Progress in Retinal and Eye Research xxx (xxxx) xxx

Contents lists available at ScienceDirect

Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/preteyeres

Efficacy in myopia control

Noel A. Brennan [a,*], Youssef M. Toubouti [a], Xu Cheng [a], Mark A. Bullimore [b]

[a] Johnson & Johnson Vision, 7500 Centurion Pkwy, Jacksonville, FL, 32256, USA
[b] University of Houston, USA

ARTICLE INFO

Keywords:
Myopia
Myopia control
Efficacy
Children
Axial length
Retinal disease

ABSTRACT

There is rapidly expanding interest in interventions to slow myopia progression in children and teenagers, with the intent of reducing risk of myopia-associated complications later in life. Despite many publications dedicated to the topic, little attention has been devoted to understanding 'efficacy' in myopia control and its application. Treatment effect has been expressed in multiple ways, making comparison between therapies and prognosis for an individual patient difficult. Available efficacy data are generally limited to two to three years making long-term treatment effect uncertain. From an evidence-based perspective, efficacy projection should be conservative and not extend beyond that which has been empirically established. Using this principle, review of the literature, data from our own clinical studies, assessment of demonstrated myopia control treatments and allowance for the limitations and context of available data, we arrive at the following important interpretations: (i) axial elongation is the preferred endpoint for assessing myopic progression; (ii) there is insufficient evidence to suggest that faster progressors, or younger myopes, derive greater benefit from treatment; (iii) the initial rate of reduction of axial elongation by myopia control treatments is not sustained; (iv) consequently, using percentage reduction in progression as an index to describe treatment effect can be very misleading and (v) cumulative absolute reduction in axial elongation (CARE) emerges as a preferred efficacy metric; (vi) maximum CARE that has been measured for existing myopia control treatments is 0.44 mm (which equates to about 1 D); (vii) there is no apparent superior method of treatment, although commonly prescribed therapies such as 0.01% atropine and progressive addition spectacles lenses have not consistently provided clinically important effects; (viii) while different treatments have shown divergent efficacy in the first year, they have shown only small differences after this; (ix) rebound should be assumed until proven otherwise; (x) an illusion of inflated efficacy is created by measurement error in refraction, sample bias in only treating 'measured' fast progressors and regression to the mean; (xi) decision to treat should be based on age of onset (or refraction at a given age), not past progression; (xii) the decreased risk of complications later in life provided by even modest reductions in progression suggest treatment is advised for all young myopes and, because of limitations of available interventions, should be aggressive.

1. Introduction

1.1. Background and aims

The epidemiology and complications of myopia have been reviewed extensively elsewhere and will not be repeated in detail here (Flitcroft, 2012; Morgan et al., 2012, 2017, 2018; Dolgin, 2015; Holden et al., 2016; Saw et al., 2019). To summarize, myopia constitutes a major threat to eye health of the global population in coming decades through its increased prevalence and its association with diseases such as myopic macular degeneration (MMD; also referred to as myopic maculopathy or myopic retinopathy) (Curtin and Karlin, 1970; Gözüm et al., 1997), posterior staphyloma (Curtin, 1977; Ohno-Matsui and Jonas, 2019), retinal detachment (Knapp, 1943; Mitry et al., 2010), cataract (McCarty et al., 1999; Kanthan et al., 2014), and glaucoma (Knapp, 1925; Grodum et al., 2001). Risk of ocular disease has been associated with myopic elongation of the eye and therefore a major research enterprise in recent times has been the search for methods of slowing myopia progression among children and teenagers rather than simply correcting vision. Whether successful implementation of these methods will reduce myopia-associated pathology later in life remains unknown and we canvass arguments on this topic in section 1.2. Notwithstanding this

* Corresponding author.
E-mail address: nbrenna2@its.jnj.com (N.A. Brennan).

https://doi.org/10.1016/j.preteyeres.2020.100923
Received 2 March 2020; Received in revised form 17 November 2020; Accepted 23 November 2020
Available online 27 November 2020

uncertainty, the potential upside of reducing risk of myopia-associated disease later in life, restricting final degree of myopia in terms of quality of life and facilitating favourable refractive surgery outcomes is substantial (Bullimore and Brennan, 2019). The opportunity has stimulated tremendous interest from clinicians, academics and industry. Treating the disorder rather than the symptoms would constitute a major disruption to standard of care in clinical practice and an important benefit for patients.

Despite many publications dedicated to the topic, little attention has been devoted to interpretation of 'efficacy' in myopia control studies and its application. Papers describing clinical trials report difference in progression between treated and untreated groups. Nonetheless, dissimilarity in endpoints, study duration, demographics of study populations and reporting protocols render genuine comparison between treatments difficult (Brennan and Cheng, 2019). For example, if one treatment is claimed to reduce progression by 0.5 D/y, another by 0.40 mm over five years and yet another by 50%, what can we say about comparative clinical benefits. While scientific analyses tend toward statement of absolute treatment effect with variable handling of the time component, the fallback position for most clinical reviews of myopia control has been to quote percentages, an inadequate and misleading metric, as will be demonstrated in sections 4 and 5 of this paper. As well as providing a basis for comparison between therapies, investigating treatment effect in myopia control studies also sheds light on a number of other related critical questions, such as (i) which endpoint should be used to assess myopia progression, (ii) how applicable is an absolute, relative or annualised effect size across populations of different age and ethnicity, (iii) does treatment effect vary depending on baseline characteristics of those treated, (iv) how can we apply group means to progression rates in individuals, (v) how much can we actually slow down progression in fast progressors, (v) is treatment effect maintained during and after treatment, (vi) do current clinical perceptions match the evidence base, and (vii) does an analysis such as this shed light on who we should treat, how we should treat and for how long we should treat?

In this paper, we conduct an in-depth review and analysis of the concept of efficacy in myopia control, using accumulated information available in the scientific literature as well as our own studies to arrive at an evidence-based approach to assessing efficacy of interventions to slow progression and explore resultant implications.

1.2. Justification for myopia control

As noted above, enthusiasm about myopia control largely relies on the unsubstantiated assumption that interventions in childhood myopia progression will reduce the prevalence of pathologies later in life. Proof that this is the case is difficult to obtain and, in its purest form, would require decades of research. The theory is reliant on the proposition that the 'newer' high myopia that has been observed in recent generations is of similar origin to the 'older' type that was found in previous generations. An alternative hypothesis is that newer high myopia is of environmental origin and found in the more extreme cases of acquired myopia and therefore different to the older type which is genetic in nature (Morgan and Rose, 2005; Morgan et al., 2017). Potentially, older myopia may genetically predispose to pathological myopia, whereas new myopia might not. The genetic link might also explain the finding of pathologic complications in eyes with low amounts of myopia and short axial length (Wang et al., 2016). Jonas et al. (2016) found support for separate types of high myopia by noting the strong association of education with the newer type but not the older type. The discovery of genetic loci related to high myopia and MMD which are not common with the more general genetic associations with all myopia is consistent with this position (Hosoda et al., 2018; Meguro et al., 2020). In a cross-sectional analysis, Nakao et al. (2020) found that extreme myopia prevalence was constant across age while prevalence of myopia and high myopia had increased in younger generations, prompting them to suggest a genetic predisposition to the extreme phenotype. However, this interpretation fails to allow for the continued increase in myopia and axial length among high myopes as they age, with greater increases observed with both increasing myopia and axial length (Lee et al., 2020a, 2020b).

On the other hand, Flitcroft (2012) provides some circumstantial support for the proposition that new and old myopia are one and the same. As well as providing multiple examples of dose-response effect where higher degrees of myopia are associated with higher levels of pathology, he points to the plausibility of the mechanisms linking high levels of myopia to risks of retinal detachment, glaucoma and MMD. Moreover, Flitcroft (2012) proposed an indirect test of causation by "determining if population shifts in myopia prevalence are followed, in future years, by increases in the incidences of glaucoma, cataract, retinal detachment and myopic maculopathy …" We believe one recent study satisfies this line of investigation. Ueda et al. (2019) measured significant increases in the prevalence of different levels of myopia over 12 years in a large, prospective, long-term, population-based study of residents of Hisayama, Japan, aged 40 years and older. This is not unexpected as the trend of increased myopia prevalence among children and teenagers over the last half century advances generationally. Accompanying this was a marked increase in MMD. Prevalence of myopia (<-0.50 D) rose from 37.7% to 45.8%, a 21% increase. But the prevalence of high myopia (<-8.00 D), excessive axial length ($\geq$26.5 mm) and MMD (grade 2 and above on the META-PM scale) increased by 100%, 66% and 112%, respectively, over this relatively short period. The sharp escalation in prevalence of MMD accompanying the generational increase in high myopia defies a separate genetic origin for MMD in this stable population. Finally, the highly linear nature of the relationship between refractive error and log of the odds of MMD across the myopic refractive error domain (Brennan, 2015) supports the proposition that all primary (non-syndromic) myopia arises from a single distribution. Features related to the distribution, such as prevalence of myopia above a certain threshold or of MMD at a certain age, are reliably predictable from probability theory as a population becomes more myopic overall, which is inconsistent with the concept of multiple large groups displaying separate traits (Brennan and Cheng, 2017; Brennan et al., 2018a).

While these arguments may not provide conclusive proof that slowing the progression of environmentally induced high myopia will reduce morbidity later in life, these considerations add support to the momentum that has driven the rise of myopia control in clinical practice.

1.3. Application of the research

The intention of this work is to study the theory underlying reporting of myopia control efficacy and implications that flow from such investigation. Interventions for slowing myopia progression that have been developed and tested to date have concentrated on low to moderate amounts of paediatric myopia where sight-threatening complications are seldom observed. Indeed, treatment is targeted at those who might normally progress to high myopia while they are still at lower levels. There is limited information on slowing progression among paediatric high myopes (Charm and Cho, 2013), so caution should be exercised in applying outcomes from this paper to that group or those with longer axial lengths. Similarly, the conclusions we reach are not applicable to eyes where substantial disease such as staphyloma is found, and where changes to axial length and ocular shape are subject to different processes compared to the early stages of myopic progression.

In keeping with the ethos of evidence-based medicine, we apply the fundamental conservative principle of assuming absence of efficacy unless demonstrated. Studies of treatments to date have generally been of limited duration and extrapolation of short-term data to the longer term should be done with caution. Any statement regarding effect size should be limited to that which has been empirically determined or can be reasonably projected from available data. Treatment effect in terms

of reduction of myopic progression should also be maintained after removal of the treatment. Resultant recommendations should be useful for the practitioner and patient to set expectations of what might be realistically achieved by myopia control treatment. This has value practically since there is no way to accurately measure the therapeutic effect achieved in an individual in practice.

Rather than endorse specific interventions by virtue of superior efficacy, this paper provides tools to enable the clinician or researcher to make efficacy evaluations in a considered manner. We report results of research studies and analyse them in the context of experimental products and scientific investigation without intent to influence commercial usage. There are a limited number of interventions that have received regulatory approval and such approvals are inevitably regional; therefore, most myopia control currently practised worldwide is off-label. We do not endorse off-label usage of any treatment discussed in this paper.

1.4. Source material

While this paper interprets a broad range of literature (see for example, section 3), there are two key sources of information that contribute to our conclusions and are analysed multiple times. The first comprises a set of reanalyses of data from our own clinical studies (sections 4.1, 4.3 and 8.2). Details of experimental design and protocols in these studies have been previously published (Cheng et al., 2016, 2019).

The second is a set of key papers that describe clinical trials of myopia control (sections 4.3, 4.4, 5.1, 5.2 and 6.1). The following criteria were applied to restrict our evaluation to those investigations listed in Table 1. Only papers describing an intervention with demonstrated efficacy were included, to reflect the objective of this investigation. Benchmark for inclusion was a minimum of statistical significance and an effect size of 0.11 mm reduction in axial elongation (equivalent to approximately 0.25 D) at any timepoint during follow-up. The rationale for restricting our review to measures of axial length is provided in section 3. Although it would be desirable to restrict

Table 1
Details of cohorts within studies meeting criteria for inclusion in our analyses.

Authors (year)	Test[a]	Cont[b]	Rand[c]	IM[d]	SM[e]	Dur[n,f] (yrs)	N[g] (cont)	N (treat)	Age[h] (cont)	Age (treat)
Aller et al. (2016)	SMCL	Y	Y	Y	Y	1	40	38	13.5	13.0
Anstice and Phillips (2011).[i]	SMCL	Y	Y	Y	N	0.8	40	40	13.4	13.4
Chamberlain et al. (2019)	SMCL	Y	Y	Y	Y	3	56	53	10.1	10.1
Charm and Cho (2013).[j]	OK	Y	Y	Y	N	2	16	12	10.5	10.5
Chen et al. (2013).[k]	OK	Y	N	Y	N	2	23	35	8.9	9.4
Cheng et al. (2014).[l]	Specs 1	Y	Y	N	N	3	41	48	10.3	10.1
	Specs 2							46		10.4
Cheng et al. (2016)	SMCL	Y	Y	Y	Y	1	57	52	9.7	9.7
Cho et al. (2005)	OK	H	N	N	N	2	35	35	9.6	9.6
Cho and Cheung (2012)	OK	Y	Y	Y	N	2	41	37	9.5	9.5
Chua et al. (2006)	Atr 1.0%	Y	Y	Y	Y	2	190	166	9.2	9.2
Hiraoka et al. (2012)	OK	Y	N	N	N	5	21	22	10.4	10.0
Kakita et al. (2011).[m]	OK	Y	N	N	N	2	50	42	11.9	12.0
Lam et al. (2014)	SMCL	Y	Y	Y	Y	2	63	65	11.0	10.9
Lam et al. (2019)	Specs	Y	Y	Y	Y	2	81	79	10.0	10.2
Leung and Brown (1999)	Specs 1	Y	N	N	N	2	32	22	10.4	10.5
	Specs 2							14		10.2
Paune et al. (2015)	OK 1	Y	N	N	N	2	21	19	13.1	13.3
	SMCL 2							18		12.3
Ruiz-Pomeda et al. (2018)	SMCL	Y	Y	N	N	2	33	41	10.1	11.0
Sankaridurg et al. (2011)	SMCL	H	N	N	N	1	40	45	10.8	11.6
Sankaridurg et al. (2019)	SMCL 1	Y	Y	Y	Y	2	50	47	10.5	10.4
	SMCL 2							45		10.4
	SMCL 3 SMCL 4							45		10.4
								47		10.3
Santodomingo-Rubido et al. (2017).[n]	OK	Y	N	N	N	7	16	14	9.6	10.4
Tan et al. (2005)	Pir 1	Y	Y	Y	Y	1	62	117	8.6	8.6
	Pir 2							119		8.8
Walline et al. (2009)	OK	H	N	N	N	2	28	28	10.5	10.5
Walline et al. (2013)	SMCL	H	N	N	N	2	27	27	10.8	10.8
Yam et al. (2019)	Atr 0.05%	Y	Y	Y	Y	1	93	102	8.4	8.5
	Atr 0.025%							91		8.5
Zhu et al. (2014)[p]	OK	Y	N	N	N	2	63	65	9.9	9.8

[a] Test, test treatment: SMCL, soft multifocal contact lenses; OK, orthokeratology; Specs, spectacles; Atr, atropine; Pir, pirenzepine. The number following those with multiple test conditions is our assigned number.
[b] Cont, was there a control arm in the study? Y, yes; N, no; H, yes but not concurrent (historical).
[c] Rand, was the study randomised?.
[d] IM, was the study investigator masked?.
[e] SM, was the study subject masked?.
[f] Durn (yrs), duration of the study in years.
[g] N (cont) sample size in the control group, (treat) sample size in the treated group.
[h] Age (cont) mean age of the control group, (treat) mean age of the treated group. Age is for subjects at enrolment in general, except for Charm and Cho (2013) and Cho and Cheung (2012), who presented data in whole years - age was adjusted upward by 0.5 years.
[i] Contralateral eye study.
[j] Study in high myopes, all other studies were restricted to myopes with at maximum -6D error.
[k] Subjects had with-the-rule astigmatism of −1.25 to −3.50 D, all other studies were for spherical correction (low astigmatism).
[l] Specs 2 included prismatic correction.
[m] Some subjects in the study of Kakita et al. (2011) were also in the study of Hiraoka et al. (2012).
[n] Santodomingo-Rubido et al. (2017). The first 2 years of this study were published as Santodomingo-Rubido et al. (2012).

inclusion to level I evidence (double-masked, controlled, randomised clinical trials), there are insufficient papers of this type to generate a solid evidence-base and so some studies that were neither masked nor randomised are included. Data from included works were either directly obtained from papers, digitised from graphs in the papers using ImageJ (National Institute of Health, Bethesda, Maryland) or kindly provided by investigators.

Treatments are often grouped for convenience into pharmacological, orthokeratology, soft multifocal contact lenses (SMCLs) and spectacles. Examination of Table 1 reveals that studies of SMCLs most often conform to best scientific practice in terms of study design, few orthokeratology studies employed randomization despite the considerable number of publications on this topic and there are relatively few studies of spectacles and pharmaceuticals that meet our criteria for inclusion. It is noteworthy that no studies of 0.01% atropine satisfied the threshold for inclusion in this analysis due to lack of efficacy in slowing axial elongation, despite widespread use in ophthalmology at this concentration (Zloto et al., 2018).

2. Problem statement

2.1. General concept of efficacy

"The primary purpose of research is to estimate the magnitude and direction of effects which exist 'out there' in the real world" (Ellis, 2010). Despite its ubiquity, statistical significance is insufficient to assess worth of a treatment. Increasing sample size escalates the likelihood of rejecting the null hypothesis of no difference even for effect sizes that are not of much interest (the much abused 'p-value'). Inadequate (small) sample size, on the other hand, can lead to increased likelihood of accepting the null hypothesis of no difference even for effect size values that produce significant benefit to the patient. True effect size is essentially independent of the number of data points and represents practical significance of a finding. A confidence interval then provides the level of precision of the estimate.

Study of effect size has become a major focus of statistical science (Batterham and Hopkins, 2006; Nakagawa and Cuthill, 2007; Ellis, 2010; Stang et al., 2010; Fritz et al., 2012). Many papers have provided guidelines for the purpose of interpreting magnitude of effect sizes across different statistical analyses, including the seminal work of Cohen (1988, 1992). Interpretation varies by field due to a range of scientific, medical and logistical factors and we have distilled available evidence on myopia control to arrive at a preferred method for expressing efficacy as we describe below.

2.2. Efficacy versus safety

Multiple treatments, including pharmacological, contact lenses, spectacles and behaviour modification, have been proposed to slow myopia onset or progression (Huang et al., 2016; Wildsoet et al., 2019). The decision to treat and which intervention to apply embodies the classical risk-benefit dilemma. On the risk side, there are safety considerations which include side-effects of the treatment as well as the potential for permanent long-term damage to the eye or even the individual. Different treatments have different risk profiles and these risks are generally yet to be fully quantified (Bullimore et al., 2013; Bullimore, 2017; Gong et al., 2017; Cheng et al., 2019; Prousali et al., 2019). On the benefit side, delay of onset or slowing of progression should result in a reduction of final degree of myopia with presumed commensurate decrease in risk of myopia-related diseases later in life. We are therefore concerned with magnitude of treatment effect and exploring that phenomenon from an evidence-based perspective is the purpose of this paper. Assessing efficacy can be challenging, as aggregate data are available in multiple formats: onset or progression; change in refractive error or axial elongation; absolute or relative; cumulative or annualised; mean progression rates or proportions meeting threshold criteria; short or long-term efficacy; with or without rebound. Sometimes progression data for emmetropes, emmetropes who become myopes and existing myopes are pooled but these populations differ in numerous ways. As the theme of this paper is slowing of progression in existing myopes, we concentrate on this group in isolation and do not consider prevention of myopia, a subsection of the field of myopia control that is still very much in its infancy.

2.3. Different descriptions of efficacy in myopia control

A major problem that hampers comparison of efficacy of myopia control modalities is the wide variation in study design, especially duration of follow-up. Heterogeneity of subject inclusion criteria, such as genetic background, levels of myopia, age, progression rate, race and environment, poses challenges to interpretation as well. These obstacles are further magnified by variation in choice and method of expression of efficacy, the subject of this paper. Despite these concerns, much of the uncertainty generated by the diversity of subjects in clinical trials is obviated by careful selection of the way in which efficacy is communicated, as we demonstrate in sections 4 and 5.

Authors of papers reporting clinical trials of interventions for myopia control typically present change in refractive error, axial length or both and report differences between change in test and untreated groups as a measure of effect size. Regularly, they also report percentage treatment effect calculated from reduction in mean progression in the treatment group compared to the untreated group. Further, results may be presented as annualised treatment effect, calculated by averaging progression over time.

The most common presentation of efficacy in clinical reviews comparing different treatments is relative reduction of progression, expressed as a percentage (Walline, 2016; Leo, 2017; Cooper and Tkatchenko, 2018; Kang, 2018; Lipson et al., 2018; Sankaridurg et al., 2018; Tran et al., 2018; Wildsoet et al., 2019; Wolffsohn et al., 2020). Implicit in this style of reporting is the assumption that relative treatment efficacy applies across the progression range and is consistent across duration of treatment. For example, a study in which an untreated group progressed by 1 D and a treated group by 0.5 D could be said to have shown a 50% reduction in myopia progression. This interpretation would suggest that a myope who was to progress by, say, 4 D over a certain time period would progress by 2 D with this intervention, a reduction in progression of 2 D. This assumption has not, to our knowledge, been validated or proven to be true. Numerous authors in other fields emphasise pitfalls in reporting treatment data as a relative effect (Faraone, 2008; King et al., 2012; Agarwal et al., 2017; Heneghan et al., 2017). They claim that relative measures are often uninterpretable or impact judgment of magnitude, significance, and implications of trial results, most often by exaggerating findings of modest clinical benefit (King et al., 2012; Heneghan et al., 2017).

Several meta-analyses of myopia control treatments have been conducted. Efficacy has been variously reported as annual progression rate (Huang et al., 2016; Gong et al., 2017; Xiong et al., 2017a), absolute progression amount at a single timepoint (Sun et al., 2015; Li et al., 2017), absolute progression amount at multiple timepoints (Walline et al., 2011; Li et al., 2016; Global Myopia Centre, 2019; Prousali et al., 2019; Kaphle et al., 2020) and mixed outcomes (Sherwin et al., 2012; Cui et al., 2017). Little attention has generally been paid to how treatment effect varies over time in these analyses with limited exceptions (Huang et al., 2016; Brennan and Cheng, 2019; Kaphle et al., 2020). In all cases, mean values are studied and virtually no attention has been paid to factors that will influence individual response to treatment.

2.4. A note on proportional analysis

Yet a further method of presentation of myopia control is expression of the proportion of subjects in each of the untreated and treated groups that progress by more or less than a given threshold, resulting in

calculation of an odds ratio. The US Food and Drug Administration (FDA) oversees regulatory approval of ophthalmic products, with two distinct branches overseeing approval of drugs and devices. Drugs are handled by the Center for Drug Evaluation and Research (CDER), specifically the Division of Transplant and Ophthalmology Products in the Office of Antimicrobial Products. Devices, including contact lenses and spectacle lenses, are the purview of the FDA's Center for Devices and Radiological Health (CDRH), specifically the Office of Ophthalmic, Anaesthesia, Respiratory, ENT and Dental Devices. The proportional analysis approach seems preferred by the FDA CDER, based on a transcript from a 2003 meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee where outcomes for myopia control studies were discussed (United States Food and Drug Administration, 2003) and three ongoing clinical trials of low concentration atropine among companies seeking FDA approval (clinicaltrials.gov NCT03350620, NCT03918915, NCT03942419), which record proportions of patients with refractive progression above a certain threshold as their primary endpoint measure of efficacy.

Using this latter endpoint requires dichotomization of measures into a binary variable. Cohen (1983) warns against this practice in an article entitled "The cost of dichotomization". In an explanatory and elaboration document to the CONSORT statement, Moher et al. (2010) state that "for binary outcomes, the effect size could be the risk ratio (relative risk), odds ratio, or risk difference" whereas "for continuous data, it is usually the difference in means". MacCallum et al. (2002) are even more strident, stating that "dichotomization is rarely defensible and often will yield misleading results". Dichotomising myopic progression into fast and slow progression implies an underlying and unstated assumption that a given odds ratio will correspond to a given magnitude of treatment effect. Likely benefits may be overestimated by this approach where significant differences arise despite effect sizes being small and clinically irrelevant. For example, Cheng et al. (2016) found a minor and statistically insignificant treatment effect of 0.14 D for a myopia control intervention after one year (see section 4.1 for more detail of this study). Yet, the odds of being a fast progressor (>0.75 D/y) in the control group in this study were 2.8 (95%CI, 1.1 to 7.4) times that in the test cohort, a statistically significant effect ($p < 0.05$). Alternatively, dichotomising leads to loss of information and so important differences could also be missed. The approach certainly contrasts with the preference of the CDRH panel which is for a mean effect size surpassing a given threshold, as evident from the FDA's co-sponsored workshop on myopia control (Walline et al., 2018) and approval order of the MiSight® (CooperVision®) 1 day contact lens (United States Food and Drug Administration, 2019). As well as potentially providing a misleading representation of clinical efficacy, expressing treatment effect as a proportion is only of moderate relevance to a practitioner, has little value in predicting likely magnitude of reduction in progression of an individual and cannot at this stage be used to predict longer term efficacy. Consequently, this approach will not be discussed further in this paper.

2.5. Summary and discussion

It is apparent from this discussion that no standardised approach to reporting myopia control efficacy has been adopted. A further confounding factor is whether myopia progression should be presented as refractive shift in dioptres, axial elongation in millimetres or both. This question is fundamental to the issue of expressing efficacy in myopia control trials and is addressed in the next section.

3. Axial elongation is the preferred outcome measure

3.1. Outcome measures in clinical trials-general

Choice of primary endpoint is crucial in maximizing value of an efficacy study and in balancing risks imposed upon both treated and untreated subjects (Fleming and Powers, 2012; Coster, 2013; Hollestein and Nijsten, 2015; Orsmond and Cohn, 2015; Hall, 2018). It has been described as "probably the single most important factor in designing a clinical trial to test whether a treatment is working for patients" (Hall, 2018), and the usefulness of a study therefore hinges on adequacy of the measure (Coster, 2013). The choice can be challenging. Oftentimes, measures are selected because they have been applied previously with similar populations or interventions and have become a *de facto* gold standard. But as technology advances, new treatments are developed and new understandings reached, there is a need to develop new measures that align with theoretical perspectives and hypothesised mechanisms of change reflected in the intervention (Orsmond and Cohn, 2015). Failure to pay adequate attention to selection of primary endpoint may result in the outcome not being congruent with the conceptual causal model of disease (Coster, 2013). The basis for choosing the primary endpoint may include statistical arguments, relation to disease processes, clinical relevance, ease of data collection, ease of interpretation, and logistical considerations but, ideally, it will involve representation of the disease process and ultimately should provide reliable evidence about whether an intervention provides clinically meaningful benefit to patient health.

3.2. Outcome measures in myopia progression trials

The two common ways of measuring myopia progression are refractive error and ocular biometry. Although the two measures are generally highly correlated, it is not possible to accurately predict one from the other. For example, in a study of 12,386 European participants, 12% of adult female eyes that were 22.6 mm or shorter were myopic, whereas 13% of adult male eyes longer than 25.7 mm were not myopic (see Fig. 2 of Tideman et al., 2018). Important differences may also exist between the two measures, such as ease and cost of obtaining data, bias and sensitivity, relation to complications of myopia, influence of accommodation and cycloplegia, and applicability to clinical practice as opposed to research. Nonetheless, when considering myopia progression rather than cross-sectional values, refractive error change and axial elongation are highly correlated. For example, Hyman et al. (2005), Lam et al. (2014), Aller et al. (2016) and Chamberlain et al. (2019) found correlation coefficients of −0.77, −0.70, −0.80 and −0.90, respectively.

Traditionally, refractive error measurement has been used to track myopia progression. This was historically appropriate as methods for biometry of the eye were of limited precision and required contact with the eye. But widespread use of interferometric techniques to measure biometric parameters potentially challenges this dominion.

The FDA CDER has shown a clear preference for functional over anatomic endpoints for drug and biologic approvals (Csaky et al., 2017). In the meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee referenced in section 2.4 (United States Food and Drug Administration, 2003), the consensus was that cycloplegic auto-refraction should be the primary outcome measure. Axial elongation was discussed as a secondary outcome measure. It is worth noting that the meeting took place soon after introduction of the Zeiss IOLMaster (Zeiss, Oberkochen, Germany), the first commercially available optical biometer. The value of interferometric measurement of axial length for monitoring myopia progression was not necessarily fully appreciated at this stage. Nonetheless, it is evident that preference for change in refractive error as the primary endpoint continues based on the three ongoing clinical trials of low concentration atropine among companies seeking FDA approval mentioned in section 2.4 (clinicaltrials.gov NCT03350620, NCT03918915, NCT03942419). The primary outcome measure for all three is proportion of treated subjects progressing by less than a dioptric criterion, such as "The proportion of primary study eyes showing less than 0.50 D (spherical equivalent) myopia progression compared to baseline measured using cycloplegic autorefraction" (NCT03942419). Only one of the three studies list axial elongation as a secondary outcome although all three studies collect these data.

On the other hand, the FDA's CDRH tend to favour anatomic outcome measures. Table 1 of the report from the co-sponsored FDA workshop on "Controlling the Progression of Myopia: Contact Lenses and Future Medical Devices" provides a "Summary of the Information Discussed and Suggestions by Each of the Three Panels". It lists the "Primary effectiveness endpoint" as "Both axial length change and refractive error change, with axial length preferred" (Walline et al., 2018). This is reflected in ongoing clinical trials seeking approval for myopia control devices. For example, a trial of novel spectacle lens designs (clinicaltrials.gov NCT03623074) lists both change in axial length and spherical equivalent refraction from baseline as primary outcome measures.

In the following discussion, we consider advantages and disadvantages of using axial elongation versus refractive error change as the primary endpoint.

3.3. Relation to myopia onset and progression

Certain established features of myopia onset and progression are unambiguously linked to the refractive state of the eye and for which axial length is minimally informative. Refractive error, ideally obtained with cycloplegia in the paediatric population, is the definitive indicator of whether an eye is hypermetropic, myopic or emmetropic, although exact thresholds remain subject to debate (Flitcroft et al., 2019). Typically, neonates are hypermetropic with the degree of refractive error reducing during early years of life (Mutti et al., 2005). Refraction stabilizes in what is traditionally considered to be normal development in the low hypermetropic range (plano to +2.00 D with mean of around +0.75 to +1.00 D) (Wolffsohn et al., 2019a). The eye continues to grow in length with thinning of the crystalline lens being largely responsible for stability of refraction in these eyes (Mutti et al., 2012). For those subjects who become myopic there is accelerated eye growth and the crystalline lens seems to stop thinning, flattening and losing power (Mutti et al., 2007). Although initially, refractive status may not warrant a diagnosis of myopia per se, the refraction deviates in the negative direction from that observed in the population that will remain emmetropic, a condition that has been termed pre-myopia (Flitcroft et al., 2019). Mean instantaneous change in refraction of myopes appears to be highest in the year prior to diagnosis (Mutti et al., 2007; Xiang et al., 2012).

While changes in axial length correlate with refractive changes and a marked increase in elongation accompanies onset of myopia, the absolute value of axial length is not useful as a metric for determining onset. Curiously, myopia onset seems to occur at approximately the same mean axial length (23.85 mm) across the age range, although considerable variation exists (Rozema et al., 2019). Once an eye has become myopic according to refraction, it is at risk of progressing to greater degrees of myopia; however, absolute value of axial length is also not especially useful in predicting the risk of accelerated progression.

The refractive criterion for high myopia is a somewhat arbitrary benchmark with multiple values having been proposed (Flitcroft et al., 2019). While categorization of high myopia is usually tied to refractive error, axial length has also been used as a threshold, with 25.5, 26.0 and 26.5 mm being most commonly used (Curtin and Karlin, 1970; Grossniklaus and Green, 1992; Silva, 2012; Ohno-Matsui, 2016; Tideman et al., 2016; Flitcroft et al., 2019). Exponential increase in risk of MMD with each dioptre increase in refractive error or millimetre increase in axial length makes a cutpoint even more arbitrary (Brennan, 2015; Bullimore and Brennan, 2019).

In summary, for categorization of refractive state and understanding processes associated with myopia onset, refractive error is clearly preferred. Nonetheless, once myopia is established and the requirement is to monitor progression, measurement of axial length by low coherence partial interferometry emerges as the definitive yardstick, as explained in sections 3.4 to 3.9.

3.4. Relation to disease risk

Despite the clear value of refraction as a guide to the onset of myopia, most experts agree that increasing axial length is the principal risk factor for myopia-associated pathology. This is a widely held belief rather than an evidence-based finding and tends to be based on associations observed in studies and logical extrapolation rather than direct causal attribution. There are numerous examples that correlate pathological myopic changes with increased axial length. In clinic-based investigations, Curtin and Karlin (1970) reported that the prevalence of posterior staphyloma increased from around 1% to over 70% of eyes as axial length increased from around 27 mm to over 33.5 mm and Gözüm et al. (1997) reported that chorioretinal atrophy, Fuchs' spot and posterior staphyloma increased significantly with axial length. In a population-based study, Numa et al. (2018) observed that only one percent of eyes with axial length of less than 26 mm had posterior staphyloma compared with nearly 50% of eyes longer than 28 mm. Studying the pathomorphology of the macular in a series of enucleated highly myopic eyes, Jonas et al. (2013) observed macular Bruch's membrane defects in some eyes, associated with complete loss of retinal pigment epithelium and choriocapillaris. In multivariate binary regression analysis, the presence of these defects was highly statistically significantly ($p < 0.001$) associated with axial length alone. Longer axial length has also been independently associated with an increased prevalence of open angle glaucoma (Perera et al., 2010; Kuzin et al., 2010) and posterior subcapsular cataract (Wong et al., 2003).

However, it is the association between MMD and axial length that has been best characterised. The most serious complication of myopia, MMD "is the only leading cause of blindness without an established treatment and therefore leads to inevitable loss of vision in some myopes, even at a young age" (Bourke et al., 2019). Grading of MMD has been systematised by an expert panel, leading to improved definition of the association with risk factors (Ohno-Matsui et al., 2015), although we do note that such classification is subject to ongoing modification (Ohno-Matsui et al., 2016; Ruiz-Medrano et al., 2019). Multiple studies link prevalence of MMD with axial elongation (Gao et al., 2011; Asakuma et al., 2012; Choudhury et al., 2018; Wong et al., 2018; Bikbov et al., 2020). Of these, three performed multivariate analysis of risk factors for MMD (Gao et al., 2011; Asakuma et al., 2012; Bikbov et al., 2020). In all cases, axial length and not refractive error remained in the final model.

To examine the role of axial length and spherical equivalent on visual impairment, which serves as an index of combined morbidity of all complications of myopia, Tideman et al. (2016) analysed population-based data from multiple large studies as well as case-control data from a third study. When axial length and spherical equivalent were both added to a logistic regression model, axial length had a significant association with visual impairment (OR, 1.46; 95%CI, 1.09–1.97) whereas spherical equivalent did not (OR, 0.98; 95% CI, 0.86–1.10). These findings may simply reflect collinearity between axial length and refractive errors and/or superior sensitivity of interferometric measurement of axial length over refraction (see section 3.6), but this does not diminish the advantage of axial length as a metric to measure risk of myopia-related eye disease. In a recent study investigating molecular processes associated with prevalence of non-neovascular MMD, Wong et al. (2019) could not identify a primary contributory species, leading them to tentatively attribute a causal effect of axial elongation on MMD.

It is notable that retinal pathologies also occur in some eyes with unexceptional axial length while other elongated eyes remain pathology free (Wang et al., 2016). As we note in section 1.2, some researchers have proposed a genetic basis for this observation. Another explanation is that there is an interaction between axial length and refractive error in risk of MMD. The reasoning is that individuals with larger stature generally have bigger eyes (Saw et al., 2002; Yamashita et al., 2019; Ye et al., 2019), meaning that their axial length may be longer before

pathology arises. It is expected that a 'larger' eye would have lower refractive error at a given axial length. For example, we calculate that 60% of females, but only 38% of males, are myopic for axial length of 24 mm or greater (from Tideman et al., 2018). Similarly, one may hypothesize that individuals with lower levels of myopia at a given axial length may be at less risk of MMD. Multivariate analyses showing axial length is sufficient to model MMD without refractive error perhaps suggest that this is not the case. Yet, we are unaware of any papers that have subjected this proposition to serious scrutiny by testing for an interaction between axial length and refractive error on pathological changes.

This review of risk factors for myopia-related disease identifies axial elongation as the principal candidate. Given this premise, inhibition of this elongation is considered the primary means of minimising risk of myopia-associated pathologies (Walline et al., 2018; Wildsoet et al., 2019).

3.5. Treatments can influence refractive error independent of axial length

Treatments for myopia control can induce changes to refracting components of the eye independently of axial length, meaning that change in refractive error is not always a suitable index to track progression and risk of myopia-associated pathologies. In particular, orthokeratology and atropine are susceptible to such impact.

3.5.1. Orthokeratology

Orthokeratology both temporarily reduces or eliminates myopia (Carkeet et al., 1995; Dave and Ruston, 1998; Swarbrick et al., 1998; Fan et al., 1999; Nichols et al., 2000; Rah et al., 2002) and slows progression (see multiple references in Table 1). Temporary reduction is achieved by flattening the central cornea – achieved by central thinning and mid-peripheral thickening of the corneal epithelium – during overnight wear of specially designed rigid contact lenses by an amount that neutralizes refractive error. Bullimore and Johnson (2020) recently published a review of the changes in the optical components and mechanisms underlying orthokeratology. The procedure leads to temporary, complex changes in optics of the cornea that remain while treatment is continued. While it is possible to undertake a washout period by removing orthokeratology treatment for a short period to assess refractive shift, there is also potential for persistent corneal shape changes on removal of treatment that prevent refraction from being an accurate indicator of progression. Myopia control with orthokeratology is therefore exclusively assessable by measurement of axial elongation. It should be noted that small reductions in corneal epithelial thickness and anterior chamber depth associated with orthokeratology may favourably bias efficacy estimates with this intervention, but these influences should be small (Bullimore and Johnson, 2020).

3.5.2. Pharmaceuticals

Pharmaceutical treatment can also influence refractive progression in a manner that does not show normal correlation with axial elongation. Recently, considerable interest has been shown in use of low-concentration (often termed 'low-dose') atropine (0.01%) for myopia control. Most studies of low-concentration atropine have measured refraction alone and noted a reduction in progression (Clark and Clark, 2015; Diaz-Llopis and Pinazo-Duran, 2018; Joachimsen et al., 2019; Larkin et al., 2019; Sacchi et al., 2019). Studies that measured axial length (ATOM2 and LAMP) did not find a significant reduction in axial elongation despite slowing of refractive error change (Chia et al., 2012; Yam et al., 2019). The ATOM2 study was confounded by absence of a concurrent placebo-control group (Chia et al., 2012). Difference in techniques used to measure axial elongation between the test group (interferometry) and the historical control group (ultrasound) is also sometimes mentioned as an explanation for the disparity; however, there is no reason to believe that ultrasound measurement of change in axial length is any less valid than interferometry despite its obvious inferiority with respect to repeatability (see section 3.6). The LAMP study design was more robust, although questions remain about the stability of low-concentration atropine in solution and the adequacy of precautions in this study to address this concern (Yam et al., 2019). To date, there are no peer-reviewed, controlled, randomised studies demonstrating effectiveness of low-concentration (0.01%) atropine for slowing axial elongation to our knowledge, despite this therapy being reported as the most popular modality among paediatric ophthalmologists in a recent survey (Zloto et al., 2018). Currently, it appears that 0.01% atropine provides little more than a moderate slowing of refractive progression or, in effect, a partial correction. Similarly, in the USA-based study of 2% pirenzepine ointment for myopia control, a significant effect was found for slowing refractive progression but not axial elongation (Siatkowski et al., 2008), although use of the less-repeatable ultrasound biometry for measuring axial length in that study may have contributed to the failure of differences to reach statistical significance.

The apparent discrepancy in refractive error change and axial elongation in these studies leads to the conclusion that the relation between the two is confounded by use of atropine. To examine this possibility, we plotted refractive error change versus axial elongation for studies in which progression was tracked among subjects wearing spectacles alone and from studies where atropine was used (see Fig. 1). Best-fit slopes of the two lines differ substantially with the slope for untreated spectacle wearers being −2.05 D/mm and that for studies using atropine being −0.83 D/mm. While the robustness of some of the studies where atropine was used may be questioned, the potential for disparity in the relationship remains and reinforces the value of axal length measurement over refractive error.

The logical explanation for our observation is that atropine results in changes to anterior optical structures of the eye. As well as use of atropine drops, study protocols required cycloplegia in both untreated and treated arms prior to refraction measurement in the studies of both Chia et al. (2012) and Yam et al. (2019) to ensure masking. Depth of cycloplegia is known to be affected by type and dosage of drug as well as duration after instillation (Auffarth and Hunold, 1992; Mutti et al.,

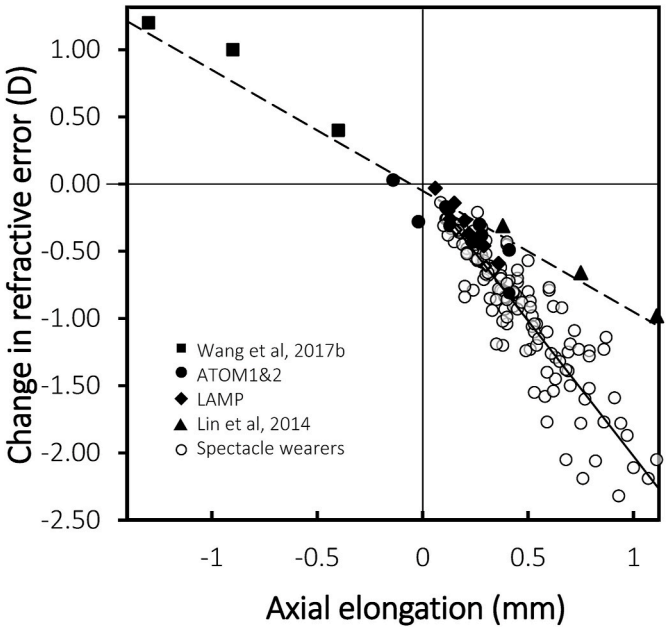

Fig. 1. Refractive error change versus axial elongation for studies where progression was tracked among subjects wearing spectacles alone (open circles, references available on request from authors), or where subjects were treated with atropine (closed symbols), showing difference in the relationship with atropine use (References – ATOM1&2 Chua et al., 2006; Chia et al., 2012: LAMP Yam et al., 2019; Lin et al., 2014; Wang et al., 2017b).

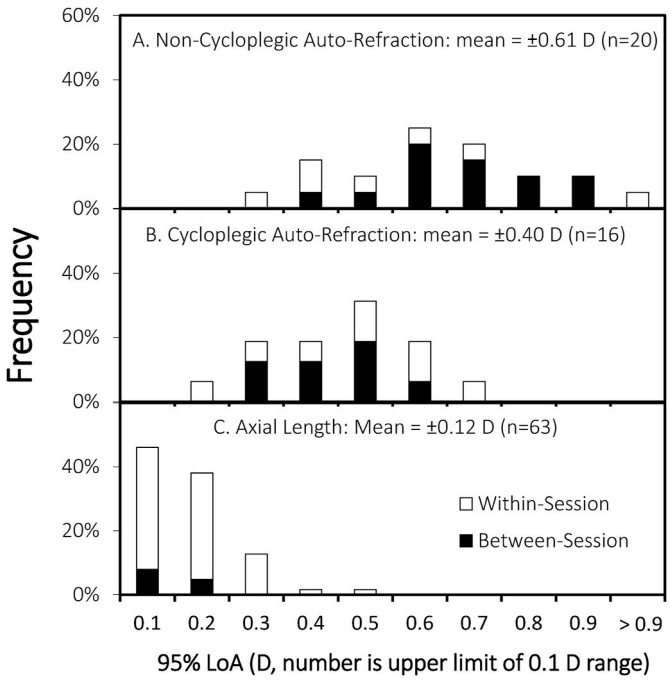

Fig. 2. Distribution of LoA for auto-refraction without and with cycloplegia and optical biometry from published studies. LoA for biometry are derived from axial length measurements converted to dioptres using the ratio of 2.5 D/mm. Interferometric biometry is clearly much more repeatable than auto-refraction.

1994; Yoo et al., 2017). These factors may come into play in these trials leading to an extreme cycloplegia in treated eyes thereby producing apparent reductions in refractive progression in the absence of corresponding reduction in axial elongation.

3.5.3. Single vision soft contact lenses

Reports also suggest that wear of soft contact lenses can lead to changes in refractive progression (Dumbleton et al., 1999; Szczotka, 2004; Blacker et al., 2009; Severinsky, 2016). While these changes were initially hypothesised to be associated with hypoxic corneal oedema induced by overnight wear of hydrogel contact lenses, the magnitude of the likely optical effect cannot explain the changes (Cheng et al., 2018). A mechanical aetiology, through corneal curvature changes associated with stiffer modulus silicone-hydrogel materials, is the more likely candidate (Szczotka, 2004; Blacker et al., 2009; Severinsky, 2016). Different optics of silicone-hydrogel lenses used in the early trials, whereby they were designed with reduced negative spherical aberration compared to hydrogel lenses (Wagner et al., 2015), may have also played a role in disparate refractive progression. Such changes are likely to be relatively small but are, nonetheless, of the order of magnitude of reduction in progression that is achieved during medium term (say, one- or two-year) myopia control studies and, so, should not be discounted. The confounding effects of soft lens wear can, to a certain extent, be mitigated by having the untreated group wear lenses of the same material (Chamberlain et al., 2019).

3.5.4. Summary

Myopia control treatments, despite beneficial influence on axial elongation, have the potential to alter the anterior optics of the eye. This can result in changes to refractive error that are not solely due to axial elongation. Intuitively, reductions in refractive progression created by such changes will not be accompanied by reduced risk of myopia-related diseases. One may also expect some of these changes to be reversible on removal of the myopia control treatment. While such effects are well accepted for orthokeratology with respect to the corrective nature of that treatment, the same cannot be said for low-concentration atropine as it continues to be the myopia control treatment method of choice for paediatric ophthalmologists. The confounding effects strongly steer the argument about preferred endpoint for tracking myopia progression to axial elongation.

3.6. Sensitivity

Measurement of axial length by optical low-coherence interferometry is relatively more sensitive than refractive error measurement by a factor of greater than three. To quantity this, a comprehensive literature search was conducted on repeatability of refractive error measurement by auto-refraction and repeatability of axial length measurement by optical, interferometric techniques. For auto-refraction, the following search terms were used in PubMed: (repeatability or reproducibility or precision) and (autorefractor or auto-refractor or automated refraction). Likewise, for axial length, the following terms were used: (repeatability or reproducibility or precision) and (axial length). The search was supplemented by searching for papers citing early, seminal papers on repeatability of auto-refraction (McBrien and Millodot, 1985; Zadnik et al., 1992; Rosenfield and Chiu, 1995; Bullimore et al., 1998) and optical biometry (Lam et al., 2001; Santodomingo-Rubido et al., 2002; Sheng et al., 2004; Buckhurst et al., 2009).

Abstracts of the resulting 194 papers on auto-refraction were reviewed and those evaluating photo-refraction, smart phone or hand-held devices excluded along with non-English sources. A total of 56 papers that appeared to have assessed repeatability of auto-refraction were reviewed in more detail. Papers were excluded that used correlation coefficients, assessed validity alone, or contained no new data. These were pared down to 25 from which estimates of repeatability, expressed as 95% limits of agreement (LoA), could be confidently extracted. Of 25 papers, two assessed two different instruments, so 27 estimates of repeatability were available: 11 without cycloplegia, 4 with cycloplegia, 9 with both, 3 on pseudophakic eyes. The most frequently evaluated devices were the Grand-Seiko/Shin Nippon models (8), Nidek (8), and Canon (5).

Fig. 2a and b shows the distribution of LoA for auto-refraction without and with cycloplegia, respectively. Mean LoA without and with cycloplegia are ±0.61 D and ±0.42 D, respectively. Data are shown separately for estimates based on within- and between-session comparisons. There is no difference between the two sets of estimates of LoA. For example, with cycloplegia, five within-session estimates average ± 0.41 D, compared with ±0.37 D for eight between-session estimates.

Abstracts of 446 papers on axial length measurement were reviewed and those evaluating only ultrasound or using IOL power or surgical outcomes were excluded along with non-English sources. A total of 108 papers that appeared to have assessed repeatability of axial length by optical means were reviewed in more detail. Papers were further excluded that used correlation coefficients, only assessed validity, or contained no new data. These were pared down to 49 from which estimates of repeatability, expressed as 95% LoA, could be confidently extracted. Of 49 papers, 12 assessed at least two different instruments, such that 63 estimates of repeatability were available: 54 without cycloplegia, 4 with cycloplegia, one with both, and four on pseudophakic eyes. The most frequently evaluated devices were the Zeiss IOLMaster (11 papers with the 700 model and 18 with earlier versions) and the Lenstar (Haag-Streit, Bern, Switzerland) (15 papers).

The mean of the LoA for axial length across all 63 estimates is ±0.050 mm (range 0.001–0.194 mm). To allow comparison with auto-refraction, LoA for axial length were converted to dioptre equivalents by assuming that 0.10 mm axial elongation corresponds to 0.25 D change in refractive error. This is based on the Gullstrand no. 1 model eye (Schulle and Berntsen, 2013) and supported by recent three-year longitudinal data on myopic children (Chamberlain et al., 2019).

Fig. 2c shows the distribution of LoA for optical biometry. The mean of the LoA is ±0.12 D. Data are shown separately for estimates based on within- and between-session comparisons. There is no difference

between these two sets of estimates of LoA. With cycloplegia, 55 within-session estimates average ± 0.13 D, compared with ±0.11 D for eight between-session estimates.

While data are not shown, cycloplegia appears to have little effect on repeatability of axial length measurement. Fifty-four of the 63 estimates were obtained without cycloplegia, with a mean of ±0.12 D. Five studies that used cycloplegia have an average LoA of ±0.13 D. Only one study compared repeatability of axial length measures without and with cycloplegia and present data for two examiners (Sheng et al., 2004). For one examiner, LoA improved from ±0.09 to ±0.06 mm with cycloplegia and, for the second, LoA are ±0.08 mm for both conditions.

As can be seen from Fig. 2, repeatability of axial length measurement by optical biometry is far superior than that for auto-refraction, even when cycloplegic is employed. LoA for axial length are less than a third of those for auto-refraction. This has a number of ramifications. For planning clinical trials, improved measurement repeatability means smaller sample sizes. For management of an individual patient, progression, and effect of any intervention, can be assessed more precisely.

Most of the above studies were conducted in adults. Four of the 25 papers reported estimates of auto-refraction repeatability in children. All assessed repeatability with cycloplegia and two also reported measurements without cycloplegia. Mean LoA with and without cycloplegia were ±0.55 D and ±1.04 D, respectively. Likewise, four of 49 studies on repeatability of axial length measurement evaluated children with average LoA of ±0.12 D. In summary, the overall superiority of optical biometry over auto-refraction extends to children.

The excellent repeatability of axial length measurement is restricted to interferometric techniques with 95% LoA for ultrasound being 3 to 6 times larger, when repeatability has been assessed in adults (Goyal et al., 2003; Sheng et al., 2004; Hussin et al., 2006; Shen et al., 2013). In children, the disparity is even greater. Carkeet et al. (2004) compared the IOLMaster with ultrasound (Echoscan 800, Nidek, Tokyo, Japan) in 179 children. Repeatability of the IOLMaster was better by a factor of almost 20 (95% LoA = ±0.043 vs. ±0.76 mm).

Finally, it is important to note that in 20 years since the introduction of interferometric axial length technology, performance has improved. The IOLMaster 700 incorporates swept-source optical coherence tomography and ten studies that have evaluated its repeatability report mean LoA of ±0.024 mm, equivalent to ±0.06 D.

3.7. Ratio of axial elongation to refractive error change

Although change in refractive error and axial elongation correlate strongly within cohorts, the ratio between the two metrics is not necessarily constant across age or axial elongation. Two different scenarios are at play here. The first is a phenomenon which has been termed ‘physiological’ eye growth. Mutti et al. (2007) observed average elongation of the eye of about 0.1 mm/y in 6- to 14-year-old emmetropes. Since emmetropia is maintained, axial elongation occurs without significant change in refractive error in this population, hence, the term physiological eye growth. Similarly, Tideman et al. (2018) reported growth at 0.19 mm/y in nine-year-old emmetropes, although the latter was associated with a small drift in refractive error. Refractive stability in these growing eyes is maintained by compensatory changes in anterior eye optics. Most notably, the crystalline lens loses power by thinning and flattening (Mutti et al., 2007, 2012; Rozema et al., 2019), a change which has been observed to continue during teenage years (Hagen et al., 2019). While eyes destined to become myopic show similar changes prior to myopia onset (Mutti et al., 2012; Xiang et al., 2012; Rozema et al., 2019), crystalline lens power loss was reported to cease abruptly at myopia onset by Mutti et al. (2012). If this observation is correct, a physiological component to eye growth is not realistic in myopes, given that there is relatively little change in corneal power during myopia development. Longitudinal observations of Rozema et al. (2019) and a cross-sectional study by Xiong et al. (2017b) tend to be consistent with the findings of Mutti et al. (2012), although the transition in their studies was observed to be more gradual. In contradiction to the findings of Mutti et al. (2012), Xiang et al. (2012) reported that the crystalline lens continues to lose power at the onset of myopia. Certainly, some researchers believe in physiological eye growth in myopes although we are unable to identify any peer-reviewed references that validate this belief. Since annual eye growth tends to slow as children get older (Twelker et al., 2009; Brennan et al., 2018b; Hou et al., 2018; Tideman et al., 2018; Sanz Diez et al., 2019), the contribution from putative physiological growth would be expected to decrease with increasing age. Overall, the net result is that the eye may enlarge from both normal growth and myopic progression with proportionate contribution from each component varying with age.

The second factor relates to optics. As well as being negatively correlated, axial length and refractive error are inversely related. Assuming constant power of the anterior optical components of the eye, a unit change in axial length requires a decreasing shift in refractive error as eye size increases, and, correspondingly, a unit increase in myopia necessitates increasing change in axial length. For example, a value of 2.7 D/mm is commonly used as a conversion between dioptres and millimetres for eyes of around 23 mm axial length. The ratio can be calculated to be less than half of this for an eye of 30 mm in length if anterior eye optics are unchanged. Age and stature are confounders in the relationship between refractive error and axial length as eyes of older and taller individuals will tend to be larger for a given degree of refractive error. Differential impacts of potential physiological growth and optical realities of eye growth on the refractive progression/axial elongation ratio have not been clearly elucidated.

To further confuse the issue, analyses conducted to quantify the ratio between refractive change and axial elongation suffer methodological challenges. Three main approaches have been taken. First, the best-fit line in scatterplots of refractive progression versus change in axial length approximates this ratio. Simple linear regression (also termed OLS or ordinary least-squares regression) has been used to estimate this slope (see, for example, Hyman et al., 2005). In theory, the intercept might also be used to assess physiological growth, assuming it is constant across the progression range. Although commonly applied, this type of regression assumes that all measurement variance lies in the ‘y’ variable and relies on ‘x’ values being true measures, that is, free of random error. Such an assumption may be violated in this application since both refraction and axial length measurements are subject to measurement variance, meaning simple regression is not an appropriate method of analysis for this purpose. Derived ratios will suffer from attenuation bias, with the magnitude contingent on which variable is designated as the dependent variable and which measurement system is used. Our review of LoA in Section 3.6 suggests that, if axial length measured by low-coherence interferometry is used as the x-variable, the slope and intercept from simple regression can provide acceptable estimates of the ratio between change in refractive error and axial elongation (the slope of the best-fit line) and physiological eye growth (the x-intercept), respectively. Analyses using ultrasound biometry or refractive error as the x-variable do not provide accurate estimates. A procedure widely known as Deming regression (also termed “total least-squares” or “errors in variables” regression) can be used to account for observations where there is error in both x- and y-variables (Adcock, 1878; Madansky, 1959; Cornbleet and Gochman, 1979). To our knowledge, such correction has not been applied to date in relating refractive change to axial elongation.

The second approach is to calculate the ratio directly from mean changes in refractive error and axial length in longitudinal studies. For example, in the study of Lam et al. (2019), refractive error and axial length changed over two years on average by −0.85 D and 0.55 mm, respectively, in the untreated group, yielding a ratio of −1.55 D/mm. This approach precludes the possibility of directly accounting for physiological eye growth (the underlying assumption being that there would be 0 mm change in axial length for 0 D change in refractive error). In the presence of such growth, the ratio would falsely be observed to

vary depending on extent of myopic progression and axial elongation. A correction obtained from another source would need to be applied, weakening validity of the estimation.

Third, scatterplots of refractive error versus axial length have been constructed from cross-sectional, as opposed to longitudinal, studies (Carroll, 1981; Atchison et al., 2004; Cruickshank and Logan, 2018). The ratio so derived is assumed to match that between change in refractive error and axial elongation during progression. The artifact noted above, in which account should be made for measurement error of the 'x' variable by Deming regression, applies here. But, in addition, there is a characteristic ledge in the curve relating refractive error and axial length at the peak of the refractive error distribution curve, that is, at low hypermetropic values (see Fig. 1 of Tideman et al., 2018). The estimate of the ratio so derived would therefore be dependent on the refractive error distribution under study.

This discussion exposes confusion in directly and accurately predicting axial elongation from refractive change, despite their generally strong correlation. An important upshot is that refractive change may not be linear with axial elongation across the range of axial length, across age and consequently over the long term. While odds of MMD tend to be exponentially related to both refractive error and axial length (Wong et al., 2018), discussion in section 3.4 leads to the conclusion that axial length is the more important risk factor. Given the additional poorer sensitivity of refraction measurements, use of refractive error as a proxy for eye length in estimating risk for MMD is evidently an inferior option.

3.8. Practicality

At some level, all eyecare practitioners can measure refraction. While all centres that perform cataract extraction have instrumentation to measure axial length, most optometry and paediatric ophthalmology practices do not. Ideally, all practitioners engaged in myopia control should obtain optical biometry equipment. Those who do not should keep in mind the limitations of refraction measurement outlined here and in section 8. Optimal refraction measurement in children requires cycloplegia, as variability is 50% higher without it (see section 3.6 and Fig. 2). Auto-refraction avoids examiner bias and is more repeatable that subjective refraction (Zadnik et al., 1992). For example, Bullimore et al. (1998) reported repeatability data on 86 subjects, aged 11–60 years, who were examined by two clinicians during one visit. Mean difference between auto-refractor readings, taken by two different optometrists, was +0.02 D with 95% LoA of −0.36 to +0.40 D. Mean difference between subjective refractions of the two clinicians was −0.12 D with 95% LoA of −0.90 to +0.65 D. In other words, auto-refraction is more repeatable by a factor of two. Moreover, two clinicians with identical training and following a uniform protocol differed by one-eighth of a dioptre. While subject to minor differences in choroidal thickness, valid and repeatable axial length measurements can be achieved with or without cycloplegia. This allows the attractive option of more frequent measurement and thus a greater capacity to monitor progression and efficacy of treatments.

3.9. Some matters of confusion around use of axial elongation

There are suggestions that a contribution from physiological growth of the eye, as discussed in section 3.7, may confound interpretation of axial elongation. Given that the same correction would be applied to treated and untreated groups, subtraction of this component of elongation certainly leads to calculation of greater percentage estimates of efficacy, which may be a motivator for this approach. For example, if a control group progressed by 0.4 mm and a treated group by 0.2 mm over a certain time period, then a treatment effect of 50% would be calculated. If allowance for physiological growth of, say, 0.1 mm over this time period is made, then the apparent growth attributable to myopic progression is 0.3 and 0.1 mm, respectively and the percentage treatment effect might be calculated as 66%. Such an approach tends to be more theoretical than material as both treated and untreated eyes are expected to be subject to the same influence and there is no evidence to the contrary. The endgame of myopia control is simply to reduce axial elongation to the maximum extent that is practically feasible and the source of that growth, whether associated with refractive progression or not, is ultimately of little consequence. Furthermore, as will be demonstrated in section 4, use of percentage reduction in progression is a flawed approach to considering efficacy.

Another uncertainty that has been raised about using axial length as the primary metric for myopia progression is that variations in choroidal thickness might negatively impact interpretation. Choroid, being a vascular tissue with spongy texture, experiences alterations in thickness under a variety of influences, including circadian rhythm, visual stimuli and pharmaceuticals. Interferometric techniques measure axial length from the anterior cornea to the pigment epithelium and, as such, will reflect choroidal thickness change in approximate antiphase. First, the magnitude of these changes is an order of magnitude smaller than the myopia control effect that is thought to be clinically important and therefore of little realistic impact. For example, Chakraborty et al. (2011) reported mean diurnal change in choroidal thickness of 0.029 (±0.016) mm in young adults. As expected, axial length underwent significant change as well (0.032 ± 0.018 mm) (Chakraborty et al., 2011). The majority of variation occurred during nighttime with daytime variation measured to be around 0.01 mm. Imposed optical defocus can also influence choroidal thickness with corresponding change in axial length measurement, but the average maximum effect does not exceed 0.013 mm (Read et al., 2010). Clinically significant reductions in axial elongation might be of the order of at least 0.1 mm, substantially larger than the observed fluctuations. Thus, choroidal thickness change is only minor consideration in using axial length as the preferred metric for monitoring myopia progression. Influence of choroidal thickness changes can also be minimised by taking measurements at a consistent time of day.

Second, not only does the choroid change thickness on a diurnal basis and in response to certain stimuli, refractive error is also a moving target. One might expect changes in refractive error to correspond directly to those observed in axial length, since retinal receptors will move in unison with the retinal pigment epithelium as choroidal thickness changes. If this was the case, refraction would be expected to be more hyperopic (by about 0.083 D) in the evening when axial length is at its shortest (Chakraborty et al., 2014). Nonetheless, refractive changes corresponding to variation in choroidal thickness have not been reported to our knowledge, presumably because of the poorer repeatability of such measurement. Furthermore, spherical equivalent refraction has been found to follow a substantial, independent diurnal pattern, being more myopic later in the day by an average of 0.37 (±0.15) D compared to the morning (Chakraborty et al., 2014). These diurnal changes in refraction clearly dwarf relative changes observed in axial length and therefore must arise from circadian changes in other ocular optical components, such as cornea (Read et al., 2005) or crystalline lens.

In summary, neither physiological eye growth nor variations of choroidal thickness detract from the use of axial length as the primary outcome to measure myopia progression. If anything, these considerations emphasise the superiority of this metric over refractive error.

3.10. Summary and discussion

Axial elongation was identified as the preferred primary endpoint measurement in both the co-sponsored FDA and IMI workshops (Walline et al., 2018; Wolffsohn et al., 2019b). Indeed, Wolffsohn et al. (2019b) stated "the end goal of all clinical trials for myopia control should be reduction of axial elongation (associated with posterior pole complications) to have the greatest effect on myopic patients' health status." Although we advocate for axial elongation as the preferred endpoint of

myopia control trials, the recommendation is limited to interferometric measurement. Ultrasound measurement was a technique of some value to complement refractive error measurements prior to development of interferometric methods, but its repeatability is sufficiently poor that only general conclusions can be drawn from its use. This presents some difficulties in the following discussion since earlier studies reported axial length measurements obtained by ultrasound techniques and adds commensurate variance in analyses.

The discussion throughout section 3 decisively points toward axial length as the preferred measure for assessing myopia progression. The supplementary question then is whether refractive error should be considered as a co-primary endpoint. There is some merit in this proposal as refractive error defines myopia and, perhaps more importantly, the degree of uncorrected visual disability. Further, equipment to measure axial length may not be available in some practices where it is desirable to conduct myopia control. Nonetheless, superior sensitivity, conflicting data observed in atropine studies, logistical difficulty in assessing refractive state in orthokeratology, the strong link between axial length and disease development, considerable diurnal variation in refractive error measurement and other considerations outlined in this section provide compelling substantiation that axial elongation alone should be the sole primary endpoint from which to judge efficacy in clinical trials. Certainly, from our work as outlined in subsequent sections below, focussing on axial elongation alone has provided great clarity and enabled us to make major progress in interpreting the meaning of efficacy in myopia control studies.

4. Absolute or relative measure of axial length?

As noted above, treatments controlling myopia progression have been described in various ways including percentage, annualised, absolute and proportional effect. With respect to viability of using percentage values to express treatment efficacy, one pivotal question is whether fast progressors have the same percentage treatment effect as slower progressors. While the need to avoid using percentage values may be obvious to statisticians, gathering evidence that this is the case for myopia progression is not a simple matter. To assess this proposition, we tackle the question in four different ways, as follows:

(i) Investigation of standardised distributions of progression from a previously published study to test the hypothesis that progression in a group treated for myopia control is a fixed proportion of progression in an untreated group across the progression range.
(ii) Reanalysis of published results of a contralateral eye study to test the hypothesis that progression in eyes treated for myopia control is a fixed proportion of progression in untreated contralateral eyes.
(iii) Use of age as a proxy for propensity to progress and examination of progression rates by age in the trial used in point (i) to test the hypothesis that absolute treatment effect varies with age.
(iv) Comparisons of standard deviations of treated versus untreated arms from published clinical trials.

4.1. Investigation of standardised distributions

The aim of this first approach was to examine whether expression of myopia control as a percentage is a valid representation of the treatment effect in a set of data from a study previously published by some of authors of the current paper (Cheng et al., 2016). For a treatment effect to be relative across the progression range (that is, percentage treatment effect is constant), the absolute treatment effect should increase with progression rate. Specifically, we compared standardised frequency distributions of progression in eyes of myopic children that were either treated with lenses designed to control myopia progression or corrected with standard spherical contact lenses and tested the hypothesis that the slopes of the distributions for the treated and untreated groups were different (Brennan and Cheng, 2018).

Comparison of frequency distributions was made assuming progression of a subject at the *n*th percentile in the untreated group was predictive of propensity to progress of the subject at the *n*th percentile in the treatment group. Use of such a method has not been attempted previously to our knowledge. We conducted simulations separately (not shown here) to assess validity of this approach. Results of the simulations showed that the technique is feasible, providing that progression of a treated eye and a matched untreated eye have a correlation coefficient of about 0.50 or greater. In a contralateral eye study (also used in section 4.2), correlation coefficients of progression in treated and contralateral untreated eyes exceeded this value (Anstice and Phillips, 2011).

The study protocol and mean results have been presented elsewhere (Cheng et al., 2016). Briefly, myopic children were randomised to wear either control lenses – conventional, daily-disposable, soft contact lenses – or test lenses, identical to the control lenses in every aspect except that they were designed with induced positive spherical aberration. This optical approach to slowing myopia progression, that is, placement of relative positive dioptric power peripherally in ophthalmic devices while providing distance vision through paraxial correction, has been used widely in various configurations in previous experimental trials (Anstice and Phillips, 2011; Sankaridurg et al., 2011; Lam et al., 2014; Aller et al., 2016). Axial length was measured at baseline, 6 months and 12 months using optical biometry. Data from 59 and 53 subjects in untreated and treated groups, respectively, at 6 months and from 57 and 52 subjects, respectively, at 12 months were available for analysis and only data from the right eye were used. Axial elongation was calculated as the change in axial length from baseline at these timepoints. Mean (95%CI: % treatment effect) treatment efficacy, expressed as retardation of axial elongation, at 6 months and 12 months was 0.11 mm (0.07–0.16: 65%) and 0.14 mm (0.10–0.19: 39%), respectively.

Cumulative frequency tables, showing interpolated decile progression values and corresponding absolute and relative treatment efficacy estimates, were constructed for both timepoints for descriptive purposes. Standardised cumulative frequency plots were generated by applying a Gaussian transformation to the cumulative frequency, where a normalised count was the count divided by the total number of observations plus one (to provide a balanced distribution and prevent an infinite z-score). Slopes of best-fit lines of these plots were compared to assess the extent to which the treatment effect falls within a relative or absolute paradigm. Parallel best fit lines are indicative of constant absolute treatment effect across the progression range, whereas diverging lines with increasing progression demonstrate a relative treatment effect.

Table 2 presents decile cumulative frequency values for both untreated and treated groups at both timepoints along with corresponding absolute and relative treatment efficacy. Relative treatment estimates for our data set range from 217% to 24%. Visual inspection of the tables shows a trend for decreasing percentage treatment efficacy with increasing rates of progression at both timepoints and higher percentage estimates for a given decile at 6 months. Absolute treatment estimates vary between 0.08 and 0.12 mm at 6 months and 0.11–0.18 mm at 12 months, showing only minor fluctuation across the range with no clear trend being evident. For 6-month refractive error data, there is a numerically greater absolute efficacy at mid-range progression values and for 12-month refractive error data, the 70th to 90th percentile show higher values. These trends are generally supportive of a constant absolute, rather than relative, efficacy across the progression range.

Fig. 3 plots the standardised cumulative frequency for axial elongation at both timepoints. The slopes of the best fit lines evidently do not deviate in a clinically meaningful way. It is worth noting that the treatment was not found to be statistically effective for reducing refractive error progression at the 12-month timepoint in our original paper (Cheng et al., 2016).

The results of this analysis are consistent with absolute, rather than

Table 2
Interpolated decile progression values for control and treatment groups at 6 and 12 months with corresponding calculated percentage and absolute treatment effects from the study of Cheng et al. (2016).

Progression Percentile	Control Group (mm)	Treated Group (mm)	Percentage Treatment	Absolute Treatment (mm)
6 Months				
10%	0.06	−0.07	217%	0.12
20%	0.08	−0.03	135%	0.11
30%	0.12	0.00	102%	0.12
40%	0.14	0.03	75%	0.10
50%	0.17	0.07	60%	0.10
60%	0.19	0.10	50%	0.10
70%	0.21	0.12	44%	0.09
80%	0.24	0.16	33%	0.08
90%	0.31	0.18	41%	0.12
12 Months				
10%	0.19	0.07	60%	0.11
20%	0.27	0.12	54%	0.14
30%	0.31	0.14	56%	0.17
40%	0.33	0.15	56%	0.18
50%	0.35	0.18	49%	0.17
60%	0.41	0.27	35%	0.14
70%	0.44	0.29	34%	0.15
80%	0.50	0.34	32%	0.16
90%	0.57	0.43	24%	0.13

relative, treatment effect across the progression range. Providing the sample size is large enough and randomization adequate to prevent selection bias, our methodology appears to be a reasonable technique to assess the underlying nature of myopia control treatment efficacy. The assumption that progression for the subject at the *n*th percentile in the untreated group is predictive of the propensity to progress of the subject at the *n*th percentile in the treated group makes intuitive sense but would benefit from further substantiation.

Percentage values at low deciles were considerably higher for the 6-month data, with efficacy values over 100%. Values above 100% are observed when subjects in a treatment group show absolute reduction in axial length (or 'shrinkage' of the globe). Examination of the distribution for the treatment group at 6 months reveals that the slowest progressing one third of the sample population showed such reduction in axial elongation. Most of these measurements are larger than the 95% LoA for biometry described in section 3.6 and are thus considered to be legitimate. Such shrinkage has been reported previously (Chua et al., 2006; Zhu et al., 2013). This observation is a necessary condition for absolute treatment efficacy to truly apply across the progression range; those individuals whose normal progression is less than the effect size must inevitably have negative axial elongation.

4.2. Reanalysis of published results of a contralateral eye study

Investigation of standardised distributions from a single study provides evidence of absolute treatment effect across the myopia progression range as observed in section 4.1. The novelty of the approach and some uncertainty in the soundness of assumptions used in that analysis motivated us to look for further evidence. A clinical trial where myopia control intervention was applied monocularly offers the opportunity to corroborate the finding (Anstice and Phillips, 2011). Although the authors of this trial derived simple regression equations to the paired data from each of the treated and untreated eyes of subjects, this methodology does not satisfy statistical requisites for predictive purposes because of variance in measurement of the x-variable. We applied Deming regression to adjust for this effect (see Section 3.7). Progression data from untreated eyes were used as proxies for propensity to progress in treated eyes. Here, we test the hypothesis that Deming regression of these data reveals increasing treatment efficacy across the progression range (Brennan et al., 2019).

Forty myopic children wore a dual-focus soft contact lens with a central zone that corrected refractive error and concentric treatment zones that created 2 D of simultaneous myopic retinal defocus in one eye for ten months. They wore a single vision soft lens in the fellow eye as a control. The dual-focus lens was a pre-cursor to the FDA-approved MiSight® lenses (Chamberlain et al., 2019). Mean axial elongation was less with dual-focus lenses (0.11 ± 0.08 mm) than control lenses (0.22 ± 0.09 mm; $P < 0.001$) over this period, which equates to a percentage treatment effect of 50% based on the mean values. Fig. 5B of the Anstice and Phillips paper plots elongation of eyes wearing dual-focus lenses versus that of partner untreated eyes for each subject in the study. Although the correlation is moderate ($R = 0.54$, $P < 0.001$) the significant association suggests that an untreated eye can serve as an indicator for the propensity of a contralateral treated eye to progress. A line of best fit from a simple regression of the data was also plotted, further promoting the concept of a percentage treatment effect of around 50% across the progression range. As noted in section 3.7, simple regression does not provide a reliable derivation of slope when there is significant variance in 'x' values. Therefore, Deming regression was performed here with the assumption of equal variance in estimates of axial elongation in both eyes. Assumptions include independence of variance between measures and constancy of variance across the data range. For ease of visualization, a Bland-Altman plot of the between-eye differences as a function of mean elongation was also created.

Data from Fig. 5B of the above study were digitised using ImageJ and

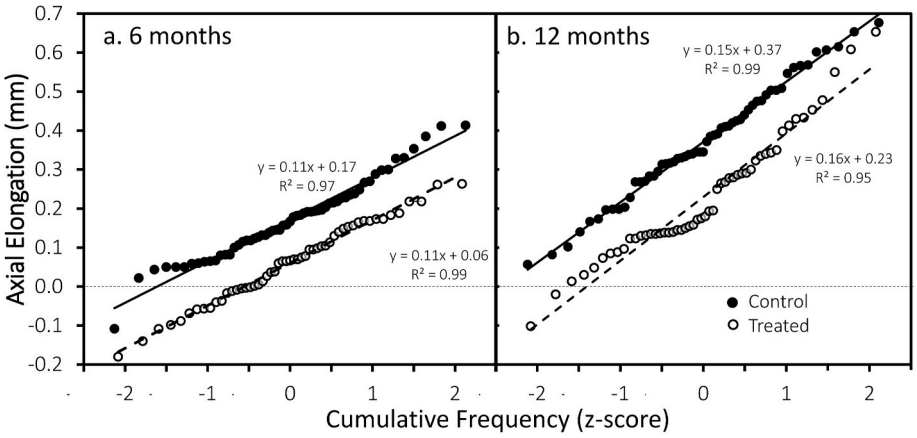

Fig. 3. Standardised cumulative frequency distribution of axial elongation for treated and control groups at (a) 6 months and (b) 12 months using data from the study of Cheng et al. (2016). The consistency of the treatment effect across the progression range demonstrates that efficacy should be expressed as absolute rather than percentage (relative) treatment effect.

a modified version of that graph is reproduced here in Fig. 4a. Deming regression was performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) and the statistical package Deming. The confidence interval for the slope was determined by bootstrapping the equation presented by Linnet (1993).

The best-fit line from the Deming regression is plotted in Fig. 4a, along with the lines of equivalence and simple regression. The slope (95% CI) was calculated to be 0.97 (0.41–1.54) and therefore not statistically different to a slope of 1. In unison, the Bland-Altman plot (Fig. 4b) demonstrates a near zero gradient. The near parallel nature of the Deming regression to the line of equivalence (and the near zero gradient of the Bland-Altman plot) demonstrate that absolute treatment effect is constant across the progression range.

The finding here is a negative result and the null hypothesis was not able to be rejected. Although contralateral trials carry limitations, this result and that of section 4.1 are consistent in their conclusion. Both analyses fail to support percentage treatment effect as a legitimate method of describing efficacy and independently point toward consistency of mean absolute effect across the progression range. Despite this, considerable variance in apparent treatment efficacy is noted across the progression range from this example. This suggests that some individuals do indeed experience greater treatment effect, but that progression rate is not a predictive factor for who may benefit most.

4.3. Use of age as a proxy for propensity to progress

Myopia progression slows with age (Saw et al., 2005; Donovan et al., 2012b; Comet Group, 2013 ; French et al., 2013; Brennan et al., 2018b). If absolute reduction in myopia progression is constant across progression rates as indicated in sections 4.1 and 4.2, then it is expected that treatment effect would also be constant across age. We tested the hypothesis that absolute treatment effect varies with age, first with our data set used in section 4.1, and then with other data available in the literature.

We analysed the impact of age on treatment efficacy using data from the study of Cheng et al. (2016). Summary details of the experimental design are described in section 4.1. Children were aged from 8 to 12 years, inclusive, and axial elongation data at 6 and 12 months were modelled. Because the rate of myopic progression decreases across time, we used log (age) as the covariate in our model. Fig. 5a and b plot progression by age at baseline for test and untreated groups at 6 and 12 months for this study. Unmodelled and modelled best-fit logarithmic regression curves are plotted for the individual groups. While axial elongation decreases with increasing age as expected, in both treated and untreated groups, consistency of the difference between treated and untreated groups across the age range is evident. By the association of age and progression rate, this observation supports the notion that interventions do not slow myopia progression on a proportionate basis but rather on a constant absolute basis across the progression range. Mixed-model regression analysis confirms that the age by treatment interaction was not significant (see Table 4 of Cheng et al., 2016).

Fig. 6a and b plot similar data from two other studies. The first is a replot of data from Fig. 1 of Santodomingo-Rubido et al. (2013), which was originally published with erroneous data for the test group. Axial elongation after 2 years is plotted by age at baseline for the test group who wore orthokeratology lenses and the control group who wore spectacles. The second data set draws on refractive error data published by the US FDA for the MiSight® pivotal study (United States Food and Drug Administration, 2019). Here mean refractive change after 3 years for the test group who wore the MiSight® lenses and the control group who wore single vision contact lenses is plotted for different ages grouped by year at baseline. In both of these examples, there is no evidence to suggest that the younger children, who can be observed to progress at a faster rate than older children, receive a greater treatment benefit. For the MiSight® data, Chamberlain et al. (2019) specifically state that the interaction of age with treatment was not statistically significant.

Other studies testing devices for myopia control in children also present data for myopia progression in treated and untreated eyes by age. Berntsen et al. (2012), while not providing data by age and not finding a large treatment effect in their study of progressive addition lenses, reported that none of age at baseline, sex, nor ethnicity interacted with treatment effect, consistent with our observation here. Hiraoka et al. (2012) plotted five-year data for groups wearing either orthokeratology lenses or spectacles by age and reported an unadjusted statistically significant effect for the interaction ($p < 0.05$). Our own digitization and analysis of this data finds the effect to be weakly significant ($p < 0.1$) when log (age) is used. Both Cho et al. (2012) and Zhu et al. (2014) plotted two-year axial elongation data from untreated and orthokeratology treated groups against age. For both studies, unmodelled linear regressions point toward decreasing treatment effect with increasing age. Nonetheless, we digitised the data from these studies, performed ANCOVA with treatment as the main factor and age as the covariate, and were unable to demonstrate that the interaction between treatment effect and age was statistically significant. Zhu et al. (2014) also divided their groups into younger and older subjects about the median to suggest better efficacy in the younger group but small changes in the cutpoint could affect their outcome considerably. For example, we digitised their data and determined that the younger and older treated groups have average elongation of 0.35 and 0.34 mm, respectively, over 2 years with the criterion of 9.9 years used by the authors. If the cutpoint is moved to 10.3 years, the average elongation is 0.41 and 0.22 mm,

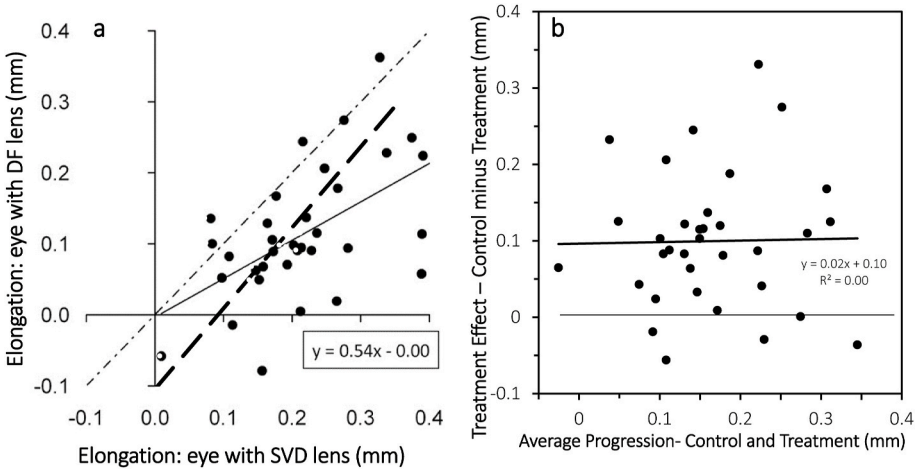

Fig. 4. (a) Reproduction of Fig. 5B from Anstice and Phillips (2011) plotting treated eye axial elongation versus contralateral control eye with overlaid white dots indicating digitised data points used for analysis. The broken line is the line of equivalence and the solid line is their simple regression. The bold broken line is the result of Deming regression showing near parallel slope to the line of equivalence and demonstrating constant absolute treatment effect across the progression range. With permission from the American Academy of Ophthalmology under licence CC BY-NC-ND 4.0. (b) Further illustration of the consistency of absolute treatment effect across the progression range using a Bland-Altman-like plot. Fast progressors are to the right and slow progressors to the left. Treatment effect is shown on the y-axis. Note the considerable stochastic variation.

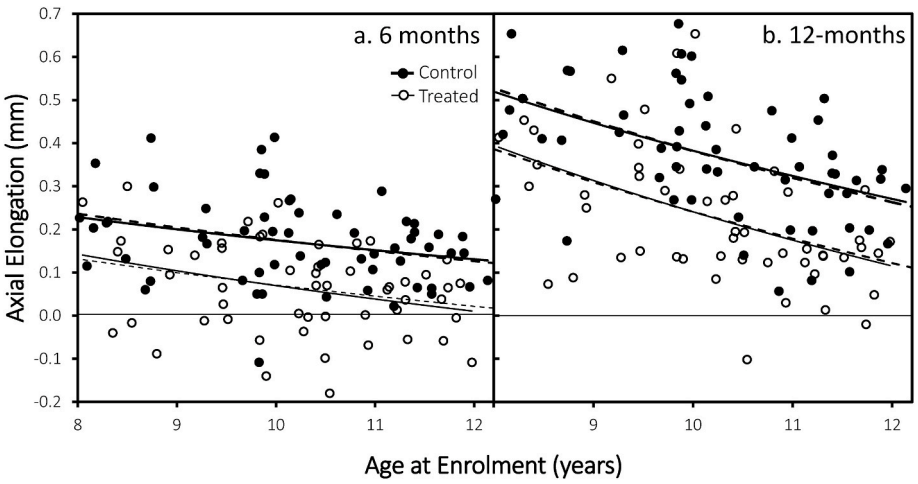

Fig. 5. Scatter plot of axial elongation at (a) 6 months and (b) 12 months in treated and control groups using data from the study of Cheng et al. (2016) by age at enrolment of the subjects. Solid lines are unmodelled best fit curves using log (age) as the dependent variable and dotted lines are modelled curves. Despite considerable variation, there is no evidence that absolute treatment efficacy varies by age.

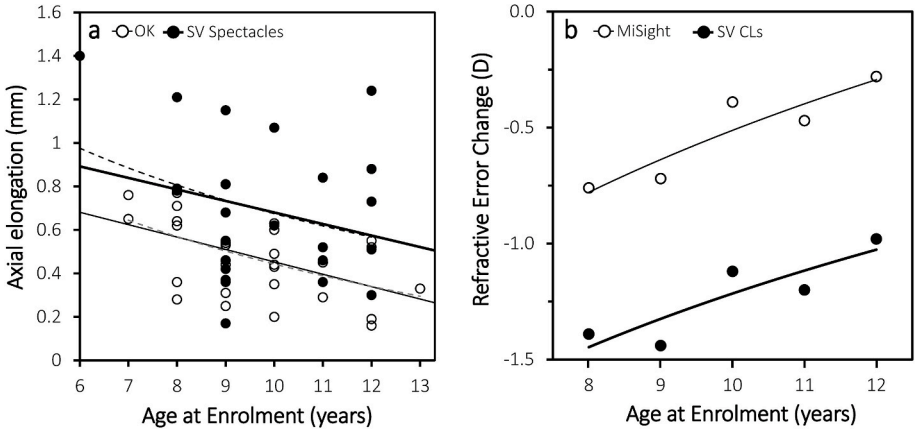

Fig. 6. (a) Scatter plot of axial elongation at two years in eyes wearing orthokeratology (OK) contact lenses or single vision spectacles (SV) by age at enrolment using data from the study of Santodomingo-Rubido et al. (2013). This is a replot of the original with corrected raw data and permission to publish kindly provided by Dr. Jacinto Santodomingo-Rubido. Solid lines are unmodelled best fit curves using log (age) as the dependent variable and dotted lines are modelled curves. (b) Mean refractive change at three years for the test group who wore the MiSight® contact lenses and the control group who wore single vision contact lenses (SV CLs) plotted against age at baseline grouped by year (United States Food and Drug Administration, 2019). For both plots, there is no evidence that absolute treatment efficacy varies by age.

respectively, a notable and important difference. Weng et al. (2019) reported two-year progression of a large sample (N = 508) of Chinese children (8–13 years old) wearing one of four different test contact lenses or single vision contact lenses, interrogating for interaction of treatment effect with age, refractive error, gender and parental myopia with a linear mixed model. None of the demographic factors significantly influenced treatment effect. Lam et al. (2020) provided scatterplots of refractive change over two years for a group using standard spectacle correction and another using Defocus Incorporated Multiple Segments (DIMS) spectacle lenses for myopia control in eFigure 1 of their paper. There was a non-significant trend toward *greater,* rather than smaller, treatment effect with increasing age.

While there is a suggestion in some of these studies that younger children, and therefore those with faster progression, may achieve better absolute efficacy than older children, the evidence is equivocal at best. An important question here is whether the absence of significant interaction between age and treatment on progression is simply a function of studies not being powered to test for this interaction. Meta-analysis of these data would be useful although this may prove difficult because of vast differences in experimental protocols between trials.

These findings again cast doubt on using percentage as an appropriate parameter for describing efficacy. For example, the data of Cheng et al. (2016), as illustrated in Fig. 5a and b, suggest that an 8-year-old could expect 20% reduction in progression after 12 months of treatment whereas an 11-year-old at 6 months derives a 75% benefitboth with the same intervention. This effect can also be observed in the other publications cited above. This finding of constant absolute but increasing relative treatment effect with increasing age helps to explain the results of Aller et al. (2016). For some time, there has been interest and intrigue over this study, which reported a treatment effect of 80% with a soft concentric-ring multifocal contact lens. On further inspection, they reported an absolute treatment effect of 0.11 mm at 6 months, the same as that observed in the Cheng et al. (2016) study at that timepoint. The high percentage efficacy reported is, at least in part, a function of the treated and untreated groups in the Aller study having considerably older mean ages (13.5 and 13.0 years, respectively) at baseline.

We have not included increased outdoor time as a treatment for slowing myopia progression in this paper, as there is some question about its efficacy and relatively few studies showing a positive effect (Xiong et al., 2017a; Deng and Pang, 2019). One study of note by Wu et al. (2018) reported myopia control among young myopes with the control group showing mean axial elongation of 0.60 mm over a year while eyes of those who were part of a program that spent increased time outdoors grew by 0.45 mm. Axial elongation over one year was therefore reduced by 0.15 mm, which is comparable in effect size to that of a number of treatments listed in Table 1 at 1-year, including SMCLs and orthokeratology (Santodomingo-Rubido et al., 2012; Chamberlain et al., 2019). Because the baseline age of subjects in this study was 6–7 years and overall progression was therefore high, percentage treatment effect

was relatively low, at 25%, despite the respectable overall reduction in axial elongation. The vastly different percentage treatment effects between Aller et al. (2016) and Wu et al., 2018 are explained, at least in part, by the age of the subjects in their studies.

Negative axial elongation above the relatively small amount that may occur with choroidal thickening implies shrinkage of the globe in some individuals (as noted above in section 4.1). This was most evident in older children. An extrapolation of this remarkable finding is that application of myopia control therapies might lead to reduction in myopia of older teenagers or young adults who show very little progression.

4.4. Analysis of standard deviations

In section 4.1, aggregate data sets of myopic progression were examined and normal Q-Q plots created. If the data of the plots in Fig. 3 are derived perfectly from a normal distribution, the slopes of these plots are the standard deviations of the distributions. Providing the assumption of normality is reasonable, such an evaluation can therefore be reduced to an analysis of standard deviations, unlocking the opportunity to test whether treatment effect is relative across a wide range of studies where subject level data are not available. For a relative treatment efficacy to apply across the progression range, the ratio of the standard deviations would need to be in proportion to the treatment effect. In this section, we conduct a meta-analysis of standard deviations from aggregate trial data to test the hypothesis that frequency distributions are consistent with the concept of relative treatment effect.

For this analysis it was assumed that all growth was positive, that growth is sufficient for frequency distributions to be well approximated by a normal distribution and that measurement error is small compared to growth (see section 3.6). The hypothesis to be tested is based on a paradigm where progression of a subject at the *n*th percentile of progression in the treated group is a constant fraction of the propensity to progress of a subject at the *n*th percentile in the untreated group. Fig. 7 presents a schematic of the different potential modes by which myopia control treatment may function. Fig. 7a portrays theoretical distributions of axial elongation for control and treatment groups where a treatment effect of 50% applies with a control group that shows axial elongation of 1.0 mm. In Fig. 7b, an absolute treatment effect of 0.50 D is depicted. Notably, the mean percentage reduction in elongation in the treated group is the same in each case but the standard deviation of the distribution is proportional to the percentage reduction in Fig. 7a, but unchanged in Fig. 7b, compared to the control group.

For the studies presented in Table 1, relative treatment effects were calculated from mean values at the final timepoints presented in the study publications by calculating the percentage reduction of progression in treated compared to untreated groups. Relative reduction in standard deviations was also calculated for these timepoints as reduction of the standard deviation in treated compared to untreated groups. If the size of the treatment effect is relative to progression rate, standard deviations for treated groups should be correspondingly smaller.

Aggregated data from the studies are presented in Table 3 in rank order of calculated percentage treatment effect. The ratio of the standard deviation in treated versus control group is also tabulated for each study. Visual inspection shows no suggestion that this ratio decreases in proportion to the treatment effect. Unadjusted mean and median reduction in progression for the studies collectively were 42.1% and 38.1%. Unadjusted standard deviations were smaller in treatment groups by a mean of 7.6% and median of 7.0%. Meta-analysis on means and log-transformed standard deviations were conducted using multi-level meta-regression models adjusting for treatment group as fixed effect. For standard deviations the log of the means was also included as fixed effect in the regression model. Pooled axial elongation mean difference (95% CI) between treated and untreated groups was −0.19 (−0.21, −0.17; $p < 0.001$), demonstrating significant treatment effects as expected. The adjusted ratio of the standard deviation ((95% CI) across groups was 1.00 (0.99, 1.02; $p = 0.56$), which does not support rejection of the null hypothesis. In summary, the meta-analysis established significant difference in means but not significant difference in standard deviations.

Consistent with the general findings of sections 4.1 to 4.3, analysis of standard deviations of myopia control studies points toward an absolute treatment rather than relative treatment effect. Examination of the distributions plotted in Fig. 3 of the paper by Chamberlain et al. (2019) are consistent with the proposition that the frequency distribution for a group treated for myopia control is merely a translation rather than compression of that for the untreated group (that is, the distributions are consistent with Fig. 7b, not Fig. 7a).

One advantage of this analysis is that it combines data from a range of studies rather than considering single studies in isolation as done in section 4.1 to 4.3 and the net result supports the interpretation from these earlier sections. We acknowledge that all of the sample set of studies showed significant treatment effect, which may introduce bias to the results. Further, lack of information as to the nature of the distributions in these other studies, that is whether they satisfactorily conform to the normal approximation, may cast some doubt about application of this approach across trials. Regardless, widespread use of means and standard deviations in the field of myopia research to describe distributions from which treatment effects are calculated, rather than medians and percentiles, as well as the use of parametric statistics as a standard statistical approach, point to an underlying assumption that the normal distribution is an acceptable approximation.

4.5. Summary and discussion

The findings of our analyses are not unique across biomedical research fields. One structured review studying health inequalities research found that 88% of abstracts reporting a quantitative treatment

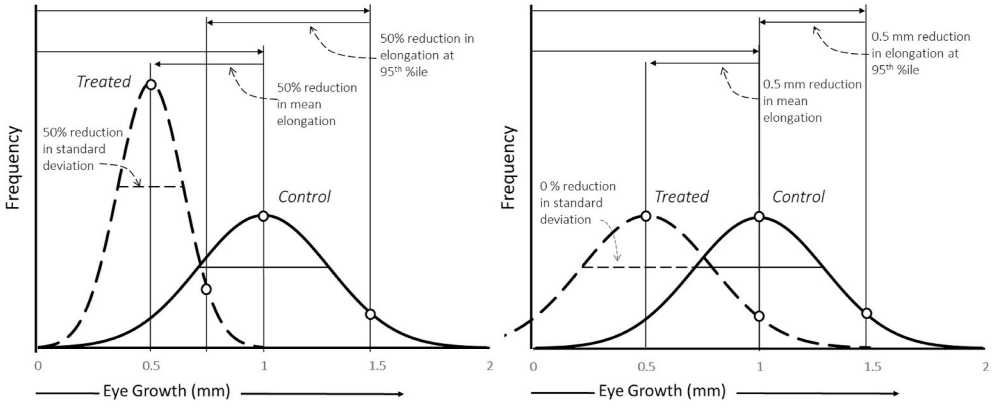

Fig. 7. Schematic of expected distributions of axial elongation where a therapy provides (a) a relative and (b) an absolute treatment effect. If all treated patients show, as in (a), 50% reduction in progression, then the distribution would be compressed and the standard deviation for the treated group would be 50% of that of the control group. If treated patients show as in (b), a 0.5 mm reduction in progression, then the distribution would simply be translated and the standard deviation for the treated group would be the same as that of the control group. Our analysis here shows that the portrayal in (b) is how myopia control treatments function.

Table 3
Mean progression and standard deviation (SDs) for treated and control groups, respectively across studies presented in Table 1. Studies are listed in order of percentage reduction in progression (%Eff). The ratio of the control group standard deviation to that of the treated group is shown. There is no apparent trend linking this ratio to %Eff, pointing away from expressing efficacy in relative terms (as shown in Fig. 7a) and towards using absolute differences (as shown in Fig. 7b).

Study	Means			SDs		
	Treated	Control	%Eff	Treated	Control	Ratio
Chua et al. (2006)	−0.02	0.38	105%	0.35	0.38	1.09
Aller et al. (2016)	0.05	0.24	79%	0.14	0.17	1.21
Charm and Cho (2013)	0.19	0.51	63%	0.21	0.32	1.52
Lam et al. (2019)	0.21	0.53	60%	0.22	0.24	1.09
Walline et al. (2009)	0.25	0.57	56%	0.19	0.23	1.21
Chen et al. (2013)	0.31	0.64	52%	0.27	0.31	1.15
Yam et al. (2019) Atr 0.05%	0.20	0.41	51%	0.25	0.22	0.88
Zhu et al. (2014)	0.34	0.70	51%	0.29	0.35	1.21
Anstice and Phillips (2011)	0.11	0.22	50%	0.08	0.09	1.13
Cho et al. (2005)	0.29	0.54	46%	0.27	0.27	1.00
Chamberlain et al. (2019)	0.34	0.62	45%	0.29	0.31	1.07
Leung and Brown (1999) 2	0.42	0.75	44%	0.31	0.38	1.23
Cho and Cheung (2012)	0.36	0.63	43%	0.24	0.26	1.08
Tan et al. (2005)	0.20	0.33	39%	0.33	0.31	0.94
Cheng et al. (2016)	0.23	0.37	38%	0.14	0.15	1.07
Paune et al. (2015) 1	0.32	0.52	38%	0.20	0.22	1.10
Ruiz-Pomeda et al. (2018)	0.28	0.45	38%	0.28	0.28	1.00
Sankaridurg et al. (2011)	0.24	0.39	38%	0.17	0.19	1.12
Kakita et al. (2011)	0.39	0.61	36%	0.27	0.24	0.89
Leung and Brown (1999) 1	0.49	0.75	35%	0.26	0.38	1.46
Cheng et al. (2014) 2	0.54	0.82	34%	0.41	0.32	0.78
Santodomingo-Rubido et al. (2017)	0.91	1.36	33%	0.63	0.63	1.00
Lam et al. (2014)	0.25	0.37	32%	0.23	0.24	1.04
Cheng et al. (2014) 1	0.57	0.82	30%	0.48	0.32	0.67
Hiraoka et al. (2012)	0.99	1.41	30%	0.47	0.68	1.45
Walline et al. (2013)	0.29	0.41	29%	0.31	0.31	1.00
Yam et al. (2019) Atr 0.025%	0.29	0.41	29%	0.20	0.22	1.10
Paune et al. (2015) 2	0.38	0.52	27%	0.21	0.22	1.05
Sankaridurg et al. (2019) 1	0.44	0.58	24%	0.29	0.27	0.93
Sankaridurg et al. (2019) 4	0.44	0.58	24%	0.25	0.27	1.08
Sankaridurg et al. (2019) 2	0.45	0.58	22%	0.29	0.27	0.93
Sankaridurg et al. (2019) 3	0.45	0.58	22%	0.28	0.27	0.96
Mean			**42.0%**			**1.076**
SD			**17.4%**			**0.180**
Median			**38.0%**			**1.070**

Table 4
Cumulative, absolute reduction in axial elongation (CARE) for various myopia control interventions listed in rank order of CARE. Bolded entries in the study design details are considered to lead to more robust studies.

Study	Tx	CARE (mm)	Study design details					
			Time (y)	Inst	Rand	LSM	N= (T,C)	Rebound
Santodomingo-Rubido et al. (2017)	OK	**0.44**	6+	**Opt**	N	N	14, 16	N
Hiraoka et al. (2012)	OK	**0.42**	5	**Opt**	N	N	22, 21	N
Leung and Brown (1999)	Specs	**0.41**	1.5	US	N	N	14, 32	N
Chua et al. (2006)	Atr 1.0%	**0.40**	2	US	**Y**	N	**166,190**	**Y**
Zhu et al. (2014)	OK	**0.36**	2	**Opt**	N	N	**65, 63**	N
Chen et al. (2013)	OK	**0.33**	2	**Opt**	N	N	35, 23	**Y***
Charm and Cho (2013)	OK	**0.32**	2	**Opt**	**Y**	N	12, 16	N
Walline et al. (2009)	OK	**0.32**	2	US	N	**Y**	28, 28	N
Lam et al. (2019)	Specs	**0.31**	2	**Opt**	**Y**	**Y**	**79, 81**	N
Chamberlain et al. (2019)	SMCLs	**0.28**	3	**Opt**	**Y**	**Y**	**48, 51**	N
Cho et al. (2005)	OK	**0.28**	2	US	N	N	35, 35	N
Cheng et al. (2014)	Specs	**0.28**	3	US	**Y**	**Y**	**46, 50**	N
Cho et al. (2012)	OK	**0.27**	2	**Opt**	**Y**	N	**37, 41**	Y*

Tx, treatment category. Inst, Instrument; Opt, optical interferometric biometry; US, ultrasound; Rand, was the study randomised; Y, yes; N, no. LSM, were the results demonstrably adjusted for confounding factors. N= (T,C), sample size in treated and control groups. Rebound, was rebound studied? *rebound was presented in Cho and Cheung (2017).

effect provided relative measures whereas only 9% offered absolute measures with just 2% reporting both (King et al., 2012). In full-text articles, 75% reported relative effects, with only 7% reporting both absolute and relative measures (King et al., 2012). The CONSORT and STROBE initiatives, both aimed at improving quality of reporting in biomedical literature, recommend reporting both absolute and relative measures of effect (Vandenbroucke et al., 2007; Schulz et al., 2010). In a task force on statistical inference, Wilkinson stated "If the units of measurement are meaningful on a practical level, it is preferable to use an unstandardised measure than a standardised measure" (Wilkinson, 1999). While the context of the statements from these initiatives may be somewhat different to myopia control treatment effect, the general principle applies.

Most papers reporting results of myopia control trials present both

absolute and relative differences, but summary clinical papers tend to use percentage treatment effect and this has become the standard way clinicians contemplate myopia control (Cooper et al., 2018; Cooper and Tkatchenko, 2018; Kang, 2018; Sankaridurg et al., 2018; Global Myopia Centre, 2019; Wildsoet et al., 2019; Wolffsohn et al., 2020). Meta-analyses provide examples of exceptions where comparative results are reported as absolute values (Walline et al., 2011; Huang et al., 2016; Li et al., 2016, 2017). The US FDA summary paper of myopia control treatments presents both relative and absolute changes (Robboy et al., 2018), and the International Myopia Institute (IMI) workshop summary paper presents a mix of both (Wildsoet et al., 2019).

Assessing the merits of relative versus absolute treatment efficacy is not straightforward. Our analysis is the first attempt to our knowledge to explore the nature of myopia control treatment across the progression range. We have used four different approaches here. Our observations indicate that reporting of relative (percentage) efficacy gives a misleading picture of treatment effect of myopia control intervention. Relative values apply to a specific sample population in terms of age and progression rate. They also apply to a specific position in the progression spectrum, usually the mean or median. Absolute treatment values appear to be robust with respect to progression rate and age but may not be constant across time (see Section 5 for elaboration), meaning that expressing efficacy as an annualised rate is also misleading. Further research is needed to ascertain whether absolute treatment efficacy is constant across ethnicities as well, although studies that have tested for this to date suggest that it may well be (Berntsen et al., 2012; Chamberlain et al., 2019).

In their MiSight® study, Chamberlain et al. (2019) stated that the "absence of significant interactions of lens type with age, sex, baseline myopia, or investigative site demonstrates that the myopia control effect is independent of these factors in this study population." This is not strictly accurate as written since the study was not necessarily powered to isolate these effects and negative results show lack of evidence to support an effect rather than proof that it does not exist. Other studies, such as Berntsen et al. (2012) and Cheng et al. (2016), are subject to the same caveat. Notwithstanding limitations of the study designs, any effect that these factors may have is likely to be modest given the lack of statistical evidence in these studies. Bearing this in mind, we reiterate that the above analyses arise from a restricted set of data, as noted in section 1.4. As noted in section 1.3, our analyses in this paper arise from studies with restricted inclusion criteria. Application of the conclusions here may not be appropriate for higher refractive errors or longer axial lengths, where different mechanisms of progression may be at play. For longer axial lengths and as a general consideration for future research, there may be a value in considering study of the change in axial length to corneal radius ratio as the outcome measure.

The observation that myopia control operates on an absolute rather than relative basis has implications for myopia management in practice. Papers that report absolute values for effect size report group means. These values provide guidance for likely treatment efficacy regardless of progression rate and age. Faster progressors including younger children, who are those most in need of treatment, will benefit less than anticipated from quoted percentage values and may receive no bigger treatment effect than slower progressors. Further research is required to fully elucidate the response to treatment across interventions and for different ages, ethnicities, refractive errors and progression rates.

From an evidence-based perspective, we find insufficient support to claim better expected treatment efficacy than the observed mean for any demographic or biometric factors. While we note that some individuals do apparently experience greater therapeutic efficacy than the observed mean based on any specific demographic, there are no predictive measures available to identify who these may be.

5. Treatment efficacy across time

5.1. Quantification of reduced efficacy with time

Another potential limitation that arises from presentation of efficacy in relative terms or in annualised terms is the assumption that results derived from limited term clinical studies can be applied across longer duration of treatment. Various calculators are available online that assume percentage treatment effect derived from short term studies endures for a decade or more (for example, the Myopia Calculator from the Global Myopia Centre, 2019). Controlled trials that run for longer than three years are uncommon, meaning that such projections are speculative.

Variation in treatment efficacy over time has been subjected to limited evaluation. In their network meta-analysis of 16 different myopia control treatments from 30 clinical trials of one-year duration or longer, Huang et al. (2016) reported that "most interventions lose their early effect in the second year, especially in protection of axial length change". They used an annualised measure of progression to make comparisons despite their own analysis showing reduced efficacy in the second year compared to the first year. Kaphle et al. (2020) conducted a systematic review and meta-analysis that was restricted to multifocal spectacle use for myopia control and concluded that "it is not appropriate to extrapolate the treatment effect observed in the first 6 months or 12 months to estimate the likely future benefit of treatment". Brennan and Cheng (2019) also presented some examples demonstrating reduced efficacy over time (see Fig. 8). Because of timing and focus, these manuscripts considered a limited number of trials. We have reviewed a more extensive catalogue of interventions demonstrating myopia control efficacy and examined time trends of treatment effect.

Studies from Table 1 with multiple timepoints were included. Different treatments were grouped as noted in section 1.3 for analysis purposes. We did not include pharmacological treatments because of dramatically different observed efficacy across the concentration range. We also note considerable variation in reported efficacies of SMCLs and spectacles but found the general patterns satisfactory for inclusion. A meta-regression using a weighted inverse variance linear mixed model with random intercept and slope was considered to model the difference in axial elongation between treated and untreated groups over time. The model was performed on the log-transformed effect size measures. Logarithm of mean age, type of treatment and logarithm of time by treatment type interaction were included in the model as fixed effects. Intercept and logarithm of time were included as random effects. An unstructured variance-covariance matrix was used to estimate the variances of the slopes and of the intercepts and the covariance between the slopes and the intercepts within each study/arm. The inverse of the sample variance of the logarithm of the axial elongation difference was used to weight each estimate.

Scatterplots for cumulative reduction in axial elongation for orthokeratology, spectacles and SMCLs and adjusted curves of best fit for each of these categories are presented in Fig. 9a. Because there ar limited data for longer periods of treatment, projections are only shown out to four years. Treatment efficacy is non-linear with time. Power functions fit the data best with the exponent approximating the square root in general. There is an initial burst of efficacy with some 31–40% of the projected four-year treatment efficacy occurring in the first 6 months and 46–54% occurring within the first year. Apparent differences in the curves should not be taken to indicate different treatment efficacies of the best performing treatments in each category.

As noted in sections 1.1 and 2.3, some authors report treatment efficacy as annual reduction of progression, expressed in D/y or mm/y, derived by averaging the reduction over multiple years. The results of our analysis here demonstrate that this approach will lead to erroneous expectations of the longer-term efficacy of such treatments. As a very general rule-of-thumb from cautious extrapolation of the data, four-year reduction in absolute progression seems to be about double that

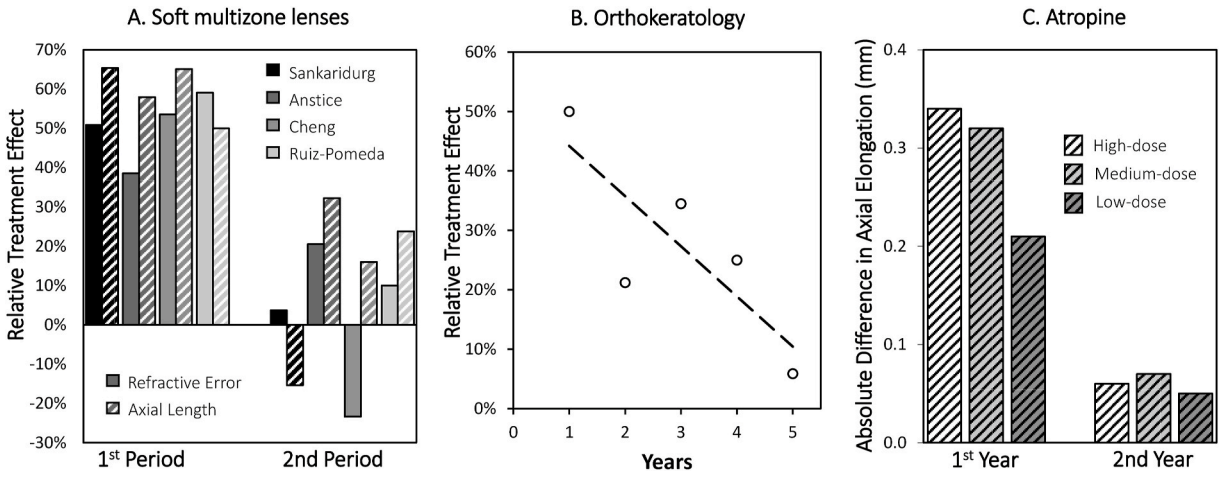

Fig. 8. Examples of reduced efficacy of investigational myopia control treatments over time shown as treatment effect during the specific time segments. (A) Relative treatment efficacy of investigational myopia-control soft lenses from 4 studies that provided data for multiple timepoints and showed over 50% reduction in axial elongation during the first period of wear. First and second periods were 0–6 months and 6–12 months for Sankaridurg et al. (2011) and Cheng et al. (2016), 0 to 5 and 5–10 months for Anstice and Phillips (2011) and first year and second year for Ruiz-Pomeda et al. (2018) (B) Relative myopia control treatment efficacy across five years in an orthokeratology investigation with yearly efficacy plotted (Hiraoka et al., 2012) (C) Absolute difference in elongation between treatment and control groups for high-dose, medium-dose, and low-dose atropine in the first and second years of treatment using data from the subgroup analysis of Huang et al. (2016). Reproduced from Brennan and Cheng (2019) with permission from the Contact Lens Association of Ophthalmologists.

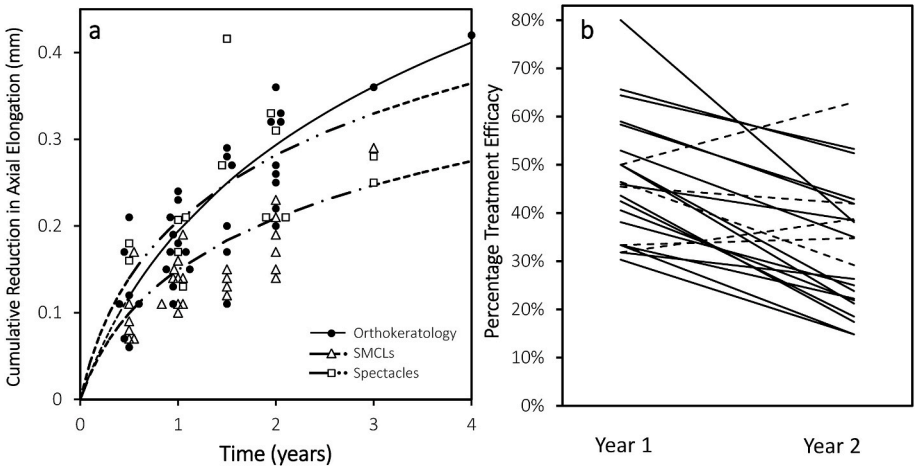

Fig. 9. (a) Cumulative absolute reduction in axial elongation for myopia control treatments with multiple timepoints listed in Table 1 by categories having at least 10 data points (orthokeratology SMCLS, spectacles). Curve fits are power functions, showing reduced efficacy across time. Apparent differences in the curves fit to the different treatment categories should not be taken as superiority of one category over another. (b) Percentage treatment efficacy for yearly intervals across myopia control treatments with one- and two-year data listed in Table 1. Not only does absolute treatment effect decrease across time, percentage treatment effect can also be observed to do the same. Dotted lines indicate where ultrasound was used to measure axial elongation. Two extremes also based on ultrasound measures are not shown– one- and two-year incremental percentage efficacy from Chua et al. (2006) were 170% and 11% and from Paune et al. (2015; SMCL2) were 7% and 50%, respectively.

observed in the first year.

The analysis presented above is based on absolute treatment effect. Since axial elongation naturally slows with time, it is reasonable to ask whether the observed reduction is simply a function of this deceleration of growth and therefore whether the relative (percentage) treatment effect remains constant across time. Fig. 9b plots the incremental first and second year percentage reductions in axial elongation for studies with relevant data from Table 1. Percentage treatment efficacy was observed to decrease in 20 of 24 eligible data sets ($p < 0.001$ by unadjusted binomial probability). Median one-year efficacy of 48% decreased to 32% in the second year. Notably, all four studies with apparent increased percentage efficacy were part of the group of six studies that had axial length measured by ultrasound. Measurement variance may in part explain why these results differ from those where optical biometry was used.

We conclude that, not only does absolute efficacy decrease with time, but that percentage efficacy also does. One theory to explain reduced percentage treatment efficacy across time is initial shrinkage of the eye as observed in section 4.1. This one-time boost to efficacy in the initial period of treatment would lead to an apparent decrease in relative treatment over time as a logical mathematical consequence. It is theoretically possible that, once the shrinkage phase has passed, a constant proportional growth rate occurs in treated compared to untreated eyes. Thus, for example, percentage effect in the second and third years of treatment might be constant. There is insufficient data available at present to test this hypothesis and further research is indicated to characterise the exact nature of the treatment versus time relationship.

5.2. *Patterns of efficacy across time of treatment*

Given that treatment efficacy decreases over time in a manner which is yet to be fully quantified, that most studies are of relatively short duration compared to the period over which myopia progresses and, indeed, that treatments are intended to be implemented for longer than the duration of the studies, there is a need to make projections of efficacy over longer periods of time. We have taken data from studies listed in Table 1 and made some preliminary observations about trends and patterns of efficacy over time.

One important preliminary observation from this exploratory analysis is considerable irregularity in efficacy for measurements at 6 and 18

months whereas data obtained at 12, 24 and 36 months follow a more regular pattern. An example of the variability of data is provided by comparing the studies of Aller et al. (2016) and Cheng et al. (2016). Both studies observed a treatment effect of 0.11 mm at 6 months. In the Aller study, this translated into a very respectable effect size of 0.19 mm at 12 months. In contrast, the effect size at 12 months in the Cheng study was 0.14 mm and the corresponding reduction in refractive progression was not statistically significant. We tentatively ascribe this phenomenon, at least in part, to seasonal effects on progression which have been widely reported (Fulk et al., 2002; Donovan et al., 2012a; Fujiwara et al., 2012; Gwiazda et al., 2014), and the improbability that subjects for studies were recruited at a uniform rate over the course of a year particularly where subjects were not randomly assigned to treated and untreated groups. Use of data obtained annually (that is, at 12, 24 and 36 months, *et cetera*) uniformly integrates growth, thereby smoothing out inconsistencies created by seasonal effects.

Of studies listed in Table 1, we included those having at least one- and two-year data and plotted cumulative absolute reduction in efficacy for each treatment out to three years where available (see Fig. 10a). Only the studies of Hiraoka et al. (2012) and Santodomingo-Rubido et al., 2017 captured data beyond three years and these are not plotted here. Observation of trends shows considerable spread of effect in the first year but a notably consistent incremental effect across studies in the second year of treatment, with that effect being generally sustained in those studies that continued for the third year. The unadjusted mean (±SE) of year one treatment for this group was 0.16 (±0.070) mm with a range of 0.02–0.34 mm of treatment effect. For year two, the unadjusted mean incremental treatment effect was 0.08 (±0.007) mm with a range from 0.04 to 0.17 mm. Notably, the study showing highest year two treatment effect used a historical control group and ultrasound measurement of axial length, increasing opportunity for random variance in the data. The second highest year two increment was 0.12 mm. In the third year, unadjusted mean incremental treatment effect was 0.07 (±0.006) mm with a range from 0.04 to 0.10 mm, although data are only available from 4 studies. These observations are noteworthy for remarkable uniformity of treatment effect after the first year, exemplified by very tight standard errors around the mean in year two and three of treatment (0.007 and 0.006 mm, respectively) compared to year one (0.070 mm). Rank order of treatment effect at years 2 and 3 is also largely conserved by virtue of this effect.

The upshot of this phenomenon is that, despite markedly different performance in the first year, interventions to slow myopia have provided notably similar treatment effect sizes in the second and third years of treatment. Fig. 10b plots incremental treatment effect in the second year against that in the first year. The unadjusted regression line does not have a statistically significant slope, leading to the quite remarkable inference that a strong first-year treatment effect does not portend a similarly strong effect in subsequent years.

The relatively small year two effect size (0.06 mm) for the treatment with greatest year one effect (0.34 mm) and the relatively large year two effect size (0.12 mm) for the treatment with smallest year one effect (0.02 mm) in our sample prompts immediate suggestion of regression to the mean. Indeed, in both cases, ultrasound was used for measurement of axial length, and low repeatability of this technique would support the proposition that regression to the mean might explain observation of uniformity in second year treatment effect. On the other hand, regression to the mean would tend to result in a negative slope of the best fit curve in Fig. 10b and that is not observed.

Because of the apparent relative consistency of effect size during the second and third years across interventions, one might assume that it is possible to predict treatment efficacy over several years based on a short study. Our investigations have led to promising progress in this direction, but lack of longer-term data have prevented us from developing a suitable model for making longer term predictions to date. The ability to project treatment efficacy over multiple years becomes urgent as time passes because retaining children untreated in a control group over multiple years while effective treatments are available is ethically unacceptable. For example, Yam et al. (2019) in their study of low-concentration atropine, reassigned children from the untreated group to a treatment group after one year for this reason. Indeed, future estimates of long-term efficacy for both clinical and regulatory purposes are likely to rely on a 'big data' approach and 'real-world evidence'.

6. Cumulative, absolute reduction in axial elongation (CARE). A proposed standard for expressing myopia control efficacy

6.1. Comparing interventions

Given that (i) axial length is the preferred metric for monitoring myopia progression, (ii) absolute efficacy is more representative than relative values for representing effect size of myopia control treatments across a range of patient factors and (iii) that efficacy of treatments decreases across time, we have converged on what we consider to be the current logical default approach to expressing efficacy; that is, the mean Cumulative, Absolute, Reduction in axial Elongation (CARE), as determined in a controlled study. This metric is not new, as it is easily extracted from studies where axial length has been measured – we are merely highlighting that it is the preferred method of expressing efficacy and the acronym can be applied to simplify its use. CARE represents an empirically demonstrated, evidence-based articulation of myopia

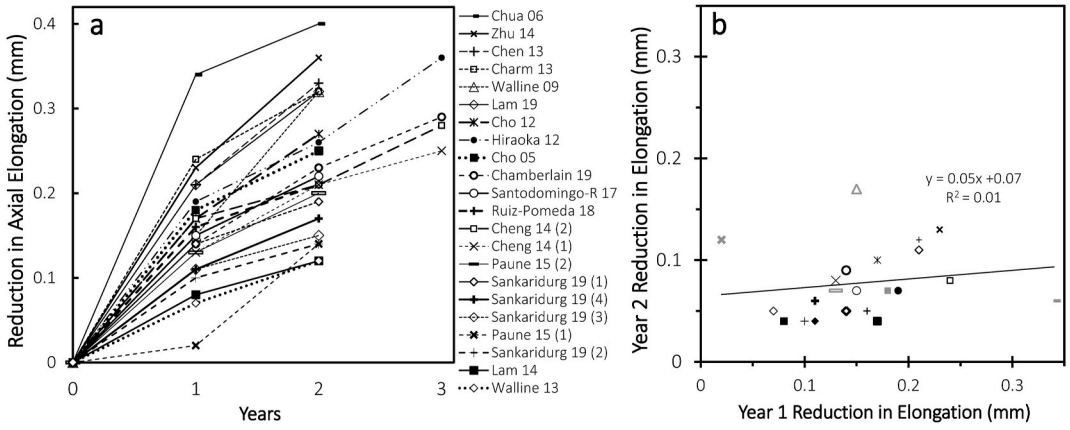

Fig. 10. (a) Cumulative absolute reduction in axial elongation at annual timepoints for myopia control treatments listed in Table 1 that reported data for one, two or three years. Note the divergence of effect size in the first year across treatments but near parallel lines after this time indicating similar measured effect size after year one. (b) Plot of incremental absolute reduction in axial elongation in year two versus year one. There is no evidence to suggest those treatments which show better efficacy in the first year continue to do so after this timepoint.

control effect. It communicates, to the best of our current knowledge, the benefit that a child receiving a specified treatment might expect independently of age, progression rate, refractive error and ethnicity over a stated time period. That is not to say that all children will experience the same treatment effect as there is considerable variance around CARE estimates but rather that the best projected efficacy for an individual child is the CARE value for that treatment and that other variables have limited impact on that estimate.

CARE should be expressed with reference to the time at which it applies. So, for example, the study of Lam et al. (2019) found a CARE of 0.31 mm at two years for the DIMS spectacles lenses in their trial and Santodomingo-Rubido et al., 2017 found a CARE of 0.44 mm at seven years in their orthokeratology trial. Thus, the metric does not enable easy comparison between treatments which have been tested over different durations. Models to predict future progression from shorter term data are not yet established and, given that there is a reduction in efficacy across time, extrapolation or comparison at common time points is required to make such comparisons.

We have constructed a table of measured CARE values from the studies in Table 1 in rank order in Table 4. In this table, study design features are provided to emphasise limitations and to facilitate interpretation. Bolded areas of the table highlight better study design features. Visual observation shows that studies demonstrating highest CARE tend to have more limitations than those with lower CARE. For example, maximum efficacy reported to date is 0.44 mm with orthokeratology (Santodomingo-Rubido et al., 2012). Nonetheless, it is important to note that study duration was some seven years, subjects were not randomised to treatment and the remaining sample size at this time was small. Some, though not all, non-randomised studies have failed to be confirmed by subsequent, more rigorous investigations (for example, Leung and Brown, 1999). Visual examination of the table suggests that those studies that have adhered to good scientific principles fall lower on the list– that is, they have measured smaller values of CARE.

The most important advantage of the CARE metric is that it provides an empirically determined, evidence-based effect size that clinicians, myopia control candidates and parents can reasonably expect for a given treatment over a given time. No other indicators in our assessment provide more guidance (see section 6.2 for further qualification regarding compliance and baseline refractive error in orthokeratology).

6.2. Implications for the clinical management of individual myopes

We have emphasised the importance of using axial length as the definitive metric for assessing myopia progression going forward. Unfortunately, there are limited published data using optical biometry to measure treatment effect and most practitioners are not yet conversant with the conceptual implications of millimetre increase in axial length in the way that they are historically with dioptre of refractive change. Since this section refers to application and interpretation of our findings in a clinical context, we include references to refractive error in this section.

Maximum reported treatment efficacy of 0.44 mm is equivalent to about 1 D of treatment over seven years. Given that (i) this mean value seems to generally apply across the progression range (see section 4), (ii) practitioners routinely treat only those that they think are fast progressors and (iii) that expected treatment efficacy may be something like 50%, there is a considerable shortfall in what the evidence base predicts compared with current expectations and projections by online calculators. Fig. 11a plots a likely refractive trajectory for a myopic six-year-old with axial length of 24.5 mm, showing a projected axial length of 27.5 mm at age 18. It also plots a calculated 50% treatment efficacy over this time, showing an axial length at 18 years old of 26.0 mm. Our conservative analysis here projects a mean maximum effect size of, say, 0.44 mm meaning that axial length is likely to exceed 27.0 mm at age 18, a substantial difference of some 1 mm compared to percentage efficacy calculation. This obviously has major implications for disease risk later in life. If considered in terms of refractive error (Fig. 11b), the child may begin at −1 D reaching −8 D at age 18. Rather than being restricted to −4.5 D, as predicted with a percentage efficacy of 50%, final refractive error is likely to be around −7 D. This represents a shortfall of around 2.5 D in reduction compared to expectations using percentage reduction as the basis for estimating efficacy.

While the ophthalmic community may be surprised to learn that expectations for myopia control efficacy should be tempered accordingly, the results are perhaps contextually not surprising. Some 80% or more of myopes do not progress to high myopia and mean long-term progression among most cohorts that have been followed for some time is generally not more than about 1.4 mm (approximately 3 D). For example, data from the 'Correction of Myopia Evaluation Trial' in 462 children aged six to 11 years at baseline revealed axial elongation to be an average of 1.26 mm (2.79 D) over 14 years (Scheiman et al., 2016). Data extracted from the 'Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error' advised mean elongation of 1.18 mm

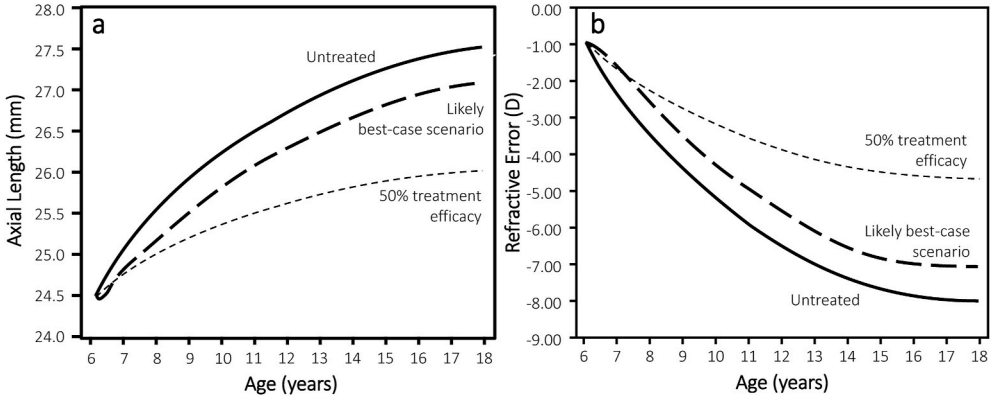

Fig. 11. Illustration showing projected trajectories for (a) axial length and (b) refractive error for a six-year-old with initial values of 24.5 mm and −1.00 D and expected 18-year-old values of 27.5 mm and −8.00 D, respectively, without treatment. Using percentage treatment efficacy, and an estimate of 50% effect based on short term data, final axial length and refractive error are expected to be 26.3 mm and −4.50 D. Nonetheless, maximum reported efficacy of any treatment is 0.44 mm or approximately 1 D so a more accurate projection using best case treatment options is a final axial length of 27 mm and refraction of about −7.00 D. Note that there is variance around the 1 D estimate so some children will achieve better results but we have limited predictive factors to identify who they may be. Furthermore, in clinical practice, it is not possible to judge how effective a treatment for a given child is because the untreated trajectory is subject to large variance.

(2.37 D) over five years in 605 myopic children also aged 6–11 years at baseline (Mutti et al., 2007). Control groups in a Japanese five-year orthokeratology study (N = 21, aged 8–12 years at baseline) and a Spanish seven-year study (N = 16, aged 6–12 years at baseline) showed axial elongation of 1.41 and 1.35 mm respectively.

In sections 4 and 5, we discussed the shortcomings of using percentage to describe treatment efficacy because of (i) its failure to accurately represent effect size across the progression range and (ii) the decrease in efficacy across time. It is worth considering the relative contributions of each of these factors. In the parlance of relative change, maximum treatment efficacy demonstrated is around 30–35% (mean efficacy of 0.44 mm compared to 1.2–1.4 mm of mean progression in untreated eyes) and only an additional 0.15–0.25 mm or thereabouts of effect size would be needed to achieve a mean of 50% efficacy. Therefore, the major issue of concern arising from our analysis involves apparent consistency of absolute effect size across the progression range and, particularly, the implications for faster progressors, rather than the decline in efficacy over time. In the example of Fig. 11a, a shortfall of around 1 mm was noted when comparing likely to projected reduction in axial elongation.

There are some other intriguing but discouraging implications from our analysis. Since treatment efficacy seems to be consistent across the progression range and, therefore, the age range, and seems to virtually plateau after some five to seven years, our analysis does not support the clinical routine of beginning treatment as early as possible. It seems unlikely that a 15-year-old beginning treatment would achieve the same longer-term efficacy as a seven-year-old but, surprisingly, we do not have an evidence base to contradict this position. We certainly would not argue against instigating myopia control treatment as early as possible despite the absence of evidence that it is likely to be of any benefit. Another curious implication is that a child who has been receiving treatment for some time will receive less benefit than another child of the same age just beginning treatment. For example, an eight-year-old may receive a treatment benefit of 0.15 mm during their first year of treatment and then 0.08 mm during the second year when the child is nine years of age. A child beginning treatment at the age of nine would be expected to receive 0.15 mm effect in their first year of treatment, a larger effect than for the first child at the same age. This raises the question as to whether swapping treatment might provide a renewed burst of efficacy. In these early days of understanding myopia control efficacy, we do not have answers to these questions.

Several worthy qualifications should be noted about the apparent effect size 'ceiling' of 0.44 mm. First, logistical constraints mean that myopia control therapies have only been investigated for relatively short periods of time, usually one or two years, and there is a possibility that some may exceed this threshold over the longer term. In addition, our conclusion of consistent average CARE across the progression range may not capture greater efficacy over longer periods among fast progressors. There is simply inadequate existing evidence to support either of these positions. Second, it should be noted that 0.44 mm is the maximum CARE that has been demonstrated, so all of the other interventions fall short of this amount. Third, CARE is a mean value and, therefore, some 50% of myopes can be expected to receive a greater benefit than this. Of course, for every child that gets a benefit of, say 0.60 mm, another child will only get 0.28 mm of benefit. Fourth, there is very limited information available for practitioners to determine the extent to which an individual will benefit from therapy. As expected, compliance with treatment seems to correlate to some extent with efficacy (Lam et al., 2014; Sankaridurg et al., 2019). With orthokeratology, there is some evidence that those with higher initial degree of myopia may obtain greater treatment efficacy (Cho et al., 2005; Kakita et al., 2011; Hiraoka et al., 2012; Fu et al., 2016; Wang et al., 2017a), although not all studies report this (Cho and Cheung, 2012; Santodomingo-Rubido et al., 2013; He et al., 2016; Lee et al., 2017). Greater efficacy at higher levels of myopia is expected with orthokeratology because of greater difference in peripheral corneal power relative to the treated central corneal power. In any case, examination of data in studies that report a significant relation shows great variability in treatment effect. Significant association of initial axial length and effect size has not been observed to our knowledge with spectacles or contact lenses. A lack of effect with baseline refractive error is specifically reported in Lam et al. (2019) and Chamberlain et al. (2019). Aside from compliance and initial refractive power in orthokeratology, no other known factors are available to assist a practitioner in predicting who will benefit most from myopia control treatment. Fifth, in practice, a clinician will not be able to measure the therapeutic effect size as there is no control for an individual undergoing treatment. As will be demonstrated in section 8, past progression does not provide guidance for future progression and so is an inadequate basis for comparison.

The maximum mean efficacies (CARE) predicted for existing treatment modalities are lower than previously thought but can still provide meaningful reductions in risk of myopia-associated disease. Bullimore and Brennan (2019) report remarkable consistency across studies whereby each increase in myopia by 1 D (approximately equivalent to the 0.44 mm maximum CARE) increases risk of MMD by 67%, regardless of the overall incidence in a study population and the criteria used to define the disease (Fig. 12). Thus, each one dioptre reduction in refractive error should reduce the risk of MMD by 40%, regardless of race or disease definition. This treatment benefit seems to be independent of the degree of myopia.

In addition to the restrained picture that these findings paint of the degree to which myopia control can be achieved, a further potential inhibiting factor that should be considered is rebound. We discuss evidence surrounding post-treatment rebound in myopia progression in the following section.

7. Rebound

Concern has been raised about long-term efficacy and potential rebound effects for both optical and pharmaceutical interventions (Gifford et al., 2019). Rebound, or post-treatment acceleration, can be loosely defined as greater progression after removal of a treatment than would have been observed at the same age in a child had treatment not been instigated.

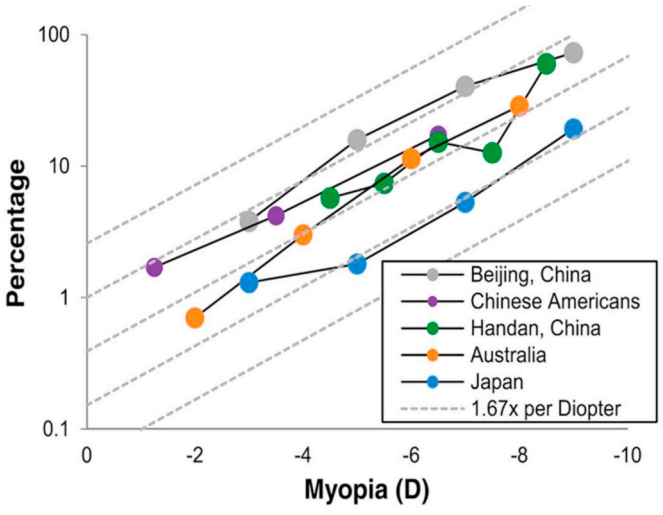

Fig. 12. The prevalence of MMD plotted on a logarithmic scale as a function of refractive error from multiple studies (Vongphanit et al., 2002; Liu et al., 2010; Gao et al., 2011; Asakuma et al., 2012; Choudhury et al., 2018). The logarithmic scale emphasizes the similar trajectory of each data set and the additional risk (approximately 67%) associated with each diopter. Reproduced from Bullimore and Brennan (2019) with permission from the American Academy of Optometry.

7.1. Atropine

In the randomised, controlled, masked ATOM1 study, Tong et al. (2009) reported myopia progression over the course of one year after stopping treatment with 1.0% atropine, which had been applied for the previous two years. The authors reported that, while a residual myopia control benefit remained, "the effect of the drug on myopia was relatively reduced after cessation for 1 year". After two years of treatment with 1.0% atropine, eyes had remained essentially unchanged (−0.02 mm) in average axial length compared with baseline (Chua et al., 2006) but, after one year following removal from treatment, had increased in length by 0.29 mm, meaning an increase in axial length of 0.31 mm in the year after cessation of treatment (Tong et al., 2009). In contrast, placebo-treated eyes increased in length by 0.38 mm during the first two years of the trial but only by an additional 0.14 mm in the third year. Not only did the rate of axial elongation in eyes removed from treatment outpace that of the untreated group by more than double (0.31–0.14 mm), but it was also numerically greater than that observed in the untreated group (0.20 mm) during the first year of the trial two years prior (Chua et al., 2006). Refractive error progression in eyes previously treated with atropine was also greater (1.14 versus 0.38 D). It is worth noting that this was a contralateral eye study design with one eye of a cohort of subjects receiving treatment and one eye of another cohort receiving placebo. The impact of such a study design on rebound is uncertain. This 'catch-up' of growth has potential to eliminate some or all of the myopia control effect obtained from treatment. Since the ATOM1 study was stopped one year after ceasing treatment, it is unclear exactly how much of the beneficial effect of treatment would be lost in the longer-term.

In ATOM2, rebound in refractive progression was also apparent at some doses (Chia et al., 2016). Because there seemed to be no impact on axial elongation from treatments with low-concentration atropine, it is difficult to draw conclusions from the work in that regard. The rebound phenomenon may arise from changes to the anterior optics of the eye.

7.2. Orthokeratology

Cho and Cheung (2017) studied axial elongation in a subset of subjects who had participated in a two-year myopia control study and who discontinued orthokeratology treatment. They compared these changes with subjects who continued with orthokeratology treatment and in an untreated group wearing spectacles. We have replotted Fig. 2 of their paper in Fig. 13, showing incremental changes in axial length by period. On average, elongation slowed down in the untreated group over the total three years of the study as it did in those who underwent orthokeratology treatment. Among those who were removed from treatment, a spike in axial elongation was apparent during the ensuing six months. As with the atropine study, the duration of follow-up on removal of treatment was limited, so it is unclear if the entire prior treatment effect may be lost over longer time periods.

It is important to note that randomization was not implemented in the orthokeratology group to decide who should be discontinued. Those who discontinued treatment were those who were measured to have benefited to a greater extent from the orthokeratology procedure. The potential for regression to the mean to artefactually generate the apparent rebound can therefore not be entirely ruled out.

7.3. SMCLs and spectacles

The studies of Berntsen et al. (2012), with progressive addition spectacles, and Cheng et al. (2016), with SMCLs, tested for rebound. Because the initial treatment effects were relatively small in both cases, little can be said about the value of the non-significant findings.

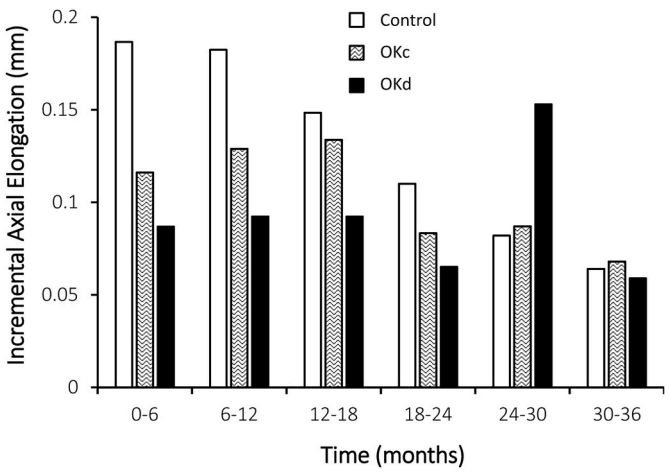

Fig. 13. Replot of Fig. 2 from Cho and Cheung (2017) using digitised data and showing incremental axial elongation for different timepoints. Children in the control group wore spectacles for the entire 36 months, those in the OKc group used orthokeratology lenses for the entire 36 months and those in the OKd group used orthokeratology lenses for the first 24 months, discontinued for 6 months and then resumed use for the final 6 months. OKc and OKd groups were chosen based in measured progression at 24 months, which creates sample bias and potential regression to the mean.

7.4. Summary and discussion

The phenomenon of rebound might be rationalised in a number of ways. While Wildsoet et al. (2019) postulate that, in refractive error terms, rebound may reflect recovery of ciliary muscle activity, they do not rule out a pharmacodynamic mechanism. This is a well-known effect, in which receptor sensitivity is altered as a result of continued exposure to drug, leading to reduced susceptibility to the effect of that drug and exaggerated symptoms following removal of treatment (Ganesan and Wildsoet, 2010). Further, in section 4, we discussed possible shrinkage of the globe in the early stages of myopia control treatment. Another theory to explain rebound would be a reversal of the mechanism leading to this initial shrinkage.

Data on rebound following removal of myopia control treatments are currently insufficient to allow generalization. Certainly, it has been observed in atropine studies although concentration-related amplitude of the effect remains unclear.

As a general principle, rebound cannot be ruled out. In keeping with the principle of evidence-based conservativism, rebound should be assumed until treatment-specific evidence to the contrary is obtained. Given limitations exposed in the above section of the extent to which myopia progression can be contained, this represents a considerable threat to overall viability of myopia control. Future research should certainly address existence of the phenomenon in optical interventions, origins of the effect, risk factors, whether tapering of treatment can mitigate the effects and whether continuing treatment beyond the normal age at which axial length stabilizes is beneficial. Issues regarding the ethics of removing myopia control treatment to study rebound complicate investigation of these questions.

8. Illusion of inflated success

In section 3, we presented arguments as to why myopia progression is best assessed by optical biometry. In this section, we present further reason for caution when using refractive error measurement. While this does not directly impact on how efficacy should be expressed, it is an interesting aspect of clinical practice and, as shown in the following discussion, can be a source of error in interpreting efficacy. Anecdotally, practitioners seem to believe that they are achieving greater myopia control treatment effect than supported by the evidence that we have

presented. This is especially true if they rely on published percentage treatment figures or online calculators (Cooper et al., 2018; Global Myopia Centre, 2019; Gifford et al., 2019). Of potential reasons for this impression, a common clinical protocol offers one potential explanation. The decision to treat myopia progression is routinely based on past history of progression (Leshno et al., 2020); that is, treatment might only be implemented for those who have exceeded, say, 0.50 or 0.75 D progression in the past year. Random variation in refractive error measurement, sample bias, and regression to the mean potentially lead to artifactual appearance of success in this scenario. We explore aspects of this artifact in this section.

8.1. Monte Carlo simulations

In the initial evaluation of potential erroneous interpretation of myopia control treatment effect, we performed Monte Carlo simulations to obtain computer-generated cases of 'measured' refractive error in a likely clinical scenario. Refractive error data were generated for 10,000 individual cases per simulation at baseline and after one year and, for a subset of cases, at two years. The clinical parallel would be the setting where a child has refractive error measured at baseline, then again one year after and, if the measured change in refractive error over this year exceeds a certain threshold, has myopia control treatment instigated with follow-up refractive error measurement at two years. In this simulation, we set treatment efficacy to zero to isolate the artifact. For each individual case, progression over the first, and second year if applicable, was generated from a mean population progression rate and a random error, derived from real population data. Refractive error estimates, as would be measured clinically, were then obtained from these values by adding a random error based also on real world measures (see section 3.6). Input variables using representative estimates derived from the literature comprised (i) population rate of progression (ii) variance in the population rate of progression (iii) threshold to treat, and (iv) variance in refractive error measurement. Variance was assumed to be normally distributed. The outcome variable was apparent reduction in mean myopia progression over the year before and after beginning treatment among cases that met the threshold to treat. No allowance was made for natural deceleration of progression.

A snapshot of the process is provided for illustrative purposes in Fig. 14. One hundred cases are shown with an arbitrary starting refraction of −1.00 D, progression rate of 0.50 D/y, zero variance in progression (that is, all 100 cases progressed by 0.50 D), a threshold to treat of −0.625 D and standard deviation of refractive error measurement of 0.25 D. The choice of −0.625 D as a threshold to treat could be considered to be somewhat representative of clinical practice if progression is measured in quarter dioptre steps and −0.50 D progression is considered insufficient to treat but −0.75 D is considered worthwhile. Some support for this position can be found in the paper of Wolffsohn et al. (2016), whose survey found that over half of practitioners in Asia, North America and South America would require at least that level of annual refractive progression to begin treatment. Fig. 14a shows the results of the simulation for the entire 100 cases, showing no bias in terms of second-year outcome compared to the first-year outcome as expected. When those who were 'measured' to have less than −0.625 D progression in the first year were excluded (Fig. 14b), a vastly different picture emerges. The median apparent progression of the remaining group in the first year is −1.02 D and in the second year, it is −0.22 D. Refractive progression naturally reduces as a child ages by around 15% per annum so, second-year progression in this simulation might be more appropriately estimated at −0.43 D rather than −0.50 D. Applying this shift of −0.07 D means that measured second-year progression is now estimated at −0.15 D. So, in this snapshot, the treated group would be measured to have mean progression of around one dioptre in the first year and less than a quarter of a dioptre in the second year – what might be promoted as a remarkable 85% reduction in progression – in the absence of any treatment effect at all, simply by virtue of random measurement variance, sample bias and regression to the mean.

Fig. 15 plots the artifact created by the common clinical paradigm used to select patients for myopia control treatment. Threshold to treat is presented on the x-axis and extends up to 1.2 D. While this threshold may seem high to some, Leshno et al. (2020) reported a progression rate of 1.1 D/y was the mean threshold for initiation of treatment in a global survey of paediatric ophthalmologists. Examples for different true progression rates from 0.4 to 1.0 D are shown. Between session repeatability (SD) of refractive error measurement and SD of annual progression were 0.25 D and 0.39 D in (a) and 0.33 D and 0.42 D in (b), respectively, with these sample figures taken from literature examples. It is evident that substantial overestimation of treatment effect can arise when using past 'measured' refractive progression as a basis to treat. It is important to note that the number of individuals who will be treated will decrease as the disparity between true progression rate and threshold to treat increases. Nonetheless, substantial artifact remains apparent for common progression rates and thresholds to treat. Given that some 80% of myopes are not destined to become highly myopic and that the illusion of success demonstrated here exists, it is not surprising that practitioners are enthusiastic about myopia control.

8.2. Using past progression to predict future progression

There are limited data correlating progression in one year to the next across individuals. Clearly individuals who progress to high levels of myopia must progress at a considerable pace for several years. Yet,

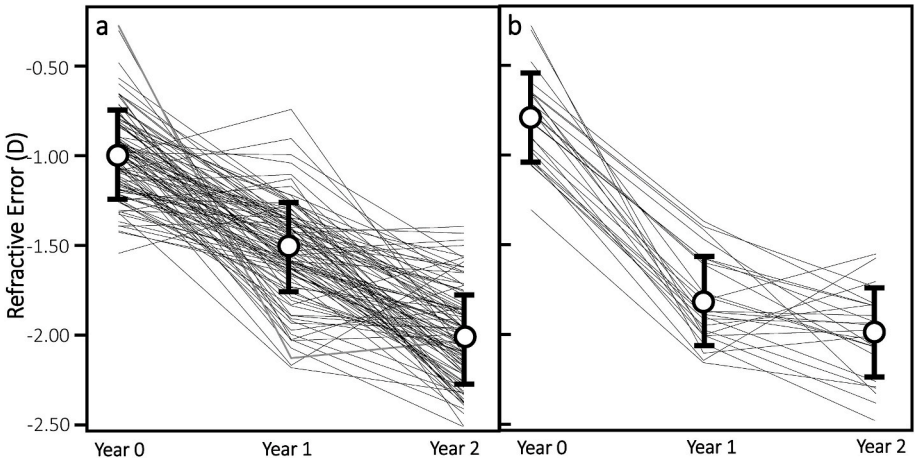

Fig. 14. (a) Simulation of 'measured' refractive trajectory for 100 cases at a starting refraction of −1.00 D with 0.50 D of progression and allowing a standard deviation of refractive measurement of 0.25 D. Refraction is measured at zero, one and two years. A treatment which has zero efficacy is notionally started at the end the first year of follow-up. (b) Replot of Fig. 1 with "slow" progressors (those progressing < 0.62 D) removed. The apparent mean progression in the first year is 1.02 D. In the second year the apparent progression is only 0.22 D. Given about natural slow-down of progression per year, second year progression would more likely be 0.15 D. In practice, one might mistakenly consider this to be treatment efficacy of about 85% when, in reality, there is no treatment effect. The artifact is caused by using previous measured refractive progression as a basis to treat, resulting sample bias, measurement accuracy of refraction that is of similar order to progression rate, and regression to the mean.

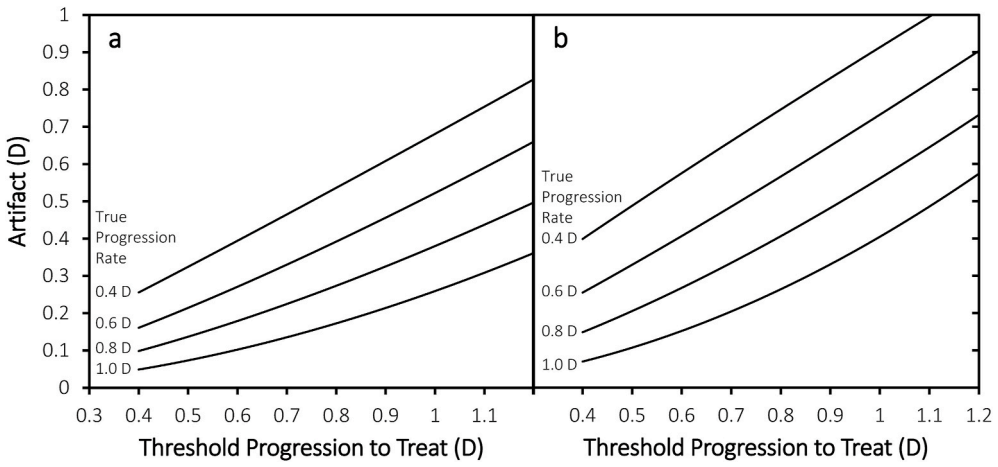

Fig. 15. Mean overestimation of treatment effect when using past 'measured' refractive progression as a basis to treat. Sample values of threshold to treat and true progression rate are shown. Between session repeatability (SD) of refractive error measurement and SD of annual progression were 0.25 D and 0.39 D in (a) and 0.33 D and 0.42 D in (b), respectively, with these sample figures taken from literature examples.

because of the considerable variance in measurement of refractive error shown in section 3.6, it is unclear whether 'measurement' of prior refractive progression can be used to predict future progression. We used a sample of right eyes from the control populations of studies published by Cheng et al. (2016, 2019) for whom refractive error measurements, obtained with autorefractor, at baseline, one and two years were available. A total of 100 data sets were available. Mean second year progression (±SD) estimates are plotted for different first year progression, grouped in half diopter steps, in Fig. 16.

The graph shows that prediction of progression using previous data is not viable. Mean second-year progression for subjects where first-year progression rate was less than 1.00 D per year was approximately half a diopter with little variation in the mean for the groups that showed no, zero to half, and half to one diopter mean progression in the first year. But the standard deviations for second-year progression across the different groupings was substantial. Indeed, probability estimates using the normal distribution suggests that some 25% of children whose measured refractive error is less than 0.50 D in a given year will progress by more than about 0.8 D in the following year. Given current prescribing trends (Leshno et al., 2020; Wolffsohn et al., 2020), the majority of these children would not be treated, despite the apparent need. Only above 1 D of measured progression in the first year was there an appreciable increase in mean second-year progression. Nonetheless, the artifact discussed in section 8.1 is evident in the data. Using probability calculations again, some 36% and 18% of those progressing 1 to 1.5 D and over 1.5 D, respectively, in the first year would be expected to progress by less than 0.5 D in the second year.

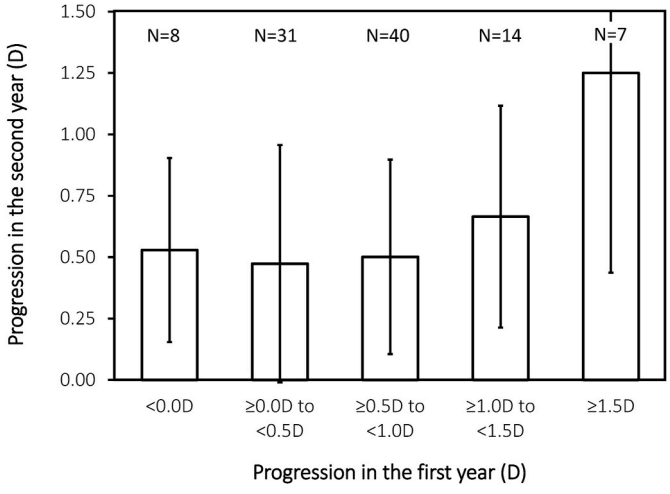

Fig. 16. Comparison of 'measured' refractive progression between year one and year two of 100 right eyes using data from the control populations of studies published by Cheng et al. (2016, 2019). Mean measured second year progression (±SD) is plotted for different measured first year progression bins. The problem of artifactual treatment effect and not treating slow progressors is revealed using 'real world' data. The basis of this problem is that measurement accuracy of refraction is of similar order to progression rate, especially for progression rates of 1.00 D or less. Higher amounts of measured progression in the first year (>1.00 D) will generally be indicative of higher progression in the second year. These data argue strongly against using past progression as a basis to treat and presents a strong case as to why all young myopic children should be treated.

8.3. Summary and discussion

Despite somewhat limited efficacy of myopia control treatments to date, practitioners are under the impression that they are achieving much better efficacy than evidence, as laid out in section 6, suggests. In part, this is due to a natural slowing of progression with increasing age and because most myopes, some 80%, do not progress to high myopia. The second feature, demonstrated here, is statistical bias introduced by the common clinical paradigm of relying on prior progression measurement. As observed in section 3.6, refractive error measurement can only be measured with repeatability of the same order of magnitude as annual myopia progression rate, making it an inefficient index of progression over anything less than, say, two years.

Perhaps of equal importance, the relatively large variance of refractive error measurement can lead to children who are true fast progressors not being treated. The best current predictor of ultimate refractive error would seem to be age of onset (Chua et al., 2016) and this should be preferred in clinical practice to previous measured progression. Using a criterion of ≤ -5.00 D, Pärssinen and Kauppinen (2019) found that over 50% of children who received their first spectacles before the age of 12.8 years became highly myopic by their early to mid-thirties. Because of the risks of complications later in life and our current inability to predict with great accuracy those who go on to higher degrees of myopia, this leads us to recommend that all young myopes (say 12 years of age and below) deserve to be treated. Following progression without treatment for an initial year would seem to be advised against, even with axial length measurement. Where age of onset is not precisely known, estimates from current age and refractive error are possible (Chua et al., 2016). Axial length may be a better predictor of future progression and further research in this area is needed.

9. Conclusions and future directions

We have conducted what we believe to be the first comprehensive review and analysis of the concept of efficacy in myopia control. This work has produced a set of evidence-based findings and recommendations. These findings should be beneficial in improving treatment for individual patients based on the group data that are presented in scientific publications. It should be emphasised that some beliefs around myopia control that exist in the practitioner community may be correct and contrary to what we say here, but there is simply insufficient evidence to support such contentions at this time (Brennan and Cheng, 2019). Our observations have far reaching implications for the field of myopia control.

Axial length is the preferred metric for tracking myopia progression. Indeed, using refractive error to gauge progression is subject to numerous pitfalls and, for scientific and regulatory purposes, axial elongation alone should ideally be used. It cannot be expected in the short term that all clinicians who wish to conduct myopia control will have access to instrumentation to measure axial length and this should not be a deterrent to practising myopia control. Nonetheless, energy should be directed toward making inexpensive instruments available for this purpose and practitioners should work toward incorporating optical (not ultrasound) biometry into practice. Practitioners should also be aware of the pitfalls of basing clinical decisions on refractive error measurements. The imperative to use axial length to monitor progression does not mean refractive error is of no value when treating myopia. It provides valuable information about onset that is not obtainable from an absolute value of axial length and, of course, about optical correction required for good vision. In the future, it may also be useful in combination with axial length to determine the threshold axial length for an individual that brings about a given risk of MMD – further research is needed to produce such a model.

There is insufficient evidence to assert that faster progressors, or younger myopes – that is, those who are most in need of progression control – experience greater treatment efficacy. It certainly appears that they will show less percentage treatment effect than the average child. Indeed, available data suggest that an intervention provides a treatment effect that is, on average, homogeneous in absolute terms across progression, age and refractive error. This has important ramifications for patients and practitioners in terms of the real-world reduction in myopia progression that can realistically be achieved through treatment. While diminishing annual treatment effect size over time plays a role (as discussed in section 5.1), uniformity of absolute treatment effect across the progression range produces efficacy projections for early onset myopes that are substantially less than those provided by percentage calculations and used by current online calculators. Further research is needed to quantify the limits to which the concept of invariant treatment effect across various demographic factors holds. More specifically, we need to establish predictive markers to identify those patients that are most likely to progress at a fast rate and those treatments that will most benefit a given patient.

While reduction in myopia control treatment efficacy over time has been mentioned in the literature, there have been limited attempts to quantify this phenomenon. Our examination of this effect suggests that some 40% of 4- to 5-year efficacy happens in the first year and indeed the majority occurs in the first few months, largely due to an eye shrinkage effect. This short-term burst of effect adds to a perception of great efficacy in practice. More research is needed to investigate the two-phase nature of myopia control treatments (that is, the initial shrinkage followed by a slower growth rate), why efficacy slows over time, and whether there are benefits to pulsing or switching treatments.

Expression of treatment as a percentage falsely suggests that 1–1.5 mm (≈3 to 4 D) reduction in myopia progression might be achievable over a period of time but consistency of treatment effect across the progression range and reduction of effect over time mean that there is only evidence to date for long-term mean efficacy of less than 0.5 mm (about 1 D). Although variation about this mean will see some individuals achieve more than this effect, for each individual that does, there will be someone who falls short by a similar amount. Further, aside from compliance with treatment, practitioners have very little in their diagnostic armoury to identify those who will receive greater benefit from a given treatment.

Given considerations around consistency of effect size across the progression range and reduction of efficacy over time, cumulative absolute reduction in elongation (CARE) emerges as the logical current default preferred metric for expressing efficacy and comparing treatments. The effect size so described appears to be independent of patient age and incorporates reduction of efficacy over time. CARE is not time independent, an important limitation, and, so, should be expressed with reference to the time scale. Considerable interpretation is required to gauge value of a given treatment over periods longer than the experimental study generating the CARE value. Given the apparently modest extent, in terms of treatment effect size, to which current techniques slow myopia progression, continued energy should be expended on the search for improved interventions. In particular, exploration of pathways that guide ocular growth during myopia progression may point to new prospects. Scientists should continue to pursue the holy grail of myopia research, that is, to identify the method by which the retina detects the sign of defocus of an optical stimulus.

Ideally, longer term efficacy of a treatment would be predicted from short term data. Part of the difficulty in predicting efficacy into the future is inconsistent treatment across time. While different treatments show divergent efficacy in the first year, they show only minor difference beyond year one. Models to predict future efficacy from short term data are yet to be developed and are sorely needed to eliminate time dependence of the CARE metric and to minimize the ethical burden of keeping children untreated for long periods during clinical trials. We are currently working on such a model and hope to update to an improved efficacy standard.

No single method of treatment shows clear superiority with the best of orthokeratology, SMCLs, spectacles and atropine showing similar effect with some caveats. Some treatments within these categories (for example, SMCLs that prioritize clear vision, progressive addition spectacles and 0.01% atropine) may provide inferior treatment effect. Side effects and potential for rebound within these categories may influence success with these different treatments. The clinician should choose the treatment based on numerous considerations such as their own skill set, preferences of parents and children, ability of the child to adapt to the treatment, as well as availability of product and regulatory considerations. Some of these issues are discussed in a recent comprehensive clinical review (Bullimore and Richdale, 2020).

Rebound is evident in at least some interventions and one possibility is that it constitutes loss of the initial shrinkage effect observed on instigation of treatment. Because it has been observed with atropine and to some extent orthokeratology, rebound should be assumed with all treatment until proven otherwise. The amount of research that has been performed on rebound with optical treatments is generally poor and needs to be augmented. There is also the need to determine whether continuing treatment well into the teenage years or beyond can reduce the extent of rebound as eye growth tends to stabilize. Combined with the modest overall treatment effect size that is revealed through our analyses in this paper, rebound is a threat to the overall viability of the myopia control movement.

An illusion of inflated efficacy is created by measurement error in refraction, sample bias in only treating fast progressors and regression to the mean. Decision to treat should be based on age of onset (or refraction at a given age), not past progression. Indeed, we recommend that treatment is recommended for all young myopic children of, say, 12 years of age or less. Consideration may also be given to ethnicity and parental myopia, but further research is required to establish the additional value of these risk factors. Use of prior axial elongation, as measured by optical biometry, is likely to be a better method for

predicting future progression in an individual and further resources should be directed to exploring this opportunity.

Despite limited efficacy of available interventions and the potential for rebound, the projected decrease in risk of complications later in life provided by even moderate reductions in progression suggests treatment should be considered for all young myopes. The paper of Bullimore and Brennan (2019) shows 67% increased risk of MMD with each increase of 1 D of myopia (Fig. 16). Even a 0.25 D reduction in myopia (equivalent to about 0.1 mm) yields close to a 10% reduction in risk. Given the relatively modest effect size expected for current treatments discussed in this paper, we recommend that practitioners should be bold in implementing myopia control therapy, utilizing the most powerful treatments available, in combination where possible, along with behavioural modifications, beginning at an early age, over extended periods of time and with encouragement of strong compliance.

Author agreement

All authors have seen and approved the final version of the manuscript being submitted. We warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

Funding

This work was funded by Johnson & Johnson Vision Care, Inc.

Declaration of competing interest

Noel Brennan, Youssef Toubouti, Xu Cheng are employees of Johnson & Johnson Vision Care, Inc.

Mark Bullimore is a consultant for Alcon Research, Inc., Asclepix, Inc., CooperVision, Inc., Corneagen, Inc., Essilor International , Eyenovia, Inc., Genentech, Inc., Johnson & Johnson Vision Care, Inc., Novartis AG, Presbia, Inc., Wells Fargo Securities, LLC and is the sole owner of Ridgevue Publishing, LLC, Ridgevue Technologies LLC, and Ridgevue Vision LLC.

References

Adcock, R.J., 1878. A problem in least squares. Analyst 5, 53–54.

Agarwal, A., Johnston, B.C., Vernooij, R.W., Carrasco-Labra, A., Brignardello-Petersen, R., Neumann, I., Akl, E.A., Sun, X., Briel, M., Busse, J.W., Ebrahim, S., Granados, C.E., Iorio, A., Irfan, A., Martinez Garcia, L., Mustafa, R.A., Ramirez-Morera, A., Selva, A., Sola, I., Sanabrai, A.J., Tikkinen, K.A., Vandvik, P.O., Zhang, Y., Zazueta, O.E., Zhou, Q., Schunemann, H.J., Guyatt, G.H., Alonso-Coello, P., 2017. Authors seldom report the most patient-important outcomes and absolute effect measures in systematic review abstracts. J. Clin. Epidemiol. 81, 3–12.

Aller, T.A., Liu, M., Wildsoet, C.F., 2016. Myopia control with bifocal contact lenses: a randomized clinical trial. Optom. Vis. Sci. 93, 344–352.

Anstice, N.S., Phillips, J.R., 2011. Effect of dual-focus soft contact lens wear on axial myopia progression in children. Ophthalmology 118, 1152–1161.

Asakuma, T., Yasuda, M., Ninomiya, T., Noda, Y., Arakawa, S., Hashimoto, S., Ohno-Matsui, K., Kiyohara, Y., Ishibashi, T., 2012. Prevalence and risk factors for myopic retinopathy in a Japanese population: the Hisayama study. Ophthalmology 119, 1760–1765.

Atchison, D.A., Jones, C.E., Schmid, K.L., Pritchard, N., Pope, J.M., Strugnell, W.E., Riley, R.A., 2004. Eye shape in emmetropia and myopia. Invest. Ophthalmol. Vis. Sci. 45, 3380–3386.

Auffarth, G., Hunold, W., 1992. Cycloplegic refraction in children: single-dose-atropinization versus three-day-atropinization. Doc. Ophthalmol. 80, 353–362.

Batterham, A.M., Hopkins, W.G., 2006. Making meaningful inferences about magnitudes. Int. J. Sports Physiol. Perform. 1, 50–57.

Berntsen, D.A., Sinnott, L.T., Mutti, D.O., Zadnik, K., 2012. A randomized trial using progressive addition lenses to evaluate theories of myopia progression in children with a high lag of accommodation. Invest. Ophthalmol. Vis. Sci. 53, 640–649.

Bikbov, M.M., Gilmanshin, T.R., Kazakbaeva, G.M., Zainullin, R.M., Rakhimova, E.M., Rusakova, I.A., Bolshakova, N.I., Safiullina, K.R., Zaynetdinov, A.F., Zinatullin, A.A., Nuriev, I.F., Khalimov, T.A., Panda-Jonas, S., Arslangareeva II, Bikbova, G.M., Yakupova, D.F., Uzianbaeva, Y.V., Jonas, J.B., 2020. Prevalence of myopic maculopathy among adults in a Russian population. JAMA. Netw. Open. 3, e200567.

Blacker, A., Mitchell, G.L., Bullimore, M.A., Long, B., Barr, J.T., Dillehay, S.M., Bergenske, P., Donshik, P., Secor, G., Yoakum, J., Chalmers, R.L., 2009. Myopia progression during three years of soft contact lens wear. Optom. Vis. Sci. 86, 1150–1153.

Bourke, C.M., Loughman, J., Fltcroft, D.I., Loskutova, E., O'Brien, C., 2019. We can't afford to turn a blind eye to myopia. QJM- Int. J. Med., hcz176

Brennan, N.A., 2015. High myopia- separate condition or part of a continuum. Cont. Lens Anterior Eye. 38 (Suppl. 1), e1.

Brennan, N.A., Cheng, X., 2017. Prediction of myopic retinopathy by age and refractive error. Invest. Ophthalmol. Vis. Sci. 58 (8), 2384.

Brennan, N.A., Cheng, X., 2018. Do relative mean progression rates published for myopia control treatments apply to fast progressors? It seems not! Ophthalmic Physiol. Optic. 38 (3), 215, O027. onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fopo.12459&file=opo12459-sup-0002-DataS2.docx. (Accessed 15 November 2020).

Brennan, N.A., Cheng, X., 2019. Commonly held beliefs about myopia that lack a robust evidence base. Eye Contact Lens 45, 215–225.

Brennan, N.A., Cheng, X., Bullimore, M.A., 2019. Myopia control intervention produces absolute, rather than relative, treatment effect across the progression range. Invest. Ophthalmol. Vis. Sci. 60 (9), 4344.

Brennan, N.A., Cheng, X., Toubouti, Y., Bullimore, M.A., 2018a. A 'universal' calculator to link data across myopia epidemiology studies. Invest. Ophthalmol. Vis. Sci. 59 (9), 4151.

Brennan, N.A., Cheng, X., Toubouti, Y., Bullimore, M.A., 2018b. Influence of age and race on axial elongation in myopic children. Optom. Vis. Sci. 95, e180072.

Buckhurst, P.J., Wolffsohn, J.S., Shah, S., Naroo, S.A., Davies, L.N., Berrow, E.J., 2009. A new optical low coherence reflectometry device for ocular biometry in cataract patients. Br. J. Ophthalmol. 93, 949–953.

Bullimore, M.A., 2017. The safety of soft contact lenses in children. Optom. Vis. Sci. 94, 638–646.

Bullimore, M.A., Brennan, N.A., 2019. Myopia control: why each diopter matters. Optom. Vis. Sci. 96, 463–465.

Bullimore, M.A., Fusaro, R.E., Adams, C.W., 1998. The repeatability of automated and clinician refraction. Optom. Vis. Sci. 75, 617–622.

Bullimore, M.A., Johnson, R.E., 2020. Overnight orthokeratology. Cont. Lens Anterior Eye. 43, 322–332.

Bullimore, M.A., Richdale, K., 2020. Myopia control 2020: where are we and where are we heading? Ophthalmic Physiol. Optic. 40, 254–270.

Bullimore, M.A., Sinnott, L.T., Jones-Jordan, L.A., 2013. The risk of microbial keratitis with overnight corneal reshaping lenses. Optom. Vis. Sci. 90, 937–944.

Carkeet, A., Saw, S.M., Gazzard, G., Tang, W., Tan, D.T., 2004. Repeatability of IOLMaster biometry in children. Optom. Vis. Sci. 81, 829–834.

Carkeet, N.L., Mountford, J.A., Carney, L.G., 1995. Predicting success with orthokeratology lens wear: a retrospective analysis of ocular characteristics. Optom. Vis. Sci. 72, 892–898.

Carroll, J.P., 1981. Regression curves for the optical parameters of the eye. Am. J. Optom. Physiol. Opt. 58, 314–323.

Chakraborty, R., Read, S.A., Collins, M.J., 2011. Diurnal variations in axial length, choroidal thickness, intraocular pressure, and ocular biometrics. Invest. Ophthalmol. Vis. Sci. 52, 5121–5129.

Chakraborty, R., Read, S.A., Collins, M.J., 2014. Diurnal variations in ocular aberrations of human eyes. Curr. Eye Res. 39, 271–281.

Chamberlain, P., Peixoto-de-Matos, S.C., Logan, N.S., Ngo, C., Jones, D., Young, G., 2019. A 3-year randomized clinical trial of misight lenses for myopia control. Optom. Vis. Sci. 96, 556–567.

Charm, J., Cho, P., 2013. High myopia-partial reduction ortho-k: a 2-year randomized study. Optom. Vis. Sci. 90, 530–539.

Chen, C., Cheung, S.W., Cho, P., 2013. Myopia control using toric orthokeratology (TO-SEE study). Invest. Ophthalmol. Vis. Sci. 54, 6510–6517.

Cheng, D., Woo, G.C., Drobe, B., Schmid, K.L., 2014. Effect of bifocal and prismatic bifocal spectacles on myopia progression in children: three-year results of a randomized clinical trial. JAMA Ophthalmol 132, 258–264.

Cheng, X., Brennan, N.A., Toubouti, Y., Greenaway, N.L., 2019. Safety of soft contact lenses in children: retrospective review of six randomized controlled trials of myopia control. Acta Ophthalmol. 98, e346–e351.

Cheng, X., Wooley, B., Brennan, N.A., 2018. Can corneal physiological changes during contact lens wear lead to myopic creep? Ophthalmic Physiol. Optic. 38 (3), 215, P021. onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fopo.12459&file=opo12459-sup-0003-DataS3.docx. (Accessed 15 November 2020).

Cheng, X., Xu, J., Chehab, K., Exford, J., Brennan, N., 2016. Soft contact lenses with positive spherical aberration for myopia control. Optom. Vis. Sci. 93, 353–366.

Chia, A., Chua, W.H., Cheung, Y.B., Wong, W.L., Lingham, A., Fong, A., Tan, D., 2012. Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (ATOM 2). Ophthalmology 119, 347–354.

Chia, A., Lu, Q.S., Tan, D., 2016. Five-year clinical trial on atropine for the treatment of myopia 2: myopia control with atropine 0.01% eyedrops. Ophthalmology 123, 391–399.

Cho, P., Cheung, S.W., 2012. Retardation of myopia in orthokeratology (ROMIO) study: a 2-year randomized clinical trial. Invest. Ophthalmol. Vis. Sci. 53, 7077–7085.

Cho, P., Cheung, S.W., 2017. Discontinuation of orthokeratology on eyeball elongation (DOEE). Cont. Lens Anterior Eye. 40, 82–87.

Cho, P., Cheung, S.W., Edwards, M., 2005. The longitudinal orthokeratology research in children (LORIC) in Hong Kong: a pilot study on refractive changes and myopic control. Curr. Eye Res. 30, 71–80.

Choudhury, F., Meuer, S.M., Klein, R., Wang, D., Torres, M., Jiang, X., McKean-Cowdin, R., Varma, R., 2018. Prevalence and characteristics of myopic degeneration in an adult Chinese American population: the Chinese American Eye Study. Am. J. Ophthalmol. 187, 34–42.

Chua, S.Y., Sabanayagam, C., Cheung, Y.B., Chia, A., Valenzuela, R.K., Tan, D., Wong, T. Y., Cheng, C.Y., Saw, S.M., 2016. Age of onset of myopia predicts risk of high myopia in later childhood in myopic Singapore children. Ophthalmic Physiol. Optic. 36, 388–394.
Chua, W.H., Balakrishnan, V., Chan, Y.H., Tong, L., Ling, Y., Quah, B.L., Tan, D., 2006. Atropine for the treatment of childhood myopia. Ophthalmology 113, 2285–2291.
Clark, T.Y., Clark, R.A., 2015. Atropine 0.01% eyedrops significantly reduce the progression of childhood myopia. J. Ocul. Pharmacol. Therapeut. 31, 541–545.
Cohen, J., 1983. The cost of dichotomization. Appl. Psychol. Meas. 7, 249–253.
Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences. Routledge, Abingdon. United Kingdom.
Cohen, J., 1992. A power primer. Psychol. Bull. 112, 155.
Comet Group, 2013. Myopia stabilization and associated factors among participants in the correction of myopia evaluation trial (COMET). Invest. Ophthalmol. Vis. Sci. 54, 7871–7884.
Cooper, J., O'Connor, B., Watanabe, R., Fuerst, R., Berger, S., Eisenberg, N., Dillehay, S. M., 2018. Case series analysis of myopic progression control with a unique extended depth of focus multifocal contact lens. Eye Contact Lens 44, e16–e24.
Cooper, J., Tkatchenko, A.V., 2018. A review of current concepts of the etiology and treatment of myopia. Eye Contact Lens 44, 231–247.
Cornbleet, P.J., Gochman, N., 1979. Incorrect least-squares regression coefficients in method-comparison analysis. Clin. Chem. 25, 432–438.
Coster, W.J., 2013. Making the best match: selecting outcome measures for clinical trials and outcome studies. Am. J. Occup. Ther. 67, 162–170.
Cruickshank, F.E., Logan, N.S., 2018. Optical 'dampening' of the refractive error to axial length ratio: implications for outcome measures in myopia control studies. Ophthalmic Physiol. Optic. 38, 290–297.
Csaky, K., Ferris 3rd, F., Chew, E.Y., Nair, P., Cheetham, J.K., Duncan, J.L., 2017. Report from the NEI/FDA endpoints workshop on age-related macular degeneration and inherited retinal diseases. Invest. Ophthalmol. Vis. Sci. 58, 3456–3463.
Cui, Y., Li, L., Wu, Q., Zhao, J., Chu, H., Yu, G., Wei, W., 2017. Myopia correction in children: a meta-analysis. Clin. Invest. Med. 40, E117–E126.
Curtin, B.J., Karlin, D.B., 1970. Axial length measurements and fundus changes of the myopic eye. I. The posterior fundus. Trans. Am. Ophthalmol. Soc. 68, 312–334.
Curtin, B.J., 1977. The posterior staphyloma of pathologic myopia. Trans. Am. Ophthalmol. Soc. 75, 67–86.
Dave, T., Ruston, D., 1998. Current trends in modern orthokeratology. Ophthalmic Physiol. Optic. 18, 224–233.
Deng, L., Pang, Y., Effect of Outdoor Activities in Myopia Control: Meta-Analysis of Clinical Studies, 2019. Optom Vis Sci 96, 276–282.
Diaz-Llopis, M., Pinazo-Duran, M.D., 2018. Superdiluted atropine at 0.01% reduces progression in children and adolescents. A 5 year study of safety and effectiveness. Arch. Soc. Esp. Oftalmol. 93, 182–185.
Dolgin, E., 2015. The myopia boom. Nature 519, 276–278.
Donovan, L., Sankaridurg, P., Ho, A., Chen, X., Lin, Z., Thomas, V., Smith 3rd, E.L., Ge, J., Holden, B., 2012a. Myopia progression in Chinese children is slower in summer than in winter. Optom. Vis. Sci. 89, 1196–1202.
Donovan, L., Sankaridurg, P., Ho, A., Naduvilath, T., Smith 3rd, E.L., Holden, B.A., 2012b. Myopia progression rates in urban children wearing single-vision spectacles. Optom. Vis. Sci. 89, 27–32.
Dumbleton, K.A., Chalmers, R.L., Richter, D.B., Fonn, D., 1999. Changes in myopic refractive error with nine months' extended wear of hydrogel lenses with high and low oxygen permeability. Optom. Vis. Sci. 76, 845–849.
Ellis, P.D., 2010. The Essential Guide to Effect Sizes: Statistical Power, Meta-Analysis, and the Interpretation of Research Results. Cambridge University Press, Cambridge UK.
Fan, L., Jun, J., Jia, Q., Wangqing, J., Xinjie, M., Yi, S., 1999. Clinical study of orthokeratology in young myopic adolescents. Int. Contact Lens Clin. 26, 113–116.
Faraone, S.V., 2008. Interpreting estimates of treatment effects: implications for managed care. P T 33, 700–711.
Fleming, T.R., Powers, J.H., 2012. Biomarkers and surrogate endpoints in clinical trials. Stat. Med. 31, 2973–2984.
Flitcroft, D.I., 2012. The complex interactions of retinal, optical and environmental factors in myopia aetiology. Prog. Retin. Eye Res. 31, 622–660.
Flitcroft, D.I., He, M., Jonas, J.B., Jong, M., Naidoo, K., Ohno-Matsui, K., Rahi, J., Resnikoff, S., Vitale, S., Yannuzzi, L., 2019. IMI - defining and classifying myopia: a proposed set of standards for clinical and epidemiologic studies. Invest. Ophthalmol. Vis. Sci. 60, M20–M30.
French, A.N., Morgan, I.G., Burlutsky, G., Mitchell, P., Rose, K.A., 2013. Prevalence and 5- to 6-year incidence and progression of myopia and hyperopia in Australian schoolchildren. Ophthalmology 120, 1482–1491.
Fritz, C.O., Morris, P.E., Richler, J.J., 2012. Effect size estimates: current use, calculations, and interpretation. J. Exp. Psychol. Gen. 141, 2–18.
Fu, A.C., Chen, X.L., Lv, Y., Wang, S.L., Shang, L.N., Li, X.H., Zhu, Y., 2016. Higher spherical equivalent refractive errors is associated with slower axial elongation wearing orthokeratology. Cont. Lens Anterior Eye. 39, 62–66.
Fujiwara, M., Hasebe, S., Nakanishi, R., Tanigawa, K., Ohtsuki, H., 2012. Seasonal variation in myopia progression and axial elongation: an evaluation of Japanese children participating in a myopia control trial. Jpn. J. Ophthalmol. 56, 401–406.
Fulk, G.W., Cyert, L.A., Parker, D.A., 2002. Seasonal variation in myopia progression and ocular elongation. Optom. Vis. Sci. 79, 46–51.
Ganesan, P., Wildsoet, C.F., 2010. Pharmaceutical intervention for myopia control. Expet Rev. Ophthalmol. 5, 759–787.
Gao, L.Q., Liu, W., Liang, Y.B., Zhang, F., Wang, J.J., Peng, Y., Wong, T.Y., Wang, N.L., Mitchell, P., Friedman, D.S., 2011. Prevalence and characteristics of myopic retinopathy in a rural Chinese adult population: the Handan eye study. Arch. Ophthalmol. 129, 1199–1204.
Gifford, K.L., Richdale, K., Kang, P., Aller, T.A., Lam, C.S., Liu, Y.M., Michaud, L., Mulder, J., Orr, J.B., Rose, K.A., Saunders, K.J., Seidel, D., Tideman, J.W.L., Sankaridurg, P., 2019. IMI - clinical management guidelines report. Invest. Ophthalmol. Vis. Sci. 60, M184–M203.
Global Myopia Centre, 2019. Myopia calculator. bhvi.org/myopia-calculator-resources. (Accessed 15 November 2020).
Gong, Q., Janowski, M., Luo, M., Wei, H., Chen, B., Yang, G., Liu, L., 2017. Efficacy and adverse effects of atropine in childhood myopia: a meta-analysis. JAMA Ophthalmol 135, 624–630.
Goyal, R., North, R.V., Morgan, J.E., 2003. Comparison of laser interferometry and ultrasound a-scan in the measurement of axial length. Acta Ophthalmol. Scand. 81, 331–335.
Gözüm, N., Cakir, M., Gücukoglu, A., Sezen, F., 1997. Relationship between retinal lesions and axial length, age and sex in high myopia. Eur. J. Ophthalmol. 7, 277–282.
Grodum, K., Heijl, A., Bengtsson, B., 2001. Refractive error and glaucoma. Acta Ophthalmol. Scand. 79, 560–566.
Grossniklaus, H.E., Green, W.R., 1992. Pathologic findings in pathologic myopia. Retina 12, 127–133.
Gwiazda, J., Deng, L., Manny, R., Norton, T.T., Group, C.S., 2014. Seasonal variations in the progression of myopia in children enrolled in the correction of myopia evaluation trial. Invest. Ophthalmol. Vis. Sci. 55, 752–758.
Hagen, L.A., Gilson, S.J., Akram, M.N., Baraas, R.C., 2019. Emmetropia is maintained despite continued eye growth from 16 to 18 years of age. Invest. Ophthalmol. Vis. Sci. 60, 4178–4186.
Hall, D., 2018. Developing outcome measures for research. ENT & Audiology News 26, 68–70.
He, M., Du, Y., Liu, Q., Ren, C., Liu, J., Wang, Q., Li, L., Yu, J., 2016. Effects of orthokeratology on the progression of low to moderate myopia in Chinese children. BMC Ophthalmol. 16, 126.
Heneghan, C., Goldacre, B., Mahtani, K.R., 2017. Why clinical trial outcomes fail to translate into benefits for patients. Trials 18, 122.
Hiraoka, T., Kakita, T., Okamoto, F., Takahashi, H., Oshika, T., 2012. Long-term effect of overnight orthokeratology on axial length elongation in childhood myopia: a 5-year follow-up study. Invest. Ophthalmol. Vis. Sci. 53, 3913–3919.
Holden, B.A., Fricke, T.R., Wilson, D.A., Jong, M., Naidoo, K.S., Sankaridurg, P., Wong, T.Y., Naduvilath, T.J., Resnikoff, S., 2016. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. Ophthalmology 123, 1036–1042.
Hollestein, L., Nijsten, T., 2015. Guidelines for statistical reporting in the British journal of dermatology. Br. J. Dermatol. 173, 3–5.
Hosoda, Y., Yoshikawa, M., Miyake, M., Tabara, Y., Shimada, N., Zhao, W., Oishi, A., Nakanishi, H., Hata, M., Akagi, T., Ooto, S., Nagaoka, N., Fang, Y., Nagahama Study Group, Ohno-Matsui, K., Cheng, C.Y., Saw, S.M., Yamada, R., Matsuda, F., Tsujikawa, A., Yamashiro, K., 2018. CCDC102B confers risk of low vision and blindness in high myopia. Nat. Commun. 9, 1782.
Hou, W., Norton, T.T., Hyman, L., Gwiazda, J., 2018. Axial elongation in myopic children and its association with myopia progression in the correction of myopia evaluation trial. Eye Contact Lens 44, 248–259.
Huang, J., Wen, D., Wang, Q., McAlinden, C., Flitcroft, I., Chen, H., Saw, S.M., Chen, H., Bao, F., Zhao, Y., Hu, L., Li, X., Gao, R., Lu, W., Du, Y., Jinag, Z., Yu, A., Lian, H., Jiang, Q., Yu, Y., Qu, J., 2016. Efficacy comparison of 16 interventions for myopia control in children: a network meta-analysis. Ophthalmology 123, 697–708.
Hussin, H.M., Spry, P.G., Majid, M.A., Gouws, P., 2006. Reliability and validity of the partial coherence interferometry for measurement of ocular axial length in children. Eye 20, 1021–1024.
Hyman, L., Gwiazda, J., Hussein, M., Norton, T.T., Wang, Y., Marsh-Tootle, W., Everett, D., 2005. Relationship of age, sex, and ethnicity with myopia progression and axial elongation in the correction of myopia evaluation trial. Arch. Ophthalmol. 123, 977–987.
Joachimsen, L., Bohringer, D., Gross, N.J., Reich, M., Stifter, J., Reinhard, T., Lagreze, W. A., 2019. A pilot study on the efficacy and safety of 0.01% atropine in German schoolchildren with progressive myopia. Ophthalmol. Ther. 8, 427–433.
Jonas, J.B., Ohno-Matsui, K., Spaide, R.F., Holbach, L., Panda-Jonas, S., 2013. Macular Bruch's membrane defects and axial length: association with gamma zone and delta zone in peripapillary region. Invest. Ophthalmol. Vis. Sci. 54, 1295–1302.
Jonas, J.B., Xu, L., Wang, Y.X., Bi, H.S., Wu, J.F., Jiang, W.J., Nangia, V., Sinha, A., Zhu, D., Tao, Y., 2016. Education-related parameters in high myopia: adults versus school children. PloS One 11, e0154554.
Kakita, T., Hiraoka, T., Oshika, T., 2011. Influence of overnight orthokeratology on axial elongation in childhood myopia. Invest. Ophthalmol. Vis. Sci. 52, 2170–2174.
Kang, P., 2018. Optical and pharmacological strategies of myopia control. Clin. Exp. Optom. 101, 321–332.
Kanthan, G.L., Mitchell, P., Rochtchina, E., Cumming, R.G., Wang, J.J., 2014. Myopia and the long-term incidence of cataract and cataract surgery: the Blue Mountains eye study. Clin. Exp. Ophthalmol. 42, 347–353.
Kaphle, D., Atchison, D.A., Schmid, K.L., 2020. Multifocal spectacles in childhood myopia: are treatment effects maintained? A systematic review and meta-analysis. Surv. Ophthalmol. 65, 239–249.
King, N.B., Harper, S., Young, M.E., 2012. Use of relative and absolute effect measures in reporting health inequalities: structured review. Br. Med. J. 345, e5774.
Knapp, A., 1925. Glaucoma in myopic eyes. Trans. Am. Ophthalmol. Soc. 23, 61–70.
Knapp, A., 1943. Retinal detachment and trauma. Trans. Am. Ophthalmol. Soc. 41, 186–197.

Kuzin, A.A., Varma, R., Reddy, H.S., Torres, M., Azen, S.P., 2010. Ocular biometry and open-angle glaucoma: the Los Angeles Latino eye study. Ophthalmology 117, 1713–1719.
Lam, A.K., Chan, R., Pang, P.C., 2001. The repeatability and accuracy of axial length and anterior chamber depth measurements from the IOLMaster. Ophthalmic Physiol. Optic. 21, 477–483.
Lam, C.S., Tang, W.C., Tse, D.Y., Tang, Y.Y., To, C.H., 2014. Defocus incorporated soft contact (DISC) lens slows myopia progression in Hong Kong Chinese schoolchildren: a 2-year randomised clinical trial. Br. J. Ophthalmol. 98, 40–45.
Lam, C.S.Y., Tang, W.C., Tse, D.Y., Lee, R.P.K., Chun, R.K.M., Hasegawa, K., Qi, H., Hatanaka, T., To, C.H., 2020. Defocus incorporated multiple segments (DIMS) spectacle lenses slow myopia progression: a 2-year randomised clinical trial. Br. J. Ophthalmol. 104, 363–368.
Larkin, G.L., Tahir, A., Epley, K.D., Beauchamp, C.L., Tong, J.T., Clark, R.A., 2019. Atropine 0.01% eye drops for myopia control in American children: a multiethnic sample across three us sites. Ophthalmol. Ther. 8, 589–598.
Lee, Y.C., Wang, J.H., Chiu, C.J., 2017. Effect of orthokeratology on myopia progression: twelve-year results of a retrospective cohort study. BMC Ophthalmol. 17, 243.
Lee, J.T.L., Guo, X., Li, Z., Jong, M., Sankaridurg, P., He, M., 2020a. Progression and longitudinal biometric changes in highly myopic eyes. Invest. Ophthalmol. Vis. Sci. 61, 34.
Lee, M.W., Lee, S.E., Lim, H.B., Kim, J.Y., 2020b. Longitudinal changes in axial length in high myopia: a 4-year prospective study. Br. J. Ophthalmol. 104, 600–603.
Leo, S.W., 2017. Current approaches to myopia control. Curr. Opin. Ophthalmol. 28, 267–275.
Leshno, A., Farzavandi, S.K., Gomez-de-Liano, R., Sprunger, D.T., Wygnanski-Jaffe, T., Mezer, E., 2020. Practice patterns to decrease myopia progression differ among paediatric ophthalmologists around the world. Br. J. Ophthalmol. 104, 535–540.
Leung, J.T., Brown, B., 1999. Progression of myopia in Hong Kong Chinese schoolchildren is slowed by wearing progressive lenses. Optom. Vis. Sci. 76, 346–354.
Li, S.M., Kang, M.T., Wu, S.S., Liu, L.R., Li, H., Chen, Z., Wang, N., 2016. Efficacy, safety and acceptability of orthokeratology on slowing axial elongation in myopic children by meta-analysis. Curr. Eye Res. 41, 600–608.
Li, S.M., Kang, M.T., Wu, S.S., Meng, B., Sun, Y.Y., Wei, S.F., Liu, L., Peng, X., Chen, Z., Zhang, F., Wang, N., 2017. Studies using concentric ring bifocal and peripheral add multifocal contact lenses to slow myopia progression in school-aged children: a meta-analysis. Ophthalmic Physiol. Optic. 37, 51–59.
Lin, H.J., Wan, L., Tsai, F.J., Tsai, Y.Y., Chen, L.A., Tsai, A.L., Huang, Y.C., 2014. Overnight orthokeratology is comparable with atropine in controlling myopia. BMC Ophthalmol. 14, 40.
Linnet, K., 1993. Evaluation of regression procedures for methods comparison studies. Clin. Chem. 39, 424–432.
Lipson, M.J., Brooks, M.M., Koffler, B.H., 2018. The role of orthokeratology in myopia control: a review. Eye Contact Lens 44, 224–230.
Liu, H.H., Xu, L., Wang, Y.X., Wang, S., You, Q.S., Jonas, J.B., 2010. Prevalence and progression of myopic retinopathy in Chinese adults: the Beijing Eye Study. Ophthalmology 117, 1763–1768.
MacCallum, R.C., Zhang, S., Preacher, K.J., Rucker, D.D., 2002. On the practice of dichotomization of quantitative variables. Psychol. Methods 7, 19–40.
Madansky, A., 1959. The fitting of straight lines when both variables are subject to error. J. Am. Stat. Assoc. 54, 173–205.
McBrien, N.A., Millodot, M., 1985. Clinical evaluation of the Canon autoref R-1. Am. J. Optom. Physiol. Opt. 62, 786–792.
McCarty, C.A., Mukesh, B.N., Fu, C.L., Taylor, H.R., 1999. The epidemiology of cataract in Australia. Am. J. Ophthalmol. 128, 446–465.
Meguro, A., Yamane, T., Takeuchi, M., Miyake, M., Fan, Q., Zhao, W., Wang, I.J., Mizuki, Y., Yamada, N., Nomura, N., Tsujikawa, A., Matsuda, F., Hosoda, Y., Saw, S. M., Cheng, C.Y., Tsai, T.H., Yoshida, M., Iijima, Y., Teshigawara, T., Okada, E., Ota, M., Inoko, H., Mizuki, N., 2020. Genome-wide association study in asians identifies novel loci for high myopia and highlights a nervous system role in its pathogenesis. Ophthalmology 127, 1612–1624.
Mitry, D., Charteris, D.G., Fleck, B.W., Campbell, H., Singh, J., 2010. The epidemiology of rhegmatogenous retinal detachment: geographical variation and clinical associations. Br. J. Ophthalmol. 94, 678–684.
Moher, D., Hopewell, S., Schulz, K.F., Montori, V., Gøtzsche, P.C., Devereaux, P., Elbourne, D., Egger, M., Altman, D.G., 2010. Consort 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. J. Clin. Epidemiol. 63, e1–e37.
Morgan, I.G., French, A.N., Ashby, R.S., Guo, X., Ding, X., He, M., Rose, K.A., 2018. The epidemics of myopia: aetiology and prevention. Prog. Retin. Eye Res. 62, 134–149.
Morgan, I.G., He, M., Rose, K.A., 2017. Epidemic of pathologic myopia: what can laboratory studies and epidemiology tell us? Retina 37, 989–997.
Morgan, I.G., Ohno-Matsui, K., Saw, S.M., 2012. Myopia. Lancet 379, 1739–1748.
Morgan, I.G., Rose, K.A., 2005. How genetic is school myopia? Prog. Retin. Eye Res. 24, 1–38.
Mutti, D.O., Hayes, J.R., Mitchell, G.L., Jones, L.A., Moeschberger, M.L., Cotter, S.A., Kleinstein, R.N., Manny, R.E., Twelker, J.D., Zadnik, K., Group, C.S., 2007. Refractive error, axial length, and relative peripheral refractive error before and after the onset of myopia. Invest. Ophthalmol. Vis. Sci. 48, 2510–2519.
Mutti, D.O., Mitchell, G.L., Jones, L.A., Friedman, N.E., Frane, S.L., Lin, W.K., Moeschberger, M.L., Zadnik, K., 2005. Axial growth and changes in lenticular and corneal power during emmetropization in infants. Invest. Ophthalmol. Vis. Sci. 46, 3074–3080.
Mutti, D.O., Mitchell, G.L., Sinnott, L.T., Jones-Jordan, L.A., Moeschberger, M.L., Cotter, S.A., Kleinstein, R.N., Manny, R.E., Twelker, J.D., Zadnik, K., Group, C.S., 2012. Corneal and crystalline lens dimensions before and after myopia onset. Optom. Vis. Sci. 89, 251–262.
Mutti, D.O., Zadnik, K., Egashira, S., Kish, L., Twelker, J.D., Adams, A.J., 1994. The effect of cycloplegia on measurement of the ocular components. Invest. Ophthalmol. Vis. Sci. 35, 515–527.
Nakagawa, S., Cuthill, I.C., 2007. Effect size, confidence interval and statistical significance: a practical guide for biologists. Biol. Rev. 82, 591–605.
Nakao, S.Y., Miyake, M., Hosoda, Y., Nakano, E., Mori, Y., Takahashi, A., Ooto, S., Tamura, H., Tabara, Y., Yamashiro, K., Matsuda, F., 2020. Myopia prevalence and ocular biometry features in a general Japanese population: the nagahama study. Ophthalmology 127 (Online ahead of print).
Nichols, J.J., Marsich, M.M., Nguyen, M., Barr, J.T., Bullimore, M.A., 2000. Overnight orthokeratology. Optom. Vis. Sci. 77, 252–259.
Numa, S., Yamashiro, K., Wakazono, T., Yoshikawa, M., Miyake, M., Nakanishi, H., Oishi, A., Nagahama Study, G., Tabara, Y., Matsuda, F., Yoshimura, N., Tsujikawa, A., 2018. Prevalence of posterior staphyloma and factors associated with its shape in the Japanese population. Sci. Rep. 8, 4594.
Ohno-Matsui, K., 2016. Pathologic myopia. Asia pac. J. Ophthalmol. 5, 415–423.
Ohno-Matsui, K., Jonas, J.B., 2019. Posterior staphyloma in pathologic myopia. Prog. Retin. Eye Res. 70, 99–109.
Ohno-Matsui, K., Kawasaki, R., Jonas, J.B., Cheung, C.M., Saw, S.M., Verhoeven, V.J., Klaver, C.C., Moriyama, M., Shinohara, K., Kawasaki, Y., Yamazaki, M., Meuer, S., Ishibashi, T., Yasuda, M., Yamashita, H., Sugano, A., Wang, J.J., Mitchell, P., Wong, T.Y., Group, M.E.-a.f.P.M.S., 2015. International photographic classification and grading system for myopic maculopathy. Am. J. Ophthalmol. 159, 877–883.
Ohno-Matsui, K., Lai, T.Y.Y., Lai, C.C., Cheung, C.M.G., 2016. Updates of pathologic myopia. Prog. Retin. Eye Res. 52, 156–187.
Orsmond, G.I., Cohn, E.S., 2015. The distinctive features of a feasibility study: objectives and guiding questions. OTJR 35, 169–177.
Pärssinen, O., Kauppinen, M., 2019. Risk factors for high myopia: a 22-year follow-up study from childhood to adulthood. Acta Ophthalmol. 97, 510–518.
Paune, J., Morales, H., Armengol, J., Quevedo, L., Faria-Ribeiro, M., Gonzalez-Meijome, J.M., 2015. Myopia control with a novel peripheral gradient soft lens and orthokeratology: a 2-year clinical trial. BioMed Res. Int. 2015, 507572.
Perera, S.A., Wong, T.Y., Tay, W.T., Foster, P.J., Saw, S.M., Aung, T., 2010. Refractive error, axial dimensions, and primary open-angle glaucoma: the Singapore Malay eye study. Arch. Ophthalmol. 128, 900–905.
Prousali, E., Haidich, A.B., Fontalis, A., Ziakas, N., Brazitikos, P., Mataftsi, A., 2019. Efficacy and safety of interventions to control myopia progression in children: an overview of systematic reviews and meta-analyses. BMC Ophthalmol. 19, 106.
Rah, M.J., Jackson, J.M., Jones, L.A., Marsden, H.J., Bailey, M.D., Barr, J.T., 2002. Overnight orthokeratology: preliminary results of the lenses and overnight orthokeratology (LOOK) study. Optom. Vis. Sci. 79, 598–605.
Read, S.A., Collins, M.J., Carney, L.G., 2005. The diurnal variation of corneal topography and aberrations. Cornea 24, 678–687.
Read, S.A., Collins, M.J., Sander, B.P., 2010. Human optical axial length and defocus. Invest. Ophthalmol. Vis. Sci. 51, 6262–6269.
Robboy, M.W., Hilmantel, G., Tarver, M.E., Eydelman, M.B., 2018. Assessment of clinical trials for devices intended to control myopia progression in children. Eye Contact Lens 44, 212–219.
Rosenfield, M., Chiu, N.N., 1995. Repeatability of subjective and objective refraction. Optom. Vis. Sci. 72, 577–579.
Rozema, J., Dankert, S., Iribarren, R., Lanca, C., Saw, S.M., 2019. Axial growth and lens power loss at myopia onset in Singaporean children. Invest. Ophthalmol. Vis. Sci. 60, 3091–3099.
Ruiz-Medrano, J., Montero, J.A., Flores-Moreno, I., Arias, L., Ruiz-Morena, J.M., 2019. Myopic maculopathy: current status and proposal for a new classification and grading system (ATN). Prog. Retin. Eye Res. 69, 80–115.
Ruiz-Pomeda, A., Perez-Sanchez, B., Valls, I., Prieto-Garrido, F.L., Gutierrez-Ortega, R., Villa-Collar, C., 2018. Misight assessment study Spain (mass). A 2-year randomized clinical trial. Graefes Arch. Clin. Exp. Ophthalmol. 256, 1011–1021.
Sacchi, M., Serafino, M., Villani, E., Tagliabue, E., Luccarelli, S., Bonsignore, F., Nucci, P., 2019. Efficacy of atropine 0.01% for the treatment of childhood myopia in European patients. Acta Ophthalmol. 97, e1136–e1140.
Sankaridurg, P., Bakaraju, R.C., Naduvilath, T., Chen, X., Weng, R., Tilia, D., Xu, P., Li, W., Conrad, F., Smith 3rd, E.L., Ehrmann, K., 2019. Myopia control with novel central and peripheral plus contact lenses and extended depth of focus contact lenses: 2 year results from a randomised clinical trial. Ophthalmic Physiol. Optic. 39, 294–307.
Sankaridurg, P., Conrad, F., Tran, H., Zhu, J., 2018. Controlling progression of myopia: optical and pharmaceutical strategies. Asia Pac. J. Ophthalmol. 7, 405–414.
Sankaridurg, P., Holden, B., Smith 3rd, E., Naduvilath, T., Chen, X., de la Jara, P.L., Martinez, A., Kwan, J., Ho, A., Frick, K., Ge, J., 2011. Decrease in rate of myopia progression with a contact lens designed to reduce relative peripheral hyperopia: one-year results. Invest. Ophthalmol. Vis. Sci. 52, 9362–9367.
Santodomingo-Rubido, J., Mallen, E.A., Gilmartin, B., Wolffsohn, J.S., 2002. A new non-contact optical device for ocular biometry. Br. J. Ophthalmol. 86, 458–462.
Santodomingo-Rubido, J., Villa-Collar, C., Gilmartin, B., Gutierrez-Ortega, R., 2012. Myopia control with orthokeratology contact lenses in Spain: refractive and biometric changes. Invest. Ophthalmol. Vis. Sci. 53, 5060–5065.
Santodomingo-Rubido, J., Villa-Collar, C., Gilmartin, B., Gutierrez-Ortega, R., 2013. Factors preventing myopia progression with orthokeratology correction. Optom. Vis. Sci. 90, 1225–1236.
Santodomingo-Rubido, J., Villa-Collar, C., Gilmartin, B., Gutierrez-Ortega, R., Sugimoto, K., 2017. Long-term efficacy of orthokeratology contact lens wear in controlling the progression of childhood myopia. Curr. Eye Res. 42, 713–720.

Sanz Diez, P., Yang, L.H., Lu, M.X., Wahl, S., Ohlendorf, A., 2019. Growth curves of myopia-related parameters to clinically monitor the refractive development in Chinese schoolchildren. Graefes Arch. Clin. Exp. Ophthalmol. 257, 1045–1053.

Saw, S.M., Chua, W.H., Hong, C.Y., Wu, H.M., Chia, K.S., Stone, R.A., Tan, D., 2002. Height and its relationship to refraction and biometry parameters in Singapore Chinese children. Invest. Ophthalmol. Vis. Sci. 43, 1408–1413.

Saw, S.M., Matsumura, S., Hoang, Q.V., 2019. Prevention and management of myopia and myopic pathology. Invest. Ophthalmol. Vis. Sci. 60, 488–499.

Saw, S.M., Tong, L., Chua, W.H., Chia, K.S., Koh, D., Tan, D.T., Katz, J., 2005. Incidence and progression of myopia in Singaporean school children. Invest. Ophthalmol. Vis. Sci. 46, 51–57.

Scheiman, M., Gwiazda, J., Zhang, Q., Deng, L., Fern, K., Manny, R.E., Weissberg, E., Hyman, L., 2016. Longitudinal changes in corneal curvature and its relationship to axial length in the correction of myopia evaluation trial (COMET) cohort. J. Optom. 9, 13–21.

Schulle, K.L., Berntsen, D.A., 2013. Repeatability of on- and off-axis eye length measurements using the Lenstar. Optom. Vis. Sci. 90, 16–22.

Schulz, K.F., Altman, D.G., Moher, D., Group, t.C., 2010. Consort 2010 statement: updated guidelines for reporting parallel group randomised trials. BMC Med. 8, 18.

Severinsky, B., 2016. A case of severe refractive changes induced by galyfilcon a silicone hydrogel contact lenses. Int. J. Ophthalmol. 9, 175–177.

Shen, P., Zheng, Y., Ding, X., Liu, B., Congdon, N., Morgan, I., He, M., 2013. Biometric measurements in highly myopic eyes. J. Cataract Refract. Surg. 39, 180–187.

Sheng, H., Bottjer, C.A., Bullimore, M.A., 2004. Ocular component measurement using the Zeiss IOLMaster. Optom. Vis. Sci. 81, 27–34.

Sherwin, J.C., Reacher, M.H., Keogh, R.H., Khawaja, A.P., Mackey, D.A., Foster, P.J., 2012. The association between time spent outdoors and myopia in children and adolescents: a systematic review and meta-analysis. Ophthalmology 119, 2141–2151.

Siatkowski, R.M., Cotter, S.A., Crockett, R.S., Miller, J.M., Novack, G.D., Zadnik, K., Group, U.S.P.S., 2008. Two-year multicenter, randomized, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. JAAPOS 12, 332–339.

Silva, R., 2012. Myopic maculopathy: a review. Ophthalmologica 228, 197–213.

Stang, A., Poole, C., Kuss, O., 2010. The ongoing tyranny of statistical significance testing in biomedical research. Eur. J. Epidemiol. 25, 225–230.

Sun, Y., Xu, F., Zhang, T., Liu, M., Wang, D., Chen, Y., Liu, Q., 2015. Orthokeratology to control myopia progression: a meta-analysis. PloS One 10, e0124535.

Swarbrick, H.A., Wong, G., O'Leary, D.J., 1998. Corneal response to orthokeratology. Optom. Vis. Sci. 75, 791–799.

Szczotka, L., 2004. Unintended ortho-k effect fromo silicone-hydrogel lenses. Contact Lens Spectr. 19 (8).

Tan, D.T., Lam, D.S., Chua, W.H., Shu-Ping, D.F., Crockett, R.S., 2005. One-year multicenter, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. Ophthalmology 112, 84–91.

Tideman, J.W., Snabel, M.C., Tedja, M.S., van Rijn, G.A., Wong, K.T., Kuijpers, R.W., Vingerling, J.R., Hofman, A., Buitendijk, G.H., Keunen, J.E., Boon, C.J., Geerards, A. J., Luyten, G.P., Verhoeven, V.J., Klaver, C.C., 2016. Association of axial length with risk of uncorrectable visual impairment for Europeans with myopia. JAMA Ophthalmol 134, 1355–1363.

Tideman, J.W.L., Polling, J.R., Vingerling, J.R., Jaddoe, V.W.V., Williams, C., Guggenheim, J.A., Klaver, C.C.W., 2018. Axial length growth and the risk of developing myopia in European children. Acta Ophthalmol. 96, 301–309.

Tong, L., Huang, X.L., Koh, A.L., Zhang, X., Tan, D.T., Chua, W.H., 2009. Atropine for the treatment of childhood myopia: effect on myopia progression after cessation of atropine. Ophthalmology 116, 572–579.

Tran, H.D., Tran, Y.H., Tran, T.D., Jong, M., Coroneo, M., Sankaridurg, P., 2018. A review of myopia control with atropine. J. Ocul. Pharmacol. Therapeut. 34, 374–379.

Twelker, J.D., Mitchell, G.L., Messer, D.H., Bhakta, R., Jones, L.A., Mutti, D.O., Cotter, S. A., Klenstein, R.N., Manny, R.E., Zadnik, K., 2009. Children's ocular components and age, gender, and ethnicity. Optom. Vis. Sci. 86, 918–935.

Ueda, E., Yasuda, M., Fujiwara, K., Hashimoto, S., Ohno-Matsui, K., Hata, J., Ishibashi, T., Ninomiya, T., Sonoda, K.H., 2019. Trends in the prevalence of myopia and myopic maculopathy in a Japanese population: the Hisayama study. Invest. Ophthalmol. Vis. Sci. 60, 2781–2786.

United States Food and Drug Administration, 2003. Dermatologic and Ophthalmic Drugs Committee. Study designs of trial in the treatment of myopia. September 25. https://wayback.archive-it.org/7993/20170404074059/https://www.fda.gov/ohrms/dockets/ac/03/transcripts/3988T1.htm. (Accessed 15 November 2020).

United States Food and Drug Administration, 2019. Center for Devices and Radiological Health. Pre-market approval, MiSight 1 day (omafilcon a) soft (hydrophilic) contact lenses for daily wear, summary of safety and effectiveness data. https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180035B.pdf. (Accessed 15 November 2020).

Vandenbroucke, J.P., Von Elm, E., Altman, D.G., Gøtzsche, P.C., Mulrow, C.D., Pocock, S. J., Poole, C., Schlesselman, J.J., Egger, M., Initiative, S., 2007. Strengthening the reporting of observational studies in epidemiology (strobe): explanation and elaboration. PLoS Med. 4, e297.

Vongphanit, J., Mitchell, P., Wang, J.J., 2002. Prevalence and progression of myopic retinopathy in an older population. Ophthalmology 109, 704–711.

Wagner, S., Conrad, F., Bakaraju, R.C., Fedtke, C., Ehrmann, K., Holden, B.A., 2015. Power profiles of single vision and multifocal soft contact lenses. Cont. Lens Anterior Eye. 38, 2–14.

Walline, J.J., 2016. Myopia control: a review. Eye Contact Lens 42, 3–8.

Walline, J.J., Greiner, K.L., McVey, M.E., Jones-Jordan, L.A., 2013. Multifocal contact lens myopia control. Optom. Vis. Sci. 90, 1207–1214.

Walline, J.J., Jones, L.A., Sinnott, L.T., 2009. Corneal reshaping and myopia progression. Br. J. Ophthalmol. 93, 1181–1185.

Walline, J.J., Lindsley, K., Vedula, S.S., Cotter, S.A., Mutti, D.O., Twelker, J.D., 2011. Interventions to slow progression of myopia in children. Cochrane Database Syst. Rev. 7, CD004916.

Walline, J.J., Robboy, M.W., Hilmantel, G., Tarver, M.E., Afshari, N.A., Dhaliwal, D.K., Morse, C.L., Quinn, C.J., Repka, M.X., Eydelman, M.B., 2018. Food and drug administration, American Academy of ophthalmology, American Academy of aptometry, American association for pediatric ophthalmology and strabismus, American optometric association, American society of cataract and refractive surgery, and contact lens association of ophthalmologists co-sponsored workshop: controlling the progression of myopia: contact lenses and future medical devices. Eye Contact Lens 44, 205–211.

Wang, B., Naidu, R.K., Qu, X., 2017a. Factors related to axial length elongation and myopia progression in orthokeratology practice. PloS One 12, e0175913.

Wang, Y.R., Bian, H.L., Wang, Q., 2017b. Atropine 0.5% eyedrops for the treatment of children with low myopia: a randomized controlled trial. Medicine (Baltim.) 96, e7371.

Wang, N.K., Wu, Y.M., Wang, J.P., Liu, L., Yeung, L., Chen, Y.P., Chen, Y.H., Yeh, L.K., Wu, W.C., Chuang, L.H., Lai, C.C., 2016. Clinical characteristics of posterior staphylomas in myopic eyes with axial length shorter than 26.5 millimeters. Am. J. Ophthalmol. 162, 180–190 e181.

Weng, R.Y.S., Naduvilath, T.J., Bakaraju, R.C., Chen, X., Sankaridurg, P., 2019. Relation between treatment effect of myopia control lenses and demographic factors in children. Invest. Ophthalmol. Vis. Sci. 60 (9), 5822.

Wildsoet, C.F., Chia, A., Cho, P., Guggenheim, J.A., Polling, J.R., Read, S., Sankaridurg, P., Saw, S.M., Trier, K., Walline, J.J., Wu, P.C., Wolffsohn, J.S., 2019. IMI - interventions for controlling myopia onset and progression report. Invest. Ophthalmol. Vis. Sci. 60, M106–M131.

Wilkinson, L., 1999. Statistical methods in psychology journals: guidelines and explanations. Am. Psychol. 54, 594–610.

Wolffsohn, J.S., Calossi, A., Cho, P., Gifford, K., Jones, L., Jones, D., Guthrie, S., Li, M., Lipener, C., Logan, N.S., Malet, F., Peixoto-de-Matos, S.C., Gonzalez-Meijome, J.M., Nichols, J.J., Orr, J.B., Santodomingo-Rubido, J., Schaefer, T., Thite, N., van der Worp, E., Tarutta, E., Iomdina, E., Ali, B.M., Villa-Collar, C., Abesamis-Dichoso, C., Chen, C., Pult, H., Blaser, P., Parra Sandra Johanna, G., Iqbal, F., Ramos, R., Carrillo Orihuela, G., Boychev, N., 2020. Global trends in myopia management attitudes and strategies in clinical practice - 2019 update. Cont. Lens Anterior Eye. 43, 9–17.

Wolffsohn, J.S., Calossi, A., Cho, P., Gifford, K., Jones, L., Li, M., Lipener, C., Logan, N.S., Malet, F., Matos, S., Meijome, J.M., Nichols, J.J., Orr, J.B., Santodomingo-Rubido, J., Schaefer, T., Thite, N., van der Worp, E., Zvirgzdina, M., 2016. Global trends in myopia management attitudes and strategies in clinical practice. Cont. Lens Anterior Eye. 39, 106–116.

Wolffsohn, J.S., Flitcroft, D.I., Gifford, K.L., Jong, M., Jones, L., Klaver, C.C.W., Logan, N. S., Naidoo, K., Resnikoff, S., Sankaridurg, P., Smith 3rd, E.L., Troilo, D., Wildsoet, C. F., 2019a. IMI - myopia control reports overview and introduction. Invest. Ophthalmol. Vis. Sci. 60, M1–M19.

Wolffsohn, J.S., Kollbaum, P.S., Berntsen, D.A., Atchison, D.A., Benavente, A., Bradley, A., Buckhurst, H., Collins, M., Fujikado, T., Hiraoka, T., Hirota, M., Jones, D., Logan, N.S., Lundstrom, L., Torii, H., Read, S.A., Naidoo, K., 2019b. IMI - clinical myopia control trials and instrumentation report. Invest. Ophthalmol. Vis. Sci. 60, M132–M160.

Wong, T.Y., Foster, P.J., Johnson, G.J., Seah, S.K., 2003. Refractive errors, axial ocular dimensions, and age-related cataracts: the Tanjong Pagar survey. Invest. Ophthalmol. Vis. Sci. 44, 1479–1485.

Wong, Y.L., Sabanayagam, C., Ding, Y., Wong, C.W., Yeo, A.C., Cheung, Y.B., Cheung, G., Chia, A., Ohno-Matsui, K., Wong, T.Y., Wang, J.J., Cheng, C.Y., Hoang, Q.V., Lamoureux, E., Saw, S.M., 2018. Prevalence, risk factors, and impact of myopic macular degeneration on visual impairment and functioning among adults in Singapore. Invest. Ophthalmol. Vis. Sci. 59, 4603–4613.

Wong, C.W., Yanagi, Y., Tsai, A.S.H., Shihabuddeen, W.A., Cheung, N., Lee, S.Y., Jonas, J.B., Cheung, C.M.G., 2019. Correlation of axial length and myopic macular degeneration to levels of molecular factors in the aqueous. Sci. Rep. 9, 1–8.

Wu, P.C., Chen, C.T., Lin, K.K., Sun, C.C., Kuo, C.N., Huang, H.M., Poon, Y.C., Yang, M.L., Chen, C.Y., Huang, J.C., Wu, P.C., Yang, I.H., Yu, H.J., Fang, P.C., Tsai, C.L., Chiou, S.T., Yang, Y.H., 2018. Myopia Prevention and Outdoor Light Intensity in a School-Based Cluster Randomized Trial. Ophthalmol 125, 1239–1250.

Xiang, F., He, M., Morgan, I.G., 2012. Annual changes in refractive errors and ocular components before and after the onset of myopia in Chinese children. Ophthalmology 119, 1478–1484.

Xiong, S., Sankaridurg, P., Naduvilath, T., Zang, J., Zou, H., Zhu, J., Lv, M., He, X., Xu, X., 2017a. Time spent in outdoor activities in relation to myopia prevention and control: a meta-analysis and systematic review. Acta Ophthalmol. 95, 551–566.

Xiong, S., Zhang, B., Hong, Y., He, X., Zhu, J., Zou, H., Xu, X., 2017b. The associations of lens power with age and axial length in healthy Chinese children and adolescents aged 6 to 18 years. Invest. Ophthalmol. Vis. Sci. 58, 5849–5855.

Yam, J.C., Jiang, Y., Tang, S.M., Law, A.K.P., Chan, J.J., Wong, E., Ko, S.T., Young, A.L., Tham, C.C., Chen, L.J., Pang, C.P., 2019. Low-concentration atropine for myopia progression (lamp) study: a randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in myopia control. Ophthalmology 126, 113–124.

Yamashita, T., Iwase, A., Sakai, H., Terasaki, H., Sakamoto, T., Araie, M., 2019. Differences of body height, axial length, and refractive error at different ages in Kumejima study. Graefes Arch. Clin. Exp. Ophthalmol. 257, 371–378.

Ye, S., Liu, S., Li, W., Wang, Q., Xi, W., Zhang, X., 2019. Associations between anthropometric indicators and both refraction and ocular biometrics in a cross-sectional study of Chinese schoolchildren. BMJ Open 9, e027212.

Yoo, S.G., Cho, M.J., Kim, U.S., Baek, S.-H., 2017. Cycloplegic refraction in hyperopic children: effectiveness of a 0.5% tropicamide and 0.5% phenylephrine addition to 1% cyclopentolate regimen. Kor. J. Ophthalmol. 31, 249–256.

Zadnik, K., Mutti, D.O., Adams, A.J., 1992. The repeatability of measurement of the ocular components. Invest. Ophthalmol. Vis. Sci. 33, 2325–2333.

Zhu, M.J., Feng, H.Y., He, X.G., Zou, H.D., Zhu, J.F., 2014. The control effect of orthokeratology on axial length elongation in Chinese children with myopia. BMC Ophthalmol. 14, 141.

Zhu, X., McBrien, N.A., Smith 3rd, E.L., Troilo, D., Wallman, J., 2013. Eyes in various species can shorten to compensate for myopic defocus. Invest. Ophthalmol. Vis. Sci. 54, 2634–2644.

Zloto, O., Wygnanski-Jaffe, T., Farzavandi, S.K., Gomez-de-Liaño, R., Sprunger, D.T., Mezer, E., 2018. Current trends among pediatric ophthalmologists to decrease myopia progression—an international perspective. Graefes Arch. Clin. Exp. Ophthalmol. 256, 2457–2466.