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The Risks and Benefits of Myopia Control

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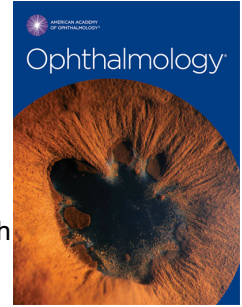


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The Risks and Benefits of Myopia Control

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Conflict of Interest:

Bullimore is a consultant for Alcon Research, Apellis, Arctic Vision, Asclepix, CooperVision, CorneaGen, Essilor, Euclid Systems, Eyenovia, Genentech, Johnson & Johnson Vision, Lentechs, Novartis, Oculus, Paragon Vision Sciences, and Presbia.

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1 Abstract

2 **Objective:** The prevalence of myopia is increasing around the world, stimulating interest in
3 methods to slow its progression. The primary justification for slowing myopia progression is to
4 reduce the risk of vision loss through sight-threatening ocular pathology in later life. The paper
5 analyzes whether the potential benefits of slowing myopia progression by one diopter justify the
6 potential risks associated with treatments.

7 **Methods:** First, the known risks associated with various methods of myopia control are
8 summarized, with emphasis on contact lens wear. Based on available data, the risk of visual
9 impairment and predicted years of visual impairment are estimated for a range of incidence levels.
10 Next, the increased risk of potentially sight threatening conditions associated with different levels
11 of myopia are reviewed. Finally, a model of the risk of visual impairment as a function of myopia
12 level is developed, and the years of visual impairment associated with various levels of myopia and
13 the years of visual impairment that could be prevented with achievable levels of myopia control is
14 estimated.

15 **Results:** Assuming an incidence of microbial keratitis between 1 and 25 per 10,000 patient years
16 and that 15% of cases result in vision loss, leads to the conclusion that between 38 and 945
17 patients need to be exposed to five years of wear to produce 5 years of vision loss. Each
18 additional diopter of myopia is associated with a 57%, 20%, 21%, and 30% increase in the risk
19 of myopic maculopathy, open angle glaucoma, posterior subcapsular cataract, and retinal
20 detachment, respectively. The predicted mean years of visual impairment ranges from 4.42 in a –
21 3 D myope to 9.56 in a –8 D myope and a one diopter reduction would lower these by 0.74 and
22 1.22 respectively. **Conclusions:** The potential benefits of myopia control outweigh the risks: the

- 23 number needed to treat to prevent 5 years of visual impairment is between 4.1 and 6.8 while
24 fewer than 1 in 38 will experience a loss of vision as a result of myopia control.

Journal Pre-proof

25 Introduction

26 There is compelling evidence that the prevalence of myopia is increasing around the world. The
27 global prevalence is projected to reach 50% by the year 2050 in the absence of effective
28 intervention measures.¹ The rising prevalence of myopia is also accompanied by earlier onset,
29 which in turn leads to an increased risk of high myopia.²⁻⁴ Increased prevalence of myopia, in
30 particular high myopia, in turn is leading to increased visual impairment due to conditions
31 associated with myopia.⁵⁻⁷ Indeed, myopic maculopathy, also known as myopic macular
32 degeneration, is an increasing cause of visual impairment.^{6, 8} The onset of myopic maculopathy
33 is earlier than other major causes of visual impairment, occurring as early as the fifth decade of
34 life,⁹ so the years of impairment are commensurately greater than later onset conditions,
35 including age-related macular degeneration (AMD).^{10, 11} In both Europe and China, visual
36 impairment from myopic maculopathy is more common than visual loss from diabetic eye
37 disease.¹²⁻¹⁴

38
39 These factors have stimulated interest in methods to slow myopia progression, with a number of
40 therapies, including topical atropine, spectacle lenses, dual-focus contact lenses, multifocal soft
41 contact lenses, and overnight orthokeratology showing clinically meaningful slowing of
42 progression.¹⁵⁻¹⁸ The preferred method varies with country and by profession.^{19, 20} Regulatory
43 approval can also play a role, although the majority of myopia control in the US is performed
44 off-label as only one device is approved for this indication. The influence of behavioral
45 modifications, such as increased time outdoors and reduced screen time, on progression rate is
46 less clear.^{21, 22}

47

48 There are, however, varying opinions regarding myopia control. Advocates for myopia control
49 say that “it is unethical not to offer myopia control” and some clinical trials have moved children
50 out of the placebo arm and into the treatment because of the significant treatment benefits.^{23, 24} In
51 contrast, some professional organizations such as the College of Optometrists in the United
52 Kingdom express caution, stating that there is “not enough evidence to support the widespread
53 roll out of myopia control.”²⁵ In addition, some clinicians feel that the increased potential risk of
54 serious ocular infections argue against prescribing contact lenses to children. Other organizations
55 are paying attention to issues related to myopia control. The American Academy of
56 Ophthalmology, for example, has published two Ophthalmic Technology Assessments related to
57 myopia control in recent years,^{26, 27} having previously reviewed the safety of one approach,²⁸ and
58 includes “Prevention of Myopia Progression” in its *Refractive Errors & Refractive Surgery*
59 *Preferred Practice Pattern*.²⁹

60
61 In a thoughtful editorial, Modjtahedi and colleagues emphasize the need to increase awareness
62 about the increasing prevalence of myopia.³⁰ They state that “creating models to accurately
63 stratify patient risk should be a significant focus for future research endeavors” and that “it is
64 essential for ophthalmologists to work with optometrists, who are frontline providers, to
65 determine a collaborative frame work and referral patterns to prevent myopic progression,
66 educate patients on the risks of myopia, and proactively address associated pathology to serve
67 the best interest of our patients.”

68 69 **Methodological Considerations in Risk-Benefit Analysis of Myopia Treatment**

70 These varying perspectives point to the central question that this paper addresses; do the
71 potential benefits of reducing myopia progression with interventions such contact lenses or

72 pharmaceutical options justify the potential risks associated with those treatments? The primary
73 justification for reducing myopia progression is to reduce the risk of vision loss through sight-
74 threatening ocular pathology in later life. Therefore, myopia is being managed because it is a risk
75 factor for visual impairment. The risk-benefit analysis of any treatment can be considered on a
76 population or an individual basis. Not every patient with a risk factor for a condition will develop
77 the condition, so a number of patients will be treated to avoid one adverse outcome, be it onset of
78 disease or visual impairment. The parameter, number needed to treat (NNT), is widely used in
79 health assessments, and is the reciprocal of the absolute risk reduction (ARR). For example, in
80 the Ocular Hypertension Treatment Study (OHTS),³¹ the five-year cumulative probability of
81 developing glaucoma was 9.5% and 4.4% in untreated and treated patients, respectively. Thus,
82 the ARR is 5.1% ($= 9.5 - 4.4$) and the NNT is 19.6 ($= 1 \div 0.051$). In other words, 20 patients
83 need to be treated for 5 years in order to prevent one case of glaucoma. The ARR and NNT can
84 be balanced by the corresponding parameters; the absolute risk increase (ARI), which is the risk
85 associated with complications of the treatment and the number needed to harm (NNH), which is
86 the number of patients who need to be treated in order to induce a single adverse event. NNH is
87 the reciprocal of ARI.

88

89 Slowing myopia progression by one diopter (D) offers the prospect of leaving a myope at -3 D
90 with treatment rather than -4 D, or achieving a final refraction of -7 D with treatment rather than
91 -8 D. On the basis of existing data, both outcomes offer potential benefits but the ARR is much
92 greater in high myopes due to the higher prevalence of myopia-related vision impairment (and
93 the NNT lower) in higher myopes. While the NNT will be greater in lower myopes, they far
94 outnumber higher myopes, even in populations with a high prevalence.¹ The values of NNT and

95 ARR are a function of the effectiveness of a myopia intervention, irrespective of the treatment,
96 and the level of myopia at the start of treatment. In contrast, the values of NNH and ARI relate to
97 the specific method of treatment and are largely independent of the level of myopia. Therefore,
98 the risk-benefit assessment of myopia treatment must consider all these elements, i.e., the
99 effectiveness of an intervention in slowing down myopia progression, the risk of vision
100 impairment associated with myopia, the level of myopia, and the treatment-modality specific
101 risks. A final consideration is that complications of myopia treatment may occur many decades
102 before any myopia-associated visual loss, so the duration in years of any treatment associated
103 complications affecting vision may greatly exceed the duration of vision loss attributable to
104 myopia later in life.

105
106 In order to answer the central question of whether the benefits of active myopia control justify
107 the risks, this review will first summarize the known risks associated with various methods of
108 myopia control, with an emphasis on contact lens wear. Based on available data, the risk of
109 visual impairment and predicted years of visual impairment are estimated for a range of
110 incidence levels. Next, the increased risk of potentially sight threatening conditions associated
111 with different levels of myopia is reviewed. Finally, a model of the risk of visual impairment as a
112 function of myopia level and age is developed, and the years of visual impairment associated
113 with various degrees of myopia and the years of visual impairment that could be prevented with
114 achievable levels of myopia control is estimated.

115

116 Risks and Side Effects of Myopia Control

117 At the time of this review, there are three commonly used myopia control therapies—spectacles,
118 atropine, and contact lenses.

119

120 Spectacles

121 Myopia control with spectacles has a 60-year history, including bifocals,³²⁻³⁴ progressive
122 addition lenses,³⁵⁻³⁷ and, most recently, novel optical designs.³⁸ In the United States, children are
123 prescribed polycarbonate spectacle lenses and the minimal physical risks associated with these
124 devices are not increased by the incorporation of a multifocal correction or other designs.
125 Spectacle wear is associated with bicycle crashes in children, although there is no association
126 between myopia or habitual visual acuity and bicycle crashes.³⁹ The study authors thus attribute
127 the increased risk to a “decrement in the peripheral visual field, thus reducing rider awareness of
128 oncoming vehicles and road obstacles.” Of course, correcting myopia and eliminating blurred
129 vision has its own benefits. Some spectacle based myopia treatments, incorporating positive
130 dioptric power will be expected to have modest effects on peripheral vision and it is important
131 that this be quantified.⁴⁰ There is also evidence that in the elderly, multifocal and bifocal
132 spectacles, can increase the risk of falls.⁴¹⁻⁴³ Progressive addition lens and bifocal wearers are
133 twice as likely to fall as non-multifocal wearers,⁴³ although there is no evidence that the same
134 risks apply in children, perhaps because they rarely wear such lenses.

135

136 Atropine

137 Atropine is an antimuscarinic agent that causes pupil dilation and loss of accommodation, even
138 in concentrations as low as 0.01%.^{24, 44} The associated symptoms of photophobia and near vision
139 difficulties vary, as expected, with concentration. This can be mitigated by photochromic lenses,
140 multifocals, or both. In the Atropine for the Treatment of Myopia 2 (ATOM2) study, among
141 children receiving 0.5%, 0.1%, and 0.01% atropine, 70%, 61%, and 6%, requested combined
142 photochromic progressive addition spectacles, respectively while the remainder chose single

143 vision photochromic spectacles.⁴⁴ In the Low-Concentration Atropine for Myopia Progression
144 (LAMP) Study, the need for photochromic or progressive addition lenses did not vary with
145 atropine concentration among the over 400 children randomized to 0.01%, 0.025%, 0.05%
146 atropine or placebo.²⁴ Between 30 and 40% children needed photochromic spectacles in all
147 groups including the placebo. Furthermore, four children needed progressive addition spectacles,
148 including one in the placebo group. The most common ocular side effect in the aforementioned
149 clinical trials was allergic conjunctivitis which occurred in 3 to 7% of children in each arm,
150 including those receiving placebo in the LAMP Study, suggesting that the preservative or other
151 excipient in the solution may be the causative agent.

152

153 With any topically applied drug, there is a risk of systemic absorption. The systemic effects of
154 atropine are well documented and include dryness of skin, mouth and throat due to decreased
155 mucous membrane secretion, restlessness, irritability or delirium due to CNS stimulation,
156 tachycardia, and flushed facial skin due to its non-selective antimuscarinic properties.⁴⁵ In spite
157 of atropine's use in a large number of clinical trials for myopia control^{24, 44, 46} and for
158 penalization therapy for amblyopia,⁴⁷⁻⁵⁰ involving hundreds of children there have been no
159 reports of systemic adverse events related to topical atropine.

160

161 The Ophthalmic Technology Assessment on Atropine for the Prevention of Myopia Progression
162 in Children by the American Academy of Ophthalmology does not list any safety concerns.²⁶

163 The review does not discuss the risks associated with increase retinal light levels and AMD with
164 atropine-induced mydriasis, but this remains a theoretical possibility, although the dilation with
165 low concentrations is modest, along with its impact on any long-term cumulative dose, and may

166 be offset by sunglasses. This theoretical risk is partly mitigated by the fact that myopia is a
167 protective risk factor for AMD,⁵¹⁻⁵³ possibly by the reduced light flux density that results from a
168 longer eye.⁵⁴ There are also potential concerns from premature presbyopia induced by prolonged
169 partial cycloplegia, but we are only aware of anecdotal reports. A seven-year review of atropine
170 in Taiwan, where atropine has been used for several decades, did not include any data on side
171 effects.⁵⁵ This is clearly an area where further data are required. In summary, the risk of vision
172 loss associated with topical atropine, particularly lower concentrations would appear to be very
173 low, but the prescription of photochromic spectacles or soft contact lenses may be required at
174 higher concentrations.

175

176 Soft Contact Lenses

177 The complications associated with soft contact lens wear have been well documented. Non-
178 infectious inflammatory events may involve the cornea, conjunctiva, and periorbital tissues.
179 Those affecting the cornea are collectively termed corneal infiltrative events and include
180 infiltrative keratitis, contact lens associated red eye, contact lens peripheral ulcers and occur at a
181 rates between 300 and 400 per 10,000 patient years in adults.⁵⁶⁻⁵⁸ These are not considered to be
182 sight-threatening and are managed by temporarily discontinuing contact lens wear, with the
183 possible addition of a topical prophylactic antibiotic. Microbial keratitis is less common, with an
184 incidence of around 20 per 10,000 patient years in adults wearing lenses on an overnight basis
185 but only between 2 and 4 per 10,000 patient years for daily-wear patients. Major studies of the
186 incidence of microbial keratitis associated with soft contact lenses are summarized in Table 1.⁵⁹⁻
187 ⁶⁶ Regardless of the incidence, 15% or fewer of cases of microbial keratitis result in vision loss.

188 ^{61, 64-66}

189

190 With respect to soft contact lenses for myopia control, three important variables influence the
191 risk of corneal infiltrative events and microbial keratitis: storage, material, and patient age. First,
192 many contact lenses designed for myopia control, though not all, are prescribed using a daily
193 disposable replacement schedule.²³ The benefits of eliminating contact lens storage as a risk
194 factor cannot be understated. For example, Stapleton et al. found that the risk of moderate and
195 severe microbial keratitis in daily wear contact lens users was increased 6.4 times by poor storage
196 case hygiene and 5.4 times by infrequent storage case replacement.⁶⁷ The authors note the
197 previously-reported associations between solution type and more severe disease for
198 *Acanthamoeba* and *Fusarium* keratitis.⁶⁸⁻⁷⁰ Again, these risks can be substantially reduced with
199 daily disposable lenses. Second, contact lens material can also affect the risk for corneal
200 infiltrative events. Over the past 20 years there has been a shift from traditional hydrogel
201 materials towards silicone hydrogel materials which provide higher oxygen transmission.⁷¹
202 Silicone hydrogels may increase the risk of corneal infiltrative events, but the broad benefits of
203 these lenses outweigh this risk for many patients.⁷²
204
205 Third, age is a significant, but non-linear risk factor for contact lens-related adverse events. A
206 retrospective, observational study evaluated the risk factors that interrupt soft contact lens wear
207 among children, teenagers, and young adults.⁵⁷ The authors reported 187 corneal infiltrative
208 events in 3,549 patients for 14,305 visits observing 4,663 soft contact lens years including an
209 average of 20 months of soft contact lens wear in 1,054 patients under the age of 18 years. The
210 corneal infiltrative events included 8 cases of microbial keratitis, 110 of infiltrative keratitis, 41
211 contact lens peripheral ulcers (CLPUs), 14 contact lens-induced acute red eye (CLARE) with
212 infiltrates, and 13 CLARE without infiltrates. The risk of a corneal infiltrative event increased in a

213 nonlinear fashion up to age 21 and then decreased, with the peak years at risk from age 15 to 25
214 years.

215

216 Figure 1 replots the published data on corneal infiltrative events in terms of incidence (cases per
217 10,000 patient years of wear).⁵⁷ The figure demonstrates the marked lower rate of corneal
218 infiltrative events in patients 8 to 12 years old (97 per 10,000 patient years, 95% CI, 31–235)
219 than in patients 13 to 17 years old (335 per 10,000 patient years, 95% CI, 248–443). The
220 incidence of microbial keratitis per 10,000 patient years varied dramatically with age group: 0
221 (95% CI, 0–70) in 8- to 12-year olds, 15 (95% CI, 2–48) in the 13- to 17-year olds, 33 (95% CI,
222 12–73) in the 18- to 25-year olds, and 7 (95% CI, 0.4–37) in the 26- to 33-year olds.

223

224 The low rate of corneal infiltrative events in patients 8 to 12 years old from the above
225 retrospective study of soft contact lens wear is supported by prospective studies. Bullimore
226 reviewed data from nine prospective studies representing 1,800 patient years of wear in 7- to 19-
227 year-olds.⁷³ The majority of the studies were at least one year in duration, fit children as young
228 as 8 years, and represented over 150 patient years.^{23, 74-82} Pooling data across the nine studies, 14
229 corneal infiltrative events were reported representing an incidence of 78 per 10,000 patient years
230 (95% CI, 44–127). None of the studies reported any cases of microbial keratitis, giving a 95% CI
231 of 0 to 21 per 10,000 patient years. A subsequent retrospective review of over 800 patient years
232 of wear in children also found no cases of microbial keratitis,⁸³ although a recent clinical trial of
233 nearly 900 patient years of wear in children reported one “presumed case.”⁸⁴

234

235 In summary, the incidence of corneal infiltrative events and microbial keratitis in children 12
236 years and younger—in whom myopia control is likely to be initiated—is no higher than that
237 observed in adults and may be lower.^{85, 86} The peak complication rate at 18-25 years suggests
238 that behavioral and lifestyle factors may have a significant influence.⁸⁷ For 8–12-year-olds,
239 parents are more likely to be involved in lens care. It is also possible that young children wearing
240 contact lenses are a pre-selected group, because they are likely to wear them responsibly. If
241 contact lenses were worn by a higher proportion, the low complication rate could conceivably
242 increase.

243

244

245 Overnight Orthokeratology

246 While the incidence of adverse events associated with soft contact lenses is well established, data
247 for overnight orthokeratology are scarce. Even in large-scale epidemiological studies, where all
248 lens types were considered, no cases of microbial keratitis in orthokeratology wearers are
249 reported.⁶⁵ Of course, this reflects the relatively small proportion of patients wearing this
250 particular modality, rather than a low level of risk. Globally, orthokeratology represented 28% of
251 all rigid contact lenses prescribed among minors between 2005 to 2009.⁸⁸ In the US, *all* rigid
252 lenses account for around 10% of all contact lenses while patients 15 years and under account for
253 only 11% of lens fits.⁷¹ Recent data suggest a steady, but small, increase in orthokeratology
254 fitting through 2017, but only represents around 1% of all contact lens fits, with large
255 geographical variations.⁸⁹ Studies of the incidence of microbial keratitis associated with contact
256 lenses typically accrue cases from hospitals and other tertiary care settings and are unlikely to
257 identify cases associated with overnight orthokeratology due to limited exposure, rather than the
258 underlying risk. Beginning in 2001, case series and case reports of microbial keratitis associated

259 with overnight orthokeratology began to appear in the literature. The first 50 published cases
260 were summarized in a 2005 paper⁹⁰ and updated with total of 123 cases two years later.⁹¹

261
262 In 2008, the American Academy of Ophthalmology published an Ophthalmic Technology
263 Assessment for on the *Safety of Overnight Orthokeratology for Myopia*.²⁸ The main source of
264 adverse events was 38 case reports or noncomparative case series, representing more than 100
265 cases of infectious keratitis. The report was unable, however, to identify the incidence of
266 complications associated with overnight orthokeratology, nor the risk factors for various
267 complications.

268
269 The only comprehensive estimate of the incidence of microbial keratitis associated with
270 overnight orthokeratology comes from a retrospective study, mandated and approved by the US
271 Food and Drug Administration (FDA).⁹² Two hundred randomly selected practitioners, stratified
272 by company and number of lens orders were asked to provide details on fitting date, and patient
273 age at fitting, and follow-up duration for up to 50 randomly-selected lens orders. The
274 practitioners were also asked to provide comprehensive information on any of these patients
275 experiencing an episode of painful red eye that required a visit to a practitioner's office. Patients
276 treated by another practitioner or with less than twelve months of documented follow-up were
277 mailed a questionnaire regarding months of lens wear, any adverse events and the name and
278 address of the treating practitioner. Data were submitted by 86 practitioners on 1494 unique
279 patients. Limiting the sample to at least three months of wear from 2005 onwards resulted in
280 1,317 patients (49% adults 51% children) representing 2,599 patient years of wear. Of the 50
281 episodes of painful red eye identified, eight presented with a corneal infiltrate of which six were

282 in children. Of these cases, two were judged to be microbial keratitis by a five-person masked,
283 expert review panel and neither resulted in any long-term loss of visual acuity. The overall
284 incidence of microbial keratitis was 7.7 per 10,000 patient years (95% CI, 0.9–27.8). Both cases
285 occurred in children giving an incidence of 14 per 10,000 patient years (95% CI, 1.7–50.4).⁹²

286

287 In summary, the incidence of microbial keratitis in children wearing overnight orthokeratology is
288 similar to that reported for other overnight modalities in adults, notably extended wear of soft
289 contact lenses (see Table 1).

290

291 **Modelling Risk of Vision Loss Associated with Myopia Treatment**

292 Given the above evidence, the risk of vision loss with spectacle lenses and atropine are
293 considered negligible, and it is assumed that the majority of risk associated with myopia control
294 will occur with contact lenses. The incidence of microbial keratitis varies with contact lens wear
295 and all available estimates have some uncertainty as indicated by the breadth of the confidence
296 intervals. Overnight orthokeratology in children carries a risk similar to other overnight
297 modalities with the only estimate being 14 per 10,000 patient years (95% CI, 1.7–50).⁹²
298 Conversely, daily soft lens wear in children appears to be at least as safe as in adults; daily
299 disposable lenses may further mitigate the risk.⁶⁵ Thus, in evaluating vision loss associated with
300 contact lens wear, a range of incidence should be considered.

301

302 The above summary of the risks associated with myopia control expresses the data in terms of
303 incidence. These data must be interpreted in terms of years of visual impairment associated with
304 said risk. In order to estimate years of visual impairment, the following assumptions were made:

- 305 • 15% of all cases of microbial keratitis result in visual impairment (two lines of visual
306 acuity or more) as this is the most conservative estimate.⁶⁵
- 307 • Each myopia control patient is exposed to 5 years of contact lens wear during the period
308 of myopia control and the risk is constant over this time. Five years was chosen so that 1-
309 diopter of control could be reasonably anticipated.⁹³
- 310 • Any serious adverse event occurs during this five year period of wear, at a mean age of
311 12 years.
- 312 • Mean life expectancy is 82 years (<https://www.mortality.org>), so each adverse event
313 causing immediate vision impairment results in 70 years lived with this vision
314 impairment.

315

316 Table 2 displays the years of vision loss for three levels of risk, expressed as annual incidence
317 per 10,000 patients. The incidence values are intended to span the range reported in the literature
318 from daily wear (1 per 10,000) to overnight wear (25 per 10,000).⁶⁵ For example, the incidence
319 of microbial keratitis with daily-disposable soft lenses could be assumed to be 1 per 10,000
320 patient years of wear.⁶⁵ The incidence of vision loss due to microbial keratitis is then estimated
321 to be 0.15 per 10,000 patient years of wear, but five years of exposure would result in a
322 cumulative incidence of vision loss of 0.75 per 10,000 patients ($= 5 \times 0.15$). Finally, this vision
323 loss is experienced for 70 years yielding a value of 53 years of vision loss per 10,000 patients ($=$
324 70×0.75). The years of vision loss are proportionately higher for incidence values of 5 and 25
325 per 10,000 patient years, the latter representing the upper limits for overnight orthokeratology.
326 The effect of increasing exposure is easily calculated, e.g., for 10 years of exposure the
327 cumulative incidence of vision loss and the number of years of vision loss would be twice that

328 for five years of exposure. Likewise, using an incidence of 50—the upper 95% limit for
329 overnight orthokeratology in children⁹²—the values in the final column would be doubled.

330

331 The NNH for one and five years of visual impairment are also shown in Table 2. For example,
332 38 patients would have to wear contact lenses with a medium risk of microbial keratitis
333 (incidence = 5 per 10,000 patient years) for five years to result in one year of visual impairment.
334 Likewise, 190 patients would have to wear them to result in five years of visual impairment.

335

336 The Potential Benefits of Myopia Control

337 Bullimore and Brennan recently summarized the benefits of lowering levels of myopia.⁹⁴ These
338 include better uncorrected and corrected visual acuity, improved vision-related quality of life,
339 and reduced dependence on correction. Likewise, a myope is likely to consider refractive surgery
340 to correct their refractive error once they reach adulthood. In this regard, the lower the level of
341 myopia, the higher the likelihood of minimal residual refractive error, leading to better
342 postoperative uncorrected visual acuity and fewer secondary surgical enhancements.
343 Furthermore, postoperative visual quality is poorer in patients with higher levels of preoperative
344 myopia.⁹⁵ Finally, higher myopia, thinner corneas, or both, can make them poor candidates for
345 LASIK due to the increased risk for postoperative corneal ectasia⁹⁶ and alternative procedures
346 may be needed. In spite of these visual and refractive benefits of lower levels of myopia, the
347 greatest benefit of lower levels of myopia is a reduced risk of blinding eye disease. The
348 following sections briefly review the association between level of myopia and myopic
349 maculopathy, cataract, retinal detachment and glaucoma. The reader is also referred to the recent
350 comprehensive review by Haarman et al.⁷

351

352 Myopia and the Risk of Myopic Maculopathy

353 There have been a number of large population-based studies of the prevalence of myopic
354 maculopathy in older patients. Bullimore and Brennan⁹⁴ summarized data from five that present
355 the prevalence as a function of level of myopia in tabular or graphical form.⁹⁷⁻¹⁰¹ Figure 2A
356 shows the prevalence of myopic maculopathy as a function of degree of myopia for these five
357 studies. Data are taken directly from each publication, digitizing figures to extract values when
358 necessary.^{99, 102} Where prevalence was presented with data for ranges of myopia, the midpoint of
359 each range was used. The highest level of myopia was often defined without an upper limit, so
360 these data are not shown. In all studies, the prevalence of myopic maculopathy increases
361 exponentially at higher levels of myopia. Figure 2B replots the prevalence of myopic
362 maculopathy on a logarithmic scale. This results in an apparent linear relationship, with all
363 studies showing a similar trajectory.

364

365 Since publication of the above data, four more reports of the relation between myopia level and
366 the prevalence of myopic maculopathy have been published,¹⁰²⁻¹⁰⁵ plus a fifth that does not
367 contain sufficient categories.¹⁰⁶ All available studies are summarized in Table 3 and represent
368 data from over 10,000 myopes. The definition of myopia varies among studies, with two limited
369 to high myopia. Likewise, the definition of myopic maculopathy varies slightly among studies
370 with data for “macular complications” used from one.¹⁰⁵ Linear regression was performed on
371 each dataset and the results displayed in Table 3. The slope of $\log(\text{prevalence})$ per diopter ranges
372 from 0.095 to 0.271. Taking the antilog of these slopes gives the ratio of prevalence to diopter—
373 a range of 1.24x to 1.87x with a crude average of 1.58x. Expressed as a percentage, each diopter

374 of myopia increases the prevalence of myopic maculopathy by 58%. Restated, controlling
375 myopia progression such that a patient's refractive error is lower by 1 D should reduce the
376 likelihood of them developing myopic maculopathy by 37% ($= 1 - 1/1.58$). Furthermore, given
377 the apparent constant slope of the data in Figure 2B, this treatment benefit is constant across a
378 range of myopia severities. Thus, while the overall risk of myopic maculopathy is higher in a -6
379 D myope than in a -3 D myope, slowing progression by 1 D during childhood should lower the
380 risk by 37% in both.

381

382 Myopia and the Risk of Other Ophthalmic Diseases

383 Cataract

384 Myopia is associated with other eye diseases. With respect to cataract, the association between
385 myopia and posterior subcapsular (PSC) cataract is the most robust.¹⁰⁷ A few studies have
386 reported the prevalence of PSC at different degrees of myopia (Table 4).¹⁰⁸⁻¹¹¹ The same
387 methodology as described in the previous section was used to determine the relation. The slope
388 of $\log(\text{prevalence})$ per diopter ranges from 0.017 to 0.103. Converting to a ratio of prevalence to
389 diopters of myopia shows a range of 1.02x to 1.40x with a crude average of 1.21x. Thus, each
390 diopter of myopia increases the prevalence of PSC cataract by 21%. While not directly
391 comparable, Pan et al. reported that each diopter of myopia increases the odds of PSC cataract by
392 1.14x in a sample of 5,474 Singaporean Malays.¹⁰⁸ For cortical cataract, three of the studies in
393 Table 4 show ratios of prevalence to diopter between 0.96x and 1.01x while one shows a ratio of
394 1.16x.¹¹¹ These same four studies show no relation between degree of myopia and nuclear
395 cataract. The ratio of prevalence to diopters of myopia ranges from 0.95x to 0.99x with a crude
396 average of 0.97x. It is important to note that many studies do show a relation between any

397 myopia and nuclear cataract.¹⁰⁷ Unfortunately, this relation is confounded by the myopic shift
398 associated with nuclear cataract. Studies that have measured the ocular components find that
399 nuclear cataract is associated with myopia, but not with axial length or its surrogates.^{107, 108, 112}

400

401 Retinal Detachment

402 The association between retinal detachment and myopia is well established. While the global
403 incidence of retinal detachment has been estimated at 0.01% per year,¹¹³ three case-control
404 studies allow quantification of the relation between myopia level and incidence of retinal
405 detachment (Table 5).¹¹⁴⁻¹¹⁶ Other studies are listed that have based estimates of the relation on
406 their cases of retinal detachment and published estimates of the distribution of refractive error.^{10,}
407 ^{117, 118} The data from the most recent study¹¹⁹ were combined with recent estimates of myopia
408 prevalence in the United Kingdom¹²⁰ to derive the relation. The slope of log(incidence) per
409 diopter ranges from 0.096 to 0.173. Converting to a ratio of incidence to diopters of myopia
410 shows a range of 1.15x to 1.49x with a crude average of 1.30x. Thus, each diopter of myopia
411 increases the incidence of retinal detachment by 30%.

412

413 Glaucoma

414 Individuals with myopia have around twice the risk of developing open angle glaucoma
415 compared with those without myopia. A meta-analysis of eight large studies estimated odds
416 ratios of 2.46 (95% CI, 1.93–3.15) and 1.77 (95% CI, 1.41–2.23) for myopia above and below –3
417 D, respectively.¹²¹ Table 6 summarizes data from five studies that present data on prevalence of
418 open angle glaucoma for three or more levels of myopia.¹²²⁻¹²⁷ The slope of log(prevalence) per
419 diopter ranges from 0.045 to 0.096. Converting to a ratio of prevalence to diopters of myopia

420 shows a range of 1.09x to 1.39x with a crude average of 1.20x. Thus, each diopter of myopia
421 increases the prevalence of open angle glaucoma by 20%. Longer axial length is independently
422 associated with an increased prevalence of open angle glaucoma.^{128, 129} Kuzin et al. estimated
423 that each millimeter longer axial length was associated with a 26% higher prevalence.¹²⁹ While
424 the association between degree of myopia and prevalence of open angle glaucoma appears
425 robust, there appears to be little or no relationship between myopia and rate of progression of
426 glaucoma,^{130, 131} although higher myopes may have more severe disease and present diagnostic
427 challenges.

428

429 Myopia and the Risk of Visual Impairment

430 Myopic maculopathy is associated with poorer visual acuity.^{97, 102} Vongphanit et al. reported that
431 39% of 67 eyes with myopic maculopathy had visual impairment, based on a definition of 20/40
432 or worse.⁹⁷ Wong et al. reported that among 119 study participants identified as having myopic
433 maculopathy, 26 (21.8%) had visual impairment in at least one eye, based on the same
434 criterion.¹⁰² Finally, Gao et al. report that visual impairment was present in 10 participants
435 (17.5%) based on the better eye, and using the criterion of worse than 20/60.⁹⁹ While most of
436 these studies, and the others in Table 3, precede the international photographic classification and
437 grading system for myopic maculopathy,¹³² the criteria used to define myopic maculopathy are
438 broadly similar: Category 2 (diffuse chorioretinal atrophy), Category 3 (patchy chorioretinal
439 atrophy), Category 4: (macular atrophy) or one of the “plus” features: lacquer cracks, myopic
440 choroidal neovascularization, and Fuchs spot. Category 1 (tessellated fundus) is not usually
441 considered to represent myopic maculopathy as it is not associated with vision loss. The risk of
442 vision loss is also dependent on age, refractive error and myopic maculopathy category.

443

444 Of course, any increase in the risk of visual impairment associated with myopia will be due to a
445 range of diseases including myopic maculopathy. Given that multiple myopia-associated diseases
446 can lead to visual impairment, the relevant parameter is the cumulative risk of all myopia
447 associated pathologies. A few studies report visual impairment from all causes as a function of
448 level of myopia.^{98, 105, 133, 134} Among these, Tideman et al. published the most comprehensive
449 data on visual impairment and myopia, analyzing data from 15,404 adults (mean age 61 ± 11
450 years) in whom refractive error and visual acuity had been measured.¹³⁴ In their Figure 2, they
451 plot the cumulative risk of visual impairment as a function of age for five levels of myopia for a
452 criterion of 20/67 (0.3 decimal acuity). Their graph was digitized, and the cumulative risk of
453 visual impairment is replotted as a function of myopia level for five ages in Figure 3. The
454 midpoint of each refractive error range was used and a value of -16 D chosen for the highest
455 range. The data show a clear exponential trend at all ages, a feature that is emphasized by
456 plotting them on a logarithmic scale. On the logarithmic scale, all ages follow a similar, near
457 parallel trajectory. The best-fit slopes of these lines (not shown) range from 1.24 to $1.31x$
458 indicating that the cumulative risk of visual impairment increases by between 24 and 31% per
459 diopter of myopia across a broad age range.

460

461 From the values in Figure 3, the odds of visual impairment were calculated using a reference
462 prevalence of 1.26%. This reference was calculated from the distribution of visual acuity among
463 the four population-based cohorts used by Tideman et al., excluding the case-control study (their
464 Table 1).¹³⁴ Figure 4 shows the \log_{10} odds ratio of visual impairment as a function of age for five
465 levels of myopia. Multiple linear regression was used to estimate \log_{10} odds ratio as a function of
466 age and refractive error. The equation for best-fit regression line shown in Figure 4 is:

467
$$\text{Log}_{10}\text{Odds Ratio for Visual Impairment} = 0.057\text{Age} - 0.122\text{Rx} - 4.03$$

468 Thus:

469
$$\text{Cumulative Odds of Visual Impairment} = 10^{(0.057\text{Age} - 0.122\text{Rx} - 4.03)}$$

470 Note that the coefficients show that the impact of one diopter of myopia is around twice that of
471 one year of aging.

472

473 Using this equation, the age-related cumulative risk of visual impairment can be modeled for
474 different myopia levels. Figure 5 shows the cumulative risk of visual impairment as a function of
475 age for seven levels of myopia and two different definitions of visual impairment. On the left is
476 the model for the criterion for visual impairment used in the original data¹³⁴ (worse than 20/67 or
477 6/20) which is similar to the WHO's ICD-11 definition of moderate visual impairment (worse
478 than 20/60 or 6/18). The model on the right is for the US definition of visual impairment (worse
479 than 20/40) which is also the WHO's ICD-11 definition of mild visual impairment. These were
480 calculated using the above equations for the odds of visual impairment but using an overall
481 prevalence of 3.63%. This value was again calculated from the visual acuity distribution among
482 the four population-based cohorts used by Tideman et al., excluding the case-control study (their
483 Table 1).¹³⁴ As would be expected both sets of curves follow a sigmoidal pattern.

484

485 In order to further assess the impact of age and myopia on the visual impairment for individuals
486 and the population, the above functions were combined with life expectancy data for the US
487 population (<https://www.mortality.org>) to estimate the number of visually impaired persons per
488 10,000 births as a function of age and myopia. A simple combination of the functions results is a
489 series of asymmetric bell curves shown in Figure 6. The peak of the distribution shifts from 86
490 years for -2 D of myopia to 81 years for -8 D, and thereafter decreases by approximately one

491 year for each additional diopter of myopia up to -15 D (not shown). The presence of an earlier
492 peak in higher myopes than in lower myopes reflects the earlier onset of myopia-related retinal
493 complications¹⁰⁵ than conditions where myopia is not a risk factor and may be protective, i.e.,
494 AMD and diabetic retinopathy.¹²⁵ Beyond the peak, the influence of mortality outweighs the
495 increased risk of visual impairment, resulting in a steadily decreasing probability of living with
496 visual impairment.

497
498 The mean number of years of visual impairment experienced by a patient over their lifetime may
499 be estimated by simply integrating the area under each curve. For example, a -3 D myope will
500 experience an average of 4.42 years of visual impairment (US definition and WHO definition of
501 moderate visual impairment), whereas a -8 D myope will experience 9.56 years of visual
502 impairment. These data are summarized in Table 7. Furthermore, the benefit of slowing myopia
503 progression by one diopter of myopia can be calculated as the difference in years of visual
504 impairment (Table 7). Controlling myopia such that a patient destined to be a -3 D myope
505 instead ends up as a -2 D myope should prevent an average of 0.84 years of visual impairment
506 ($= 5.25 - 4.42$). Likewise, one diopter of myopia control such that, ultimately, a -8 D myope is
507 instead a -7 D myope would save 1.22 years of visual impairment ($= 9.56 - 8.35$).

508
509 Table 7 also shows the number of patients needed to treat (NNT)—the number slowed by one
510 diopter—to prevent five years of visual impairment. For -3 D of myopia the NNT is 6.75, while
511 for -8 D of myopia the NNT is 4.11. Finally, the reduction in myopia needed to prevent one year
512 of visual impairment in a given patient can be estimated. For -3 D of myopia a 1.38-D reduction
513 is needed, but for -8 D of myopia, only a 0.82-D reduction is required. To put these figures in

514 context, the NNT for preventing one nonfatal heart attack in asymptomatic adults 40 years or
515 older with statin medications is 217, and the NNT to prevent one nonfatal stroke, 313.¹³⁵

516

517 The corresponding data for the WHO definition of moderate visual impairment are shown in
518 Table 8. Both the mean years of visual impairment and the years of visual impairment prevented
519 by a 1 diopter reduction in myopia are smaller than for the US definition. Likewise, the NNT to
520 prevent one year of visual impairment and the reduction in myopia needed to prevent one year of
521 visual impairment are higher.

522

523 Comparing the Risks and Benefits of Myopia Control

524 The above model shows the potential benefit of slowing myopia progression such that a patient
525 ends up with one diopter less than their original refractive trajectory. Recent randomized clinical
526 trials suggest that one diopter of myopia control is achievable given that a 0.73 D reduction in
527 progression was achieved with three years of treatment with a daily-disposable soft contact lens
528 incorporating a dual-focus optical design,²³ a 0.71 D reduction with three years of executive
529 bifocal spectacle wear,³³ and a 0.82 D reduction with two years of 1% atropine therapy.⁴⁶ While
530 few studies have reported myopia control on patients beyond 3 years,^{136, 137} the above results
531 suggest that one diopter is feasible, but would take up to five years of treatment.⁹³

532

533 The above model predicts that one diopter of myopia control can prevent between 0.74 and 1.22
534 years (9 to 15 months) of visual impairment for myopia levels between -3 and -8 D. Referring
535 back to the years of visual impairment that might be associated with five years of contact lens
536 wear (Table 2), the range corresponding to the published range of incidence levels of microbial
537 keratitis is between 53 and 1,312 years of visual impairment per 10,000 patients. This represents

538 a range of 0.0053 to 0.1312 years per patient. This leads to the reasonable conclusion that the
539 benefits of myopia control far outweigh the risks of the five years of contact lens wear required
540 to achieve this one diopter of control. Another way to compare risk and benefit is using NNH
541 and NNT. For the range of values in Table 2 the NNH for five years of visual impairment is
542 between 38 and 945. In other words, even for the highest incidence of microbial keratitis (25 per
543 10,000 years), 38 patients would need to be exposed to induce five years of visual impairment. In
544 contrast, only 4.11 to 6.75 patients would need to have their ultimate myopia level reduced by
545 one diopter to prevent five years of visual impairment. For the level of risk that might be
546 expected for myopia control using daily disposable contact lenses, (1 per 10,000 years) the
547 NNH outweighs the NNT by a ratio of 140 for a -3 D myope ($=945/6.75$) and 230 for a -8 D
548 myope ($=945/4.11$). Thus, for therapies that carry low risk, the benefits are compelling, but for
549 smaller amounts of myopia control, or higher levels of risk, the benefits are still meaningful. For
550 example, slowing myopia by 0.50 D—equivalent to slowing axial elongation by 0.18 mm^{138} —
551 would still lower the risk of myopic maculopathy by 20% and, on average, prevent six months of
552 visual impairment.

553
554 This comparison reflects conservative estimates of the total treatment benefit from myopia
555 control derived from current methods of management.⁹³ The benefits would scale up if a greater
556 level of myopia control could be achieved, especially for higher myopes. For example, the data
557 in Table 7 can be used to calculate the benefit of 2-diopters of control in a patient destined to be
558 a -7 D myope ($8.35 - 6.19 = 2.16$ years of visual impairment) or 3-diopters of slowing in a
559 patient who would otherwise end up at -6 D myope ($7.22 - 4.42 = 2.8$ years of visual
560 impairment).

561
562 An important consideration is that values for visual impairment associated with myopia are for
563 bilateral impairment (tables 7 and 8), whereas the estimates of vision loss associated with contact
564 lens wear in Table 2 are monocular and correspond to rates based on two lines loss of visual
565 acuity.⁶⁵ Bilateral cases of contact lens-related microbial keratitis are rare. For example, among
566 the 367 cases reported by Dart et al., only one was bilateral.⁶⁶ Even in large case series of
567 acanthamoeba keratitis bilateral infection occurs in only 5 of 183¹³⁹ and 3 of 154 cases.¹⁴⁰
568 Furthermore, while some cases of vision loss due to contact lens-associated infections require
569 corneal transplants, less severe cases might be ameliorated with rigid contact lenses or
570 phototherapeutic keratectomy.^{141, 142} In summary, the binocular visual impairment associated
571 with contact lenses is far lower than the binocular visual impairment associated with each
572 additional diopter of myopia. Of course, a patient who has reduced vision in one eye is then at
573 greater risk of bilateral visual impairment throughout the rest of their life as a result of other
574 causes¹⁴³ and the loss of binocularity could impact future career choices and quality of life.

575
576 Limitations of Model

577 A number of assumptions are required to produce a model of risk/benefit from myopia control
578 and the accuracy of such a model is dependent on the validity of these assumptions. Our model
579 of visual impairment and myopia uses some interpolation regarding age as only data through 75
580 years were available. It is possible that relation between myopia and visual impairment is
581 different at older ages, for example, the prevalence of age-related macular degeneration is lower
582 in myopes.¹²⁵ The rising worldwide prevalence of myopia is leading to secular trends. A large
583 population-based Japanese study reported that the age-adjusted prevalence of myopic
584 maculopathy doubled in a decade.⁸ Likewise, there has been a 44% increase in the incidence of

585 retinal detachment in the Netherlands over a 7-year period that the authors attribute to myopia,
586 although this is a small contributor to visual impairment.¹⁴⁴ A similar increase was previously
587 reported in Scotland.¹⁴⁵ The inclusion of both age and myopia level in the model of visual
588 impairment should make it relatively robust moving forward.

589

590 The assessment of vision loss associated with contact lens wear assumes that the risk is constant
591 over time and independent of refractive error. As demonstrated in Figure 1, the incidence of
592 contact lens-related adverse events increases as children become teenagers,⁵⁷ presumably due to
593 engaging in behavior likely to increase the risk of adverse events.⁸⁷ Likewise, higher myopes are
594 more likely to engage in risky behavior related to their contact lenses.^{146, 147} A value of 15% for
595 the proportion of cases of microbial keratitis was chosen, based on the two lines loss of visual
596 acuity.^{64, 65} Other studies have reported rates of 4% for a criterion of 20/40 or worse⁶⁶ and 5%
597 based on 20/70 or worse.⁶¹ The calculations in Table 2 are all linear, so the effect of replacing
598 0.15 with a different value is easily calculated. Our model of visual impairment associated with
599 contact lens assumes that the design of the lens does not play a role and that the increased risk is
600 due to increased exposure. Intuitively, those additional years of wear would occur when the child
601 is younger and their myopia relatively low.

602

603 The current model assumes a fixed treatment effect with myopia control. While the efficacy of
604 these technologies show a reduction in subsequent years of treatment,⁹³ a more sophisticated
605 model or simulation could explore variations in treatment duration, treatment effect, or both. The
606 model also uses data from only one paper reporting predominantly white Europeans, although a
607 recent clinic-based French study of nearly 200,000 myopic adults show a similar relationship

608 between myopia level and visual impairment.¹⁰⁵ Both studies include all causes of visual
609 impairment and thus account for age-related increases in AMD and the potentially protective
610 effect of myopia. It will be important to extend these results to other populations as data become
611 available, particularly Asians where the prevalence of myopia is higher. It should be noted that
612 the prevalence of visual impairment in this Dutch population¹⁴⁸ is lower than other comparable
613 populations.^{149, 150}

614

615 Recent comprehensive reviews of the efficacy of myopia control are available,^{17, 93, 151} but long-
616 term data on myopia control and whether the benefits are sustained are scarce. Few published
617 studies are longer than three years in duration. Of the 26 studies considered by Brennan et al.,
618 only four exceed two years and the majority of reports in the literature are one year in duration.⁹³
619 Likewise few studies demonstrate more than 1 D of treatment effect,^{136, 137, 152} and caution must
620 be exercised when extrapolating the findings of shorter duration trials, as slowing of progression
621 in the first year of treatment is greater than in subsequent years.⁹³ Nonetheless, a recent report of
622 the only FDA-approved myopia control device demonstrates a six-year 0.53 mm slowing of axial
623 elongation, which in dioptric terms approaches 1.50 D.¹⁵²

624

625 The extent to which benefits are sustained once treatment is withdrawn is not settled. Dramatic
626 post-treatment acceleration, or rebound, has been reported with 1% atropine, but does not seem
627 to occur with spectacle³⁵ or soft contact lens therapies.^{75, 153} Nonetheless, some level of rebound
628 should be assumed until proven otherwise.⁹³ The choice of treatment will be ultimately be
629 determined by a discussion among practitioner, parent, and patient, but influenced by regional
630 practice patterns and scope of practice.

631
632 The use of NNT and their comparison with NNH is not beyond reproach.¹⁵⁴⁻¹⁵⁶ NNTs vary with
633 baseline or event rate and a NNT without the treatment period and follow-up period is difficult to
634 interpret. For these reasons, a range of rates of visual impairment was explored, with care to
635 specify the duration of treatment and calculate years living with any impairment. Comparisons
636 between different outcomes, for example, risks of microbial keratitis in contact lens wear with
637 risk of vision impairment due to increasing myopia could also be criticized.¹⁵⁷ In contrast, the
638 analyses express both NNH and NNT in a single metric—years of visual impairment. A further
639 valid criticism of the presentation of NNH and NNT is the absence of confidence intervals. The
640 naive approach to calculating a confidence interval for NNT is by inverting the limits for ARR,
641 but this does not yield a valid interval. Our approach has been to explore a range of underlying
642 assumptions and present data for a range of risks and benefits. Finally, the analysis assumes that
643 all years of visual impairment are created equal, which may or not be valid. For example, visual
644 impairment earlier in life may impact earning potential and comparing this with later-onset
645 visual impairment where comorbidities may exist is a complex problem.¹⁵⁸
646

647 Finally, this is not a cost-benefit analysis and future work should consider the cost associated
648 with myopia control, including those associated with adverse events, along the potential savings
649 associated with any reduction in ocular morbidity. Nonetheless, some brief comment is
650 warranted. First, there have been few attempts to estimate the costs of visual impairment. Frick et
651 al.¹⁵⁹ used Medical Expenditure Panel Survey data to estimate the effect of visual impairment
652 with total medical expenditures, components of expenditures, days of informal care received
653 (direct costs), and health utility (indirect costs) among patients 40 years and older in the United

654 States. The direct costs of visual impairment (individual excess medical expenditures) were
655 estimated to be \$1,037 (for 2004). Adjusted for 2021, this is \$1,446. For indirect costs, Frick et
656 al. assumed visual impairment corresponds to a loss of 0.05 quality-adjusted life years (QALYs)
657 and use a “common but arbitrary value for a QALY in the US of \$50,000” resulting in \$2,500¹⁶⁰
658 Adjusted for 2020 gives \$3,779. Frick et al. acknowledge that their estimate of the economic
659 impact is limited, because it does not include productivity loss.¹⁵⁹ Furthermore, all estimates can
660 vary dramatically with the underlying assumptions. For example, other authors apply an upper
661 limit of \$100,000 per QALY and consider the difference between 20/20 and 20/40 to represent
662 0.12 QALYs.¹⁵⁸

663
664 The costs associated with myopia control are also challenging to estimate. At the time of writing
665 only one device or drug is FDA-approved for myopia control in the US and was only launched in
666 the past year, although it has been available in other countries for some years. Analyses would
667 need to include costs of drugs or lenses, but these are incremental as the child will already be
668 wearing spectacles or contact lenses. The cost of additional office visits and measurements,
669 including axial length will also need to be incorporated. All these costs will vary across
670 countries.

671
672 The cost to families of myopia control when that treatment is not generally covered by vision or
673 medical insurance may mean that the prevention or slowing of myopia to reduce the risk of
674 visual impairment later in life may be at the expense of other medical conditions, such as oral
675 care.¹⁶¹ This can potentially exacerbate health disparities in underserved communities as
676 highlighted in a recent Prevent Blindness report, particularly minority communities.¹⁶² The

677 supplemental material in the recently published report of the American Academy of
678 Ophthalmology Task Force on Myopia,¹⁶³ includes a number of goals, including “Encouraging
679 government and commercial insurers to cover myopia control as part of their medical and vision
680 benefits would further expand the interventions available to clinicians and might allay future
681 vision loss and costs associated with higher degrees of myopia. Health disparities in myopic
682 minority children in the United States are likely to be amplified unless insurance coverage for
683 myopia treatments is expanded.” We feel that all stakeholders should consider this issue.

684

685 Finally, those at the greatest risk of developing maculopathy and visual impairment are those
686 with higher levels of myopia.¹³⁴ Likewise, our model shows that the greatest individual
687 reductions in visual impairment from myopia control are accrued in higher myopes. Given the
688 strong relation between age of onset and ultimate severity of myopia,^{2, 4} it is most important to
689 direct efforts at those children who develop myopia relatively early. As Brennan et al.⁹³ recently
690 stated, “Because of the risks of complications later in life and our current inability to predict with
691 great accuracy those who go on to higher degrees of myopia, this leads us to recommend that all
692 young myopes (say 12 years of age and below) deserve to be treated.”

693

694 One question that is currently unresolvable, is whether the observed associations of refractive
695 error and ocular disease are directly causal and whether a reduction in myopia with treatment
696 will reduce the associated risks. Due to the 40 or more-year delay between myopia treatment and
697 the increased risk of vision loss, this is a challenging question to address. One suggestion that
698 there is a causal relationship is the increasing prevalence of myopic maculopathy associated
699 vision loss in countries that have experienced the most rapid increases in myopia prevalence and

700 severity such as China where myopic maculopathy has risen to become the leading cause of
701 vision impairment.^{14, 164} Myopic maculopathy is also the leading cause of uncorrectable visual
702 impairment among Chinese Americans.¹⁶⁵

703

704 **Conclusion**

705 In summary, we have reviewed the risks associated with various myopia control therapies,
706 particularly contact lenses, and the predicted visual loss from five years for therapy. We have
707 examined the increased risk of ocular disease associated with increasing levels of myopia and,
708 more importantly, the relation between visual impairment and myopia level. Finally, we compare
709 the potential benefits of reducing a patient's ultimate level of myopia by one diopter. Our model
710 suggests the potential benefits of myopia control outweigh the risks: the number needed to treat
711 to prevent 5 years of visual impairment is between 4.1 and 6.8 while fewer than 1 in 38 will
712 experience the same loss of vision as a result of myopia control.

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Figure Legends

Figure 1.

The incidence of different inflammatory events involving the cornea and iris as a function of patient age. Data are replotted from Chalmers et al.⁵⁷ CLARE = contact lens-induced acute red eye, CLPU = contact lens peripheral ulcer.

Figure 2.

The prevalence of myopic maculopathy plotted with both linear (left) and logarithmic (right) scales, replotted from Bullimore and Brennan⁹⁴. The logarithmic scale emphasizes the similar trajectory of each data set, the additional risk associated with each diopter.

Figure 3.

The cumulative risk of visual impairment as a function of level of myopia for five ages. The left panel uses a linear scale, while the right panel uses a logarithmic scale. Data are from Figure 2 of Tideman et al.¹³⁴

Figure 4.

The \log_{10} odds of visual impairment as a function of level of myopia for five ages plotted a logarithmic scale. Based on data from Tideman et al.¹³⁴

Figure 5.

Model of visual impairment as a function of age (years) for different levels of myopia and two different definitions of visual impairment. The left panel is ¹³⁴ (worse than 20/67 or 6/20) which is similar to the WHO's ICD-11 definition of moderate visual impairment (worse than 20/60 or 6/18), while the right panel is for the US definition (worse than 20/40) which is also the WHO's ICD-11 definition of mild visual impairment.

Figure 6.

By combining the risk of visual impairment as a function of age for different levels of myopia with mortality data, the probability of a patient living with visual impairment (VI) can be

determined. The mean number of years of visual impairment experienced by a patient over their lifetime may be estimated by integrating the area under each curve.

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Table 1. Incidence of microbial keratitis in adults associated with daily and regular overnight wear of soft contact lenses. Two studies distinguish between hydrogel and silicone hydrogel soft contact lenses, so both values are shown.^{63, 65} When available, the percentage of cases leading to vision loss is shown. Vision loss is defined as two lines loss of visual acuity^{64, 65}, 20/40 or worse⁶⁶, or 20/70 or worse.⁶¹

Country of Study	Year	Number of Cases	Incidence of microbial keratitis (per 10,000 years of wear)		Percentage of Cases Leading to Vision Loss
			Daily Wear	Overnight Wear	
United States ⁵⁹	1989	137	4.1	20.9	—
Scotland ⁶⁰	1999	20	2.4	—	—
Netherlands ⁶¹	1999	92	3.5	20.0	5%
Hong Kong ⁶²	2002	59	3.1	9.3	
England ^{63, 64}	2005	38	6.4/0.0	96.4/19.8	0%
Australia ⁶⁵	2008	244	1.9/11.9	19.5/25.4	15%
England ⁶⁶	2008	349	—	—	4%

Table 2. Vision loss associated with three levels of risk of microbial keratitis (MK). It is assumed that 15% of cases of microbial keratitis result in vision loss, that exposure is five years, and that any vision loss is experienced for 70 years after the event. All values are per 10,000 patients.

Variable	Multiplier	Low Risk	Medium Risk	High Risk
Annual incidence of MK		1	5	25
Annual incidence of vision loss	× 15%	0.15	0.75	3.75
Accumulated incidence of vision loss	× 5 years	0.75	3.75	18.75
Years of vision loss accrued	× 70 years	53	263	1,312
NNH for one year of vision loss	10,000/ years vision loss	189	38	7.5
NNH for five years of vision loss	5 × 10,000/ years vision loss	945	190	38

MK: microbial keratitis; NNH: number needed to harm.

Table 3. Summary of studies of the relation between degree of myopia and the prevalence of myopic maculopathy.

Population	Age Range (Mean)	N	Myopes (definition)	Slope (logPrevalence per Diopter)	Ratio of Prevalence to Diopter	Increase per Diopter	Decrease per Diopter
Australia ⁹⁷	≥49 (66)	3,583	603 (< -1 D)	0.271	1.87x	+87%	-46%
Beijing, China ⁹⁸	≥40 (56±10)	4,319	1,191 (< -0.5 D)	0.213	1.63x	+63%	-39%
Chinese Americans ¹⁰¹	≥50	4,144	1,523 (≤ -0.5 D)	0.192	1.56x	+56%	-36%
Handan, China ⁹⁹	≥30 (52±12)	6,409	1,705 (< -0.5 D)	0.228	1.69x	+69%	-41%
Hisayama, Japan ¹⁰⁰	≥40 (63±11)	1,892	1,619 eyes (≤ 0 D)	0.199	1.58x	+58%	-37%
Singapore ¹⁰²	40 to 80 (57±10)	8,716	3,108 (≤ -0.5 D)	0.095	1.24x	+24%	-20%
Zhongshan, China ¹⁰³	40 to 70 (22±12)	96	96 (≤ -6 D)	0.230	1.70x	+70%	-41%
France ¹⁰⁵	60+		(≤ -0.5 D)	0.143	1.39x	+39%	-28%
Germany ¹⁰⁴	35 to 74 (51±10)	519	519 (≤ -6 D)	0.182	1.52x	+52%	-34%

Table 4. Summary of studies of the relation between degree of myopia and the prevalence of posterior subcapsular cataract.

Population	Age Range (Mean)	N	Myopes	Slope (logPrevalence per Diopter)	Ratio of Prevalence to Diopter	Increase per Diopter	Decrease per Diopter
Beaver Dam, US ¹¹¹	43 to 84 (61±11)	4,470	1,149	0.145	1.40x	+40%	-28%
Singapore Chinese ¹¹⁰	40 to 79	1,029	340	0.009	1.02x	+2%	-2%
Salisbury, US ¹⁰⁹	65 to 84 (73±5)	5,040 eyes	736 eyes	0.103	1.27x	+27%	-21%
Singapore Indian ¹⁰⁸	40 to 84 (59±10)	5,768	1,498	0.060	1.15x	+15%	-13%

Table 5. Summary of studies of the relation between degree of myopia and the incidence of retinal detachment.

Population	Cases	Controls	Slope (logIncidence per Diopter)	Ratio of Incidence to Diopter	Increase per Diopter	Decrease per Diopter
Japan ¹¹⁴	1,166	11,671	0.113	1.30x	+30%	-23%
EDCCS, US ¹¹⁵	253	1,138	0.110	1.29x	+29%	-22%
China ¹¹⁶	61	61	0.059	1.15	+15%	-13%
Switzerland ¹¹⁸	195	—	0.096	1.25x	+25%	-20%
England ¹⁰	452	—	0.173	1.49x	+49%	-33%
Iowa, US ¹¹⁷	172	—	0.156	1.43x	+43%	-30%
Scotland ¹¹⁹	1,202	—	0.096	1.25x	+25%	-20%

Table 6. Summary of studies of the relation between degree of myopia and the prevalence of primary open angle glaucoma.

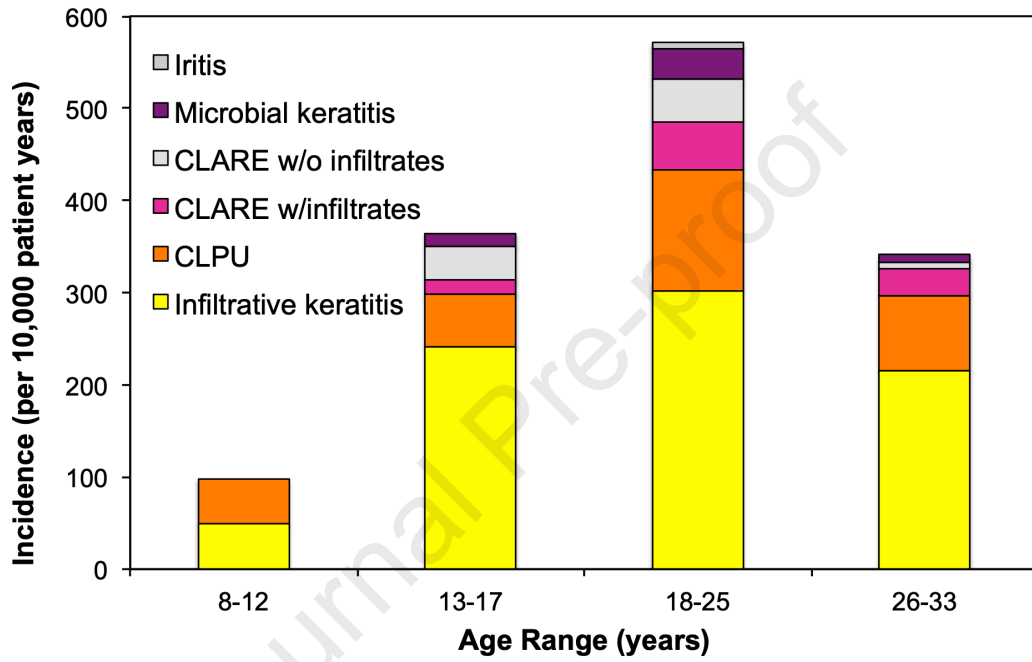
Population	Age Range (Mean)	N	Myopes	Slope (logPrevalence per Diopter)	Ratio of Prevalence to Diopter	Increase per Diopter	Decrease per Diopter
India ¹²²	40 to 90 (51)	5150	—	0.032	1.08x	+8%	-7%
Beijing ¹²³	40 to 101 (56±10)	4,319	978	0.066	1.16x	+16%	-14%
NHANES, US ¹²⁴	40 and older	5,277	1,241	0.053	1.13x	+13%	-12%
Singapore Indian ¹²⁵	40 to 84 (59±10)	5,768	1,498	0.144	1.39x	+39%	-28%
South Korea ¹²⁶	40 and older	13,433	2,986	0.082	1.21x	+21%	-17%
Kaiser, US ¹²⁷	35 and older (58±12)	437,438	—	0.037	1.09x	+9%	-8%

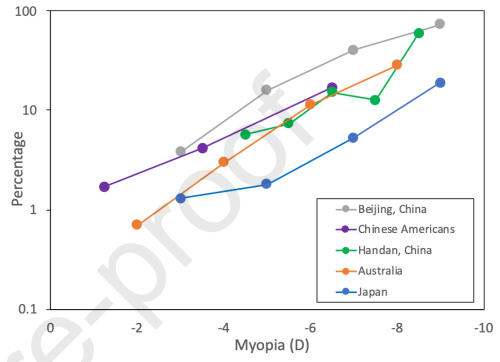
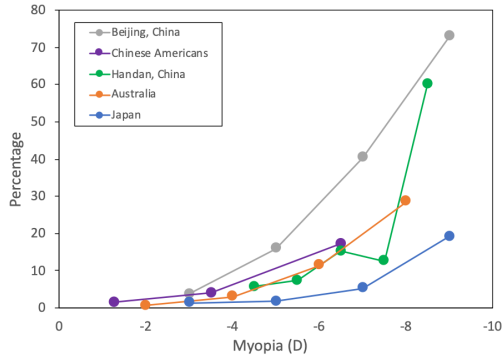
Table 7. Mean lifetime years of visual impairment (VI) as a function of level of myopia using the US definition of 20/40, which is WHO definition of mild visual impairment. Also shown are mean years of visual impairment prevented by a 1 D reduction in a patient's ultimate level of myopia, the number of patients needed to treat (NNT) in order to prevent 5 years of visual impairment, and the reduction in myopia needed to prevent one year of visual impairment.

Myopia Level (D)	Mean Years of VI per Patient	Years of VI Prevented by 1 Diopter Reduction	Number Needed to Treat to Prevent 5 years of VI	Reduction Needed to Prevent One Year of VI (D)
-3	4.42	0.74	6.75	1.38
-4	5.25	0.84	5.97	1.22
-5	6.19	0.93	5.35	1.07
-6	7.22	1.03	4.85	0.97
-7	8.35	1.13	4.44	0.88
-8	9.56	1.22	4.11	0.82

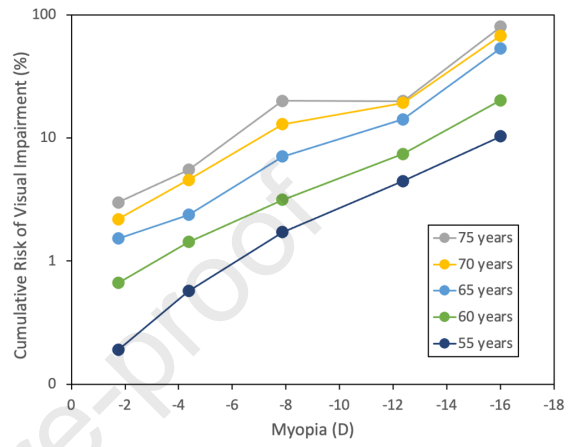
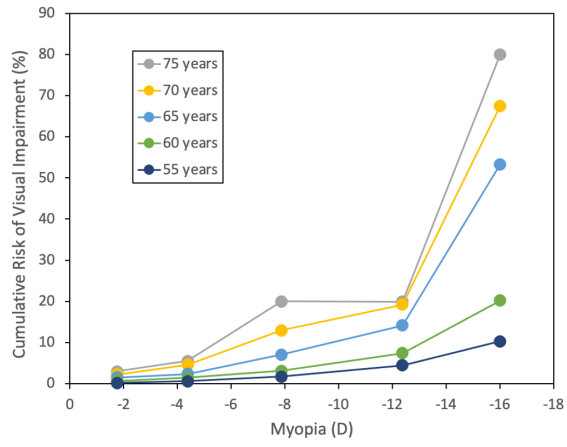
Table 8. Mean lifetime years of visual impairment (VI) as a function of level of myopia using the WHO definition of moderate visual impairment: 20/60. Also shown are mean years of visual impairment prevented by a 1 D reduction in a patient's ultimate level of myopia, the number of patients needed to treat (NNT) in order to prevent 5 years of visual impairment, and the reduction in myopia needed to prevent one year of visual impairment.

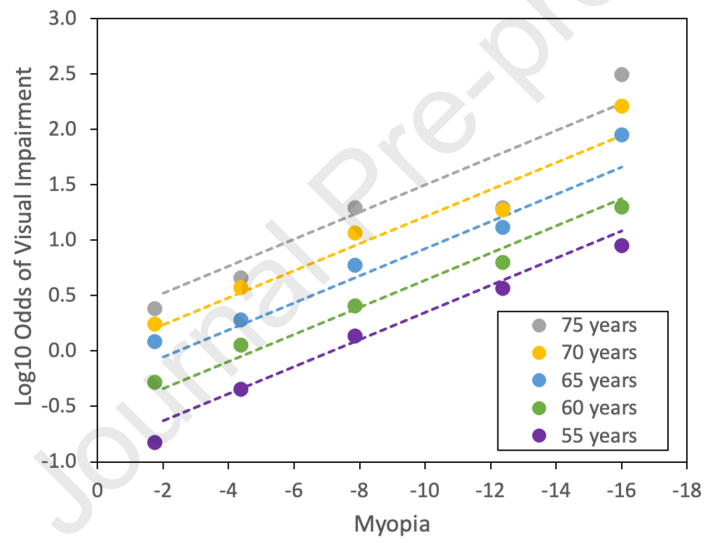
Myopia Level (D)	Mean Years of VI per Patient	Years of VI Prevented by 1 Diopter Reduction	Number Needed to Treat to Prevent 5 years of VI	Reduction Needed to Prevent One Year of VI (D)
-3	2.06	0.41	12.24	—
-4	2.55	0.49	10.29	2.33
-5	3.12	0.57	8.77	1.88
-6	3.78	0.66	7.58	1.58
-7	4.53	0.75	6.63	1.36
-8	5.39	0.85	5.87	1.18

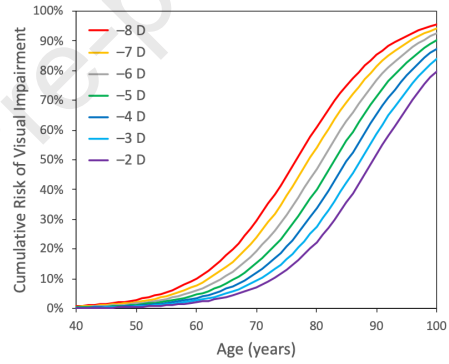
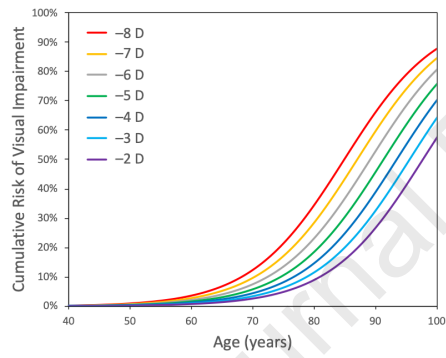


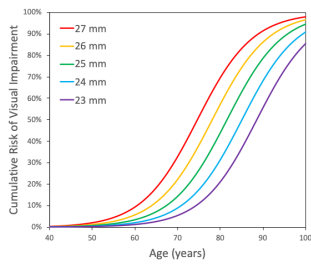


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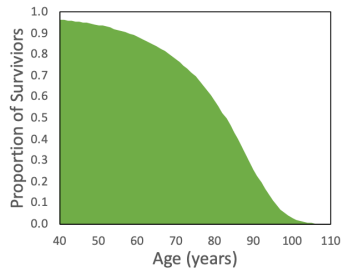




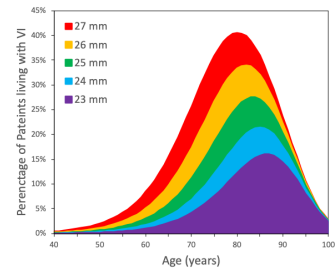




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We consider whether the potential benefits of slowing myopic progression by one diopter justify the potential risks associated with treatments, based on published data on risks and the relation between visual impairment and myopia.

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