Emmetropization and nonmyopic eye growth

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## Abstract

Most eyes start with a hypermetropic refractive error at birth, but the growth rates of the ocular components, guided by visual cues, will slow in such a way that this refractive error decreases during the first 2 years of life. Once reaching its target, the eye enters a period of stable refractive error as it continues to grow by balancing the loss in corneal and lens power with the axial elongation. Although these basic ideas were first proposed over a century ago by Straub, the exact details on the controlling mechanism and the growth process remained elusive. Thanks to the observations collected in the last 40 years in both animals and humans, we are now beginning to get an understanding how environmental and behavioral factors stabilize or disrupt ocular growth. We survey these efforts to present what is currently known regarding the regulation of ocular growth rates.

**Key words:** Emmetropization, refractive development, refractive error, ocular growth, animal model

# 1 Introduction

The newborn eye awaits a long series of refractive changes. At birth most eyes are out of focus, likely due to a lack of visual feedback *in utero*. Once the eye begins perceiving retinal images, growth typically brings the refractive error from moderate to low hypermetropia. This process intrigued Amsterdam ophthalmologist Manuel Straub, who after briefly mentioning[266] it in 1889, wrote an important treatise on the topic 20 years later.[268] Based on the literature available to him at the time, Straub noticed that emmetropic eyes varied considerably in both axial length and crystalline lens shape. However, since these parameters should be closely matched to reach emmetropia, he deduced that their variations could not be random, but rather guided by a mechanism he called **emmetropization**. In his own words:

> *"Men heeft het veelvuldig voorkomen der emmetropie als van zelf sprekend beschouwd. Wanneer men echter bedenkt, dat de pasgeborene meestal hypermetroop is, dat de emmetropische instelling bij de meerderheid der volwassen oogen, ondanks belangrijke verschillen in bouw, met zeer groote nauwkeurigheid is bereikt en dat een aanzienlijke minderheid der emmetropen in de school bijziend wordt, dan wordt men genoopt tot het aannemen van een mechanisme, dat de refractie toename van het pasgeboren oog op een wijze leidt, waardoor emmetropie ontstaat en bovendien de emmetropische oogen der scholieren zoodanig beheerscht, dat de meerderheid dezer oogen tegen de oorzaken der myopie bestand blijft."*[268]
>
> [*"The high frequency of emmetropia has always been taken for granted. However, if one considers that the newborn is usually hypermetropic, that the emmetropic state is accomplished with great accuracy in the majority of adult eyes, despite important structural differences between individual eyes, and that a sizeable minority of emmetropes become myopic at school, one is compelled to assume there is a mechanism that directs the refractive increase in the newborn eye in a way that emmetropia arises and also controls the emmetropic eyes of students in such a way that the majority of these eyes can resist the causes of myopia."*] *(authors' translation)*

Straub further postulated that emmetropization is the result of dynamic adaptation of the crystalline lens power and axial length, controlled by the nerve system, but he was unable to tell which of these was the driving factor. Around the same time, Adolf Steiger wrote a seminal work,[264] postulating that the normal variations in ocular biometry add up to form either emmetropia or ametropia, supported by significant correlations between ocular parameters. Seemingly unaware of Straub's 1909 work,[268] Steiger assumed this process was controlled by hereditary factors and stature, eventually leading to a Gaussian refractive error distribution. Although Wibaut disproved the latter assumption by reporting a skewed and leptokurtic refractive error distribution instead,[312] later reports by Tron,[296] Stenström[265] and Sorsby[262] confirmed Steiger's ideas about the correlations between parameters, which are essential for a tight refractive error distribution.[261] These authors also confirmed that the main ocular dimensions (intraocular distances and surface curvatures) are normally distributed, but that the fit is not as good for axial length due to an excess of eyes with a longer axial length.[262, 265] This causes the skewed and leptokurtic refractive error distribution.[223]

Although all authors agreed that the refractive power loss of the eye closely matches its growth, there was much disagreement about how this was accomplished. Sorsby, for example, considered all eye growth as genetically predetermined without feedback,[260] while for Hofstetter[93] and Mark[156] emmetropization was a geometric artefact, where the cornea automatically becomes flatter as the globe expands. Others, like van Alphen[298] and Medina,[162] saw indications of an active feedback system that corrects for minor refractive discrepancies, much as Straub

had envisioned. This discussion continued until animal experiments were able to induce myopia by altering the way light enters the eye,[207, 307, 309, 314] e.g. by imposing a refractive lens or a filter. From such experiments it became clear that retinal feedback plays an essential role in refractive development, modulated by the position of the sharpest image with respect to the retina.[309] If a negative (concave) lens is placed in front of a chicken eye, the sharpest image is moved behind the retina, triggering quick alterations in the choroidal thickness and axial growth rate until the refractive influence of the negative lens is fully compensated.[230] In humans the evidence for defocus-guided emmetropization is weaker, but still sufficient to assume that a similar process is at work.

From this short description it is clear that early refractive development is a complex process, with many interactions between components that have to be just right in order to work. It is therefore remarkable how well Straub's century-old conclusions still match the current understanding of the topic. But despite being the 'father' of emmetropization, his ideas are often overlooked in favor of the equally impressive work by Steiger. Meanwhile, the topic of emmetropization is often considered in function of myopia research, which is understandable in light of the ongoing myopia pandemic.[94] A review of emmetropization in its own right is therefore long overdue.

## *1.1 Definitions*

The term 'emmetropization' is a source of ambiguity in the literature as it suggests targeting zero refractive error without clarifying whether this refers to cyclopleged or non-cyclopleged refraction. Since cycloplegia is the clinical standard in children, the endpoint of emmetropization is often reported as *+1 diopter (D)*, corresponding with the loss in accommodative tonus.[172] Few would consider *+1D* emmetropia, however, making emmetropization under cycloplegia a contradiction in terms.

Straub also struggled with this issue, but also gave a thought that may help address it:

> *"Het doel der aanpassing is namelijk de instelling voor de verte. (…) De behoefte om de verst verwijderde voorwerpen scherp te zien voert tot de dynamische aanpassing, die op den duur den vorm van het oog helpt vaststellen en dan grotendeels een statische wordt."*[268]
>
> [*"The goal of the adaptation is namely the setting for afar. (…). The need to see the most distant objects clearly leads to a dynamic adaptation that eventually helps determine the shape of the eye and then becomes mostly static." (authors' translation)*]

He considered sharp distance vision as key to the entire process and, since children obviously do not spend their days cyclopleged, it is reasonable to assume that the target is non-cyclopleged emmetropia. Moreover, since cyclopleged and non-cyclopleged refraction represent fundamentally different physiological conditions, one could consider having 2 different definitions for emmetropia. Non-cycloplegic emmetropia is then given by the classic definition of *0.0 ± 0.5D*, while cycloplegic emmetropia should consider the accommodative tonus (*AT)* in its definition: *AT ± 0.5D*, or [*+0.5D*, *+1.5D*] assuming a tonus of *+1D* for children. The latter definition is supported by the fact that low hypermetropia under cycloplegia appears to have a protective effect in school children,[173] while a cycloplegic refractive error below *+0.5D* is typically considered 'pre-myopic' as it could lead to myopia later on.[185] In accordance with the conventions in the literature, the following only considers cycloplegic refraction and non-cycloplegic emmetropia unless specified otherwise.

## 2 Phases of refractive development

Since it is not possible to conduct a full longitudinal study of the refractive error before birth up until the age of *18* years, the only way to get a complete picture of early refractive development is by combining the spherical equivalent refractive error (*SER*) data published in previous studies in the literature. In this study we collected the cycloplegic *SER* data of *35* studies (*51 761* participants; details in Supplement A) with data from pre-term infants measured immediately at birth, full-term infants, and children from cohorts with a low myopia prevalence (Figure 1). Although the reliability of the cycloplegia and measurement protocols of the individual studies is not always clear, the synthesis demonstrates that refractive error goes through three stages: rapid perinatal hypermetropization (prenatal – *3* months), rapid emmetropization (*3* – *15* months), and **homeostasis**, a period where the refractive error is stable and gradually eases towards emmetropia (*1.25* – *18* years).[73, 76, 180] The following discusses each stage in more detail.

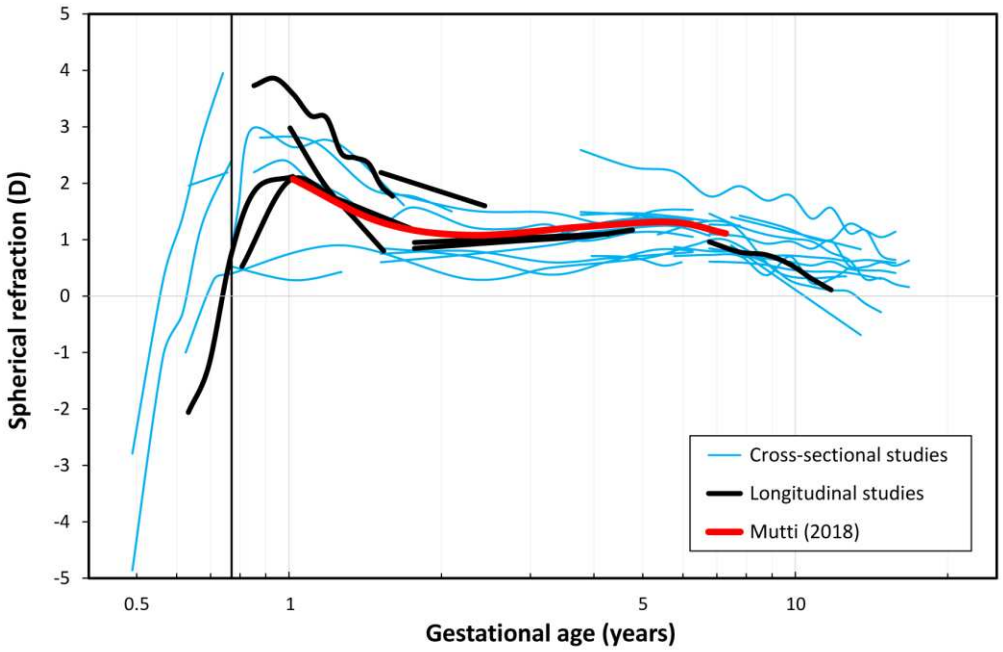


*Figure 1: Combined graph based on 35 literature reports presenting mean refractive error data for pre-term infants (measured at birth), full-term infants and children as a function of gestational age. Vertical black line represents normal time of birth (40 weeks of gestation). Study details available in* ***Supplement A****.*

### *2.1 Perinatal hypermetropization*

To understand the evolution of refractive error directly after birth, the earliest available source of information is required, which is pre-term infants whose refractive error was determined immediately after birth. Although their refractive development is different from that of full-term children,[57, 76] their birth refraction can still be considered as a close proxy for the normal refractive error in utero. Pre-term children are generally myopic at birth[28, 37, 46, 75, 234] and the degree of myopia increases with the degree of prematurity.[299, 300] This corresponds with a rapid change in refractive error towards hypermetropia at a rate of *40* – *50D/year* around *10* weeks before birth, which slows down to *12.8D/year* at birth and ends around the age of *3* months. For a large part, these changes are probably associated with scaled eye growth without visual feedback.

## 2.2 Emmetropization

Once the highest mean hypermetropic refractive error has been reached at about *+2.37 ± 0.12D* (*95%* confidence interval, CI) at *0–3* months after birth, it is immediately followed by a rapid decrease that brings the refractive error back down to around *+1.10 ± 0.07D* at *15* months of age.[33, 50, 52, 177, 198, 323] This refractive loss occurs at a considerably slower rate than the previous increase, with a maximum rate of *–2.12 D/year* at *6* months. This quickly brings the refractive error close to low hypermetropia (or non-cycloplegic emmetropia) through modulated growth.

## 2.3 Homeostasis

During this phase the remaining mild hypermetropia is preserved by a balance between axial growth, pushing refraction towards myopia, and lens power loss, pushing refraction towards hypermetropia.[173] As the eye continues to grow from a length of *20.71 mm* at *18* months[180] to *23.80 mm* at *17* years,[73] corresponding with an axial power change of about *–9.00D*,[215] homeostasis requires a considerable amount of coordination between the growth rates of the different ocular components. This is especially important to avoid cycloplegic pre-myopia (i.e. *0.00 ± 0.50D*) and the risk of later myopia development.[173, 332]

During homeostasis two subtle refractive changes may be distinguished: an initial increase in hypermetropia and a subsequent decrease that together form a slow, *6*-year long refractive fluctuation (Figure 1). The first indication for the existence of this fluctuation can be found in the Berkeley Infant Biometry Study that followed children longitudinally between the ages of *3* months and *6.5* years.[177, 180] In their seminal 2018 paper Mutti and coworkers showed that after an initial phase of emmetropization to a refraction of *+1.08 ± 0.11D* (*95%* CI) at *18* months, refractive error significantly increases to *+1.31 ± 0.16D* at *5* years (*t* test, *p = 0.015*) and slowly decreases again to *+1.11 ± 0.14D* at *6.5* years. Although Mutti and coworkers never explicitly discussed this, 2 older longitudinal papers also reported a minor, but significant, increase between the ages of *1* and *4* years.[1, 105]

One might think that the refractive decrease after *4 to 5* years is associated with an increased prevalence of myopia, though the same is seen in populations where myopia is rare.[65, 183, 201] Instead, the continuous lens power loss and hypermetropic stragglers are more likely reasons for this slow emmetropization. Axial growth typically ends between the ages of *15–20* years for emmetropes and hypermetropes, but myopes could still experience minor growth and continued myopization for another decade.[84, 88, 225] This is supported by a retrospective study in Buenos Aires office-workers where approximately *50%* of myopes had their myopia onset after the age of *20* years.[109] Environmental and behavioral factors may therefore continue to affect refractive development well into adulthood.

## 2.4 Endpoint

The natural target of cycloplegic emmetropization results from the preprogramed eye growth controlled by a combination of genetic factors, each nudging the refractive error towards either the myopic or hypermetropic side[278] depending on environmental and behavioral factors. It typically lies between *+0.50D* and *+1.00D*,[173] corresponding with the normal accommodative tonus of the accommodative system[194, 274] This is seen in native populations in rural areas who typically do not experience myopogenic influences and where adults have low hypermetropia, such as a mean *SER* of *+0.65D* in Amazonian Brazil [283] or *+0.59D* in Malawi.[133] Similar values

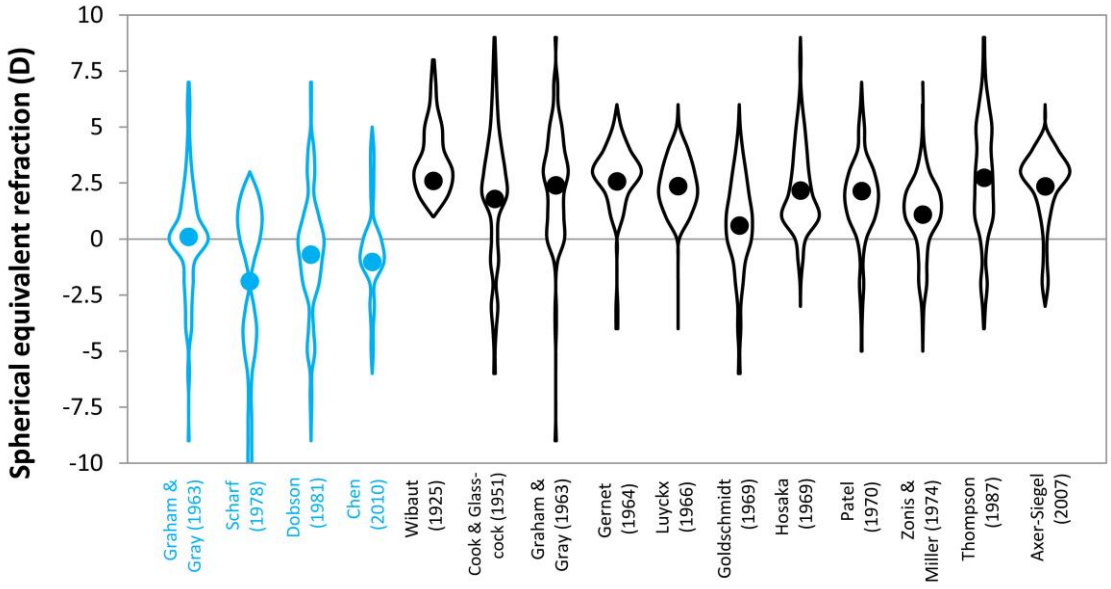


*Figure 2: Overview of refractive distributions of infants below one week of age reported in the literature. Round markers: average; blue lines: pre-term data at max 2 weeks after birth; black lines: full-term data at max 1 week after birth.*

were reported in White children with a high outdoors exposure, with *SER = +0.82D* in *11-15* year-olds in Sydney[106] and *+0.74D* in *16*-year-old Norwegian boys,[82] both populations with a low myopia prevalence. Given that zero refractive error under cycloplegia is a risk factor for future myopia,[185] this target may be a natural protection against myopization.[173]

# 3 Refractive clustering

## *3.1 Population changes*

The refractive distribution of full-term infants at birth is generally broad and centered on a mean hypermetropia of *+2.19D* (range *+0.60D to +2.74D*),[15, 39, 68, 71, 75, 97, 151, 197, 282, 312, 339] while in pre-term children these are centered on low myopia or emmetropia, depending on the degree of prematurity (Figure 2).[28, 46, 75, 234] The broadness of these distributions and the prevalence of myopia vary considerably between studies, but may be affected by variations in the cycloplegia protocols used and the difficulties in accurately measuring refractive error in infants.[172] In the first six years of life most of these eyes emmetropize into a tighter distribution, a process called ***refractive clustering*** or tight emmetropization.[173] The effects of clustering are best illustrated by the chick data of Wallman and coworkers who observed an initial distribution with a range of *18D* narrowing to *3D* during the first eight weeks of life, while the mean refractive error reduced from *+9.2D* to *+1.9D* (Figure 3a).[305] Clustering was also demonstrated in humans,[168, 169] but mostly during the first year with little change thereafter (Figure 3b).[159]

## *3.2 Individual changes*

Emmetropization appears universal at the population level, but much more variation can be seen on the individual level, with hypermetropic peaks and homeostasis occurring at different moments. Considering the longitudinal refractive data by Pennie and coworkers,[198] 4 different developments can be distinguished (Figure 4). A first group of *5* out of *19* infants underwent all

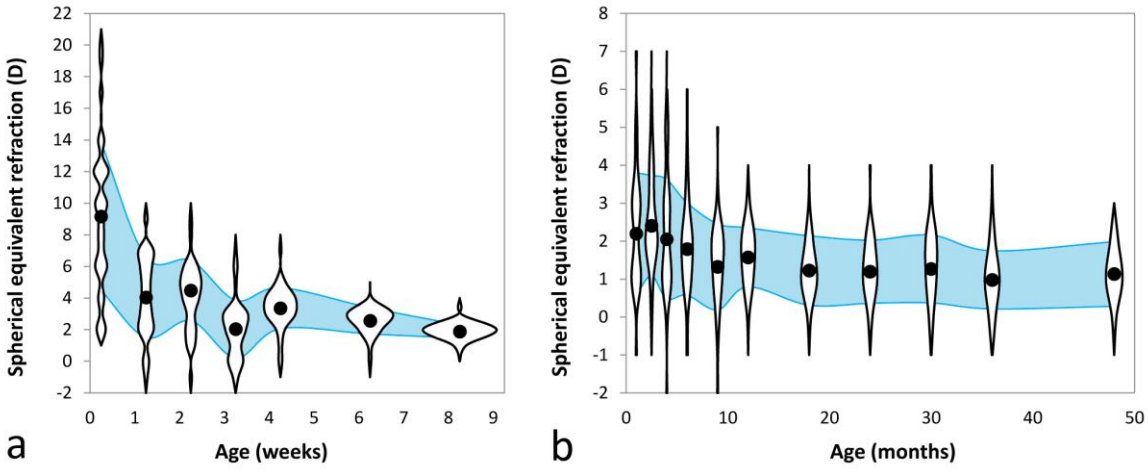


*Figure 3: a. Longitudinal refractive changes in chicks reported by Wallman et al.305; b. Cross-sectional refractive changes in children reported by Mayer et al.159 Black markers indicate the average, the blue zone corresponds with the standard deviation.*

3 stages of hypermetropization, emmetropization, and homeostasis (modulated development), while for a second group of *9* children the hypermetropic peak had already passed before the start of the study (instant emmetropization). Another *3* children were already close to low hypermetropia at the beginning and experienced instant homeostasis, and the final *2* children saw a rapid increase towards a high hypermetropia that persisted over the entire follow-up period. Most eyes reached the interval between *+1.00* and *+2.00D* within the one-year follow-up, while several others were still trending towards it. Recent longitudinal work suggests that this trend towards mild hypermetropia may even continue in *3 – 6*-year-olds[152] or even in *6 – 12* year-olds,[155] albeit at a diminished rate.

Since publicly available longitudinal data are scarce, we extracted the raw data of refractive change as a function of baseline refraction and age from the scatter plots of several prospective longitudinal studies, providing data for *742* measurements of children with ages between *2* weeks and *20* months.[52, 177, 198, 323] These data illustrate how emmetropization leads to the clustering into a tighter distribution as Straub[267] foresaw (Figure 5). For example, most eyes with a baseline refractive error near *+1.00D* will retain this value in the long term, while more hypermetropic eyes generally move towards *+1.00D* at a rate proportional to the initial refractive er-

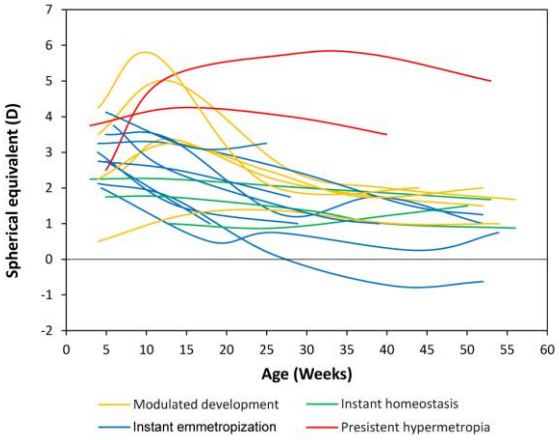


*Figure 4: Refractive changes in 19 infants during the first year. Replotted from Pennie et al.[198]*

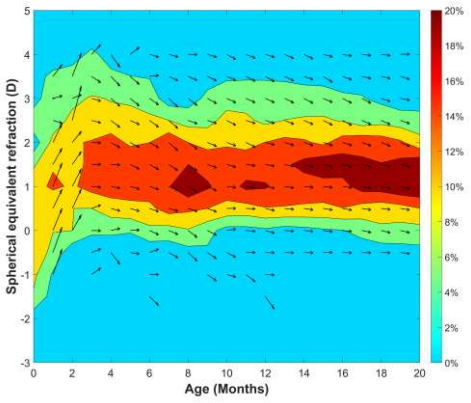


*Figure 5: Longitudinal refractive changes in a group of 742 infants. Colors indicate prevalence and arrows the mean refractive change during follow-up in bins with at least 3 eyes.*

ror.[227, 235] Some overshoot the target and become emmetropic or myopic, while others are emmetropic at baseline and become hypermetropic over time. Emmetropization therefore works in both directions,[51, 168] naturally compensating the neonatal refractive errors, regardless of their sign, provided they occur early enough (Figure 3).[168] Although these processes are mostly active during the first few years, they may form the basis for school age myopization if triggered by specific environmental or behavioral pressures as discussed in later sections.

# 4 Growth of ocular structures

The developmental stages described in the earlier sections all originate from underlying biometric changes that have been described in countless longitudinal and cross-sectional studies from around the world. A complete overview of these sources is outside the scope of this review, but is provided elsewhere.[215] For now, we will use an earlier literature synthesis by Weale[311] that shows all the relevant trends for current discussion.

## *4.1 Sclera and axial length*

During the first years of life the human eye grows from an initial axial length of *17 mm* at birth to *21 mm* (Figure 6a) and increases the tunic surface area from about *900 mm²* to *1400 mm²*. Simultaneously, the sclera increases its thickness from about *500 µm* at birth to *700 – 800 µm* in adults.[14, 70, 186] From this it should be clear that ocular growth is inextricably linked with scleral expansion and remodeling, which gradually slows as the sclera stiffens with age due to natural cross-linking of its collagen.[77, 78, 270] Since young scleras are more pliable,[195] children are at considerably higher risk of myopia than adults, while the severity of this myopia increases with earlier onset.[32]

The scleral development is likely similar to that of other structural connective tissues, with a developmental growth and remodeling according to the use or disuse of that tissue.[43] Scleral growth occurs in two ways: *appositional growth*, that causes dense connective tissues to grow thicker through deposition and resorption at the surface, and *interstitial growth*, where soft tissues grow thicker and longer by internal adding and remodeling of the interstitial extracellular matrix and collagen. The exact growth stimulus remains unclear for now, but developing and mature connective tissues both tend to remodel their extracellular matrix components according to their mechanical load, like in e.g. bone morphogenesis.[43] Consequently, the gradual deformation of tissue with age occurs through a combination of normal growth and elastic deformation by external influences. The sclera is especially interesting in this sense as its continuously subjected to the load produced by the pressure differential between the eye (*10 – 15 mmHg*) and the orbit[127, 340] (*3 – 5 mmHg*). Chicks, for example, require a normal vitreous cavity pressure during early development to develop a normal eye shape,[6, 41] while high intraocular pressure leads to excessive posterior sclera elongation (*'creep'*).[78, 176 85, 200] In humans, the sclera of infants may also interact with the expansive force of the intraocular pressure,[202] as seen in congenital glaucoma where the high intraocular pressure leads to axial elongation.[226] This process cannot explain school age myopia, however, since at that age normal eye growth has already slowed to *0.10 mm/year* and growth modulation is hampered by increased scleral stiffness.[112]

At the histological level, animal models suggest that excessive scleral growth is a combination of active growth that adds new interstitial tissue and a remodeling that reduces the creep rate and minimizes the refractive error.[26, 77] While the exact mechanism is unclear, it is known that an imposed negative lens up-regulates the matrix metalloproteinase turnover and degrades

intercellular proteoglycans and collagen fibers in the sclera.[77, 200] Meanwhile, an imposed positive lens produces an opposite response, with a down-regulation of the matrix metalloproteinase turnover and increased synthesis of proteoglycans and collagen, causing the connective tissue to be less extensible, decreasing or even stopping further ocular growth.[85] As will be discussed in Section 5.2.1 the most important trigger for these responses is visual feedback in the form of retinal blur and accommodation. This was confirmed by Bryant and McDonnell using a finite element model of the tree shrew eye that used visual feedback to control scleral growth and remodeling, producing a realistic simulation of posterior pole growth under normal eye pressure.[26] A similar model for human eye growth was published recently.[124]

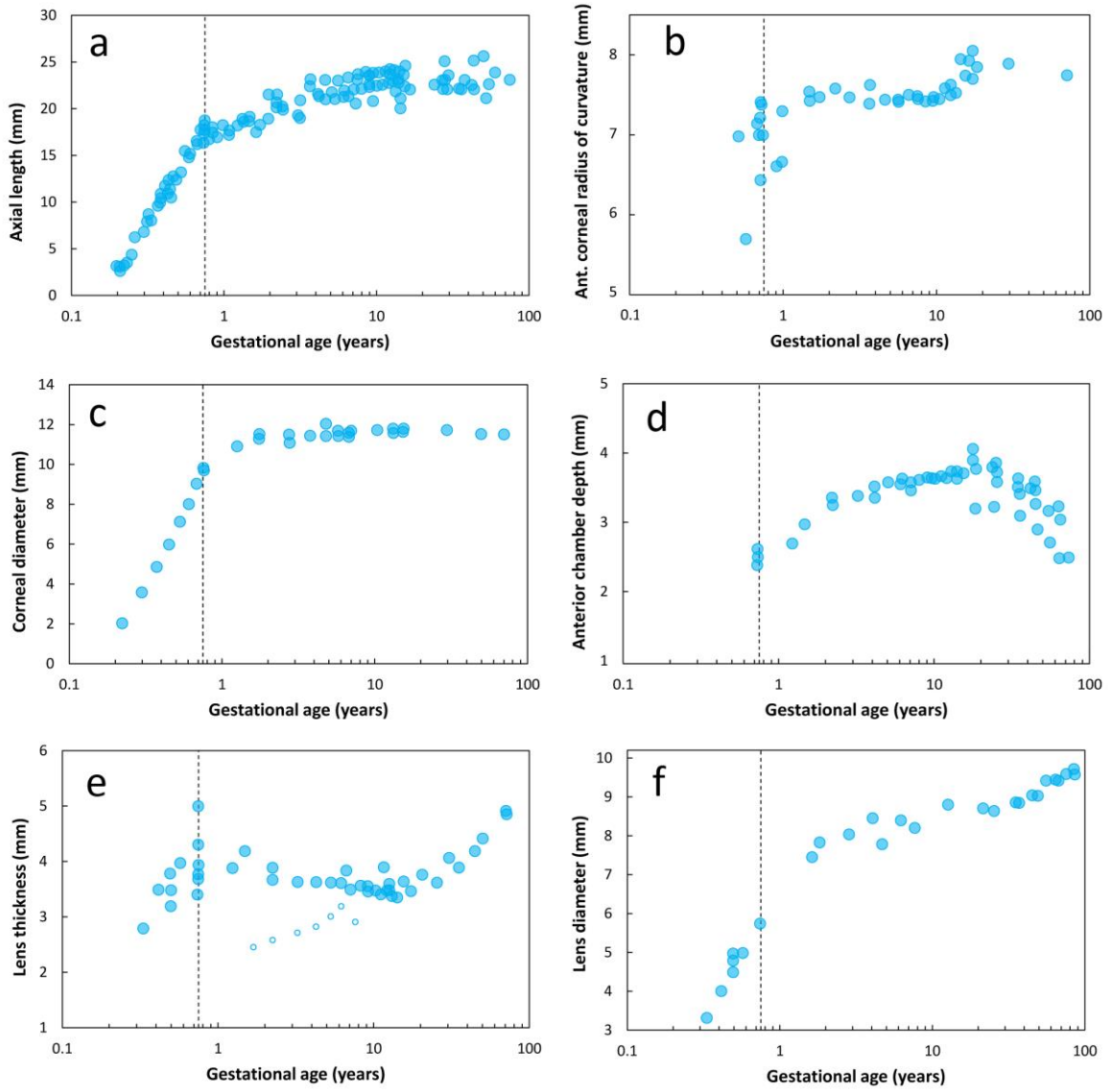


*Figure 6: Changes in ocular biometry before and after birth obtained by combining multiple previously published datasets for: a. axial length; b. anterior corneal radius of curvature; c. corneal diameter; d. anterior chamber depth; e. lens thickness; f. lens equatorial diameter. Dashed line represents time of birth. Open markers in panel e correspond with dataset with atypical behavior. Replotted from Weale.[311]*

### 4.2 Cornea

The cornea is a dense transparent tissue that provides the bulk of the ocular refractive power and helps maintain the ocular structure. Anatomically, this structure consists mostly of stromal tissue made of tightly packed collagen fibrils and specialized fibroblasts called keratocytes. The anterior epithelium has a basement membrane attached to the collagen fibers of the anterior limiting lamina. Posterior to the stroma, the Descemet membrane forms the basement membrane of the endothelium that pumps water and ions to maintain corneal transparency.

In embryos the cornea is steep and spherical in shape, but it quickly flattens until the adult curvature is reached, on average by the age of 2 years (Figure 6b).[73, 104, 129, 213] The corneal asphericity continuously increases with age due to a slight peripheral thinning.[246] Its central thickness does not change much with age, however, apart from a brief period of deswelling after birth.[210]

The mechanism to modulate the corneal curvature may be based on the clear association between the corneal curvature and its diameter.[110] This diameter is probably determined by the scleral growth near the limbus, which in turn may be modulated by signals from the peripheral retina.[112] During embryonal growth both areas are adjacent until the retinal mitosis begins to slow down at *7* months of gestation,[38] gradually pulling away the peripheral retina to from the limbal region and widening the space containing the *ora serrata* from a width of *2 mm* in newborn infants to *7 mm* in adults. It is conceivable that this increasing distance attenuates the retinal metabolite signals towards the cornea, thus slowing its growth. This could explain why the corneal power is determined during the first years of life without much change thereafter beyond the influence of eyelid pressure[239] or contact lenses. Although in humans this mechanism has yet to be observed, there is a similar process in chicks by which the peripheral retina regulates the equatorial expansion of the eye globe, independently of axial elongation.[56]

### 4.3 Crystalline lens

The crystalline lens is a structure with a unique set of features such as its deformability, gradient refractive index, and suspension within the ciliary ring, all of which make it essential for refractive development and accommodation. It is also the most variable optical structure in the eye as it undergoes drastic shape changes with age. The lens thickness increases before birth,[95] reduces until *10 – 12* years,[180, 333] and increases again thereafter (Figure 6e).[244] The lens diameter increases rapidly before and slowly after birth (Figure 6f),[13] while the lenticular radii of curvature initially become flatter[180] and then gradually steepen.[10, 48] Considered together, this means that the lens stretches from a small, nearly spherical structure in the embryonal stage to a thin, flat shape[181] that becomes thicker and rounder after the early teenage years.[108] The net result is a continuous lens power loss after birth.[108, 170, 176, 179, 180] which is easily understood when the lens is flattening, but appears contradictory once the lens steepens again. This *lens paradox*[126] can only be understood by looking at its structural changes.[47]

The crystalline lens consists mostly of densely packed fibers that develop from the anterior lens epithelial cells. These cells divide and migrate towards the equator, where they transform into lens fibers that gradually elongate until they reach the anterior and posterior poles of the lens. *In utero*, the differentiation and orientation of these fibers is guided by a diffusion gradient of fibroblast growth factor (FGF), excreted by the peripheral retina into the vitreous and aqueous humors.[148] Similar to the cornea, the increasing distance between the retinal periphery and the lens equator across the *ora serrata* during eye growth gradually decreases the FGF diffusion

gradient, stimulating the lens to reshape itself from a sphere early in the embryonal development to an asymmetric ellipsoidal shape during gestation. This reshaping is so robust that even a surgical inversion of the developing lens in a chick embryo, flipping the anterior and posterior poles, cause the fibers to reorient along the gradient within days and form a normal lens shape despite the intervention.[42] The epithelium continuously adds new cells that transform into fibers with a relatively low refractive index located right between the lens surface and the deeper, more mature fibers that have been compacted over time. This increase in fibers density from the surface to the lenticular nucleus creates a gradient refractive index that gradually bends passing light, almost doubling the surface power with a gradient power.[108] With age, the endless deposition of new fibers increases the density in and around the nucleus until the highest possible density is reached. This leads to a steeping gradient.[122] Since gradient power depends on pathlength, shallow gradients provide more power than steep gradients for the same peak index, and thicker lenses have more gradient power than thinner lenses.[108] Consequently, gradient power is lost with age, explaining the lens paradox.[108] In addition to age, gradient steepness and lens thickness are likely determined by the fiber growth rate as well. Hence, slowly-laid fibers would have a higher percentage of compacted fibers, leading to a thin lens with a steep gradient and a high central peak index.[108] Indirect evidence for this are children with longer eyes, such as those with myopia, taller born individuals or men, all of whom have thinner and less powerful lenses compared to their peers to compensate for their longer axial lengths.[108, 135]

The final factor affecting lens shape is the external stretching force applied by the zonulae to the capsular bag containing the lens. As the sclera expands during growth, the increasing pull of ciliary body pulls the lens into a flatter shape, despite the expected thickness increase due to the deposition of new lens fibers. Once the sclera approaches its final diameter, the zonular pull for distance vision becomes constant, and the lens thickness can slowly increase again (Figure 6e).

Despite its obvious importance, the lens' optical properties are relatively understudied *in vivo* due to its internal position and the lack of suitable or affordable clinical equipment. Consequently, most reports on this topic are either based on incomplete data, assumptions, and indirect calculations,[218] making many lens power values reported in the literature inconsistent and not comparable. The introduction of standardized methodology for clinical lens measurements is therefore long overdue.

### *4.4 Anterior chamber*

The anterior chamber is the fluid-filled space that separates the cornea and the crystalline lens. In embryos the lens and cornea are in direct contact with one another until the corneal endothelium is developed and the lens begins to recede. This, along with the gradual thinning of the lens, leads to an increase in anterior chamber depth. At around the age of *12* years, these trends reverse, with an increasing lens thickness and decreasing chamber depth (Figure 6d&e). The changes in anterior chamber depth directly affect the total power of the eye as an increased separation between cornea and lens will reduce the total power, while a decreased separation will increase it.

## 5 Ocular growth patterns

In adults, emmetropia is found in axial lengths ranging between *21 – 26 mm*,[128, 262] requiring a corresponding optical power range of *55 – 70D* to reach emmetropia.[217] The fact that refractive development is able to adapt to these extremes clearly highlights the flexibility of human eye

growth under favorable circumstances.[62, 63, 259, 262] Emmetropization consists of an interaction between the axial and refractive components of the eye according to passive and active mechanisms that together form the biometric growth patterns (Figure 6). **Passive or scaled growth** is dictated by the geometry of the eye globe, which decreases in curvature as it grows in diameter. Meanwhile, the limbus increases in diameter, thus proportionally flattening the cornea.[93, 110] **Active or coordinated growth**, on the other hand, refers to a retinal feedback system that modulates corneal, lenticular, and axial growth rates to maximize retinal image quality.[298] Several authors incorporated these processes into ocular growth models,[49, 86, 92, 101, 162] but they were often hampered by the limited availability of suitable data to test their hypotheses. The steep rise in the number of clinical studies since that time allowed new ideas about eye growth to be developed that will be discussed in this section.

### *5.1 Scaled growth*

Human body growth is largely genetically programmed, but is modulated by environmental factors and hormonal interactions. Growth rates vary considerably with age and the structure being considered. Infancy and puberty see especially fast growth spurts, separated by a slower period. During the first 2 years of life, for example, infants grow about *15 cm/year* in length, which slows down to *6 cm* per year during middle childhood and increases again to *7 – 11 cm/year* in puberty. Body growth slows down at about *14 – 15* years in girls and at *16 – 17* years in boys, leaving a mean height difference of *13 cm* between adult males and females.[209] Most tissues follow the growth pattern of the body as a whole, with the exception of the head and the brain.[193, 229] Instead, these structures undergo a rapid, exponentially decreasing growth (Figure 7). The brain quadruples in weight during the first *3* years of life, but adds only *25%* more weight during the subsequent *15* years.[45, 276] The eye closely follows the growth pattern of the head and brain, which is not surprising given that the retina, the coordinator of ocular growth, is neural tissue.

The human body also respects certain proportions, such as when taller people have longer arms, and larger heads. The same is true for the eye, where infants and adults with larger heads also have longer eyes,[22, 131, 228] along with flatter corneas and lower lens powers, irrespective of their refractive error.[53, 113, 114, 132, 184, 192, 228, 322, 324] Conversely, women are typically shorter than men, and have shorter eyes with more powerful optics while achieving the same refractive error.[108] These observations suggest that, at least during the early stages of development, the eye undergoes scaled growth during which it preserves its general layout and proportions, much like a balloon being inflated. This is confirmed by the refractive error distributions of pre-term and full-term infants, which have about the same width (Figure 2).

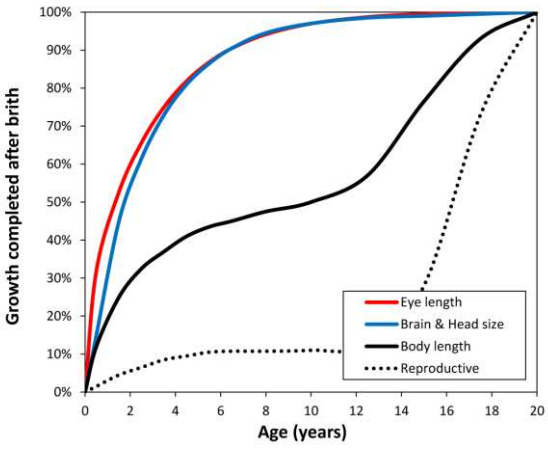


*Figure 7: Growth patterns of various parts and systems of the human body combining data from Tanner[276] and Weale.[311]*

It is unclear whether eyes that were relatively long at birth will still be relatively long at later ages, with one study reporting no correlation

between axial length at birth and during childhood[139] and another finding a strong correlation.[180] Given that, unlike the former, the latter study was conducted with the same equipment over the entire follow-up period, it seems more likely that the larger eye size at birth is retained in later life.

### *5.1.1 Nutrition and hormones*

Recent publications confirmed that urban children, who tend to be taller and weigh more than those in the countryside, have significantly longer eyes with flatter corneas for the same refraction.[143, 222, 275] Since corneal power is mostly determined during the first 2 years of life, the biometric differences between both groups are likely determined by early environmental factors,[286] such as prenatal conditions (e.g., mother's weight, nutritional and smoking habits, infectious diseases, education, socio-economic development, and inherited predispositions[199]), but also the babies' early eating and activity patterns. Urban children in developing societies consume more animal protein and dairy products than those in the countryside, leading to higher levels of insulin-like growth factor in their blood streams.[157, 211, 212] Similarly, switching from a traditional Asian diet to a Western diet, with a higher consumption of saturated fat in meat, cheese, and cow milk, is associated with increase axial growth.[140, 280] Hence, the consumption of foods with a high glycemic index may affect insulin sensitivity, which in turn could stimulate excessive eye growth and myopia.[40] Insulin is also known to speed up axial growth in chicks with imposed lenses or form deprivation, while a related hormone, glucagon, has the opposite effect. This suggests that insulin and glucagon may affect the growth regulation of the retina, choroid and sclera.[337] The positive correlation between body length and eye size suggests that there may be a systemic effect on ocular growth, but this is not necessarily the case for school myopization as that is mainly caused by external optical environmental factors such as illumination, defocus, and contrast.

Other interesting aspects can be found in hormonal diseases, such as growth hormone receptor deficiency (Laron syndrome), leading to adults with a short stature but otherwise normal body proportions.[79] The eyes of these individuals are generally shorter than those of matched controls, but with a more powerful cornea and lens, so their ocular refraction remains near emmetropia.[23] In another syndrome, isolated growth hormone deficiency, a failure in the release of growth hormones and insulin leads to a short adult stature with a relatively large head and eye size (albeit close to that of typical individuals). This confirms that eye and head size follow a different growth path from the rest of the body, possibly involving a greater role for insulin-like growth factor II[44] or other local growth factors that override insulin, reflecting a physiologic hierarchy between body and brain growth.[2, 3] Cortisol, estrogens and thyroid hormones could also play a role, as they also affect tissue growth.[3]

## *5.2 Coordinated growth*

The active components of ocular growth have already been the topic of several review articles.[59, 309, 315] The following intends to give a cursory overview of this challenging topic.

### *5.2.1 Growth triggers*

Emmetropization and homeostasis are largely controlled by retinal defocus. The prevailing theory suggests that if the focal point is predominantly located behind the retina (hypermetropia), it triggers an increased growth rate to compensate, and when the focal point is predomi-

nantly in front of the retina (myopia) the growth rate is reduced. Consequently, cycloplegic refraction was found to be the best predictor for longitudinal refractive change during emmetropization.[52, 177, 178, 323] While cycloplegia may be considered as a 'calibrated' refractive state essential for follow-up studies and comparisons, it also represents a form of distance vision without accommodative tonus that the eye rarely experiences in everyday life. Hence, any description of the optical feedback mechanisms that modulate ocular growth rates must start from a combination of cyclopleged refraction and accommodative performance.

The ability to accommodate develops gradually during early childhood from being unreliable in the first *3 – 4* months of age,[89] to better suited for near than for far vision at *1* year,[64] eventually reaching accurate accommodation for near and far. This evolution closely follows the distances at which childhood activities take place, such as eating and grasping toys in the early years, to interactions with people and objects at a distance as they grow older.

The idea that accommodation is involved in refractive development was first proposed in *1988* when Schaeffel and Howland presented a mathematical model of the chick eye that incorporated optical feedback mechanisms.[232] Clinical confirmation came later from Mutti and coworkers, who found a lack of correlation between non-cycloplegic defocus at baseline and refractive change in infants between *3* and *18* months old.[178] Meanwhile, infants with low to moderate refractive errors were able to maintain accurate levels of accommodation at near targets and were considerably more likely to grow towards the target refractive error of *+1D*. This suggests that a direct, defocus-driven model for emmetropization must be complemented by the normal accommodative tonus. Horwood and Riddell later confirmed these observations and reported that, under natural binocular conditions, accommodative behavior at baseline may predict successful emmetropization.[96] Persistently emmetropic infants accommodated well for all distances at baseline, emmetropizing hypermetropic infants accommodated better for near than for far, while the same was seen in persistent hypermetropic infants, but with more under-accommodation at all distances (Figures 8). This was suggested by an earlier report that *3 – 12* month-old infants lagged more for distant targets (*57 cm*; *1.75D*) than near targets (*33 cm*; *3D*).[64] Finally, animal experiments demonstrated that normal eye growth can still compensate for an imposed defocus when accommodation is blocked, albeit with lower accuracy.[309] These observations all suggest that accommodative lag presents a complementary feedback trigger for growth rate changes. Recent experiments add some nuance to this idea, however, as the amount of accommodative lag does not

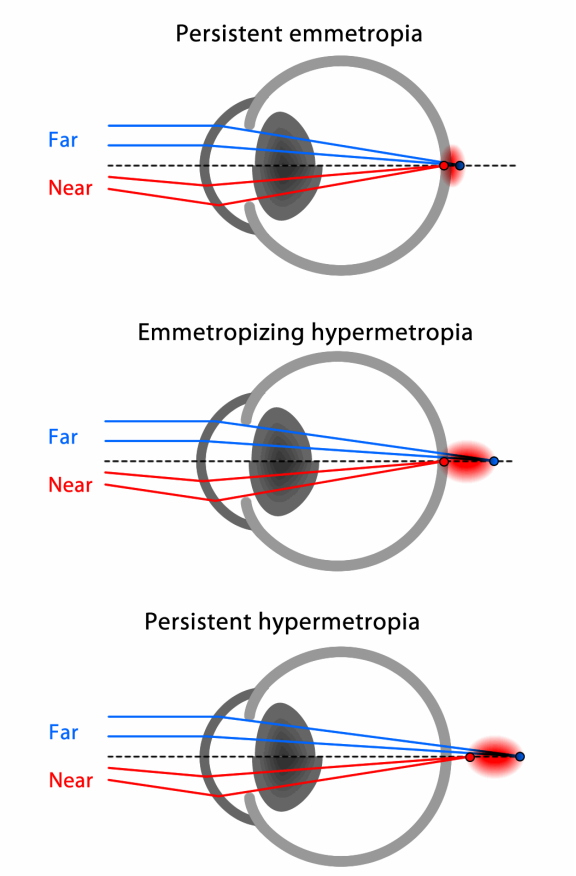


*Figure 8: Overview of the average focal point positions (red area) in persistent emmetropia, emmetropizing hypermetropia and persistent hypermetropia.*

necessarily lead to accelerated eye growth.[4] Instead, the number of hours spent in myopic and hypermetropic defocus may have a larger influence than the amount of lag itself.[335]

There are several ways these triggers could integrate into a growth regulator. One possibility is that retinal blur and accommodation are perturbations to a genetically preprogrammed scaled growth rate.[232] The posterior scleral growth would then be controlled by retinal blur integrated over time, while the metabolic factors from the peripheral retina control lenticular growth. Another, simpler possibility is that the growth rate is controlled by retinal blur alone through a wide spatial and temporal integration over the entire retina, which is in turn affected by both refraction and accommodation. In this description, the hypermetropic defocus in infants forms a growth signal that, along with the lack of scleral stiffness,[290] accounts for the rapid axial increase during the first years. Accommodation would then be a short-term modulating factor, as it attenuates hypermetropia in both near and far vision, reducing the risk of excessive ocular growth. Meanwhile, eyes that cannot accommodate away their hypermetropia are at risk of increased growth rates and myopic shifts due to time-integrated hypermetropic defocus.[96]

### *5.2.2 Influencing factors*

Although the concept of retinal blur as a growth trigger is easy to understand, it is important to note that the process is affected by the blur's cause, direction, chromaticity, luminosity, and temporal changes, all integrated into a single growth response by the retina. These influences have each been thoroughly examined in animal studies, allowing a more detailed understanding of the underlying mechanisms. Table 1 gives a brief introduction to the most relevant studies.

Clear proof that emmetropization is **driven by refractive blur** is found in experiments initiated by Schaeffel, who placed a refractive lens in front of the eyes of newborn chicks during emmetropization and reported that these eyes were able to compensate imposed refractive powers between *–10D* to *+15D* by adjusting their axial growth.[83, 116, 231] Even though this process takes several days to complete, chick eyes are able to determine the sign of imposed lenses within a matter of minutes.[336] Blocking accommodation reduced the efficiency of the mechanism, but did not stop it,[231] confirming its role in emmetropization. Additional proof comes from animals raised in an environment that forced them into a permanent state of accommodation, leading to myopia.[165, 214, 330] Interestingly, defocus-driven modulation of axial growth not only occurs in young, but also in adolescent animals.[196, 249, 294] Similar results have been observed for the eyes of other species (Table 1).

Another type of experiment, called **form deprivation**, allows animals to perceive light but not to see a clear image. These studies, performed either by suturing the eyelids of an infant animal or covering it with a frosted plastic occluder, invariably leads to myopia (Table 1). In human infants, myopia may occur a similar situations, such as in ptosis,[100, 191, 204] dense corneal scars, excessive eye patching[175] or after a vitreous hemorrhage.[55] These observations suggest that the eye is unable to distinguish between blur caused by refraction or by scatter, and that it interprets form deprivation as extreme hypermetropia. Curiously, subjecting rhesus monkeys to milder degrees of pattern deprivation in the form of reduced contrast led to an increase in hypermetropia rather than myopia,[24] possibly pointing at another misinterpretation of non-refractive blur. Lens-induced or form deprivation myopia can usually be reversed after removal of the lens or sutures, provided the eye is left uncorrected.[160, 203, 304] As the flexibility of the growth process decreases with age, both the formation of experimental ametropia, as well as the potential for recovery is greatly reduced in older animals.[293, 304, 313, 314] These experiments all show the remarkable robustness of defocus driven eye growth in young animals.

**Table 1: Global overview of animal studies and their outcomes**

| Observation | Chick | Mouse/ rat | Tree shrew | Guinea pig | Rab-bit | Cat | Mar-moset | Rhesus monkey | Human equivalent |
|---|---|---|---|---|---|---|---|---|---|
| Myopia after form deprivation (lid suture) | Yes[308, 328] | Yes[16, 279] | Yes[243] | Yes[98] | Yes[301] | Yes[72, 125, 166, 313] | Yes[292, 294] | Yes[284, 314] | Ptosis, patching, scars,... [55, 100, 175, 191, 204] |
| • *(Partial) recovery after suture removal* | Yes[317] | | | | | **Mixed**[166, 313] | **Mixed**[205, 292, 294*] | Yes[203*] | |
| Myopia after form deprivation (filter) | Yes[31, 231, 304] | Yes[27, 287, 288] | Yes[188, 190] | Yes[150, 325, 334] | | | Yes[74] | Yes[249,256] | Myopia in pediat-ric cataract[277] |
| • *(Partial) recovery after filter removal* | Yes[304] | | Yes[248] | Yes[334] | | | | | |
| • *Protective effect of bright ambient light* | Yes[8, 17] | Yes[27,288] | Yes[247] | | | | | Yes[256] | |
| • *Aggravating effect of dim ambient light* | | | | | | | | **No**[241] | |
| • *Hypermetropia after mild form deprivation* | | | | | | | | Yes[24] | |
| Compensation of imposed myopic lens | Yes[83, 116, 231] | Yes[16, 288] | Yes[160, 238] | Yes[99, 149, 325] | | Yes[118] | Yes[74] | Yes[103, 255] | |
| Compensation of imposed hypermetropic lens | Yes[83, 116, 231] | | Yes[164] | Yes[99] | | **No**[118] | Yes[74] | Yes[103] | Yes, but weakly[81] |
| • *(Partial) recovery after imposed lens removal* | Yes[304] | | Yes[160] | Yes[149] | | | | Yes[103, 258] | Recovery of mild myopia in infants |
| • *Protective effect of bright ambient light* | Yes[9] | | Yes[247] | Yes[137] | | | | **No**[255] | |
| • *Protective effect of dim ambient light* | | | | | | | | Yes[242] | |
| • *Protective effect of constant light* | **No**[17] | | | | | | | | |
| • *Protective effect of blue/violet ambient light* | Yes[289] | Yes[117] | | | | | | | Yes[289] |
| • *Lens compensation with inhibited accommodation* | Yes[233, 236] | | | | | | | | |
| Myopia when restricted to near vision | Yes[165] | | | | | Yes[19, 214] | | Yes[245, 329, 330] | School myopia[107] |
| Refractive change when reared in constant light | Yes ⊕ 136 | Yes ⊖ 182, 287 | | | | | | **No** 253 | |
| Refractive change when reared in dark/ dim light | Yes ⊖ 31, 30 | Yes ⊕ 287 | Yes ⊖ 189, 247 | Yes ⊖ 137 | | | | Yes ⊖ 206, 240 | Yes ⊖ 35, 219 |
| Myopia when reared in red light | Yes[61, 237] | **No** ⊕[327] | Yes[66] | Yes[147] | | | | Yes[102, 254] | |
| Hypermetropia when reared in blue/ violet light | Yes[61, 237] | Yes[269] | Yes[67] | Yes[145] | | | | Yes[144] | |
| Regional refractive response to half-field lens | Yes[306] | | Yes[187] | | | | Yes[20] | Yes[257] | Possibly[141] |
| Regional myopic response to half-field form deprivation | Yes[31] | | | Yes[161] | | | | Yes[250] | |
| • *Same, after inhibiting optic nerve/ fovea* | Yes[291] | | | | | | | Yes[257] | |

*Occasionally, a hypermetropic response was reported.

⊕: hypermetropic change; ⊖: myopic change.

**Ambient illumination** appears to play a double role. By itself, it forms another trigger for excessive or reduced ocular growth, such as in chicks reared under constant light that develop severe hypermetropia,[136] while rats become myopic under the same circumstances,[182] and rhesus monkeys see no change.[253] In dim or dark conditions, on the other hand, most animals tend to become myopic, with the exception of mice,[287] who become hypermetropic (Table 1). The closest human equivalent is the recent observation that preschoolers in kindergartens with a low ambient illumination (*300 lux*) have on average lower hypermetropia values than those attending brightly lit kindergartens (*700 lux*),[35] along with the well-known observation that time spent outdoors reduces the risk of (continued) myopia development.[174] The other role of illumination can also interact with other environmental influences and modulate the growth response.[146] For example, high ambient lighting slows lens-induced or form deprivation myopia in chicks[8, 9] and tree shrews,[247] while in rhesus monkeys it protects against form-deprivation myopia.[255, 256] Dim ambient light does not affect form deprivation myopia in rhesus monkeys,[241] but it does attenuate lens induced ametropia.[242] This association with low light intensity is likely related to the sensitivity of the photoreceptors. Since the cones in the fovea are less sensitive to low intensities than the rods in the periphery, this may increase the relative importance of peripheral defocus and potentially increase the risk for myopia development. Bright lights, on the other hand, gradually increases the dopamine level in the retina, which is a well-known stop signal for eye growth.[21, 54, 138]

**Pupil size** is also important in this context since smaller pupil sizes reduce the ocular wavefront aberrations, and hence the size of the retinal focus, leading to a sharper retinal image. Smaller foci also lead to less light spilling between adjacent photoreceptors,[302] forming an additional way bright environments may affect emmetropization.

Finally, a sufficient quantity of environmental **higher spatial frequencies** may be needed for proper refractive development. These frequencies correspond with the finer details in the retinal image and are essential to provide the retina with visual cues to assess blur. Since natural scenes typically have more details, while urban scenes generally have more uniform surfaces with fewer details, this was proposed as an aggravating factor in myopia development.[60]

The overview in Table 1 is by no means complete and omits many other experiments that combine the aspects mentioned above, or look at the genetics, proteomics and biomechanics under these circumstances.[230, 295] Although informative, it is important to keep in mind that animal experiments may not reflect all aspects of human refractive development.[230, 331] Regardless, these results suggest that the combination of external influences has to be just right to accomplish an optimal refractive development, while compensation failures lead to large degrees of ametropia.

### *5.2.3 Response*

There are clear signs that emmetropization is **controlled locally** by signals that go straight from the retina to the sclera. Half-field occluders or half-field minus-lenses cause ocular elongation and myopia only in the corresponding section of the fundus,[161, 250-252, 306] even after severing optic nerve[291] or ablation of the fovea.[252] In children a similar phenomenon may exist in the form of a longitudinal myopization of the superior refraction that was attributed to read-

ing behavior.[141] The peripheral retina is especially interesting in the context of myopia control since peripheral hypermetropic defocus leads to central axial myopia[20] since perimacular myopic growth will automatically drag the central foveal zone along with it.[124]

This raises the question as to how positive or negative refractive errors lead to a retinal growth response, given that similar degrees of myopia and hypermetropia produce the same amount of retinal blur. The answer lies in multiple factors that each show a different aspect of the defocus sign. Chromatic aberrations, for example, cause red light to be focused behind the retina in an emmetropic eye, while blue light is focused on front. Hence, one would expect that animals raised in red light to become myopic while those raised in blue light would become hypermetropic, which is confirmed in chicks[61, 237] and mice,[269] but not in tree shrews or monkeys.[224] Another way to estimate the defocus sign is through accommodation, which can partially compensate hypermetropia but not myopia, or through-focus changes in higher-order wavefront aberrations.[281, 319] Moreover, the emmetropic human eye produces a different physiological response to optical blur than to a blurred image on a screen,[271] as well as to different contrast polarities of a text,[272] confirming that the retina is also sensitive to optical phase information via the ON/OFF pathways.[5, 310] The **spatial and temporal variations** in these visual signals are then **integrated** into a growth signal, as illustrated by the experimental results in section 5.2.2. There may be limits to the efficacy of this process, however. Based on the observation that an imposed positive lens and an imposed scatter filter both lead to myopization, it is possible that the retina cannot distinguish between different forms of blur. Since in form deprivation there are no clues to the sign of the blur, the retinal processing may respond in the same way as to an extreme form of hypermetropia and start growing in a fruitless attempt to reach to a sharp image.

Once optical blur is detected, there are 3 compensating mechanisms that either change the accommodative state, choroidal thickness, or axial length. These responses differ considerably in speed, amplitude and reversibility.[309] Accommodation can compensate several diopters of negative defocus almost instantly, but is ineffective against positive defocus. Meanwhile, choroidal thickness changes can compensate positive or negative defocus in a reversible manner within a few hours. In chicken experiments this response can compensate several diopters of defocus, while in humans a similar, but more limited response can occur until early adulthood.[5, 208] Finally, axial length changes may cancel out fairly large amounts of defocus of any sign, but the response's amplitude and reversibility greatly depend on the age and scleral distensibility of the individual,[309] as well as on the type and duration of the retinal blur signal it perceives. For example, in chickens a short period of positive defocus can lead to a far more potent growth response than *12* hours of negative defocus,[338] which may be associated the inability of accommodation to compensate positive defocus, or the more rapid decay of negative retinal blur signals compared to positive signals.[335] Environmental circumstances such as low ambient light reduce the accuracy of the accommodative response, with overaccommodation for distance vision and underaccommodation for near vision in humans,[119] thus distorting the visual cues to the retina. Since accommodation requires some effort to maintain and is associated with higher levels of optical aberrations,[29] a long-term blur signal may be more efficiently compensated by adjusting the axial growth speed, leading to permanent changes.

Even so, some degree of accommodative tonus is generally well tolerated, as latent hypermetropes typically do not develop myopia.

It remains unclear whether the human axial response to blur occurs according to a graded process, where the response is proportional to the amplitude of the defocus, or rather a binary ('*bang-bang*') process[83] where the growth response occurs at a fixed rate until the defocus is fully compensated.[178] The reason for this lack of clarity, at least in humans, lies in the relatively long periods between follow-up measurements that make it impossible to distinguish between immediate and slow growth. Chick eyes can compensate for imposed lenses at a constant speed within a few days, suggesting that eye growth is indeed controlled by a binary rather than a graded process,[83] but since imposed lenses do not represent a realistic physiological situation, this observation may also correspond with the maximal scleral growth rate, and the growth response will still be graded for minor amounts of defocus.

To some degree the influences that trigger myopization seem to align with the luminous environment before birth. For example, when unhatched chicks open their eyes, they will mostly see darkness (if mother hen is brooding) or low-intensity red light passing through the eggshell. Coincidence or not, these circumstances are all axial growth signals in chicks. In monkeys, on the other hand, red light is not an axial growth signal, while low light intensity is. This aligns with the expectedly much darker environment they experience *in utero*, as the womb is located deep inside the mother's fur-covered body, and it is likely too dark for red cone vision.

### *5.2.4 Therapeutic consequences*

Based on the animal experiments in section 5.2.2, it might seem reasonable to undercorrect ametropic children to forcefully adjust the ocular growth speed and gradually reach a more appropriate axial length. While this idea has some ardent supporters,[163] refractive undercorrection has a mixed track record for myopia control, with randomized controlled trials reporting both slower and faster progression.[316, 320] To the best of our knowledge, there has yet to be a similar trial on the undercorrection of hypermetropia in schoolchildren, but in infants no difference was found between children that experienced either full correction or undercorrection.[12] The therapeutic translation of some of these animal experiments to humans remains therefore controversial until randomized control trials become available. One exception to this are the recently developed spectacles and contact lenses with some peripheral plus power to slow myopia axial growth by creating a perimacular myopic defocus. These designs have proven effective in slowing the progression of myopia in several randomized trials and are being introduced in clinical practice, along with diluted atropine drops.[30, 134, 316, 321] Similarly, center-near multifocal soft contact lenses for presbyopia may be useful to accelerate axial growth when fitted in children with in hypermetropic eyes.[18]

### *5.2.5 Other aberrations*

Ocular growth not only minimizes refractive sphere, but also astigmatism[221] and other wavefront aberrations, [7, 11, 273] by finding the optimal balance between the corneal and lenticular aberrations. This balance generally works well in young adults, but it is slowly lost due to age-related changes, such as the corneal change from with-the-rule to against-the-rule astigma-

tism.[221] Unlike the sphere, these are not axial processes, but rather gradual surface changes. This was confirmed by longitudinal imposed cylinder lens experiments in monkeys that did not lead to much refractive compensation.[123]

## *5.3 Relative contributions*

### *5.3.1 Scaled vs. coordinated growth*

Although scaled and coordinated growth likely occur simultaneously for a while, it is clear that their relative contributions change with age. Since the retina can only receive visual feedback after birth, it is reasonable to assume that ocular growth is mainly determined by scaled growth before and shortly after birth. Consequently, at birth there should be strong correlations between scalable biometry parameters, such as corneal curvature and axial length, while unscalable parameters, such as refractive error, are expected to have a low correlation with biometry. The literature indeed shows relatively low correlations between refractive error and axial length at birth, ranging between *–0.188* and *+0.03*,[91, 151, 220] while the correlation between corneal radius and axial length is relatively high at *0.575 – 0.678*.[22, 220] In the months and years that follow the active processes gain importance as indicated by the increased correlation between refractive error and axial length (Table 2). In school children this is easily understood because of the increased prevalence of myopia, but at *3* months, long before school myopia, these higher correlations may be associated with the shortest eyes being more hypermetropic. At the same time, a weakly positive correlation between refractive error and lens power is gradually established,[108] while the negative correlation between lens power and axial length seems fairly stable, probably due to the lens power loss while the eye grows. Increased myopization causes the initial correlation between refractive error and corneal radius to gradually decrease. Finally, refractive clustering causes the correlation between corneal radius and axial length to increase at first but subsequently decreases due to myopization.

Note that it is important to be cautious when comparing correlation values as they may be affected by population size and sampling artifacts. Even so, multiple references and datasets show similar correlation values, suggesting these trends are likely correct.

**Table 2: Age-related changes in Pearson correlation between biometric components taken from Ma et al.,[153] Mutti et al.[180] and Rozema et al.[220, 223]**

| | **Rozema 2018** | **Mutti 2018** | **Ma 2016** | **Ma 2016** | **Ma 2016** | **Rozema 2014** |
|---|---|---|---|---|---|---|
| Age | *0-3 days* | *3 mths* | *3 yrs* | *6 yrs* | *10 yrs* | *25 yrs* |
| *N* | *66* | *286* | *278* | *861* | *686* | *242* |
| *Spherical equivalent (SER)* | *2.78 D* | *2.07 D* | *1.25 D* | *1.08 D* | *–0.83 D* | *–1.61 D* |
| *Axial length (AL)* | *16.53 mm* | *19.19 mm* | *21.94 mm* | *22.67 mm* | *23.83 mm* | *23.98 mm* |
| *Corneal radius (CR)* | *6.93 mm* | *7.69 mm*[*] | *7.81 mm* | *7.84 mm* | *7.83 mm* | *7.75 mm* |
| *Crystalline lens power ($P_L$)* | *49.34 D* | *40.30 D* | *27.00 D*[†] | *24.87 D*[†] | *23.22 D*[†] | *23.60 D* |
| *Correlation SER vs. AL* | *–0.114* | ***–0.39*** | ***–0.416*** | ***–0.456*** | ***–0.705*** | ***–0.715*** |
| *Correlation SER vs. CR* | *0.204* | ***0.21*** | *0.031* | ***0.073*** | ***–0.145*** | ***–0.099*** |
| *Correlation SER vs. $P_L$* | *–0.116* | *0.04* | *0.035* | ***0.109*** | ***0.286*** | ***0.184*** |
| *Correlation CR vs. AL* | ***0.575*** | ***0.46*** | ***0.732*** | ***0.680*** | ***0.439*** | ***0.438*** |
| *Correlation $P_L$ vs. AL* | ***–0.681*** | ***–0.69*** | ***–0.745*** | ***–0.708*** | ***–0.748*** | ***-0.638*** |

Significant correlations ($p < 0.05$) given in **boldface**

[*] Value converted from diopters; [†] Value at the second principal plane of the eye

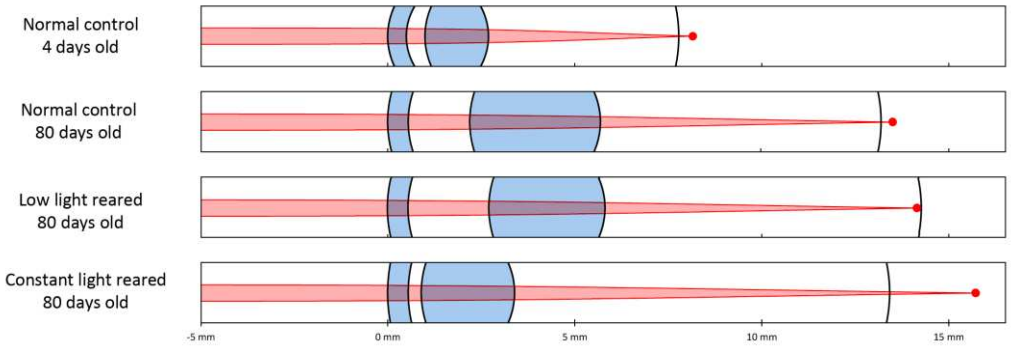


*Figure 9: Comparison of eye growth in chicks at age 80 days in normal, low light (50 lux) and constant light conditions based on data from Cohen[34, 36] and Li.[136]*

### *5.3.2 Anterior vs. posterior segment growth*

Another important aspect to consider is the relative contribution of the anterior and posterior segments to emmetropization. Corneal power, for example, is mostly defined by scaled growth until it reaches its final values at an age of about *3 to 4* years (Figure 6b). Because the cornea is the major refractive element of the eye, this sets the stage for the continued refractive development of the axial length and lens power. Both are determined by a combination of scaled and coordinated growth, but whereas axial length stops growing during adolescence (Figure 6a), lens power loss will continue throughout life.[112, 121, 216, 297] This combination of scaled and coordinated growth leads to a balance between the anterior and posterior segments of the eye during homeostasis that is eventually lost during adult-onset hypermetropia later in middle-age due to the continued lens power loss.[87, 167]

Although the homeostasis between the anterior and posterior segments is quite robust in healthy eyes, it may fail under certain experimental or pathological conditions (see also Sections 5.2.2 and 5.2.3). For example, eyes with otherwise normal axial lengths will become myopic if their corneal or lenticular powers are too high, e.g. in keratoconus, lenticonus, or age-related nuclear cataract.[25, 108, 111, 114] Anterior segment growth can also be affected by external factors such ambient light. If chicks are reared under constant light, their anterior segment growth slows down, leading to shallower anterior chambers, as well as lower corneal and lens powers (Figure 9).[115, 136] Much like in lens-imposed hypermetropia, these eyes develop deeper vitreous chambers to compensate for the lower powers, but insufficiently for a full compensation, resulting in severe hypermetropia. Chicks reared under dim lights, on the other hand, experience faster axial growth and increased corneal and lens power losses to compensate (Figure 9).[34, 36] This compensation holds up reasonably well for 1 or 2 months,[36] but when the lens power loss can no longer keep up with axial growth myopia begins to form. Normally, the emergence of myopia would quickly slow down the posterior segment growth, but the momentum of the accelerated axial growth may extend the stopping time and increase the final degree of myopia. Other experiments demonstrated that posterior segment growth in chicks is dissociated from equatorial growth, since the destruction of peripheral retinal neurons led to wider eye globes while axial growth remained the same as in healthy controls.[56] Similar experiments, using intravitreal injections of kainic acid to dissociate anterior and posterior

segment growth in chicks, found changes in equatorial diameter and either steeper or flatter corneas, depending on the concentration.[318]

The dimensions of the anterior and posterior segment also seem dissociated in humans, since the anterior segment length remains roughly constant between *2* and *12* years of age,[130] while the axial length continues to grow considerably. Premature infants, on the other hand, tend to have shallower anterior chambers and steeper corneas at a gestational age of *40* weeks compared to full-term infants,[37] a difference that persists at *7* to *9* years of age.[28] Myopia of prematurity may therefore result from higher corneal and lenticular powers rather than excessive axial length.[108] Although there could be other growth abnormalities, e.g. resulting from laser treatments of retinopathy of prematurity, it is likely that the early exposure to light in these eyes stagnates their anterior segment growth into an immature state with high-powered optics. Another example is adult myopes, whose scleral tissue posterior to the equator has thinner collagen fibrils, while the anterior sclera remains normal.[120] This results in different shapes of the vitreous chamber, which is more prolate in emmetropes and spherical in myopes, while their anterior segments are similar in shape.[69] These examples suggest that, although the anterior and posterior segment growth patterns are typically balanced to produce long-term refractive stability, these may be dissociated by environmental factors and retinal response, eventually leading to ametropia.

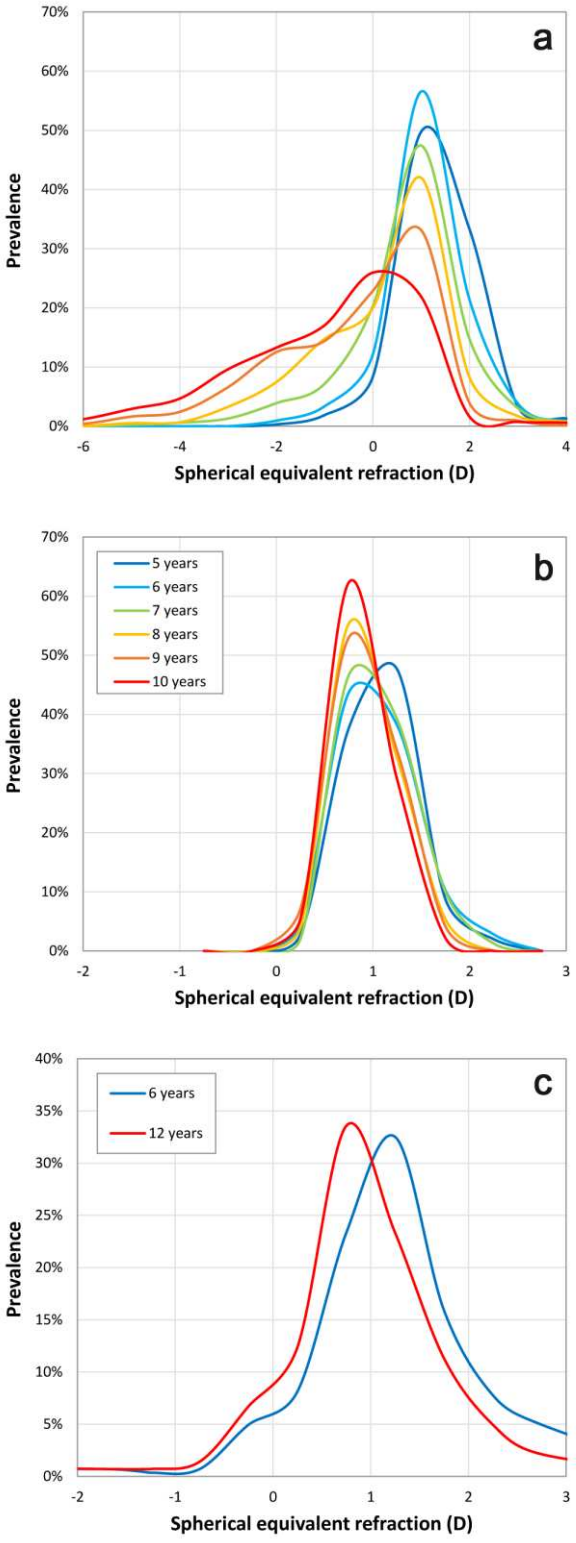


*Figure 10: Comparison of the changes in refractive distribution in a) an urban environment (Shanghai); b) a rural environment (Nepal); c) Marcos Juarez, Argentina. Data taken from Guo et al.,[80] Ma et al.,[153] Pokharel et al.201 and Magnetto et al.[155].*

## 6 Emmetropized and dysregulated eyes

Ideally, scaled and coordinated growth cluster the cycloplegic refractive error of a population into a narrow refractive distribution centered at *+1.00D* during the first years of life when axial growth and refractive power loss are at their

fastest (see Section 4). Over time, some children develop ametropia, gradually broadening the distribution.[58] Based on their refractive development history, people may therefore be classified as either **emmetropized**, meaning those who experienced successful emmetropization, or **dysregulated**, referring to those who were or became ametropic.[58] This is determined by developmental or genetic factors (e.g., hypermetropic stragglers), but also environmental and behavioral factors. The relative proportions of the emmetropized and dysregulated are reflected in the shape of the refractive distribution. A population that predominantly experienced an optimal refractive development produces a sharp and narrow distribution, while a sizeable dysregulated component leads to a leptokurtic and skewed distribution that can no longer be described by a single Gaussian function, but rather a sum of two Gaussians that each represent one group.[58, 223] This difference is best seen when comparing the distributions of rural and urban regions.[80, 154] Urban environments see the first cases of school myopia appear after the age of *6* years, leading to a gradual broadening of the distribution (Figure 10a),[90, 158] while in rural areas such as Nepal the prevalence of myopia remains low at less than *3%* between the ages of *5* to *15* years (Figure 10b).[201] Consequently, rural distributions remain narrow and peaked, much like those reported in mid-20th century Europe, before the introduction of most modern myopogenic influences.[263] The Nepal cohort also shows a loss in hypermetropia at school ages without changes at the myopic side of the distribution (Figure 10b). This was confirmed by a recent prospective study in Argentinian children followed longitudinally between the ages of *6* to *12* years (Figure 10c).[155]

### *6.1 Myopia*

The most common form of dysregulated refractive development is school age myopia, which forms an extensive field of study.[171, 295] There is a general agreement that myopia is usually triggered by behavioral factors such as a lack of outdoor exposure, intense reading habits,[142, 171] or environmental factors such as spatial frequencies,[60] but the evidence for results is not equally convincing.[174]

Myopia is likely caused by the same coordinated growth mechanisms described earlier, interacting disadvantageously under environmental and behavioral pressures. Although many postulate a possible genetic predisposition for myopia, over *500* genes have been identified[278] that are distributed evenly in the population and explain less than *20%* of the phenotypic variance, so it seems unlikely that school myopia is genetic in origin.[174, 285] Myopia is often presented as a condition with a sudden onset once refraction decreases below a certain threshold. This idea seems incorrect, however, as the first indicators for future myopia may already be present years before 'official' onset, such as a higher axial growth rate compared to those that will remain emmetrop-

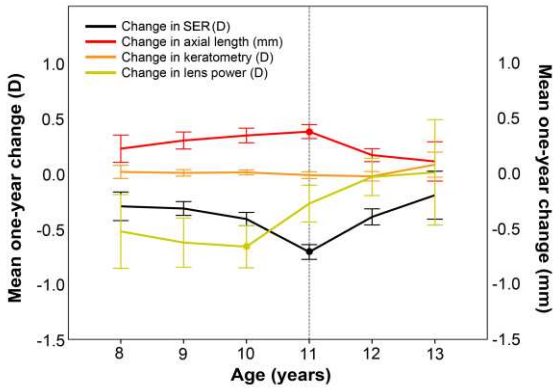


*Figure 11: Mean changes in spherical equivalent refraction and ocular biometry data over the previous 12 months for children with a myopia onset at age 11 years. Figure taken from Rozema et al.[216]*

ic.[216] This excessive axial growth remains unnoticed, however, as the refractive error remains stable due to accelerated lens power loss.[179, 216] Axial elongation continues at a high rate until lens power loss reaches a peak one year before myopia onset, after which the power loss suddenly slows down, producing in a myopic shift (Figure 11). This myopic shift is initially fast, but gradually slows down as the axial elongation rate slows down to a more appropriate level. Given the faster axial growth in younger children, it takes longer to slow down in early-onset myopes, resulting in worse myopia compared to later onset cases.[109] So, while in school children myopia development begins with excessive axial growth, it only becomes apparent once the crystalline lens is no longer able to lose power efficiently. Since the lens loses its power at a near constant rate after the age of *12* to *15* years,[108, 326] any increase in the axial growth rate after that age would inevitably lead to myopia.[303]

# 7 Conclusion

It is clear that Straub's original ideas about emmetropization through coordinated growth of the different ocular components were largely correct. He also envisioned the necessity of a feedback mechanism that brings the eye to sharp distance vision, although its exact nature eluded him. Straub can be easily forgiven, however, since it is only after a hundred years and many experiments that the scientific community began to understand its complexity. While researchers originally thought that the feedback was only controlled by the relative position of best focus with respect to the retina, it became obvious that this is a gross oversimplification. Instead, retinal blur is a far more accurate controller, containing influences of the ocular wavefront aberrations, illuminance, chromaticity, spatial frequencies, and contrast (Table 1, Figure 12). These mostly environmental factors are integrated over time by the retina to account for behavioral factors, such as the amount of near work and accommodation. Integration occurs at a local rather than a global level of the retina, occasionally leading to a regionally different growth response. Under the right, typically pre-industrial, circumstances this feedback system will direct the eye towards sharp unaided distance vision, while a dark environment and excessive near work may trigger myopization.

Although different growth phases may be distinguished based on changes in refractive error (Section 2), the underlying eye growth seems to follow a far simpler biphasic course with rapid growth before birth and slow (or no) growth after *1* to *2* years of age (Figure 6; more information in reference [215]). The relatively smooth transition between these 2 phases of eye growth, along with the ability of certain animals to recover from imposed blur, seems to confirm that prenatal growth, emmetropization and homeostasis are all the one and the same process. Hence, it would perhaps be more correct to consider these as the **rapid and slow phases of emmetropization** instead. Together, the successfully and unsuccessfully emmetropizing eyes shape the distribution of the refractive error, and transforms it from a broad Gaussian distribution at birth to a narrow distribution at *6* years, followed by an asymmetric broadening when school age myopia sets in. Local differences in myopization then explain the widely varying shape of refractive distributions around the world.

In the future, we foresee that new optical models of normal and pathological eye growth will be developed to help warn clinicians whether a child is at risk of becoming myopic. In this

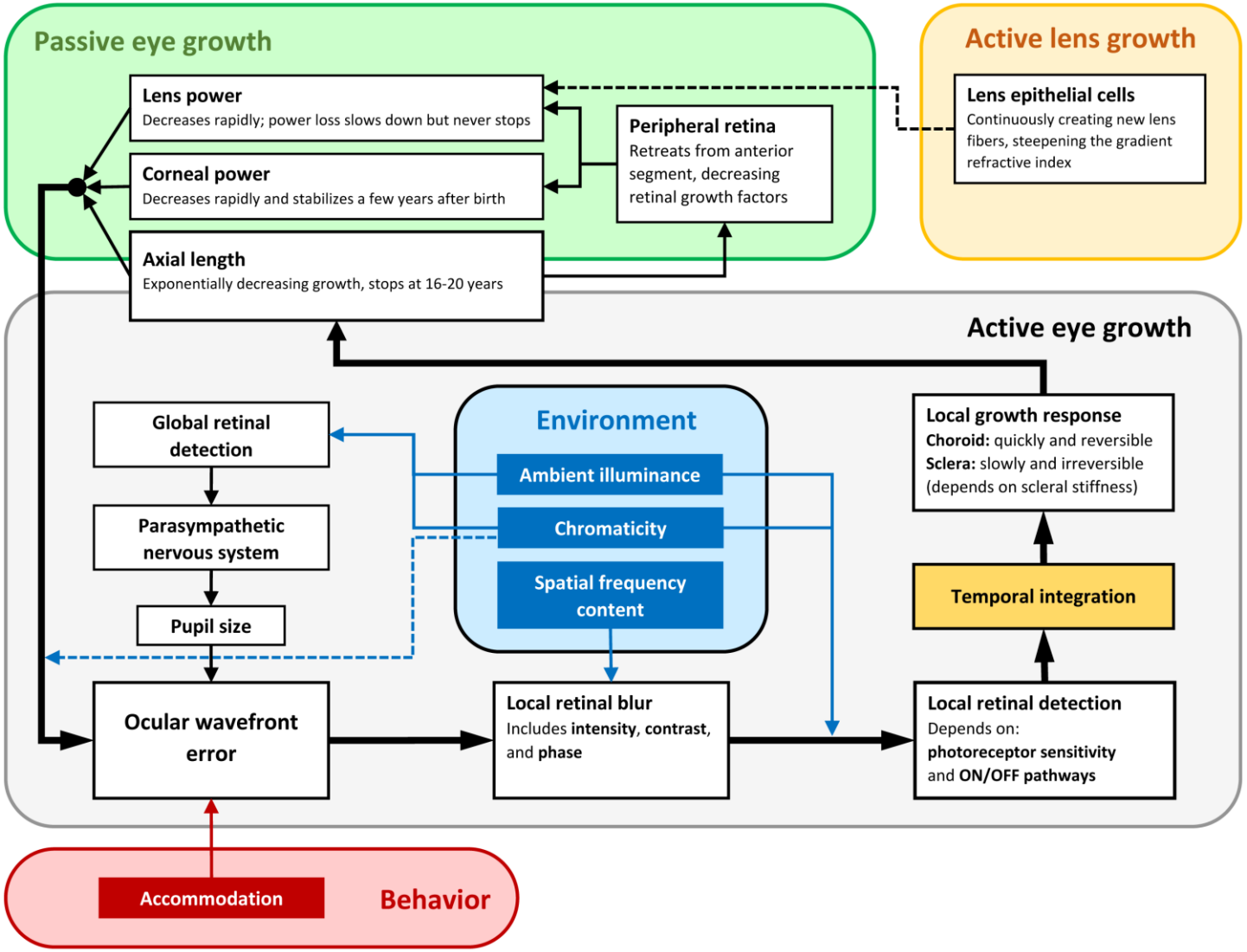


*Figure 12: Schematic overview of the processes affecting emmetropization discussed in this work.*

context, it would be especially interesting if new clinical tools would be developed to assess the shape, power, and gradient index of the crystalline lens. Because of its location inside the eye, this structure is often disregarded, despite its essential role in emmetropization. Reliable and easy to use lens measurement devices are therefore of great importance for future research into refractive development.

## Literature Search

We collected the references for this work with PubMed, Web of Science and Google Scholar using a large variety of search terms depending on the needs of each section. Additional references were obtained from the manuscripts found, to trace back to the original reports as much as possible. For this reason, we did not impose a date restriction. References in English were preferred, but non-English references were considered as well if we were either proficient in that language or it could be translated with an online dictionary.

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- *Wallman J, Winawer J. Homeostasis of eye growth and the question of myopia. Neuron 2004;43:447-68*
  Despite its age, this seminal review still holds up very well. It was one of the first to give a detailed synthesis of the processes of emmetropization and homeostasis based on the animal data available at the time.
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  The most complete overview of animal experiments on refractive development to date.
- *Morgan IG, Rose KA, Ellwein LB. Is emmetropia the natural endpoint for human refractive development? An analysis of population-based data from the refractive error study in children (RESC). Acta Ophthalmol 2010;88:877-84*
  This work confirmed that the endpoint of cycloplegic emmetropization is mild hypermetropia using the data of 8 large scale population studies around the world.
- *Flitcroft D. Is myopia a failure of homeostasis? Exp Eye Research 2013;114:16-24*
  Provides a systematic overview of refractive clustering. This work was later complemented by our own work on ocular biometry.[223]
- *Mutti DO, Sinnott LT, Lynn Mitchell G, et al. Ocular component development during infancy and early childhood. Optom Vis Sci 2018;95:976-85*
  This is the only study we know of that followed newborn infants during emmetropization and part of homeostasis. In a way, this work was the inspiration for this review, and we hope more such studies will be undertaken in the future.

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We also wish to acknowledge the contribution of the countless laboratory animals sacrificed to obtain the crucial results in Table 1.

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