


Review Article

# Laser-based refractive surgery techniques to treat myopia in adults. An overview of systematic reviews and meta-analyses

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## ABSTRACT.

Systematic reviews (SRs) and meta-analyses (MAs) are of great importance for basing clinical decisions. However, misleading interpretations may result when informed decisions rest on biased review papers with methodological issues. To evaluate which treatment is optimal, an overview was made of SRs and MAs to establish the quality and certainty of meta-evidence published on the efficacy of laser-based refractive surgery techniques for treating myopia in adults. A search was made in five databases and was updated using Really Simple Syndication (RSS) feed appliances up to April 2021; SRs with or without MAs were included. Methodological quality was appraised using the AMSTAR-2 tool. The best available reviews were summarized using the GRADE approach. The corrected covered area (CCA) was used to determine the degree of over-representation of publications. The risk of bias of the primary studies was disclosed visually. Thirty-six studies published between 2003 and 2021 were included. Twenty SRs (56%) were conducted in China. The most studied comparisons were SMILE versus FS-LASIK (19%) and FS-LASIK versus MM-LASIK (11%). Of the 251 overlapping index publications, 165 were unique (CCA = 0.015%), representing a negligible risk of skewed reporting. The AMSTAR-2 tool showed most SRs to have critically low or low quality. Nine reviews presented moderate quality. The GRADE approach of the 41 *a priori* outcomes evidenced critically low and low certainty of evidence. Only the spherical equivalent refraction changes at 12 months between LASEK and PRK showed moderate certainty of evidence, favouring PRK (mean difference 0.06, 95%CI [−0.02 to 0.14],  $I^2 = 0\%$ ;  $p \geq 0.05$ ). Index trials among less biased reviews are prone to selection, performance and reporting bias. The appraised techniques exhibit comparable results in terms of efficacy. There is moderate certainty of evidence in favour of the use of PRK over LASEK in terms of the spherical equivalent refraction error changes at 1 year of follow-up. Most appraised SRs presented methodological flaws in critical domains, resulting in a low to critically low certainty of evidence after GRADE appraisal. Therefore, investigators need to study and compare the different laser-based refractive techniques to provide better evidence-based medicine. Further well-designed, high-quality clinical trials and SRs are needed to reappraise the current findings.

**Key words:** adults – evidence-based medicine – myopia – refractive error – refractive surgery – systematic review

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[Correction added on 11 May 2022, after first online publication: The affiliations were corrected for Antonio Vidal-Infer and Adolfo Alonso-Arroyo in this version.]

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## Introduction

### Description of the condition

Myopia or nearsightedness is the most prevalent refractive error. In 2000, a total of 22% of the world population was myopic. By 2050, it is estimated that 50% will be short-sighted and 10% will be highly myopic (Holden *et al.* 2016). High myopia is generally defined as a spherical equivalent error  $\leq 6$  diopters when ocular accommodation is relaxed (Flitcroft *et al.* 2019). The worldwide economic burden of myopia totals approximately USD 202 billion annually (Smith *et al.* 2009), versus USD 139 billion in the USA alone (National Academies of Sciences Engineering *et al.* 2016).

### Description of the intervention

The refractive power of the eye can be modified by altering the curvature of the refractive surface or by introducing intraocular implants such as intraocular lenses (Bower *et al.* 2001).

Laser corneal refractive surgery is an effective alternative to the correction of refractive errors with spectacles or contact lenses, especially in patients with myopia. A wide range of surgical techniques have been developed that modify the refractive error of the eye by removing corneal tissue and reshaping the cornea (Fig. 1).

These procedures can be broadly divided into three categories: corneal surface ablation surgery (PRK, T-PRK, LASEK and Epi-LASIK) (McAlinden & Moore 2011), corneal stromal ablation surgery (techniques involving the creation of a corneal flap, such as LASIK or FS-LASIK) (McAlinden 2012) and refractive corneal lenticule extraction procedures such as FLEx or SMILE (Blum *et al.* 2019).

Adjuvants to refractive surgery used to enhance the postoperative outcomes (e.g. topical timolol, mitomycin C and topical corticosteroids) have also been assessed in clinical settings (Chansue *et al.* 2015, Hofmeister *et al.* 2013, O'Brart *et al.* 1994, Sharma *et al.* 2013).

### Why is it important to do this overview?

Evidence-based medicine seeks to base clinical decisions as much as possible on the most current and highest level of evidence (Sackett *et al.* 1996). Systematic reviews (SRs) and meta-analyses (MAs) constitute powerful tools for decision making because they are able to overcome the limitations of underpowered studies and allow professionals to keep abreast of the literature while basing their decisions on the available specific evidence (Bastian *et al.* 2010).

Nowadays, in consonance with the technological innovations and changes in surgery techniques, the synthesis of healthcare information constitutes a challenge, as over 75 clinical trials and 11 systematic reviews are published on a daily basis (Bastian *et al.* 2010). An overwhelming number of primary studies and systematic reviews on refractive surgery for the treatment of myopia in adults have been published in recent years. Regrettably, SRs and MAs are often not correctly conducted, and their findings may be affected by design and execution bias – causing them to not truly represent what was published in the first place.

The number of people with myopia worldwide is expected to reach 4.76 billion by 2050 (Holden *et al.* 2016) – a trend that has important economic (Ioannidis 2016) and public health

implications. As there appear to be no overviews of systematic reviews (OoSRS) in the available literature, it is of great importance to appraise the methodological quality and summarize the best available SRs and MAs on laser-based refractive surgery for myopia control in adults.

## Material and Methods

### Study protocol

The present study protocol was registered in the INPLASY (INPLASY202150095) database, and was developed according to the Preferred Reporting Items for Overviews of Systematic Reviews (PRIO-harms) checklist (Bougioukas *et al.* 2018). The term 'overview' was used as proposed by the Cochrane collaboration for the synthesis of multiple intervention systematic reviews and meta-analyses.

### Information sources

A search in duplicate by two investigators (SPO and RSP) was made of the main electronic databases and grey literature, including Medline (*via* PubMed), EMBASE, Web of Science (WOS), the Cochrane Library, Google Scholar and Open Grey, up until April 2020. The search included thesauruses such as Mesh (PubMed) and Emtree (EMBASE), as well as other free-text terms that were combined whenever possible and adapted for each database (Table S1). The search string employed for PubMed was as follows: ('Refractive Errors'[Mesh] OR 'Myopia'[Mesh] OR myopia OR nearsightedness) AND ('Refractive Surgical Procedures'[Mesh] OR 'Keratotomy, Subepithelial, Laser-Assisted'[Mesh] OR Laser-Assisted Subepithelial Keratectomy OR Laser Subepithelial Keratomileusis OR Laser-Assisted Subepithelial Keratomileusis OR LASEK OR epipolis laser in situ keratomileusis OR Epipolis laser in situ keratomileusis OR Epi-LASIK OR 'Photorefractive Keratectomy'[Mesh] OR Photorefractive Keratectomy OR PRK OR TransPRK OR transepithelial PRK OR transepithelial photorefractive keratectomy OR refractive surgery OR laser surgery OR small incision lenticule extraction OR SMILE OR femtosecond lenticule extraction OR FLEx) AND (Efficacy OR 'best corrected visual

Refractive surgery techniques included in the Overview	
Abbreviation	Name
Epi-LASIK	Epipolis laser in situ keratomileusis
FLEx	Femtosecond lenticule extraction
FS-LASIK	Femtosecond laser in situ keratomileusis
LASEK	Laser epithelial keratectomy
LASIK	Laser in situ keratomileusis
PRK	Photorefractive keratectomy
SMILE	Small-incision lenticule extraction
T-PRK	Transepithelial photorefractive keratectomy

Fig. 1. Refractive surgery techniques.

acuity' OR BCVA OR visual acuity OR safety OR predictability OR pain scores OR 'Quality of life measures' OR dry-eye OR 'glare' OR 'halo' OR adverse events OR haze OR pain OR visual recovery OR heal OR target refraction OR diopter OR mean spherical equivalent OR Myopia degree) AND (systematic review or meta-analysis or meta-analyses).

In addition, complementary sources such as topic-related journals and reference lists of included studies were consulted to retrieve titles not detected through the electronic search. In order to identify new potential titles consistent with the research strategy, the electronic search was kept updated using the Really Simple Syndication (RSS) feed appliance for PubMed. Ongoing review protocols were also sought in the PROSPERO database. No restrictions referred to language or year of publication were applied.

### Eligibility criteria and outcomes of interest

#### Population

Adults (>18 years of age) diagnosed with myopia, defined as the spherical equivalent of  $\leq -0.50$  diopter (Holden *et al.* 2016), with or without astigmatism but without any other comorbidities (e.g. strabismus, amblyopia, keratoconus and pathological myopia subjected to photocoagulation therapy) were included. Systematic reviews focused on myopia but including study subgroups with myopic astigmatism or hyperopia were also considered.

#### Intervention and comparators

Studies assessing two or more laser-based refractive surgery techniques for myopia with or without astigmatism, as well as publications assessing the use of mitomycin C or adjuncts, were included.

#### Outcome measures

The primary outcomes of the present OoSRs were the determination of the methodological quality of the eligible systematic reviews, the degree of study overlap, meta-biases during the review process, the disclosure of the methodological quality of the index titles included among less biased systematic reviews, and the determination of the certainty of evidence referred to the following parameters, as secondary outcomes:

Efficacy was measured in terms of the mean change in refractive error,

uncorrected visual acuity (UCVA 20/20 or better and UCVA 20/40 or better), the UCVA Logarithm of the Minimum Angle of Resolution (LogMar), corrected distance visual acuity (CDVA) LogMar, spherical equivalent refraction changes  $\pm 0.5$  diopter, the proportion of eyes within  $\pm 0.50$  diopter /  $\pm 0.1$  diopter of target refraction, loss of one or more lines of best corrected visual acuity (BCVA) and final BCVA (20/40 or less).

#### Study design

The units of analysis were systematic reviews with or without meta-analyses, and those with network meta-analyses, if any. All of them were based on randomized controlled trials (RCTs) or nonrandomized studies of interventions (NRSIs) in adults ( $\geq 18$  years of age). On the other hand, narrative reviews without systematic electronic searches and evidence appraisals were excluded. For the present overview, a systematic review was defined as such based on the following methodological criteria:

- It must be a secondary analysis of primary studies, consulting at least two main databases and critically assessing the methodological quality of the included studies.
- It must have a clearly formulated question or aim.
- It must use systematic and explicit methods to identify, select, extract and analyse data from the studies.
- When two SRs involving the same topic and the same authors are found, the most recent SR is considered.

#### Study selection and data management

The selection of studies was performed independently and in duplicate by two investigators (SPO and RSP). The citations retrieved through the electronic search were compiled by a reference manager application for the removal of duplicates (Mendeley desktop 1.19.4 for Mac). After the duplicates were removed, the potential eligible citations were transferred to Excel spreadsheets (Microsoft® Excel for Mac ver. 16.33) in order to perform title and abstract and full-text screening.

The selection process consisted of two steps. Firstly, titles not related to

the topic of the overview, other types of primary studies (e.g. experimental and observational clinical studies, *in vitro*, *in vivo* and finite-element studies) and dissertations and theses without systematic reviews were excluded. The second step involved the full-text assessment of those studies lacking enough information to be excluded on the basis of the title and abstract alone, in order to decide their final inclusion or exclusion according to the predefined eligibility criteria.

With respect to unavailable titles from databases or journal pages, a request was sent to the corresponding author to obtain the full manuscript and, in the case of no response, the title was deemed excluded. Kappa scores were used to determine the level of agreement between reviewers (SPO and RSP), and were interpreted according to the Landis and Koch scale. Discrepancies were resolved by discussion with a third advisor (AVI).

#### Data collection process and data items

Data were extracted in duplicate (SPO and RSP) using predefined Excel spreadsheets and considering the following aspects: author and year, study type, country, review comparison, consulted databases, sample size (patient/eyes), myopia range, primary studies frequency, risk of bias (RoB) tool employed, intervention and control groups, review outcomes, follow-up in months, conclusions and review quality score. Disagreements were resolved by discussion with a third advisor (AVI). In the case of missing data, an Email request was sent to the corresponding author of the publication.

A glossary of terms related to the methods used in the present work is provided in Table 1. Moreover, a summary of the methodology employed is visually depicted in Fig. 2. The full description of the methods used in meta-evidence appraisal (e.g. risk of bias appraisal and data synthesis) is provided in the online appendices (Appendix S1). Discrepancies were resolved by discussion with a third advisor (AVI).

## Results

After the removal of duplicates, a total of 293 titles were screened by title and abstract. Of these publications, 74 were full-text appraised against the eligibility

**Table 1.** Glossary of terms of the present overview of systematic reviews.

Glossary of terms	
Abbreviation	Meaning
OoSR	Overview of Systematic Reviews
PRIO-harms	Preferred Reporting Items for Overviews of Systematic Reviews
AMSTAR-2	Appraisal of the Methodological Quality of Systematic Reviews (version 2) (Shea <i>et al.</i> 2017)
PICO	Population, Intervention, Comparison and Outcomes (acronym to address and conceptualize an electronic search based on a focused question)
GRADE	Grading of Recommendations, Assessment, Development and Evaluations (approach to integrating in a transparent manner essential methodological issues that allow researchers/clinicians to move from evidence to clinical recommendation) (Castellini <i>et al.</i> 2018, Lunny <i>et al.</i> 2020)
CCA	Corrected Covered Area (a mathematical method to quantify the degree of primary studies overlap among systematic reviews; it is based on a citation matrix approach) (Bougioukas <i>et al.</i> 2021)
ISPOR	International Society for Pharmacoeconomics and Outcomes Research Indirect Treatment Comparisons Good Research Practices Task Force (it is used to assess the hints of meta-bias in a network meta-analysis) Jansen <i>et al.</i> (2014), Zarin <i>et al.</i> (2017)
TSA	Trial Sequential Analysis (a statistical approach to formally appraise the degree of imprecision based on the weight of accrued data in a meta-analytical subset; this approach tests the propensity to types I and II statistical errors, analysing the power of available evidence) Miladinovic <i>et al.</i> (2013), Wetterslev <i>et al.</i> (2017)
JADAD	JADAD scale or Oxford Quality Punctuation System (an approach to independently assess the quality of a randomized controlled clinical trial)
NOS	Newcastle–Ottawa Scale (a risk of bias tool for observational studies such as cohort studies, cross-sectional studies, case–control studies and case series)
CHALMERS	The Chalmers scale has been constructed to evaluate the design, implementation and analysis of randomized controlled clinical trials (RCT)
CONSORT	Consolidated Standards of Reporting Trials (a checklist of items for proper reporting of clinical trials)
STROBE	Strengthening Reporting for Observational Studies (a checklist of items for proper reporting of observational studies)

criteria, including 30 systematic reviews. In addition, seven potentially eligible titles were retrieved by using the RSS feeds appliances among the databases up until 10 April 2021. A total of six of these publications met the inclusion

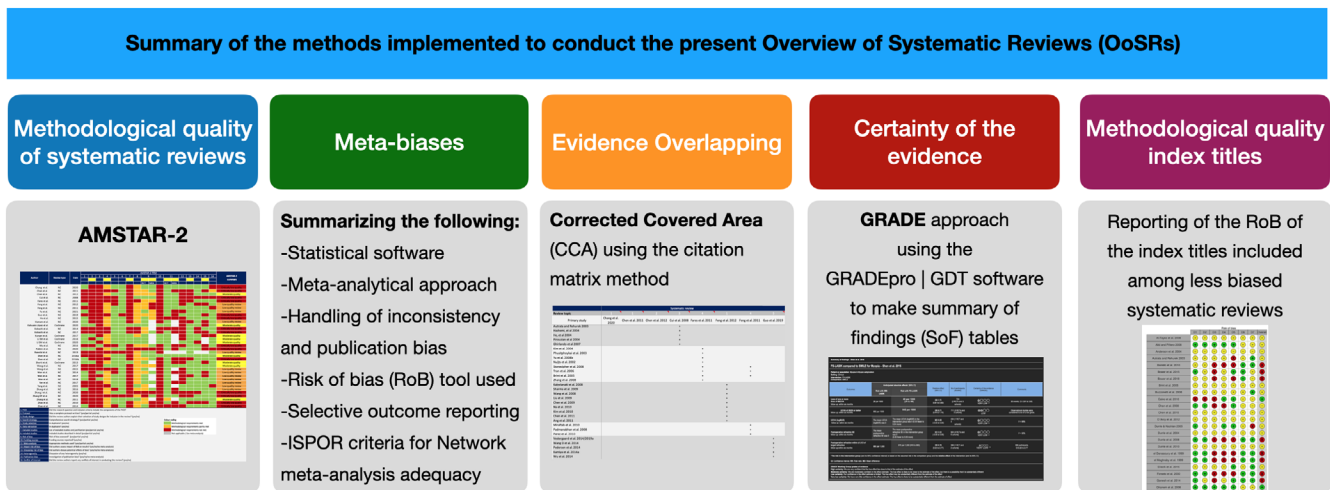
criteria (Chang *et al.* 2021, Fu *et al.* 2021, Hamam *et al.* 2020, Li *et al.* 2020, Zhang *et al.* 2020a, Zhang *et al.* 2020b). Finally, 36 systematic reviews were included in the qualitative synthesis (Fig. 3). The level of agreement was

almost perfect (kappa = 0.92). Details of the excluded studies, including reasons and the selection process, are provided in Supplementary Material (Table S2–S4).

The included systematic reviews were published between the years 2003 and 2021. Thirty-three were systematic reviews with meta-analyses, two performed network meta-analysis (Wen *et al.* 2017, Wen *et al.* 2018) and one conducted a qualitative synthesis (Raevdal *et al.* 2019). With regard to the country of origin of the publications, over 50% corresponded to China ( $n = 20$ ; 56%) or were collaborations between Chinese authors and authors from other countries ( $n = 5$ ; 14%).

Concerning the refractive surgery target disorder, 16 reviews assessed myopia as a single condition, 19 focused on myopia and myopic astigmatism, 1 review addressed myopia and hyperopia and 1 focused on all three conditions together. A descriptive summary of the included systematic reviews is provided in Supplementary Material (Table S5).

Regarding comparison of the interventions, the meta-evidence was grouped into six categories, tagged with letters in order to enhance the visibility of the distribution of comparisons (Fig. 3). The most frequently reported comparison was between SMILE and FS-LASIK (representing 19% of the included reviews) (Fig. 4), followed by FS-LASIK versus MM-LASIK (11%). More detailed information can be found in Fig. 5A,B.



**Fig. 2.** Summary of the methods employed for meta-evidence synthesis.

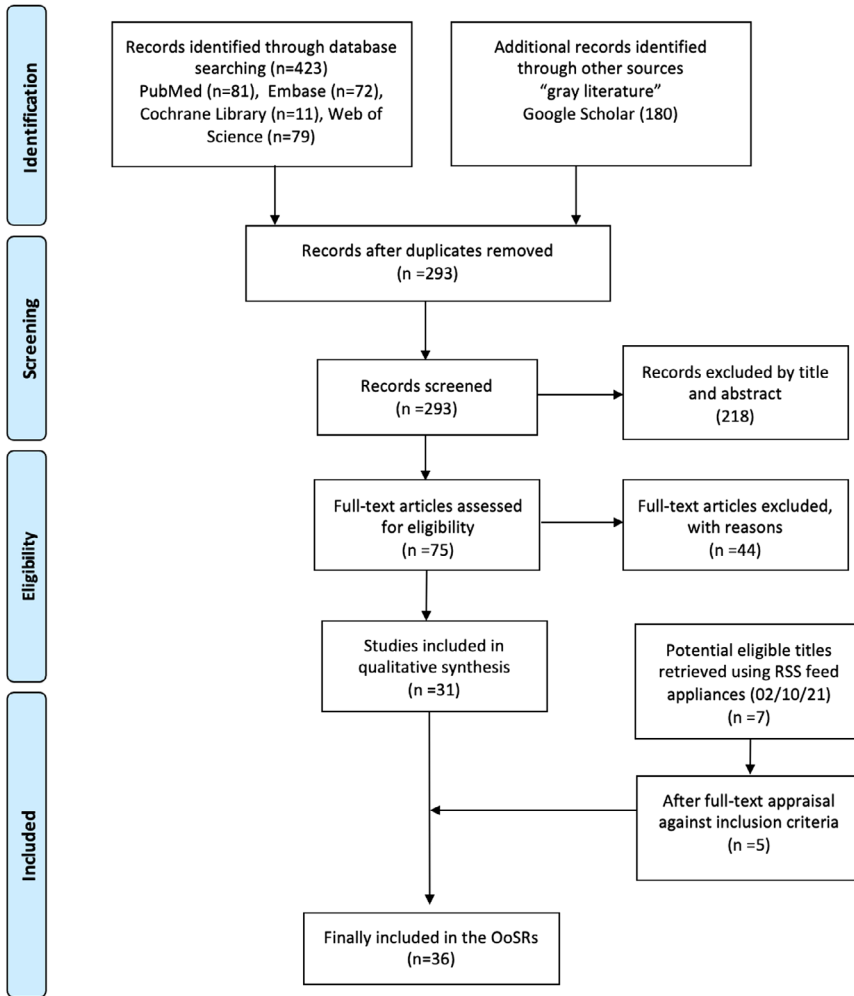


Fig. 3. PRISMA flowchart.

**Overlapping**

The 36 included SRs and MAs comprised 251 index publications, of which 165 were unique. A citation matrix, provided in Supplementary Material (Table S6), depicts the included systematic reviews in columns and the index titles in rows. Overlapping studies included in one or more reviews were identified in the citation matrix. The degree of overlapping was estimated by calculating the corrected covered area (CCA). The CCA was 0.015%, corresponding to a negligible risk of skewed reporting.

**Assessment of methodological quality of the systematic reviews**

The risk of bias of the included studies was appraised using the AMSTAR-2 tool. The methodological quality was found to be moderate in nine of the papers, of which five were Cochrane systematic reviews (Kahuam-López

*et al. 2020, Kuryan et al. 2017, Li et al. 2016, Li et al. 2020, Shortt et al. 2013*). Twelve studies had low quality and 16 reviews had critically low quality. No high-quality reviews were identified. Among the 16 items contemplated in the AMSTAR-2 tool, the critical domains were item 2 (review protocol), item 4 (search strategy) and item 7 (list of excluded studies), which presented the highest number of concerns among the included studies (Fig. 6). Moreover, 9 of the 36 included reviews evaluated certainty of evidence using the GRADE approach; 4 of them were non-Cochrane reviews (Chen *et al. 2012, Shen et al. 2016, Wang et al. 2017, Zhang et al. 2020b*).

**Meta-bias during the review process**

The risk of meta-biases during the review process is summarized for each included review in Table S6. A total of 17 reviews did not perform any formal

analysis of publication bias; one mentioned its implementation but provided no further details (Feng *et al. 2011*); 5 performed no analysis due to a lack of data ( $\leq 10$  studies) (Kahuam-López *et al. 2020, Kuryan et al. 2017, Li et al. 2020, Li et al. 2020*); and 1 review did not provide any information in this respect (Chen *et al. 2011*).

A propensity for selective outcome reporting bias was considered possible in 28 reviews – in most cases due to the implementation of methodological tools that did not cover this aspect (e.g. Jadad score, NOS, Chalmers scale, CONSORT and STROBE). On the other hand, such bias was considered unlikely in eight SRs, most of which used the Cochrane tool for risk of bias. In turn, dual co-authorship (i.e. one or more review authors participating in at least one primary study included in the systematic review) was detected in eight reviews.

Another no less important aspect was the reporting of the unit of statistical analysis. Seven studies offered information about the unit of analysis: three studies reported the eye as the unit of analysis and considered the inclusion of nonpaired eye design studies (Kuryan *et al. 2017, Ma et al. 2016, Pakbin et al. 2020*); two considered participants rather than eyes for the analysis (Kahuam-López *et al. 2020, Li et al. 2016, Li et al. 2020*) and one study considered the eyes for paired analysis (Shortt *et al. 2013*). The remaining 28 studies did not explicitly indicate whether the analysis was based on eyes or patients (Table S6).

There were only two network meta-analyses (Wen *et al. 2017, Wen et al. 2018*), and the appropriateness of the statistical approaches used was appraised based on the ISPOR criteria (Jansen *et al. 2014*). Both papers were from the same author, and did not account for inconsistencies (e.g. meta-regression analysis) or state the rationale for the use of both random- or fixed-effects models.

**Disclosure of methodological quality of index titles**

This was conducted based on those primary studies provided by the best available reviews. The nine least biased reviews (those with moderate quality) comprised 102 indexed titles. Five reviews used the Cochrane collaboration tool to calculate the risk of bias (RoB) (Kahuam-López *et al. 2020,*

Refractive surgery SRs and MA		N	(%)	Authors
Other parallel arm comparisons		22	61	
A	SMILE vs FS-LASIK	7	19	He et al. 2015, Kobashi et al. 2017, Shen et al. 2016a, Shen et al. 2016b, Yan et al. 2017, Zhang et al. 2016, Fu et al. 2021
	FS-LASIK vs MM-LASIK	4	11	Yang et al. 2020, Chen et al. 2012, Kahuam-Lopez et al. 2020, Zhang et al. 2011
	LASEK vs PRK	3	8	Cui et al. 2008, Li SM et al. 2015, Zhao et al. 2010
	LASIK vs PRK	1	3	Short et al. 2013
	LASIK vs LASEK	2	6	Kuryan et al. 2017, Zhao et al. 2014
	LASIK-timolol vs LASIK-non timolol	1	3	Wang et al. 2015
	PRK-steroids vs PRK- non steroids	1	3	Pakbin et al. 2020
	LASEK vs epi-LASIK	1	3	Wen et al. 2014
	Q-adjusted LASIK vs standard LASIK	1	3	Zhang KP et al. 2020
Pupil center LASIK vs Corneal vertex LASIK	1	3	Zhang J et al. 2020	
B	Indirect and mixed comparisons (NMA)	2	6	Wen et al. 2017, Wen et al. 2018
Wavefront vs Non-Wavefront		3	8	Fares et al. 2011, Kobashi et al. 2014, Li SM et al. 2020
C	LASIK	1	3	
	PRK	1	3	
	LASIK, LASEK, PRK	1	3	
D	Wavefront-guided vs Wavefront-optimized	2	6	Feng et al. 2011, Hamam et al. 2020
E	LASIK	1	3	
	PRK	1	3	
Mitomycin C		3	8	Chen et al. 2011, Feng et al. 2012, Chang et al. 2020
E	LASEK, PRK, epi-LASIK	1	3	
	On-Flap / Off-Flap epi-LASIK	1	3	
	PRK-MMC vs PRK-non MMC	1	3	
Biomechanical properties		4	11	Guo et al. 2019, Ma et al. 2016, Raevdal et al. 2019, Wang et al. 2017
F	SMILE vs FLEX, LASIK, LASEK, PRK	1	3	
	SMILE vs FLEX	2	6	
	SMILE vs LASIK, FS-LASIK, FLEX	1	3	
Total		36	100	

Fig. 4. Intervention comparison categories. Number of studies, N; percentage by category / technique comparison, %.

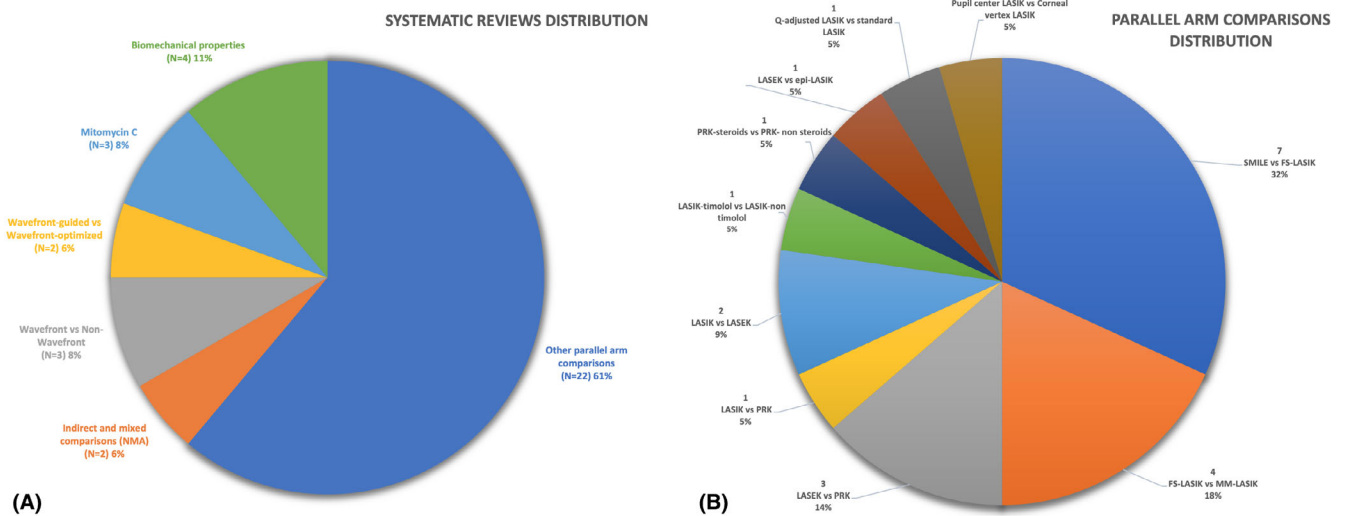


Fig. 5. Distribution of interventions.

Author	Review type	Date	AMSTAR-2 ITEM																AMSTAR-2 summary	
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16		
Chang et al.	NC	2020	Green	Red	Red	Yellow	Green	Green	Red	Yellow	RCT	NRSI	Red	RCT	NRSI	Green	Green	Green	Green	Critically low quality
Chen et al.	NC	2011	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Critically low quality
Chen et al.	NC	2012	Red	Red	Red	Yellow	Green	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Moderate quality
Cui et al.	NC	2008	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Critically low quality
Fares et al.	NC	2011	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Critically low quality
Feng et al.	NC	2012	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Low quality review
Feng et al.	NC	2011	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Low quality review
Fu et al.	NC	2021	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Low quality review
Guo et al.	NC	2019	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Critically low quality
He et al.	NC	2015	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Critically low quality
Hamam et al.	NC	2020	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Low quality review
Kahuam-López et al.	Cochrane	2020	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Moderate quality
Kobashi et al.	NC	2014	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Critically low quality
Kobashi et al.	NC	2017	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Critically low quality
Kuryan et al.	Cochrane	2017	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Moderate quality
Li SM et al.	Cochrane	2016	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Moderate quality
Li SM et al.	Cochrane	2020	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Moderate quality
Ma et al.	NC	2016	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Critically low quality
Pakbin et al.	NC	2020	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Critically low quality
Raevdal et al.	NC	2019	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Low quality review
Shen et al.	NC	2016a	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Moderate quality
Shen et al.	NC	2016b	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Critically low quality
Shortt et al.	Cochrane	2013	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Moderate quality
Wang et al.	NC	2017	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Moderate quality
Wang et al.	NC	2015	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Low quality review
Wen et al.	NC	2014	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Low quality review
Wen et al.	NC	2017	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Low quality review
Wen et al.	NC	2018	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Low quality review
Yan et al.	NC	2017	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Low quality review
Yang et al.	NC	2003	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Low quality review
Zhang et al.	NC	2016	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Low quality review
Zhang J et al.	NC	2020	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Critically low quality
Zhang KP et al.	NC	2020	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Critically low quality
Zhang et al.	NC	2011	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Moderate quality
Zhao et al.	NC	2010	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Critically low quality
Zhao et al.	NC	2014	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Critically low quality

1. PICO	Did the research question and inclusion criteria include the components of the PICO?
2. Protocol	Was a complete protocol written? (yes/partial yes/no)
3. Study design	Did the review authors explain their selection of study designs for inclusion in the review? (yes/no)
4. Search strategy	Comprehensive search strategy? (yes/partial yes/no)
5. Study selection	In duplicate? (yes/no)
6. Data extraction	In duplicate? (yes/no)
7. Excluded studies	List of excluded studies and justification (yes/partial yes/no)
8. Included studies	Included studies described in detail (yes/partial yes/no)
9. Risk of bias	Risk of bias assessed? (yes/partial yes/no)
10. Funding sources	Funding sources reported? (yes/no)
11. Meta-analysis	Appropriate methods used? (yes/partial yes/no)
12. Impact risk of bias	Did authors assess impact of RoB on results? (yes/no/no meta-analysis)
13. Discussing risk of bias	Did authors discuss potential effects of bias? (yes/no/no meta-analysis)
14. Heterogeneity	Discussion of any heterogeneity (yes/no)
15. Publication bias	Investigation of publication bias? (yes/no/no meta-analysis)
16. Conflict of interest	Did the review authors report any conflicts of interest in conducting the review? (yes/no)

Colour coding	
Green	Methodological requirements met
Yellow	Methodological requirements partly met
Red	Methodological requirements not met
Grey	Not applicable / (no meta-analysis)

Fig. 6. Summary of methodological appraisal with the AMSTAR-2 tool. Critical items are differentiated with yellow colour boxes.

Kuryan *et al.* 2017, Li *et al.* 2016, Li *et al.* 2020, Shortt *et al.* 2013); two used the Jadad score (Chen *et al.* 2012, Wang *et al.* 2017); one used the Cochrane RoB tool combined with the Newcastle–Ottawa scale (Shen *et al.* 2016) and one used the NOS for cohort studies (Zhang *et al.* 2020b). One study used the Jadad scale to assess both randomized and nonrandomized studies, but it provided only the summary score – not the full assessment of each item (Wang *et al.* 2017). In this scenario, full-text appraisal and reporting was performed using the same methodological tool. The quality of index publications showed low risk of bias for the random sequence generation item ( $\geq 50\%$ ), allocation concealment (25%) and selective outcome reporting (almost 25%). Nevertheless, fewer than

25% of the trials conducted proper blinding of either participants or outcome assessors, while almost 50% of the trials showed low risk of bias due to incomplete outcome data (Fig. 7A). Nine studies were assessed using the NOS scale for cohort studies, showing moderate-to-high quality for scores of 7 to 9 stars (Fig. 7B). The Jadad scale was used by two reviews comprising nine studies, with scores of 0–2 suggesting moderate-to-low methodological quality (Fig. 7C). Additional information is provided in the online appendix (Fig. S1 and Tables S7–S8).

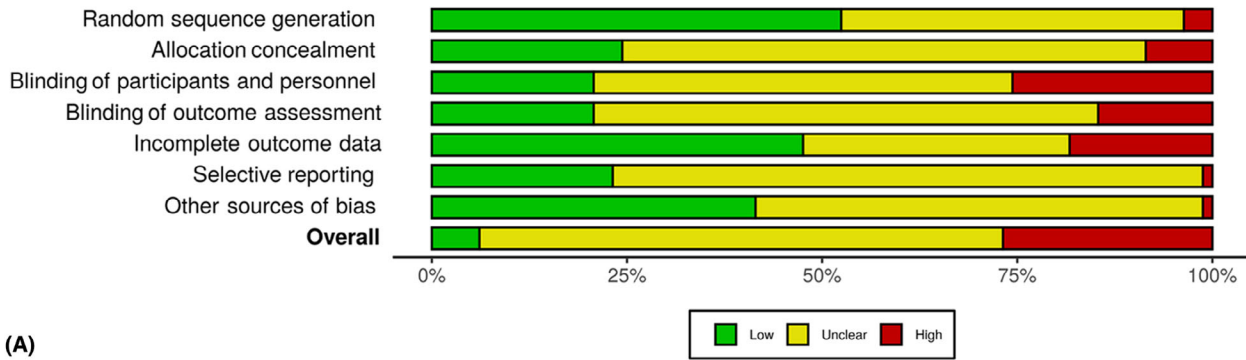
**Synthesis of results**

The overview outcomes were retrieved from the less biased reviews and were summarized using summary of findings

(SoF) tables according to the GRADE approach, with the inclusion of meta-analytical data of *a priori* study outcomes for the following comparisons:

PRK versus LASIK, Wavefront versus conventional (PRK, LASIK), Wavefront-optimized versus Wavefront-guided (PRK, LASIK), Wavefront-guided LASIK versus Wavefront-guided PRK, LASEK versus LASIK, LASEK versus PRK, MM-LASIK versus FS-LASIK, FS-LASIK versus SMILE and SMILE versus FLEx.

The comparisons were listed according to the order in which each type of surgery was developed: PRK was the first refractive surgery developed (1996), followed by LASIK and LASEK (1998). Soon after, laser femtosecond was introduced on the market



(A)

Study	Selection				Comparability	Outcome			Total score
	Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Chan 2015	*	*	*	*	**	*	-	*	8
Denoyer 2015	*	*	*	*	**	*	*	*	9
Hu 2013	*	*	*	*	*	*	-	*	7
Li 2013	*	*	*	*	*	*	*	*	8
Li 2014	*	*	*	*	*	*	-	*	7
Sefat 2015	*	*	*	*	*	*	-	*	7
Shen 2014	*	*	*	*	*	*	-	*	7
Xia 2016	*	*	*	*	**	*	*	*	9
Zhang 2016	*	*	*	*	**	*	-	*	8

\*Risk of bias was assessed with use of the Newcastle–Ottawa Scale.

(B)

Quality Assessment of Included Studies Using the Jadad Scale

Study	Appropriateness			Appropriateness of Blind	Analysis Reasons for Withdrawals	Overall Jadad Score
	Randomization	of Randomization	Blinded			
Lim et al. 2006	0	0	0	0	1	1
Kezirian and Stonecipher 2004	0	0	0	0	1	1
Tanna 2009	0	0	0	0	0	0
Li et al 2010	0	0	0	0	0	0
Rosa et al. 2009	0	0	0	0	1	1
Agca et al. 2014*	1	0	0	0	1	2* (4)
Kamiya et al. 2014	1	0	0	0	1	2* (4)
Kobashi t al. 2015	1	0	0	0	1	2* (4)
Ang et al. 2014	1	0	0	0	1	2* (3)

\*, score obtained after full-text appraisal because full rating was not provided in the original paper.

( ), original score provided in the original paper.

(C)

Fig. 7. Risk of bias of primary studies included among less biased reviews. (A) Cochrane collaborations RoB tool; (B) Newcastle–Ottawa scale and (C) Jadad score.

(2002), allowing the corneal flap to be produced by femtosecond laser instead of a microkeratome (FS-LASIK). In 2008, the FLEX surgical procedure was reported, and in 2011 a new procedure developed from FLEX and named SMILE was described by Shah *et al.*, and approved in 2016 (Guo *et al.* 2019).

The GRADE SoF tables were not implemented in three systematic reviews; the grading of evidence was

thus conducted by two authors (SPO and RSP) (Chen *et al.* 2012, Wang *et al.* 2017, Zhang *et al.* 2020b). A meta-evidence summary and grading of the 41 outcomes reported in the systematic reviews are provided in Table 2.

The most common reasons for evidence downgrading were related to the risk of bias, imprecision, indirectness and inconsistency. A full description of the GRADE appraisal is provided in Supplementary Material (Table S11).

PRK versus LASIK

One study established this comparison at 12 months postsurgery (Shortt *et al.* 2013). The proportion of eyes with UCVA 20/20 or better, ±0.5 diopters of target refraction, the loss of one or more lines of BCVA and final BCVA 20/40 or less showed very low to low certainty of evidence favouring the LASIK group. Spherical equivalent refraction changes ±0.5 diopter



revealed no specific effect direction for either of the interventions. Heterogeneity was not estimated due to the limited number of included studies. The differences were not statistically significant.

**Wavefront versus conventional (PRK, LASIK)**

This comparison was made by one review at 12 months postsurgery (Li *et al.* 2020). The proportion of eyes with UCVA 20/20 or better showed low certainty of evidence favouring Wavefront PRK versus conventional PRK. For the other outcomes retrieved, the certainty of evidence was low to very low. There was no specific effect direction for either PRK or LASIK. Heterogeneity was not estimated due to the limited number of included studies.

**Wavefront optimized versus Wavefront guided (PRK, LASIK)**

This comparison was made by one review at 12 months postsurgery (Li *et al.* 2020). The certainty of evidence was low for all outcomes. The spherical equivalent refraction error changes showed low certainty of evidence favouring Wavefront-optimized LASIK. The results were observed in a context of low heterogeneity  $I^2 = 0\%$ .

**Wavefront-guided LASIK versus Wavefront-guided PRK**

This comparison was made by one review at 12 months postsurgery (Li *et al.* 2020). The certainty of evidence was very low for all outcomes. There was no specific effect direction for either of the interventions. Heterogeneity was not estimated due to the limited number of included studies.

**LASEK versus LASIK**

One study established this comparison at 12 months postsurgery (Kuryan *et al.* 2017). The proportion of eyes with UCVA 20/20 or better, UCVA 20/40 or better and eyes with  $\pm 0.5$  diopter of target refraction showed very low to low certainty of evidence favouring the LASEK group. Heterogeneity was not estimated due to the limited number of included studies. The differences were not statistically significant.

**LASEK versus PRK**

Only one review established this comparison (Li *et al.* 2016). Certainty of evidence was very low to moderate among the assessed outcomes and favoured the PRK group. Spherical equivalent refraction error change was the only outcome of the present overview of systematic reviews showing moderate certainty of evidence in favour of the PRK group. The results were not statistically significant, in a context of low heterogeneity  $I^2 = 0\%$ .

**MM-LASIK versus FS-LASIK**

The proportion of eyes with UCVA 20/20 or better was reported in two reviews based on data corresponding to 3193 (Chen *et al.* 2012) and 321 eyes (Zhang *et al.* 2011), with the observation of no statistically significance differences. Low certainty of evidence suggested a trend favouring the MM-LASIK group over a range 3–48 months postsurgery, in a context of low heterogeneity  $I^2 \leq 14\%$ .

The UCVA LogMar for this comparison showed very low certainty of evidence over a period of 3–48 months in favour of the FS-LASIK group (Chen *et al.* 2012). However, on only including data corresponding to 12 months postsurgery, certainty of evidence proved to be low in favour of MM-LASIK (Zhang *et al.* 2011). These results proved discordant.

Changes in spherical equivalent refraction  $\pm 0.50$  diopter showed very low to low certainty of evidence – in both cases favouring the FS-LASIK group over a range 3–48 months postsurgery. The proportion of eyes with  $\pm 0.5$  diopter of target refraction was evaluated in three reviews over a range 3–48 months postsurgery. The effect direction favouring the MM-LASIK group showed very low to low evidence quality (Chen *et al.* 2012, Kahuam-López *et al.* 2020), but favouring the FS-LASIK group at 6 months of follow-up (Zhang *et al.* 2011). There were no statistically significant differences among the analytical subsets.

**FS-LASIK versus SMILE**

One review established this comparison (Shen *et al.* 2016). The proportion of eyes with the loss of one or more lines of best spectacle-corrected visual acuity (BSCVA), or eyes with  $\pm 0.1$  diopter of

target refraction revealed very low certainty of evidence favouring FS-LASIK and SMILE respectively. The proportion of eyes with UCVA 20/20 or better showed low certainty of evidence, favouring SMILE. In relation to the quantitative outcomes, UCVA LogMar and spherical equivalent refraction changes  $\pm 0.1$  diopter revealed no specific effect direction for either of the interventions. The heterogeneity context of these results ranged between  $I^2 = 0$  and 68%. The differences were not statistically significant.

**SMILE versus FLEx**

One review established this comparison (Shen *et al.* 2016). The proportion of eyes with the loss of one or more lines of BSCVA, or eyes with  $\pm 0.1$  diopter of target refraction, showed very low certainty of evidence favouring FS-LASIK and SMILE respectively. The proportion of eyes with UCVA 20/20 or better showed low certainty of evidence, favouring SMILE. In relation to the quantitative outcomes, UCVA LogMar and spherical equivalent refraction changes  $\pm 0.1$  diopter revealed no specific effect direction for either of the interventions. The heterogeneity context of these results ranged between  $I^2 = 0$  and 68%. The differences were not statistically significant.

**Discussion**

The present overview of systematic reviews (OoSr) was carried out to summarize the best available evidence on laser-based refractive surgery techniques for treating myopia in adults. An analysis of this kind is of great importance in order to clarify the quality of the current evidence, as no studies have addressed this topic to date.

**Main findings and quality of the evidence**

The overview compiled the information of 36 systematic reviews comprising 251 overlapping studies, of which 165 were unique. The CCA was 0.015%, representing a negligible risk of skewed reporting.

The findings of the present study suggest that the quality of the available evidence is not methodologically rigorous, as evidenced by the AMSTAR-2 tool. In fact, 15 reviews (42%) showed

**Table 2.** Summary of findings according to the GRADE approach and level of certainty of evidence.

Comparison	Outcome	Author	Months	Eyes (studies) (T/C)	Effect size	Mean value	95% CI		I <sup>2</sup>	Effect direction	Evidence certainty
							Lower	Upper			
PRK versus LASIK	UCVA 20/20 or better	Shortt <i>et al.</i> (2013)	12	1007 (7) (402/605)	OR	1.64	1.10	2.45	0%	Favours LASIK	Low
	Proportion eyes $\pm 0.5D$ of target refraction	Shortt <i>et al.</i> (2013)	12	1007 (7) (402/605)	RR	1.45	0.99	2.10	0%	Favours LASIK	Low
	SE refraction changes $\pm 0.5D$	Shortt <i>et al.</i> (2013)	12	589 (6) (295/294)	MD	-0.01	-0.06	0.04	0%	-	Low
	Loss one or more lines BCVA	Shortt <i>et al.</i> (2013)	6 or more	746 (6) (366/380)	OR	0.88	0.51	1.50	0%	Favours LASIK	Low
Wavefront versus conventional	Final BCVA 20/40 or less	Shortt <i>et al.</i> (2013)	6 or more	442 (6) (222/220)	OR	0.12	0.01	1.93	N/A	Favours LASIK	Very Low
	UCVA 20/20 or better (PRK)	Li <i>et al.</i> (2020)	12	70 (1) (35/35)	RR	1.03	0.86	1.24	N/A	Favours Wavefront	Low
	UCVA 20/20 or better (LASIK)	Li <i>et al.</i> (2020)	-	-	-	-	-	-	-	-	-
	Loss one or more lines BSCVA (PRK)	Li <i>et al.</i> (2020)	12	70 (1) (35/35)	RR	0.94	0.81	1.09	N/A	-	Low
Wavefront optimized versus Wavefront guided	Proportion eyes $\pm 0.5D$ of target refraction (PRK)	Li <i>et al.</i> (2020)	12	70 (1) (35/35)	RR	1.03	0.86	1.24	N/A	-	Low
	Proportion eyes $\pm 0.5D$ of target refraction (LASIK)	-	-	-	-	-	-	-	-	-	-
	SE, refraction error changes	Li <i>et al.</i> (2020)	12	70 (1) (35/35)	MD	0.04	-0.11	0.18	N/A	-	Very Low
	Loss one or more lines BSCVA (LASIK)	-	-	-	-	-	-	-	-	-	-
Wavefront-optimized versus Wavefront-guided	UCVA 20/20 or better	Li <i>et al.</i> (2020)	12	618 (5) (309/309)	RR	1.00	0.99	1.02	0%	-	Low
	Loss one or more lines BSCVA	Li <i>et al.</i> (2020)	12	622 (5) (311/311)	RR	0.99	0.96	1.02	0%	-	Low
	Proportion eyes $\pm 0.5D$ of target refraction	Li <i>et al.</i> (2020)	12	480 (4) (240/240)	RR	1.02	0.95	1.09	33%	-	Low
	SE, refraction error changes (PRK)	Li <i>et al.</i> (2020)	12	334 (2) (167/167)	MD	0.07	0.03	0.18	50%	-	Low
Wavefront-guided LASIK versus Wavefront-guided PRK	SE, refraction error changes (LASIK)	Li <i>et al.</i> (2020)	12	472 (4) (242/230)	MD	0.14	0.19	0.09	0%	Favours Wavefront-optimized	Low
	UCVA 20/20 or better	Li <i>et al.</i> (2020)	12	66 (1) (33/33)	RR	1.03	0.93	1.15	N/A	-	Very Low
	Loss one or more lines BSCVA	Li <i>et al.</i> (2020)	12	66 (1) (33/33)	RR	1.03	0.93	1.15	N/A	-	Very Low
	Proportion eyes $\pm 0.5D$ of target refraction	Li <i>et al.</i> (2020)	12	66 (1) (33/33)	RR	0.97	0.82	1.14	N/A	-	Very Low
LASEK versus LASIK	UCVA 20/20 or better	Kuryan <i>et al.</i> (2017)	12	57 (1) (28/29)	RR	0.96	0.82	1.13	N/A	Favours LASEK	Low
	UCVA 20/40 or better	Kuryan <i>et al.</i> (2017)	12	57 (1) (28/29)	RR	0.90	0.67	1.21	N/A	Favours LASEK	Very Low

Table 2 (Continued)

Comparison	Outcome	Author	Months	Eyes (studies) (T/C)	Effect size	Mean value	95% CI		I <sup>2</sup>	Effect direction	Evidence certainty
							Lower	Upper			
LASEK versus PRK	Proportion eyes $\pm 0.5D$ of target refraction	Kuryan <i>et al.</i> (2017)	12	57 (1) (28/29)	RR	0.69	0.48	0.99	N/A	Favours LASEK	Very Low
	UCVA 20/20 or better	Li <i>et al.</i> (2020)	12	102 (1) (51/51)	RR	0.98	0.92	1.05	-	Favours PRK	Low
	Proportion eyes $\pm 0.5D$ of target refraction	Li <i>et al.</i> (2020)	12	152 (2) (76/76)	RR	0.93	0.84	1.03	-	Favours PRK	Low
	Loss one or more lines BSCVA	Li <i>et al.</i> (2020)	12	102 (1) (51/51)	RR	3.00	0.13	71.96	-	Favours PRK	Very Low
MM-LASIK versus FS-LASIK	SE, refraction error changes	Li <i>et al.</i> (2020)	12	386 (3) (193/193)	MD	0.06	-0.02	0.14	0%	Favours PRK	Moderate
	UCVA 20/20 or better	Chen <i>et al.</i> (2012)	3-48	3193 (9) (1514/1679)	RR	1.02	0.99	1.06	14%	Favours MM-LASIK	Low
		Zhang <i>et al.</i> (2011)	6	321 (3) (161/160)	OR	1.17	0.40	3.42	0%	Favours FS-LASIK	Low
		Kahuam-López <i>et al.</i> (2020)	12	-	-	-	-	-	-	-	Very Low
FS-LASIK versus SMILE	UCVA LogMar	Chen <i>et al.</i> (2012)	3-48	716 (7) (349/367)	MD	-0.01	-0.02	0	0%	Favours FS-LASIK	Very Low
		Zhang <i>et al.</i> (2011)	12	42 (1) (21/21)	MD	0.01	0.06	0.04	N/A	Favour MM-LASIK	Low
	SE refraction changes $\pm 0.5D$	Chen <i>et al.</i> (2012)	3-48	1050 (9) (430/620)	MD	-0.03	-0.08	0.02	46%	Favours FS-LASIK	Very Low
		Zhang <i>et al.</i> (2011)	12	168 (3) (84/84)	MD	0.09	-0.01	1.19	0%	Favours FS-LASIK	Low
FS-LASIK versus SMILE	Proportion eyes $\pm 0.5D$ of target refraction	Chen <i>et al.</i> (2012)	3-48	3487 (11) (1650/1837)	RR	1.05	1.00	1.10	62%	Favours MM-LASIK	Very Low
		Zhang <i>et al.</i> (2011)	6	321 (3) (161/169)	OR	7.37	0.37	147.61	N/A	Favours FS-LASIK	Very Low
	Loss one or more lines BSCVA	Kahuam-López <i>et al.</i> (2020)	12	79 (1) (39/40)	RR	0.97	0.85	1.11	N/A	Favour MM-LASIK	Low
	UCVA 20/20 or better	Shen <i>et al.</i> (2016)	6	724 (5) (345/379)	OR	1.71	0.81	3.63	0%	Favours FS-LASIK	Very Low
UCVA LogMar		Shen <i>et al.</i> (2016)	6	711 (6) (323/388)	OR	0.71	0.44	1.15	50%	Favours SMILE	Low
		Shen <i>et al.</i> (2016)	6	434 (4) (201/233)	MD	0.00	-0.03	0.04	68%	-	Very Low
	SE refraction changes $\pm 0.1D$	Shen <i>et al.</i> (2016)	6	924 (9) (452/472)	MD	0.00	-0.05	0.05	50%	-	Very Low

Table 2 (Continued)

Comparison	Outcome	Author	Months	Eyes (studies) (T/C)	Effect size	Mean value	95% CI		I <sup>2</sup>	Effect direction	Evidence certainty
							Lower	Upper			
SMILE versus FLEX	Proportion eyes ±0.1D of target refraction	Shen <i>et al.</i> (2016)	6	399 (3) (202/197)	OR	0.78	0.22	2.77	0%	Favours SMILE	Very Low
	UCVA LogMar	Wang <i>et al.</i> (2017)	3–12	212 (4) (106/106)	MD	-0.01	-0.04	0.01	45%	Favours SMILE	Very Low
	UCVA 20/20 or better	Wang <i>et al.</i> (2017)	3–12	237 (5) (119/118)	OR	1.49	0.78	2.86	0%	Favours FLEX	Very Low
	CDVA LOGMAR	Wang <i>et al.</i> (2017)	3–12	205 (4) (102/103)	MD	0.00	-0.01	0.01	0%	-	Very Low
	SE refraction changes ±0.1D	Wang <i>et al.</i> (2017)	3–12	192 (4) (97/95)	MD	0.03	-0.12	0.07	0%	Favours SMILE	Very Low
	Proportion eyes ±0.5D of target refraction	Wang <i>et al.</i> (2017)	3–12	244 (5) (123/121)	OR	1.34	0.58	3.14	0%	Favours FLEX	Very Low

*GRADE Working group grades of evidence:* High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

95% CI = 95% confidence interval, I<sup>2</sup> = I-squared index for heterogeneity, MD = mean differences, OR = odds ratio, RR = relative risk, T/C = sample size for either test or control group.

critically low methodological quality, 12 low quality (33%) and 9 (25%) moderate quality. No high-quality systematic reviews on this topic have been identified to date. Over half of the studies come from China (56%) or correspond to collaborations between Chinese researchers and authors from other countries ( $n = 5$ ; 14%). The most frequently reported comparison was between SMILE and FS-LASIK (19%), followed by FS-LASIK versus MM-LASIK (11%).

The narrative synthesis of the pre-defined OoSR outcomes was based on the less biased reviews. The SoF tables according to the GRADE approach summarized 41 outcomes retrieved from the best available reviews. Certainty of evidence was 'low' to 'very low' for most outcomes. Only the spherical equivalent refraction error changes outcome showed 'moderate' certainty in the comparison between LASEK and PRK, favouring PRK at 12 months of follow-up (Li *et al.* 2016).

A critical issue in grading evidence is the formal assessment of imprecision, which is often not reported (Castellini *et al.* 2018). Evidence was downgraded by imprecision in four reviews (Kahum-López *et al.* 2020, Kuryan *et al.* 2017, Li *et al.* 2016, Li *et al.* 2020), but the rationale for downgrading due to imprecision was only reported by two papers referring to 'wide confidence intervals' (Kuryan *et al.* 2017, Li *et al.* 2016). Given the relevance of imprecision assessment in establishing solid recommendations on healthcare interventions, transparent reporting should be expected. Often, review authors are lenient, or the accrued data are insufficient to draw firm conclusions (Castellini *et al.* 2018). In this sense, trial sequential analysis (TSA) was used to estimate the optimal information size in the imprecision assessment of those reviews which *a priori* failed to implement the GRADE approach (Chen *et al.* 2012, Wang *et al.* 2017, Zhang *et al.* 2011). It was seen that the required information size after TSA was not met among the data subsets of the assessed reviews – more information being needed in order to establish solid recommendations.

Overviews often neglect the reporting of discordant results (Lunny *et al.* 2020). Some divergent results were observed in the comparison between FS-LASIK and MM-LASIK (Chen *et al.* 2012, Kahum-López *et al.* 2020,

Zhang *et al.* 2011) – the second most frequently reported comparison (Table 2). Such discordance could be attributable to the information size between meta-analytical outputs. The lower the information size, the greater the tendency to overestimate the findings. Also, pooled data in one study covered an interval of 3–48 months – a fact that may have biased the estimations.

### Meta-biases

A propensity towards selective outcome reporting bias was considered possible in 28 reviews, as the reported risk of bias tools among several reviews did not assess this aspect (e.g. Jadad score, NOS, Chalmers scale, CONSORT and STROBE). Selective outcome reporting can result in outcome reporting bias, which is bias generated after choosing the outcomes based on the results (Hutton & Williamson 2000), or when the outcome is incompletely reported in the protocol – creating the opportunity of ‘cherry-picking’, i.e. the reporting of only some of the outcome measurements or metrics (Mayo-Wilson *et al.* 2017).

### Unit of analysis

It is highly desirable for future reviews to explicitly specify the unit of analysis used in the included studies, as this information was rarely found among the included reviews and would be really useful to differentiate and adjust outcomes according to trial design (e.g. nonpaired eye / paired eye). Furthermore, it would be useful for the unit of analysis to specify whether it was based on patient or on eye; such information was infrequently stated, but intuitively interpreted in some SRs.

Only two of the included reports performed indirect comparisons using network meta-analysis (NMA). These reviews were of low quality according to the AMSTAR-2 tool. The appropriateness of analysis was appraised using the ISPOR guidelines for indirect treatment comparison (Jansen *et al.* 2014). The two included NMAs did not account for inconsistency (e.g. assessment of treatment-by-covariate interactions that act as ‘effect modifiers’, using meta-regression models) – a fact which may have biased the results of indirect comparisons. Also, both reports failed to provide the rationale

for use of the meta-analytical model (random-effects or fixed-effects model).

### Potential biases in the overview process

The present OoSRS has some strengths, such as *a priori* protocol registration, comprehensive electronic screening, data extraction and critical methodological appraisal of systematic reviews, the disclosure of methodological quality of primary studies, the proper assessment of study overlapping and the appraisal of meta-biases among reviews. All these aspects are in adherence to the most recent guidelines for the conduction of OoSRS referred to healthcare interventions (Bougioukas *et al.* 2018).

Notwithstanding, some limitations should be underscored when interpreting the findings of the present work. There are hints for skewed information due to the overlapping of primary studies among systematic reviews. This issue was addressed estimating the corrected covered area (CCA = 0.015%), suggesting a negligible risk of skewed reporting.

Moreover, most of the systematic reviews with meta-analyses (47%) did not properly test the hints for publication bias, in particular due to the limited body of information (< 10 studies), no mention or no performing of tests, or mention of testing but no use of Egger’s test. Thus, there was a risk of false-positive results in those reviews.

This propensity towards type I and type II errors in meta-analysis outcomes was tested using the trial sequential analysis (TSA) as formal assessment of imprecision adopting the GRADE approach, proving a need for more evidence for the outcomes assessed.

On the other hand, the quality of the primary studies raised some concerns: less than 25% of the studies properly reported allocation concealment, the blinding of participants and personnel/outcome assessment and selective outcome reporting. This may have biased the results obtained.

It is important to emphasize that depending on the clinical setting and type of study outcome, the determined methodological drawbacks (e.g. performance bias due to a lack of or unclear double blinding) could influence the intervention effect sizes to one degree

or other (Wood *et al.* 2008). It is well known that blinding of the surgeon to the allocated intervention is not always possible, while contrarily inappropriate blinding of the participants and staff overestimates the results of subjective outcomes (e.g. pain or quality of life) (Savović *et al.* 2012, Wood *et al.* 2008).

### Implications for future evidence improvements

Methodological flaws identified in this overview must be improved in future studies in order to enhance the quality of evidence-based medicine referred to this topic. Some practical recommendations and consulting links to upgrade the quality of future studies are provided below:

- Improve the quality of reporting of primary studies (e.g. randomized clinical trials, nonrandomized studies and observational studies) by using CONSORT and STROBE checklists (<https://www.equator-network.org>). However, it is of utmost importance to integrate these checklists along with the propensity of risk of bias during study design and execution. The Cochrane collaboration risk of bias (RoB) tools are suitable for this purpose (e.g. RoB 2.0, ROBINS-I). These tools include selective outcome reporting (e.g. trials registration and publishing cherry-picking results). (<https://methods.cochrane.org/methods-cochrane>).
- Adhere to the PRISMA ([www.prisma-statement.org](http://www.prisma-statement.org)) and AMSTAR-2 ([www.amstar.ca](http://www.amstar.ca)) guidelines when performing systematic reviews with or without meta-analysis. Consider the prospective register of the review protocol using registries like PROSPERO ([www.prospero.org](http://www.prospero.org)) or INPLASY ([www.inplasy.com](http://www.inplasy.com)).
- Meta-biases (e.g. hints of publication bias, specification of the unit of analysis and selective outcome reporting) in reviews should be monitored and strictly adjusted (e.g. sensitivity analysis, subgroup analysis and meta-regression) in order to avoid biased results.
- Implement the GRADE approach to move from initial certainty of evidence (meta-analytical findings) to final certainty, clearly integrating the risk of bias, inconsistency/heterogeneity, indirect evidence, imprecision (e.g. the

sample size of accrued data), publication bias or other confounding elements in the results (<https://gdt.grade.pro.org/app/handbook/handbook.html>).

### A claim of postpublication culture

Postpublication culture is the opposite of passive consumption of scientific papers. It can appear within future articles or through more immediate channels to respond to published research, such as letters and comments to the editor, commentaries, editorials in journals and discussions in blogs. The withholding of adequate information by authors precludes science from advancing. However, postpublication culture is about commenting and giving feedback to published research. The criticism and comments about our responses to research reports are the science's vibrant and compelling intellectual core (Bastian 2014).

In a clinical setting, informed decisions for patients' benefits should be based on the best available evidence. Many studies are published every day (Bastian *et al.* 2010), and it is no longer possible to read all the relevant individual studies. Thus, keeping up with the fast-evolving evidence is more challenging than ever for practicing physicians.

Systematic reviews and meta-analyses are positioned at the top of the evidence hierarchy. However, not every published review has a proper design and execution or may not have enough accrued data (e.g. few randomized participants or studies) to obtain sufficient statistical power to allow reliable assessment of large anticipated intervention effects (Turner *et al.* 2013). Therefore, filtering and discerning the evidence certainty provided in a published paper should not be exclusive to systematic reviewers but clinicians.

The present formal synthesis reflects an example of strong postpublication culture. It makes us aware of important published works. Still, it also traces a roadmap both visually and descriptively of strong and weak aspects of published papers in laser-based refractive surgery for treating myopia in adults.

This overview of systematic reviews may help clinicians and researchers figure out the core of the evidence transparently for better informed decisions for patients' benefit. Also, it may

shed light on new research considerations from the limitations detected in the present study.

## Conclusions

The continuous technological innovations and changes in surgical techniques have increased the range of possibilities available to treat refractive errors. Laser-based refractive surgery is

one of the most frequently used ocular surgeries, with excellent visual results and safety profiles. Furthermore, it is also associated with improved quality of life and high patient satisfaction.

Advances in imaging and preoperative assessments have allowed customized laser ablation to improve visual acuity and quality. Surgeons need to choose the method to treat the refractive error considering the

### Box 1: Key insights and guidelines for future practice and evidence improvements.

#### What is new?

##### Key findings – Take home messages

- 25% ( $n = 9$ ) of the SRs appraised ( $n = 36$ ) had a moderate quality.
- Publication bias was not formally tested due to scarce of information ( $n \leq 10$  studies) in almost half (47%) of published meta-analyses.
- The propensity of selective outcome reporting bias is considered possible in 77% ( $n = 28$ ) of the reviews. Most SRs appraised the methodological quality with tools or checklists not covering this issue. Less than 25% of randomized clinical trials appraised among systematic reviews fulfil this criterion.
- Information about the statistical unit of analysis (e.g. eye, participant and paired eyes) was explicitly provided only by 20% ( $n = 7$ ) of the SRs with MA.
- The two available NMA included did not account for the inconsistency of results (e.g. meta-regression analysis) to explain sources of heterogeneity. Also, these reviews did not properly justify the rationale of the meta-analytic approach (e.g. random or fixed effects).

#### What are the contributions to what is already known?

- Knowing the methodological quality of 36 SRs about laser-based refractive surgery approaches to treat myopia in adults.
- Knowing the evidence certainty appraisal of predefined outcomes retrieved from the less biased SRs with MA according to the GRADE approach and accounting the formal assessment of imprecision (weight of accrued data) using the trial sequential analysis (TSA) approach.

#### How could clinicians/researchers apply this information?

- It is highly desirable that evidence certainty of a research paper should be contemplated based on the critical appraisal and proper interpretation of: a) the propensity of risk of bias, b) the heterogeneity/inconsistency of the results 'Is the heterogeneity explained by a factor?', c) the hints of indirect evidence (e.g. differences in outcomes measures 'surrogate outcomes'), d) the imprecision of the results 'Is the accrued data from the meta-analysis enough?' and e) other sources (e.g. hints of publication bias, spurious effect of interventions due to confounders and dose–response effect).

#### How could this overview be applied to improve the evidence?

- The identified deficiencies should be consciously considered, especially in SRs updated and new clinical trials.
- Strict adherence to the methodological – and reporting – quality guidelines should be mandatory. It is highly recommended this to be ascertained before paper submission by authors and during the peer-review process by the Journal's editors and peer reviewers.
- Future clinical trials protocols on this topic should be *a priori* registered (e.g. [www.clinicaltrials.gov](http://www.clinicaltrials.gov), EU Clinical Trials Register and Eudra CT) to account for selective outcome reporting bias.
- Implementing the GRADE approach in future meta-analyses is highly recommendable to determine the degree of evidence certainty that allows us to move from meta-evidence to clinical recommendations in transparent manner.

preoperative examination characteristics and personal values and preferences and keep up to date with these emerging trends.

There is moderate certainty of evidence in favour of the use of PRK over LASEK in terms of the spherical equivalent refraction error changes at 1 year of follow-up. Laser-based refractive surgery techniques to treat myopia in adults afford comparable results in terms of efficacy. Notwithstanding, most appraised SRs presented methodological flaws in critical domains according to AMSTAR-2 guidelines and reflected by the low to critically low certainty of evidence established by GRADE appraisal.

Further well-designed, high-quality clinical trials and SRs are needed to reappraise these findings. Therefore, investigators need to study and compare the different laser-based refractive techniques to provide better evidence-based medicine. According to the findings drawn out from the present overview of systematic reviews, some guidelines and main recommendations are provided in the Box 1.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

### Data S1

**Fig. S1.** Considerations for grading the evidence using the GRADE approach.

**Fig. S2.** Risk-of-Bias Assessment of randomized controlled trials using the Cochrane's collaboration tool.

**Table S1.** Electronic search strings used among databases.

**Table S2.** Excluded studies with reasons.

**Table S3.** Included studies after full-text assessment.

**Table S4.** Potentially eligible titles retrieved using RSS feed appliances among databases.

**Table S5.** Descriptive summary of included reviews.

**Table S6.** Citation matrix for the detection of overlapping studies among included systematic reviews.

**Table S7.** Primary studies included among less biased reviews.

**Table S8.** Handling of heterogeneity and meta-biases.

**Table S9.** Risk of bias was assessed with use of the Newcastle–Ottawa Scale for cohort studies.

**Table S9.** Risk of bias was assessed with use of the Newcastle–Ottawa Scale for cohort studies.

**Table S10.** Summary of risk of bias appraisal of non-randomized studies of intervention according to the Jadad scale.

**Table S11.** Summary of findings tables (SoF) according to the GRADE approach.

**Appendix S1.** Material and methods of the risk of bias assessment and data synthesis.

**Appendix S2.** Formal assessment of imprecision using the Trial Sequential Analysis (TSA).