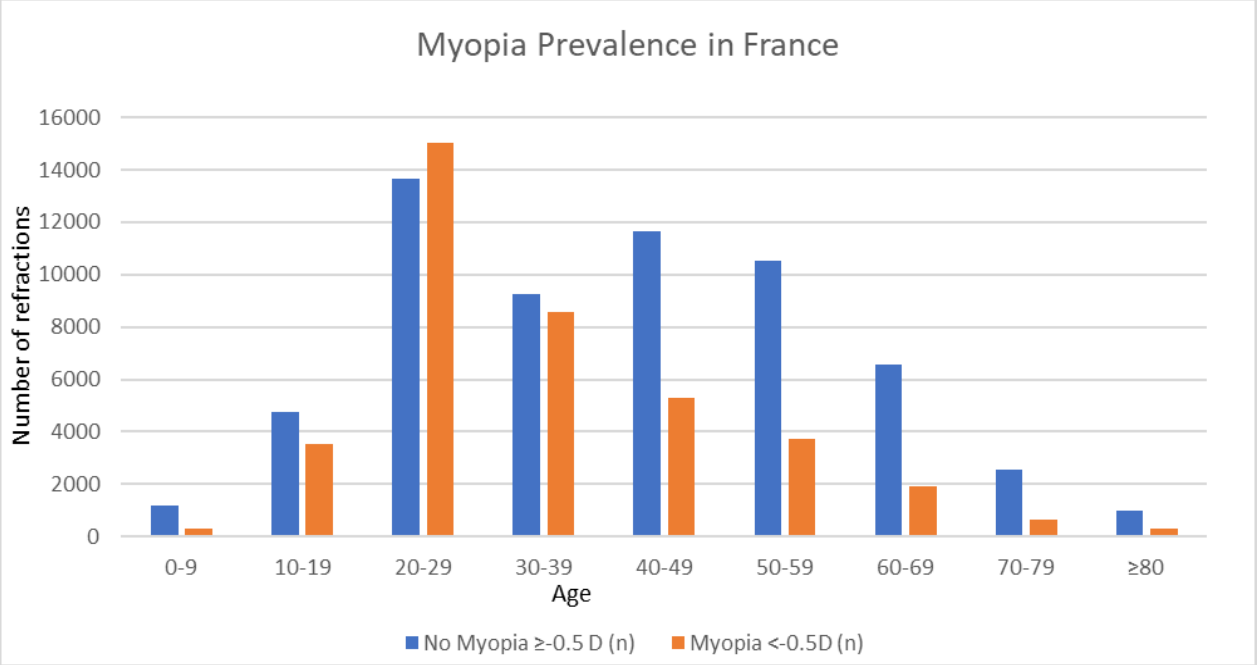

Figure 1: Myopia Prevalence in France

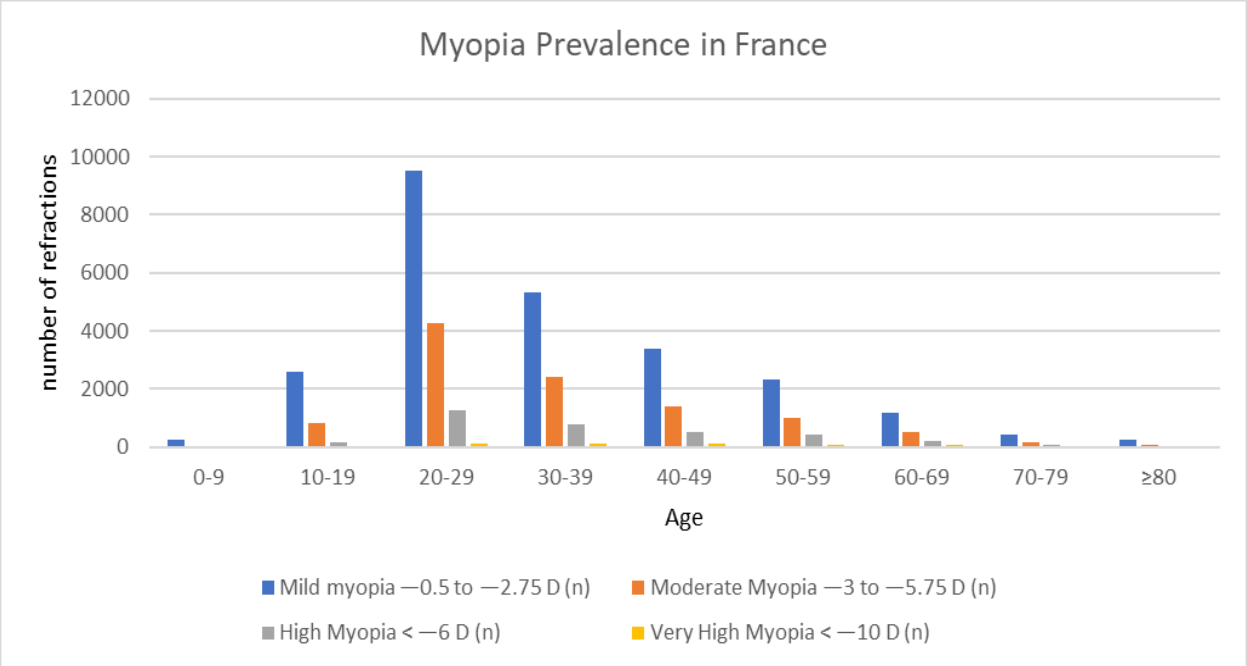

Figure 2: Myopia Prevalence in France, by magnitude

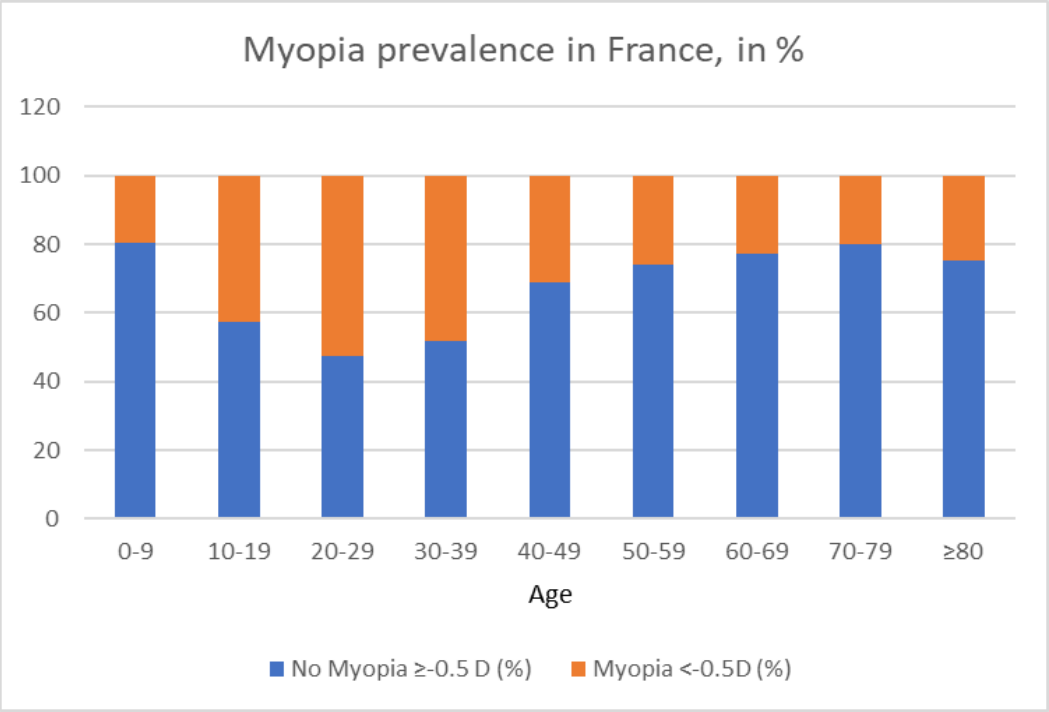

Figure 3: Myopia Prevalence in France, confrontation with hyperopia, by age

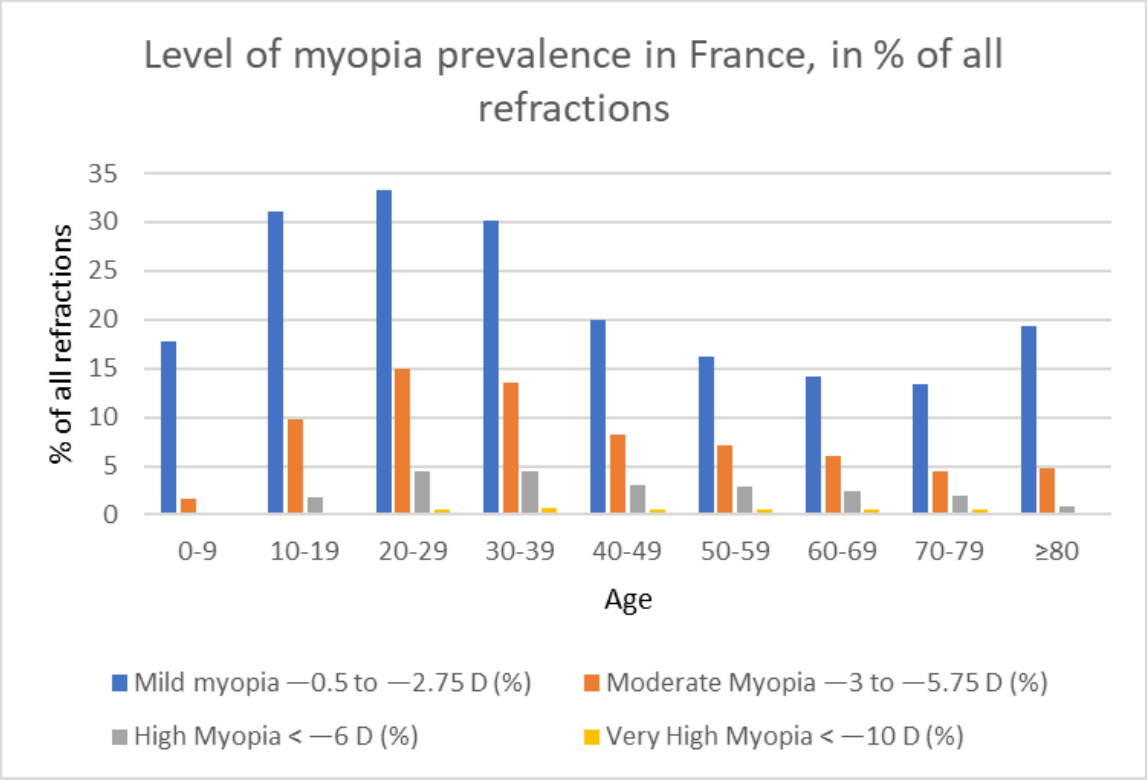

Figure 4: Level of Myopia Prevalence in France, in % of all refractions

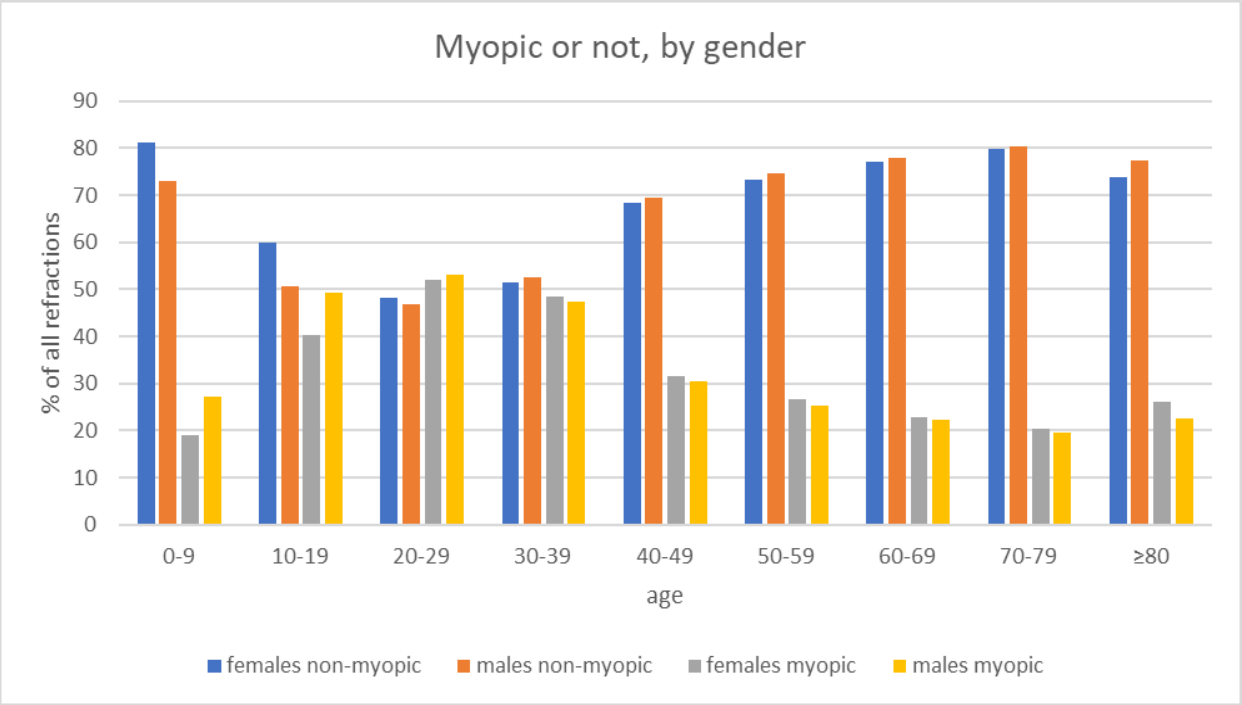

Figure 5: Myopic or not, by gender

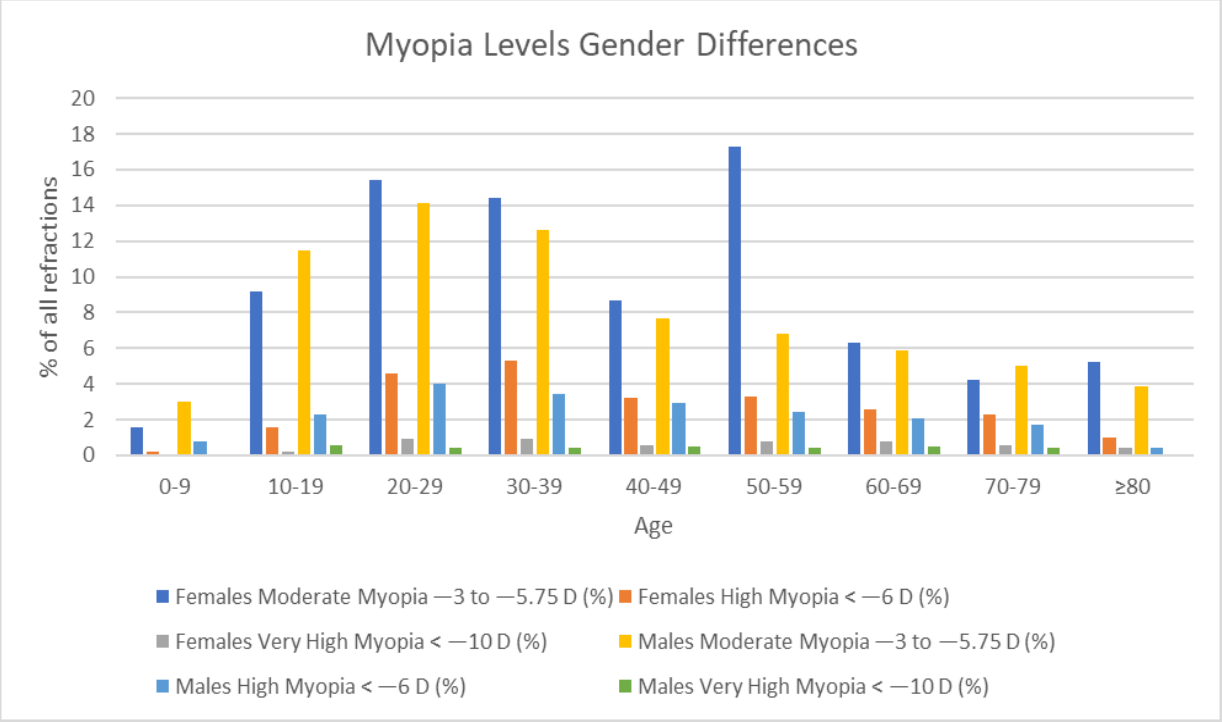

Figure 6: Myopia levels gender differences

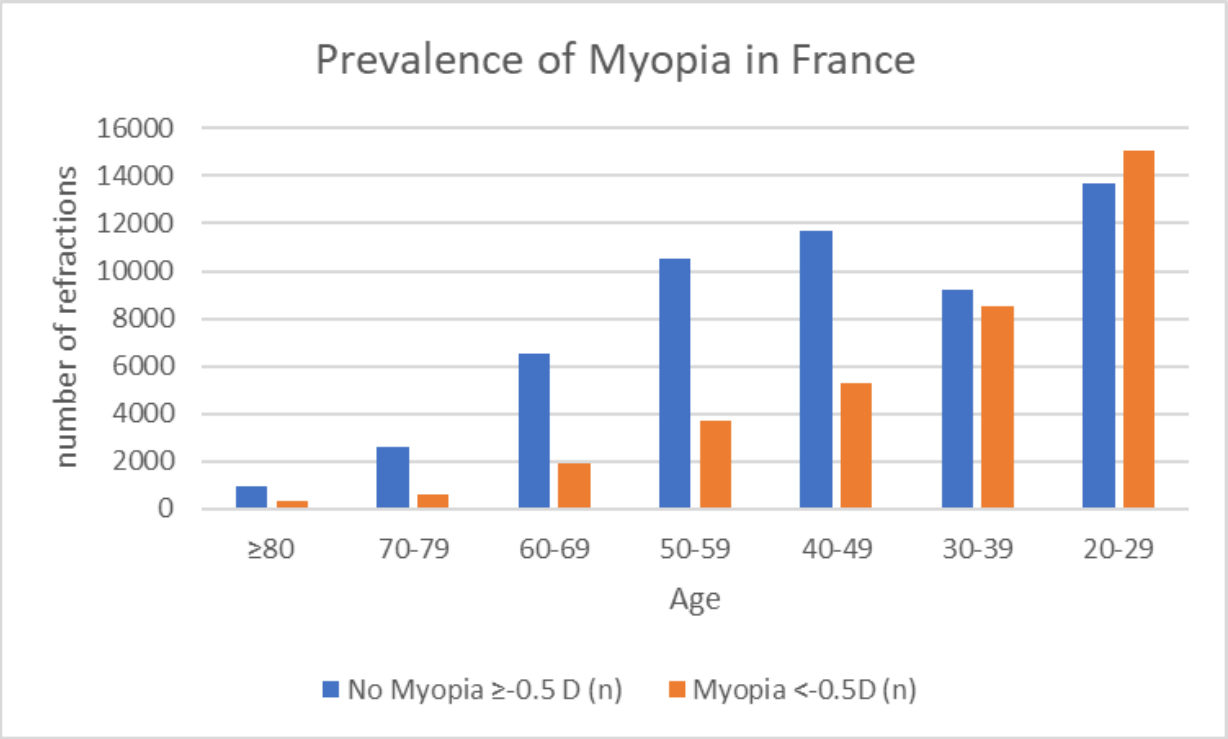

Figure 7: number of myopic and non-myopic refractions, by age

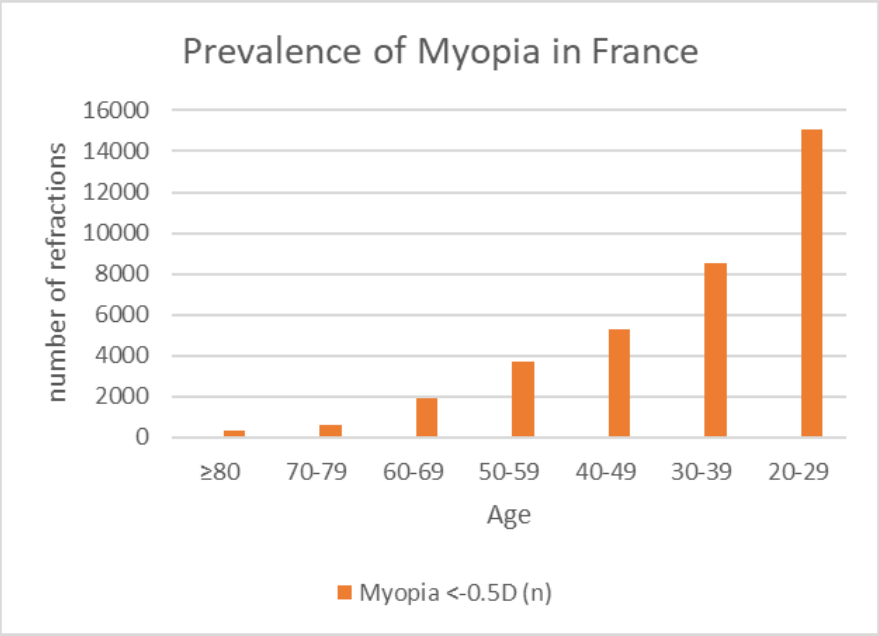

Figure 8: Number of myopic refractions

Myopia is the most common eye condition in the world (36,62–64). Just over a half of all European adults are affected by refractive error. The greatest burden of refractive error is due to nearsightedness, with high prevalence rates in young adults (65). And its prevalence is significantly increasing worldwide, especially in Southeast Asia (63,66–69); Especially young adults show an increasing prevalence in the United States and elsewhere (37,65,70,71). In the USA, about 37% of the population in ages between 20 and 59 are myopic (69). Ascending evidence shows the enlarged frequency of nearsightedness in many populations across ethnicities and all around the world (72).

We have to take care of it because nearsightedness is associated with an increased number of sight threatening diseases, such as glaucoma, myopic maculopathy, cataract and retinal detachment, even if we have corrected it appropriately (39).

The visual problems and impairment in working-age adults caused by the associated diseases like the currently untreatable myopic maculopathy (73) have an economic impact, on health care systems as on patients.

Myopia is highly heritable (74,75), and already a number of genetic polymorphisms have been associated with refractive error. But these can only explain a part of this heritability (76,77). Because the myopization happened so fast, within one generation (78–80). The rest of the explanation are environmental factors, they play a key role in myopia development. Only with them we can clarify the actual changes in prevalence (81). Some factors associated with myopia are: education, urbanization, near work, prenatal factors, cognitive ability, socioeconomic status, season of birth, light, and time spent outdoors (67,81–90). A very strong risk factor is the level of education (81,91), and scientists found evidence of interaction between the level of education and genetic factors (92). Since we see students spending a longer time in school over the 20th century, we see increasing numbers of myopic patients (93). The change in mean refraction is towards myopia. Among 14- to 15-year-old Finnish school children, myopia doubled to about 21% within 30 years (65).

Using the data from more than 60'000 participants of the European Eye Epidemiology (E^3) Consortium (94), there were 227.2 million expected myopic people across Europe in the year 2015.

In this large study the mean spherical equivalent was collected as refractive data. Patients were excluded if they had refractive or cataract surgery, retinal detachment, or other factors that might influence their refractive status. The following classifications for myopia were made: myopia ≤-0.75 diopters (D), high myopia ≤-6 D; hyperopia ≥1 D and astigmatism ≥1 D. The 61'946 individuals with median age ranging from 44-81 had minimal ethnic variation (98% Caucasian).

The patient born closer to today were analyzed to be more myopic. Myopia prevalence increased from 17.8% (95% confidence interval [CI], 17.6–18.1) to 23.5% (95% CI, 23.2–23.7) in the group born between 1910 and 1939 compared with the group born between 1940 and 1979 (P = 0.03). The association of education and myopia was significant: for participants completing primary, secondary, and higher education, the age-standardized prevalence was 25.4% (CI, 25.0–25.8), 29.1% (CI, 28.8–29.5), and 36.6% (CI, 36.1–37.2). Individuals born in the 1960s with completed higher education had approximately 4 times the reference risk: a prevalence ratio of 3.76 (CI, 2.21–6.57).

A higher level of education seems to be not the explanatory, but an additive factor.

Williams et al. (94) investigated myopia prevalence (spherical equivalent ≤−0.75 D) by birth cohort and 3 educational levels in individuals aged 45 to 65 years: primary education, leaving education at age <16 years; secondary education, leaving school at age ≤19 years; higher education, leaving school at age ≥20 years.

In the age category of ≥25 and <90 years (n = 61,476), the myopia prevalence 24.2 % (95 % confidence interval (CI) CI 19.9–28.5), with a European age-standardized myopia prevalence of 30.6 % (95 % CI 30.4–30.9). In younger patients aged 25–29 years, myopia was most commonly seen, with 47.2 % (95 % CI 41.8–52.5). This was almost twice the prevalence of those of middle and older age [27.5 % (95 % CI 23.5–31.5) in those aged 55–59 years. In those aged 20–24 years, 34.2 % myopia prevalence was found (95 % CI 27.9–40.6). High myopia had an age-standardized prevalence across all age groups of 2.71 % (95 % CI 2.69–2.73), with 3–5 % in young and middle-aged patients and 1–2 % in older individuals. The increase of myopia, the decline of hyperopia and the risen numbers of astigmatism in the very eldest patients is most likely related to developing cataracts.

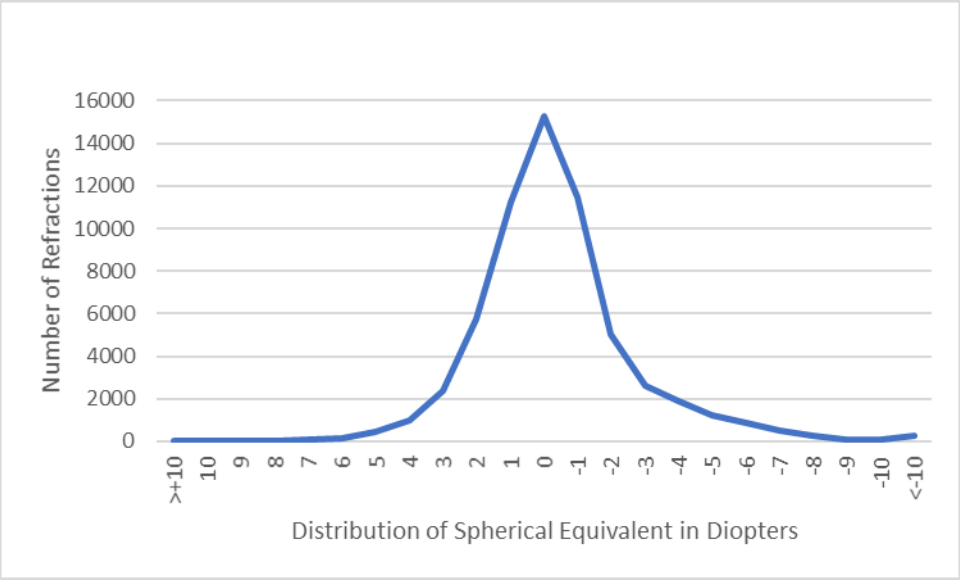

Figure 9: Distribution of Refractive Error

Figure adapted from Williams (89): distribution of refractive error.

Hyperopia was present in 34.7% (95% CI 27.9-41.6) of all cases, with an age-standardized commonness of 25.2% (95% CI 25.0-25.4). Less hyperopia was found in younger participants aged 25-29 years (6.4% (95% CI 3.8 - 9.0) than in those in middle to older age. High hyperopia was affecting 1-3% younger and 10-13% elderly patients. Across all age groups, the commonness of astigmatism was 27.3% (95% CI 22.6-32.1) with an age-standardized estimate of 23.9% (95% CI 23.7-24.1). Astigmatism showed a quite stable rate of prevalence of 15-25% in young and middle-aged participants. Over all ages, no significant differences in myopia commonness were found between men and women. More astigmatic eyes were found in men (p=0.001; 3.8% mean difference), women were more often hyperopic (p=0.04; a mean difference of 2.5%).

The COMET group (33) found that at elementary school age, myopia causing eye growth usually starts. 1mm of eye growth leads to -2.7 D myopia (3). After puberty this progression usually stops. Further progression after the age of 25 years is unusual (33). The result of an eyeball that was growing too long is that the focal point is falling in front of the retina. Due to this, far away objects appear indistinct, while objects in the near appear clear and sharp. The treatment options for myopia are using concave glasses lenses or contact lenses, or in selected cases surgical options. Surgery does not change the length of the eyeball, but the patients see distant objects clear again (33). Asian children have later onset of myopia, but then faster progression than Caucasians. At the age of 16, about 60% and at the age of 20, about 80% of Asians and Caucasians have stabilized their myopia (33). The overall cumulative proportion distributions of the 426 participants are significantly different across ethnicity groups ($P < 0.0001$, log-rank test).

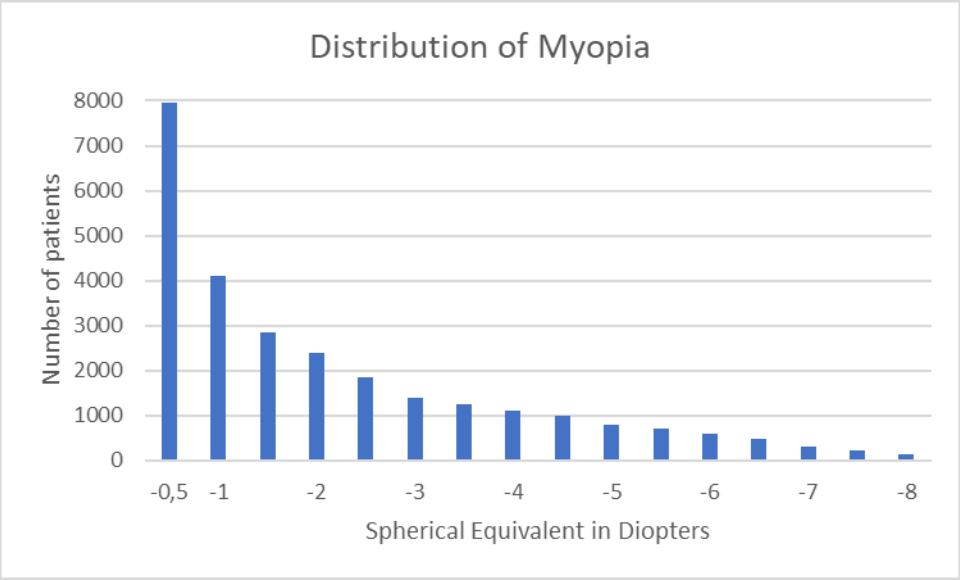

Figure 10: Distribution of Refractive Error

Figure based on Dhakal (90): distribution of myopes based on degree of refractive error.

In Australia, the rate of nearsightedness in 12-year-old Caucasian children doubled from 2005 to 2011. Today, more than half of Australian children of East Asian decent are myopic (95). In urban English areas, 30% of the same age group show myopia (96). In 12 to 54 year old Americans, myopia prevalence grew 40% in the past 30 years (37). In South-East Asia, 80% to 90% of the population are myopic by the end of adolescence and puberty (97–99).

In a pilot study to determine the prevalence of myopia, Yang et al. (100) searched the proportion of uncorrected myopia and pertinent environmental factors among children in a suburban region in Canada. Refraction was done with cycloplegia and ocular biometry were measured in children of two age groups (83 aged 6-8 and 83 aged 11-13). Myopia was considered at a spherical equivalent refraction (SER) ≤-0.50 D in at least one eye. Parents completed a questionnaire that captured the child's daily activities.

Mean subjective SER in myopic children was -1.10 D (95% confidence interval (CI), -0.34 to -1.86 D) at ages 6-8 and -2.44 D (95% CI, -1.71 to -3.18 D) at ages 11-13. Mean axial length (AL) increased by 1.03 mm from ages 6-8 (mean 22.62 mm; 95% CI, 22.45 to 22.79 mm) to ages 11-13 (mean 23.65 mm; 95% CI, 23.45 to 23.84 mm; $p < 0.01$. Myopia prevalence increased from 6% at ages 6-8 to 29% at ages 11-13. Thirty-five per cent of the myopes in this study were uncorrected, this represented 6.0% of the entire group of children. More time outdoors may be beneficial to protect against myopia onset: one additional hour of outdoor time per week lowered the odds of a child having myopia by 14.3% ($p = 0.007$).

The Brian Holden Vision Institute (72) predicts, that by 2050 half of the world’s 5 billion people will have myopia. From those nearly 1 billion will be at risk of myopia-related ocular pathology (101).

Jung et al. (99) conducted research on association of myopia and body stature in South Korea. Nearsightedness was not associated with height (P = 0.159); weight (P = 0.571); or BMI (P = 0.323). Myopia was associated with educational level, not with body stature. 96.54% of the young Korean males (19 years old) were myopic:

Prevalence of Myopia		
Classification	Number of Subjects	Prevalence (%, 95% CI)
Myopia (> −0.50 D)	22’800	96.54 (96.30, 96.78)
Mild myopia (−0.5 D to −2.99 D)	7’323	31.00 (29.94, 32.06)
Moderate myopia (−3.0 D to −5.99 D)	10’372	43.92 (42.96, 44.88)
High myopia (> −5.99 D)	5’105	21.62 (20.49, 22.75)
Moderately high myopia (−6.0 D to −7.99 D)	3’541	14.99 (13.81, 16.17)
Severe myopia (−8.0 D to −9.99 D)	1’228	5.20 (3.95, 6.44)
Severely high myopia (> −10.0 D)	336	1.43 (0.16, 2.70)

Table 1: Prevalence and Classification of Myopia

Table with data from Jung (99)

1.4.4 How to Manage Myopia

Treatment options for myopia progression management include PAL, bifocal, and special spectacle lenses; surgical solutions; orthokeratology; soft bifocal or multifocal contact lenses; pharmacological interventions like atropine eye drops; and others. It is important to know that standard single-vision spectacles, soft and GP contact lenses do not help to slow any myopia progression (102–104), and prescribed for progressing myopes is not a good evidence-based practice (72).

When reading studies about myopia management, it is important to check what threshold values of spherical equivalent (SE) they use to define myopia. Cumberland et al. (105) investigated the impact of varying the definition of myopia on estimates of prevalence. They found that just a little shift of 0.25 D changes the results and the association with risk factors significantly. So, changed in their sample the prevalence of mild myopia from 28% to 47%, the association with highest educational attainment was lowered and with higher social class became stronger. The changes in risk ratios were about 20%.

TABLE Summary of myopia control intervention studies				
Treatment	**Duration of studies**	**Reduction in axial elongation progression**	**year**	**References**
Stand. spherical GPs and soft contact lenses	2 to 3 years	0% to 5%	2003 2004 2008	Katz et al. (102) Walline et al. (103) Walline et al. (104)
Atropine	2 to 5 years (mode 2 years)	30% to 77%	2006 2009 2011 2016	Chua et al. (106) Tong et al. (107) Chia et al. (108) Chia et al. (25)
Atropine rebound effect	1 year	1% atropine reduces to a 30% total control effect Lower rebound frequency with 0.01% atropine compared to with higher concentrations (109)	2009 2016	Tong et al. (107) Chia et al. (25)
Spectacles: PAL, bifocal, and novel lens designs	1 to 2 years	12% to 55%	2003 2002 2009 2010 2010	Gwiazda et al. (19) Edwards et al. (110) Yang et al. (111) Cheng et al. (112) Sankaridurg et al. (113)
Soft contact lenses: bifocal and multifocal	6 months to 2 years	29% to 95%	2011 2011 2013 2016 2013 2018	Anstice et al. (56) Sankaridurg et al. (114) Walline et al. (115) Aller et al. (116) Lam et al. (117) Ruiz-Pomeda et al. (118)
Ortho-K	1 to 10 years	30% to 100% (meta-analysis 45%) (119–129)	2005 2009 2011 2015 2015 2018	Cho et al. (119) Walline et al. (120) Kakita et al. (121) Si et al. (126) Sun et al. (127) Hiraoka et al. (129)

Table 2: Summary of myopia control intervention studies

Table based on Gifford (72)

This research data was revealed around a decade ago on average, it has not found its place in eye care practices (72). A recent survey, undertaken across a dozen countries with almost 1'000 respondents, of myopia control strategies and attitudes in eye care practice uncovered that most practitioners (67% ±37%) still prescribe single-vision contact lenses and glasses as the primary mode of correction for myopic patients. Practitioners sold these objects with the acknowledgement that single-vision spectacles and under-correction of myopia were least effective for myopia control. But increased cost, inadequate information, and unpredictable outcomes were justifications for what is non-evidenced-based management of progressing pediatric myopia (41). The increased cost may include both the prolonged chair time and the prescribed corrections type (72). Eye care practitioners may be concerned about the time they shall invest extra in fitting contact to children; however, children (8 to 12 years) take only 15 minutes more to fit compared to teens (13 to 17 years). The biggest part of this occurs with prolonged contact lens handling instruction (130).

Yes, myopia is a lifelong cost burden, being around $709 per person per year (131). So, prepare your practice for myopia control practice for seeing these patients more frequently and for more costly contact lens corrections, implementing extended payment systems like a monthly payment option may be helpful (72). These costs seem to be high, but are in fact much lower compared with costs for blinds or vision impairment patients of about $12'000 annually per patient, increasing with the severity of the vision impairment (132).

ECP who want to learn about myopia management find a lot of data and summaries of recent myopia control research readily available at www.myopiacontrol.org and through practitioner communication tools at www.myopiaprofile.com (72). The concerns of practitioners regarding unpredictable outcomes of myopia control strategies can be resolved by knowledge of theory and experience (72). ECP shall speak with their clients about risks and benefits. This must be presented to make sure that the long-term message about ocular health is not lost in the short-term concerns about time, cost, and safety (133,134).

Mathematical modeling has shown that the use of a 33% effective myopia control strategy would result in a 73% reduction in the frequency of nearsightedness greater than 5 D, and a 50% efficacy would result in 90% less high myopia. The consequence would be a significant reduction in ocular pathology risk across the population (135).

From future research we expect to have practitioner protocols on treatment time, duration, and appropriate treatment option selection based on analyzing the risks. Safety concerns and side effects of atropine and contact lens treatments can reduce practitioner confidence in active myopia control. No myopia control strategy has an U.S. Food and Drug Administration today (136). But a big amount of scientific support already exists. "For the current and lifelong benefit of our clients, we must ensure that we are not myopic about myopia control", says Kate Gifford (72).

Epidemiology

In 2015, "Nature" reported that the prevalence of nearsightedness a in large Southeast Asian urban areas had risen from around 20% in the years after World War II to an actual level of over 80% (3,137).

Genetics alone cannot explain such quick changes; There must be an ability of the visual system to adapt fast to new environmental conditions, specifically a shift in distances from long to short. We live now more inside and are not so much outside any more (3). The E^3 consortium presented in 2015 prevalence figures indicating a clearly higher incidence of myopia in Europe too: 15% in those aged 75 years, 34% in age group

50 years, and 46% in the 25 years young (94). European figures for children or adolescents indicate currently no further increasing numbers.

In the year 2016, a meta-analysis was published by Brien Holden et al., expecting myopia prevalence changes up to the year 2050. The worldwide myopia prevalence rate is expected to be 50%; the proportion with high myopia (more severe than –6 D) is estimated at 10%. Holden expects 2050 in western Europe 56% of all persons having myopia (35).

Prevalence of myopia by region

Region	**Prevalence (%) at 3 points in time**		
	2010	**2030**	**2050**
Asia-Pacific. high-income	29	58	66
East Asia	47	57	65
North America. high-income	35	49	58
Western Europe	29	45	56
Australasia	27	44	55
Central Latin America	27	42	55
Central Europe	27	42	54
North Africa and Middle East	23	39	52
Worldwide	28	40	50
Central Asia	17	33	47
Southern Africa	8	18	30
Central Africa	7	14	28
West Africa	7	14	27
Oceania	7	13	24

Table 3: Expected Prevalence of Myopia in 2050 by Region

Table from data of Holden (35) and Lagrèze (3)

In the past 30 years, in the US the prevalence of nearsightedness increased by 145%. The rate of high myopia (over –6 D) increased by enormous 820% (37,71,138). In the same 30 years, the prevalence of myopia in South Korea was 334% higher and high myopia increased by 891% (138). The equal trends were registered all over the world, also in Africa and Europe (38,139–141).

But how is the situation for myopic children today? 329 Parents of 8–13-year-old kids in 8 Irish schools taking part in this study completed a questionnaire designed to ask their knowledge of and attitudes towards nearsightedness and its risk factors. Only 46% of the parents give thought to that myopia is a health risk to their children. The same number (46%) regarded it as an optical problem only. 4% of the mothers and fathers thought, myopia was also a sign of intelligence. Only 14% of parents would be concerned should their son or daughter be diagnosed with myopia. Compared to parents without myopia, parents with myopia viewed myopia as more of an optical inconvenience ($p < 0.001$), an expense ($p < 0.005$) and a cosmetic inconvenience ($p < 0.001$). Myopic parents tended to limit TV and computer time use at home more than non-myopic parents ($p = 0.05$). Older ($p = 0.001$), urban ($p = 0.0005$) myopic ($p=0.04$) kids spent significantly more time with digital screens than younger non-myopic children from a rural background. Parents were typically nonchalant in relation to health risk of nearsightedness. This demonstrates an acute need to speak about the importance of myopia management (142).

2 Myopia, Myopia Control Contact Lens Design and Functionality

2.1 Development of Myopia in Humans

At elementary school age, myopia causing eye growth usually starts between 5 and fifteen years, and after puberty this progression usually stops (143,144). Further progression after the age of 25 years is unusual (33). The prevalence of myopia increases with age (145).

To evaluate the refractive development of 1'019 children aged 7-9 years, the Singapore Cohort of Risk Factors for Myopia (SCORM) study (56) followed them prospectively for three years. At baseline 331 (32%) of the children were myopic and 688 (68%) were either emmetropic or hyperopic (143). After 3 years, 842 children completed the study. The findings of the study showed 42.7% of children having emmetropia or hyperopia at baseline developed nearsightedness over the 3 years. The overall progression of myopia in children with myopia at baseline was 2.03 D, an annual progression of 0.68 D. The axial length elongated in this 3-years' time 0.89 mm.

At beginning of the study, most progression was seen, with only little changes for refractive error and vitreous chamber growth in the last study year. Evidence suggests, that the numbers of children in East Asian nations suffering from myopia, especially high myopia, is increasing, while the age of onset is shifted to a younger age (98).

To characterize the change of the refraction during myopia development Thorn et al. (146) used a sample of kids with diverse refractive histories for their mathematical modelling. The scientists found that the age of onset for the myopization process occurs between the ages 5 and ten years for more than 4 of 5 children; the onset of myopia progression happens when the young persons are still having emmetropia or a slight hyperopia. The process is characterized by a rapid acceleration of changes in refraction. The time with the most rapid myopia progression is normally within two years of onset. After this phase progression slows and at a mean age of 15 years the eye become stable.

The patient records from three optometry practices suggest that myopia progression stops earlier in girls than in boys. But a wide variety of cessation age was found, overall (147).

The age of the children at onset is essential. With early-onset myopia the kids eyes tend to progress myopia for a longer period, and the deceleration phase is slower. This leads to a bigger amount of myopia. Late-onset myopes show a shorter time period of rapid progression and mostly small amounts of final myopia (146). Bullimore and Mutti found evidence that in some persons myopia develops or progresses significantly after childhood. Normal nearsightedness develops during the school years and gets stable as the patient reaches their late teenage years (148,149). Thorn's study is based on data on a mostly Caucasian population. In Caucasians is generally lower prevalence and slower progression of myopia seen than East Asian populations. Myopic progression rates can be captured well before the onset of a myopia, is one of the most important findings from the Thorn study. Intervention at this point may be best effective for myopia management.

This fact interested me, I found another study on that topic: In 2018 Li et al. (150) published their study in which they investigated the incidence of myopia and biometric characteristics of pre-myopic eyes. More than 2000 grade 1 and grade 7 students living in the southwest part of China participated. As myopia Li defined a SE of less than - 0.50 D. The incidence of myopic eyes was 33.6% (95% confidence interval [CI]: 31.7-35.5) in grade 1 students. The myopia incidence for grade 7 students was 54.0% (95% CI: 51.5-56.5). Myopia progressed in this one-year study - 0.97 D (95% CI: -1.22 to - 0.71) in grade 1 children and - 1.02 D

(95% CI: -1.07 to - 0.96) in grade 7 students. Per mm increase in baseline axial lengths increased the risk of myopia onset by 28% among grade 1 students and 22% among grade 7 students after 1 year. Grade 7 students which had thinner pre-myopic lenses had higher incidence rates of myopia. In conclusion, the incidence and progression rates of myopia were very high in this sample. Pre-myopic eyes were characterized with thinner lenses and longer axial measurements.

Risk factors

We think today, myopia is caused by nature and nurture together. Environmental factors are more and more seen as triggers for onset and progression of nearsightedness (151,152).

The costs of treating myopia and its associated additional diseases, including glaucoma, rhegmatogenous retinal detachment, and chorioretinal atrophy, are conservatively estimated to be over $4.6 billion dollars in the United States (153,154). In the United Kingdom approximately 200'000 people have pathological myopia (National Institute). This is why we want to identify the risk factors for myopia (155), to modify these risk factors to lessen the prevalence and impact of myopia (156).

However, we should keep an eye not only on myopes (72); measuring less than +0.50 D of hyperopia at age 6 to 7 years is the most significant risk factor for future myopia. This risk factor is independent of visual environment and family history (157). In the year before the onset of myopia, the children show the fastest rate of refractive change (158). That requires to monitor children closely, who are less hyperopic than age normal. If the children have an additional risk factor like family history or binocular vision status, an extra close monitoring is necessary.

For urban children come some factors together: children with myopia spend less time outdoors than kids with normal vision, and they do more near work at an earlier age (81). Exactly why being outdoors is a protection against myopia is not clear. Some animal experiments suggest that dopamine release from high light intensity outdoors slows axial growth (159,160). Why near work is causing higher levels of myopia is unclear as well, but studies with animals suggest that working in close distances increases hyperopic defocus in the peripheral retina. This is expected to be the trigger for axial elongation (161).

Degree of hyperopia in D	**Age**
≤ +0.75	6 years
≤ +0.50	7-8 years
≤ +0.25	9-10 years
Emmetropia or myopia	11 years

Table 4: CLEERE groups cut off points for cycloplegic SER

Table with data from Zadnik (157): cut off points of the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) group for cycloplegic spherical equivalent refractive errors to identify children at risk of high myopia. The use of this table will allow appropriate myopia control interventions at the right moment.

The next table gives an overview of risk factors for development and/or progression of myopia in childhood.

Summary of risk factors for development and progression of myopia			
Risk factor	Description	Year	References
Family history	One myopic parent – threefold greater risk of myopia development. Two myopic parents – sixfold greater risk of myopia development. Two myopic parents – greater risk of progressing to high myopia.	2005 2007 2007 2009 2015 2018	Morgan et al. (81) Jones et al. (155) Kurtz et al. (162) He et al. (163) Loh et al. (164) McCrann et al. (142)
Time spent outdoors	Less than 1.6 hours per day increases risk two- to three times	2007 2008	Jones et al. (155) Rose et al. (165)
Time spent on near work	More than 3 hours per day (excepting time at school) – only when combined with other factors like low time spent outdoors.	2007 2009 2019	Jones et al. (155) Dirani et al. (166) Guan et al. (167)
Age of onset	Younger onset (ages 6 to 7 years) versus older (11 years) age of onset gives a 6.6 times risk of progression to high myopia.	2014 2015 2017	Pärsinnen et al. (168) Zadnik et al. (157) Rotolo et al. (169)
Current refraction	The fastest refractive change is seen in the year prior to myopia onset. Less than +0.50 D found in 6 to 7 years old is a risk for myopia development.	2007 2015	Mutti et al. (158) Zadnik et al. (157)
Ethnicity	Asian ethnicity is probably linked to faster progression. The risk factors of time spent outdoors, current refraction, and family history risk of high myopia are independent of nationality and race.	2008 2010 2011 2015	Ip et al. (170) Rudnicka et al. (171) Logan et al. (96) Zadnik et al. (157)
Binocular vision characteristics	Increased accommodative lag and higher AC/A ratio may predict myopia onset. The presence of accommodative lag and esophoria predicts faster myopia progression as well as more favorable responses to myopia control strategies.	2000 2006 2011 2018	Mutti et al. (172) Mutti et al. (173) Gwiazda et al. (174) Ruiz-Pomeda et al. (175)
Further references in text			

Table 5: Summary of risk factors for development and progression of myopia

Table with data from Gifford (72).

If kids have a strong family history of nearsightedness, this results in stronger treatment effects in studies investigating efficacy of progressive and novel spectacle lens designs for myopia control (113,162). Recent data indicates that progression in Asian and Caucasian children may be similar (95), from previous studies we thought Asian ethnicity has been linked to faster myopia progression (72,176,177).

Spending a lot of time on near-work activities has been appraised a risk for myopia development and progression (72,84); but when controlled for parental myopia and time spent outdoors, it shows that it is not an independent risk factor (155,165). No matter what kind of outdoor activity, regardless of the type of activity, combined with low and moderate levels of near work can protect against myopia development. This relationship has been affirmed regardless of ethnicity, gender, parental myopia, employment, and education in Australian, American, and Asian studies (155,165,166). Children with only a bit outdoor activity (0 to 1.6 hours per day) and many hours near work outside of school (>3 hours per day) at age 12 have a two- to three times higher risk for nearsightedness compared to the group with a lot of outdoor activity (>2.8 hours per day) and low near work (0 to 2 hours per day) (165).

Further risk factors include accommodative and binocular factors: higher accommodative convergence (AC/A ratio) at near, the presence of esophoria and accommodative lag (72). Pre-myopes show a higher accommodative lag compared to their peers who do not develop myopia. This correlation gets stronger after myopia onset, indicating that this may be an attribute rather than a cause of myopia (173). Kids who have higher response AC/A ratios have a more than 20 times higher risk of myopia development within one year (172). Children with esophoria progressed their myopia more quickly in single-vision spectacle control groups than with progressive addition spectacle lenses (PALs)(111). The greater treatment effect was seen in kids with a larger baseline accommodative lag in the PALs groups (19).

Other genetic and environmental factors have been shown to be associated with higher numbers of myopia (156), including socioeconomic status (89,178), body stature (179), degree of urbanization (180), level of physical activity (181), low birth weight (182), parental smoking status (183), parental education and birth order (184), and lack of breastfeeding (185). Ethnicity (96,170,171) and family history of myopia (170,186,187) are as well recognized risk factors for nearsightedness. Relationships with age and sex also have been described (188). Numerous narrative reviews describe these risk factors in some detail (39,62,66,67).

The long list of environmental factors that may influence the development of nearsightedness can only explain a small part of the broad variations found in myopia prevalence (156). For the relationship of many of the risk factors conflicting evidence exists, including boobfeeding (184) and intensed near work (170). Probably genetic predispositions let some patient's eyes result in greater susceptibility to the environmental impacts (189), which may partly explain worldwide variation in myopia prevalence (67).

The Northern Ireland Childhood Errors of Refraction (NICER) study (190) has shown that there is a high prevalence of myopia in Caucasian children in Northern Ireland (NI) compared to white children of the same age in Australia. The levels of physical activity and the prevalence of myopia was found to be associated (P for trend = 0.027). The children with regular physical activity were less myopic compared to the ones who reported a sedentary lifestyle. (OR = 0.46; 95% confidence interval [CI], 0.23–0.90). Children with younger brothers or sisters were less likely to have myopia (OR = 0.77 per younger sibling; 95% CI, 0.60–0.99). Parents with myopia are a strong genetic risk factor; compared to kids with no myopic parents, children with one or both parents being myopic were 2.91 times (95% CI, 1.54–5.52) and 7.79 times (95% CI, 2.93–20.67) more likely to develop nearsightedness. The associations of myopia prevalence with sex and economic deprivation were not statistically significant, but in the expected direction (37,89). Girls were more likely to be myopic (170,184,191–193). Those kids who had richer parents were at higher myopia risk (184,191,192).

Nearsightedness has been long time associated with inaccurate and insufficient near accommodation. Myopes show more accommodative convergence than emmetropes (15,17,172,194,195); finding these conditions in both myopic and at-risk emmetropic children can help to name the myopia progression risk (72).

The ideal starting point for myopia management treatments should be before the children become myopic. At-risk emmetropes may exhibit every or any of the following: lower than age-normal hyperopia, one or two myopic parents, esophoria at near and accommodative lag (72).

2.1.1 Normal Myopia progression

By looking up 'normal progression data', I found very different numbers. Usually were these participants the placebo or control group in studies. Asian children showed faster progression, Caucasians a slower one. Here just a part of the data found:

Study or source	Annual progression in D	Notes, ethnicity, age
Aller (116)	0.79 ±0.43	Control group, American mixed ethnicity, 8–18
Tan (196)	0.84	Control group, Asian, 6-12
Donovan (177)	0.55 (-0.39 to -0.72)	SV glasses group, predominantly Caucasian, 9.3
Chua (197)	1.20 ±0.69	Control group, Asian, 6-12
Anstice (56)	0.7	SV lens group, mixed ethnicity, 11-14
Katz (102)	1.28 ±0.55	SV spectacles, Asian, 6-12
Siatkowski (198)	0.53	Placebo group, mixed ethnicity, 8-12
Walline (199)	0.80	Placebo group Review, mixed ethnicity and ages

Table 6: Normal myopia progression rates, from literature

Donovan et al. (177) published in 2012 a formula to calculate the expected myopia progression for Europeans (Caucasians): $y = 0.04x^2 - 0.56x - 0.002$. y is the cumulated progression, x the time in years. The formula based on 9.3 years old children, with cycloplegic autorefraction. The progression rates decreased as older the child got or as later the child was enrolled in the study. Donovan found gender differences: for the combined ethnicities with an average age of 8.8 years at study start, his estimated annual progression was -0.80 D for girls (95% CI, -0.51 to -1.10), and a significantly less ($p < 0.01$) -0.71 D for boys (95% CI, -0.42 to -1.00).

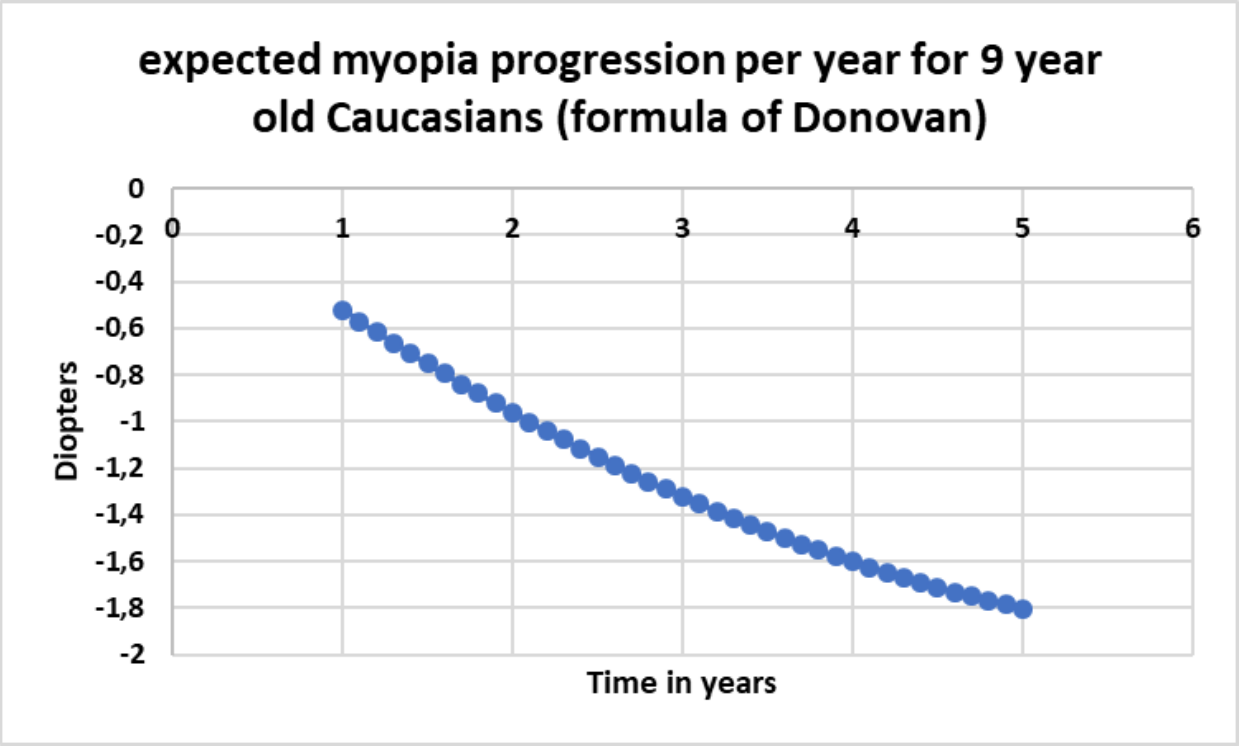

Figure 11: expected annual myopia progression for 9-year-old Caucasians

The problem with the formula of Donovan from 2012 is, that its results say that there is no more myopia progression in 16-year-old children, and after that the children become less myopic. As a practitioner I see other results in real life.

So I was searching further data: Gwiazda et al. (19) reported -1.48 D in 3 years, 0.49 D per year. Fulk et al. (200) reported 1.24 D for single vision in 30 months, so 0.50 D per year. In the study of Walline et al. (103) -2.19 ±0.89 D in 3 years, 0.73 D per year was found. In 2011, Walline et al. included 23 studies (4'696 total participants) in a review, and reported -0.80 D (95% CI -0.70 to -0.90 D) yearly myopia progression in placebo groups (199). Yam et al. (201) reported recently -0.81 ±0.53 D per year in their control group. In Finland, Mäntyjärvi (202) found 1985 a myopia progression rate of −0.93 D per year in 8 year old and −0.52 D in 13 year old.

Reports of Myopia Onset and Progression

After myopia onset, children show fast progression. This progression is faster in younger children, and a young age of onset is a significant risk factor for developing high myopia in the future (203,204). Asian children progress myopia generally faster than Caucasian children (177). Progression stabilizes usually after puberty (205). But in adults with high myopia, axial elongation is still seen because of the thinned sclera (206).

The CLEERE data set includes 4'927 children in the age range of 6 to 17 years old (207).

Data of the CLEERE study on the youngest age at which myopia was registered:

Age, in years	Spherical equivalent -0.5 D or more (n=1006)	Both principal meridians -0.75 D or more (n=749)
7	25 (2.5 %)	11 (1.5 %)
8	80 (8.0 %)	59 (7.9 %)
9	150 (14.9 %)	100 (13.4 %)
10	175 (17.9 %)	122 (16.3 %)
11	161 (16.0 %)	136 (18.2 %)
12	157 (15.6 %)	112 (15.0 %)
13	142 (14.1 %)	111 (14.8 %)
14	91 (9.0 %)	80 (10.7 %)
15	23 (2.3 %)	12 (1.6 %)
16	2 (0.2%)	6 (0.8%)

Table 7: Age of myopia onset

Onset of myopia was registered from children aged 7 to 16 years. The highest percentage of new cases of myopia was seen in 10 and 11 years old, depending on the definition of myopia. The largest percentage increase in occurred between ages 7 and 9 years, the largest increase in percentage of new cases was reported. After ages 10 to 11 years, the list shows a steady decrease in the percentage of new cases (208).

In nearsightedness developing eyes a different relative peripheral refraction (RPR) has been found. In myopic eyes hyperopic RPR is seen, while hyperopic and emmetropic eyes show myopic RPR. The results of the study of Rotolo et al. (169) suggest that RPR cannot predict development or progression of nearsightedness in Caucasian children.

Comparison of Rates of Myopia Progression for Adult-Onset and Childhood Myopia

In the 23-year follow-up study of Pärssinen et al. (168) regarding myopic children, nearly half of the cases of myopes starting their profession at a young school age continued to progress in adulthood. Female sex, parental nearsightedness and less time spent outdoors in childhood were related to higher adulthood myopia. Reading during childhood with reduced accommodation stimulus, like taking off glasses or using bifocals, was not influencing adulthood refraction. Short reading distance in childhood caused higher myopia among adult females only. Time spent on reading and close work in childhood cannot predict adulthood myopia, but increased myopic progression during the first 3 years.

Young adults progress their nearsightedness slower after onset in adulthood than children do. The Derby study (1985) reported, that the majority of students progressed myopia at a rate of -0.25 D per year or less. In the O'Neal report (1986), monitoring Air Force Academy cadets, this rate of myopia progression was confirmed. The annual progression rate was lowest in cadets entering the academy with +0.50 SER (0.15 D), entering with a -1 D refraction led to 0.32 D progression, and myopes entering with -3.0 D showed a progression of 0.4 D (209).

Useful for comparison purposes, Donovan et al. (210) published data of the actual progression rates of Asian and Non-Asian children. The analysis of Donovan et al. from 2010 showed higher myopia progression rates in urban Asians as compared with urban Caucasians. The younger the child the greater was the annual rate of progression of myopia.

The older formulae of Donovan, for Asians: expected annual myopia progression = $14.64e^{-0.52xAge}$ +0.50.

And for Caucasians: $7.33e^{-0.40xAge}$ +0.28. In both formulae, e stands for 'Exponent'.

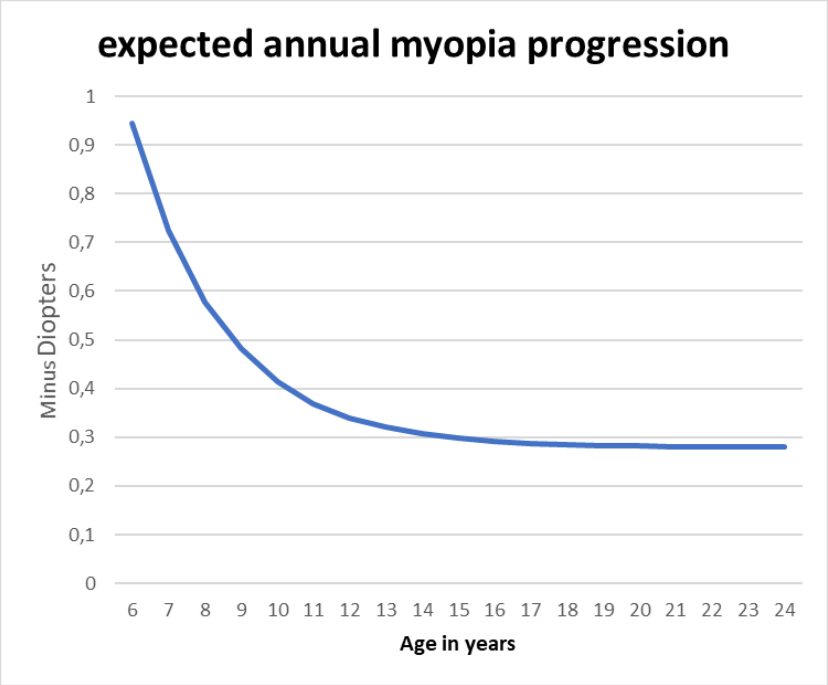

Figure 12: expected annual myopia progression for young Caucasians

In the figure above, calculated with the formula of Donovan from 2010, is a 20-year-old still progressing.

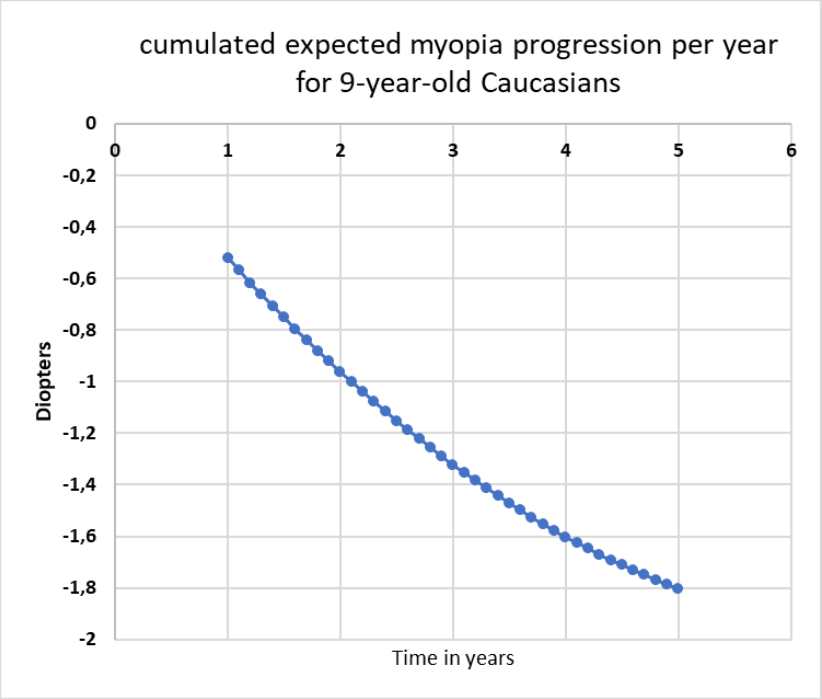

Figure 13: cumulated expected annual myopia progression for young Caucasians

Still not perfectly happy with the formula, I continued my search: A group of scientists around Donovan searched the National Library of Medicine's PubMed literature database for publications on myopia progression using the terms 'myopi*progression' and MeSH terms 'myopia' and 'disease progression'. Only publications from later than January 1990 and only for children under 16 years were accepted. Exclusion criteria were: non-randomized studies, use of non-cycloplegic autorefraction, small sample size, including high myopia (>-6.0 D) or special subject groups, myopia as part of a syndrome or condition, retrospective study design, or using control groups wearing other than spectacles. They found 175 publications, from which 25 remained after applying exclusion criteria. The analysis showed an approximated yearly myopic progression rate of -0.53 D (95% C.I. -0.32 to -0.74) for Caucasians and -0.87 D (95% C.I. -0.73 to -1.01) for Asians. The progression rates were leaning on baseline age with decreasing progression rates the older the children were. In mixed ethnicity, Girls progressed -0.66 D and boys -0.58 D per year (210).

Temporal variations in nearsightedness progression of school children were reported occur during the course of a full year. Probably this is the result of seasonal differences in intensity of close work, or due to factors related to being outdoors in sunshine. Summer has a different, much higher ambient light level than winter. Higher ambient light levels produce higher levels of light-induced retinal dopamine (211) and help hypothetically to maintain a sufficient concentration of cutaneously derived vitamin D in the blood (212). These results show the need for a myopia study duration of at least 12 months, to take seasonal variations into account (213).

2.2 Etiology of Myopia

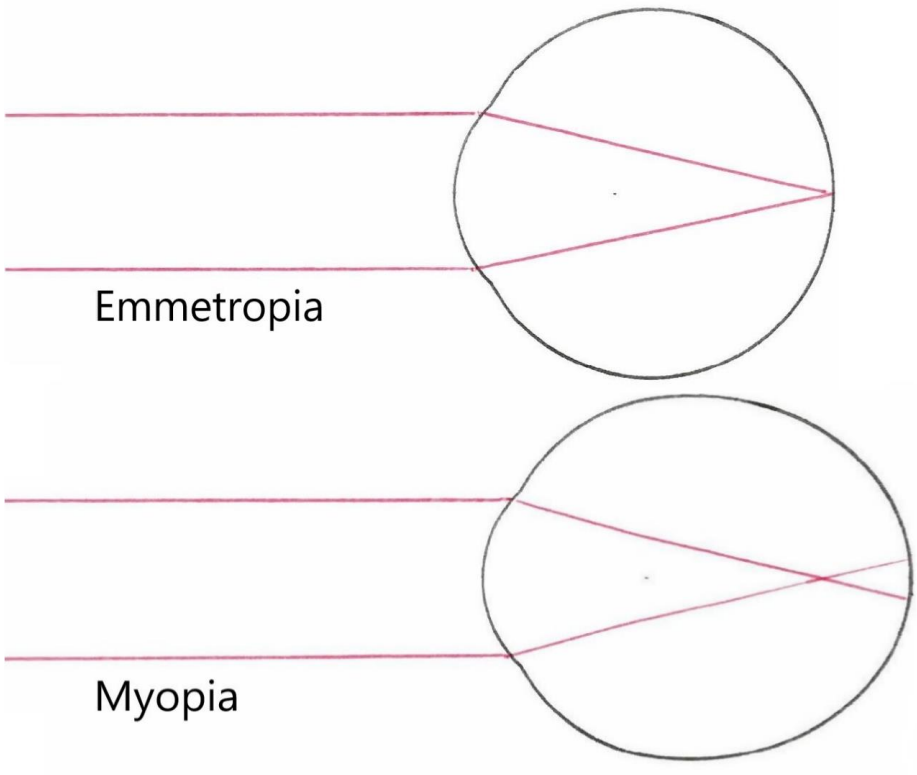

Figure 14: Myopia

Myopia, hyperopia, and astigmatism, the so-called refractive errors, are complicated miscellaneous disorderliness of the human eye. Myopia or nearsightedness is an ordinary eye condition mostly caused by a too long grown axial length. If the collimated light entering through the pupil is focused on a too short distance in front of the retina and not on the correct distance at the retina, patients can see distant objects unclear and the condition is called myopia. Myopia is usually corrected with contacts, negative glasses or by a refractive surgeon. The problem with myopia is that this eye growth can lead to structural damages in the retina, the lens or optic disc, seen more frequently in clients with a high myopia over -5 or -6 D (141).

The cornea and axial length are most responsible for the refractive status (214–216). Eye length and the central curve of the eye are highly correlated. If one of these parameter changes, a large effect in refractive error follows (217,218). Axial length is the main determinant of refractive status and is dependent on a combination of the anatomy of anterior chamber depth, lens thickness, and vitreous chamber depth (Figure below).

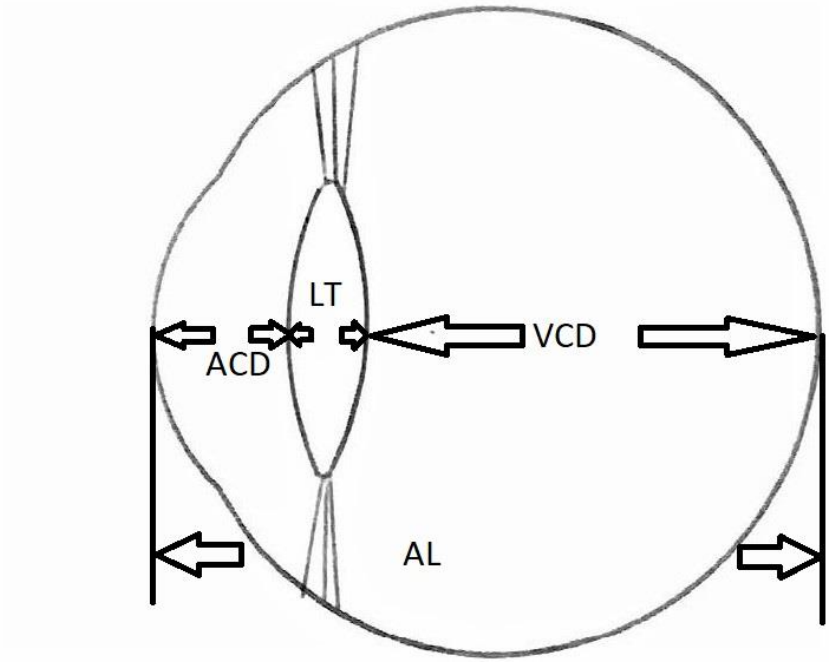

Figure 15: Anatomical fractions of axial length

Figure: anatomical fractions of axial length, adapted from Meng et al. (215): ACD = anterior chamber depth; LT = lens thickness; VCD = vitreous chamber depth; AL = axial length (141)

Even if axial length measuring is more objective, accurate, and reproducible compared to assessment of refraction, eye care practitioners usually use refractive status to define nearsightedness. Autorefractors are widely spread, they measure refractive error mostly automatically in diopters (D or dpt). Diopters are the reciprocal of a distance measured in meters (141).

Refractive status is normally analyzed in terms of spherical equivalent (SE), which is the result of the formula: SE = [sphere + (½ cylinder)].

The retina is a part of the brain, a neurosensory tissue. It detects contrast, movement and colors and is processing the signals locally through different spatial and temporal filters. This pre-processed visual signal is then sent to the retinal ganglion cells, from where it proceeds to the visual cortex. When the retina is exposed to visual signal degradation during early ocular development, it registers contrast deterioration and gives neurotransmitters free to signal eye growth. These signals have to pass through the underlying

retinal pigmented epithelium, travels through the vascular choroidea to reach the whitish fibrous membrane called sclera. The response is scleral tissue remodeling and eye length growth.

2.2.1 Course of refractive error and the onset of myopia

Children are usually born with hyperopia and shall develop emmetropia by ages 6-9 years. This process is called emmetropization (219). The front tissue of the eye, the cornea, is grown up at the age of six (220). But still the crystalline lens power continues to change until age twelve, and the eye's axal length can change even in adulthood (usually until 20-25 years of age) (219,221). The age of onset delivers us the expectation about the grade of myopia: the severity of adult nearsightedness is inversely correlated with it. High myopia has its onset usually in the first 10 years of life, whereas mild myopia often develops in the teenage years or a bit later (141).

2.2.2 Current hypothesis regarding the pathogenesis of myopia

The actually accepted hypothesis for the pathogenesis of myopia is: "excessive eye growth is induced by a visually evoked signaling cascade that originates in the retina, traverses the retinal pigment epithelium (RPE) and choroid, and terminates in the sclera, where active remodeling of the extracellular matrix (ECM) causes the eye to become elongated" (141). We have currently not enough knowledge about the physical events that fire this cascade, about the kind of cells involved, and the biochemical transmitters.

The possible roles of light intensity and cycles in eye growth are discussed (222). Rhythms in axial length growth, choroid thickness changes and also rhythmic changes in the sclera, dopamine and melatonin levels and IOP may be involved in eye growth.

Incompletely understood retinal functions influence eye growth after birth. Muscarinic and nicotinic mechanisms seem both to affect refractive development. Retinal dopamine signaling and light exposures influence refractive development. There were daily rhythms of eye dimensions found, this may be linked with refraction and eye growth. Clock genes and intrinsic retinal rhythms may be fundamental to refractive control (223).

The age of onset is essential: the younger children become myopic, the faster will be their progress. A progress of at least 1 D per year is normal for 7-year-old children. They will half this amount by age 11 to 12 years (177). An early onset of myopia requires an early as possible myopia management strategy (72).

2.2.3 Genetics of refractive error

Nearsightedness is highly heritable; the risk of developing myopia is increased at least three times as high among children with two myopic parents, compared to kids with non-myopic parents (75,92,224).

The genetic background predicts the probability of becoming myopic (162). Myopic parents have a higher probability of having myopic children. The refractive error of monozygotic twins is correlated in a high grade (75). But the effects of genotype are not the most important factor, studies have shown that the effect of visual behavior is many times greater, in one study for example by a factor of 7.2 versus 51.3 (3,92).

The scientific community currently has an understanding of the basics of mechanisms that cause nearsightedness (28). Studies on twins show that about 90% of myopia inheritance is explained by the one's genetic background. This is supported by the fact that children with one myopic parent have a 2.08 times

increased chance of developing myopia. Children who have two parents with myopia show a 5.07 times increased chance of developing myopia, both numbers compared to children with non-myopic parents. These data suggest that we have in myopia a strong underlying genetic factor (155,225). As said before, we know that environmental factors such as higher education and IQ, living in a citylike environment, and spending only short time periods outdoors have all been associated with developing nearsightedness (155,226–228).

Myopia is reported in all races and ethnicities, the most myopia show persons from Asian descent especially those who live in developed areas (28,35,63,69,98,229). The increase in prevalence of myopic patients is not likely to be related to genetics alone. The changes in prevalence came too fast and has only recently increased; more likely a change in our behavior let the prevalence of myopia rise, e.g. we spend much less time outside (35). Rose et al. (229) reported lower incidence of myopic children of Asian descent in Sydney than Singapore, the children in Sydney spent more time outdoors.

Epidemiological studies have shown strong correlations in myopia along families (216,224,230–234) and in myopic populations a number of possible genes have been identified (235–237). Several authors have discussed these genes (81,238–240). The proportion of phenotypic variation is estimated at >90% and can be attributed to biodiversity, respecting refractive status (231).

Nearsightedness is a common feature of some heritable connective tissue disorders like Marfan and Stickler syndrome. Many studies searched for the loci of the responsible myopia causing genes (62,234,241–256). Those studies looking at genetic factors in myopic family found a very heterogenic picture.

Another interesting myopia fact I found was this here: Pan et al. (257) studied the relation of iris color and myopia, and published the results 2018. Over two thousand Chinese students participated in their study. After adjusting for sex, body stature, parental myopia, time spent on computer and watching TV, time spent outdoors, and time spent in reading and writing, students with a darker iris have shown tendency for a higher prevalence of nearsightedness, a more myopic refraction and a prolonged AL. Also dose-response relationships were found in all regression models (p for trend <0.05).

2.2.4 Environmental factors and gene-environment interactions

Most scientists agree that nearsightedness is not alone determined by genetics, but that environmental influences play an important role in development of nearsightedness (8,81,233). Environmental risk factors such as close distance work (15,258) and time spent outdoors (165,229) have been identified as possible etiological factors in the development of nearsightedness (4).

As usual in diseases that have both genetic and environmental factors, these two elements generally have substantial interactions (81,243,259). Neither gene-gene nor gene-environment interactions have been studied systematically for nearsightedness. The great variation of the correlations between genes and environment explain the variance we see in myopia (260). But only with a change from the current approach of a purely genetic analysis to the identification of gene-environment relationships helps to find the missing links in myopia management (141).

Motivated by pharmacological links already found in studies about nicotinic acetylcholine receptors in chicks and their association to myopia progression, the authors around Stone implied a study about myopic progression in children with smoking parents and compared them to children not exposed to cigarette smoke. Prenatal and childhood exposures to tobacco smoke correlated with less prevalent myopia (183).

Near Work and Myopia

ECPs should assess near point vision of progressing myopic children accurately: measuring accommodative posture, lag of accommodation, and binocular status gives an overview of child's ocular response to near tasks. If a great lag and / or near esophoria was found, PALs, bifocal glasses or multifocal contact lenses can be prescribed. These treatments relieve near point stress of the patients and probably help to slow myopia progression (261).

The Amount of near work (192,262) and the level of education (263,264) have one as well as the other been described as possible risk elements in myopia development, even though direct evidence of the alliance between near work and myopia is difficult to secure (86,233). In specified employment groups like clinical microscopists, high prevalence of myopic refractive error and increased rates of myopia progression have been described (265). Other studies have found no strong correlation of myopia and near work (266). Even in the large multi-center COMET study no association between the amount of near work and myopia was found, the scientists reported difficulties to measure the exact amount of near work over a three year period (4,16,56).

Short interruptions like the rule of 20 – 20 – 20 – 20 (look each 20 minutes for 20 seconds at an object in 20 feet distance and blink 20 times) can help in situations of sustained near work (261).

As we know from animal studies of eye development, hyperopic retinal defocus is a causative element in axial growth (43,267). Lag of accommodation could be an important element in producing the retinal defocus values experienced in humans when looking at close objects. Children with recently started myopia progression accommodated significantly less than children with emmetropia when looking at close objects (268). Gwiazda et al. (56) measured that at the two nearest object distances (33 and 25 cm) children with myopia accommodated significantly less than children with emmetropia (0.22 D less at 33 cm and 0.39 D less at 25 cm). They found that when accommodation was stimulated with minus lenses this lag of accommodation was even more evident. Probably can blur cues not be handled well with myopic eyes accommodation, suspect the authors. The effect would cause a chronic retinal defocus which accelerates axial elongation and myopia alike we have seen it in animal models.

Newer studies on accommodation of myopic eyes clarified that they respond less well to minus lens-induced defocus than emmetropic or hyperopic eyes (269–271). Viewing the target through their distance correcting glasses, myopic children tended under binocular viewing conditions to have larger lags of accommodation than emmetropic kids. A little help had most of the myopic patients due to their spectacle under-correction (270,272). Gwiazda et al. described the effect of increased accommodative lags being present up to 2 years before the onset of myopia. Possibly accommodative convergence may also be changed before the myopia is measured (4,15,17,56).

Reports show that the interplay of lag of accommodation, target distance, near heterophoria and time spent on near tasks all can be relevant elements that control myopia development and progression (56). Myopes have tendentially higher accommodative-convergence to accommodation (AC/A) ratios than children with emmetropia (17,200). Gwiazda et al. (17) described the possibility that AC/A ratio decreases once myopia has stabilized, due to either better accommodative responses or less esophoria at near. In myopic kids with high AC/A ratios, it has been proposed that a child with esophoria must relax accommodation muscles to reduce accommodative convergence for the reason of holding the binocular picture together, unfortunately this effect costs clarity. The result is an enlarged lag of accommodation and sessions of too long hyperopic retinal defocus at near.

Other authors like Langaas and Weizhong (265,273–275) found no firm correlation between accommodative lag and myopia development. Mutti et al. (173) investigated in their CLEERE study the

accommodative response in 568 children who had emmetropia at study start and later became myopic, and compared them with 539 children who stayed emmetropic. Both groups had the same amount of accommodative lag at study start and at onset of myopia. The significant difference was found in kids who became myopic from one year after myopia had been measured the first time, they showed an increased lag of accommodation. This shows that was rather an adaptation to myopia than a cause (4).

My interest was now to find a link between reading time and myopia. Ip et al. (85) examined the association of time spent in near work and reading with spherical equivalent refraction (SER) in a population-based sample of 12-year-old schoolchildren in Australia. With the use of questionnaires, data on the weekly time spent in near-work or outdoors and estimates for the duration of continuous reading and reading distances were collected in the Sydney Myopia Study between 2004 and 2005; 2339 children were controlled with a comprehensive eye examination, including cycloplegia. In conclusion, Ip et al. discovered that even myopia was not significantly associated with time spent in working in close distances but there exist significant independent relationships with very near reading distance and continuous reading. These relationships may indicate that the intensity rather than the total time of near work is an important element.

A new idea about why eyes become myopic I found in the work of Aleman et al. (276): from animal models they knew that selective activation of ON or OFF pathways has also selective out-turn on axial prolongation. Aleman found that ON and OFF inputs were mostly balanced out in the nature. They presented black text on white paper and overstimulated with this the retinal OFF pathways. Conversely, they presented now white text on black paper, to overstimulate the ON pathways. Using an OCT in their young human volunteers, they realized that the choroid becomes about 16 µm thinner in only 1 hour when subjects read black letters on white background but about 10 µm thicker when they read white letters from a dark background. These thinner choroids are associated in animal studies with axial prolongation, leading to myopia. Those studies found a slower myopia progression in animals with thicker choroids. Therefore, presenting white text on a black display may be a way to hinder myopia, while the classic way, black letters on white background, may activate myopia progression.

All the studies I read until here were focused on central accommodation. Then helped the study of Whatham et al. (277) to understand the changes in off-axis refraction during accommodation. Corrected myopic eyes are seen generally with relative peripheral hyperopia, but does this change with accommodation? Peripheral refractive error, compared to central refraction, became less hyperopic the greater the eccentricity was (20°, 30°, and 40°) and with increasing accommodation. Lag of accommodation grew bigger with accommodation ($p < 0.001$), shifting the image-shell backwards. So, myopic persons show hyperopic shifts in the center and near peripheral field while looking at close targets.

Myopia and Outdoor Activity

Pärssinen et al. (278) reported in the 90's a correlation between more time outdoors and slower myopia progression in Finnish children, a lot of epidemiological studies followed assuring that spending more time outdoors as a child has protective character against the development of nearsightedness (54,88,165,229,279–282).

But in 2018 Hagen et al. (283) argued that if this is true, myopia prevalence must be higher in grown-ups living in high latitude nations with only few daylight hours in the autumn-winter. He examined in a representative Norwegian region of 60° latitude North Norwegian Caucasians aged 16 to 19 years (n = 393, 41.2% males). In this region, summer is 50 days shorter than winter; however, they found a quite low prevalence of myopia (≤-0.50 D) of 13%. The short summer daylight exposure seems to outweigh longer winter period, must the effects leading to this must be investigated further.

A meta-analysis (284) of 19 cohort studies evaluated the strong effect of a lack of light on the development of myopic conditions. Indoor standard illumination is around 500 lx, while it reaches outdoors levels of 5'000 lx on a cloudy day and 100'000 lx in bright sunlight. Each hour exposure to daylight per week extra is helpful. Third-grade children can lower the risk of developing nearsightedness by around 10% within 5 years for each hour outdoors, discovered the US American Orinda Study, included in the meta-analysis (3,233).

Statistically significant associations were found by Guan et al. (167) between outdoor time at midday and lower amounts of myopia, which supports the idea that light intensity is important to protect eyes from getting myopic.

Seasonal aspects count as well: 358 US children with a mean age of 10 years showed more progression (0.35 D) during the six winter months than during the 6 summer months (0.14 D) (285). Donovan et al. (210) found children progressing their myopia in summer months approximately 60% of that seen in winter. This indicated that myopia control studies must have a duration of at least 12 months, to take these variations into account.

So, sunlight is a possible factor in myopia progression. The question, if more time spent outside helps to manage myopia, was answered by Wu. 571 Taiwanese children at ages 7 to 11 years were randomly told to spend their break time in school differently. One half had to stay outdoors; the others had to stay inside the house. The "outside"-group spent 80 minutes more each school day outside the building. Their risk of getting myopic fell by half, after study end after one year (88). Comparable studies are available from China: half of 1903 children at age 7 years had to stay 40 minutes per day more outdoors than normal. They showed a risk reduction for myopia from 40% to 30% in 3 years. In already myopic kids, progression was 1.4 D in the group that stayed longer outdoors and 1.6 D in the group that stayed inside (286). A comparable study of over three thousand children aged around 8 years discovered that 20 minutes' additional sunlight exposure each day lowered the risk of getting myopic from 9% to 4% in one year and progression from 0.3 D to 0.1 D per year (287).

Animal studies indicate that frequent exposure to bright light is also related with an increasing thickness of the choroid (288), and eye growth was slowed, potentially from light-induced retinal dopamine production (34,289). In 2018, Landis et al. supplemented, that it is probably necessary to add to dim light sessions to the sessions with bright light (290). They concluded that rod pathways stimulated by dim light exposure could be important to manage myopia progression.

Schaeffel et al., Li et al., Schwahn et al., Schmid et al. (291–294) and other authors suspect that in the time spent outdoors in sunlight dopamine is released in the retina. We know dopamine as an inhibitor to myopia progression. The time spent outdoors is more important than doing sports. According to Xiong et al. (280), sunlight exposure is the key factor to slow myopia progression. Following this idea, spending time inside like in schools should progress myopia faster. Lack of daylight shows a higher risk for myopia progression than the duration of near work, confirmed the Sydney Adolescent Vascular and Eye Study, a 5 years' follow-up study (295). Some cohort studies like the Gutenberg Health Study (91) have established that the rate and grade of myopia are positively associated with school and training results.

As we know that light is a factor in myopia progression, does it matter what kind of light source is used? In a recent study, Pan et al. (296) compared the types of lamp used for homework including incandescent lamp, fluorescent lamp, and light-emitting diode (LED) lamp. The result was, that the use of LED lamps can accelerate the progression and development of myopia among school-aged Chinese children.

In the beginning stage of myopia before onset, staying outdoors reduces the risk of progression of myopia (261).

Each child's behavior outside is different, so new wearable light sensors and accelerometers worn by the youngsters will allow a more accurate measurement of light exposure and distance, including time spent outdoors, as well the child's physical activity, compared with traditional studies based on questionnaires. Different tools were already utilized in studies, including a customized spectacle-frame mounted distance sensor, the so-called Cloudclip, the HOBO and Actiwatch (281,297,298). Fit-Sight, a smartwatch linked with a smartphone app, displays the amount of time children spent during the day in sunlight, and seems to motivate children to go more outdoors (299).

As described in early reports, a link exists between habitually short working distances and pronounced head tilts with a higher risk of myopia progression. From this comes the interest to measure working distances (300). Also causes prolonged near work in short distances greater myopia (301). To quantify the amount of near work activity like reading, writing, computer use, or playing video games on myopia development, Zadnik, Mutti et al. calculated a weighted variable by adding three times reading, two times computer use, and two times video games use in hours per day as diopter hours (186). This was in 1994: but in the past 25 years, the world of a child has changed, smaller smartphones, mostly held in close distances, should be added to the list.

On the other side, new techniques like the use of computer screens for reading, give us two new possibilities:

First, the newer bigger screens are further away from the child's eye and asks for less accommodation. And second: it offers a solution for the idea to present text in invers colors: that means white letters on black background (276). Aleman et al., Wang et al. and Schaeffel et al. used in 2018 optical coherence tomography (OCT) in children, and found that the choroid becomes about 16µm thinner in only 60 minutes when children read black text on a white background, but about 10µm thicker when they read white text from a black background. Thinner choroids are a signal for myopia development, and thicker choroids a signal for myopia inhibition (302–307). Therefore, reading white letters from a black background screen, e-reader or tablet may be an option to slow myopia progression, while conventional black text on white background may stimulate axial elongation.

2.2.5 Myopia and level of education

As seen before, the time spent inside school is leading to more myopia. Are persons spending more years in school more myopic than those with only basic education? The E^3 Consortium for Refractive Error and Myopia (CREAM) calculated the genetic risk score on the base of twenty-six single nucleotide polymorphisms correlated with myopia. The level of education was captured by survey form and divided into primary, intermediate, and higher education (92). The Consortium investigated the distribution of the highest educational level absolved, per birth decade (1900–1989), and divided in three groups: primary education, leaving school at age <16 years; secondary education, leaving education at age ≤19 years; higher education, leaving university at age ≥20 years. While persons born in the years 1900 to 1909 have less than 10% higher education, is about half of the persons born 1970 to 1989 higher educated. More and more participants absolved the level "higher education", the closer they were born to today (94).

Every of the 26 genome-wide significant single nucleotide polymorphisms (SNPs) correlated with refractive error and myopia described by the CREAM consortium were taken into calculation of the genetic risk score. Involved were totally 45'758 participants (76), higher scores indicate a greater risk for myopia development (92). The results of this and other studies show: yes, an individual's genetic risk of getting myopic is significantly affected by the level of education (94,308).

2.3 Visual consequences of refractive errors in the general population

In adults nearsightedness is the main risk factor other than age for some degenerative eye diseases, a strong link was found between myopia and a higher risk of cataracts, retinal detachment, and myopic maculopathy (39,309–311). However, data about the absolute risk of visual impairment among patients with (high) myopia are not available. Asian countries see already increasing rates of blindness and vision impairment due to myopia (312,313).

At least 10% of the estimated 2.5 billion people will suffer from high myopia in the next decade, and 49 million will develop severe visual problems as a result of this disease (63). Families and patients will have a lower quality of life, and the loss of vision will lead to major financial consequences (314,315). We cannot offer adequate treatment modalities worldwide, but we expect more new myopic patients each year. This will create a significant burden in the next decade for economy and our public health system (141).

For our patients it is important to take myopia control seriously, because as little as 1 D of myopia doubles the risk of myopic maculopathy (MM) and posterior subcapsular cataract (PSCC) (72). And compared to emmetropes it gives a threefold risk of retinal detachment (RD). Higher levels of myopia bring much more of the sight-threatening risks. These odds ratio risks show that there is no safe physiological level of nearsightedness (39).

TABLE Odds ratios of increased risk of ocular pathology with increasing levels of myopia*

Myopia (D)	Glaucoma	Cataract (PSCC)	Retinal detachment	Myopic maculopathy
–1.00 to –3.00	2.3	2.1	3.1	2.2
–3.00 to –5.00	3.3	3.1	9.0	9.7
–5.00 to –7.00	3.3	5.5	21.5	40.6
< –7.00	–	–	44.2	126.8

* summarized from Flitcroft (39)

Table 8: Odds ratios of increased risk of ocular pathology with increasing levels of myopia

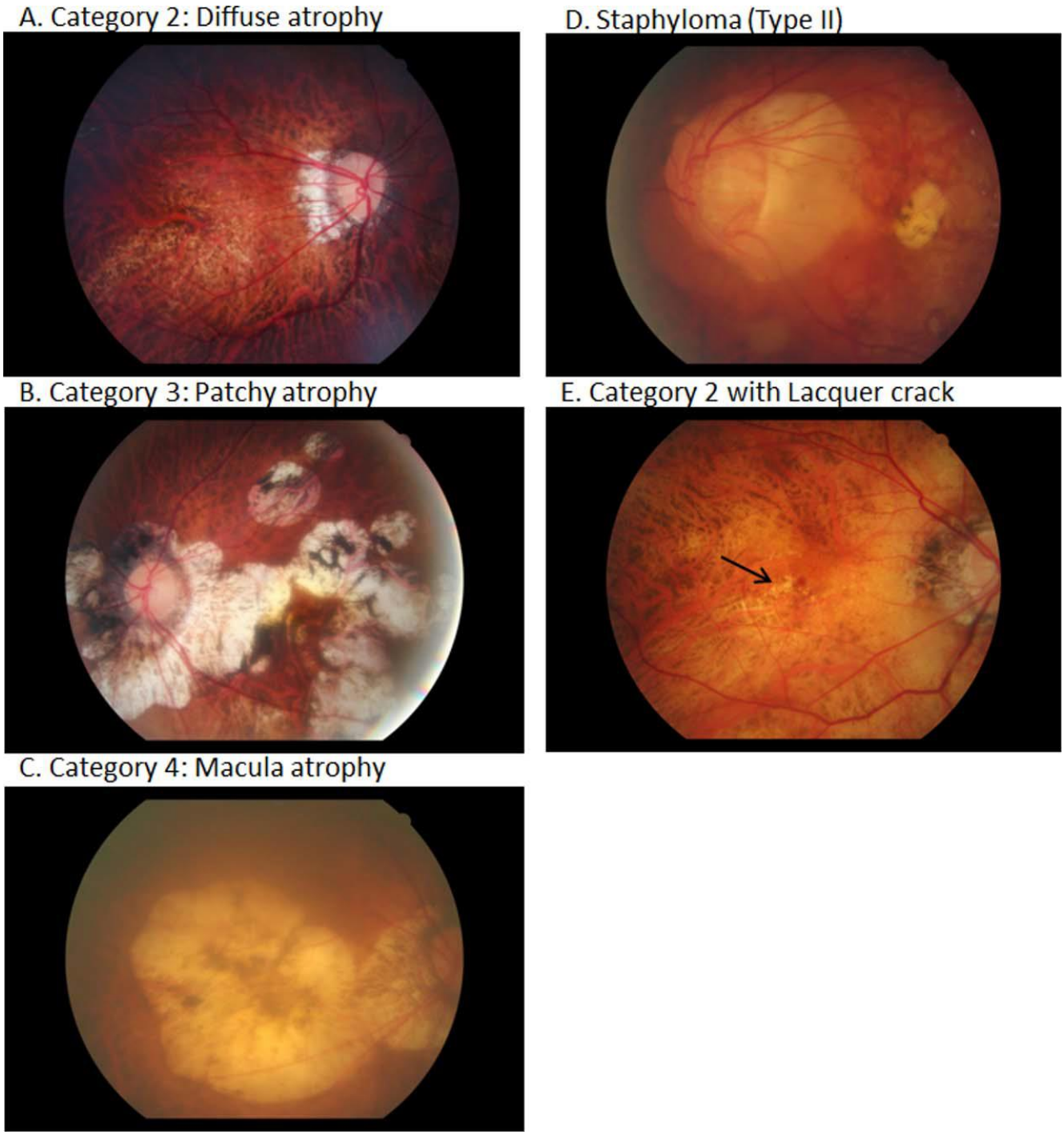

Figure 16: fundus photos of consequences of myopia

Picture from Saw, Prevention and Management of Myopia and Myopic Pathology, 2019 (316). Used under Creative Commons Attribution 4.0 International License. (Text added, and changed.)

The figure above shows examples of fundus photographs based on the International Classification of Myopia Maculopathy:

(A) Diffuse atrophy (Category 2); (B) Patchy atrophy (Category 3); (C) Macula atrophy (Category 4); (D) Left fundus of a 61-year-old Malaysian man with SE-18.25 D and an AL 31.73 mm presenting staphyloma (Type II); (E) Right fundus of a 55-year-old Malaysian woman with SE-13.75 D and an AL 28.24 mm presenting category 2 with lacquer crack (black arrow).

Every growth in axial length towards myopia rises the risk of pathology (72). This because of the lengthening and thereof thinning of the eye tissue. To avoid this effect is the main goal of myopia management. The population-based Rotterdam Eye Study discovered that 2.3% of the adults were severely visually impaired (vision in better eye lower than 0.3). Myopic patients in the range between –6 D and –10 D (1.8% of adult population) showed a triple risk for visual impairment. Severely high myopia patients with myopia over –10 D (0.4% of adult population) had a 22 times increased risk for developing ocular diseases (154). In those high myopia patients the sensitivity and specificity of OCTs is reduced due to the very long eyeball; this makes is hard to detect degenerative changes in the optic nerve early enough (317). Dhakal (318) confirmed recently that lesions like staphyloma and retinal detachment increase the higher the myopia degree gets. The proportion of findings of pathologic changes across different grades of myopia show need for exact peripheral fundus examinations.

Mostly, bilateral visual impairment was caused by myopic macular degeneration (in 39% of cases); followed by cataract (17%) and glaucoma (5%) (3). The major causes of visual impairment in highly hyperopic persons were age-related macular degeneration (AMD), cataract, and combined causes (each 25%). In 2018, pathologic myopia was the 4th most common cause of unrepairable blindness in developed nations. The two main factors steering the development of pathologic myopia are: 1) growth of the eye ball length and 2) posterior staphyloma (319). The definitions of the World Health Organization (WHO) for unilateral and bilateral low vision are VA < 0.3 and VA ≥ 0.05; for blindness VA < 0.05. High myopia is the cause for the most severe visual consequences of all refractive errors (154).

I was interested in the correlation between glaucoma and myopia: the Blue Mountain study (320) confirmed that there is a strong relationship between myopia and glaucoma. Myopic subjects had a twofold to threefold increased risk of glaucoma compared with subjects which were not myopic. The risk was independent of the IOP or other glaucoma risk factors.

And these findings were confirmed: a Belgian study of Detry-Morel (321) confirmed these data in 2011. Existing epidemiologic evidence suggests that moderate and especially high myopia over -6 D is a risk factor for the development and the progression of glaucomatous optic neuropathy. In myopic eyes, although probably not clinically relevant, but slightly higher IOPs than emmetropic or hyperopic eyes were found. High myopia gives weakness of the fibroglial matrix of the nerve fibers at the optic disc. Together with the structural variations in the choroid and lamina cribrosa the interpretation their visual field is difficult. Probably is glaucoma better diagnosed in myopic patients because they see their ophthalmologists more frequently than hyperopes or emmetropes. Cave: special attention must be given to patients with low myopia who present together elevated IOP levels and a positive family history. At closer intervals shall high myopic subjects be screened for glaucoma. After adjustments for deviations in central corneal thickness have been made, patients with IOP greater than 17 mmHg are critical and initiation of medical treatment is considered.

In conclusion, myopia is a major independent lifelong risk factor for eye disease. Nearsightedness is the most important factor in MM and RD, and for causing cataracts and glaucoma it is on rank two behind age (39).

Parents are normally interested in myopia control because they don’t want to change their children’s glasses every few months. Those parents must be explained why we should control the progression of axial growth: for their child’s lifelong ocular health (72).

2.4 Current Therapies to Inhibit Myopia Progression

Nearsightedness is not just a genetically given condition. As shown in many human and animal studies, several environmental factors affect the process of emmetropization. “Time spent outdoors, specific light spectrum, time spent in reading, hyperopic retinal defocus during near work, and intrinsic factors as near esophoria or great lag of accommodation are considered responsible for the disruption of emmetropization processes and for the promotion of myopia progression”, explains Mihelčič from the Velika Gorica University of Applied Sciences, Velika Gorica, Croatia (261).

We usually correct the refractive anomaly of myopia with glasses, contact lenses and refractive surgery; however, these treatments don’t heal or stop the underlying axial growth, they just adjust the focal point of the eye to provide clear far vision. Very different treatment options have been tried to stop or slow myopia progression. Ortho-K and myopia control contact lenses reducing hyperopic retinal defocus as well as muscarinic antagonists like atropine and pirenzepine showed good results (322). These latters are not widespread because of their unwanted ocular and systemic effects. Many studies on bifocal spectacle lenses, PALs and SV RGP contact lenses have been conducted, with no clinically significant results (4).

Since the early 1900’s many different attempts have been made to control and slow the progression of myopia (4,56,108,279,282,323–326). Recently, a range of clinical interventions have been introduced to slow eye growth and reduce myopia progression through optical, environmental or pharmacological means. Some of the clinical trials have shown promising results for a number of these methods (327). New research technologies like high-resolution OCT imaging has also provided important insights into the possible mechanisms underlying these treatment options (34).

Table: Percent reduction in myopia progression relative to control group

Treatment group	**Study / year**	**% of reduction**
More outdoor activity	Wu et al. (282)/ 2018	26
	He et al. (286)/ 2015	11
Atropine 0.01%	Chia et al. (108)/ 2012	59
	Yam et al. (201)/ 2019	27
Atropine 1%	Chua et al. (197)/ 2006	77
	Tong et al. (107)/ 2009	10 (after rebound)
Ortho-K	Santodomingo et al. (124)/ 2012	31
	Hiraoka et al. (129)/ 2018	30
Multifocal soft contact lenses	Aller et al. (116)/ 2016	79
	Anstice and Phillips (56)/ 2011	50
	Cooper et al. (328)/ 2017	96
Spectacles	Hasebe et al. (329)/ 2014	20
	Cheng et al. (330)/ 2014	39

Table 9: Percent reduction in myopia progression relative to control group

The table above shows the percentual reduction in myopia progression relative to control group with standard, single vision spectacles or contact lenses.

For kids who are already myopic it is important to find a myopia-controlling strategy that fits the child. Depending on a child’s characteristics and capability, correction of myopia can be actively combined with myopia management options, using special spectacles, multifocal or bifocal contact lenses, pharmacological treatments, and visual environment modifications (72).

In 2016, Huang et al. (327) found in their comparison of the efficacy of myopia control treatments, that peripheral defocus modifying contact lenses and Ortho-K were the best non-pharmacological options to decrease axial length growth. In total Huang found 2435 publications on the topic, the 30 best were used for his comparison. The most effective treatments were pharmacological intervention, specifically the ones with atropine in different concentrations. The following table compares differences in myopia progression for atropine eye drops, multifocal lenses, exposure time to sunlight, varifocal glasses and placebo treatments (3).

Of these different interventions, CLs show a very good risk-benefit ratio compared with other interventions for myopia management. Further research is necessary to investigate possible rebound on discontinuation. Wearing CLs is generally safe for children and improves quality of life and self-esteem. The number of CL complications is not higher than in adults (331).

Atropine is more effective in the first year than CL wear but has more risk of side effects compared with CLs and myopia rebounds after treatment has been stopped (108,323).

Atropine 0.01% eye drops seem to be the most useful current way to reduce progression for ophthalmologists, but they don't prescribe it that much because it is an off-label treatment in many countries. Neither we know enough up to which age atropine drops should be given, or about the optimal duration of treatment. Nor we know the effects why rebound happens when patients discontinue the treatment (3).

As we know from animal experiments (3), the retina controls the axial elongation of the eye throughout the visual field. Due to this, peripheral VA is important (332). Opposite to this, accommodation is steered nearly exclusively by the fovea and shifts the whole image over the complete visual field (333). Additionally, multiple simultaneous focal planes exist (similar to multifocal contact lenses), and the retina determines the average position and will adjust growth on the result (334).

Huang et al. (327) studied with a network meta-analysis the efficacy of sixteen interventions for myopia management in children. They found:

1. Statistically significant effects in myopia control were found in high-dose atropine (1% and 0.5%) moderate-dose atropine (0.1%), and low-dose atropine (0.01%); peripheral defocus modifying contact lenses, pirenzepine and ortho-k showed moderate effects. Cyclopentolate and prismatic bifocal spectacle lenses had lesser effects; progressive addition spectacle lenses, bifocal spectacle lenses, peripheral defocus modifying spectacles, and additional outdoor activities showed weak effects. RGP contact lenses, soft SV contact lenses, under-corrected SV glasses and timolol were not effective.
2. Asian children responded better to myopia control treatment than white children, and
3. most treatments lose their early effect in the second year.

During the last decade, myopia control soft CLs that create additional myopic defocus on the retina are in the focus of interest in myopia control (56). Such lenses worked better than peripheral defocus modifying glasses (113,327).

2.4.1 The Idea to Present Myopic Defocus to the Retina

The results of many trials provide convincing evidence, that a number of optical interventions for myopia management are efficient, even with unknown underlying mechanisms. These interventions include the relative contributions of the central and peripheral regions of the retina to regulate axial elongation, like the influences of peripheral myopic defocus seen with Distance-Center Multifocal Soft Contact Lenses or Ortho-K, or glasses or lenses with a peripheral addition.

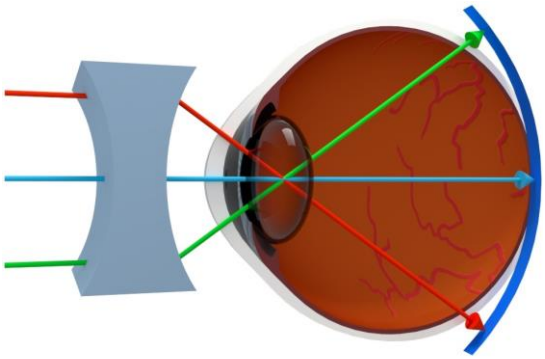

Image shell with SV contact lens

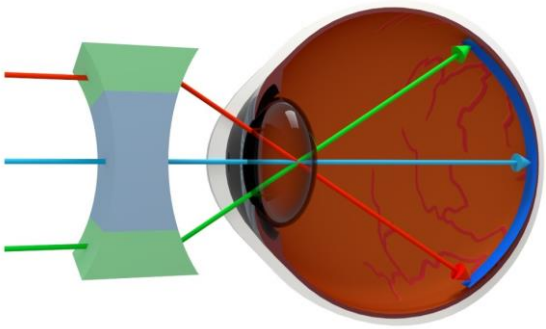

Image shell with peripheral defocus contact lens

Figure 17: Image shell with peripheral defocus contact lens

Figure: Swisslens

Ortho-K and MFSCLs bring the image shell inside the retina, change hereby the relative peripheral refraction from relative hyperopia to relative nearsightedness by the reshaped cornea and the peripheral treatment (add) zone. This seems to be consistent with the assumption that relative peripheral hyperopia is the driver of the progression of nearsightedness (335).

This assumption is based on the results of studies following the hypothesis that presenting myopic defocus to the peripheral retina slows myopia progression. This necessitate a fundamental shift in how refractive errors are defined. If we want to understand eye growth, a single sphero-cylindrical definition of foveal refraction is not enough. Instead of correcting a simple central refractive error, the image must be calculated across the curved surface of the retina. By planning and interpreting the results of clinical trials on myopia prevention we must keep in mind that local retinal image defocus can only be determined once the shape of the eye, the 3D structure of the viewed scene and off axis performance of the eye has been accurately defined (39).

Animal models have shown that there are biological and molecular signals present that are able to increase or decrease ocular axial growth and thereby steer the rate of myopia progression (336), these biochemical and cellular pathways have not been identified yet (4). The idea that near work plays a role in the development of nearsightedness is supported by animal studies which decovered that imposing hyperopic defocus on the retina stimulates ocular axial elongation and myopia development (11,43,45). It has been suggested that this condition is similar to the lag of accommodation faced by children when reading, and that this hyperopic defocus at near is a stimulus for developing nearsightedness (15). Trials to modify these environmental risk factors, for example by the use of near spectacle correction, have shown largely

unsuccessful outcomes (19,337,338). Confirmation of the potency of myopic retinal defocus has been mentioned by changes in refraction in animals wearing lenses and then allowed short sessions of normal, unlimited vision (4). Plus and minus lenses were both compensated (13).

Schmid and Wildsoet (13) speculated that myopic retinal defocus builds a 'stop' signal which causes decreased axial elongation and vitreous chamber growth. This 'stop' signal seems to be stronger than the 'grow' signal built by hyperopic defocus.

The effect of soft contact lens with concentric ring bifocal and peripheral add multifocal designs on controlling myopia progression in school-aged children was evaluated by Li et al. (339) in 2016. They systematically searched in MEDLINE, EMBASE, Cochrane Library and reference lists of included trials. The quality of the methods used in the included trials was assessed using Newcastle-Ottawa Quality Assessment Scale items and Jadad Scale.

The scientists identified three cohort studies and five randomized controlled trials (RCTs) with a total of 587 myopic young persons. Concentric ring bifocal soft contact lenses showed less myopia progression with a weighted mean difference (WMD) of 0.31 D (95% CI, 0.05-0.57 D, $p = 0.02$) and a smaller axial elongation with a WMD of -0.12 mm (95% CI, approximately -0.18 to -0.07 mm, $p < 0.0001$) at 12 months, when compared with the control group. With peripheral add multifocal soft contact lenses less myopia progression was found, with a WMD of 0.22 D (95% CI 0.14-0.31 D, $p < 0.0001$) and also the axial elongation of -0.10 mm was smaller (95% CI -0.13-0.07 mm, $p < 0.0001$) at 12 months, relative to the control group. In children wearing these myopia control contact lenses with concentric ring bifocal and peripheral add multifocal designs a 30-38% smaller myopia progression rate and a 31-51% lesser axial elongation was found within 24 months.

So, Li et al. confirmed that both concentric ring bifocal and peripheral add multifocal soft contact lenses are clinically effective for controlling myopia in children in school-age. The overall myopia control rates were 30-50%, controlled over 2 years. Concentric ring bifocal soft contact lenses seem to have a little bigger effect than peripheral add multifocal soft contact lenses.

Multifocal contact lens designs may reduce binocular VA, stereopsis and CS compared with spectacles. This has an impact on wearers' visual function quality, inducing ghosting, halos and visual fluctuation. To wear a multifocal contact lens, neural adaptation is necessary (340).

The effect of eye and head rotation evaluated in peripheral refraction with contact lenses, but no difference was found. Lopes-Ferreira (341) confirmed that multifocal center-distance soft contact lenses induce peripheral myopization. Multifocal concentric near center soft contact lenses (Acuvue Oasys for Presbyopia) did not show changes in peripheral refraction.

An interesting finding in an animal model presented Zhu, Winawer and Wallman (342). They investigated the potency of interrupting continuous negative lens wear with short sessions of either positive or plano lens wear. The results especially of the positive lenses worn for short sessions several times a day showed that this cancels the effect of much longer sessions of negative lens wear (4). Chicken eyes wearing plano lenses in the non-negative sessions became double as myopic as eyes wearing +6 D lenses (-3.4 D compared with -1.8 D). So, the authors came to the conclusion that presenting myopic retinal defocus, here by a positive lens, is the most effective mechanism for prevention of myopia development. Even when the sessions of myopic retinal defocus were very short like a total of eight minutes a day, the effects of myopic defocus dominated hyperopic defocus. So, Zhu et al. (342) showed in 2005 that in chicken eyes short sessions of positive lens wear can reduce the ocular axial growth for up to 48 hours after the lens is removed.

A completely other way chose Phillips (20). He investigated myopia progression in New Zealandish school children. His attempt was to give the children monovision spectacles, the dominant eye corrected for far distance, the other for near. The non-dominant, near eye encountered sustained myopic defocus because of the under-correction, progressed myopia significantly less than the fellow eye. This experiment also showed that in children accommodation was steered by the dominant, distance corrected eye. Unfortunately, this idea of monocular under-correction therapy is not useful as a myopia control therapy form because it treats only 1 eye (4). Attempts at under-correcting myopia in kids binocularly failed (343,344). A treatment form was required to simultaneously deliver myopic defocus, combined with clear distance vision; Simultaneous bifocal and multifocal contact lenses, each with distance correction in center, have such optics. The term simultaneous CLs describes contact lenses presenting 2 or more powers within the pupil at the same time, the powers are usually annularly concentric arranged. The light rays travelling through such a lens are focused on different spots (345). One focus should be on the retina, for clear distance vision. The second focus should be in front of the retina to present myopic defocus to the eye, this for the myopia control effect.

The wear of simultaneous MFSCLs resulted in a relative myopic shift in peripheral retinal refraction compared with glasses or single vision contacts. This myopic shift may give an explanation of the reported reduced myopia progression rates in wearers of MFSCLs (346,347).

Diffractive spectacles providing peripheral defocus were not as good accepted as MFSCLs as the spectacle lenses reduce vision (4), contrast sensitivity and stereopsis (348,349). Children preferred MFSCLs over spectacles because they deliver a better cosmetical result (350,351), which was helpful for a good compliance with treatment regimens. Aspheric lenses have been produced included a more positive peripheral power (333,352) to compensate the more hyperopic peripheral refraction often found in children with myopia (353).

The role of the choroid

Diether at al. (354) have tested whether defocus presented to local retinal areas can produce local differences in eye prolongation, even if the available accommodation is able to clear the imposed defocus partially. Chickens hatched eleven to fifteen days ago started wearing hemi-field lenses for 4 days. That defocus from negative and positive lenses was locally compensated, suggests that the retina can admit the sign of defocus without help of accommodation. Bowrey et al. (355) confirmed, that peripheral defocus-induced ocular elongation circumscribes the peri-papillary zone, no matter what sign of the inducing defocus. Tse et al. (356) concretized: the chick retina can recognize both the sign and the power of optical defocus and adapt their refractive development accordingly. Nickla et al. (357) from the NECO, Boston, see predictable changes in choroidal thickness too, happening in response to visual stimuli that are also known to influence axial growth and refractive error development.

Recent research (34) utilizing methods to image the choroid have confirmed that the human choroid can change rapidly its thickness in response to a blurry retinal image at least in the short-term (302,358), found recent research using high-resolution OCT technique. But the magnitude of reaction is smaller than expected from animal models. The next figure provides an overview of these changes in choroidal thickness observed in response to received blur. The short-term nature of these thickness adaptations is not to be seen as a definitive link between choroidal adaptations and myopia, it seems to be rather a biomarker for the signals underlying changes in longer-term axial growth.

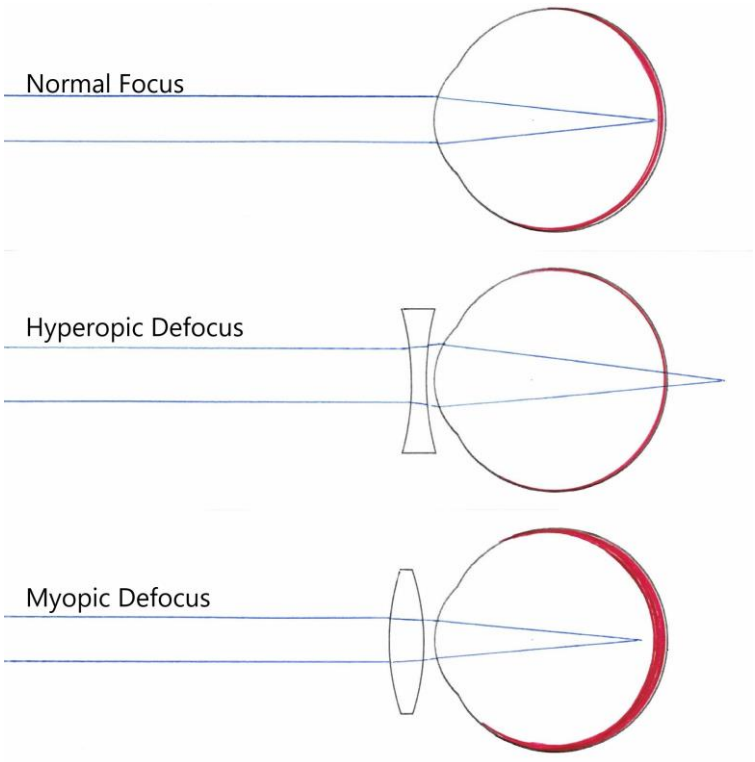

Figure 18: short-term adaptations in choroidal thickness

Figure adapted from Read et al. (34): this diagram illustrates the short-term adaptations in choroidal thickness (red tissue) that occur in humans as reaction to optical blur. With clear distance focus (top), the image is focused directly on the retina, choroidal thickness remains at base level. With hyperopic defocus (middle), the image is focused more behind, and a minimal thinning of the choroid occurs. With myopic defocus, the image is focused too early, and a minimal choroidal thickening happens. The observed choroidal adaptations move the retina in the direction of the focus point. In animals, these choroidal adaptations are the first step to longer-term changes in axial growth and refractive error development responding to optical blur.

New information I found in the study of Sander et al. (359). They found recently, that homatropine blocks the thinning effect of hyperopic defocus on choroidal thickness, but it was not able to enhance the thickening effect of myopic defocus.

Many different cross-sectional studies using OCT imaging in confirmed in healthy adults the association with thinner choroidal thickness with higher myopic refraction (34) and longer eyeballs (360). Accordingly, children with myopia show thinner choroids compared to children with no refractive error, proposing that choroidal thickness reduction associated with developing myopia is likely to be one of the first steps in the process of refractive error development (361,362).

Only a small number of longitudinal studies of choroidal thickness in childhood have been published (34,363,364). Examined over a one-and-a-half-year period, the choroid of more than 100 Australian children aged 10 to 15 years underwent a significant increase in thickness over time. Eyes with more choroidal thickening were significantly related to less myopia development, in eyes with less thickening faster axial elongation happened (363). An inverse association was found between choroidal thickness changes and the rate of axial elongation in children (363): the more quickly the eye grows, the thinner the choroid. These findings were confirmed by Fontaine et al. (364). Children exhibiting thinning of the choroid need to be monitored closely for possible myopia development and progression, because a small thickening over time is normal and not a thinning (34).

In children with high myopia over 6 D or an axial length of more than 26mm, the choroid is substantially thinner than normal (365–367). There is confirmation that this marked choroidal thinning plays a role in the pathogenesis of vision loss (366) and there are associated pathologies like staphyloma, myopic maculopathy, and lacquer cracks (303,365,367,368). Choroidal thickness measurements in high myopes are supposed to be useful in the recognition of patients at risk of developing ocular myopia associated pathology. Wang and colleagues (303,368,369) found a strong relationship between the presence of lacquer cracks and thinned choroid in high myopic patients, if the central choroidal thickness was less than 59µm; this is predicting the presence of lacquer cracks with solid sensitivity and specificity.

In a recent study, Breher et al. (370) investigated the effect of the optical design of multifocal contact lenses on human choroidal thickness. They did not find a proof that the hypothesized choroidal thickening happens significantly in short-term wear of MFSCLs. The difference between the SV distance CL control group (+0.9 ±11.2 µm) and the most effective MFSCL (+2.1 ±11.1 µm) was too small (all p >0.05). Therefore, they concluded, changed choroidal thickness might not be the main driver to the protective effect of MFSCLs in myopia management.

Although the choroid's exact role in visually guided eye elongation is still not completely understood, it has been suggested that the choroid may send signals or growth factors from the retina to the sclera (34).

2.4.2 Distance-Center Bifocal, Multifocal or Progressive Contact Lenses

In the last years many different soft contact lenses have been tested for their potential to reduce myopia progression in children (34,328,331,339,371). CLs used for myopia management can be either the rigid contact lens designs used in ortho-K (see chapter 2.4.3.), or also bifocal or MFSCLs (372). Probably such lenses reduce the myopia progression rate in children because of the reduction of accommodative lags (373). The alternative hypothesises say they decrease the peripheral hyperopic retinal defocus, which is associated with increased risk of axial elongation by shifting the image closer to the retina; and that the lenses present myopic defocus to the peripheral areas of the retina, which is considered to inhibit axial elongation (325,326). If eyes wear myopia control contact lenses, they show a significantly reduced axial growth and myopia progression than eyes wearing normal lenses. MFSCLs and Ortho-K lenses don't reduce the visual acuity much and allow normal accommodation to targets in close distances. A good myopia control lens must provide both distance correction and treatment zones within the pupil, this not only under mesopic but also under photopic conditions and during near work (56,374,375).

How bifocal SCLs work, I found in the study of Ji et al. (376). They describe bifocal SCLs as having a quite small impact on myopic shift in peripheral refractive error, while increasing depth of focus (DoF) significantly. Hypothetically an increase in DoF and a reduction of the directionally dependency of peripheral optical blur is the reason for the good myopia control effect such lenses show. Many studies describe the effects seen if peripheral defocus is presented. As an example, Ho et al. (377) described the potential of the human eye to detect optical defocus at the level of the retina. They confirmed that the retina can differentiate defocused signals signs. And Ho et al. support the idea that paracentral retina reacts more energetic to optical defocus than the macula, the center of the eye.

Distance viewing vision quality was in the study of Faria-Ribeiro et al. (378) only minimally affected by the diameter of the central distance correction and not by the chosen addition. Higher addition helped only when looking at very near distances. Faria-Ribeiro recommends higher adds just for patients with accommodation problems or those working a lot at near distances. Several different CL designs have been trialled, the successful designs have usually a distance center and a peripheral addition to produce such a

myopic defocus on peripheral retina. Test series included custom lens designs (56) and commercially available bifocal or multifocal lenses (115). Clinical trials examined the impact on myopia progression and axial growth in children, comparing to either SV spectacles or contact lenses in the control group. These studies have shown significant positive myopia control effects, with decreasing axial growth of about 30% to 50% over 2 years observed across these trials. The effect of concentric ring bifocal soft CLs is probably a little bit more intense than in MFSCLs (339). Here some examples:

Cooper et al. (328) tested the NaturalVue Multifocal 1 Day extended depth of focus (center distance) multifocal soft contact lenses (from Visioneering Technologies, Inc., Alpharetta, GA) for the slowing effect in myopia progression. The retrospectively analysed 32 children aged 6 to 19 years showed progression of -0.50 D or more with current corrections and were followed up to 25 months (mean 10.98 ±2.95 months). In this group, the annualized rate of myopia progression decreased from -0.85 ±0.43 D to -0.04 D per year ±0.18 D (P<0.0001) OD, and from -0.90 ±0.57 D to -0.03 D per year ±0.17 D (P<0.0001) OS. Cooper et al. calculated reduction rates 95.4% OD and 96.25% OS. More than 98% of the children in his group showed a decrease in myopia progression; 91% showed a reduction in myopia progression rate of 70% or more. 81.25% of the group showed complete stop in progressing myopia, included are 6.25% showing myopic regression.

In 40 children at ages 11 to 14 years already having myopia, Anstice and Phillips (56) reported a myopia progression reduction from 0.7 D per year with SV contact lenses to 0.4 D per year with multifocal contact lenses. She determined that these special lenses granted normal acuity and contrast sensitivity and helped the eyes to accommodate to near targets. Myopia progression and axial elongation were reduced significantly with these lens types. Her data suggest that myopic defocus can decrease myopia progression without reducing visual function relevantly. In 128 children aged 8 to 13 years with pre-existing myopia the near-sightedness progressed with mono-focal CLs 0.4 D per year, while with multifocal CLs only 0.3 D per year, investigated Lam et al. (117). Aller et al. found yearly progression rates of 0.8 D per year with SV contact lenses and 0.2 D with multifocal contact lenses in 86 myopic children and adolescents at ages 8 to 18 (116). These are just a few controlled clinical trials providing solid evidence (3).

So, bifocal or multifocal CLs have proven effective for myopia management (4,114,115,117,325,326,379,380). A MFSCL for myopia management shall provide:

1. an effective, financeable and save way to reduce myopia progression in patients
2. good vision at all distances
3. constant myopic retinal defocus over the largest possible area while looking in near and far distance.

Research on lens design found center-distance multifocal designs with two distinct portions within the optical zone to be effective for myopia management. They need a central part for distance correction and an outer part that has to be relatively more positively powered than the central zone (4,114,115,117,379,380). The theory of peripheral defocus says that this positive power in the periphery induces myopic defocus across the non-central retina (115,379).

In RELAX contact lenses, the diameter of the central distance zone can be chosen individually. ECP have to choose the peripheral addition wanted in the lens. The addition usually chosen are between +1.50 D to +2.50 D. Unclear remains whether increasing the addition is delivering improved myopia control (372).

If myopic children had esophoria at near were fitted with bifocal soft contact lenses with an add that was chosen to neutralize the associated phoria, the result was a up to 79% reduction in axial elongation over 12 months compared to single-vision soft contact lens-wearing controls (116).

Some research gave not clear results: Ozkan et al. (381) did not find consistent changes in the static accommodative measures lag and phoria, that's why they speculate that accommodative adaptation is unlikely to happen with long-term multifocal soft CL wear.

As the result of their comparison Vistakon Acuvue Oasys for Presbyopia (AOP) and ALCON Air Optix Aqua Multifocal (AOAMF) on new MF clients, Zollinger et al. found AOAMF had better distance vision while AOP had better comfort. CL users chose their lens on these differences and not based on clinical finding of the eye care practitioner (382).

Another new product was tested by Tom Aller (383), he found a clinically significant reduction in progression of myopia and axial elongation in children when switching to the NaturalVue Multifocal (Visioneering Technologies, Inc, Alpharetta GA), a soft contact lens with peripheral defocus. Such lens types seem to be an effective treatment for myopia management. No adverse events were reported and all children continued wear of the lenses.

The customer satisfaction was targeted by Kang and Fedtke et al. (346,384). They described, that MiSight, Proclear Multifocal Distance center and other lenses showed good VA in high contrast test situations, but patients subjective vision was reduced. For practice, quality of vision with multifocal contact lenses has to be measured with low contrast charts. Experiments with two custom-made lenses with a gradual slope instead of a steep slope of addition power helped to rise customer satisfaction.

In another study, Fedtke et al. (385,386) were evaluating the association between decentration of several commercial MFSCLs and their objective and subjective visual performance in presbyopic and non-presbyopic volunteers. Some decentred more, other less. Compared to the control, a significant decentration in inferior direction was found for the Proclear® MFSCL Distance lens in the group of non-presbyopic (non-presbyopic =-0.69 mm). In this group, a moderate but significant correlation with total MFSCL decentration was found, indicating that vision quality became worse the more the lens decentred. Such an association exists between decentration and seven out of nine vision variables.

How do children wearing multifocal contact lenses use their accommodation, and change the lenses the binocular status? Gong et al. (387) measured reduced accommodative responses and more exophoria than in children wearing SV contact lenses. Maybe the multifocal CL wearers relax their accommodation and use the addition or increased depth of focus from added spherical aberration of the special lenses.

The new demands for a peripheral calculation of a soft lens inspired engineers to produce new machines to measure the peripheral cornea. Correction of the off-axis wave front aberration is expected to be important for peripheral vision, for the diagnosis of the imaging quality of the retina, and for the influence of refractive development. A new technique with the name ocular wave front tomography (OWT) was adapted to enhance the design of contact lenses to improve the eye's peripheral optical quality. The OWT technology successfully calculated bifocal contact lens designs, from center to the periphery. This technique can be used to calculate the desired level of myopia in the peripheral field up to 45° to produce myopia control lenses of the desired level (388).

Daily multifocal soft CLs for myopia control are available from Cooper Vision too and called MiSight™ (Cooper Vision, Fairport, NY, US), presenting two zones for distance vision and two addition zones for treatment (389). Beyond 2.0 mm of diameter for distance vision, there is only one complete addition ring at around 4.0 mm, followed by another negative ring at around 5.0 mm. Again another addition ring is available for apertures over 6.0 mm. Large pupil diameters allow more effects of the treatment zones (374,389). The peripheral adds in these lenses produces a bit of blur, but most kids adapt to this in a short time. To be effective for myopia control, the lenses must be worn at least 10 hours a day, 6 days a week. Each 6 month a visit in the optometry practice is required (320) (see information brochure of CooperVision,

available at https://coopervision.com.sg/sites/coopervision.com.sg/files/misight_-_consumer_brochure_fa.pdf) (was available at 2019-05-25 18:20). Such a MFSCL is a powerful tool for myopia management: the rate of myopia progression and axial elongation was reduced in the group of 41 children aged 11.01 ± 1.23 years, SE -2.16 ± 0.94 D (21 boys, 20 girls), wearing MiSight™ lenses, compared with the single-vision spectacle group of 33 children aged 10.12 ± 1.38 years, SE -1.75 ± 0.94 D (12 boys, 21 girls). After 24 months, the myopia progression rate in the MiSight group compared to the control group was 0.45 D vs 0.74 D, $p < 0.001$, 39.32% reduction. The axial elongation was reduced in the MiSight group compared to the single-vision group, 0.28 mm vs 0.44 mm, $p < 0.001$, 36.04% reduction. The study is still ongoing. The three- and four-year results published in 2018 still show good reduction rates similar to the first 2 years, and showed that such a lens is effective in elder children, too (390). Another good thing about MFSCLs is, that we expect no rebound effects after finishing treatment, found Cheng et al. (391).

The power profiles of MFSCLs are very different: Plainis et al. (392) measured standardized plano MFSCLs from four manufacturers (Air Optix AQUA, Alcon; PureVision multifocal, Bausch & Lomb; Acuvue OASYS for Presbyopia, Vistakon; Biofinity multifocal- "D" design, Cooper Vision) to assess their sagittal power profiles. The "low" add PureVision and Air Optix lenses display even parabolic profiles, in correspondence to negative spherical aberration. The "mid" and "high" add PureVision and Air Optix CLs show bi-aspheric designs, producing different rates of power change for the portions in center and periphery. In all OASYS lenses a series of zones with the same center were measured, separated by sudden discontinuities. Biofinity lenses were measured having constant power over the central circular zone of radius 1.5 mm, followed by a circular zone where the power increases nearly linearly, the ascent increasing with the add power, and finally a peripheral zone showing a slow, linear increase in dioptric power nearly independent of the add power. The variation in power across the MFSCLs enhances depth of focus. Further factor can affect this depth of focus: decentration, pupil diameter and inherent ocular aberrations.

New strategies to combine treatments (i.e., central and peripheral defocus, spectral filters, delivering pharmaceutics, and active lens-borne illumination) in a single unit will be tested for additional effectiveness in myopia control (393).

Single Vision Soft Contact Lenses and Myopia Progression

Different studies found no statistically significant effect to slow myopia progression in children wearing single vision distance soft contact lenses (4,394). A study of Walline et al. (104) on 454 children aged 8-11 years, showed 0.06 D per year more myopia in children wearing SV lenses than in those who wore glasses, the difference after 3 years was not clinically relevant. Following the hypothesis of peripheral myopic defocus, SVSCLs do not produce myopic defocus and cannot lower myopia progression because of that lack, but MFSCL with distance view in the center and orthokeratology can.

Rigid Contact Lenses and Myopia Progression

Wearing flat fitted rigid gas permeable (RGP) lenses changed the corneal curvature in the central part, improved image quality of the retina and led to an over-correction of nearsightedness (102). Some clinical trials have been conducted on the effects of such rigid and gas permeable lenses on controlling myopia progression. The study outcomes often were limited by high drop-out rates (4).

Only 45 out of 105 children in the study of Khoo et al. remained at the final measurement after 3 years (395), the others discontinued because of bad comfort, lens dislodgement, handling difficulties, puffy lids

and lack of motivation. After study end, children wearing RGPs progressed myopia by 1.32 D compared with 2.32 D in children with spectacles. In both groups axial elongation was reported, 0.22 mm for RGP group and 0.31 mm for spectacle wearers. The difference found of 0.09 mm (P = 0.008) equals 0.23 D per year average reduction in myopic progression, but children responded very differently to RGP (4).

Other studies have found RGPs as not efficient for myopia control. A large randomized controlled clinical trial by Katz et al. (102) investigated children six to twelve years old either wearing RGP lenses or spectacles. At the final visit after 24 months myopia progressed -1.33 ± 0.84 D for RGP wearers compared with -1.28 ± 0.55 D for children wearing glasses (p = 0.64) the axial length grew similar in both groups and related good with the changes in refraction (4).

One hundred and forty-seven children aged 8 to eleven years were enrolled in the Contact Lenses and Myopia Progression Study (CLAMP) of Jeffrey J. Walline et al. (103). This randomized controlled clinical trial investigated the use of RGP lenses in myopia up to -4.00 D. The children had to wear either RGPs or soft CLs. After three years, the RGP group added -1.56 ± 0.95 D to the pre-existing myopia compared with -2.19 ± 0.89 D for the soft CL group. Myopia progression was 28.8% less in the RGP group, this was statistically significant (P < 0.001). Axial length growth was not affected by wearing RGP lenses, the effects seen in the CLAMP study could be therefore caused by changes in corneal curvature. This may give a rebound effect when RGP treatment is discontinued (4).

2.4.3 Orthokeratology

The definition of modern overnight orthokeratology (Ortho-K) is ‘controlled corneal reshaping using computer-designed RGP contact lenses to produce a controlled effect on the cornea’ (396). The FDA of the USA has approved Ortho-K in 2002 for up to -6.00 diopters of myopia and a maximum of 1.75 diopters of astigmatism. The higher the initial astigmatism power was the lower myopia control effects in long term were reported (397). Ortho-K can be used to control myopia progression and lead to a reduction of myopia progression of about 50% (122,398). The effect is produced by the specifically designed ‘reverse geometry’ by reshaping the corneal curvature (399). The lens is worn during sleep, and the central corneal shape stays for many hours in the form that was induce overnight. First to correct myopia and to see distance objects clear during the day. The Ortho-K lens shifts central tissue to the mid-periphery, which induces peripheral myopic defocus. Optically, the cornea works now like a multifocal lens with distance center. This effect does not treat the cause of nearsightedness, but some studies have also shown reduced rates of axial elongation in patients fitted with orthokeratology lenses (119,400). To make Ortho-K a clinically safe option for myopic reduction and myopic control, this requires combined efforts from practitioners, parents, and contact lens wearing children (401). The long-time successful outcome of Ortho-K is depending on a combination of correct fitting of the lenses, strict compliance to lens use and care regimen, respecting routine follow-ups, and the correct treatments to unwanted events (397,402). Adverse effects in the cornea have been associated with Ortho-K; safety and efficacy of Ortho-K lens wear in children is uncertain (399,403). Different infectious keratitis types can be caused by micro-organisms adherent to the Ortho-K lenses combined with insufficient over-night tear film exchange (402,404–406). Other unwanted events like corneal abrasions, sterile infiltrative keratitis and toxic keratitis have been reported in children wearing Ortho-K, too. Even with the new materials providing more oxygen to the cornea, the risk of developing of keratitis still exists, overnight wear seems to be the causative factor. Orthokeratology may be putting children and young adults at risk for ulcer formation and reduced visual acuity upon resolution (4). Na et al. (407) were using a contralateral eye study design in 2018, which prevented the influence of potential confounding factors, and proofed effectiveness of the Ortho-K lenses with their study. The little number of

only 9 subjects followed-up for two years in this study showed significant less axial growth (+0.16 ±0.25 mm) in the Ortho-K wearers (P = 0.095) than in the control eyes (+0.38 ±0.26 mm; P = 0.002).

Children having a lower baseline accommodative amplitude gave a greater myopia control response to orthokeratology contact lens wear, if compared to children with normal accommodation (408). Subjects that responded to orthokeratology with a larger magnitude of corneal relative peripheral power change along specific axes showed less axial growth, over 2 years. The reason therefor is probably the induction of greater amount of relative myopic defocus on the peripheral retina (409).

Another aspect is the choroidal thickness: two recent reports from China indicate significant choroidal thickening in children wearing Ortho-K for 6 months, not only peripheral as also increased sub-foveal choroidal thickening was registered (410,411). The long-term effects of this thickening are not clear, but probably leads this mechanisms to the good myopia control effects (34).

Children wearing Ortho-K lenses for 1 to 6 months showed improved accommodation functions, which could be one of the mechanisms for myopia control. Accommodative sensitivity and amplitude, accommodative lag, positive and negative relative accommodation improved seriously (412). A retrospective clinical record analysis of Ortho-K wearers (413) aged 18 to 30 years found them to be significantly more exophoric than wearers of single vision soft contact lenses (Ortho-K -2.05 ±2.38Δ; SVSCL 0.00 ±1.46Δ, p=0.005). The Ortho-K group in this study showed again better accommodative accuracy. (Ortho-K 0.97 ±0.33 D; SVSCL 1.28 ±0.32 D, p=0.009).

Ortho-K is today surveyed for a very long time: Hiraoka et al. (129) presented 2018 a long-term study of 10 years of overnight Ortho-K wear. 104 eyes of 53 participants were treated with Ortho-K, the control group were 78 eyes of 39 participants wearing soft CLs. The Ortho-K group showed a myopia progression of -1.26 ±0.98 D over the 10-year period, while the control group progressed -1.79 ±1.24 D. The difference was 0.05 D per year. The number of unwanted events was nearly the same: 119 in the Ortho-K group and 103 in the soft lens group.

Discontinuing Ortho-K lens wear at or before the age of 14 years led in the 2017 ‘Discontinuation of orthokeratology on eyeball elongation (DOEE)’ Study by Pauline Cho et al. (414) to a more rapid increase in axial length. The amount of this ‘rebound effect’ was comparable to those wearing spectacles during the initial 2-year myopia control study and greater than the Control and continuous Ortho-K wearing group. Eyeball elongation slowed again with recommenced lens wear after 6 months and reached the normal elongation level of Ortho-K wearers and control group again.

2.4.4 Bifocal and Multifocal Eyeglasses (PAL), Under-correction

In theory, binocular under-correction reduces near accommodation, thereby reducing the accommodative lag and the hyperopic defocus while viewing close targets should be reduced. Studies have tested this possible effect on the myopic progression rate of children in school ages (343,344,415). These studies found that under-correction increased, rather than decreased the rate of myopia progression (4).

Phillips (20) investigated in a small clinical trial (13 children) the effect of monovision glasses, the dominant eye was fully corrected for distance, the other eye 2 diopters under-corrected. Results indicated that the mean difference in myopia progression was 0.37 D/year (95% CI: 0.19-0.54 D/year) between the eyes, with much less progression in the under-corrected eye (P = 0.0015). As good these results were, for daily use in clinical practice is a binocular reduction needed and not just in the nondominant eye (4).

Bifocal lenses were tested for their myopia control potential in the late 1980's. Grosvenor et al. (18,416) used randomly SV glasses and bifocals with additions 1 and 2 diopters on 207 children. After three years no group was statistically different from the others. For young girls aged 6-11 years myopia progression decreased a bit, but young boys of the same age showed an increase (4).

I found a study, that found no good myopia managing effect in eyeglasses: Pärssinen et al. (337) investigated the impact of different use of myopia correcting spectacles and accommodation on myopia progression in 237 school children 9-11 years old. One group wore full distance correction for the whole day, the second group wore the glasses just when distance view was needed and the third group wore bifocal glasses with +1.75 D addition. After three years, the children wearing their distance correction for the whole day showed the slowest myopia progression, but changes in myopia progression were not statistically significant in any group (4). Similar not relevant differences between the SV and PALs groups were found by Edward et al. (27).

Cosmetically acceptable lenses for distance and near vision, Progressive addition lenses (PALs), have been used as an alternative to bifocal lenses in the study of Leung et al. (417) in Hong Kong. 79 children wore either PALs with add 1.50 or 2.00, or SV glasses for 2 years. The SV (control) group showed a statistically greater amount of myopia progression than the two PALs groups ($P \leq 0.0001$). For the SV control group, the mean changes in refraction were -1.23 D ±0.51 D; -0.76 D ±0.43 D for the group of +1.50 add PALs and -0.66 ±0.44 D for the children with the +2.00 D add, with statistically significant differences between the groups ($P < 0.0001$). There was a high correlation between refractive change and axial elongation (4).

To evaluate the effect of PALs on myopia progression in American children in America the Control of Myopia Evaluation Trial (COMET) study was launched, a randomized, multi-center, double-blind trial (418–420). During three years, four hundred and sixty-nine children were measured every six months. The results of this study showed a statistically significant lower myopia progression in children wearing PALs than wearing SV glasses ($P <0.0001$) (19). But this "statistically significant" difference was only 0.18 D and, in this value, not clinically significant. PALs showed better myopia control effects in children with lower baseline nearsightedness (≤ 2.25 D). The treatment effect was here 0.32 ± 0.11 D over three years, and only 0.07 ± 0.10 D in kids with higher baseline myopia. Children with lower accommodative responses benefited more than others from PALs ($P = 0.03$) by 0.26 D (16). The best myopia control effects showed PALs in children with larger lags of accommodation and near esophoria. No treatment effect was found in children with small lags of accommodation or near exophoria. This supports the idea for the importance of hyperopic retinal defocus at near in human myopia progression rates (4).

Different Japanese studies on myopia control with PALs (338,421,422) found also statistically significant, but clinically irrelevant, treatment effects. The efficacy of PALs was found to be better when first wearing 18 months of PALs and then SV glasses, than the other way around. Hasebe's study registered children wearing largely downward displaced PALs, in the mean glasses were 3.7 ±2.0 mm worn too deep. This decreased the near add effect on myopia retardation significantly.

It seems that bifocal glasses with near prisms are useful for a special group of patients: Cheng et al. (423) found bifocal and multifocal glasses limiting myopia progression in young persons with near esophoria, fast progression and/or high lags of accommodation. The most important step was to define the individual lens/prism combination, that produced perfect focus at close distances. This special bifocal/multifocal lens design was the best selection for myopia control. In Switzerland, such special lenses can be ordered via the swiss representative of the Swedish MultiLens company: Optidea, Gsteiggasse 2, 4523 Niederwil.

A new technique, the Defocus Incorporated Multiple Segments (DIMS) Spectacle Lens developed by the Hong Kong Polytechnic University (PolyU), shows promising first results. These spectacle lenses slowed down myopia progression by 60% in a group of children; 21.5% of the children stopped fully their myopia progression. This offers a new non-contact, spectacle lens solution to children with myopia. This new kind of lens was designed by Lam et al. (424). The Lens provides a central optical zone for the correction of the refractive error and multiple small segments surrounding the central zone for constant myopic defocus, extending to mid-periphery of the DIMS lens, declares Professor Lam, the designer of the lens. A total of 160 Chinese children at ages between 8 and thirteen wore either the DIMS lens or SV spectacles over two years. The children wearing DIMS showed 0.38 D mean myopic progression, the SV group 0.93 D.

2.4.5 Pharmacological Interventions

Atropine

The non-specific muscarinic receptor antagonist atropine can be applied by drops to the eye surface and is an effective treatment for myopia control (327,425,426). Atropine blocks the muscarinic receptors, which are found in the central nervous system and in many parts of the eye, can cause mydriasis and block accommodation (427,428). Atropine reduces the rate of axial elongation of the eye (and therefore myopia) in different species including chick (429–431), monkey (432) and humans (23). Because of atropines side effects (24,323) like photophobia due to fixly enlarged pupils and blurred vision while reading due to limiting accommodation, compliance of the children can be reduced (52,141).

How atropine really works is unclear; the theoretical amount of atropine necessary for myopia control requires much lower doses than expected from receptor binding possibilities. This leads to the suspicion that atropine does not inhibit nearsightedness by muscarinic mechanisms at all. Other binding options may be relevant including binding to alpha-2 adrenergic receptors. Agonists other than atropine binding primarily to alpha-2 adrenergic receptors slow myopia progression equally efficient (3).

An animal study on chicken discovered that the myopia-slowing effect of atropine required the gaseous transmitter nitric oxide available in the retina: if the synthesis of nitric oxide is blocked, atropine is not effective any more (433). Nitric oxide signals light to the retina, similar to dopamine. Tyrosine hydroxylase, the key enzyme in the synthesis of dopamine, controls the agitation of adrenergic receptors too, and with this the dopamine level in the retina (433).

Atropine is clinically used since the late 60's (434,435), and has been for a long time the only available therapy to slow myopia progression statistically and clinically significant, with reduced axial growth and refractive changes (4). Atropine drops can be instilled in eyes of persons of any age and are not dependent on the ability to handle contacts correctly (130). Conversely, some parents and patients are not willing to use a drug with unknown mechanism to control myopia progression (30). Most of the atropine trials show only little or none myopic progression compared with children wearing spectacles (22,436,437). The Atropine in the Treatment of Myopia (ATOM) study used either 1% atropine or placebo eye drops in one eye only, once nightly for 24 months, 400 children six to 12 years old participated (197). After two years the mean progression and axial elongation of, respectively. In the 1% atropine group myopia progression was only -0.28 ± 0.92 D, with nearly stable axial length (-0.02 ± 0.35 mm), the control group showed -1.20 ± 0.69 D and 0.38 ± 0.38 mm. The high atropine dose was tolerated well, because only 1 eye was treated at the time. No serious unwanted events were reported, intraocular pressure did not change significantly, no lenticular, optic nerve head or macular changes were reported. For allergic reactions or discomfort (4.5%) and glare (1.5%) reasons, or disturbed by blurred near vision or other reasons 15% of the children did not

use atropine until study end. Most atropine studies enrolled East Asian children; there is some evidence proposing that atropine (at least in concentrations as 0.5%) is also effective in non-Asian pediatric population (30,438–440). The higher 0.5% or 1.0% concentrations of atropine allow a treatment form with only 1 or 2 drops per week, before sleep (109,426,441,442). The problem of 1% Atropine is the big rebound effect after cessation. This effect is nearly as big as the treatment effect before, so nearly the same amount of myopia is seen after discontinuation of the drug in the treatment and placebo group. This makes Atropine 1% a good option in amblyopia treatment, but not necessarily for myopia management (107).

Low dose atropine 0.01%

Atropine 0.01% eyedrops were more effective in slowing myopia progression compared with higher doses of atropine because of less rebound effect, with less visual side effects over 5 years (109,443). This dose was generally well tolerated bilaterally (30,444). Loughman et al. (445) looked at the effects of low-dose atropine in Caucasian eyes. They found in their study no serious adverse effect. The effect of atropine 0.01% was statistically significant for responsiveness ($p<0.01$) and pupil size ($p=0.04$). A not statistically significant reduction of the amplitude of accommodation was reported. Reading speed and VA for distance and near were not reduced. Even as glare symptoms increased a bit, there was no impact on quality of life felt by the patients. Therefor this dose of atropine appears to provide a viable therapeutic option for myopia control among Caucasian eyes. Low-dose 0.01% atropine is usually not commercially available, specialized pharmacies like the Bichsel Laboratorium in Interlaken, Switzerland, have to dilute it in clean conditions (28). Atropine 0.01% appears to be most effective in pediatric population of different ethnicities with low initial myopia and is not able to control rapid myopic progression in some children; Higher concentrations of atropine could be required in such cases (446). Children eight to 13 years old should undergo at least a 2-year course of atropine treatment (447).

In the ATOM 2 study, using low dose atropine, Chia et al. (426) found the mean myopia progression over the whole five years was less in the 0.01% group (1.38 ±0.98 D) than in the 0.1% (1.83 ±1.16 D, $P =0.003$) and 0.5% (1.98 ±1.10 D, $P < 0.001$) groups. 7% of children had accommodation problems and had to wear PALs, tinted ones for the children feeling glare. 60 days after the last use of atropine, pupil size and accommodation were measured at original levels (109). In 2013 Cooper et al. (448) defined 0.02% atropine as the maximum concentration accepted for daily administration without a clinical effect. Nishiyama et al. (449) found in a small group of children receiving 0.01% atropine eye drops every day only minimal side effects after two weeks. Loughman and Flitcroft (445) found quality of life not significantly negative affected with low-dose 0.01% atropine drops. Clark and Clark (446) enrolled ethnically diverse US 60 children for their retrospective work about use of 0.01% atropine. The findings were -0.1 D myopia progression in the treatment group compared to -0.6 D per year in the control group. But 5% of the treated children showed rapid myopic progression. Low-concentration 0.025% atropine showed its potential for myopia prevention in pre-myopic children (450). The weaker efficacy during treatment is sometimes seen with anxiety (425).

Low-dose 0.01% Atropine showed in the ATOM2 study a 59% reduction in the myopia progression rate, but controversially no effect on axial growth (108). Kaymak et al. (451) found a wider pupil size in children using low dose Atropine drops: the pupil size changed from 3.2 to 4.5mm. This nearly doubled the field of the pupil, from 10.24mm^2 to 20.25mm^2.

The popular ATOM 2 study of Chia et al. (109) was limited, because of the lack of a placebo group. Nevertheless, the use of atropine 0.01% was much more popular after this study. Yam et al. (201) found in 2019 in a randomized placebo-controlled trial, that all 3 concentrations of low dose atropine (0.05%, 0.025%, 0.01%) were well tolerated by the children. After 12 months, there was a concentration-dependent response measured with a reduction of 67%, 43%, and 27% in mean SE progression and 51%, 29%, and 12% in axial elongation, when compared with the placebo group. The difference in axial elongation between the

0.01% atropine and placebo groups was not significant. But even with this fact is low-concentration atropine an effective and safe treatment to control myopia progression.

Now that atropine has shown to be effective, would there be an additional effect if combined with optical treatment option? A recent meeting abstract reported an additional axial elongation control effect after twelve months for the combination of Ortho-K and 0.01% atropine drops (452). Another study is underway (Bifocal & Atropine in Myopia BAM Study) (453) to evaluate the additive effect of the combination of 0.01% atropine with a soft multifocal lens (454). Atropine and Ortho-K are both individually useful in myopia control. Chen et al. (455), Tan et al.(456) and Wan et al. (457) studied the adjunctive effects. Wan et al. studied the combined effects on 84 patients and compared to 95 patients wearing Ortho-K alone for 24 months. Axial elongation was significantly better controlled in the combination group, the lower the myopia was the better the effect.

As an example for a combination therapy, Cheng and Hsieh (458) treated patients in two groups, one group with 0.125% atropine eye drops alone and the other with 0.125% atropine eye drops and added auricular acupoint stimulation. 73 of 110 patients finished the study. The patients of the second group had less myopic progression, less axial length elongation (-0.41 D and 0.24 mm/year) than those treated with 0.125% atropine alone (-0.66 D and 0.32 mm/year). The 2nd group showed more IOP reduction (-1.01 mmHg vs. -0.13 mmHg/year, p = 0.007). Decreasing the IOP by 1 mmHg correlated with a decrease of the myopia progression rate of 0.021 D/year (p = 0.006). The 2nd group increased the anterior chamber depth more than the 0.125% atropine alone group (0.076 mm vs. 0.023 mm/year, p = 0.0004). The combination of added auricular acupoint stimulation with low-concentration topical atropine was beneficial for myopia control.

Significant choroidal thickening has been reported by the short-term use of atropine (34,359,459). There is also interaction between anticholinergic agents and choroidal reaction to optical blur, which supports the potential involvement of the choroid in the myopia control mechanisms. Atropine seems to inhibit ocular response to hyperopic image blur (459,460).

All concentrations of atropine cause some side effects. Cooper et al. (388) explored different concentrations of atropine and reported 0.02 % was the highest concentration to get a clinically acceptable level of mydriasis and loss of accommodation. At this or lower concentration, children reported no subjective symptoms.

Atropine can slow or stop myopia progression, but it does not correct the refractive error. For this the children with atropine treatment need an additive solution for distance vision like myopia control lenses (32).

Eye doctors need to inform the parents about the off-label use, because 0.01% atropine has no FDA approval for myopia control. Most families accept this circumstance, according to Dr. Epley (461), MD, in private practice in Kirkland (near Seattle, State Washington, USA). The price for a bottle of atropine drops of typically between $55 and $85 does not hinder parents from choosing the medication.

The actual WHO clinical guidelines for children aged 6–10 years with myopia over -1.0 D and documented myopia progression over 0.5 D/year:

Treat children with Atropine 0.01% for 2 years:				
Good response:		**Moderate response:**		**Poor response:**
Almost no myopic progression (<0.5 D over second year)		myopic progression of 0.5 D to 1.0 D over second year		myopic progression >1.0 D over second year
What to do:				
Taper and stop Atropine		Continue Atropine 0.01% for a further 1–2 years, then taper and stop Atropine		May be a non-responder. Consider taper and stop Atropine
Follow subject for a year post stopping Atropine				
Recommence Atropine if significant rebound and continue frequent controls				

Table 10: clinical guideline for the use of low dose 0.01% atropine in children

Data modified from the ATOM2 study (109,427)

Atropine seems to be the better option for myopia management than Cyclopentolate: Yen et al. (462) published in 1989 a randomized comparison of 1% Atropine and 1% Cyclopentolate eye drops on the effectiveness of cycloplegics in myopia control. After 1 year, the ninety-six patients, 32 in each group, showed a mean myopic progression of -0.219 D in the atropine group, -0.578 D in the cyclopentolate group, and -0.914 D in the control group. Cyclopentolate is effective in slowing axial growth, but the effect of Atropine is better. The side effects of 1% Cyclopentolate are similar to 1% Atropine.

Pirenzepine

Pirenzepine is a relatively selective M1 muscarinic antagonist, and does not affect accommodation and pupil diameter as much as atropine, but has shown promising effects in controlling myopia progression in children (196,198,463). The safety profile of pirenzepine seemed well known from stomach ulcers and intestinal problems treatment in children (198). But several side effects were noted with 2% pirenzepine gel (twice a day) (196), but none in an US-based clinical trial (464). Pirenzepine shares part of the mydriasis effect with other muscarinic antagonists. Research found that 2% pirenzepine increases pupil size and produces a nearly complete cycloplegia in rhesus monkeys (465). Thus, the effect of pirenzepine in lowering the intraocular pressure was possibly because of the mydriatic effect on thick guinea pig lenses (those have thicker lenses than humans and other primates have) eliminating pupil block and promoting flowing aqueous fluid (466). In theory, this more selective antimuscarinic drug should result in less cycloplegia, the scientists noted that children using pirenzepine gel drops still reported difficulties with accommodation and mild mydriasis. Disappointingly, the effect on axial elongation control was small. A study found 0.19 mm in the treatment group and 0.23 mm in the control group over one year (198). A US-based, two-year multisite clinical trial found a similar small reduction in myopia progression. The axial elongation was 0.28 vs. 0.40 mm in the treatment vs control group, and didn't reach statistical significance (463). Better results showed a study from Asia: this double-masked, placebo-controlled, randomized study used 2% pirenzepine gel,

twice a day. The study found a 44% reduction of myopia progression and 39% axial elongation reduction over a time of 1 year, compared with the control group (196).

Brimonidine, Latanoprost and Timolol

In 2017, Liu et al. (467) controlled myopia progression in guinea pigs with 0.1% of the α-adrenergic agonist brimonidine alone and 0.2% brimonidine alone, furthermore in combination with 2% pirenzepine, was effective in inhibiting progressing myopia. Brimonidine reduces intraocular pressure in humans (468). The results indicated that reducing the intraocular pressure is probably a mechanism and potential option for myopia control.

The prostaglandin analog Latanoprost is very effective in reducing human intraocular pressure by improving the quality of uveoscleral flow at the ciliary body. This leads to a better control of accommodation via the ciliary muscle. This effect seems to decrease also myopia progression in guinea pigs and humans. This result opens the door for a new possible myopia control therapy form (469–471). 0.005% Latanoprost eye drops can be used to control myopia regression after LASIK treatment (472), but Timolol 0.1% gel yielded more efficient outcome compared to Latanoprost.

Timolol, a beta-blocker, is used to treat glaucoma, by reducing the IOP. A randomized study by Jensen (473) had three groups in the study: bifocal spectacles (n = 57), SV glasses combined with 0.25% timolol maleate, twice a day (n = 51), and SV glasses as control group (n = 51). The subjects were followed for 2 years, and got a measurement 1 year after study end. The results found were generally disappointing. The Timolol (1.14 D) and placebo group (1.18 D) showed nearly the same mean myopia progression over the 24-months study period. The use of Timolol reduced IOP significantly, by about 3 mm Hg, with best effects in children with high IOP. Five children showed ocular side effects of Timolol, like stinging, itching, and foreign body sensations, the cause was possibly the formulation rather than Timolol by itself (473). Alterations in ciliary muscle tone with Timolol have been reported (474), but with tendentially small magnitude. One child showed more serious systemic side effects of headaches and difficulty in breathing. These are side effects seen often with beta-blockers (464,474).

7-Methylxanthine (7-MX)

The randomized Danish study of the oral adenosine antagonist 7-MX tested 400 mg once per day over 1 year in a small human group (n = 68). The drug has been tested for myopia control in animal studies before (475). The group of shortsighted children aged 8 to 13 years included a placebo control group (476). In the second year, all children took once or twice per day 7-MX, before the treatment was terminated in all children.

The treatment effects found in this study were relatively small. The reduction in annual progression was 0.07 D. Nor reduction of axial length, neither reduction of progression in diopters reached statistical significance. The results are hard to read, because all children had been treated for at least 1 year, only from the first year was placebo data available. Children with moderate baseline axial growth rates showed a reduction in growth rates, but no effect was seen in children with high baseline axial growth rates. The treatment appears to be safe, no ocular or systemic side effects were reported (464,476).

2.4.6 Surgical Interventions for Controlling Myopia Progression

Because myopia is caused by abnormal long axial length as a by-product of lower collagen synthesis and higher collagen degradation (475), a thinner sclera and more biomechanical instability are the result. After the emmetropization process, most myopia is irreversible. The axial elongation leads to thinner retina and choroid (366,477,478), which leads to complications like retinal detachment, retinoschisis, myopic maculopathy, and choroid atrophy (310,479). In patients with higher myopia, the ocular motility can be disturbed by the stretching of the muscles, this can lead to strabismus. The orbital space is more and more filled by the prolonged eyeball.

There are 3 procedure categories for rising the stability of the sclera, by preventing further axial elongation:

1. scleral reinforcement surgeries, such as posterior scleral reinforcement (PSR),
2. injection-based scleral strengthening (SSI), and
3. collagen cross-linking scleral strengthening (CCL)

Clinically, only PSR has been used frequently in high myopia. But PSR can only be performed under general anesthesia. Very different materials have been used, like fascia lata, lyophilized dura, strips of tendon, aorta, and donor sclera (464).

Posterior Scleral Reinforcement (PSR)

Ward et al. (480) published in 2009 a retrospective study of adult myopes (-9 to -22 D), comparing 4-year results. Eyes operated with PSR showed an average axial growth of 0.1 mm compared with 0.8 mm for the untreated other eyes.

The challenging surgery can lead to minor complications, like elevated IOP, anterior uveitis, choroid edema, retinal hemorrhage and detachment as well as muscle imbalance (481).

Injection-based Scleral Strengthening (SSI)

This treatment involves injections of chemical reagents under Tenon's capsule. The idea is to biomechanically stabilize the collagen matrix of the sclera. There are not many reports about the efficacy of SSIs in controlling myopia: Golychev et al. (482) reported stabilization in 61% of eyes after approximately 24 months, while Avetisov et al. (483) found nearly 80% of the treated eyes stable after 12 months of injection.

Collagen Cross-linking for Scleral (CCL)

Unstable corneas are worldwide more and more treated with CCL, to strengthen the structure of the tissue (484). The reason for instability can be diseases like keratoconus, or complications of refractive surgery. The good results of CCL use on corneae led grow interest to use this method for scleral tissue as well. Wollensak et al. performed in 2004 scleral CCL with different agents, like glyceraldehyde, genipin, or riboflavin and ultraviolet-A light (485). This cross-linking was very effective, and strengthened the sclera over a time of 8 months. An animal study on rabbits has proofed the positive effect (486). But the effect depends on concentration and treatment time, and most testing of CCL has been limited to animals (464) or human sclera outside a living body (487).

2.5 New Ideas

This section introduces new ideas. These are just ideas and most of them are far from being used in everyday practice. However, they are promising, so further studies in this direction are desirable.

In 2018, Liu et al. (488) found in a cross-sectional study of children at ages 6-12 years in China that the prevalence of nearsightedness was significantly lower in breastfed children (51.8%) than in non-breastfed children (64.7%) ($P = 0.029$). Additionally, the duration of breastfeeding (never, <6 months, 6–12 months, and >12 months) was correlated with the prevalence of nearsightedness ($P = 0.043$).

Spending time outdoors with any kind of activity is one of the most important environmental factors for managing nearsightedness. We know from Torii et al. that violet light (VL, 360–400 nm wavelength) suppresses the progression of nearsightedness. First was an animal study, they confirmed that VL slowed axial length (AL) elongation in chicks. As a next step, they analyzed retrospectively the AL elongation among children with nearsightedness who wore eyeglasses (VL blocked) and 2 types of CLs (partially VL blocked and VL transmitting). By comparing the data, they found, that the VL transmitting CLs suppressed nearsightedness progression best. These results suggest that VL should be one of the important outdoor environmental factors for managing nearsightedness. Because VL can be excluded from our modern society due to excessive UV protection, exposure to VL may be a preventive strategy against the progression of nearsightedness (489,490).

The progression of nearsightedness and axial elongation showed significant correlations with many components of corneal higher-order aberration (HOA) ($P < 0.0001$ to $P = 0.0270$). Multivariate analysis showed that the total HOA of the cornea was the most relevant variable to myopia progression and axial length growth ($P < 0.0001$). Eyes with larger amounts of corneal HOAs showed less progression of nearsightedness and smaller axial elongation. This suggests that corneal HOAs play a role in the refractive and ocular developments in kids (491). The findings of Lau et al. (492) support the potential role of HOAs, image quality and a vision-dependent mechanism in eye growth in kids.

Zorena (493) presented 2018 her ideas about nonpharmacological therapeutic possibilities of nearsightedness prevention in young adults. Her special focus was myofascial therapy, osteopathy, and massage of acupuncture points surrounding the eye.

Mesenchymal stem cells (MSCs) are well known in several clinical fields in regenerating or reconstructing of connective tissue. This makes them excellent candidates for scleral treatment, transplanted MSCs are expected to differentiate into fibroblasts and strengthen the sclera by producing collagen and extracellular matrix. This should help against axial growth and control myopia progression (494). Genetic Engineering of MSCs could make it possible, that MSCs can also produce dopamine, a substance shown to be effective for myopia control. The injection of these engineered MSCs into the sub-scleral space with a micro-needle is only minimally invasive. The use of engineered MSCs is an attractive concept, could be a safe technique and is expected to be available in the near future (494).

Omar et al. (495) investigated in 2018 the effect of oral Difrarel, a bilberry extract, on myopia progression of highly myopic children and its course after discontinuation. The treatment and control group had each 32 eyes of 32 patients. The mean age was 9.34 ±2.27 years in the treatment group, 9.33 ±2.2 years in the control group. Mean refraction and axial length at beginning of the study were −10.78 ±2.6 D and 23.7 ±1.2 mm, respectively, in the treatment group, and −10.5 ±2.55 D and 23.9 ±1.4 mm in the placebo group. Refractive error and axial growth measurements were taken every 6 months. The treatment group used Difrarel for 1 year, followed by 1 year without the drug. After 2 years, the treated eyes showed a mean annual progression of 0,195 D, the placebo group 0.9. The difference was statistically relevant (p=0.01).

3 Example for fitting a Customized Myopia Control Contact Lens

3.1 Fitting Parameters

Fitting CL

All clients presenting with nearsightedness should be judged for their risk of myopia progression based on age, ethnicity, family history of nearsightedness and past history of progression. A non-cycloplegic refraction can result in too high myopic refraction, the difference to cycloplegic results is greatest in younger children and those showing low myopia, emmetropia and hyperopia (496). Because of this, ECPs should know that their patient classified incorrectly as having myopia has probably none, or the magnitude of nearsightedness could be lower than the amount found in non-cycloplegic measurement. A (modified) Humphriss binocular balancing technique can reduce the difference to cycloplegic refraction (497). Based on the risk profile, ECPs can decide to recommend the fit of MFSCLs (372).

Just more than 90% of lenses fitted are soft CLs (498). Soft lens fitting as a science and as a skill has played nearly no role in science over the last twenty years. The share of frequent replacement and disposable soft lenses in the contact lens market has grown, so the fitting process of soft lenses has been reduced on the choice of the brand of the lenses and handling instructions in many cases. “Silicone hydrogel materials accounted for 76% of soft lenses prescribed and for more than 90% of fits in four markets”, writes Morgan (498) in his 2018 report. Because these new materials have a higher modulus than conventional soft lens materials and are stiffer on the eye due to this, some basic knowledge of lens fitting is useful. Measuring techniques developed in the last years, from having only central keratometry to limbal-to-limbal topographs, and now to instruments that deliver additional information of the area beyond limbus such as OCTs (499–501) and superficial eye profilometry (502,503). These new instruments help us to analyze the shape of the corneo-scleral profile (CSP) also known as corneo-scleral junction (CSJ) and the anterior surface. Each CSP is unique, significant differences are found among quadrants and ethnic groups, so have Caucasians deeper and/or more irregular CSP than Asians and Latinos do. The deepest CSP profile and/or most irregular CSP surface are found in the nasal direction. The less vertical CSP heterogeneity, the more comfortable is the soft contact lens wear (504).

Studies by Hall et al. (505) have shown that there is a direct association between CSP shape and soft CL fitting characteristics. And we have also a better understanding of the shape and geometry of the soft CLs we use today (506). A lot of new materials, contact lens solutions and even new replacement frequencies came on market, but we face still high drop-out rates (507,508) as implied at the 2014 BCLA Conference.

Fitting of traditional (like RELAX) or silicone hydrogel CL requires slightly less visits and diagnostic lenses than fitting RGPs. The number of visits and diagnostic lenses required between traditional and silicone hydrogel CLs is the same (509).

New fitting and evaluating ideas can be helpful (510). 2014, a workshop was held in the Netherlands with Helmer Schweizer, from EUROMCONTACT, Matthew Lampa, Mark André, both from Pacific University College of Optometry in Oregon (USA), and Marco van Beusekom, conference president of the Nederlands Contactlenzen Congres, building a “consensus group”. The goal was to find out how soft CLs are fitted today. Results were published in the Contact Lens Spectrum issue of June 2014 under the title ‘The Future of Soft Contact Lens Fitting Starts Here’ (511). Here the highlights:

1. Keratometry

Measuring central corneal curvature is still necessary for the fit of soft CLs. But it is needed for the documentation, to realize later changes. It is the main myth in the contact lens field that this central keratometry measurements are enough to be able to fit a soft CL correctly. It can also be used to decide what type of lens to choose: RGPs are another option for the correction of corneal versus refractive astigmatism. But alone with central corneal data, the performance of the soft lens on the eye surface cannot be predicted. Young (512) and Gundel et al. (513) stated that they found a very weak correlation between the central and peripheral corneal curvature and SCL fitting characteristics. Using sagittal height data instead of central keratometry has been suggested for many years (512,514,515). The IACLE basic module on soft lens fitting (516) of the international association of contact lens educators is teaching the sagittal height fitting method to better understand the soft CLs behavior in vivo. Registering the total sagittal height of the lens makes sense in theory. But most CL producers give no information about the sagittal height of their product, and the method is useless to separate one lens from another, because lenses can have the same sagittal height but different diameters and/or different back side geometries. It remains unclear how a dehydrated lens would have changed the movement on the ocular surface (506).

Diameter

From a clinician's standpoint, the lens diameter can be most useful measurement to approximate the relative sagittal height of the cornea. Taking the horizontal white-to-white measurements of the cornea is one of the most used options. Typical horizontal WTW diameters are between 11mm to 12mm. Caroline and André (517) found an average WTW of 11.8mm, ranging from 10.2mm to 13.0mm. Half of the 200 right-eye corneas measured between 11.6mm and 12.0mm. A quarter was smaller than 11.6mm and another quarter bigger than 12.0mm. Clients with the normal WTW between 11.6mm and 12.0mm showed a high fitting success rate, while for the other groups fitting had to be corrected for final fitting (42). If the iris isn't an exact circle, a good measurement direction is at axis 45 or axis 135 for the average corneal diameter. It is in the responsibility of the ECP, that eyes with non-standard values are fitted with custom-made lenses. The association between visible iris diameter and corneal curvature is: the steeper the cornea, the smaller the corneal eccentricity, the larger the diameter, the bigger the sagittal height.

The normal value that is added to the horizontal WTW diameter to calculate the soft lens diameter is 3 mm, for each side 1,5 mm overlap. The findings of Wolffsohn et al. (518) suggest that soft lenses may be worn larger than optimal without any loss of either comfort or ocular physiology. This is important to know when we cannot access an optimal fit otherwise.

2. Base curve

Ensuing up on the myth discussed before: the notation of the base curve on a monthly soft lens package may be different from the real curvature of the back-surface radius, at least not equaling the one in the back-surface optic zone. In many cases, '8.3' or '8.6' mm is the calculated base curve equivalent, indicating the radius of a sphere that would have the same sagittal height over the given diameter. The sagittal height is driven by the back-side curvature and the lens diameter. So, a single number on the lens box cannot describe the lens design or its fitting behavior; total sagittal height and back surface form are therefore more important. The base curve of a soft CL shows a very low correlation with the central keratometry of an eye (519,520). Theoretical success rates for a single available base curve lens range from 60.7% (95% CI 7.2%) to 90.2% (95% CI 3.7%) (521). These calculations are based on classic hydrogel and newer SiH SCLs and an on-eye shrinkage of 1.0 to 2.3%.

As Legerton (522) describes, the more away from corneal center, the greater is the variation in corneal sagittal height. So can a variation of 3 mm be seen at a 14 mm chord.

3. Lens centration

The corneo-scleral junction or profile (CSP) is very often reported as having tangent angles, instead of concave or convex forms. New study results (500,501) showed that the CSP in an average eye beyond the cornea is normally nonrotational symmetrical. OCT imaging has showed that the transition from cornea to sclera is relatively straight shaped (523). Hall et al. (501) showed in 2013 that different CSP shape produces different CL movement.

The so-called chord is the defined diameter on which the calculations for the total sag height are performed. The distance from this base, the chord, to the top of the sagitta is the sagittal height. Normal eyes show roughly 3,700 microns for a 15 mm chord with a standard deviation of about 200 microns, according to studies at Pacific University (524).

Ritzmann (525) has analyzed the anterior scleral shape with a Zeiss Visante AS-OCT. The anterior eye was found to be nearly rotationally symmetric at chord length 12.8 mm, and became more asymmetric at a chord of 15.0 mm the shape became more asymmetric and individual. The median sagittal heights of the different segments at a 12.8 mm chord were between 2890 µm and 2940 µm; at the 15.0 mm periphery between 3680 µm and 3790 µm. The nasal segment showed more concave corneoscleral transitions, whereas temporal segments had usually tangential or convex corneoscleral transitions.

The whole nasal portion shows typically flatter curves compared to the other quadrants. Consequently, due to the greater elevation in this area, the lenses are decentered to the temporal side. This decentration is of interest by fitting the multifocal RELAX contact lenses.

Another myth says that SCLs with larger diameters lead to less lens decentration. Using todays knowledge about the nasal ocular portion can pilot us to rethink. Larger lenses probably just decenter more temporally. As white to white diameter are very individual, different lens diameters are to be chosen. For example, Asian eyes show a smaller average diameter than Caucasian eyes, and need smaller lens diameters. In summary, CL diameter can be a better predictor for lens centering than the base curve.

4. Lens movement

With the old, not as oxygen permeable lens materials, a soft CL with 1 mm of movement was suggested as a healthy optimal fitted lens. But because an average white-to-white corneal diameter is around 11.8 mm while an average soft CLs diameter is around 14 mm, this let the lens touch the limbal zone during blinking, leading to discomfort. Today's soft CLs are often moving around 0.3 mm during blinking process. CL wearers with lenses that move in the 0.1–0.4 mm range have the best comfort, discovered Troung et al. (526) in their study.

The fact that silicone hydrogel (SiH) lenses move less than the classic hydrogels is not only due to the material component, says the consensus group. Factors like lens edge shape and back surface form and many more seem to be involved.

Soft contact lenses that show no or minimal movement may be the most comfortable ones (527). Unfortunately, this allows only very little tear exchange. Fresh tears all around the lens is considered essential for good eye health. Too tight lenses can lead to inflammations, and corneal infiltrates, whose may be a response to the toxins liberated from the debris held back in the tear film behind the CL. A significantly higher level of corneal staining was found in tight fitted lenses, in 68% of the wearers (P=0.001) (528).

Non-moving lenses in general should make us nervous, says the consensus group unison. A tight lens or lens edges that press into the conjunctiva may be more pleasant to patients than a well-fitting lens, but is not good for their long-term ocular health. Initial comfort is not a good predictor of fortunate long-term CL

wear. And as clients don't like to have their comfort lowered during fitting process, the fitting of a tight, high initial comfort CL has to be chosen carefully.

Further factors to judge the lens fit are physiological signs like wider blood vessels, impingement of the blood vessels of the conjunctiva and corneal staining. Impression rings on the conjunctiva show not enough evidence as a useful indicator of a soft CL success or failure. As we see in scleral lens fitting wearers can be very happy and comfortably wear their lenses even with significant impression into the conjunctiva.

Soft CLs can alter the corneal topography, similar to RGPs. This "corneal warpage" caused by a suboptimal soft CL fittings are more common as many may think. If CL wearers would be asked to remove their soft CLs at every follow-up visit and ECPs measure the corneal topography, the amount of unwanted changes beneath a soft CL would be surprisingly high (529–532). The better the lens fit; the less changes are expected. Many unsuccessful refractive surgery results are caused by corneal warpage by bad fitted lenses and wrong corneal readings because the corneas didn't have had sufficient time to reorganize (524). And how long to wait? Ng et al. suggested in 2007 to wait on average 35.1 ± 20.8 days until pachymetry reached stability (533).

Loose fitted lenses caused on the eye a higher level of corneal staining: 69% vs 39% (P=0.04) and more bulbar (P=0.03) and limbal hyperemia (P=0.006) (528).

Thickness, material, and optic zone size, among others, influence the overall fit of a CL.

Lens Thickness: the optimal lens thickness is the thinnest possible one by fulfilling the requests of good manipulation, durability, comfort, oxygen permeability and patient skills (42).

5. Potential future steps

For lens designs with lower success rates, incompatible lens diameter was the most seen contributor to failure (521). More diameter options would be highly preferred for daily and monthly lenses, respecting this. Sagittal height information may be not the perfect measurement, but information on this would be a good indicator for changes can be expected when switching from one lens brand to another. To know the back-surface design, mono-curve, bi-curve, tri-curve, aspherical or spherical, helps ECPs to better serve their clients. The big overview listings like the ACLM Contact Lens Year Book (available through the BCLA for members) or US-based Tyler's Quarterly miss this information. Fitting CLs perfectly is not solving all of the Cl problems (534), but can lower the drop-out rates.

Examination flow

All scheduled patients shall first get an ocular health examination. All myopia management evaluations should begin with a patient education that includes all aspects of myopia management options, risk factors and costs.

Because myopia management leads to a long-term relationship between ECPs and patients, latters should be inspired to ask questions. ECPs have to take as much time as necessary to explain myopia management. The parents of pediatric clients must be involved in the process from the beginning to help ensure compliance.

The measurements

Next, a complete myopia control evaluation is to be done, first the evaluating of the spherical equivalent refractive error adjusted for vertex distance and the amount of astigmatism (372). Regular or irregular astigmatism has to be separated (for irregular astigmatism a thickened MFSCL can be a solution). Next measurements include distance and near VAs, pupil testing, cover test, accommodation tests. After this a slit lamp bio microscopy for safety and binocular vision monitoring reasons has to be done. Scientific research showed that clients who have large pupils may benefit more from Ortho-K compared with small pupil clients, so the result of the pupil test will also guide an ECP's myopia management selection (374). Further on, corneal topography is performed to guide CL selection, also by the corneal eccentricity, the rate at which the cornea becomes flatter from center to periphery. This is the anatomical feature that has the second most impact. If available axial length is measured with non-contact biometry, and refractive status is evaluated whenever possible in cycloplegia.

Staff education is relevant to run a successful myopia management practice because staff members are usually the first persons who interact with clients. Good educated staff makes sure that clients are receiving correct information about myopia and myopia management.

After this first evaluation, the results are presented to the patients and suitable myopia management treatments are proposed. All clients should be scheduled for a half-yearly check-up to observe myopic progression and axial elongation as well as compliance.

Pucker states, to his experience, that MFSCLs are the cheapest option, followed by atropine and Ortho-K CLs (28). If the client chooses CLs, today's contact lens types include RGP corneal, hybrid, soft or scleral lenses. For myopia control reasons the last two offer solutions to be worn as MFSCL or Ortho-K lens.

Patients generally don't like the first minutes of wearing CLs but adapt usually quickly (372). ECPs should wait with visual performance testing until about half an hour after putting the lens on the eye. Because MFSCLs symptoms like ghosting, poor contrast and haloes are highly associated with decentration, clinicians should measure and reduce the lens decentration and movement before directing their interest on visual performance. If ECPs perform over-refraction, they should use a trial frame for this rather than a phoropter, to reduce errors related to head tilt and maneuvers behind the phoropter.

Fitting strategies

For soft CLs fit exists no sound scientific basis compared to GP lenses, which are typically fitted based on keratometry. Fitting soft lenses calculated on predictable ocular factors may limit the trial-and-error aspect of fitting soft CLs (42). Aberrometers, which can measure refractive errors very exactly, are more and more available in eye care practices.

What we know is:

First, lens diameter and base curve are the most used parameters describing the CL design.

Second, the major corneal shape measurement is the corneal sagittal height because it is defining the most appropriate contact lens-to-cornea fitting association. Central radius, corneal eccentricity, horizontal white-to-white diameter, peripheral corneal slope and radius of the para-limbal sclera (CSP) all contribute to the sagittal height.

The reason why fitting soft CLs just on central keratometry is difficult, is that these parameters come from four measurement points within the central 3mm of the cornea (42). Choosing contact lenses on this obviously thin data base leads to error. Even if fitting on keratometry data is over-simplified, the majority of clients are successfully fitted. But for some patients with data out of the norm this technique doesn't work.

Factors that Improve Soft Lens Fitting

Base Curve Choice on K readings and WTW Diameter

A popular method of base curve selection is adding about 0.8mm for small diameter lenses to 1.0mm for large diameter lenses to the flatter corneal radius. Material type, lens thickness and water content all affect base curve calculation. Lens dehydration, lens glide and stiffness, tensile strength and fitting parameters are differently dependent on the lens material characteristics (42).

Corneal Diameter	Add to flat K
10.2mm	-7.00 dpt
10.6mm	-5.00 dpt
11.0mm	-3.00 dpt
11.2mm	-2.00 dpt
11.4mm	-1.00 dpt
11.6mm	0.00 dpt
12.0mm	0.00 dpt
12.2mm	1.00 dpt
12.4mm	2.00 dpt
12.6mm	3.00 dpt
13.0mm	5.00 dpt

Table 11: Corneal Diameter Compensation

Table adapted from Davis et al. (42) - Corneal Diameter Compensation, adapted from data of Caroline and André (517)

The conversion table from the Contact Lens Manufacturers Association for radius in K reading to mm is available at https://www.gpli.info/conversion-charts/ (was available at 2019-05-25 18:30) or in the appendix.

As an example, for a WTW of 12.2mm and K readings of 43 D x 44 D, as seen in the table above, 1 D must be added to the 43 D flat base curve. The corrective base curve is calculated as 44 D or 7.65mm.

Now, for the final hydrophilic base curve a further correction is calculated: because an ellipse is the base for the measurements and not a straight line, 0.3mm are added to the adjusted base curve radius of curvature to the final curvature of the back side of the lens. We ordered a soft lens base curve for this patient of 7.95mm. These calculations were based on GMA (hioxifilcon A 59 percent) material that shows little lens shrinkage throughout the wearing day. The lens will now fit 1.00 D to 2.50 D flatter than the adjusted base curve. The flatter the central K values, the smaller the adaptation in diopters. The steeper the central K values, the larger the adaptation in diopters (42).

To recall these soft lens fitting guidelines is the "Rules of 3" (42):

- Adjusted base curve in mm + 0.3mm = soft lens base curve
- Corneal diameter (WTW) in mm + 3.0mm = lens diameter

Determining Lens Power

ECPs usually convert the sphere and cylinder to cross-cylinder form and then calculate the strongest and weakest meridian separately to convert it to the corneal plane using the calculation formulas, Vertex Charts or apps before reconverting to a minus-cylinder refraction in CL vertex distance (42). The formula is:

$F_c=F/(1+x*F)$, here is F_c the power corrected for new vertex distance, F is the original lens meridian power, and x is the change in vertex distance in meters. For x: coming closer to the eye results in a negative value for x (535).

English converting software from CooperVision is here https://coopervision.com/practitioner/tools-and-calculators/spectacle-conversion-calculator to find, a German version here: https://www.linsenrechner.de/

Fitting the Lens

As described previously, for any soft lens choice, many factors together form the total sag height of that cornea and lens; central keratometry, numeric eccentricity, CSP and the shape of the sclera are involved (524).

With a simple push-up test is verified that the lens is moving and not fit too tight, because most lens materials can lose up to eleven % of their water content over the course of the day and are tighter after hours of wear (42). The VA test and over-refraction with the in vivo lens has to be done after total lens adaptation.

A good indicator for CL fit is the quality of the keratometer mires (for those who still own a keratometer…) or retinoscopic reflex. A steep fit shows clear but wobbly mires instantly after the blink, but then begin to be distorted and blurry. Oppositely, flat fitted CLs show mire distortion that begin to be more distorted short after the blink. Visual acuity will sharpen after blinking, but then drop and the vision will be blurry. Additionally, more dehydrated lenses show a dull reflex, and less VA is measured the longer the CLs are on the eye (42).

Patient comfort is affected by lens edge awareness upon the lower lid. If the client is disturbed too much, the lens edge can be moved away from the lower lid edge by choosing a larger lens diameter or fitting the lens closer to the eye surface so the lid can slide easier over the CL to improve the comfort (42).

Discomfort can also be caused by environmental factors. The classic example is a computer worker who can't wait to get out his lenses at home, although he reports to wear them without discomfort on the weekends. Such wearers blink not frequently enough during computer use, and the air in many offices is not as humid as at home or outside, so the soft CLs dry out more in office environment.

Studies at Pacific University have promoted five main anatomical features that contribute to the sagittal height of the frontal eye segment, they are: (1) central keratometry (the inner 3.0 mm) of the cornea, often referred to as “K”; (2) corneal numeric eccentricity of the mid-peripheral, that describes the corneal shape from apex to a chord of around 10.0 mm; ; (3) the WTW horizontal corneal diameter; the corneoscleral profile CSP beginning with the corneal angle (4), that starts at the 10.0 mm chord and extends to the limbal zone, reaching finally the scleral angle (5) that begins at the limbus and is extending out to the chord of choice, i.e. 14.0 to 16.0 mm (536).

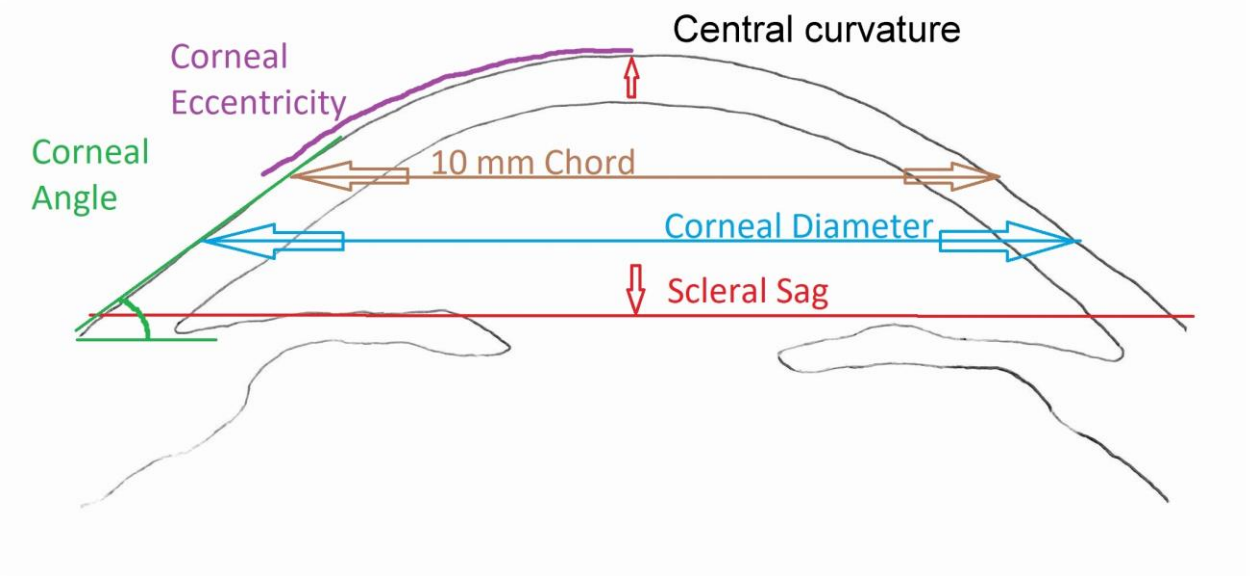

Figure 19: Five Anatomical Features that Contribute to the Sagittal Height of the Anterior Eye

Figure adapted from Contamac (536): five anatomical features that contribute to the sagittal height of the anterior eye.

Young et al. (537) discovered that for aspheric soft CLs, the numeric eccentricity has a larger influence on total sagittal height than central keratometry has. So leads a 0.12 change in eccentricity to a 0.2mm lens back curve radius change. But the lens diameter had the biggest influence. Changing the lens diameter from 14.0mm to 15.0mm in an 8.3 mm base curve CL can increase the sag height by up to a 700- or 900-micron increase depending on the lens design. The flatter the lens, the smaller this effect (524).

By keeping the diameter, changing from 8.3mm base curve to 8.7mm causes the sag height to decrease about 300 microns, the lens flattens. The impact of a changed diameter is larger than the impact by another base curve. So, if lens fit has to be adjusted: diameter change first is a good choice.

If a cornea is measured larger than normal, with small central corneal radii and with a low eccentricity, there will be the need for a lens with a huge sag height.

Horizontal and the vertical corneal diameters are not the same, the vertical is usually the smaller one. In practice the use of an oblique meridian gives some sort of an average value.

The sagittal height might become the new standard in SCL fitting, as this factor seems to be more relevant as others. Lathes, machines that manufacture CLs and that produce molds for cast-molded SCL production calculate already exclusively in height - not in curves. With an accuracy of about 1/1000 of a micron, the height can be calculated as long as there is an x, y and z coordinate. Diameter is one of these variables (524).

Low-water-content SiH materials and other new materials tighten up less than the traditional hydrogels. The lens base curve should be selected only 0.4mm flatter than the corneal central radius, rather than the usual 0.7mm for traditional hydrogels.

On objective and subjective analysis, lenses fitted between 0 and 200µm bigger than the eyes sag height were considered optimally fitted and the best option. Patient eyes can be effectively fitted with Soft CLs with ocular sagittal height as a reference instead of the central corneal curvature (527).

Theoretical Ocular Sagittal Height Considerations

The theoretical ocular sagittal height can be resolved on using the mathematical formula: Total Ocular Sag = S1 + S2 – S3 (as seen in the figure below). S1 is the corneal and S2 the scleral sagittal height, S3 the overlap zone. This is the equation to compute the theoretical ocular sagittal height:

$$S = \frac{r - \sqrt{(r^2 - p(\frac{d}{2})^2)}}{p}$$

In this formula r stands for corneal or scleral radius of curvature, p for corneal or scleral shape factor (where $p = 1 - e^2$), e for eccentricity and d for diameter (538).

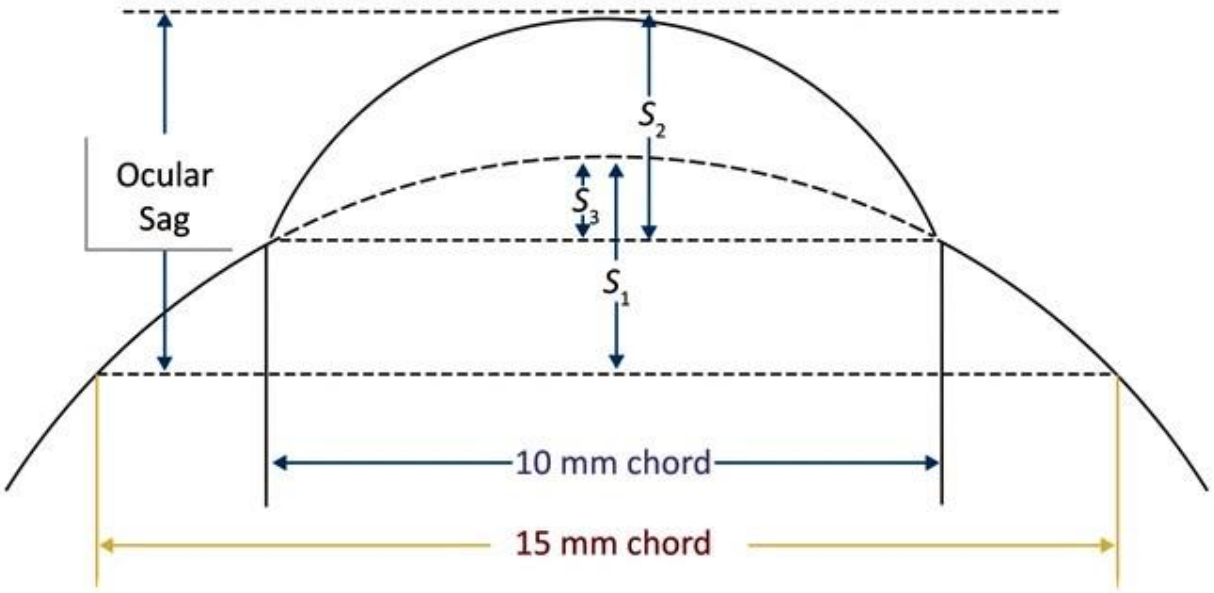

Figure 20: How to calculate the sagittal height

Figure from Gillan et al.: "The sag: A forgotten parameter in need of resurrection?" (539). Used under Creative Commons Attribution 2.0 International License.

Based on this model, Young (512) systematically evaluated the effect of different factors on sagittal height and ranked them: the biggest influence has the corneal diameter, followed by corneal eccentricity, central curvature, scleral curvatures, and scleral eccentricity.

The "normal" eye in Youngs study had a horizontal WTW corneal diameter of 11.90mm, a central corneal radius of 7.85mm, and showed a 0.55 eccentricity. A scleral radius of 18.0mm over a 15.0mm chord can be assumed. The normal ocular sagittal height in this typical eye was 3'150 µm. A variation in the diameter of this 11.9mm cornea of only 1mm larger or smaller results in very different sagittal heights of 3'510 and 2'880 µm (540–542).

Different eccentricities of the cornea have a slightly weaker effect on ocular sagittal height. So are eccentricity values of 0.30 (more spherical) and 0.70 (more aspheric) leading to ocular sagittal heights of 3'275 µm and 3'060 µm in a "normal" eye, a still clinically significant change. For the same small change, the radius of the central corneal curvature must be about 0.40mm different.

Such a mathematical model helps to understand what we calculate, but is over-simplified. A normal cornea is elliptic, a usual sclera spherical. Advances in technology help to measure quicker and more accurately the actual ocular sagittal height.

Further studies (499,505,543) provided detailed accurate corneal sagittal height measurements about the data of the anterior eye.

Nevertheless, the fitting of CLs with the sagittal height as the central fitting parameter cannot yet be described as the gold standard. The main reasons for this are: First, the contact lens manufacturers usually do not state the sagittal height of their lenses (sometimes not even on request). On the other hand, the measuring devices for determining the sagittal height of the CSP are still quite expensive and little common in ECP practices. Also, there are no definitive guidelines as to what sagittal height must have a soft CL so that it has a good fit in one eye with a given CSP (544).

Sagittal height as a central fitting parameter

One challenge in choosing the first soft fitting CL is to choose the lens to fit well, given the steepness it experiences on the eye after touchdown. An ideal individual adaptation of a soft contact lens with respect to the pressure distribution would theoretically be achieved if the back-surface profile of the contact lens on the eye (after reaching the state of equilibrium of evaporation and resumption of water) would follow exactly the CSP stress-free.

However, according to a recent mathematical model by Young (541,545), such a synchronization would provide a highly down-decentered and excessively mobile contact lens. To counteract that, for a good lens fitting, the lens must have a greater sagittal height than the ocular corneoscleral profile in the bearing area of the lens. The lens must be more exposed at the edge than at the center, which is equivalent to a slight steep adjustment, but Youngs model does not give an idea of how much higher the sagittal height of the contact lens must be in order to get a good fit. Information that the fitters need, but unfortunately this is not yet available.

First studies at the Pacific University and Maastricht University (531) showed that the sagittal height difference of lens and eye in conventional lenses must be between 200-400 microns. Using monthly CL, a difference of about 130 µm seems sufficient, whereby the spread of the value for replacement lenses was immense (546).

In order to make good predictions for the fit of a particular soft contact lens, many factors must be considered. The sagittal height alone cannot be sufficient as a criterion.

But even base curve, diameter and sagittal height together are not sufficient. The final behavior is highly dependent on material-specific properties such as modulus, temperature-dependent change in shape and water binding capacity. Future research must show how (material-) specific a crest-depth-based fitting formula must be, and what simplifications are allowed without too much error.

Corneo-scleral profile CSP

The five profiles of the CSP were defined by Meier in 1992 based on observations of the limbus using the naked eye or a biomicroscope/slit lamp. Meier only described the superior CSP. But the CSP is quite difficult to classify by eye, and lacks reproducibility (547). Anterior OCT are here helpful.

Meier described five different possibilities of corneo-scleral transition: gradual transitions from cornea to sclera, either with convex (Profile 1) or tangential (Profile 2) scleral portion; marked transitions with either convex (Profile 3) or tangential (Profile 4) scleral part; and a sinusoidal profile, with a convex cornea blending into a concave sclera (Profile 5). The profiles are arranged in decreasing sagittal depth across the classification. Profile 1 represents the greatest sagittal height and Profile 5 the smallest.

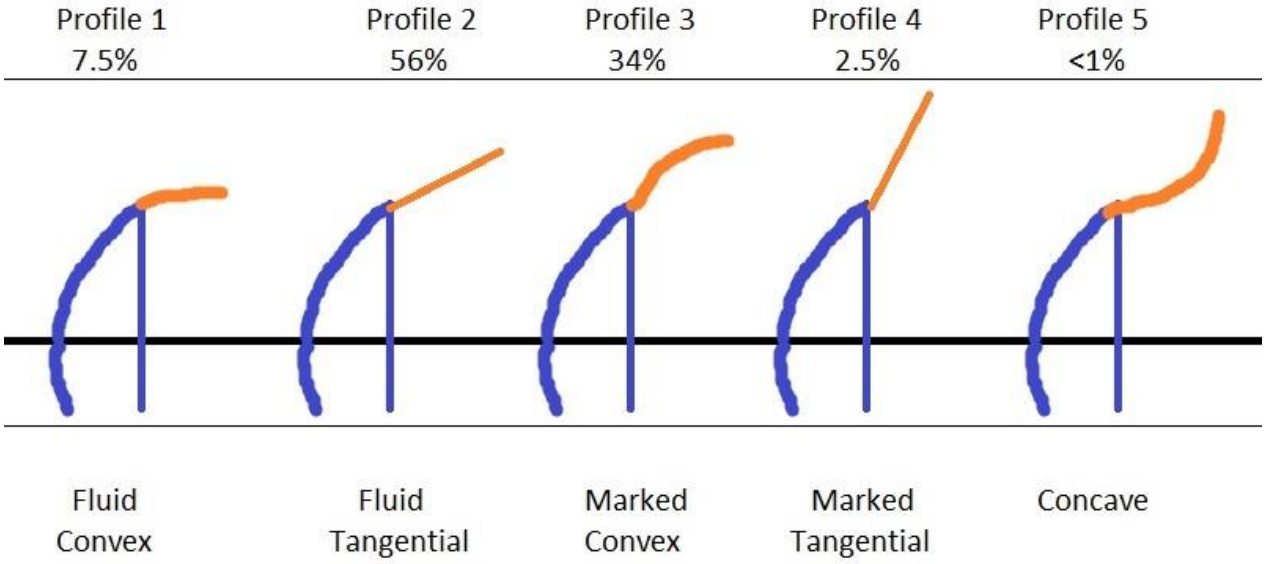

Figure 21: Corneo-scleral Profile CSP, the 5 profiles of Meier

A 2013 study by Hall et al. investigated the superior, inferior, nasal, and temporal junction angles (501). 77% of all transition angles were within ±5° of 180° and demonstrated the predominance of almost tangential profiles.

The CSP accounted for up to 24% of the variance in lens movement. The fit of the stiffer SiH material CLs was better predictable and was more varied than the classic hydrogel CLs (505).

To date, the Oculus Pentacam can detect the corneoscleral profile, thus providing the basis for an individual CL fitting. The measurement yields corneoscleral profile lines in different meridians. The CSP Report Software Module can be purchased as an option.

Recording fitting characteristics

The characteristics of a CL fit in daily practice are often simplified recorded as good, acceptable fit or poor, unacceptable fit. These records vary greatly between individual ECPs (510). We know that a lens fit cannot be predicted based on lens base-curve or material type, and that different patient react differently on these lenses (510,548). But it is necessary to record fit characteristics properly and to avoid future lens complications and drop-outs (549). From different studies we know that poor fitted soft CLs are cause discomfort, poor vision (542) and drop outs (550). Such lenses impact ocular physiology, causing bulbar and limbal hyperemia and corneal staining, compared to well-fitted lenses (528). A certain lens mobility is required to remove trapped debris, inflammatory cells and others. And it provides additional oxygen to the cornea (551). The better tear layer underneath the lens reduces also the friction between the surfaces and mechanical interaction. The tear layer on the outer lens surface prevents lid tissue disturbance (552). Previous attempts to evaluate the CL fit metrics have been mostly subjective ones, concentrating on factors such as lens centration, movement on blink, lag and push-up (542,553,554). The objective grading was differently from ECP to ECP (555). This led to the try to overcome clinical bias and lack of precision by recording the movement on blink objectively from video (556). The usual way was to film the lens movement through a slit lamp and using a ruler to make measurements off a monitor (556–558). Other factors of lens movements like lag and push-up recovery speed have not been objectively assessed (557–560).

The hypothesis of the study of Belda-Salmeróna (560) was that objective assessment of CL fit deliver the same key parameters as subjective analysis, but with higher repeatability and resolution. For the 4 main lens fit factors, objective and subjective assessment delivered similar results. Surprisingly, subjective measures were as repeatable as objective measures. But with lower precision as with objective measurements. In conclusion, the outcomes of the study show that objective image analysis is precise in evaluating soft contact lens fit, showing higher sensitivity and reliability than subjective grading.

Decentration

Certain MFSCLs like e.g. the Proclear® Distance-type lens showed more temporal-inferior decentration in than others in non-presbyopic patients, found Fedtke et al. The decentration in this case of 0.69 mm induced significant aberrations of the third order, about tenfold the lens-induced vertical coma (3,-1). MFSCL decentration is associated with seven out of nine vision variables in young non-presbyopic patients. Young adults with larger pupil diameters and less third-order corneal aberrations by nature wore the most decentered lenses, decreasing vision the more the lens decentered (385).

Non-presbyopic MFSCL wearers unlikely adapt their accommodative behavior in long-term lens wear (381).

Searching the database of 11'624 spectacle prescriptions, Young et al. found commonness of patients showing astigmatism of 0.75 D or greater in at least one eye was 47.4% and in 24.1% both eyes. Myopes showed nearly double the prevalence of astigmatism >0.75 dpt than hyperopes: 31.7% vs. 15.7% (561).

3.2 Manufacturer-specific fitting guidelines

Contact lens producers usually provide fitting guides, to help ECPs finding the final lens faster. Here some examples, let's first have a look at Swisslens:

3.2.1 The SWISSLENS Fitting Guide

The SWISSLENS fitting guide is not only for the RELAX contact lens. The lens has to be calculated like a normal individual customized contact lens.
Especially for the RELAX myopia control lens exists also the free "Toolbox" calculator: https://www.swisslens.ch/experts/toolbox/ (was available at 2019-05-26 13:33).

Step 1: Finding Diameter and Base Curve

The needed measurements are: corneal diameter = visible iris diameter +0.6 mm; and keratometer readings K_{flat} and $K_{steep.}$

Calculation of the lens parameters:
Spheric: Contact lens diameter = Corneal diameter +2.1 mm; Base curve (BC) = K_{flat} +0.6 mm
Toric: Contact lens diameter = Corneal diameter +2.5 mm; Base curve (BC) = K_{flat} +0.8 mm

Step 2: Central optical zone for distance vision (Zoc)

Pupil size measured in room lighting:
- small pupil (< 5.00 mm): Zoc = 4.00 mm
- medium pupil (5.50 to 6.50 mm): Zoc = 4.50 mm
- large pupil (> 6.50 mm): Zoc = 5.00 mm

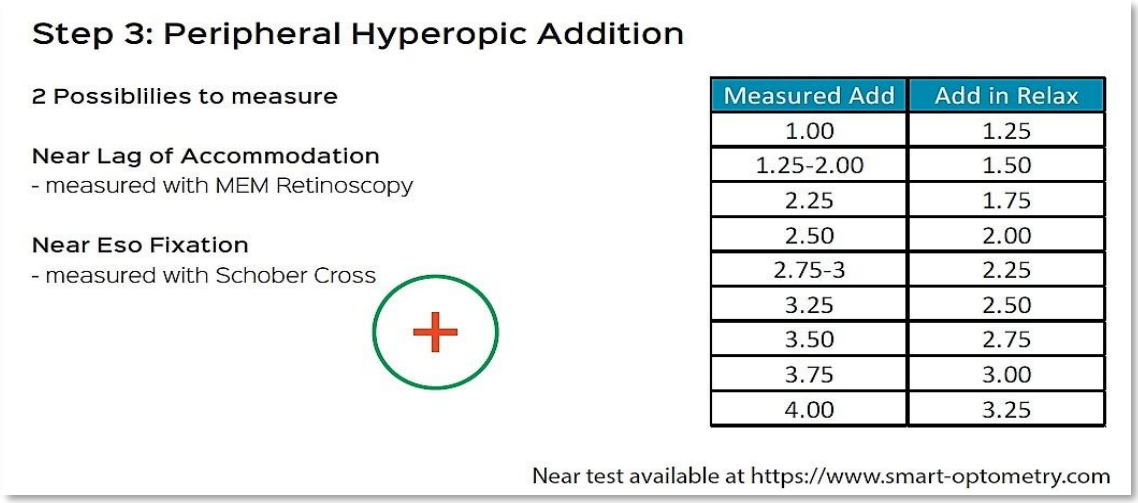

Figure 22: The Swisslens fitting guide

Figure: Swisslens

If myopia increase is >0.5 D after the first 6 months of wear, the Zoc can be reduced and/or a higher Add can be chosen.

How to choose the Hyperopic Addition

Near Lag of Accommodation measured with MEM Retinoscopy

Position yourself 33-40 cm away from the client (2.50-3.00 dpt accommodative demand). Have the patients either look at your nose or a near fixation card at your retinoscope. The client should wear his common (near) correction. Use now ±1.00, ±1.50 and ±2.00 flippers and look at the reflex without a correcting lens, sweeping quickly along the horizontal and vertical, checking right then left eyes and repeat then. Try the +1.00 flippers first. If still 'with' movement is seen, quickly change to +1.50. If the reflex reverses, your answer is +1.25. Once you've found neutralization or reversal, your last lens is your answer.

Near Eso Fixation - measured with Schober Cross or other fixation disparity tests: Use the Schober test or similar to measure the needed addition to bring the cross into the center of the circle. The Patient holds the test in reading distance (33-40 cm) in front of the eyes, in normal gaze position. Use a red/green or polarization filter (depending on the test). Ask the patient to look on the cross and circle. Let the patient explain where they are. Try with the binocular flippers plus power until the cross is exactly in the middle of the circle.

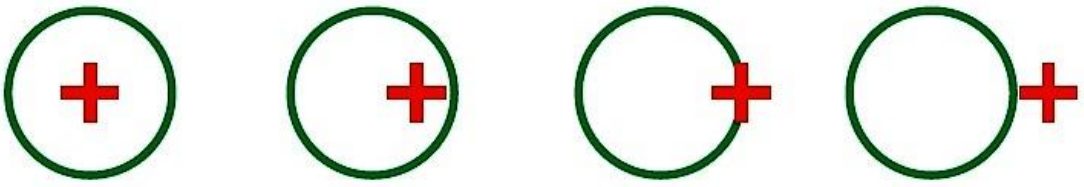

Figure 23: eso fixation, measured with Schober cross

Figure: Swisslens

If the disparity indicates a near exophoria, then is this test not useful for the fitting process and the RELAX lens will probably not work as expected. All the words in this section follow the hypothesis, that accommodation plays a role in myopia progression.

3.2.2 Other Fitting Guides for soft Multifocal Contact Lenses

Appenzeller Kontaktlinsen

Appenzeller recommends the diameter of the soft, individual contact lens should be 2.5 mm larger than the visible, horizontal iris diameter (HVID).

Materials: Benz G; GM Advance; Contaflex; Definitive 65; HEMA:

Mean Corneal radii $_{rh1 + rh2/2}$	7.20	7.30	7.40	7.50	7.60	7.70	7.80	7.90	8.00	8.10	8.20	8.30	8.40	8.50	8.60	**AF**
Corneal Diameter 11,0‑11,4	7.70	7.80	7.90	8.00	8.10	x	x	x	x	x	x	x	x	x	x	AF 2
Corneal Diameter 11,5‑12,1	7.70	7.80	7.90	8.00	8.10	8.20	8.30	8.40	8.50	8.50	8.60	8.70	x	x	x	AF 2
Corneal Diameter >12,1	x	x	x	8.00	8.10	8.20	8.30	8.40	8.50	8.60	8.70	8.80	8.90	9.00	9.10	AF 1

Materials: SiH 74%; Igel 77%:

Mean Corneal radii $_{rh1 + rh2/2}$	7.20	7.30	7.40	7.50	7.60	7.70	7.80	7.90	8.00	8.10	8.20	8.30	8.40	8.50	8.60	**AF**
Corneal Diameter 11,0‑11,4	7.70	7.80	7.90	8.00	8.10	x	x	x	x	x	x	x	x	x	x	AF 1
Corneal Diameter 11,5‑12,1	7.70	7.80	7.90	8.00	8.10	8.10	8.20	8.30	8.40	8.50	8.60	8.70	x	x	x	AF 1
Corneal Diameter >12,1	x	x	x	7.90	8.00	8.10	8.20	8.30	8.40	8.50	8.60	8.70	8.80	8.90	9.00	AF 1

Designation	Geometry
AF 1	bi-curve with slight edge flattening
AF 2	bi-curve with normal edge flattening (standard)
AF 3	bi-curve with high edge flattening

Table 12: Appenzeller fitting guide

Galifa Contactlinsen

The evaluation of 29'239 fitted Galifa Individual lenses in Benz G3x material, showed the following relationship: most lenses with a certain diameter were ordered with similar base curves:

- Diameter 13.50 -> base curve 8.00 +/- 0.20 mm
- Diameter 14.00 -> base curve 8.20 +/- 0.20 mm
- Diameter 14.50 -> base curve 8.40 +/- 0.20 mm

Because studies showed that the CSP is in most cases tangential, (Meier (1992): Das Corneo Skleral Profil – ein Kriterium individueller Kontaktlinsenanpassung. Die Kontaktlinse 1992: 4-11.; Rott-Muff et al. (2001): Das Cornea-Skleral-Profil und seine Auswirkungen auf die Form von Weichlinsen. Die Kontaktlinse 2001:26-34.), Galifa recommends to start with their flattening type B, made for tangential CSPs (523).

Galifa developed an app, helping the ECP to find a good starting lens.

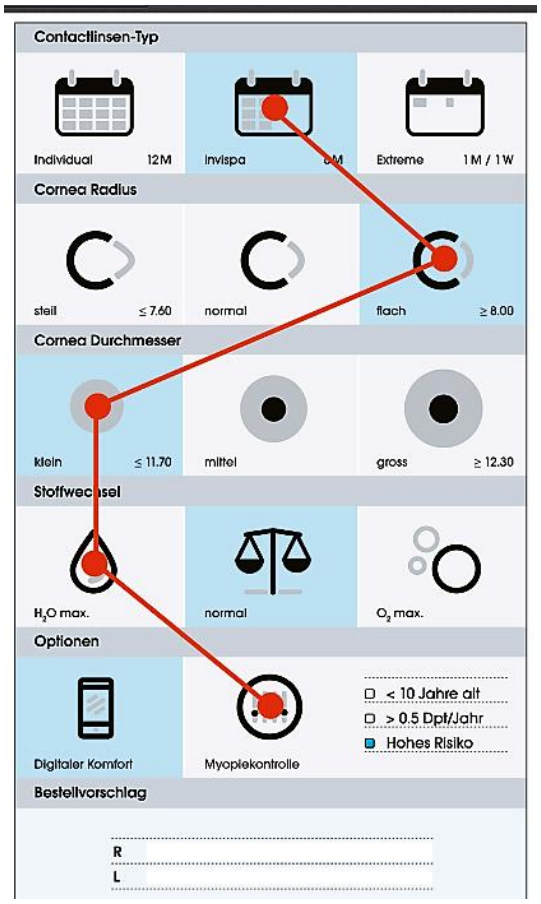

Figure 24: Galifa fitting app

3.3 Progressive contact lens parameters

As an example, the Swisslens Relax lens can be ordered with the following parameters, as a spheric or toric customized lens:

Technical data

- Total diameter: 12.00 -> 15.00… 19.00 mm (according to material)
- Base curve: 7.00 -> 12.00 mm
- Sphere: plano -> -40.00 D
- Cylinder: -0.25 -> -8.00 D
- Axe: 0° -> 180°
- Flattening: (-) flowing/ (+) pronounced/ (- -) monocurve
- Addition: 0.75 to 4.50 D (default 1.50 D)
- Center distance diameter: 2.50 to 5.50 mm (default 4.50 mm)
- Renewal: Each 3 / 6 / 12 months

In steps of 0.01 mm / 0.01 dpt / 1°
(see: https://www.swisslens.ch/wp-content/uploads/2017/03/Relax_2017_en_01a.pdf) (was available at 2019-05-25 13:29)

The Swisslens fitting advice: fitting is identical to a unifocal contact lens. The adjustment period for the patient will be usually about 1-2 weeks (e.g. halos). Some patients reported slightly reduced distance VA's at the beginning. The best results are seen in near esophoric children and young adults. The use of the free Online Toolbox to calculate the optical treatment zone is recommended.

3.3.1 Contact Lens Backside Design

Choice of base curve and total lens diameter

The base curve and diameter of MFSCLs lenses have to be chosen to minimize, but still allow lens movement (4). Due to the nature of all MFSCLs, they provide otherwise unstable and distorted vision (562).

As presented in chapter 3.1., the base curve alone is not very suitable for predicting a good contact lens position because it does not give any information about the back shape in the periphery of the CL (544). The lens diameter and the chosen flattening have a much greater influence on the sagittal height, and thus on the behavior of a soft CL on the eye (541).

Nevertheless, it is still worth to take the base curve into account, together with diameter, material and numeric eccentricity. Depending on the material, tear film and ambient conditions, the contact lens loses part of its water content during the wearing time. With that, the lens shrinks on the eye and the sagittal height increases.

This steepening effect is bigger with larger contact lens diameters. To counteract the steepening, the base curve of the contact lens must be flatter than the central flat corneal radius.

The well-known rule of thumb radius of CL = flatter corneal radius + 1 mm is too much generalized. Strictly speaking, for each contact lens material, contact lens diameter, corneal curvature and n.e. a different rule of thumb is needed for the customer. But this would be too complicated. Müller-Treiber describes a very meaningful, and in the fitting practice successful simplification in the following tables (563).

Contact lens diameter [mm]	Base Curve [mm]
13,0	Flat central corneal radius + 0,5
13,5	Flat central corneal radius + 0,7
14,0	Flat central corneal radius +0.9
14,5	Flat central corneal radius + 1,2

Table 13: Simplified base-curve finding of Müller-Treiber for conventional hydrogels

Rule of thumb for the selection of the base curve on contact lens diameter in conventional hydrogel contact lenses. These are all hydrogels that contain neither the water-binding substance GMA (or other water binding properties strongly improving components) nor belong to the group of silicone hydrogels. The rule of thumb applies only to average corneal diameters.

Contact lens diameter [mm]	Base Curve [mm]
13,0	Flat central corneal radius + 0,1
13,5	Flat central corneal radius + 0,3
14,0	Flat central corneal radius + 0,5
14,5	Flat central corneal radius + 0,7

Table 14: Simplified base-curve finding of Müller-Treiber for high performance hydrogels

Rule of thumb for the selection of the base curve on contact lens diameter for high performance hydrogels. These non-silicone hydrogels with very good water-binding properties contain GMA or alternative elements for improved water binding. The rule of thumb applies only to average corneal diameters.

There is no table for silicone hydrogels (SiH) Materials, because the material properties of the SiH are very inhomogeneous, and thus the extent of the steepness on the eye. Therefor the indication of a rule of thumb seems to make little sense here.

The back-surface profile of the KL is decisive for how well the KL fits especially in the periphery, i.e. on the limbus and on the conjunctiva. Therefore, it is important to select the correct posterior surface shape based

on the CSP and the flattening of the cornea. This can be done freely according to Müller-Treiber (563) according to the following clues:

• Fluent convex / tangential CSP and low n.e.: spherical single-curved back surface shape

• Fluent convex / tangential CSP and higher n.e.: aspherical or bi-curved back surface shape

• Distinctive convex / tangential CSP: poor suitability of strongly marked profiles for soft CL, see fluent concave CSP. For moderately prominent profiles, a small diameter and aspheric back surface shape with appropriate flattening or a two or more-curve back surface shape should be chosen.

• Fluent concave CSP: very poor suitability for soft CL. However, if soft CLs have to be fitted, a very small diameter and a strongly flattening aspherical back surface shape or a strongly opening multiple-arc back surface shape should be chosen.

• The subsequent evaluation of the contact lens shows whether the selection was correct. A market overview of different contact lenses including information on the back-surface geometry are available from the FHNW Fachhochschule Nordwestschweiz, Olten, Switzerland (Institut für Optometrie FHNW Kontaktlinsenkatalog). Available under https://blogs.fhnw.ch/io/klk/, in German and French.

Assessment: criteria of a good lens fit

The evaluation of a soft contact lens is more difficult than with dimensionally stable lenses, because the fit cannot be estimated via the fluorescein image. Therefore, with soft lenses, indirect criteria are more important. An additional complicating factor is that the fit initially changes from the point in time of placement through the already described steepening. It therefore makes sense to perform the final assessment of the contact lens only from a time of about 30 minutes.

A well-adjusted soft contact lens should objectively:

• Move 0.5 - 0.8 mm spontaneously during the blink of an eye (a very thin lens or a lens with a low coefficient of friction may also move less)
• Do not touch the limbus with the edge of the lens when looking straight ahead or when looking around
• For horizontal saccades, after a short decentration, re-center with only a slight delay
• Do not sag more than approx. 1 mm when looking upwards
• Have a relative movement to the bulbar conjunctiva during their movement
• Do not squeeze the bulbar conjunctival vessels
• Do not leave any fluorescently stainable conjunctival impressions after weaning
• Do not cause redness or other changes to the eye.

In addition, a well fitted soft contact lens should subjectively provide the customer

• good vision
• good spontaneous comfort and good comfort at the end of the day

The final objective criterion and the two subjective criteria are important for customer information. The ECP should ask the customer to pay attention to these signs at home. This can be done with the very catchy formula:

"The eyes should
- see well (good vision)
- look good (no redness)
- feel good (comfort). "

If these criteria are met, and also after-checks show no abnormalities, it can be assumed that the adaptation is successful and long-term compatible.

3.3.2 Options for Front Side Optic Zone Diameters

The front addition zone can be produces in MFSCLs in a bifocal or progressive style. The profiles of the addition are very different from manufacturer to manufacturer. For example, the RELAX lens has a progressive peripheral addition zone. The main data to choose the zone diameters are the pupil and corneal diameter.

In simultaneous multifocal myopia control CLs, the image produced on the retina are blurry circles. It is difficult for the CL wearer to separate the picture parts. The plan is to place the image of the myopic peripheral defocus enough away from the normal focus point, to produce a broad low-frequency background which reduces primarily the contrast, and is so much soften that it is easy to neglect (564). While wearing MFSCLs, the patient has to well suppress the blurriest image. The indistinct this image the easier it is to reach this. So, the greater the amount of addition in the peripheral zone, the indistinct will be the image (4).

Rehnert et al. found in a master thesis at Aalen University that the type and magnitude of refractive error has no influence on the success rate of fitting MFSCLs. Likewise, the magnitude of the used addition and the age of the patient was irrelevant, too. The success rate was associated with the loss of contrast: the less contrast the patients lost, the happier they were.

3.3.3 Options for Addition

From a study of Li et al. (339) we know, that both concentric ring bifocal and peripheral add MFSCLs are clinically effective for slowing myopia progression in school-aged children, with overall reduction rates of 30 to 50% over 2 years. Concentric ring bifocal soft contact lenses seem to be slightly more effective than MFSCLs.

Jeff Walline recommends to use the strongest tolerable add for soft bifocal CLs (30,115). See also his PDF available at: http://www.coavision.org/files/102%20Myopia%20Control.pdf (was available at 2019-04-08 18:21).

Which addition the most effective is, remains unclear. Today, only studies are published with additions from 2 to 2.5 D. Only the MiSight™ lenses have a proof for being effective over years, all other producers of lenses have to finish their studies or produce some.

The lower the power of the peripheral addition, the better is the success rate, the less contrast lost, the less the dropout rate. Even small additions like 1.25 or 1.5 D show good results in controlling myopia progression in my daily practice, but sometimes children ask for more peripheral add to reach the level of defocus and a control effect. The BLINK Study (565) will provide further information about lower additions. Already successfully tested are additions of 2.0 D and above (4,20,118). The range of acceptability seems to end under 3 D of addition. Turpin (566) wrote in his 2016 Thesis "Assessment of Three Multifocal Soft Lens Designs for Myopia Control", that his subjects rejected distance center MFSCLs with additions 4.0 and 5.0 D. One Concentric Constant Addition Design was rejected also with add. 3.0 D, while they still accepted Concentric Aspheric Addition and Concentric Linear Addition Design. Turpin found the low contrast near acuity test the best objective predictor of subjective success. A good accepted MFSCL shall be under the

limit of +3.00 D add power. Best accepted design was Aspheric Add Design. In these cases, the visual quality ratings and visual acuity are similar to those of a single vision soft lens. The amount of addition does not influence the accommodation of the child (373,567).

3.4 Pupil Size

Because the simultaneous principle of MFSCLs asks light rays from central correction (Zoc) and peripheral add zone fall through the pupil at the same time, a certain size of pupil diameter is necessary. Speaking in other words: the diameter of the Zoc is directly related to the pupil size.

In literature, photopic pupil size in bright light measures in young adults about 3.44 mm for persons younger than 20 years old (568) and 3.75 mm for patients younger than 25 years old (569).

The results of the large study of MacLachlan and Howland (4,570) presenting the normal variations in mesopic (15.9 ±0.5 lux) pupil size in infants, children and teenagers are shown in the following table:

Age in years	Number of subjects	Pupil Diameter **Girls** (mm) Mean ± Std Dev	Number of subjects	Pupil Diameter **Boys** (mm) Mean ± Std Dev
12.5	36	7.36 ± 0.90	34	6.88 ± 0.88
13.5	35	7.34 ± 1.00	20	7.18 ± 0.75
14.5	20	7.22 ± 1.08	14	7.25 ± 0.82
15.5	9	7.13± 0.81	13	7.45 ± 0.65

Table 15: Mesopic pupil diameters in teenage children

The table above shows mesopic pupil diameters in teenage children, with data from MacLachlan & Howland The difference between pupil sizes of boys and girls was marginally not significant ($p < 0.054$).

The optic zones of a MFSCL follow the principles:

1. The distance, central correction is large enough to provide clear distance vision, so that the lenses are accepted and worn.

2. The peripheral addition zone is within the pupil, in mesopic conditions.

A Relax lens, for example, with 4.5 mm central zone covers with this about 38% of the circular pupil area in a 7.3 mm pupil. MacLachlan et al. (570) found a mean mesopic pupil in about that size, 7.3 mm.

Human pupil diameters range usually between 2 and 8 mm. This diameter is a large factor of the optical transfer function of the eye. Pupil size also affects directly the depth of field, as well as the retinal illuminance, which in turn influences sensitivity for contrast. Various formulas have tried to predict pupil diameter. However, none of the formulas found take all significant points into account. These are: The observer's age, the size of the adapting field, and monocular versus binocular stimulation. Studies report in general the size of the eye's entrance pupil, which is the virtual image of the physical pupil as seen through the cornea (569). The light that reaches the retina, the retinal illuminance, is proportional to the area of the entrance pupil (571). Overall can be said, the younger the person, the larger the pupil size.

As Charman et al. (375) explored that in young, myopic adults accommodative miosis was weaker. Following this, is leading to relatively greater degradation of the retinal images in myopes. No evidence for any systematic refractive dependence of pupillary characteristics or accommodative responses was found.

Myopes don't have other pupil diameters than hyperopes: Orr et al. (572) confirmed, that refractive error has no influence on pupil diameter, irrespective of accommodative demand. This suggests that the pupil is not controlled by retinal blur but by the pupillary light reflex.

No associations were found by Zhao et al. (573) between disk halo size and initial diameter, amplitude, latency, duration and velocity of contraction, latency, duration and velocity of dilation, maximum pupil, average pupil, dark pupil and age ($P>0.05$). But they found patients with a high myopia and large minimum pupil size (minimum pupil ≥4 mm) suffered more glare than those with a low myopia and small minimum pupil size. Neither static nor dynamic pupillometry data were gender different, state Tekin et al. (574).

In patients with large pupil diameters Ortho-K showed better myopia control effects than in patients with small ones. Chen et al. (374) speculate that this is probably because of enhanced myopic shift in the peripheral retina.

3.5 Accommodation Measurement, lag of Accommodation

Accommodation should be measured to evaluate the correct addition for the peripheral zone (4). Gifford wrote on this topic on myopiaprofile.com (https://myopiaprofile.com/measuring-near-lag-of-accommodation/) (was available at 2019-05-26 14:30).

Measuring the accommodative function at near is an important component of understanding the myopia profile of the patient. Binocular vision functions influence the myopic progression in children and adults. Studies reported relationship between higher levels of esophoria and accommodative lag at near in children and young adults with myopia as compared to emmetropes (15,194,270,575,576). On lens-induced blur, children and young adults with myopia respond insufficiently (15,269,577,578), show more variability in accommodative response (579), have less accommodative facility (575,578) and more accommodative convergence (elevated AC/A ratios) when compared to emmetropes of the same age (17,172,580). Probably exists an accommodative lag prior to onset of myopia, but this is speculation in the literature. There is evidence for a higher accommodative lag in progressing myopes, no matter if they started as an emmetrope or myope (575), however one other study does not find this significance (581).

The simplest way to measure accommodative lag is with MEM near retinoscopy (582). The use of near fixation cards will usually provide a slightly less plus result. Another way to measure accommodative lag is using the fused cross-cylinder card in the phoropter. An old paper from 1989 found significantly lower results with fused cross-cylinder measurement of the near accommodative response than with MEM or Nott retinoscopy techniques (583). The phoropter is not a free-space technology and is more time consuming than MEM retinoscopy. Normal MEM results are between +0.50 and +1.00 D. Higher results indicate an increased risk for developing myopia (16,17,173,575,576).

Late-onset myopes were measured by Culhane et al. (584) with significantly extended accommodation response times after continuous near vision work. The extended response times observed in this study were consistent with previous reports of findings in late-onset myopes and early-onset myopes. They provide an inference between reflex and adaptive components of the accommodation response.

Altoaimi et al. (585) fitted young eyes with MFSCLs, that contained significant transition zones in the pupil regions. The young eyes accommodated to focus between the near and distance optics. This resulted in reduced retinal image quality and defocus in either the pupil center or margins.

For myopia and hyperopia, soft CLs change wavefront parameters in different ways. Neroev et al. (586) found elevated accommodation parameters in wearers of soft CLs for myopia and hyperopia. The improved accommodative response is due to the CL induced negative spherical aberration.

MFSCLs do not alter the binocular and accommodative function in children, found Ruiz-Pomeda (175) in MiSight wearers. A study of Koomson et al. (587) showed no association between lag of accommodation and the myopia progression rate of kids with progressing myopia.

3.6 Orthoptic status, lag of fixation

At-risk emmetropes have no correctable refractive error, but we have to take care of the risk factors: one or two myopic parents, lower than age-normal hyperopia, accommodative lag, and esophoria at near. In such children, we can start by providing advice on visual environment and by reducing the problems with their esophoria and accommodative lag at close distances. Starting with a prescription with a near add for near tasks during school hours and homework, usually in the form of bifocal or PAL glasses, is helpful. This will neutralize the fixation disparity and bring the child's accommodative lag at near back within the normal area of +0.50 D to +0.75 D (588,589). Sending the kids out for at least 90 minutes of outdoors play per day, together with limiting homework and leisure near-work activities to less than three hours after school, will lower myopia risk. This is the present limit of evidence-based practice knowledge today (72).

Sustained near work is related with myopia development in children and young adults, but the reason underlying this relationship is unknown. The 2 potentially important factors are the near work induced adaptations of contrast and accommodative adaptation of the eye. The study of Hong et al. (590) measured in myopic and emmetropic children and young adults in Singapore the degrees of contrast and accommodative adaptation during and following reading.

In children and young adults with myopia, reading led to significantly greater contrast and accommodative adaptations than in emmetropic children of the same age. Greater adaptations were found in children than in young adults, following this Hong suggests that children are more susceptible to changes of the eye induced by reading. These greater adaptations show a potentially greater risk of developing refractive errors.

Myopic children need longer accommodative adaptation regression times than emmetropic children. This could drive myopia progression in susceptible children performing considerable amounts of near work.

Because Chinese text is more complicated to write and read than English text, it was hypothesized that Chinese text would cause greater adaptation. However, for both texts similar amounts of accommodative and contrast adaptation were found in young adults (590).

The study of Kang et al. (591) wanted to characterize the effects on accommodation and binocular vision in young non-presbyopic adults of 2 distance center multifocal soft contact lenses (MFSCLs) with different addition power. She tested twenty-four young adult myopes (18–28 years; 20 females, 4 males) for their baseline visual acuity, accommodation, near phoria, fixation disparity and stereopsis. The data was collected with single vision (SV) SCLs. The same set of measurements was repeated directly after subjects

were fitted with each of two MFSCLs. The lenses had either +1.50 or +3.00 D add. Each lens type was worn in a daily wear mode for 2 weeks. Between the trials was one week as a wash-out phase, the order of testing was randomized. Differences in near and distance acuities with MFSCLs compared to SVSCLs were clinically insignificant and small. MFSCLs increased accommodative lags with this change. The lens with the +1.50 D addition reached statistical significance. The near phorias were shifted in the exo direction with both MFSCLs significantly. No significant differences in stereopsis and fixation disparity with MFSCLs compared to SVSCLs were found. With these results, we can expect good tolerance of MFSCLs in young, non-presbyopic patients fitted with them for myopia control.

3.7 Safety and Compliance

How safe are myopia control options? Research shows that children (8- to 12-year-olds) and teens (13- to 17-year-olds) have both an equally low risk of being noncompliant with their CLs or evolve a CL complication (592). CL wearing children and teens report improved social acceptance, ability to play sports; and their appearance and overall satisfaction with their vision correction was better (28,593,594).

In 2013, Bullimore et al. (595) determined the relative risk of microbial keratitis in overnight Ortho-K based on reports of a 3-year period. 2 red eyes in children were determined by an expert panel to be cases of microbial keratitis. The calculated overall estimated incidence of microbial keratitis in Ortho-K was 7.7 per 10’000 patient-years of overnight Ortho-K wear, but with very wide confidence intervals. Stapleton and colleagues (596) published estimates for the incidence of microbial keratitis of 1.2 per 10,000 patient-years for rigid daily wear, 11.9 per 10’000 patient years for silicone hydrogel daily wear, and 19.5 per 10’000 patient years for hydrogel extended wear. The findings of Bullimore et al. (597) provided some confidence amongst Ortho-K prescribing ECPs, that Ortho-K did not in itself present an inappropriate risk for children. But the ECPs must be good skilled in fitting and managing these children, fitting after accepted international standards for safe CL wear, and good compliance is absolutely necessary in Ortho-K lens wearers.

The long-term wear of Ortho-K was investigated by Hiaroka et al. (129), they found in 2018 no significant difference in the number of adverse events found in 10 years of wear between the Ortho-K and soft CL groups ($p = 0.72$), in 104 patients.

Low-dose atropine (0.01%) is also considered safe, even that it has an effect on accommodation and light sensitivity (108,449,461).

The visits for medical device-associated adverse events in the pediatric population were investigated in 2010 by Wang et al. (598). Contact lenses of all kind were the largest group accounting for events (23%), followed by hypodermic needles (8%).

None of the discussed treatments had in march 2019 a U.S. Food and Drug Administration (FDA) approval specifically for myopia treatment, even though they are approved for other uses (32).

3.7.1 Safety of MFSCLs

Wear time of MFSCLs, and replacement schedule

To have a good myopia control effect, patients should wear their myopia control contact lenses for all waking hours. So, the myopia control effect of MFSCLs is dose-dependent (117). For me, it seems that the reason for this is the longer exposition to myopic defocus, this slows myopia progression more than shorter ones.

For occasions the patients cannot wear the lenses, they need also an up-to date spectacle. Contact lens wear in this form does not expose children to an increased risk of complications compared with adults (599,600). First, the contact lens fitters should focus on properly training patients in appropriate lens care and proper handling techniques. To avoid complications, patients should avoid overnight wear of the contact lenses. A frequent replacement schedule is often the most successful way to wear lenses. It is highly recommended to teach both the child and the parent. But very important that the child understood each step of lens wear such as insertion/removal and lens disinfection. Parents and children must know the necessary steps in case of an adverse event (372).

Adverse effects

Nearly all the anterior ocular structures can be affected by wearing CLs (601). Adverse effects caused by wearing CLs can be acute or chronic (602). The impact ranges from a mere annoyance to a disabling permanent ocular damage or even loss of an eye. CL complications are the result of one or more of these factors:

- mechanical factors that cause irritation or abrasion of the ocular tissue or lid due to: CL materials, inappropriate designs, or incorrect fitting; CL interactions with foreign bodies such as fine powder or other particulates; and physical forces like high G-forces;
- physiological factors, such as the eye's response to reduced oxygen levels under old hydrogels; infection; or chemical interaction, including the preservatives in many CL care solutions;
- immunological factors like allergies, that can lead to general lens intolerance; tear film alterations due to low humidity, too much wind or similar factors; changing the tear film can disturb the normal function of removing waste products and clearing foreign matter from the ocular surface, lubricating it, and preventing the cornea from drying out (570).

The upper and lower eyelids contain the meibum secreting meibomian glands. Meibum thickens the lipid layer of the tear film. Eye with meibomian gland dysfunction show symptoms such as fatigue, dryness and burning sensation. Studies have found that wearing CLs is changing meibomian gland morphology, the lid margin and meibum quality, suggesting that wearing CLs negatively affect meibomian glands. Such CL induced meibomian gland dysfunction-like changes are probably responsible for at least some of the ocular symptoms in CL wearers (603).

We know two categories of contact lens-related adverse events: serious and non-serious. The difference makes the potential for vision loss. Microbial or infectious keratitis are serious. The common definition of microbial keratitis is: pain more than mild; one or more corneal stromal infiltrates greater than 1mm; and one or more of following: mucopurulent discharge, anterior chamber reaction more than minimal, or positive corneal culture. Around one in seven cases of microbial keratitis results in permanent vision loss (596).

Non-serious adverse events include allergic conjunctivitis, contact lens-induced acute red eye (CLARE) and infiltrative keratitis.

Infection

A large study of Stapleton et al. (604) estimated the incidence of severe microbial keratitis (with permanent loss of visual acuity) in daily wear of soft lenses to eight per 10'000 patient years (95% CI: 6.7, 9.8) (596,605). Overnight wear, increased exposure in daily wear, smoking and poor hand hygiene (606) were significant risk factors for microbial keratitis.

Microbial corneal infection is a recognized danger of CL, especially in soft lens wearers. Wearers of extended-wear hydrogel lenses are at highest risk. Infections can cause corneal ulcers, reducing VA acutely or chronically. Serious cases may end in surgery or loss of an eye (602). Wearing CLs contributes to infections by compromising of the corneal surface either through mechanical abrasion or oxygen deprivation and contaminating the cornea with bacteria (607). A high percentage of hydrogel CLs from patients without symptoms of infection show bacterial contamination (607) and bacteria can also be found in bottles of lens solutions (608–610). Even a patient with good compliance and strict lens cleaning procedures can have an infection (611).

Bacteria adhere readily to the superficial deposits on soft CLs and can multiply rapidly there, creating a biofilm (607) able to provide infectious agents to a stressed cornea. Microorganisms adhere to the CL surface, transfer to a damaged corneal epithelial surface, penetrate into the deeper layers of the cornea and damage the cornea. The resulting microbial keratitis can cause to permanent blindness (612). The CL environment also seems to support some of the more harmful bacteria, such as pseudomonas (613,614).

Conjunctivitis causes irritation, itching, foreign body sensation, and increased tear flow or discharge of the ocular region. Most adults have a viral conjunctivitis, while children are more likely to have bacterial conjunctivitis than viral. The bacteria mostly seen are Staphylococcus species in adults, and Hemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis in children. If eyelids are like glued together and don't itch, a bacterial cause is more likely than a viral. A watery discharge is seen more often with viral conjunctivitis; itching is also seen with allergic conjunctivitis (615).

To define the incidence or prevalence of bacterial conjunctivitis, Epling et al. (616) were not able. Bacterial keratitis is estimated to occur in 10 to 30 out of 100'000 CL patients. The prevalence of conjunctivitis is influenced by the customer's age, as well as the month of the year. Viral conjunctivitis is more prevalent in summer months. Bacterial conjunctivitis is more frequently observed from December through April. Allergic conjunctivitis is reported more frequently in spring and summer months (615). Viruses provoke up to 80% of all acute conjunctivitis cases (615). One study of Smith et al. (617) estimated the incidence of bacterial conjunctivitis to be 135 in 10'000. In the USA it is estimated that 23% of bacterial conjunctivitis cases happen in the youngest, up to 2 years age range; 28% occur in 3-9-year-old children, and 13% happen in the 10-19-year range. The remaining 36% of all cases occur in adults (617).

Recovery from infection can happen quickly or take a lot of time, depending on the rapidity of treatment. It is usually needed to discontinue CL wear for the duration of the treatment.

In the USA, an incidence of 11 per 100'000 individuals (618) for microbial keratitis and 5.3 per 100'000 individuals per year for ulcerative keratitis was reported. Daily wear contact lens users show the lower rate of ulcerative keratitis of 1 in 2'500, while extended wear contact lens users show a rate of 1 in 500 per year (619).

Incidence rates for bacterial microbial keratitis ranging from two/10,000 per year for RGPs, 2.2-4.1/10'000 per year for daily-wear soft CLs, to 13.3-20.9/10'000 per year for overnight-wear soft CLs were reported by Liesegang (620). In literature, he found the relative risk of microbial keratitis described as 1 for RGPs (referent), 1.0-4.2 for daily-wear soft CLs, 2.7-36.8 for overnight-wear soft CLs, and 13.0-13.3 for disposable

soft CL wear. In the study of Liesegang the most significant risk factors were overnight wear, smoking and male sex.

Factors that cause contamination of CL storage cases like low frequency of storage case replacement, inadequate hygiene, and solution type are associated with moderate and severe microbial keratitis in daily use CL wearers (621).

Red eye

The term "Red eye" is used to report irritated or bloodshot eyes. It is a noticeable sign of an acute or chronic, localized or systemic underlying inflammation. Poorly fitted lenses can cause this too (622). Conjunctival injection is usually driven by dryness, allergy, CL over wear, and local infections. In some cases, red eye can represent a true eye emergency that should be seen as soon as possible by an ophthalmologist. A correct treatment is required to preserve the patients VA. Severe painful eyes, significant photophobia, lower VA and reports of ocular trauma are warning signs demanding immediately an ophthalmologist (623).

Extended wear of high Dk/t SiH lenses did not increase microcyst numbers, report Keay et al. (624) Patients changing from low to high Dk/t CLs can increase the number of microcysts is transitory, these disappear without changing anything.

Infiltrates

Infiltrates are hazy, grey areas in the stroma of the cornea and are most likely clusters of inflammatory cells. While infiltrates themselves don't cause symptoms, they are often accompanied by other complications, such as scratchiness, pain, photophobia, and tear flow (602). The cause of infiltrates is unknown, but hypoxia over a long time, immune responses, physical irritation, and local infection are discussed factors in its development (601). The presence of infiltrates requests discontinuation of lens wear until the infiltrates have disappeared. This can take up to 2 months. To prevent recurrence, ECPs can reduce the wear time, change the lens type or change the lens care system for their patients. 3%-4% wearers of reusable soft CLs have corneal infiltrative events in a year, report Chalmers et al. (625).

Risk factors for infiltrates have been identified by Morgan et al. (626):

- Wearing modality type: extended-wear hydrogel lenses had a 7.1-fold risk vs. daily wear.

- Male gender (relative risk 1.4x), smoking (1.4x), the absence of relevant ocular (1.8x) and general health (2.4x) problems, and the late winter months (highest risk in March, 3.6 fold of July).

The incidence of corneal infiltrative events has been estimated as 300 to 400 per 10'000 patient years in some large-scale studies for adults in daily wear soft contact lenses (600,608,626,627).

Efron et al. (628) found an annual incidence for corneal infiltrative events for all wearing modalities and lens types of 21.3 per 10'000 CL wearers (95% CI 17.8 to 25.5).

In 1.6% of the 2'324 patients examined during unscheduled visits found Cutter et al. (629) corneal infiltrates with overlying staining. These 38 events were milder than expected from studies of specialty eye care centers. The patients reported redness, fear of light, pain, and foreign body sensation. Infiltrates were found in all corneal zones, 44.7% involved the central zone. Not one of those infiltrates left a reduced VA at follow-up. The already known risk factors of wearing the lenses overnight, lens modality and smoking have been confirmed.

GPC

Giant papillary conjunctivitis (GPC) is an inflamed conjunctiva, an immunological-allergic disorder. It is caused by the deposits of contact lenses in predisposed wearers. The incidence of GPC was much higher in former days in wearers of soft hydrogel CL, fortunately manufacturers have developed CL systems with better materials and shorter replacement schedules, leading to much lower numbers of GPC (630).

Corneal Vascularization

The normally avascular cornea has sometimes blood vessels in the 2 mm around the edge. Invasion of blood vessels further inside is abnormal (631). Vascularization is usually symptomless until the vessels cover the pupil and reduce with that the visual acuity (602). ECPs should search for signs of early neovascularization, and change the patient in this case to a SiH material (632). If vessels reach the pupil, lens wear use must be permanently ended (601).

How 536 medical students in Saudi Arabia handle their CLs investigated Ibrahim et al. (633). 40.5% of the students wore lenses. Of these wearers, 45.6% did not renew the lenses on time, 29.9% were sleeping, showering (29.0%) or swimming (24.6%) with the lenses. And 16.6% of the students shared their lenses with other students. Of the CL using students, 30.4% reported at least one CLs' related complication like acute red eye (19.8%), conjunctivitis (18.9%) or corneal abrasion (8.3%).

As I have shown over the last pages, yes, contact lenses can cause problems and in bad cases even vision loss. But they help us that the eyes are not getting as myopic. And with an aged, prolonged myopic eye, changes are also expected. The numbers of clinically relevant events with lenses is quite small, the impact of a disease like myopic maculopathy is high – for me rather a reason to fit contact lenses than to avoid it.

Comfort

The study of Lubis et al. (634), using the CLDEQ-8 questionnaire (635,636), showed that “dry eye syndrome was not correlated with daily lens wear duration, but affected by many factors such as contact lens, lens care solution, eye drops usage and environment”.

3.7.2 Compliance of the Customers

Lens Wear Time

In general, wearing the contacts for a longer time translates to a higher risk of unwanted events. The Food and Drug Administration in the USA expects 10 times more complications developed in extended-wear hydrogel CL wearers than in those with daily-wear hydrogel CLs (613). Schein et al. showed in their controlled case study that the relative risk of ulcerative keratitis is ten to 15 times greater if CLs are worn in extended -wear mode (602,637).

Lens-free recovery periods of up to 80 minutes during a 12-hour lens wear day did not positively impact end-of-day comfort in the study of Stahl et al. (638).

Anstice and Phillips (4) selected for their study clients wearing their CLs for at least two years continually. They had to change their lenses at the scheduled moments in time. Because incompliant children would

not follow this regime, the DIMNZ study does probably not reflect whole real CL world. In general, the compliance of the children was very good. After ten months of CL wear, wear times of 12.66 ±2.21 hours per day, on 6.87 ±0.45 days per week were reported. At the visit after 20 months, 13.15 ±2.83 hours per day, and 6.63 ±1.25 days per week. The compliance continued to be good during the whole period.

The waking hours of the young clients were expected to be about 15-18 daily waking hours (639). American teenagers sleep nearly 8.5 hours per day (640), European children have even longer sleeping periods (641).

Causes of CL dropout

The causes of CL dropout are often misunderstood, and ECPs tend to underestimate or be unaware of the incidence of CL wearers who drop out. CL wearers that discontinue lens wear fade away silently, their dropouts are not obvious in most practices. Historically, dropout rates as low as 5% to 10% have been estimated for CL wearers dropouts (642–644). But the survey of Rumpakis et al. (645) found dropout rates as high as 16% to 30%. The economic loss for an ECP if only one single patient is discontinuing lens wear can be as much as $24'000 over the patient's lifetime.

The mean dropout rates found by the worldwide survey of Rumpakis were 15.9% in the USA, 31.0% in Asia and Pacific region, and 30.4% in Europe, the Middle East and Africa.

The most important reasons for discontinuation of contact lens wear were discomfort (41.9% to 52.9%), costs (11.6% to 17.5%) and insufficient vision (3.8% to 17.5%). The need for recurring eye exams was a real infrequent reason for dropouts (0.0%-1.8%).

Dropout reason	**Europe** / Middle East / Africa	USA	Americas (incl. USA)	Asia/Pacific
Comfort/fit	45.6%	50.0%	52.9%	41.9%
Vision not as good as with glasses	17.5%	15.9%	14.2%	3.8%
Costs	17.5%	12.3%	11.6%	11.9%
Handling problems	7%	7.2%	8.4%	7.5%
Fear or history of infections	3.5%	0.7%	0.6%	17.5%
Need for regular eye exams	1.8%	0%	0%	0%
Easy to lose	1.8%	0%	0%	0.6%
No astigmatism correction	1.8%	0%	0%	0.6%
Lens care is too difficult	0%	0.7%	0.6%	0.6%
Multifocal lenses don't work as well as glasses	0%	5.1%	4.5%	0.6%
Inconvenient to wear	0%	5.1%	4.5%	10%

Table 16: reasons for CL dropout

Figure adapted from Rumpakis (645)

I searched for data about which lens types cause highest drop-out rates: Sulley et al. (646) investigated in 2017 dropout rates in the first year in patients wearing multifocals (43%), spherical CLs (21%) and torics (27%). Most drop out (47%) was seen in the first 2 months. In another Sulley study (647) the dropout rate was 22.4% in the first year, visual problems were the main reason. In 71% of dropout cases, no alternative lens or handling/cleaning strategy had been tried.

A 2007 study of 730 CL patients at the Ohio State University found a 24% CL patient dropout rate (648). In Asia and Europe, the numbers of dropouts are as high or higher than the numbers of new fits (645). The Dry Eye Workshop Study (DEWS) reported discomfort and dryness as the main reasons for CL intolerance (649). Other patients find lens handling to be bothersome or the cleaning too complicated (645). In new wearers of spherical CLs, handling and comfort were the most common dropout reasons, while this was visual problems in new wearers of toric and MFSCLs (646).

Because patients reported discomfort as their main reason for dropout, ECPs should select CLs and lens care products that increase comfort, and provide good cleaning and disinfection options.

Using the Ocular Surface Disease Index (OSDI) questionnaire (650), Dumbleton evaluated the diurnal decrease in comfort and subjective vision. Dryness, grittiness, and irritation increased over the day, significantly more for CL wearers than non-CL wearers (651).

With a self-administered questionnaire, Wu et al. (652) surveyed 210 contact lens wearers. The questionnaire was constructed to collect information regarding contact lens wearer demographics, attitudes toward lens care and contact lens hygiene behaviors. Major non-compliance aspects identified were lens storage cases (61%), inadequate cleaning of lenses (13%) and poor hand hygiene (11%). 50% of the wearers were not remembering how often or when they were advised to return for an aftercare. CL wearers purchasing their CLs from the internet were 3.8 times more likely to forget their aftercare schedule than those who purchased CLs direct from the optometrists (95% CI=1.2-12.2, p=0.024).

3.7.3 Fitting MFSCLs to children

Nearly all (97%) practicing optometrists in the American Optometric Association answered in a survey that they have fitted CLs to children. For children younger than 10 years old, the optometrists used glasses as the primary method of myopia correction and CLs as additional form of correction. But in children ten years old and older, correcting myopia with CLs was the method of choice. Today, data on the safety of CL wear in children and about the improved quality of life with CLs are available, but the number of use of lenses in children is often not reaching the expected amount, and is often restricted by parents, doctors and ECPs for certain situations, such as in sport (653).

Children at the age of 8 can successfully insert, remove and clean lenses, that showed different studies (114,115,117,130,379,380,391,654). In other clinical studies was confirmed that children achieve the required duration of lens wear, and their duration of lens wear was similar to that seen in adults (593). No increased risk of complications was found in CL wearing children compared with adults (350,593).

Even if ECP teach parents and children to handle the lenses, the children should be able to independently manage all aspects of CL wear.

Unfortunately, not every child can be a successful CL wearer. Allergic conjunctivitis and other diseases have their onset in childhood, and CL wear may increase the risk of flare-up in such instances. ECPs should ask about any former history of allergic or vernal conjunctivitis, and the bio microscopy flow should include control of the everted tarsal conjunctiva (372).

In a recent review, Bullimore et al. (655) analyzed many studies about safety of CL wear in children, including large-scale epidemiological studies of CL-related complications, hospital-based case series, long- and short-term prospective studies, and retrospective papers. Children show no higher incidence of corneal

infiltrative events than adults, and the youngest wearers of ages eight to eleven years showed even a noticeably lower incidence.

Age and other risk factors for corneal infiltrative and inflammatory events (CIEs) in young, soft contact lens (SCL) wearers were inspected Chalmers et al. (600). They reviewed charts from 14'305 visits observing 4'663 SCL years yielded 187 CIEs in 168 wearers. The significant associations were: patient age, use of multipurpose care products, years of lens wear, extended wear and silicone hydrogels were all significantly associated with corneal infiltrative and inflammatory events. Young patients aged 8 to 15 years using soft contact lenses were associated with a lower risk of infiltrative events compared with teens and young adults. Looking at safety outcomes, SCLs appear to be an acceptable method of serving optics designed to manage the progression of nearsightedness in children and young teens. In the overall picture, is shows that the incidence of corneal infiltrative events in children is not seen more frequently than in adults. In the youngest age range of 8 to 11 years, it was reported to be markedly lower (655).

Wearing CLs significantly improves the quality of life in children and teens (391). The used 'Pediatric Refractive Error Profile' showed no difference in improvement between eight- to twelve-year-old children and teens aged 13 to 17 years. How these young persons feel about their appearance and participation in activities was dramatically improved by the wearer of CLs, leading to greater satisfaction with their refractive error treatment. Children should therefore be offered contact lenses as often as teens (593).

Children have a better long-term adaptation to soft contact lenses than to Gas Permeables (GP) (656).

The retrospective Contact Lens Assessment in Youth (CLAY) study (657) was a multicenter, meticulous, observational, retrospective study that evaluated risk factors that interrupt soft contact lens wear among young adults, teenagers and children in North America. The study's goal was to assess in a pediatric population the safety profile of soft contact lens wear. The investigators like Chalmers reviewed charts from 3'549 patients. Those were representing 14'276 office visits (600). New fitted patients were 21% of the young persons, 79% existing soft contact lens wearers. Across all patients there were 187 corneal infiltrative events over 4'663 soft contact lens patient years. The incidence varied dramatically with age! The eight- to 12-year-olds have much lower rates of adverse events than teenagers. Young adults had even higher rates. The incidence of corneal infiltrative events for eight to 12-year-olds was 97 per 10'000 patient years (95% CI: 31, 235) compared to 335 per 10'000 patient years (95% CI: 248, 443) in 13 to 17-year-olds.

Only eight of these events were classified as microbial keratitis. No cases of microbial keratitis were observed in the younger children. In the group of teenagers were two cases registered (incidence = 15 per 10'000 patient years) and five cases among the university-age patients (incidence = 33 per 10'000 patient years). In summary, both microbial keratitis and corneal infiltrative events are much less common in the group of eight- to 12-year-old children.

Not biology, but changes in behavior are the cause for the higher number of adverse events in teenagers and college kids (658). As a father, this is not a big surprise for me… The much riskier behaviors included: having a shower and sleeping in lenses, in elder kids came more problems due to travelling, drinking, and being away from home.

In the ACHIEVE study, Walline (104) assessed the influence of soft lenses on self-esteem in 584 myopic children aged eight to 11 years. There were no cases of microbial keratitis in the young contact lens wearers. And he reported just six presumed cases of corneal infiltrative events – an incidence of 83 per 10'000 patient years (95% CI: 34, 173).

The Brien Holden Vision Institute (599) reported adverse events on 240 children aged seven to 14 years. The children wore silicone hydrogel lenses on a daily wear–monthly replacement schedule. In the two-year study were no cases of microbial keratitis reported. Among the 55 non-serious events, there were 13

instances of asymptomatic infiltrates and five cases of infiltrative keratitis. Sankaridurg et al. (599) calculated the incidence of symptomatic corneal infiltrative as 136 per 10'000 patient years (95% CI: 50, 300).

CooperVision (390) recently completed their MiSight Three-Year Clinical Trial on children aged eight to 12 years randomly wearing MiSight or Proclear daily lenses. Just four asymptomatic corneal infiltrative events giving an incidence of 116 per 10'000 patient years (95% CI: 37, 280) and again no cases of microbial keratitis were found. The study is still ongoing.

Now, I was searching for data about dry eye symptoms in children. Greiner and Walline (659) tried to determine whether children who wear contact lenses truly have fewer dry eye complaints than adults do. The recruited ninety-four paediatric contact lens wearers, aged 8 to 14 years, was given the Contact Lens Dry Eye Questionnaire (CLDEQ) short form. This survey is designed to diagnose dry eye syndrome by collecting information on the frequency of dryness and light sensitivity and asks for their corresponding intensity levels. The control points were: within the first 2 hours of putting in the lenses; in the middle of the day; and at the end of the day. The results were compared with those of adult samples from the literature. "The average (±SD) age of the sample was 11.7 ±1.5 years, 56.4% were female, 59.6% were white, and 19.1% were black. The mean CLDEQ composite score was 0.25 ±0.50 (range = −1.20 to 1.45). In the literature, the adult mean CLDEQ composite score was 1.02 ±0.80 (range = −0.74 to 4.50). Of the 94 surveys collected, 4.3% of children were categorized as having dry eye compared with 56.2% of the adults who completed the CLDEQ survey in the adult study", reported Greiner and Walline. In conclusion, paediatric contact lens wearers have fewer dry eyes than adult contact lens wearers. This could be because of an improved tear film, modality of contact lens wear, or differences in reporting of symptoms.

In conclusion, by comparing a number of different studies, it is possible to make a valid assessment of the safety of soft contact lenses in children (655). Four of six studies observed no corneal infiltrative events. In children, the overall picture is that the incidence of corneal infiltrative events is markedly lower than in adults. The estimated incidence in older patient groups was never reached by the upper confidence interval. The prospective studies of children represent over 2'000 patient years of soft contact lens wear. Combining the six prospective studies, the estimated incidence of corneal infiltrative events in children is 54 per 10'000 patient years and the upper 95% limit is 86 per 10'000 patient years. In other words, each year, no more than 86 cases of corneal infiltrative events each year per 10'000 patients. In contrast, we would expect to see 300 such events in adults.

Chair time and communication with a child

Practitioners must communicate with both the parent or guardian and the child. In the first session it is important to find an understanding of who is the "driver" for the contact lens fitting. Is it the parent guardian or is it the child? The child wants the lenses and wants to lead? Then make sure that all the parental questions and concerns are answered as early in the process as possible. So, the parent or guardian is supporting, removing the risk of skepticism. Due to the financial involvement and possible parental support required, this is the way to get successful child contact lens wearers. A good paper about successful fitting contact lenses to children from Black is available at https://www.abdo.org.uk/wp-content/uploads/2012/06/CET153.pdf (was available at 2019-04-08 20:52).

In case the parent is the leader then the child needs to be reassured and questioned to understand that she or he has a 'voice'. So, the child should know that the practitioner is their advocate if required. If the child is not ready at this point to wear contacts or handle them correct reassure them that contact lenses may be a good supplement for their glasses now, or in the future.

By giving the child a lens to feel and handle, the patient realizes of what the lens is and that it will not harm the eye. If the child has questions answer them in this situation. To go on with an insecure child will waste the time of all and not lead to success.

My last question for this section was, if it matters at what age children are fit with lenses. Walline et al. (660) collected data about the comfort and compliance of patients as well as adverse events. They compared those who were fitted in contact lenses as a child (≤ 12 years of age) versus those who got their lenses as a teenager (≥13 years of age). Fitting children at 12 years or younger was not associated with a greater frequency of current poor comfort, prior adverse events, or poorer compliance, even after 10 years of soft contact lens wear. In the CLIP (Contact Lenses in pediatrics study) found Walline et al. (130) the time needed to fit contacts nearly the same in children and 13-17 years old teens. Children needed just about 15 minutes more chair time, most of this extra time was needed for the insert and removal training. Nearly three-quarters of children aged 8 to 11 preferred contact lenses to spectacles. After 3 months, none of the teens and Children needed help to remove the contacts. 10% of the children and 4% of the teens needed help to insert them.

For young patients with progressive myopia a follow-up control is necessary every three to six months. Any over-refraction of 0.25 D or more indicated to adjust the lens power to avoid blurred vision.

3.8 Production of a SWISSSLENS RELAX Lens

3.8.1 Manufacturing

The company SwissLens manufactures contact lenses exclusively in the turning process. Hervé de Malm developed his first fully automatic lathe in the mid-nineties. The computer-controlled lathes used today have nanometric precision, which are optimally suited for the production of customized contact lenses and do not require additional polishing at the end of production (661).

Production process:

(Picture: SwissLens)

Figure 25: Turning of a contact lens

Calculation of the contact lens geometry: the desired contact lens parameters are read in the database, calculated and with a specific software, the contact lens is displayed in the two main sections.

Blocking the blank: using a special wax, the blanks are glued in an apparatus exactly on the flat brass holder.

Rotate the contact lens back surface: during the first turning process, a coarse diamond is first rough-cutting the blank, then the fine diamond is used to finish the edge of the contact lens and the back surface (base curve, asphere and possible correction).

Transferring the half-finished workpiece: to turn the front surface, the half-finished contact lens must be turned over and thus re-attached to a convex chuck. Before that, the center thickness of the semi-finished contact lens in the micron range must be measured in order to finally obtain the required center thickness of the final contact lens. Then the contact lens is attached to the convex chuck by targeted heat addition and removed from the plane chuck.

Turning the front surface: in the case of the front surface as well, the coarse diamond is first cutting the rough form, then the final cut is made with the fine diamond.

First control and hydrogenation: in the dry state, the RGP, but also the soft contact lenses are controlled optically and to the parameter accuracy. Thereafter, the soft contact lenses come for at least 5 hours in distilled water for hydrogenation (swelling). Hydrogel materials can grow between 20 - 70%.

Final check: during the final inspection, all parameters of the swollen and final contact lens are again measured and a visual check carried out.

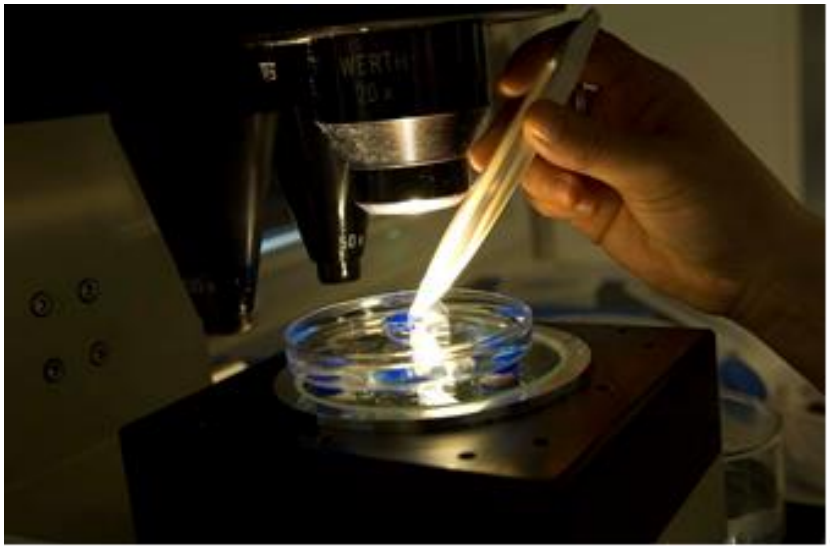
(Picture: SwissLens)

Figure 26: control of a contact lens

Sterilization: now, every contact lens must be sterilized at the end in the supplied liquid. Under steam (> 121 ° C), the contact lenses are heated for 20 minutes in a hot air sterilizer.

Lathed lenses like the REALAX provide sharper transitions between the central distance correction and the peripheral addition zone than molded lenses (4,662,663).

3.8.2 The Materials

In 2013, Jones described end-of-day dryness symptoms in about 50% of CL wearers as a major hindrance to the expansion of the CL market (664,665). This is often decreasing the comfort for the last 2-3 hours of wear (665,666) and is causing CL dropout, which occurs in 20-25% of all CL wearers (644,648). Many new materials and care products were introduced to the market over the past decade, but no big reduction in the of clients who complain of end-of-day dryness and discomfort has been registered.

The historical problem of low water content, poor oxygen transmission soft CLs causing limbal hyperemia, stromal striae, neovascularization, epithelial microcysts and endothelial changes (667–670) was tried to solve with new higher water content, increased oxygen permeable (higher Dk) lens materials (671). This solved not yet the level of significant overnight corneal swelling, and marked corneal staining due to dehydration (672,673). High water content lenses needed to be made thicker, to reduce this – but now the benefit of better oxygen transmission was reduced again. The majority of wearers of such materials showed no edemas any more on a daily wear basis (674–676).

The todays silicone hydrogel (SiH) materials bring increased oxygenation to the cornea and allow in some cases overnight wear. These products with improved Dk/t eliminated most of the hypoxic signs, on a daily wear or overnight mode (677,678).

SiH CLs show a less pronounced effect on corneal homeostasis compared to other lens materials, but mechanical interaction with eye tissue and the impacts on tear film structure and physiology are interchangeable to that usually found in soft CL wearers (679).

These SiH materials increased their market share since 1999 and were used in 2018 in over 76% of all new fits in many markets worldwide, in some markets over 90% (498). Since 2013, this increase reached a plateau, showing that many practitioners are still fitting the classic hydrogel materials. Probably because silicone materials are generally more hydrophobic than the classic hydrogels (680–682) and show increased deposition of certain lipids (683,684) and more denaturation of deposited protein (685).

Classic hydrogels and silicone materials show mechanical differences. The higher modulus and stiffness of SiHs (680,686,687) result in a number of mechanical reactions (688–690), especially with lower water content SiHs (687) "*These mechanical complications include superior epithelial arcuate lesions* (691–693)*, mucin balls* (694–698)*, epithelial flaps* (699–702) *contact lens associated papillary conjunctivitis* (703–705) *and corneal erosions* (689,690)", wrote Jones et al. (680).

The study of Tan et al. (698) is indicating that a part of the population is predisposed to create mucin balls no matter what soft contact lens type worn, but the lens type is influencing the degree of building up mucin balls. The association between lens wettability, back side superficial deposits, and steeper corneal curvature with mucin balls assists the hypothesis that the mechanical interchange of a lens with the superficial layer of the epithelium and the tear film linked with the blinking forces of the eyelid is involved in building up mucin balls.

Wearing SiH materials combined with preserved care systems can lead to solution-induced corneal staining (SICS) (706,707). It seems unclear how clinical important these SICS are (708–710), but with the change to a preservative free H_2O_2 solution the SICS disappear in nearly all cases.

The risk of microbial keratitis is rather not related to the lens material (711–714). Several reports (600,715–717) have shown that SiH wearers double their risk for infiltrative keratitis (718). Today, no custom soft lens material (hydrogel or silicone hydrogel) has a FDA clearance for the overnight use with closed lids (719).

For the modern materials we can calculate an on-eye shrinkage of 1.0-2.3% for typical, current, hydrogel and silicone hydrogel SCLs (521).

Examples for customizable contact lens materials

Definitive 74% Silicone Hydrogel

This material is produced by Contamac. Other names for this product are Filcon V3 or Efrofilcon A. The oxygen permeability (ISO) at 35°C (barrers) value is 60, the oxygen transmissibility (ISO) at 35°C is 75, it contents 74% water, its refractive index at 20°C (hydrated) is 1.375, the hardness (Shore D) is 84 and it shows 99% light transmission at 380-780nm. The modulus is 0.35.

GM3 49% and 58%

Contamac, the material producer, describes GM3 a terpolymer, based on high-purity glycerol methacrylate. Resultant lenses are durable, resilient to protein build-up and can be used for a variety of wearing regimens.

Property	Contaflex GM3 49%	Contaflex GM3 58%	Definitive 74	IGel 77
Classification	Filcon I 2	Filcon II 2	Filcon V3	Filcon II 3
USAN	Acofilcon B	Acofilcon A	Efrofilcon A	
Oxygen permeability (ISO) @ 35°C gas to gas (barrers)	15.9	25.5	60	39
Swell factor @ 20°C	1.29	1.38	1.615	-
Water content by refractometer @ 20°C	50%	59%	74%	-
Refractive index @ 20°C dry	1.522	1.523	1.510	-
Refractive index @ 20°C hydrated	1.416	1.402	1.375	-
Light transmission (%) @ 380-780nm	>94%	>95%	99%	-

Table 17: Examples for customizable contact lens materials and their properties

3.9 Other Customized Soft Multifocal Myopia Control Contact Lenses

Galifa Contactlinsen AG in St. Gallen, Switzerland, offers the app SmartFit soft for the calculation of an 'Individual' or 'Invispa Scalia 2' customized myopia control lens (www.galifa.ch).

Appenzeller Kontaktlinsen AG, Speicher, Switzerland, produces the 'Personelle proASSIST' MFSCL in a spheric, toric dynamic and prismatic version.

Hecht-Contactlinsen GmbH, Freiburg i. Br., Germany, produces lenses with a new myopia control concept. The 'myLIFE' RGP lenses were developed in cooperation with the Brian Holden Institute as part of a clinical study and incorporated into the eponymous contact lens concept. This type of lens will come from mid-2019 as MFSCL on the market.

None of these lenses has a reviewed proof of effectiveness. Until today.

3.10 Accommodation and progressive lenses

My interest was to find out, if MFSCLs change the accommodative behavior of the patients. Montés-Micó et al. (720) evaluated accommodative response and facility in presbyopic and non-presbyopic patients fitted with several types of simultaneous-image multifocal contact lenses. The unadapted wearers of simultaneous-image bifocals were fitted with the low- and high-addition Pure Vision and Focus Progressives simultaneous vision MFSCLs. Each patient wore each of the three types of CLs in random, successive order. Accommodative response, VA, accommodative facility, and contrast sensitivity at distance and near were evaluated for every lens. The mean age was 28.6 ±2.72 years in the non-presbyopic patients, they showed for all situations relatively linear 1:1 stimulus response. Distance and near accommodative facility rate for the presbyopic participants was zero for all conditions. The results of the study of Montés-Micó suggest that the simultaneous-image MFSCLs studied do not change accommodative functions.

To evaluate lens related changes in pupil and accommodative response for different accommodative stimuli with three different MFSCLs, Madrid-Costa et al. (721) checked accommodative and pupil responses. Young subjects were fitted with PureVision Low Add, PureVision High Add and Focus Progressives. No differences were found in accommodation response for accommodative stimuli studied between the SV lens and the three different MFSCLs ($p > 0.05$ for stimuli -2.5 D and -4 D). The data collected suggest that in young wearers, the MFSCLs studied do not alter the accommodative system or change pupil size compared with the SV lens.

In 2018, Gong et al. (387) found in 10 to 15 years old Children wearing MFSCLs reduced accommodative responses and more exophoria at increasingly higher accommodative demands than with SV CLs. This was probably because the children may relax their accommodation and use the positive peripheral addition or increased depth of focus from their multifocal CLs.

Another study regarding accommodation comes from Tarrant et al. (567). They tried to assess the effect on the accommodation of young adult emmetropes and myopes wearing bifocal soft CLs. With a Grand–Seiko optometer they measured accommodation responses for 4 target distances: 100 cm, 50 cm, 33 cm and 25 cm in 36 subjects (11 emmetropes and 25 myopes). Each of the measurements were made with 3 different types of corrections: single vision distance contact lenses, bifocal contact lenses (BF; +1.50 D add) and SV near contact lenses (+1.50 D added to distance prescription). Accommodation demands were set side by side with accommodation responses, the compensation offered by the lenses was calculated. Overall,

myopes tended to accommodate less than emmetropes for all distances, no matter what lens type worn. Tarrant found three main outcomes: 1. Myopes tend to accommodate less than emmetropic patients, 2. Accommodative demand is reduced with Bifocal contact lenses and SV near contact lenses 3. all subjects tend to overaccommodate with BF contact lenses (for 2 conditions only). We know from bifocal lenses, that they are an effective method of reducing accommodative effort. But if they also improve the accuracy of accommodation remains unclear.

20 normal pre-presbyopic patients under 35 years were tested by Lindskoop Pettersson et al. (722) for their accommodative responses when wearing a multifocal soft contact lens with a +1.00 D add, with distance center. Statistical analyses showed no difference in accommodative lag ($t = 0.8479$, $p = 0.407$) with and without the lens. In conclusion, young normal patients don't relax accommodation when fitted with a MFSCL with addition +1.00 D.

During accommodation, Aldossari et al. (723) found an increased eye length out to at least ±30° visual angle in young adult myopes and emmetropes (higher myopes 41 ±14 µm, emmetropes 30 ±12 µm, $P = 0.005$). Higher myopes showed significantly greater increase of axial length than the other groups at some positions. There were significant associations between nearsightedness and accommodation-induced changes in eye length at all positions.

The hypothesis that the state of peripheral refraction during accommodation may play some role in myopia development was investigated by Mathur et al. (724). They found for most of the adult emmetropes in the study only little changes with accommodation in relative peripheral refractive error and aberration. Hence it seems unlikely that such small changes can cause late-onset myopization.

In patients wearing a SV near lens on one eye and a MFSCL on the other eye, Anstice (4) found that the children actively accommodated on the near target. This implies that accommodation was driven through the distance part of the MFSCL. She concluded that if MFSCLs are worn binocularly, patients would continue to accommodate on near targets. Accommodation measurements committed the presence of myopic retinal defocus in the MFSCL wearing eyes, for distance as for near targets. Young patients use their MFSCLs different than presbyopic users do.

If accommodation was purely triggered by blur, then the young patients would not have needed to accommodate for the near target when the other eye was corrected with the SV near CL. But convergence and proximal cues drive accommodation as well. Probably these factors triggered the accommodative response seen.

The position of the focus points when a MFSCL is on the eye of a pre-presbyopic or presbyopic patient when looking at a distance target is positioned on the retina, while the second focus point, created by the peripheral addition zone of the MFSCL, is located in front of the retina resulting in myopic retinal defocus. In a pre-presbyopic patient, because this patient still can accommodate, the focus point of a far object is maintained on the retina and the focus point of a near object in front of the retina, so that myopic retinal defocus is also produced by near targets. The position of the focus points of a near object in a MFSCL wearer that is completely presbyopic are different: due to this he is not able to accommodate, the focus point created by the peripheral addition zone of the MFSCL is located at the retinal plane, while the focus point of the central distance zone is located behind the retina (resulting in hyperopic retinal defocus). Beginning presbyopes still do have a bit of accommodation, although not enough to keep a clear and comfortable view for sustained near work. In this case, the addition zone in the lens periphery is helping the remaining accommodation, so for reading a book one focal point is located on the retina (formed from the addition zone of the lens) while the second focal point is located posterior of the retina. In distances further away, early presbyopes can still use their remaining accommodation, which shifts the focus point of the lens

center back on the retina again. In this case there is no difference between a child and early presbyopes. Only a few patients are confronted with nearsightedness progression in their 40's.

Hyperopic retinal defocus at short distances has been suggested to play a role in the development and progression of nearsightedness in kids in school ages (17,271,580) and would have been an unwanted situation in MFSCL wearers. No kid in the DIMENZ study of Anstice (4) wearing MFSCLs was ever measured with hyperopic retinal defocus.

It is possible that some kids can relax their accommodation fully and use the peripheral addition zone of the MFSCL to focus on near objects. This would produce hyperopic retinal defocus when looking at near objects, even if it still produces myopic retinal defocus by looking at distant objects. This possibility asks for caution in the binocular fitting process of MFSCLs. To evaluate the presence of myopic retinal defocus for both distance and near objects precise measurements of accommodation should be done with kids wearing MFSCLs.

A study from 2008 (373) has evaluated the effect of MFSCLs on the lag of accommodation in 35 young adult patients (mean age 22.8 ±2.4 years). This study on distance center soft bifocal lenses with add 1.5 D showed that myopic patients accommodated less than emmetropes, irrespective of the lens type worn or the target viewing distance (15,269). In the Tarrant study the near addition part of the lens produced lower lag of accommodation measurements in emmetropes and myopes, and by looking at reading distance in some cases leads of accommodation were found. A greater reduction in accommodative lag was found while wearing the ACUVUE® bifocal CL than the SV near lens, even with the same amount of addition. In the idea of the authors this may be due to the bifocal CL gives greater depth of focus and is with this artificially extending the accommodation range of the patient. Another explanation is that bifocal CLs show greater amounts of spherical aberrations than SV lenses, which would produce more positive dioptric values in the near zones. Spherical aberrations are normally more negative when eyes accommodate on near objects, and adding positive spherical aberration in the bifocal CL could produce a better retinal image quality. This reduces the accommodative lag encountered by producing more accurate blur-driven accommodative response.

The idea behind fitting MFSCLs is not to change lags of accommodation by using the peripheral addition zone. Many studies have investigated the effect of lag of accommodation on myopia progression (173,268,275,373). Even if accommodative lag is enlarged in myopic patients, myopia treatments that reduced accommodative lag have been widely unsuccessful (19,200,416). Myopic retinal defocus is seen in uncorrected myopic children at distance, while it may not occur at near if the amount of nearsightedness is less than about 2 diopters and regardless of this progresses nearsightedness in the majority of subjects (343,344). If a child is wearing MFSCLs, myopic retinal defocus is also always present for near work. This is the possible key to the reduced rate of nearsightedness progression reported in children wearing MFSCLs.

3.11 Lens Care System

Worn contact lenses other than one day lenses must be cleaned and stored overnight. A solution is needed to disinfect the lens and to remove colonizing microbes from the lens outside, to have a wearable lens the next morning. Another job for the solution is to remove contaminations from tear film components like proteins and lipids, or environmental deposits from the lens surface.

Contamination can happen at each step of CL use. The use of CL solutions provides clean, decontaminated and preserved lenses. This prevents from infectious problems and improves the comfort of wear. CLs are contaminated essentially from dirty hands and cases, the use of water and environmental factors. The microorganisms causing sickness are in most cases Gram-negative bacteria, fungi and amoebae. CL deposits must not have an organic origin. These deposits are responsible for discomfort during wear and serve as a nutrient matrix for microbes. CLs with deposits cause more infections (725). Two main groups of solutions can be separated: the multi-purpose disinfecting solutions (MPS), using biguanides or polyquaternium-1. Those substances disrupt the microbial membranes which kills the microbes. Hydrogen peroxide (H_2O_2) is the second group, is strongly oxidizing proteins, lipids and microbial DNA, and killing the microbes in this way. To promote lens cleaning, solutions can enclose surfactants.

Each CL solution is unique in its composition, mechanism of action and shows different concentration of the ingredients. To select the best CL solution for a wearer, the ECP must be familiar with the different options. MFSCLs have to be cleaned in the same way as all other soft contact lenses.

Nichols et al. (726) reviewed and evaluated in 2019 the available data, indicating that in comparison with MPS, one-step peroxide solutions seem to promote better compliance, efficacy, comfort, and ocular surface outcomes for most of the users. Regarding the current published evidence, the recommendation is that ECPs make one-step peroxide solutions their first-line CL care recommendation for most patients wearing reusable lenses.

Contamac, the lens material producer, recommends:

For Definitive (Silicone-Hydrogel) 74% materials: Multi-Purpose Solutions. All tested solutions showed good compatibility. Enzymatic cleaners are no problem for Definitive 74% lenses. Contamac is not recommending the use of cleaners on alcohol base for Definitive 74%.

Peroxide solutions are compatible with Definitive 74%, but platin disc systems are preferred. If a tablet system is used, the pill has to be put into the container at the same time as the solution. Otherwise the stability of the CLs will be compromised.

The Johnson and Johnson Acuvue Oasys Lens is made of Senofilcon A, and tests discovered that the clinical response is modulated by the cleaning solutions. All lens care products tested reduced subjective comfort relative to daily disposables. Additionally, in patients using multi-purpose solution (MPS) increased incidence of corneal infiltrative events and solution-induced corneal staining was reported (727).

H_2O_2 systems provide usually better comfort compared with MPS solutions (728) and have been prescribed for CL wearers with reactions to preservatives (729,730). Other studies found no significant differences between H_2O_2 and MPS (731). Steele et al. (732) found a 2.86-3.8 fold risk for corneal infiltrative events with the use of multipurpose solutions.

The results of Guillon et al. (733) showed that in wearers of ACUVUE(®) OASYS(®) and PureVision™ lenses the CLEAR CARE(®) 3% hydrogen peroxide cleaning and disinfecting system significantly improved the CL wettability compared with Renu(®) fresh™ multi-purpose system, the mean median pre-lens non-invasive break-up time PL-NIBUT was 5.8 sec instead of 4.0 sec, $p<0.001$).

The external eye condition of contact lens wearers using H_2O_2 can decrease. The cause can be its insufficient cleaning efficacy. To solve this a contact lens detergent solution may be added (734).

In 2016, Berntsen et al. (735) found comparable CLUE scale comfort levels between the latest generation of MPSs compared to H_2O_2 disinfection. The tested three MPS/material combinations resulted in increased corneal staining <grade 1 of up to 0.57 units versus a H_2O_2 solution. Willcox et al. (736) collected about 70 cases per lens type after 1 month of use, they found the rate of contamination not affected by the type of contact lens (lotrafilcon A, balafilcon A, or comfilcon A) worn.

The effectiveness of 3% H_2O_2 (CLEAR CARE® of Alcon) platinum star system solution with and without HydraGlyde® Moisture Matrix was tested in 2018 by Gabriel et al. (737) with 5 compendial microorganisms required by the Food and Drug Administration (FDA) 510(k) and International Organization for Standardization (ISO) 14729 stand-alone procedures, 4 clinical isolates of Gram-positive and Gram-negative bacteria, and trophozoites and cysts of 2 Acanthamoeba strains causing microbial keratitis. Evaluation of microbial loads was done after disinfection and neutralization. After only 1.5-hour disinfection/neutralization time in the 3% H_2O_2 solution, Gabriel reports: *"Bacteria were reduced by 4.4 to 5.1 logs, yeast by 4.4 to 4.9 logs, and mold by 2.9 to 3.5 logs with and without organic soil. In addition, both solutions eliminated or effectively reduced populations of clinically relevant ocular bacterial isolates (4.5-5.0 logs), Acanthamoeba trophozoites (3.4-4.2 logs), and cysts (1.5-2.1 logs*)". The addition of HydraGlyde® (EOBO-21) to the 3% H2O2 lens care solution had no impact on antimicrobial activity.

From 2006 to 2015, the proportion of patients using H_2O_2 systems has nearly doubled (738).

Sometimes, switching the patient to an alternative CL- lens care product combination makes sense: Tilia et al. (739) described perceptibly improvement in ocular comfort and symptoms in symptomatic CL patients.

3.12 Questionnaires

The contact lens fitter survey

In a survey, I asked contact lens fitters in Europe about their fitting practice. The survey wanted to investigate how Swisslens RELAX lenses are fit. The survey was in German language, translation/original version: see appendix. The survey was sent to over 1'700 fitters, ophthalmologists and optometrists in Europe, 14 answered.

1. During the last 10 fittings, in how many cases did you follow the official fitting guide?

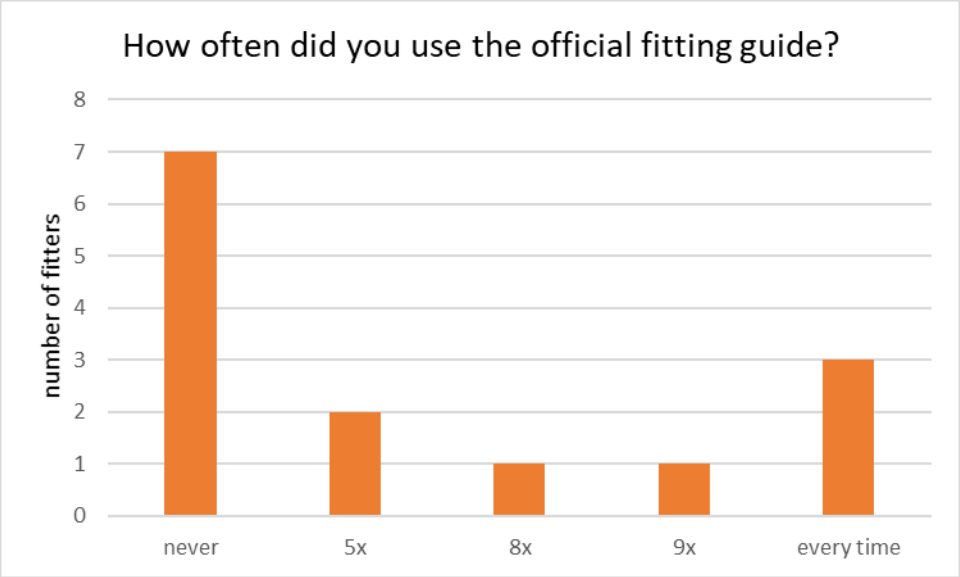

Figure 27: The use of the fitting guide

If not following the official fitting guide, what are you doing instead?

2. – Use another fitting guide: 6 use another fitting guide, 8 not
3. – calculate myself: 7 yes, 7 not
4. – sending the data to the lens company: 4 send data to Swisslens

5. How to choose peripheral CL design: 7 choose CSP, 5 the corneal diameter, 2 use each time the same standard

6. Trial lenses needed till final lens: 6 fitters need 1 lens, 7 fitters usually 2 lenses 7x, 1 fitter declared to use 8 trial lenses to find the correct lens

7. How many clients rebuy the lenses: 2 fitters declare 100%, 7 answered 90%, 4 fitters had 80% rebuys, one fitter reported 60% rebuys

8. What was the main cause if a customer did not rebuy the lenses? 4 fitters reported VA, for comfort, price, and not enough myopia control effect voted in each case 2 fitters. 3 fitters had no idea, 1 suspects moving away of customers as cause

How are patients selected for MFSCLs?

Selection criteria:

9. Patients are not hyperopic enough: for no fitter
10. Patients show already elevated myopia: for 9 yes, for 5 not
11. Fast myopia progression: for 9 yes, for 5 not
12. customers idea: for 1 fitter yes, for 13 not
13. parental idea: for no fitter
14. If fast myopia progression is the reason, what is the minimal annual myopia progression to choose MFSCLs? For 2 fitters ≥0,25, for 9 fitters ≥0,50, 2 reported ≥0,75 and one ≥1 D.

What are the motivations to fit MFSCLs for myopia control?

15. Because patients benefit: all reported yes
16. Because higher income: 3 answered yes, 11 no
17. Because it shows competence: 6 fitters agree, 8 not
18. Because of no internet availability: 4 reported yes, 10 no

19. After how many months do you see the patient again? 2 fitters after 3 months, 10 after 6 months, 2 want to recheck after 9 months

20. How complex is the official fitting guide?

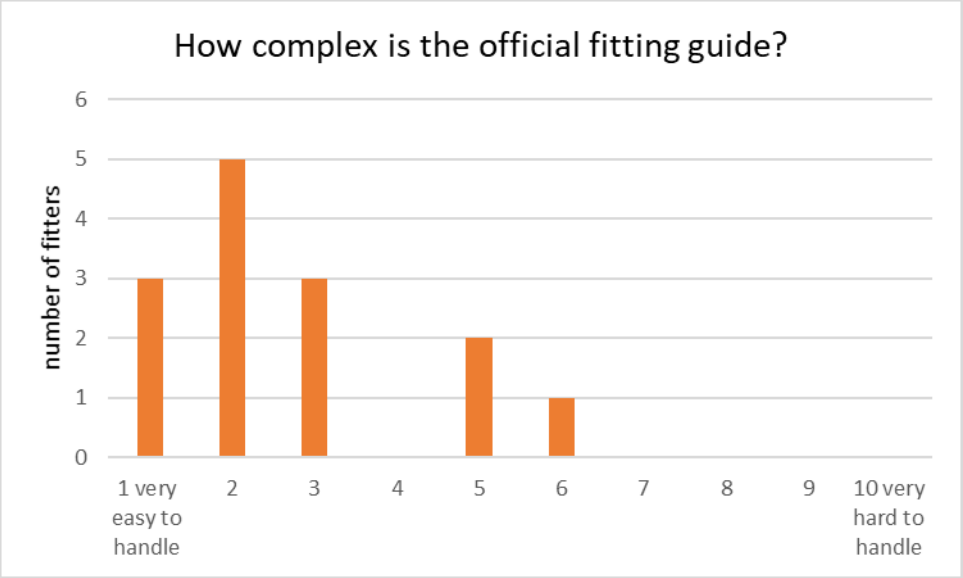

Figure 28: How complex is the official fitting guide?

21. Know the customers of the expected benefits? Every fitter informed the client about the benefits of RELAX MFSCLs.

The MFSCL wearer survey

In this survey I asked patients to answer questions about comfort and compliance. Most questions were adapted from CLDEQ-8 (635,636) and the CLUE (740) surveys. 18 Patients replied.

1. How long may you wear the lenses as recommended by your contact lens fitter? ___ Hour/day

Hour/day	14	12	11	10	9	8
Number of fitters	1	7	1	6	1	1

Table 18: How long may you wear the lenses?

This means that over 50% of the patients should wear the lenses more than 11 hour per day.

2. How often did you follow the instructions of your fitter regarding wearing time? (1 every time - 10 never)

Points	1	2	3	4	5	8	9
Number of clients	6	1	3	3	3	1	3

Table 19: How often did you follow the instructions of your fitter?

More than half of the clients follow the recommendations of the fitter.

3. When your eyes felt discomfort with your contact lenses, how intense was this feeling of discomfort at the end of your wearing time? (Never have it = 0; not at all intense = 1; very intense = 5)

Points	0	1	2	3
Number of clients	3	7	7	1

Table 20: How intense was this feeling of discomfort?

4. When your vision was blurry, how noticeable was the changeable, blurry, or foggy vision at the end of your wearing time? (Never have it = 0; not at all intense = 1; very intense = 5)

Points	0	1	2	3	4
Number of clients	4	3	7	3	1

Table 21: How noticeable was the changeable, blurry, or foggy vision?

How much do the following statements apply to your lenses:

Question: Answers:	Never	Rarely	Some-times	Fre-quently	Con-stantly
5. During a typical day in the past 2 weeks, how often did your eyes feel discomfort while wearing your contact lenses?	7	8	3	0	0
6. During a typical day in the past 2 weeks, how often did your vision change between clear and blurry or foggy while wearing your contact lenses?	7	9	2	0	0
7. During a typical day in the past 2 weeks, how often did your eyes bother you so much that you wanted to close them?	14	4	0	0	0
8. These lenses felt smooth in my eyes	0	0	0	5	13
9. The discomfort of the lenses caused me to be distracted from a task	13	4	1	0	0
10. On a typical day, I was aware of these lenses	7	8	2	0	0
11. I had to blink more often because these lenses were uncomfortable	5	9	4	0	0
12. I was able to very clearly see at the movies/cinema	2	2	3	5	6
13. I see with the lenses as well as with the glasses	1	2	2	2	11
14. Caring for these lenses was very straight forward	0	0	0	2	16
15. I always wash my hands before putting on the lenses	2	0	1	6	9
16. On a normal day I'm happy with my lenses	0	0	0	1	17
17. I sleep with these lenses on the eye	16	1	1	0	0
18. When wearing lenses, I forget that I have these on	1	0	1	6	10
19. The comfort of the first hour of wear is the same as in the last one	0	3	3	9	3
20. My lenses feel soft throughout the day	0	0	1	8	9
21. These lenses increase my quality of life	0	0	0	3	15
22. Do you have eye irritation when you wake up?	17	1	0	0	0
23. I use wetting drops	13	2	1	2	0
24. How often during the past 2 weeks, did your eyes bother you so much while wearing your contact lenses that you felt as if you needed to stop whatever you were doing and take out your contact lenses?	14	4	0	0	0

Table 22: MFSCL wearer survey

In the fields after the question stands the number of patients answers for that field. The questions 3 to 7, and 24 are from the CLDEQ-8 questionnaire (635,636). Questions 8 to 12 and 14 are taken from the CLUE scales (740). All other questions are own questions.

Questions 1 and 2 concerned the verification of customer compliance. We have specified the recommended wearing time of glasses between 10 and 14 hours, depending on the material and other factors. The customers remembered a shorter wearing time than we indicated, about 2 hours less. Answers for question 2 included 2 ways of not following the instructions: I expected the wearers leaving the lenses too long on the eye. But a third of the clients reported, they have no time to have the lenses long enough on the eye.

	Compliance	Comfort	Vision	Dryness	Handling
Literature question		3, 5, 7, 8, 9, 10	4, 6, 12,	11,	14
Own control	1, 2, 15, 17	16, 18, 19, 20, 24	13,	22, 23	

Table 23: questionnaires question types

I missed in the CLDEQ-8 and CLUE questionnaires questions targeting compliance. So I added them.

The own questions about comfort, vision and dryness topics were used to ensure the results of the questionnaires from literature. So I asked the same question very similarly twice. The answers were consistent.

Most wearers reported a contact lens wear without significant problems. This could be, because unsatisfied users have finished their lens wearing and are not active contact lens customers any more.

The clients that were more uncompliant are young adults, in this sample.

4 Discussion / Conflicts

4.1 Myopia progression

The predicted fast increases in myopia and high myopia are expected to be caused by environmental factors and altered lifestyle. This problem is seen in Asian and Europe as well. Today we spend less time outdoors and have more near-work activities (66). The genetic factors cannot be the explanation for the rapidly rising prevalence seen in such a short time period. Possibly is the pressure given to the children in Asian countries by the school system a cause. Intense use of electronic devices over a prolonged period could also be a driver in myopia progression. Possible other factors causing higher amounts of myopia progression are light levels and specific wavelengths, time spent in sun, vitamin D and others. Providing peripheral hyperopic defocus to the retina is accelerating axial growth. As we see a gradual slowing of myopic progression in normal patients with age, which is a natural process, it is difficult to separate this natural process from the treatment effect in studies using a myopia control treatment in both eyes (119–122,177). Better would be to give the treatment in one eye, and a placebo option in the other. However, this is more for animal models, as it seems unethical to use this in children.

I also acknowledge the retrospective design of this thesis perhaps carry the potential bias.

Not each study measuring children with cycloplegic agents used the same drug: a previous study of Manny et al. (741) has shown 1% tropicamide is an effective cycloplegic agent for myopic children, but most studies use cyclopentolate. How and if this choice of the agent influences the result is unknown to me.

As Cooper et al. (742) found, it is good to stabilize myopia around -4 D, above this range the possibility to suffer from a concomitant disease of myopia is exponentially larger.

4.2 Normal myopia progression rates versus own progression data

Not all children and young adults show the same progression rate. Asians have a greater risk to reach high myopia levels than Caucasians, and show higher annual progression rates. A Malaysian study (743) showed that children with a significant near esophoria are more likely to develop myopia.
By looking up ‘normal’ progression rates, I found a lot of different numbers, usually was it the result of control groups:

Study	Annual progression in D	Ethnicity	Age group in years	notes
Clark et al., 2015 (446)	−0.60 ±0.4	Asian	6 - 15	based on noncyclo-plegic refraction
Chia et al., 2012 (108)	-0.60 ±0.35	Asian	6 - 12	
Lee et al., 2006 (437)	-0.75 ±0.35	Asian	6 - 12	
Yam et al., 2019 (201)	-0.81 ±0.53	Asian	4 - 12	
Aller et al., 2016 (116)	-0.79 ±0.43	Americans	8 – 18 (13.5 ±2.2)	
Chen et al., 2013 (744)	-0.86 ±0.42	Asian	6 - 12	
Ruiz-Pomeda et al., 2018 (118)	-0.37 ±1.13	Caucasians	8 – 12 (11.01 ±1.23)	

Table 24: Normal myopia progression, found in literature

My idea was to compare the progression rates of MFSCL wearers (like RELAX) with a historical control group. Because none of the found control groups fitted in ethnicity, age groups or selection criteria, I analyzed existing historical data from the next 100 myopic customers.

The inclusion criteria:

- 4 to 21 years old, inclusive, at baseline examination
- Providing a complete historical dataset, covering a 18- to 70-moths study period
- 0.2 logMAR or better best-corrected visual acuity in each eye
- A historical annual myopia progression rate of at least 0.5 D in the two years before study period

Exclusion criteria were:

- Any form of refractive surgery
- Any form of myopia management
- previous gas permeable CL wear for longer than 1 month
- Myopia over 6.5 D, astigmatism over 3 D
- Any disease or condition than influences the refraction or VA of the eye
- Binocular vision problems e.g., strabismus, amblyopia, oculomotor nerve palsies, etc.
- Systemic disease that may affect vision or vision development (e.g., diabetes, Down syndrome, etc.)
- Chronic use of medications that may affect refraction

So, the following results show my patients data of myopia progression, without any kind of treatment. The results can be taken as a reference, to compare the results of patients with a myopia management option.

For the following statistics, IBM SPSS Statistics version 25 was used.

Range, min and max (females and males)

	N	Range	Minimum	Maximum
	Statistic	Statistic	Statistic	Statistic
Study time in months	188	51	18	69
Prescription at study start SE	188	5.04	-4.67	.37
Prescription at study end SE	188	6.00	-6.50	-.50
Difference SE	188	4.62	-4.87	-.25
Annual progression in D	188	1.687	-1.77	-.0857
Age in months at study start	188	186.0	57.0	243.0
Age in months at study end	188	175.0	92.0	267.0
Middle (mean) age in months	188	180.5	74.5	255.0

Table 25: Range, min and max (females and males)

Std-deviations and variance (females and males)

	Mean		std.-deviation	variance	kurtosis
	statistic	std.-error	statistic	statistic	statistic
Study time in months	31.76	.712	9.759	95.245	2.371
Prescription at study start SE	-1.568	.07292275	.9998	1.000	.726
Prescription at study end SE	-3.481	.09016	1.236	1.528	-.510
Difference SE	-1.913	.06713278	.921	.847	.582
Annual progression in D	-.734	.02227	.3053	.093	.001
Age in months at start	136.511	2.4528	33.6305	1131.011	.961
Age in months at study end	168.266	2.5296	34.6846	1203.020	.576
Middle (mean) age in months	152.388	2.4659	33.8113	1143.204	.814

Table 26: Std-deviations and variance (females and males)

Range, min and max (females)

	N	Range	Minimum	Maximum
	Statistic	Statistic	Statistic	Statistic
Study time in months	114	48	21	69
Prescription at study start SE	114	5.04	-4.67	.37
Prescription at study end SE	114	6.00	-6.50	-.50
Difference SE	114	4.25	-4.75	-.50
Annual progression in D	114	1.566	-1.77	-.21
Age in months at study start	114	156	57	213
Age in months at study end	114	157	92	249
Middle (mean) age in months	114	156.5	74.5	231

Table 27: Range, min and max (females)

Std-deviations and variance (females)

	Mean		std.-deviation	variance	kurtosis
	statistic	std.-error	statistic	statistic	statistic
Study time in months	31.39	.863	9.219	84.982	4.214
Prescription at study start SE	-1.70	.10	1.07	1.146	.141
Prescription at study end SE	-3.68	.12	1.23	1.516	-.420
Difference SE	-1.98	.087	.927	.860	.253
Annual progression in D	-.76	.029	.31	.096	.263
Age in months at study start	132.05	2.76	29.52	871.342	.534
Age in months at study end	163.44	2.74	29.20	852.815	.481
Middle (mean) age in months	147.75	2.72	28.997	840.833	.612

Table 28: Std-deviations and variance (females)

Range, min and max (males)

	N	Range	Minimum	Maximum
	Statistic	Statistic	Statistic	Statistic
Study time in months	74	44	18	62
Prescription at study start SE	74	4.49	-4.37	.120
Prescription at study end SE	74	5.25	-6.00	-.75
Difference SE	74	4.62	-4.87	-.25
Annual progression in D	74	1.26	-1.35	-.0857
Age in months at study start	74	165.0	78.0	243.0
Age in months at study end	74	171.0	96.0	267.0
Middle (mean) age in months	74	168.0	87.0	255.0

Table 29: Range, min and max (males)

Std-deviations and variance (males)

	Mean		std.-deviation	variance	kurtosis
	statistic	std.-error	statistic	statistic	statistic
Study time in months	32.32	1.230	10.578	111.893	.761
Prescription at study start SE	-1.36	.0985	.847	.717	2.242
Prescription at study end SE	-3.17	.1378	1.185	1.405	-.283
Difference SE	-1.80	.105	.905	.819	1.512
Annual progression in D	-.689	.03425	.2946	.087	-.606
Age in months at study start	143.4	4.4564	38.3355	1469.608	.396
Age in months at study end	175.7	4.7493	40.8551	1669.143	-.200
Middle (mean) age in months	159.5	4.5640	39.2607	1541.402	.081

Table 30: Std-deviations and variance (males)

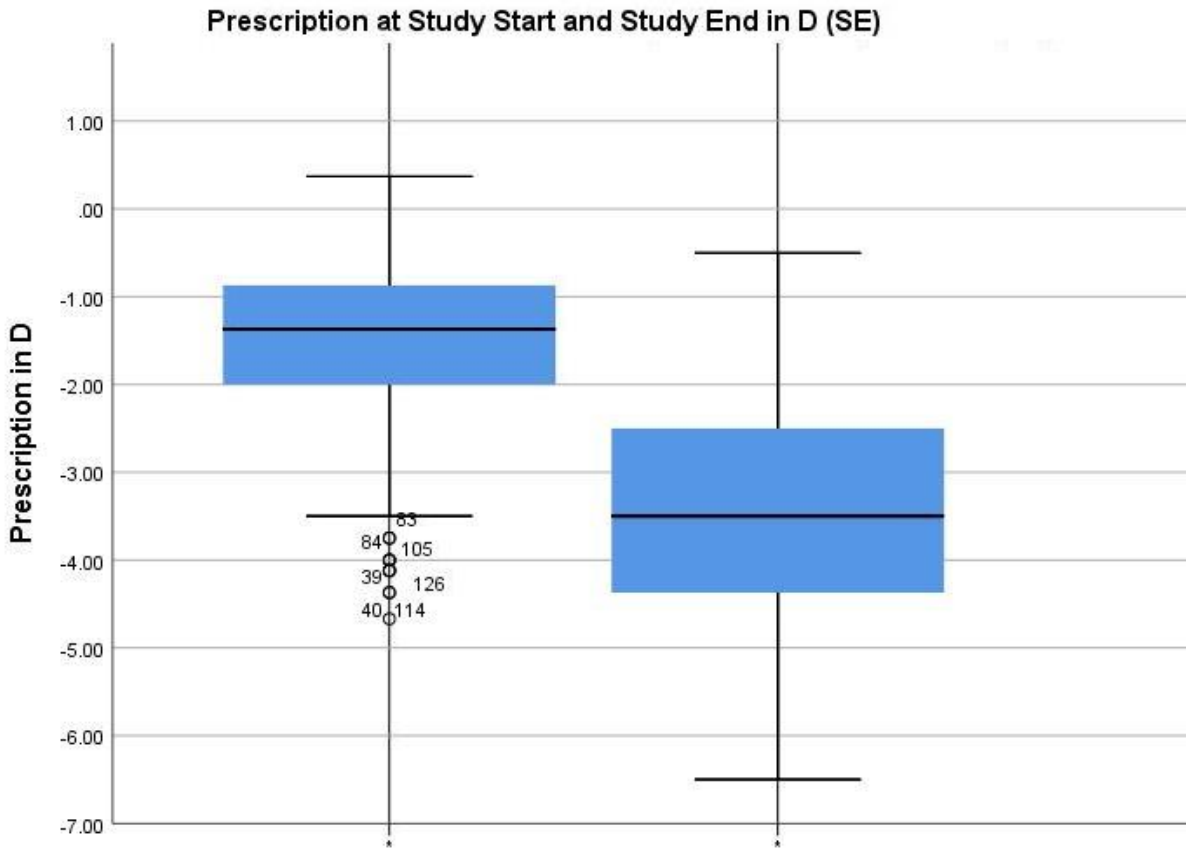

Figure 29: boxplot prescription at study start and study end

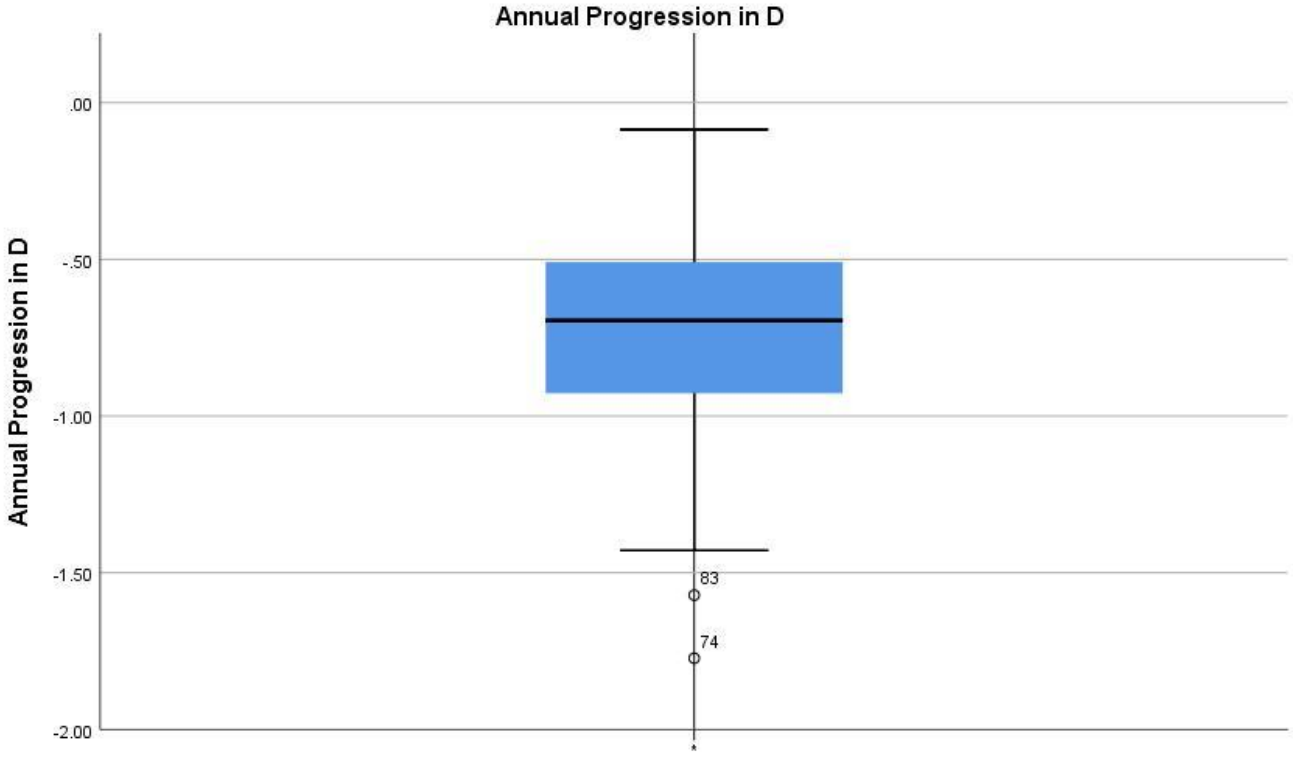

Figure 30: boxplot annual progression in D

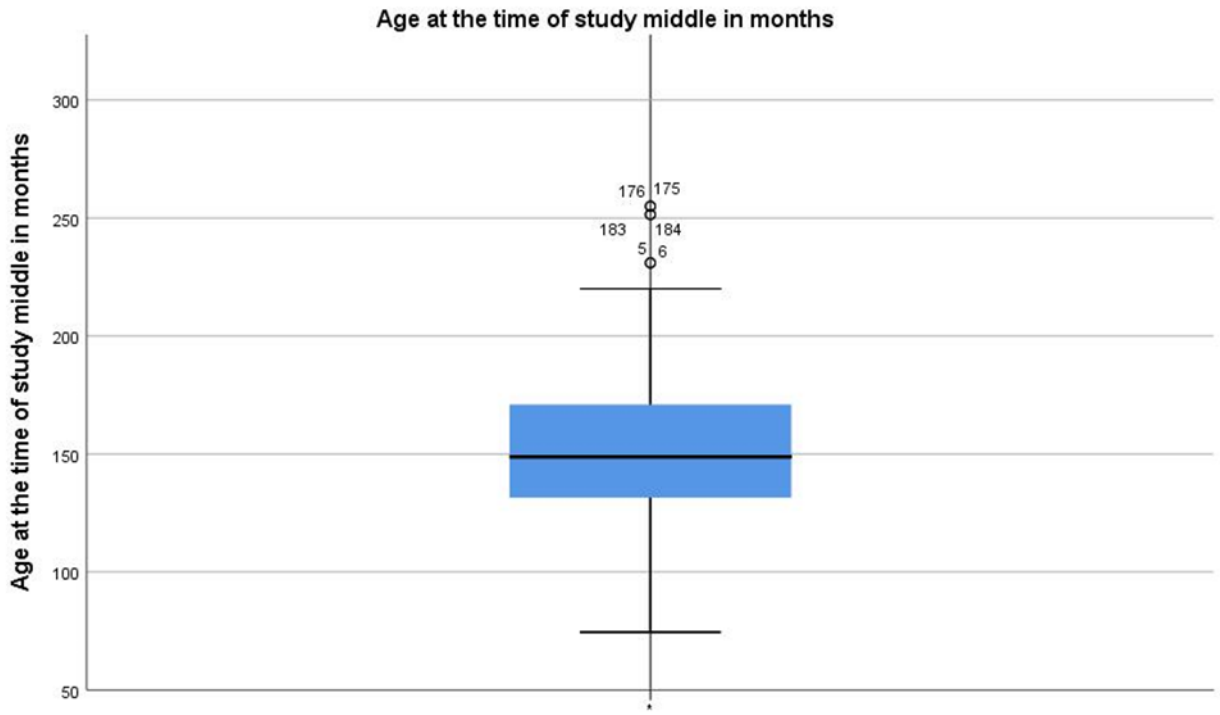

Figure 31: boxplot middle (mean) age in months

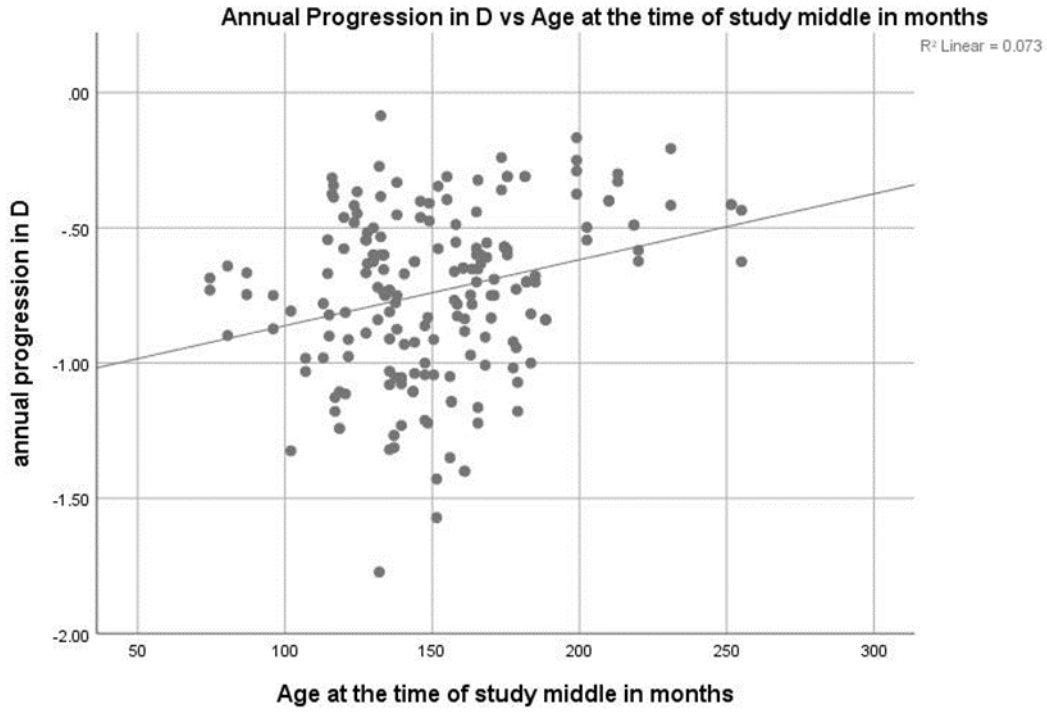

Figure 32: annual progression vs middle (mean) age

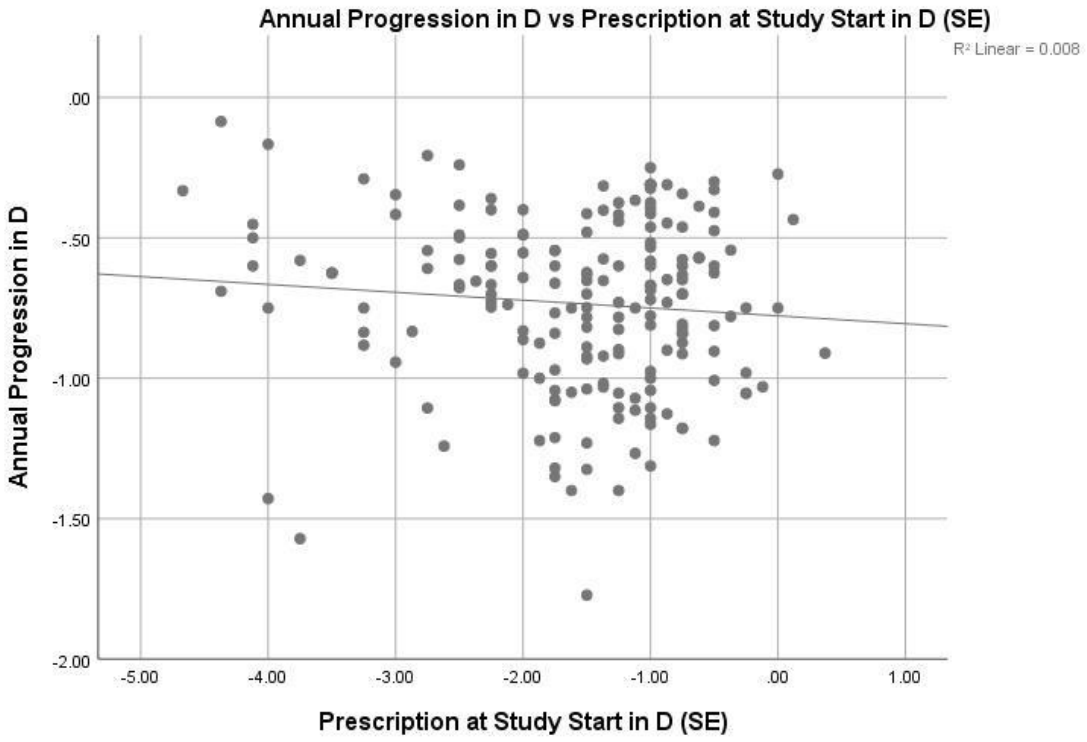

Figure 33: annual progression vs prescription at study start

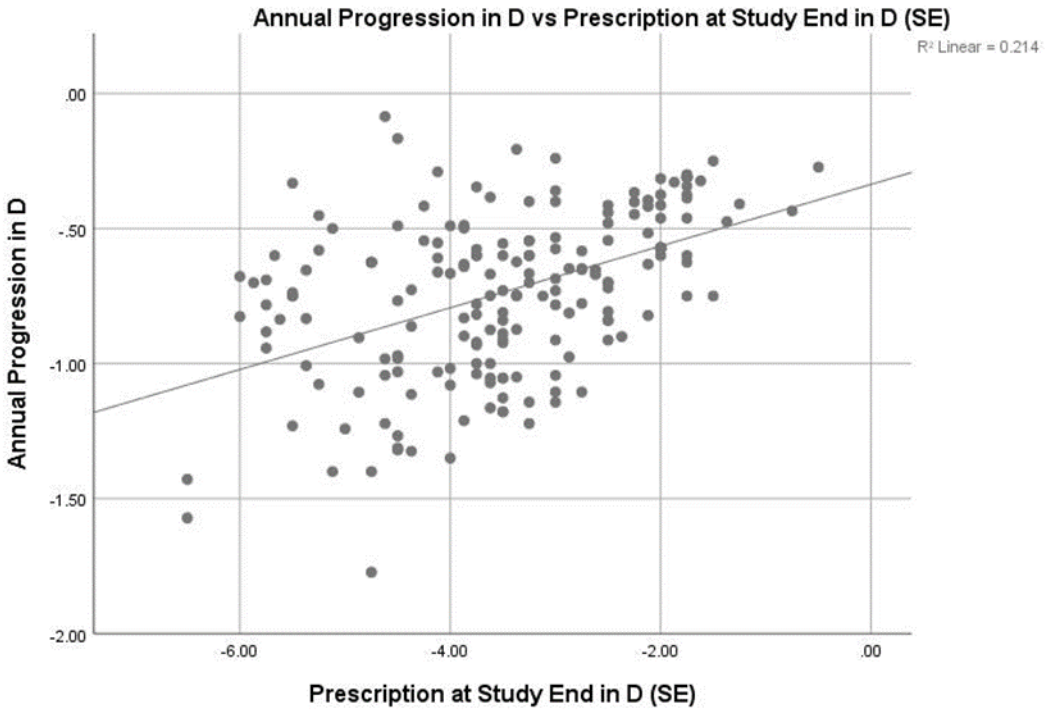

Figure 34: annual progression vs prescription at study end

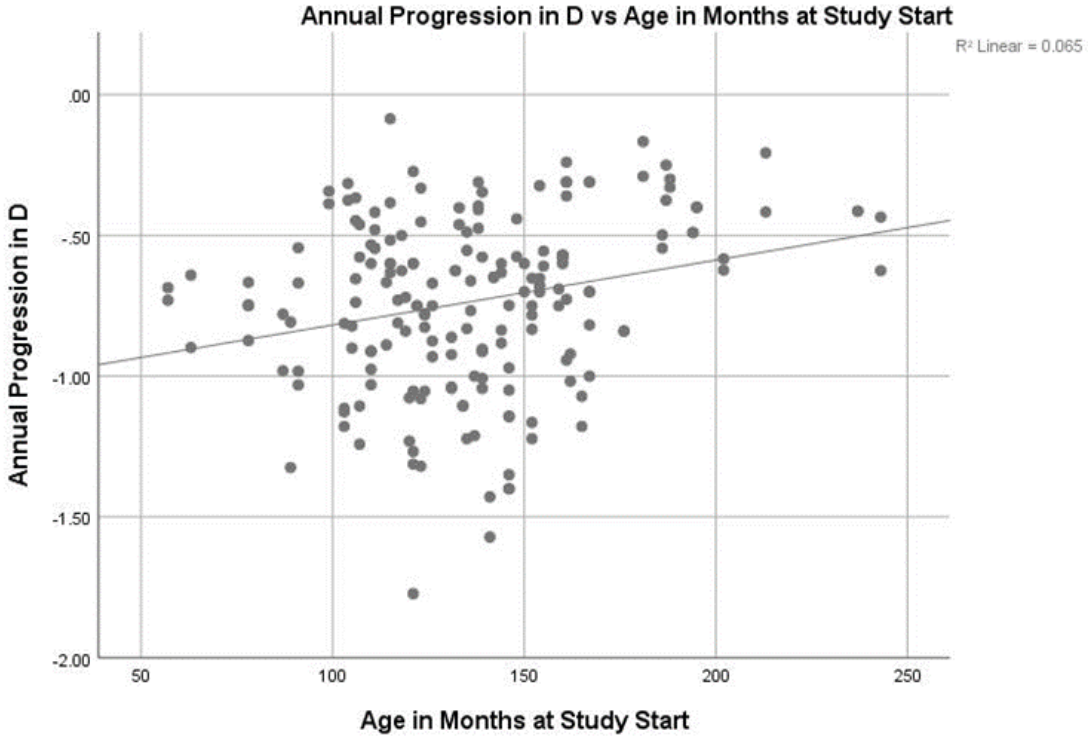

Figure 35: age at study start vs annual progression

The ANOVA test (one factor, annual progression) showed a statistically significant correlation between annual progression and refraction at study end. Patients with higher myopia at study end showed higher progression rates (significance=0.001).

Test of the homogeneity of the variances

		Levene-Statistic	df1	df2	Significance
Age in months at study end	Based on the mean	3.728	29	48	.000
Age in months at start	Based on the mean	3.357	29	48	.000
Difference months	Based on the mean	18.209	29	48	.000
Prescription 1 SE	Based on the mean	3.344	29	48	.000
Prescription 2 SE	Based on the mean	3.287	29	48	.000
Middle (mean) age	Based on the mean	3.659	29	48	.000

Table 31: Test of the homogeneity of the variances

One-factorial ANOVA (factor: annual progression)

		F	Significance
age in months at study end	Relation to annual progression	1.745	.014
age in months at study start	Relation to annual progression	1.665	.022
study time in months	Relation to annual progression	3.061	.000
prescription at study start SE	Relation to annual progression	1.575	.036
prescription at study end SE	Relation to annual progression	2.159	.001
middle age	Relation to annual progression	1.689	.019

Table 32: One-factorial ANOVA

After applying the criteria, 94 patients with 188 eyes remained in the study. 57 patients were female (60.6%). The ethnicity was Caucasian. The mean age of the study group was 12.7 years (152 months). The mean study period was 31.8 months. Due to the retrospective character of this study, the timespan this work covers was different for each eye pair, between 18 and 69 months. So I used the age the patient had in the middle of the covered time to compare the results ("Age at the time of study middle in months" or "middle (mean) age in months"). The children and young adults started with a median SE of -1.57 D, and ended with a median SE of -3.48 D. The mean annual progression rate was 0.73 D.

The progression rate I found was in the expected range. Ruiz-Pomeda et al. (118) found a lower mean progression rate, but I had preselected patients with a reported underlying annual progression of at least 0.5 D over two years. So, it was expected to find values of more than 0.5 D. If I compare the progressing Caucasians with Asians, the difference is not big (to e.g. Yam et al. (201): 0.08 D). Compared to mixed ethnicities like the data from Aller et al. (116), the difference was even smaller (0.06 D).

Principally can placebo groups of intervention trials not represent the general population. So were these children enrolled in the studies, because the parents wanted that because of their concern of e.g. about the rapid myopia progression. Studies based on a broad population or all children of a school tend to report lower progression rates. Such did for example Fan et al. (745) by testing more than 7'500 myopic Asian/Chinese children aged 5 to 16 (mean, 9.3) years in Hong Kong, reporting an annual progression rate of 0.63 D, and Donovan and colleagues (177) found in a Meta-analysis an annual progression rate for Europeans of about 1 D in 7 year old, 0.8 D in 8 year old, 0.65 D in 9 year old, 0.55 D in 10 year old and 0.5 D in 11 year old.

But what do these progression rates tell us? Must a child with a high progression rate reach high myopia in adult life? Isolated tells the progression rate not much.

Jensen (746) analyzed data over a 10-year period. At study start, the Danish children were 9 to 12 years old and controlled over two years. At study end, the patients are now 17 to twenty years old, the mean refractive error increased from -2.77 D to -5.14 D. All parameters were controlled at study start and study end: age at début, myopia level, IOP, changes at the fundus, status of phoria, near-point of convergence and accommodation. The only parameter predicting high myopia was 'age at début'. The refractive error among the children with a début (age of onset) below 7 years of age was -6.60 D, but only -3.72 D in children with an age of onset after 10 years. The refractive change over the second, 8-year period was not statistically related to the age of onset. The annual progression rate depended not on the degree of myopia, the changes at the fundus or the intraocular pressure. Nevertheless, by using a combination of these parameters, some patients could be found who had a high rate of progression.

4.3 The Peripheral Defocus Hypothesis

The peripheral defocus hypothesis remains uncertain in humans, while different studies have demonstrated that the axial length in animals eyes has the ability to respond to myopic and hyperopic defocus by modification (565).

In a normal optometrist practice, it is not possible to measure if the myopic defocus induced by MFSCLs or Ortho-K was sufficient to cover most part of the retina. Therefore, the treatment zones are calculated by the contact lens producers for a normal myopic retinal profile. But in the uncommon case that the profile is very steep toward the periphery ('prolate' shape), the effect of the lens may be not strong enough and will still produce hyperopic peripheral defocus (117,353).

The relatively large pupil sizes of the children must be taken into account. Probably show children with larger pupil diameters better response to optical myopia control treatments, because in each case enough myopic defocus is present (56,374,375).

Lam et al. (117) found a better retardation effect when daily wearing hours increased. And if this both is true; this advocate again the peripheral defocus hypothesis: constant myopic defocus presented to the retina can act to decrease myopia progression.

4.4 Distance-Center Multifocal Soft Contact Lenses vs Other Interventions

Different methods to decrease myopia progression have been investigated in the past. But the results are difficult to compare. Unequal ethnicity, placebo groups, environments, study duration, and even definition of myopia contribute to different results. A way to try to reduce these factors is comparing the results on the reduction in percent (56).

All myopia management options may be the strongest the sooner they are initiated (493,747).

Optical Myopia Control Interventions

Multifocal soft contact lenses MFSCLs

The rate of myopia control with MFSCLs as quite linear, as Lam et al. (117) described, and no plateau effect was observed. This is brilliant for the wearers and fitters of such lenses, and it is also valid for Ortho-K: if the patients wear the lenses, the myopia management effect is active, no matter how many years the lenses are worn.

Fresnel principle dual-power lenses studies using myopic defocus in experimental animals (356,748,749) support the hypothesis that the retinal location could be less important than the total area of the involved retina. But this would lead to the idea, that also multifocal near center soft contact lenses should be effective in controlling myopia. Thomas A. Aller is planning to finish the study "Myopia Progression in Children Wearing Near Center and Distance Center Multifocals - a Randomized Controlled Clinical Trial: Can Distance Center and Near Center Multifocal Contact Lenses Control Myopia Progression in Children?" on that topic in summer 2020 (750). The "total area hypothesis" can explain, why more than one brand of lenses or power profile is effective.

Many health institutions like the WHO, the AAO, the Brien Holden Vision Institute in Australia and the British Association of Optometrists have published advices for the use of myopia management CLs. Although research into peripheral refraction associated with myopia control has not been completed, several studies have clearly shown that MFSCLs and Ortho-K positively influence the slowing down of myopia progression. Walline reviewed the peer-reviewed literature of studies, finding a reduction of up to 50%, and Aller showed a success rate of over 70% in his trial, for myopia progression reduction. However, not 100% of the children responded positively to the products in these studies. Why do not such lenses work for all children? And how can the products be improved to make the myopia-controlling effect visible to every wearer? Although we have today strong evidence that MFSCLs slow progression of myopia and axial elongation, the mechanism of the control effect is quite unknown (751). The time of MFSCL wear in studies is critical. In many MFSCL myopia control studies, the patients wore the lenses for only 1 year or less (565). As known from other myopia management options, the best effect is seen in the first year (19,197). This demands for a minimum study duration of 2 years in order to measure the myopia control efficacy, during the years a child would normally progress (147,752).

The significantly lower myopia progression and axial growth found in children wearing MFSCLs compared with SV distance CLs, propose that sustained myopic defocus is efficiently controlling myopia progression. It does not matter whether it is presented to the retina at the same time with a clear distance image. MFSCLs provide normal acuity and contrast sensitivity. Such lenses can slow myopic progression in a relatively safe and effective way. Fitting soft CLs is an established method for optically correcting myopia. MFSCLs can be worn for decades, the safety risks are well known, and if a potential complication occurs, ECPs are familiar with their handling (56).

Ortho-K

Another optical solution is Ortho-K, it was thought to be an effective treatment in controlling progression of myopia (119,123). Orthokeratology presses the central cornea flat, shifts cells to the side in the midperiphery and steepens like this the cornea there. This produces a myopic defocus, similar to MFSCLs. This is thought to slow the axial elongation of the eye (114,753). Fitting Ortho-K requires additional skills of the CL fitter, and the discomfort during overnight wear, the higher cost, and the risks of infective keratitis reduce the possibility of a widespread use (754–758). And recently published Hiraoka et al. (129) a study covering 10 years of Ortho-K wear. The study from Japan reported less unwanted events than expected, but also an annual myopia progression reduction of only 0.07 D.

Ortho-K wearers show slower axial elongation when they have higher baseline myopia (119,121,124). “Because uncorrected refractive error extends across the retina (753,759,760), greater baseline myopia may have led to greater peripheral myopic blur for orthokeratology contact lens wearers but not for single-vision spectacle or contact lens wearers whose peripheral refractive error was corrected”, write Walline et al. (565). This hypothesis would say, that higher dioptric power of the treatment zone of the lenses, producing more myopic blur, would lead to better myopia progression control. But this has not been proofed to date.

Another open question is whether Ortho-K lenses can be developed to further improve myopia control effects. New Ortho-K lens designs are in the testing phase, for example a lens that wants to provide simultaneously a vision correction area and a myopic defocus area (US 9753309 B2 Patent by Drs. Martin Lörtscher and John R. Phillips). Unknown is the effect of interrupting multifocal or Ortho-K wear from time to time on treatment efficacy. Another idea is, that Ortho-K wearers with rapidly recovering corneas could wear MFSCLs, to possibly combine the myopia control effects and extend the time of treatment effects. New ideas and methods to analyze the relative corneal refractive power and its role in myopia control with

orthokeratology are developed. Wang et al. (761) published, that their new method tells that how the combination of spherical equivalent, corneal asymmetry, and astigmatism determines modulation of the maximal relative corneal refractive power and a large amplitude of modulation is associated with a higher probability of effective control of myopia progression.

Discontinuing Ortho-K lens wear at or before the age of 14 years led to a more rapid increase in axial length. And this 'rebound effect' was greater than the SV glasses wearing control group (414). Normally could be expected a return to the amount of the control group. But why does this rebound overshot that point? Probably an effect of the cornea, an overcompensation after Ortho-K pressure over the study time? To measure axial length in Ortho-K is difficult anyway, because the pressure of the lens changes the place of the starting point.

Pharmacological Control of Myopia

Atropine

Many myopia management studies regarding the effects of atropine for control are published, and many more will follow soon. But some important questions are still unanswered. At this time, we don't know the exact site of action of atropine in myopic eyes (762). Possible sites for the inhibitory effect on myopia progression of atropine are the sclera, the choroid, the retina or others. Older studies have suggested that the Atropine is working on lens accommodation, whereas more recent works have shown that the myopia controlling effect is rather via a nonaccommodative pathway in the retina or sclera (430,763). Also unclear are the underlying cellular and pharmacological mechanisms (764,765). Until the answers to the open questions of the site of action and mechanisms of atropine are found, not many advances in drug formulations can be expected. And more studies are needed to find the correct atropine dosing and treatment regimens. How long atropine treatment should be continued, when and how it should be stopped is not clearly defined yet. Also discussed should be the option and effects of ''prescribing'' short drug holidays (766) to prevent tolerance with higher concentrations (52,443).

Atropine in high and medium doses showed the best controlling effects, but the side effects like glare, photophobia, unclear near vision and the strong rebound effect after cessation of the treatment have ended its option for a widespread clinical use (107,441,767).

Because the response to Atropine is concentration-dependent, what would cause an increased frequency of 0.01% Atropine eye drops, like twice per day? In theory it should give a better myopia control effect. This is an idea for a further study.

More studies are also needed to clarify the effects and safety of Atropine for the extended chronic use in children under 6 years, and its efficacy in adolescents over 12 years. What about the Atropine effects in those who are still hyperopic, as a preventative strategy, and in children with myopia over 6 diopters, can they also benefit? The effects and very long-term side-effects of low dose Atropine in later adulthood are not yet known and require investigation. Actual guidelines for the application of topical Atropine are available (768).

Only 2% of patients stop treatment due to side effects of low dose Atropine in the 2018 study of Diaz-Llopis et al. (769).

Pirenzepine

The increasing demand for myopia control options is a good argument for further studies on the efficacy and safety of topical pirenzepine, which showed promising early results (196,198,368,463). It is less likely to produce mydriasis and cycloplegia, but still produces moderate effects in myopia management (770,771). However, the search for pirenzepine studies was limited to a few older articles (196,198,465). Further trials and registration of 2% Pirenzepine gel drops were not pursued, and pirenzepine gel is no longer on the market (772). To add pirenzepine to the favorites, further good controlled trials with larger sample sizes are necessary to certify its effect. For the use of atropine, a much lower dose had still enough treatment effect, but much less side effect. Would it be possible to find such a smaller concentration also for Pirenzepine?

7-Methylxanthine (7-MX) and Timolol

There is need for more studies on 7-MX and related compounds. One of the problems is the relatively short half-life, this needs automatically a frequent dosing over the day. Even twice per day dosing is not sufficient enough to hold the effective serum concentration level of 7-MX. Best would be an improved formulation like a sustained-release formulation (476). Further research is needed to clarify underlying mechanisms, the systemic side effects in children with longer-term use of 7-MX. The combination effects of 7-MX with other myopia control options have to be explored.

Animal studies have shown that ‘‘myopic growth’’ occurs mostly at night (773). The results of the timolol trial by Jensen (473) were probably disappointing, because the beta-blocker Timolol is known for his clinically little effect on night-time IOP (774). New on-going experimental studies are promising, involving other ocular hypotensive drugs with better night-time IOP lowering effects like latanoprost, a prostaglandin analogue (469), and brimonidine, an alpha2-adrenoceptor agonist (467). These drugs help not only to reduce myopia progression, they also protect the eye from primary open-angle glaucoma, for which myopic persons are at increased risk (775–777).

Environmental Influences

Outdoors

There are as much answers as questions about the environmental influences on myopia and the possible protective potential for outdoor exposure to protect against myopia onset and to slow axial elongation. Further research is needed to find the underlying mechanism of action and the key temporal factors. At the moment, it is unknown if 2 hours per day outdoor light presented in one block is more or as effective as two 1-hour daily sessions. What is the best time in the day to go out (midday?), or what minimum light intensity is necessary? What spectral components? Does it matter to do sports outside or using the phone? Has the age of the child an influence on the success of this therapy form? Is there only a protection against myopia onset or also against axial elongation?

Instruments or gadgets like the smart garments (known from spinal and posture alignment therapy), Cloudclip or an eye tracker with attached distance sensor were presented at the 16th International Myopia Conference (Birmingham, UK, 2017). The idea is that such instruments give a signal to the user, if the reading distance is too close (778,779). All these smart gadgets and technologies could be soon integrated into myopia management. An assessment of efficacy for each individual tool will be needed to slow the progression of myopia.

In the evening is the human body more susceptible for myopic retinal defocus, the STOP signal for myopia progression, while in the earlier daytime more for the GO signal, the hyperopic defocus (55,780). Could this be the effect of different Dopamine levels?

Near work

As Guan et al. (167) found, the use of smart phones and computers reduce the children's VA, while watching television viewing had no negative effect. While Lin et al. (98) and Huang et al. (301) found that intense near work is leading to higher amounts of myopia, Wojciechowski et al. (62) stated that these changes are possibly more related to genetic factors. Further studies may find the real cause.

Surgical Interventions for Controlling Myopia

Posterior Scleral Reinforcement (PSR) is partially effective in stabilizing high myopia, but studies reporting on the efficacy of this procedure have limitations (781–783). Scleral reinforcement surgery is not very popular. Donor sclera material is also difficult to acquire and store, and include the risk of rejection. Artificial materials like Gore-Tex (784,785) have been tested. PSR can cause severe surgical trauma. This procedure is much more popular in other countries, such as Russia and Japan. It remains unclear in what developmental stage this operation should be performed (786).

For the other two surgical options, sclera strengthening injection (SSI) (483) and Collagen Crosslinking (CCL) technique (787,788), clinical evaluation is either limited (SSI) or nonexistent (CCL). CCL is already used for corneal applications (789) and interest in its use in the control of human myopia has led to ongoing studies on animal models of myopia (790–792).

For all these options, general anesthesia is needed. There is need to find a simple and safe surgical technique that requires only local anesthesia. The even bigger need is to find a synthetic scleral implant that is as biocompatible as biostable. Only with materials like that can the risk of infection and rejection be reduced.

There is concern about potential ocular toxic effects on nearby tissues, including the choroid and retina, when using sclera strengthening injections. Russian studies on chicks did not show slowing of axial growth in either of two studies (793,794). The use of a thermo-responsive material (poly[N-isopropylacrylamide-co-acrylic acid]) produced a significant thickening of the outer fibrous layer of the chick sclera, a good finding to possibly prevent staphyloma in human eyes. Another study with no need for general anesthesia is ongoing, tested is the effect of a more biocompatible, hyaluronic acid–based polymer in a guinea pig model. The study showed slowed axial growth, but curiously, so did the control group, the sham injected eyes (795). These interesting results argue for further investigations into this approach, to find a method with no need for general anesthesia, better benefits and less adverse ocular effects.

Actually, two different CCL techniques are used. The one has need for UV radiation, the other not. Eyes with high myopia show thinned scleral thickness or staphyloma, which possibly does not block all the UV radiation before it can damage the retina. The biggest technical problem is, how to reach the posterior sclera of highly myopic eyes with the light activator, as required in all current protocols. And the most important questions are: how long does the treatment prevent axial elongation? Are the structural changes sufficient to slow axial elongation (792,796–799)?

Combination Therapies for Myopia Control

Because no myopia control treatment available (optical, pharmacological, or behavioral) has proven effective in giving full halt in myopia progression, nor in refractive error or axial growth (327), it is time to think about exploring combination therapies to improve treatment efficacy.

The exact mechanism of action of topical atropine as a myopia management option is unknown, this offers the possibility that sites other than the retina may be involved. So, it would be interesting to test topical atropine in combination with optical solutions like Ortho-K or MFSCLs. Actually, the study of Kinoshita "Combined Atropine With Orthokeratology in Childhood Myopia Control (AOK)" (800,801), and the "Bifocal & Atropine in Myopia (BAM) Study" (453) are collecting data.

The first short-term results for the AOK trial, which combines low dose 0.01% atropine with Ortho-K is being compared with Ortho-K alone in children and with 1.00-4.00 D myopia, are promising. It seems that the combination therapy is better than the use of Ortho-K alone (reduced axial elongation) (456,801). Wan et al. (457) found in their study in 2018, that the combined treatment achieved a slightly better myopia control.

In a 3 years trial of Lin et al. (802), high myopia patients benefited more from both OK lenses and 0.125% atropine applied every night than did low myopia patients. But the patient had either atropine or Ortho-K treatment. What will be the outcome of the combination therapy?

Another idea is that MFSCLs could directly release atropine on the cornea (803), the lenses could be used as a drug-delivery device. The effectiveness and safety should be ensured with longitudinal studies in children. If such a contact lens–based combination option works, other drugs can be tested too (464).

Comparison of MFSCLs with Other Methods of Slowing Myopia Progression

In direct comparison, MFSCLs have been more successful in reducing axial growth than Pirenzepine (198).

Intervention, compared to SV glasses	Mean difference Axial length	Mean difference refraction
Low-dose Atropine	**0.15 mm**	0.53 D
Ortho-K	**0.15 mm**	(0.4) D
MFSCLs	**0.11 mm**	0.21 D
bifocal spectacle lenses	0.06 mm	0.09 D
progressive addition spectacle lenses	0.04 mm	0.14 D
SV soft CL	-0.01 mm	-0.09 D
undercorrected SV spectacle lenses	-0.02 mm	-0.11 D

Table 33: Intervention, compared to SV glasses

Table with data from Huang (327). Annual rates of difference from a meta-analysis of 2016. MFSCLs, low-dose Atropine and Ortho-K are similar effective in axial length control. To transform these dioptric data to elongation: an amount of 2.7 diopters corresponds to 1 mm axial change (705,706).

But are these facts enough to support the use of myopia management options? Former reviews by Saw et al. (804) and the Cochrane review by Walline et al. (199) concluded that the existing clinical trials of that time do not deliver sufficient enough information to support myopia management interventions. This literature review is not the first of its kind (199,215,804,805). But new information is available.

Huang et al. found in 2016 (327), that atropine, in all used concentrations, produced significantly myopia controlling effects. Pirenzepine, Ortho-K and MFSCLs are statistically significant reducing myopia progression. Likewise moderately, but not statistically relevant, reduce cyclopentolate and prismatic bifocal glasses. PALs, bifocal glasses, peripheral defocus modifying glasses, and more time spent outdoor produced weak effects. RGPs, soft CLs, undercorrected SV glasses, and timolol were ineffective or favored myopic

progression. Asian children seemed to benefit more from myopia control options than Caucasian children. Most myopia management options lose their good effect from the first year in the second year.

The trials found for myopia management were highly heterogenic, but Huang et al. did not find any statistically significant inconsistencies in the works, so that the results seem to be relatively reliable.

For multifocal glasses, very different efficiencies can be determined depending on the trial. Sometimes, the results are controversial (23,110,112). A small reduction of about 0.25 D per year compared with SV glasses wearing children was found by Li et al. (806) in a meta-analysis. Bifocal and progressive addition glasses showed similar, weak results. Better results were found in bifocal glasses with 3 prism base-in in the 1.5 D addition part, but not statistically significant. Further good quality data is missing, only one RCT was found. In terms of results, multifocal eyeglasses do not show enough substance to be a preferred option for myopia management.

Huang et al. (327) showed that MFSCLs were more effective than peripheral defocus modifying glasses. Similar to other myopia control options, more relevant RCTs are required to ensure its efficacy.

Spending more time outside is more a prevention than a myopia progression treatment. The time spent outside in the midday sun is the most important. It seems to delay the onset of myopia. The myopia control effect found in studies was unassuming (152,166,167,284,286,287,297,299). Randomization in such studies is difficult. The patient realizes that he or she is spending more time outside. The way chosen in Taiwan was to select randomly one school class to spend 80 minutes a day more outside, while the other class followed the usual schedule.

Racial differences between myopia prevalence in young Asians and white patients within the same region show ethnic differences. Epidemiological studies examined this (163,176,187,207,807). According with previous studies (806), Asians progressed faster but also responded better on myopia management options than Caucasian children. The increased genetic perceptivity of Asians to myopia or the faster rate of progression in Asians can be the explanation for this. As seen in many myopia management options, the faster the progression the better is the effect of the treatment. Confirming the results of previous reviews (106,121,327), most myopia management options lose their early effect after one year, increased age could be the explanation.

4.5 Choice of Ideal Optic Zone Diameters

In this thesis I reviewed studies on MFSCLs. My special interest are customized lenses. With such lenses comes the problem, that each lens is individual. So, this means that the CL fitter must choose what to order. Contact lens company, replacement schedule, material, diameter, base curve, flattening, power, diameter of central optical distance zone, addition power and lens color are the minimal decisions the ECP must make. Many producers offer also different style of the addition/treatment zone, like bifocal, and different styles of progression. The companies offer help, they provide fitting guides. Once a patient is happy and myopia progression slows down, the reproduction quality is good today.

A large central distance correction zone diameter provides normal visual acuity and does not influence accommodation for near work. But this inner zone does not have to be too big, otherwise would not fall enough light through the peripheral treatment zone. Luckily are pupils of children usually big enough to provide a simultaneous image of the peripheral treatment zone and the central far vision zone. As a rule of thumb, we fit the lens zone that the central far vision zone covers about 50% of the field of the mesopic pupil, usually 4 to 4.5 mm. This size produces a constant myopic defocus, even in moments of near work.

4.6 Choice of Contact Lens Material and Lens Care Solution

Materials

Blacker et al. (808) found in 2009, that silicone hydrogel lens material produced less myopia progression in adult contact lens wearers than other hydrogels, after three years of wear. But because the effect of a MFSCL is dose-dependent, highly gas permeable materials like silicone hydrogels are needed, to give the child the possibility, to wear the lens for a longer time per day (117). Children in their growth phase need much more oxygen than adults. The today silicone hydrogels provide enough oxygen to the cornea. But these SiH lenses tend to break and do not provide the same comfort to the eye as other hydrogels. But these softer hydrogels bring not as much oxygen to the cornea, must be fit loser to bring water under the lens (and with the water further oxygen). But this let the lens slip down, and the optical zone is displaced. And the time of wear has to be limited. So, ECP have to make a choice…

Today, one day lenses (like MiSight™, Cooper Vision, Fairport, NY, US), monthly lenses (like MYLO from MARK'ENNOVY) and classic customized 3-6 months lenses (like RELAX of Swisslens) are all available in silicone materials.

Further material details can be found in the appendix.

Solutions

When comparing MPS with peroxide systems, it is important to know whether the peroxide is measured before or after contact with its neutralization component. Not neutralized, the peroxide systems show better microbial killing rates than the MPS solutions (809,810). But this is not the way to compare these solutions. Because the customers use usually a platinum catalyst star in their cases (one-step), converting the peroxide to water over time. These 4 to 6 hours prolongation of storage time make the big difference between the solutions. Two-step peroxide solutions, using another liquid or a catalyzing pill are a very efficient way to clean the lenses, and can kill even otherwise resistant large inocula of Acanthamoeba cysts (811). In the storage case of a one-step peroxide can microbes re-grow, if the lens was not used for more than 6 days (812). In contrast, MPS disinfectants are not decomposing and continue in their disinfection activity. In two-step peroxide solutions, the users can forget to neutralize the peroxide or could use the solution directly on the eye or take it to rinse the lens. This causes pain and redness in affected eyes for some hours, but does not cause permanent damage. But peroxide systems also result in the lowest level of solution induced corneal staining (SICS) compared to any of the many MPS solutions, no matter what contact lens material was worn (707). Patients with SICS show a three to six fold risk for corneal infiltrates (813,814).

Rubbing the lens with a MPS results in nearly the same level of cleanliness as seen in peroxide solutions used with a protein removal rub step, found Nichols et al. (815).

4.7 Possible Mechanisms for Inhibition of Myopia Progression

Mechanical

Axial growth in nearsightedness comes together with a 'non-reversible, biomechanical softening' of the sclera, found Levy et al. (816) recently. These biomechanical transformations, in this study in tree shrew sclera, could be guarded by scleral crosslinking with the low-toxic agent genipin. But as discussed in chapter 4.4., the best way to strengthen the sclera is not found yet.

Cholinergic

The study of Sander et al. (359) investigated the role of muscarinic receptors in the choroid and confirmed: "choroidal thickness changes caused by hyperopic defocus had a muscarinic involvement". The authors found that the changes in the choroidal thickness may relate to the various pathways in ocular response to myopic and hyperopic blur. It could also show a maximum of the capacity of the short-term choroidal thickening. The results help to better understand the role of the cholinergic system in the choroidal response to optical blur (817).

Myopic retinal defocus

In animal models was seen that even short periods of myopic retinal defocus can almost completely stop the axial elongation of the eye associated with negative lens wear in newborn animals (48,334,818,819). Axial length changes are highly correlated to myopic progression (420).

In difference to animal models using neonates, the optical myopia control options are worn after the emmetropization process (11,14,43). Human children over-shoot emmetropia in the emmetropization process and develop nearsightedness. It is imaginable that both environmental (165,270) and genetic factors (186,224) contribute to juvenile-onset nearsightedness, and that these processes are different from the effect that lens defocus has on the emmetropization process in newborn animals. Such differences can probably explain the incomplete stop of myopia progression in users of optical and pharmaceutical myopia management options.

Peripheral Refraction

Some studies describe the role of peripheral refractive error in the development of nearsightedness (161,353,820). Eyes of myopic persons don't have only prolonged axial length, but also a more prolate shape as the ocular growth is longer axially than equatorially (821). At least in the horizontal meridian show shortsighted eyes more hyperopic peripheral refractions than their foveal refractive error (264,822). Earl L. Smith the 3rd destroyed the fovea of rhesus monkeys by laser photocoagulation (821), but the emmetropization process was not altered. Animals wearing an occluder in front of the treated eye developed the normal form deprivation myopia. In conclusion, visual inputs from the fovea are not obligatory for normal refractive development in newborn animals. This study suggests that peripheral defocus may be an important thought in refractive development. In humans, some studies have shown no significant different measurements between peripheral refraction in eyes with emmetropia and myopia (820). But other studies have found significantly more hyperopic peripheral refractions in patients with myopia compared with emmetropes (353,823). The large CLEERE study (158) described that children who developed myopia had axially longer grown eyes and more hyperopic peripheral refractions than emmetropic children 24 months before the onset of nearsightedness. In the year before myopization starts, the fastest changes of refractive error, eye length and peripheral refraction were found. The relative peripheral refraction was found to stay stable after the onset of nearsightedness, even though spherical refractive equivalent and eye length persisted to change.

The possible mechanism of action of MFSCLs with distance center and Ortho-K is the amelioration of the relatively hyperopic peripheral refractive error. The peripheral treatment zone with addition is producing the focus point in front of the peripheral retina, instead of behind the retinal plane as it would normally occur with a SV distance lens. This form of correction could act as a stimulus to halt axial growth and inhibiting further myopia progression.

We know from the CLEERE study, that peripheral refraction was relatively constant after the onset of nearsightedness. Even if myopic refractive error and axial eye length continue to increase for at least 5 years after the onset of nearsightedness (158). This could explain why correcting peripheral refraction is probably not the correct way to prevent progression once nearsightedness has developed.

The equatorial expansion of the eye globe may also be simply limited by the extra-ocular muscles or limitations from orbital size (353,823). The significance of peripheral refraction in nearsightedness development and progression in children remains unclear and future studies of nearsightedness treatments should measure central and as well as peripheral refraction.

We know now for decades that localized retinal defocus can cause localized refractive error alterations (824), studies are published since then on measuring peripheral refractive error (353,825,826). Future studies of MFSCLs in the control of nearsightedness should evaluate changes in peripheral refraction that are responsible for the reduced nearsightedness progression seen in eyes wearing such lenses, as an important theory in the development of nearsightedness in children.

No rebound effect after cessation of MFSCLs was reported by Cheng et al. (391). But until what age is this true? Is it true for all kind of MFSCLs or only the lens chosen for the Cheng study? Important questions, to be answered by further research.

Lowering IOP

Regardless of many factors like family history and age: IOP was discovered to play a role in myopia, found a cross-sectional survey in 1995 (827). But the relationship between intraocular pressure and nearsightedness is controversial: several studies found no proof for the influence of IOP between groups of patients with emmetropia and myopics, or between groups with different levels of nearsightedness (828,829). And other studies showed that the IOP was statistically significantly higher relative to the group of the emmetrope and associated with the axial length (830–832). Despite conflicting results from various studies, a prospective study showed that IOP was higher in the myopia group after the onset of myopia than before the onset of myopia; However, there were no differences in IOP between myopic and non-myopic children (833). The results stipulate that IOP is possibly decisive to myopia progressing after onset, so had youngsters with elevated IOP a higher progressing rate of nearsightedness (473). A study by Yan et al. (834) demonstrated that accommodation could temporarily elevate the IOP in children with progressing nearsightedness, including a shortening of the anterior chamber depth and a narrowing of the anterior chamber angle at the same time. But these effects were not found in the emmetropic group. So, it can't be that IOP is the stand-alone cause for myopia. What about the reading distance? Does a shorter reading distance cause higher IOP (and from this more myopia) than reading further away? In consequence, these results proposed that IOP could be an intermediate factor for nearsightedness establishment and development. IOP is a little lower in preschool children, and reaches then the level of the adulthood IOP: Normal values are usually between 10 and 22 mmHg (835).

Older studies yielded that elevated IOP induced by injection of a liquid is able to cause eyeball prolongation and nearsightedness in chicks (836). Also the opposite worked: after trabeculectomy to reduce the IOP, the axial length decreased statistically significantly and was smaller than before the surgery (837). So, there is a direct relationship between IOP and axial length. In conclusion, reducing IOP should be effective in stabilizing myopia progression and axial elongation.

A study discovered, that nearsightedness and axial elongation are closely associated with scleral extracellular matrix remodeling (838). Myopic patients show reduced levels in glycosaminoglycan and collagen content (839). The actual research of Liu et al. (467) implies that brimonidine prevents the thinning of sclera, which can prevent from complications of pathological myopia.

4.8 Thesis Limitations

There are some key limitations in this review that should be listed here. The correct myopia control treatments are different for each patient. For the optical interventions example, multifocal glasses have different dioptric powers for each patient, and the peripheral effects of Ortho-K vary with refractive power and during the day. The trials and studies contained a variety of ethnicity, number of participants, year of publication and the style to report. Some studies were randomized, double-blind, placebo-controlled, so the "gold standard" (840). But the biggest amount of the studies and trials did not reach this standard. By the wide variation in children's age ranges was it not possible to compare the different treatment or to clarify how a treatment effect changes in older children. It was easier to find information about the efficacy in the studies than about the safety of the treatments. To choose a treatment for a patient, it is absolutely necessary to know the efficacy, short-term/long-term benefits, and the risks of side effects. Additional information about the safety of all interventions is important. Usual studies did compare one myopia control treatment with another, but not using the same group of children (like age, ethnicity, …). More trials are needed to compare the results from previous studies. Also, more information is needed on the rebound effect, after cessation of a treatment.

At a certain moment in writing this review, I needed a "normal myopia progression rate". After finding so different data, ranging from about 0.2 dpt to 1.28 D per year, I decided to have a retrospective look at the existing customer data in our optometry store. Selected were children which I would today fit with myopia control lenses. To find enough participants, the data was collected from refraction over a time period of more than 10 years. But over this time period, our life has changed: we use today smaller smartphones for a long time in very near distance, compared with the former generation reading books in a further distance. Near tasks were existing before, myopes existed before, but the number of near tasks and myopes has risen since.

New trials with a greater number of participants would be helpful provide data of a good quality, especially for the combination therapies. Only this would proof the possible additive effects of different combinations of myopia control options. This gives a solid base for the most effectful and best tolerated treatment combination to control myopia progression easily tolerated by the patient.

I think it is unlikely that all the questions of the text above will be answered. Way over 100 clinical trial must be run, to compare the myopia control options against each other. Without them, this review is an approach to close this gap as good as possible.

As seen in many studies, Asian children respond better to myopia control treatments than Caucasians. But they show higher progression rates as well. To compare Asian population-based studies with others, is difficult.

Today, very different definitions of high myopia are in use: < –5.00 D, ≤ –5.00 D, < –6.00 D, ≤ –6.00 D, <-6.5 D and ≤ –8.00 D of myopia (427). High myopia has also been defined on the basis of an axial length > 26 mm. But axial length can't be measured by most optometrists, and the data can be inaccurate because even in normal eyes a big variation is seen.

5 Conclusion

5.1 Conclusions

The main objectives of this literature review were as follows:

1. To review and collect actual information about the myopia control options for optometrists in Switzerland.
2. To collect information about the safety of fitting soft (customized) myopia control lenses to children
3. To add own collected data to the findings

The myopia control options are presented in chapter 2.4., and discussed in chapter 4. The safety aspects were illuminated in chapter 3.7., while own added data are in chapter 3.12. and 4.2.

The fast, documented increase in myopia prevalence is a worldwide serious public health concern. Myopia (nearsightedness) is usually caused by an eye with prolonged axis length and highly common refractive error. Normally, myopia is just corrected with negative glasses spectacles, SV CLs or surgery. But myopia can damage the ocular structures, the retina and optic disc. The result can be severe problems such as retinal detachment, myopic macular degeneration, staphyloma and glaucoma. Myopia is the result of an interaction between genetic and environmental risk factors. It is still poorly understood, how the relation of these factors is and how it can cause ocular damage. There is a big need to find evidence-based strategies to reduce the prevalence of myopia and high myopia, to reduce its associated vision impairment and diseases.

The best myopia progression slowing methods to-date are topical pharmaceutical agents, Ortho-K, and MFSCLs. However, none of these treatments has an FDA approval for myopia control. ECPs use topical pharmaceuticals not frequently due to possible unwanted effects like photophobia and near work problems due to decreased accommodation. Less side effects are registered with lower concentrations. Ortho-K and MFSCLs reduce the annual myopia progression rate in a similar way and with similar effectiveness. This gives ECPs a choice to discuss with the myopic child and its parents. Bifocal and PAL glasses are slowing the progression of myopia, but usually not with a clinical significance. Undercorrection of myopia, RGP lenses, single vision glasses and lenses are ineffective to reduce the progression of myopia.

Many questions about the progression of myopia in youngsters remain unanswered (30). Many studies are underway or should be run in future to try to find the answers to questions like: may MFSCLs with near part in the optical center reduce myopic progression as well? Which combination of myopia management options reduces the progression rate better than the standalone effects? Is it possible to shift the date of onset to a date, that children do not reach high myopia values anymore? What are the reactions of the children's eyes after cessation of the therapy form? Any diopter progression reduction cuts down the health risk for the children.

Many studies have been conducted to test the safety, efficacy, and practicality of several myopia control treatments for childhood myopia. But only few have shown sufficient results beyond the first two years of use. Most studies were not tracking myopia progression beyond three years. And some treatments failed: undercorrection of myopia either increases progression or fails effectivity (415) and should never be used.

In most children, axial length increases fast at younger ages, then slows down and stabilizes. A direct relationship exists between growth and stabilization of axial length of the eyeball and the amount of myopia. This implies that axial growth is the main ocular component in myopia progression and stabilization (200).

By reading through several hundred documents, a lot of terms describe similar conditions. But this makes it difficult to find the next document on that specific topic. The WHO (427) recommends to use the term “myopic macular degeneration” instead of the different other terms in current use for the categorization of the blindness causing retinal diseases in high myopia.

MFSCL

Multifocal CLs seem to be the most safe and effective in slowing myopia progression. The ongoing BLINK study will reveal the long-term effects and safety of MFSCLs on myopia progression (115). As all contact lenses do, MFSCLs do come with a certain risk of infection. Corneal neovascularization is not expected any more, if a modern silicone hydrogel material is used. Children have not more problems in CL wear than adults. They learn quick how to use their lenses in a safe and effective mode, with their parents and ECPs as guides (115,383,655). This lens type does not compromise the vision quality of the youngsters and gives children a better self-esteem (30,199,380). These lenses create a potentially beneficial myopic blur from the peripheral addition power zone and may support the reduction of eyestrain from accommodative work as well. Peripheral myopic defocus has been proofed to slow axial elongation and myopia progression in both animal and human studies (841). MFSCLs are quite inexpensive when compared to other myopia treatments (30). Further improved CL materials could lengthen the safe wearing time, which will increase the amount of defocus per day. Lam asked for customizable lenses: those are available today, and offer a myopia control option independent from refractive error or anatomical situation (117).

MFSCLs with a distance center design provide clear vision and may slow the average axial growth of the myopic child, and studies like the IMI white papers (464), BLINK (565), Anstice et al. (56) and Sankaridurg et al. (114) suggest that the treatment effect for axial elongation control is still active after the first year of treatment. The average myopia control effect is similar in magnitude to Ortho-K wear and greater than several other types of myopia control (115), and is less invasive than pharmacological treatments. Intense patient education can improve patient motivation and compliance, and probably the treatment effect. The optimum amount of peripheral myopic defocus needed to stop myopia progression is not found yet, further work is needed to possibly find the amount. The new improved contact lens materials allow to wear the lenses longer, and can produce a greater dose-dependent effect (117).

Are MFSCLs helping to reduce a fixed amount of annual myopic progression? No, Walline et al. found such lenses more effective in patients with a lower amount of myopia at treatment start. Unfortunately, I found no other studies to compare this finding.

It is unclear why MFSCLs slowed the progression of myopia nearly twice as much as ocular axial growth. An explanation may be the less precise measurement of ocular axial growth with a-scan ultrasound. Probably MFSCLs provoke alterations to eye shape and change the refractive status in this way. In a few myopia management options including multifocal spectacles (19) and atropine (106) is the good progression controlling effect mainly seen in the first year of treatment. In the second year, no relevant differences between treatment and placebo groups was found. The results for MFSCLs are different: the rates of myopic progression reduction remain over 5 years on the same good level of the first year (117).

No study was found that measured near accommodation and peripheral refraction through the MFSCL wearing eye at the same time. Additionally, I found no study comparing directly different MFSCL designs in lenses with otherwise same parameters. Is bifocal concentric ring design really the better option than the different designs of progressive peripheral plus power?

Ortho-K

Ortho-K increases the risk of many eye infections and other diseases of the eye (594,805), but not in a big difference to soft contact lenses, in a long term (129). Ortho-K may be similar effective in slowing axial elongation in children and young adults compared with MFSCLs. The younger the age of treatment start, the bigger the effect. The best effect is seen in 6–8 year-old (842).

Other optical myopia control options

Studies with bifocal glasses with added prisms in the near part have discovered that those glasses are more effective than normal bifocals (330). The outcome of studies regarding the effect of progressive lenses has been very heterogenous. Because of the good results of the COMET study, the effectiveness test was repeated in COMET2, but these results showed that the PALs were not as effective in slowing myopia progression (19,174).

Pharmacological treatments

High dose atropine and pirenzepine have unwanted effects and are not widely used. In Asia, high-dose atropine eye drops are used for myopia management, but in Europe this treatment form is usually used in amblyopia treatment (843). The low-dose atropine drops are much less used in Europe than in Asia, too. This could be because of the lack of enough European studies, parents are critical if their child is to receive a drug, care much more about the possible side effects and the availability is also sometimes a problem. For a child, it is hard to keep the initial motivation to take the atropine drop each day, but to be long-term compliant. Education about the impact of high myopia to both, the young patient and caregivers, is needed. Inviting children and parents together to check-up visits is one possible way to ensure that both are informed identically.

Other myopia management options

Children with myopic parents should have more frequent refractive exams, spend more time outdoors in the sunlight, and less near work activities. These actions are preventative, and help controlling and slowing the myopia progression (844).

The combination of early interventions at pre-myopes or early myopes, and the later use of myopia management options shall prevent the eye from reaching higher levels of myopia. This is to protect the eye from vision-threatening changes, the so-called myopic pathology. Pre-myopes and early myopic children can modify their amount of time spent outdoor to shift the date of myopia onset. And can take the near work in a prolonged distance to the eye and may interrupt their near work frequently and look on far objects, following for example the 20-20-20 rule: every 20 minutes, look at something 20 feet away for 20 seconds (845). This rule is to release eye-stress and was not intended to reduce myopia progression. But it directs to the goal to interrupt continuous near work. To motivate children to spend a greater amount of time outdoors is a good strategy for the prevention or delay of myopia onset.

All the discussed strategies use probably different pathways. Regarding this thought, the best way to fight high myopia is the use of different methods in combination to delay myopia onset and later reduce its progression. A young Child should spend a lot of time in sunlight, a beginning myope can get low dose atropine drops in combination with Ortho-K or MFSCLs. If a child does not develop high myopia, it not only saves money, but also multiplies the chances of seeing well in the course of working years.

Even if we have promising approaches for the treatment of pathological myopia today like anti-VEGF and surgical treatment, the challenge remains to avert lasting visual damage. In order to delay the progression of myopia, appropriate intervention measures must be taken in good time (316).

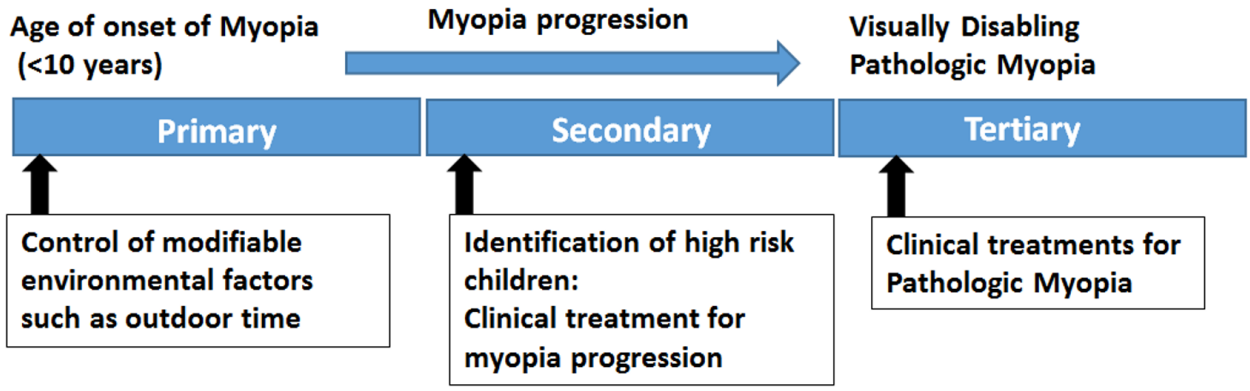

Figure 36: Diagram on prevention (primary, secondary, tertiary)

Figure from Saw, Prevention and Management of Myopia and Myopic Pathology, 2019 (316). Used under Creative Commons Attribution 4.0 International License. (Text added and changed.)

Lens Care Solutions

In conclusion, the two-step peroxide solutions provide the best antimicrobial action, the one-step peroxides are good for persons wearing the lenses frequently and provide the best long-term comfort, while MPS can be used for patient wearing their lenses infrequently or don't have 6 hours until they have to re-use the lenses. All systems are relatively safe (846). So, there is more than one possibility, make your choice…

5.2 Major Outcomes

In conclusion after reading hundreds of documents, taking the outcome of many studies including my own data as a base, the following evidence-based major outcomes are:

(1) Multifocal distance center soft contact lenses are a safe, financeable and efficient method to manage myopia progression in children. These lenses show no rebound effect. Appropriate care is important to avoid adverse effects. The lenses cause not more unwanted effects than in adults, are well accepted and give the children a good self-esteem. This option is used more and more in optometry.

(2) Atropine, pirenzepine, Ortho-K, MFSCLs with peripheral defocus modifying designs, and in some cases PAL glasses and bifocal glasses with added prisms in the near part are effective and produce a statistically significant reduction of myopia progression in refraction or axial length.

(3) The use of myopia management options may be limited by side effects (atropine 1%), cost and complexity (Ortho-K), and limited effectiveness (PAL). The todays Top-3-choices for a myopia management option are: low-dose atropine (0.01%), MFSCLs with peripheral defocus modifying designs and Ortho-K as viable options for the active management of myopia progression.

(4) RGP contact lenses, SV soft CLs, timolol, and under-corrected single vision spectacle lenses are ineffective in slowing the progression of myopia in children.

(5) There are promising new ideas in the trial phase or new on the market, like the DIMS glasses.

(6) More trials on the combination effects of treatment options shall be conducted, because not one of the existing methods can stop myopia progression. All options just slow.

(7) Most treatment options lose some effectivity in the second year. So, trials must be conducted for at least a 2 years' time.

(8) The myopia control effect of MFSCLs with distance center is similar in magnitude to Ortho-K wear.

(9) Time spent outdoors can delay the onset, but is also a risk factor.

(10) Excessive near work increases the risk of myopia.

5.3 Future Directions

The WHO Myopia Report of 2015 (427) asked for more epidemiological data on the prevalence of myopia, high myopia and vision impairment caused by high myopia in Africa, Oceania, Central and South America. There is no standardized protocol how to use cycloplegic agents in myopia care examinations, including the cycloplegic agent, the concentration (how many drops) and time before measurement. And there is no guideline to use such agents at all, even that the level of myopia differs in a small amount when cycloplegics are used. Studies should define the protocol, and if cycloplegia is needed, the law in many countries should be changed in a way, that it allows skilled optometrists to us the agents as well.

Future studies should look into more effective and accessible safer options for myopia control. Especially in Asian countries, a combination of low income, rising prevalence of myopia and lower drinking water quality and cleanliness awareness allow many families not to buy contact lenses to their children, and the next ophthalmologist may be far away to prescribe Atropine.

We need also further studies focusing on an improved MFSCL design. The scientists should investigate which effects affect eye growth and solve the mystery of myopia development. More trials are needed to understand the interactions between CL optics, accommodation, and convergence. With this result possibly new optical devices for near work can be produced. A CL design should be found, that allows MFSCL wearers to see at night as comfortable as in daylight.

The ongoing BLINK study is comparing MFSCLs with different add powers with SV CLs, to make it clear that higher addition powers lead to better myopia control (565). MFSCLs slow ocular axial growth, but no myopia control studies have examined the peripheral growth. The BLINK study will deliver information about ocular growth patterns centrally and in 20° and 30° periphery, horizontally and vertically.

To date, I found not one single study regarding the rebound effect of MFSCLs. What happens after cessation of the lens type? Further studies on that topic are required to be able to compare MFSCLs with e.g. atropine. MFSCLs of the future should be carefully designed with an optical profile that provides good myopia controlling effects while presenting a good image quality.

My wishes to the contact lens industry:

- More information about the sagittal height of a lens. This parameter would be the best to compare contact lenses with each other
- To invest in the research for new materials

Most need for clinical trials:

- Combination therapy
- Rebound effects after cessation of therapy form

We will see what all these studies will find. And probably does not stand this sentence at the end of a thesis any more:

Multifocal soft contact lenses with a distance center and peripheral defocus modifying designs have been found to be the most viable and effective, current treatment for slowing myopia progression in children and young adults for optometrists in Switzerland.

Appendix

COLLECTION OF DATA FOR THE STUDY "DATA ANALYSIS OF THE EFFECTIVENESS OF THE RELAX CONTACT LENS FOR REDUCING MYOPIA PROGRESSION"

Clinical Research Director: Andreas van der Heide, Dipl. Augenoptiker SBAO

Firma: TSIOUNIS_GLARUS Patienten Referenz: [redacted]

Auge Rechts Studiennummer: 21656

Geschlecht	Geburts jahr	Pupillendurchmesser im Raum (mm)	HH-Radien (mm) vorher	jetzt	Hornhaut Ø WTW (mm)	Augenlänge (mm)
M / W		2–4 / 4–6 / >6	/	/		

Phorie in der Ferne Exo/exo				Phorie in der Nähe Exo/Eso				lag of Acc. / Akkommodationsdefizit			
> 2Ba	≤ 2Ba	> 2Bi	≤ 2Bi	> 2Ba	≤ 2Ba	> 2Bi	≤ 2Bi	Keinen	< 0.75D	≤ 1.5D	> 1.5D

Compliance des Kindes				
Keine	Wenig	Geht so	Gut	Sehr gut
Compliance der Eltern				
Keine	Wenig	Geht so	Gut	Sehr gut

Was wurde getragen vor der Relax?			
Nichts	Brille	Einstärken KL	Andere Myopekontroll KL

Dioptrienwerte			
6 Monate vor der Relax	12 Monate vor der Relax	18 Monate vor der Relax	24 Monate vor der Relax

Tragemodus			
Unregelmässig und weniger als 5 Stunden/Tag	Unregelmässig aber mehr als 5 Stunden/Tag	Fast täglich aber weniger als 5 Stunden/Tag	Fast täglich aber mehr als 5 Stunden/Tag

Wechselwirkungen			
Relax wurde alleine verwendet	Relax wurde mit Atropin verwendet	Relax wurde mit Nahrungsergänzungsmittel verwendet	Relax wurde mit Naturprodukten verwendet

Gesundheit: Auffälligkeiten während den Kontrollen

Während dem 1. Jahr mit den Relax Kontaktlinsen		
Entzündungen, augenärztlich behandelt	Infiltrate	Ulcera
Während dem 2. Jahr mit den Relax Kontaktlinsen		
Entzündungen, augenärztlich behandelt	Infiltrate	Ulcera
Während dem 3. Jahr mit den Relax Kontaktlinsen		
Entzündungen, augenärztlich behandelt	Infiltrate	Ulcera
Kontaktlinsen Pflegemittel		
Peroxid	All in One	Weiss nicht

Anpasserspezifische Fragen **Anpasser:** _____

Bei den letzten 10 Anpassungen der Relax Kontaktlinsen, bei wie vielen sind sie dem offiziellen Anpassleitfaden gefolgt?

Nie 1 2 3 4 5 6 7 8 9 10

Falls nicht: O benütze anderen Leitfaden (welchen?_____)

O rechne selber (wie?_____)

O sende Daten an Swisslens

Wie bestimmen Sie die Abflachung +, - oder mono ?

gar nicht, stets gleicher Standard / Nach dem CSP / nach Stärke / nach Durchmesser Hornhaut

Nach wie vielen Versuchen haben Sie normalerweise die definitive, sphärische Linse gefunden?

1 2 3 4 5 6 7 8 9 10

Wie viele % der begonnenen Anpassungen kauften diese normalerweise nach 6-12 Monaten nach?

10 20 30 40 50 60 70 80 90 100

Wenn RELAX nicht nachgekauft wurden, woran lag das?

O Preis O Komfort O Sicht/Visus O Myopie wurde nicht gebremst O Wegzug des Kunden O weiss nicht

Wie selektionieren Sie Kunden für die RELAX?

Sind nicht hyperop genug für Alter / Bereits erhöhte Kurzsichtigkeit mit dem Wunsch den Refraktionsfehler zu stabilisieren / schnelle Myopiezunahme / Kundenwunsch / Elternwunsch

Falls nach Myopiezunahme: Bei: >=0.25 / >=0.50 / >=0.75 />=1.00 dpt/Jahr

Was motiviert Sie, RELAX Linsen anzupassen? Mehrfachnennungen möglich

Nutzen für Kunden / Zusätzliches Einkommen / zeigt Kompetenz / keine Internetverfügbarkeit

In welchen Abständen führen Sie Nachkontrollen durch?

3 Monate / 6 Monate / 9 Monate / 1 Jahr / >1Jahr

Wie beurteilen Sie die Handhabung des Anpassleitfadens?

Sehr einfach 1 2 3 4 5 6 7 8 9 10 sehr komplex

Wissen die Kunden vom erwarteten Nutzen der RELAX Linse?

O JA O Nein O nur die Eltern

Fragen an den Kunden **Nummer:** _____

Wie lange dürfen Sie die Linsen gemäss der Empfehlung Ihres Anpassers tragen? _____ Stunden/Tag

Wie oft folgten Sie den Anweisungen Ihres Anpassers bezüglich Tragezeit?

Immer 1 2 3 4 5 6 7 8 9 10 nie O keine bekommen

Wenn Ihre Augen ein Stören oder Kratzen beim Linsentragen verspürten, wie stark war das Gefühl des Störens oder Kratzens am Ende der Tragezeit?

0 hatte nie welches 1 gar nicht intensiv 2 eher schwach 3 eher stark 4 intensiv 5 sehr intensiv

Wenn Ihre Augen verschwommene Sicht beim Linsentragen verspürten, wie bemerkbar war die wechselhafte Sicht oder Unschärfe am Ende der Tragezeit?

0 hatte nie welche 1 gar nicht intensiv 2 eher schwach 3 eher stark 4 intensiv 5 sehr intensiv

Wie sehr treffen folgende Aussagen auf Ihre Linsen zu:

Frage: **Antworten:**	Nie	Selten	Manchmal	Oft	Immer
Während eines typischen Tages in den vergangenen 2 Wochen, wie oft fühlten Ihre Augen ein Stören oder Kratzen während Sie Kontaktlinsen trugen?					
Während eines typischen Tages in den vergangenen 2 Wochen, wie oft wechselte die Sicht während dem Kontaktlinsentragen zwischen klar und verschwommen?					
Während eines typischen Tages in den vergangenen 2 Wochen, wie oft störten Sie Ihre Augen so sehr, dass Sie diese schliessen wollten?					
Diese Linsen fühlten sich in meinen Augen geschmeidig an					
Das Unbehagen der Linsen hat mich von einer Aufgabe abgelenkt					
An einem typischen Tag war ich mir dieser Linsen bewusst					
Ich musste öfter blinzeln, weil diese Linsen unangenehm waren					
Ich konnte abends sehr deutlich im Kino sehen, wenn ich die Linsen am Morgen bereits eingesetzt hatte					
Ich sehe mit den Linsen gleich gut wie mit der Brille					
Ich kann die Linsen gut ein- und aussetzen					
Ich wasche die Hände stets vor dem Aufsetzen der Linsen					
An einem normalen Tag bin ich zufrieden mit meinen Linsen					
Ich schlafe mit diesen Linsen auf dem Auge					
Beim Linsentragen vergesse ich, dass ich diese anhabe					
Der Komfort der ersten Tragestunde ist gleich wie in der letzten					
Meine Linsen fühlen sich weich an, über den ganzen Tag					
Diese Linsen steigern meine Lebensqualität					
Haben Sie Augenirritationen wenn Sie aufwachen?					
Ich benütze Nachbenetzungstropfen					
Während eines typischen Tages in den vergangenen 2 Wochen, wie oft störten Sie Ihre Augen so sehr, dass Sie die KL heraus nehmen wollten?					

K Readings Diopters to mm conversion chart

Radius in Diopters	Radius in mm
34.00	9.92mm
34.25	9.85mm
34.50	9.78mm
34.75	9.71mm
35.00	9.64mm
35.25	9.57mm
35.50	9.50mm
35.75	9.44mm
36.00	9.37mm
36.25	9.31mm
36.50	9.24mm
36.75	9.18mm
37.00	9.12mm
37.25	9.06mm
37.50	9.00mm
37.75	8.94mm
38.00	8.88mm
38.25	8.82mm
38.50	8.76mm
38.75	8.70mm
39.00	8.65mm
39.25	8.60mm
39.50	8.54mm
39.75	8.49mm
40.00	8.44mm
40.25	8.39mm
40.50	8.33mm
40.75	8.28mm
41.00	8.23mm
41.25	8.18mm
41.50	8.13mm
41.75	8.08mm
42.00	8.04mm
42.25	7.99mm
42.50	7.94mm
42.75	7.89mm
43.00	7.85mm
43.25	7.80mm
43.50	7.76mm
43.75	7.71mm
44.00	7.67mm
44.25	7.63mm
44.50	7.58mm
44.75	7.54mm
45.00	7.50mm
45.25	7.46mm
45.50	7.42mm
45.75	7.38mm
46.00	7.34mm
46.25	7.30mm
46.50	7.26mm
46.75	7.22mm
47.00	7.18mm
47.25	7.14mm
47.50	7.11mm
47.75	7.07mm
48.00	7.03mm
48.25	6.99mm
48.50	6.96mm
48.75	6.92mm
49.00	6.89mm
49.25	6.85mm
49.50	6.82mm
49.75	6.78mm
50.00	6.75mm
50.25	6.72mm
50.50	6.68mm
50.75	6.65mm
51.00	6.62mm
51.25	6.58mm
51.50	6.55mm
51.75	6.52mm
52.00	6.49mm
52.25	6.46mm
52.50	6.43mm
52.75	6.40mm
53.00	6.37mm
53.25	6.34mm
53.50	6.31mm
53.75	6.28mm

Source: https://www.gpli.info/conversion-charts/

	Definitive (silicone 74)	Igel 77	CTF 67	GM3 58	Igel 58	GM3 49
DK Fatt ISO 9913-1	60*/44**	39*/29**	30*/22**	25*/19**	21*/16**	16*/12**
Material type	Silicone Hydrogel	Hydrogel	Hydrogel	Hydrogel	Hydrogel	Hydrogel
Manufacturer	Contamac	Contamac	Contamac	Contamac	Contamac	Contamac
Classification	Filcon V3	Filcon II3	Filcon II2	Filcon II1 (Acofilcon A)	Filcon II1	Filcon I1 (Acofilcon B)
Water content	74%	77%	67%	58%	58%	49%
Refractive index	1.37	1.37	1.39	1.41	1.4	1.42
Handling tint	klar / blau	klar	klar	klar / blau	klar	klar / blau
UV	√ (blau)	√	√	√	√	√
Normal tear film	+++	++	+++	+++	++	++
Reduced tear film	+++	+	+	++	+	+++
Watery tear film	+++	+++	+++	++	++	++
Tear film with lipid	+	+	+	+++	++	+++
Tear film with protein	+	+	+	++	+++	+++
Durability	+	+	++	++	+++	+++
Initial comfort	+++	+++	+++	++	+	+
Low dehydration	+++	+	+	+++	++	+++
Moistening	+++	++	++	+++	+	+++
Dry eye	+++	+++	++	++	+	+++
Non-ionic	√	√	√	√	√	√

* $\times 10^{-11}$ (cm^2/sec) [ml O_2/(ml × mm Hg)]

** $\times 10^{-11}$ (cm^2/sec) [ml O_2/(ml × hPa)]

Figure (www.swisslens.ch/wp-content/uploads/2018/05/Soft-Materials-en.pdf): Soft contact lens materials

Survey	Question/Wording	Translation Sebastian Felgner	Translation by: Andreas Tsiounis
Anpasserspezifische Fragen	Anpasserspezifische Fragen	contact lens fitting questions	Fitter-specific questions
	Anpasser	name of contact lens fitter	fitter
	Bei den letzten 10 Anpassungen der Relax Kontaktlinsen, bei wie vielen sind sie dem offiziellen Anpassleitfaden gefolgt?	During the last 10 fittings, in how many cases did you follow the fitting guide?	For the last 10 fittings of Relax contact lenses, how many times have you followed the official fitting guide?
	Nie	never	Never
	Falls nicht:	if not	If not:
	benütze anderen Leitfaden	use of another fitting guide	use another fitting guide
	welchen	which guide do you use?	which
	rechne selber	calculate on my own	calculate on myself
	Wie?	how	How?
	sende Daten an Swisslens	sending data to swisslens	send data to Swisslens
	Wie bestimmen Sie die Abflachung +, - oder mono ?	how do you calculate the excentricity	How do you determine the flattening +, - or mono?
	gar nicht, stets gleicher Standard	never always the same	not at all, always the same standard
	Nach dem CSP	by CSP	By CSP
	nach Stärke	by power	by power
	nach Durchmesser Hornhaut	by corneal diameter	according to corneal diameter
	Nach wie vielen Versuchen haben Sie normalerweise die definitive, sphärische Linse gefunden?	after how many tries have you found the definitve lens	After how many trials did you normally find the definitive spherical lens?
	Wie viele % der begonnenen Anpassungen kauften diese normalerweise nach 6-12 Monaten nach?	how many patients did reorder the lens the past 6-12 months? (in percentage)	How many % of the started fittings did normally buy again after 6-12 months?
	Wenn RELAX nicht nachgekauft wurden, woran lag das?	if not reordered, why	If RELAX was not bought again, why was that?
	Preis	price	price
	Komfort	comfort	Comfort
	Sicht/Visus	VA / vision	VA / vision
	Myopie wurde nicht gebremst	myopia could not be stopped	Myopia was not slowed down
	Wegzug des Kunden	patient moved	Departure of the customer
	weiss nicht	dont know	I do not know
	Wie selektionieren Sie Kunden für die RELAX?	how do you choose patient for Relax?	How do you select customers for the RELAX?
	Sind nicht hyperop genug für Alter	not age appropriate hyperopic	Are not hyperopic enough for age
	Bereits erhöhte Kurzsichtigkeit mit dem Wunsch den Refraktionsfehler zu stabilisieren	already higher myopia combined with the wish to stabilize	Already increased myopia with the desire to stabilize the refractive error
	schnelle Myopiezunahme	fast increase in myopia	fast myopia increase
	Kundenwunsch	patient request	customer request
	Elternwunsch	parents request	parents desire
	Falls nach Myopiezunahme: Bei: >=0.25 / >=0.50 / >=0.75 />=1.00 dpt/Jahr	If after myopia progression: At: >=0.25 / >=0.50 / >=0.75 />=1.00 D/year	If after myopia increase: At:> = 0.25 /> = 0.50 /> = 0.75 />=1.00 dpt / year
	Was motiviert Sie, RELAX Linsen anzupassen?	what is your motivation to fit relax lenses	What motivates you to adjust RELAX lenses?
	Mehrfachnennungen möglich	multiple choises possible	multiple choices possible
	Nutzen für Kunden	patients benefit	Benefits for customers
	Zusätzliches Einkommen	additional income	Additional income
	zeigt Kompetenz	increase in competence	shows competence
	keine Internetverfügbarkeit	cant be bought online	no internet availability
	In welchen Abständen führen Sie Nachkontrollen durch?	how often do you do follow ups ?	At what intervals do you conduct follow-up checks?
	Monate / Jahr	month /years	Months / year
	Wie beurteilen Sie die Handhabung des Anpassleitfadens?	how do you judge the lens fitting guide	How do you assess the handling of the fitting guide?
	Sehr einfach	very easy	Very easy
	sehr komplex	very complex	very complex
	Wissen die Kunden vom erwarteten Nutzen der RELAX Linse?	do your patients know about the advantage of the relax lenses	Do the customers know about the expected benefits of the RELAX lens?
	Ja / Nein / nur die Eltern	yes no only parents	Yes / no / only the parents
	Bitte senden an:	please send to	Please send to:
	Herzlichen Dank!	Thank you very much	Thank you very much!

Survey	Question/Wording	Translation Sebastian Feigner	Translation by: Andreas Tsiounis
Fragen an Kontaktlinsenträger / Kontaktlinsenträgerin	Name/Nummer:	Name / number	Name / Number:
	Geschlecht: m/w	Gender Male/Female	Gender: M / F
	Geb.Jahr:	date of birth	Year of birth:
	Wie lange dürfen Sie die Linsen gemäss der Empfehlung Ihres Anpassers tragen? _____Stunden/Tag	how long are you allowed to wear the contacts	How long may you wear the lenses as recommended by your fitter? _____Hour(s)/day
	Wie oft folgten Sie den Anweisungen Ihres Anpassers bezüglich Tragezeit?	how often do you follow the recommendations of the contact lens fitter?	How often did you follow the instructions of your fitter regarding wearing time?
	Immer	always	always
	keine bekommen	none recieved	do not get any
	Wenn Ihre Augen ein Stören oder Kratzen beim Linsentragen verspürten,	Do the contacts feel itchy or bother you?	If your eyes felt a jarring or scratching lens wear,
	wie stark war das Gefühl des Störens oder Kratzens am Ende der Tragezeit?	If yes how intense is this at the end of the day?	how strong was the feeling of jamming or scratching at the end of the day/wear?
	hatte nie welches	never had one	never had any
	gar nicht intensiv	not intense at all	not intense at all
	eher schwach	rather weak	rather weak
	eher stark	rather strong	rather strong
	intensiv	intense	intensive
	sehr intensiv	very intense	very intensive
	Wenn Ihre Augen verschwommene Sicht beim Linsentragen verspürten,	If your eyes felt a blurred vision when wearing lenses,	If your eyes felt a blurred vision when wearing lenses,
	wie bemerkbar war die wechselhafte Sicht oder Unschärfe am Ende der Tragezeit?	how noticeable was the changeable vision or blur at the end of the day/wear?	how noticeable was the changeable vision or blur at the end of the day/wear?
	Wie sehr treffen folgende Aussagen auf Ihre Linsen zu:	How often are these statements correct, regarding your contact lenses:	How much do the following statements apply to your lenses:
	Frage: Antworten:	Questions: Answers:	Question: Answers:
	Selten	very rare	Rare
	Manchmal	sometimes	Sometimes
	Oft	often	Often
	Immer	always	always
	Während eines typischen Tages in den vergangenen 2 Wochen,	On a typical day how often did you feel uncomfortable or scratching of the lens?	During a typical day in the past 2 weeks,
	wie oft fühlten Ihre Augen ein Stören oder Kratzen während Sie Kontaktlinsen trugen?	(regarding the last 2 weeks)	how often did your eyes feel a disturbance or scratching while wearing contact lenses?
	Während eines typischen Tages in den vergangenen 2 Wochen,	On a typical day how often did the lens switch between blurry and clear vision?	During a typical day in the past 2 weeks,
	wie oft wechselte die Sicht während dem Kontaktlinsentragen zwischen klar und verschwommen?	(regarding the last 2 weeks)	how often did the view change between clear and blurry during contact lens wear?
	Während eines typischen Tages in den vergangenen 2 Wochen,	On a typical day how often did they feel uncomfortable that you need to close the eye?	During a typical day in the past 2 weeks,
	wie oft störten Sie Ihre Augen so sehr, dass Sie diese schliessen wollten?	(regarding the last 2 weeks)	how often did you disturb your eyes so much that you wanted to close them?
	Diese Linsen fühlten sich in meinen Augen geschmeidig an	my eyes felt good and smooth	These lenses felt supple in my eyes
	Das Linsentragen hat mich kein einziges Mal von meiner Aufgabe abgelenkt	Lens wasn't uncomfortable and distracted me from my work	The discomfort of the lenses hasn't distracted me from a task
	An einem typischen Tag, war ich mit meinen Linsen zufrieden	on a typical day I was happy with these lenses	On a typical day I was happy with these lenses
	Ich musste öfter blinzeln, weil diese Linsen unangenehm waren	I needed to blink more because they have been uncomfortable	I had to blink more often because these lenses were uncomfortable
	Ich konnte abends sehr deutlich im Kino sehen, wenn ich die Linsen am Morgen bereits eingesetzt hatte	I could see very clearly if I inserted the lenses in the morning	in the evening I could see very clearly in the cinema, if I had already used the lenses in the morning with my lenses
	Ich sehe mit den Linsen gleich gut wie mit der Brille	There is no difference between CL and glasses	I see with the lenses as well as with the glasses
	Ich kann die Linsen gut ein- und aussetzen	There is no problem inserting and removing the lens	I can put the lenses on and off well
	Ich wasche die Hände stets vor dem Aufsetzen der Linsen	I always wash my hands before inserting the lens	I always wash my hands before putting on the lenses
	An einem normalen Tag bin ich zufrieden mit meinen Linsen	I am satisfied with the lenses	On a normal day I'm happy with my lenses
	Ich schlafe mit diesen Linsen auf dem Auge	I do sleep with lenses inserted	I sleep with these lenses on the eye
	Beim Linsentragen vergesse ich, dass ich diese anhabe	while wearing lenses I forget that I have them inserted	When I carry the lens I forget that I have this on
	Der Komfort der ersten Tragestunde ist gleich wie in der letzten	comfort of the lens is similar no matter if inserted or wearing them for a longer time	The comfort of the first carrying hour is the same as in the last one
	Meine Linsen fühlen sich weich an, über den ganzen Tag	my lenses feel soft all day long	My lenses feel soft throughout the day
	Diese Linsen steigern meine Lebensqualität	these lenses increase my quality of life	These lenses increase my quality of life
	Haben Sie Augenirritationen wenn Sie aufwachen?	do you have any irritations because of the lens?	Do you have eye irritation when you wake up?
	Ich benütze Nachbenetzungstropfen	i am using wetting drops	I use wetting drops
	Während eines typischen Tages in den vergangenen 2 Wochen,	regarding the last 2 weeks, how often were the lenses as uncomfortable,	During a typical day in the past 2 weeks,
	wie oft störten Sie Ihre Augen so sehr, dass Sie die KL heraus nehmen wollten?	that you had to remove them?	how often did you distract your eyes so much that you wanted to take the contact lens out?

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Declaration

Master Thesis

Declaration

I, Andreas van der Heide, assure herewith, that my final thesis with the topic “Fitting Soft Multifocal Customized Contact Lenses for Myopia Control: A Literature Review” was issued by myself and that I did not use any other sources or help except those indicated. Sentences or parts of sentences quoted literally are marked as quotations; identification of other references with regard to the statement and scope of the work is quoted. The thesis in this form or in any other form has not been submitted to an examination body and has not been published.

Issue of the master thesis	……12.07.2019……..
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Signatures

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