Influences of SMILE and FS-LASIK on Corneal Sub-basal Nerves: A Systematic Review and Network Meta-analysis

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ABSTRACT

PURPOSE: To compare postoperative corneal sub-basal nerve density and number between small incision lenticule extraction (SMILE) and femtosecond laser–assisted in situ keratomileusis (FS-LASIK).

METHODS: A search was made in PubMed, EMBASE, and the Cochrane library for prospective comparative studies. The analysis was divided into two parts: network meta-analysis and traditional meta-analysis of the studies directly comparing two surgical groups. Stata 16 (Stata Corporation) and RevMan 5.4 (Cochrane) software were used to analyze the data.

RESULTS: Twelve studies (n = 775) were included. In the network meta-analysis, the SMILE group showed a significant increase compared with the FS-LASIK group in corneal nerve density at 1 month postoperatively (mean: 4.23; 95% CI: 0.06 to 8.39, $P < .05$), and in the number of corneal nerve trunks at 6 months postoperatively (mean: 13.25; 95% CI: 10.20 to 16.30, $P < .05$). In the traditional meta-analysis, the SMILE group showed significant improvement compared with the FS-LASIK group in corneal nerve density at 1 (weighted mean difference [WMD]: -2.05, 95% CI: -3.11 to -1.00, $P < .05$) and 3 (WMD: -0.90, 95% CI: -1.30 to -0.50, $P < .05$) months postoperatively, and in the number of corneal nerve trunks (WMD: -2.52, 95% CI: -4.91 to -0.14, $P < .05$) and corneal nerve branches (WMD: -2.80, 95% CI: -3.41 to -2.19, $P < .05$) at 1 month postoperatively.

CONCLUSIONS: The corneal nerve injury in the FS-LASIK group was worse than that in the SMILE group. The corneal nerve recovery in the SMILE group was better at 3 months postoperatively. However, there was no significant difference in corneal nerve density and number between the two groups at 6 months postoperatively.

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Corneal nerves are densely distributed in the sub-basal layer of the corneal epithelium, and there are more than 7,000 nerve receptors per mm^2 on the corneal surface. In vivo confocal microscopy (IVCM) has been used to examine changes in the sub-basal nerve plexus.[1] As a non-invasive technique, IVCM is widely used in the follow-up of patients' corneal nerve morphology.

Refractive surgery is prevalent in the treatment of myopia, especially small incision lenticule extraction (SMILE) and femtosecond laser–assisted in situ keratomileusis (FS-LASIK). Meanwhile, refractive surgery is a common cause of corneal nerve injury that will affect corneal function and cause dry eye symptoms. In the past 20 years, although significant progress has been made in this technology, corneal nerve injury is

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not always avoided. Unlike FS-LASIK, in SMILE there is no need to make a corneal flap, but a lateral incision is made on the cornea to remove the lenticule.[2] Many studies have shown that rates of corneal nerve injury and corresponding symptoms are lower after SMILE, which may be due to the smaller incision and less damage to the corneal nerves.[3] However, some studies have reached the opposite conclusion.[4]

To evaluate corneal nerve damage and recovery after refractive surgery, many clinical studies have been performed. However, there is still a lack of large-scale meta-analyses to analyze and compare SMILE and FS-LASIK with regard to corneal nerve injury. We conducted this systematic review and meta-analysis to examine the influences of SMILE and FS-LASIK on corneal nerve density and nerve number.

PATIENTS AND METHODS

Study Selection

Two reviewers (XJ and YW) independently searched the PubMed, EMBASE, and Cochrane library databases for relevant publications from January 1, 2000 to August 30, 2021, using a combination of the following search terms: "SMILE," "LASIK," "corneal nerve," and "corneal re-innervation." We retrieved full articles that seemed to meet the objectives of this review, and studies that met the inclusion criteria were included. The review is registered with PROSPERO (CRD42021277452).

Inclusion and Exclusion Criteria

The inclusion criteria were: (1) population: myopic patients with or without astigmatism; (2) intervention: studies comparing FS-LASIK and SMILE or where participants in one of the experimental groups underwent FS-LASIK or SMILE; (3) control group: the control is the preoperative morphology of corneal nerve tissue; (4) outcomes: outcome indicators include at least one of the following: corneal nerve density, the number of corneal nerve trunks, and the number of corneal nerve branches (outcomes had to be measured using IVCM); (5) study type: either randomized or non-randomized trials; and (6) follow-up time: at least 1 month.

The exclusion criteria are as follows: FS-LASIK surgeries without femtosecond laser technology, studies without complete data, and animal experiments.

Assessment of the Risk of Bias and Quality

We used the Cochrane bias risk tool to assess the quality of the included studies. Two independent observers (YW and XJ) assessed the risks, and any disagreement was discussed with a third researcher (HY). The assessment tool includes seven aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential biases. According to the established criteria in the *Cochrane Systematic Assessment Intervention Handbook*,[5] each article was evaluated as low, high, or unknown risk according to seven aspects. In addition, because the articles included in this meta-analysis were mainly cohort studies, we adopted the Newcastle-Ottawa Scale[6] to evaluate the literature quality.

Data Extraction

Two independent reviewers (XJ and YW) extracted the following information: authors' name, publication year, trial location, study design, follow-up time, intervention, and the characteristics of the study population. Among the 12 studies, four directly compared the corneal nerve injury and repair after SMILE and FS-LASIK. Four studies focused on corneal nerve changes only in the FS-LASIK group preoperatively and postoperatively, or in the FS-LASIK group and another surgery group. We only extracted the data pertaining to variables before and after FS-LASIK surgery in these studies. Similarly, four studies focused on corneal nerve changes only in the SMILE group preoperatively and postoperatively or in the SMILE group and another surgery group. We only extracted the data pertaining to variables before and after SMILE surgery in these studies.

Statistical Analysis

Stata 16 (Stata Corporation) and RevMan 5.4 (Cochrane) software were used to perform this meta-analysis. Heterogeneity was assessed by calculating the I^2 statistic, and a value of I^2 greater than 50% or the P value for heterogeneity less than .10 was considered significant. According to whether I^2 is greater than 50%, we used a random- or fixed-effects model, respectively. We tested the inconsistency of the study through the instruction "network meta i" and "network meta c" in Stata 16 software, and a chi-square value of greater than 0.05 was considered to be acceptable. We first analyzed the results of the 12 studies and a P value of less than .05 was considered statistically significant. Sensitivity analysis was performed by excluding each study in turn. The weighted mean differences (WMDs) and 95% CIs were used to compare each parameter.

RESULTS

Results of Search

The flowchart of the literature retrieval process is shown in **Figure A** (available in the online version of this article). We retrieved 233 articles related to

TABLE 1
Characteristics of Included Studies

Study	Region	FU (mo)	No. of Eyes			Preoperative SE, Mean ± SD (D)			Average Age, Mean ± SD (y)			NOS Score
			FS-LASIK	SMILE	Control	FS-LASIK	SMILE	Control	FS-LASIK	SMILE	Control	
Recchioni et al, 2020[16]	UK	1	16	13	N	-3.48 ± 2.89	-4.67 ± 2.12	N	32.6 ± 9.1	32.2 ± 5.3	N	8
Agca et al, 2015[3]	Turkey	6	15	15	N	-3.62 ± 1.56	-4.06 ± 1.59	N	Unknown	Unknown	N	7
Li et al, 2013[13]	China	6	42	32	N	-8.46 ± 2.15	-6.56 ± 1.28	N	28.3 ± 5.5	27.1 ± 4.0	N	8
Denoyer et al, 2015[9]	France	6	30	30	N	-4.42 ± 1.78	-4.65 ± 2.38	N	32.2 ± 7.5	31.1 ± 4.7	N	8
Chao et al, 2015[7]	Australia	6	19	N	19	-5.21 ± 2.69	N	-5.21 ± 2.69	22.0 ± 4.3	N	22.0 ± 4.3	8
Hu et al, 2015[10]	China	3	28	N	28	-4.55 ± 0.88	N	-4.55 ± 0.88	26.03 ± 4.69	N	26.03 ± 4.69	8
Patel et al, 2010[15]	USA	36	21	N	21	Unknown	N	Unknown	38 ± 10	N	38 ± 10	8
Darwish et al, 2007[8]	UK	6	20	N	20	0.78 ± 0.31	N	0.78 ± 0.31	40 ± 10	N	40 ± 10	8
Vestergaard et al, 2013[17]	Denmark	6	N	35	35	N	-7.56 ± 1.11	-7.56 ± 1.11	N	35 ± 7	35 ± 7	8
Li et al, 2021[12,a]	China	12	N	38	38	N	-5.50 ± 1.85	-5.50 ± 1.85	N	18.45 ± 0.69	18.45 ± 0.69	8
				84	84	N	-5.42 ± 1.89	-5.42 ± 1.89		24.90 ± 2.56	24.90 ± 2.56	
				58	58	N	-5.37 ± 1.73	-5.37 ± 1.73		32.38 ± 2.42	32.38 ± 2.42	
				36	36	N	-5.30 ± 1.78	-5.30 ± 1.78		45.14 ± 3.51	45.14 ± 3.51	
Ishii et al, 2015[11]	Japan	12	N	30	30	N	-3.90 ± 1.60	-3.90 ± 1.60	N	31 ± 6	31 ± 6	8
Liu et al, 2015[14]	China	8	N	30	30	N	-4.84 ± 1.69	-4.84 ± 1.69	N	25.77 ± 4.13	25.77 ± 4.13	8

SE = spherical equivalent; SD = standard deviation; D = diopters; FU = follow-up; FS-LASIK = femtosecond laser–assisted LASIK; SMILE = small incision lenticule extraction; NOS = Newcastle-Ottawa Scale; N = no data
[a]The study divided all of the patients into four groups according to age.

key words and excluded 205 articles after abstract evaluation. Twenty-eight articles were initially considered potentially relevant. Among them, a total of 16 studies were excluded. Three articles had a follow-up period that was too long or too short, nine articles did not use IVCM to evaluate corneal nerves, one did not have complete data, and two were animal experiments. Finally, 12 studies were included in this meta-analysis.[3,7-17]

Characteristics of Included Studies

Table 1 shows the characteristics and quality scores of our included studies. All patients were myopic with or without astigmatism and underwent FS-LASIK or SMILE. Follow-up time was at least 1 month. We assessed the risk of bias and the literature quality of the 12 included studies, and the results are shown in **Figure B** (available in the online version of this article) and **Table A** (available in the online version of this article).

Corneal Nerve Density

Corneal nerve density was defined as the total length of corneal nerve per unit area of visual field (μm/mm^2). We extracted corneal nerve density data 1, 3, and 6 months postoperatively and performed the network meta-analysis. As shown in **Figure 1**, the postoperative corneal nerve density in the SMILE and FS-LASIK groups was significantly lower than the preoperative level. Corneal nerve density was significantly better in the SMILE group than the FS-LASIK group at 1 month postoperatively, but no significant difference was observed at 3 or 6 months postoperatively.

Four studies[3,9,13,16] directly compared the differences of postoperative corneal nerve injury between the FS-LASIK and SMILE groups. We conducted a separate meta-analysis of these four articles. Significant differences could be observed at 1 and 3 months postoperatively (1 month = WMD: -2.05, 95% CI: -3.11 to -1.00, $P < .05$; 3 months = WMD: -0.90, 95% CI: -1.30 to -0.50, $P < .05$). However, there was no significant difference in cor-

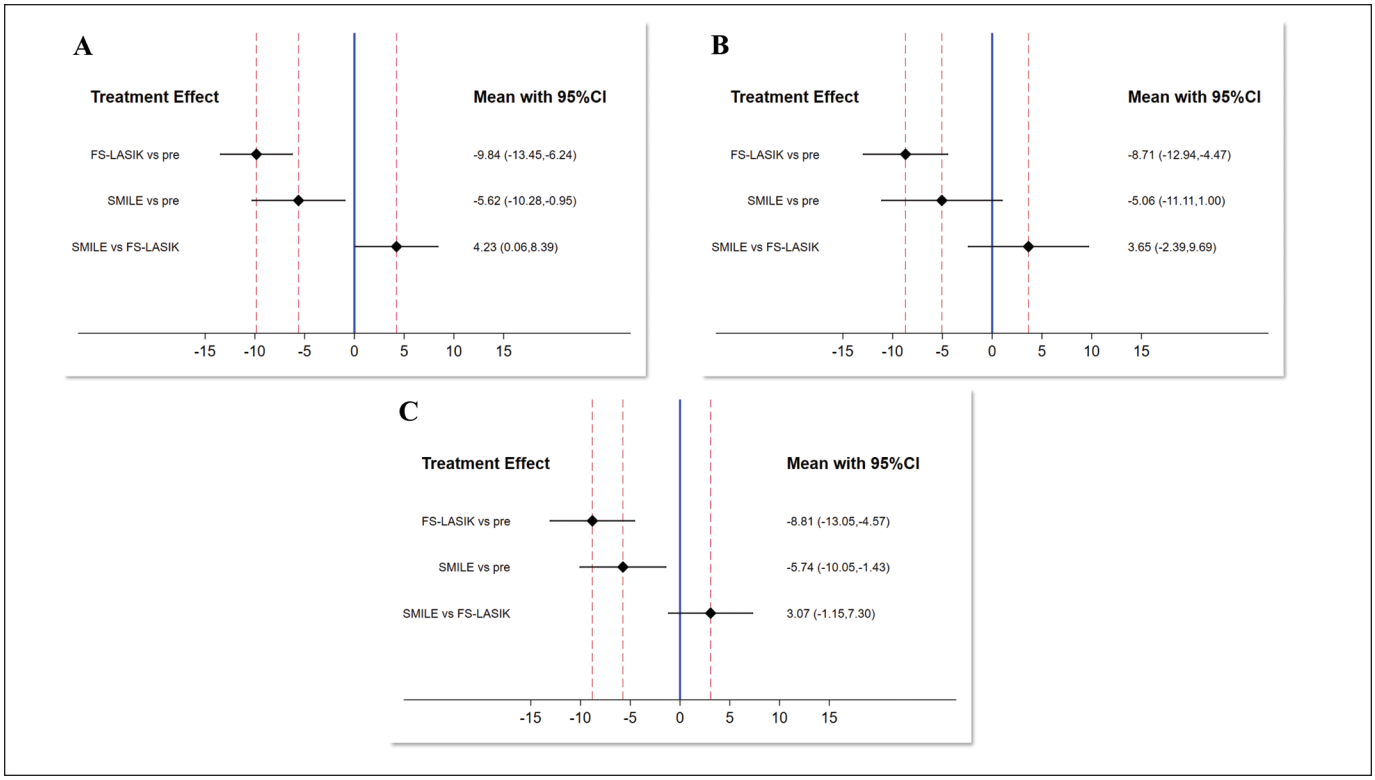

Figure 1. Corneal nerve density in the femtosecond laser–assisted in situ keratomileusis (FS-LASIK) and small incision lenticule extraction (SMILE) groups at (A) 1, (B) 3, and (C) 6 months postoperatively.

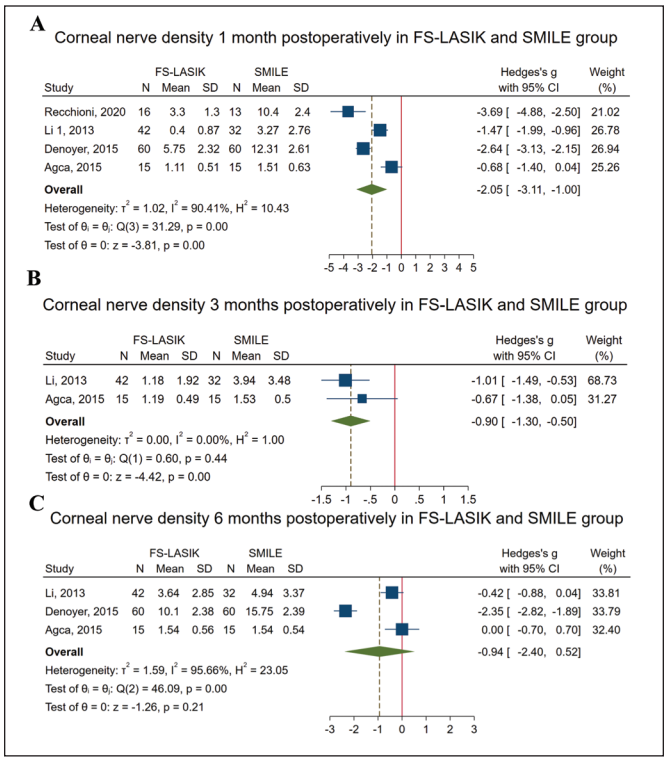

Figure 2. Corneal nerve density in the femtosecond laser–assisted in situ keratomileusis (FS-LASIK) and small incision lenticule extraction (SMILE) groups at (A) 1, (B) 3, and (C) 6 months postoperatively. SD = standard deviation

neal nerve density between the SMILE and FS-LASIK groups at 6 months postoperatively (WMD: -0.94, 95% CI: -2.40 to 0.52, $P > .05$), as shown in **Figure 2**.

Number of Corneal Nerve Trunks

The number of corneal nerve trunks was defined as the number of corneal nerve trunks per mm^2. Five studies[8,9,12,16,17] evaluated the number of postoperative corneal nerve trunks. We analyzed the data at 1 and 6 months postoperatively, as shown in **Figure 3**. At 1 and 6 months postoperatively, both the FS-LASIK and SMILE groups showed significant decreases in the number of corneal nerve trunks. There was no significant difference between the two groups at 1 month postoperatively. However, there was a significant difference at 6 months postoperatively.

Number of Corneal Nerve Branches

The number of corneal nerve branches was defined as the number of nerve joints per mm^2. Four studies[8,9,12,16] evaluated the postoperative corneal nerve branches. The results of the network meta-analysis are shown in **Figure 4**. Compared with preoperative levels, the FS-LASIK group showed a significant decrease in the number of corneal nerve branches at 1 (mean: -25.09; 95% CI: -41.64 to -8.54, $P < .05$) and 6 (mean: -30.69; 95%

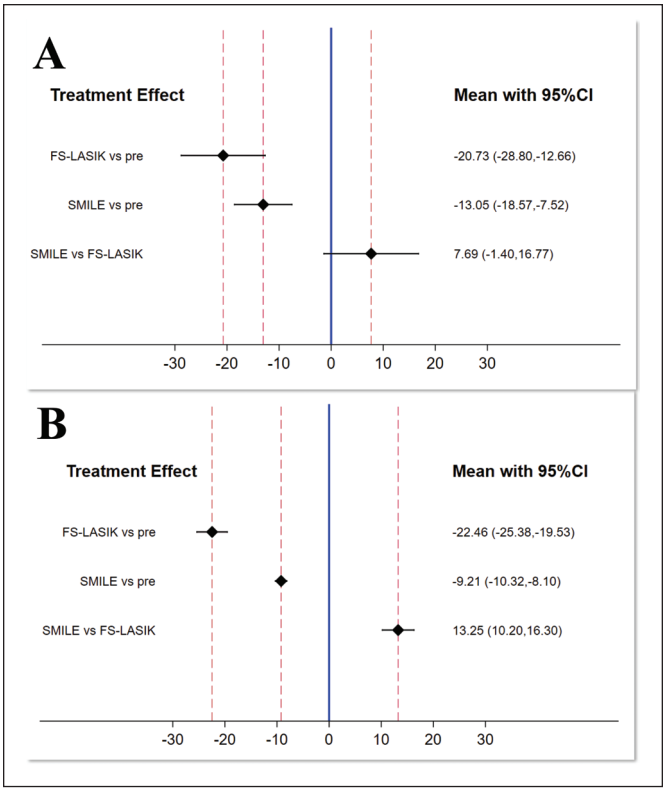

Figure 3. The number of corneal nerve trunks at 1 and 6 months postoperatively in the preoperative group (pre), femtosecond laser–assisted in situ keratomileusis group (FS-LASIK), and small incision lenticule extraction group (SMILE). The number of corneal nerve trunks at (A) 1 and (B) 6 months postoperatively.

CI: -49.30 to -12.07, $P < .05$) months postoperatively. In contrast, no significant difference was found between the preoperative levels and the SMILE group at 1 month postoperatively (mean: -3.92; 95% CI: -23.07 to -15.22), but there was a significant decrease in the SMILE group at 6 months postoperatively (mean: -26.48; 95% CI: -38.23 to -14.73, $P < .05$). There was no significant difference between the SMILE and FS-LASIK groups at 1 (mean: 21.17, 95% CI: -0.79 to 43.13, $P > .05$) and 6 (mean: 4.21, 95% CI: -15.74 to 24.16, $P > .05$) months postoperatively.

Only two studies[9,16] directly compared the number of nerves between the FS-LASIK and SMILE groups at 1 month postoperatively. The results are shown in **Figure 5**. There was significant difference between the SMILE group and FS-LASIK group at 1 month postoperatively (trunks = WMD: -2.52, 95% CI: -4.91 to -0.14, $P = .04$; branches = WMD: -2.80, 95% CI: -3.41 to -2.19, $P < .05$).

Among the four studies that directly compared the SMILE and FS-LASIK groups, none recorded the number of corneal nerve trunks and corneal nerve branches at 3 months postoperatively, so we could not perform a network meta-analysis on these two indexes for this time point.

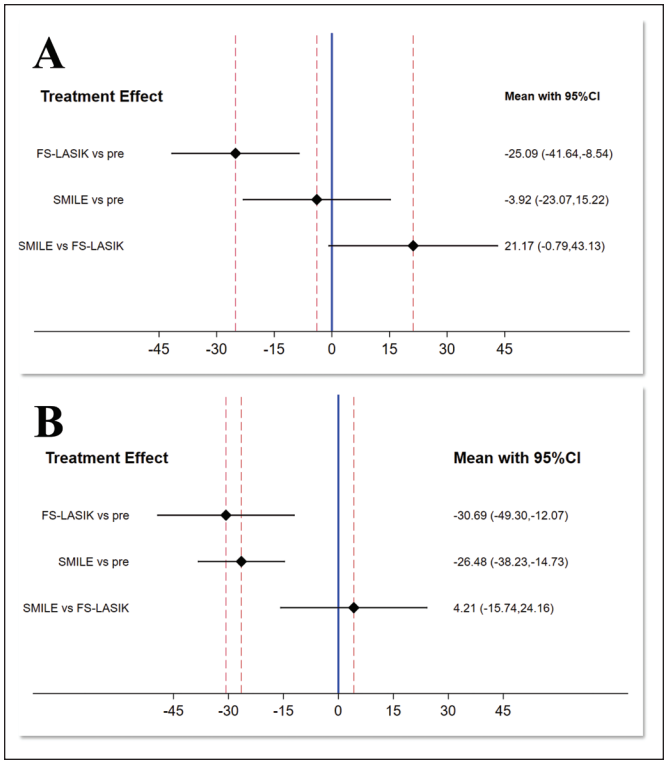

Figure 4. The number of corneal nerve branches in the preoperative group (pre), femtosecond laser–assisted in situ keratomileusis group (FS-LASIK), and small incision lenticule extraction group (SMILE) at (A) 1 and (B) 6 months postoperatively.

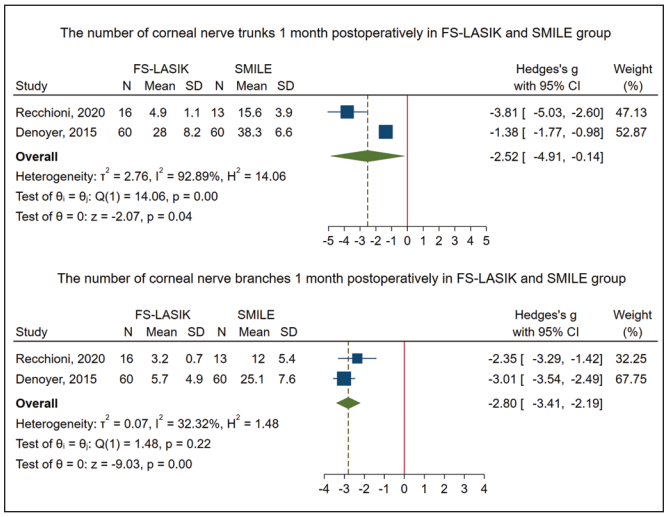

Figure 5. The number of corneal nerve trunks and branches at 1 month postoperatively in the femtosecond laser–assisted in situ keratomileusis (FS-LASIK) and small incision lenticule extraction (SMILE) groups. SD = standard deviation

DISCUSSION

Due to the need to make an incision or corneal flap on the cornea, refractive surgery will inevitably damage the corneal nerves. IVCM can clearly observe the decrease in corneal nerve density, the number of corneal

nerve trunks, and the number of corneal nerve branches. Previously, several meta-analyses compared SMILE and FS-LASIK.[18-24] However, most meta-analyses focused on clinical outcomes such as dry eye symptoms, final refractive spherical equivalent, and corneal sensitivity. There are few meta-analyses involving the corneal or sub-basal nerves. Furthermore, many studies compared one of the refractive surgeries with the preoperative baseline level, whereas there are few studies directly comparing the FS-LASIK and SMILE groups. We conducted a network meta-analysis to compare the corneal nerve injuries between SMILE and FS-LASIK surgeries and concluded that SMILE showed better results regarding corneal nerve damage and reinnervation within 3 months, whereas no significant differences were observed at 6 months postoperatively between the two surgeries.

During the process of refractive surgeries, damage to the cornea is inevitable.[25] In our study, both the SMILE and FS-LASIK groups showed a significant decrease in the corneal nerve density and the number of corneal nerve trunks and branches at 1, 3, and 6 months postoperatively. Previous studies have reached similar conclusions. Calvillo et al[26] suggested that the sub-basal corneal nerve density and the number of corneal nerve trunks and branches decreased more than 90% in the first month after LASIK and began to recover at 6 months postoperatively. Other researchers suggested that the corneal nerve damage caused by FS-LASIK could not be repaired to the same level as that before FS-LASIK even 10 years postoperatively.[19] Long-term studies are limited for SMILE, but it is suggested that the nerves keep regenerating even 2 years postoperatively.[17,19]

Corneal nerve density is defined as the total length of corneal nerve per unit area of the visual field ($\mu m/mm^2$), which reflects corneal nerve injury caused by surgery and the recovery of the corneal nerves. The higher the corneal nerve density, the lesser the degree of corneal nerve damage. As mentioned before, there were differences in the results of the network and traditional meta-analyses. The results of the network meta-analysis showed that the corneal nerve density in the SMILE group was higher than that in the FS-LASIK group only 1 month postoperatively ($P < .05$), whereas traditional meta-analysis showed that the SMILE group was better than the FS-LASIK group at both 1 and 3 months postoperatively ($P < .05$). Both analyses showed there was no difference at 6 months postoperatively. In FS-LASIK, the surgeon creates a flap in the anterior cornea stoma. Then the flap is lifted, and photoablation of the corneal stroma is performed. The photoablation will damage the stroma nerve and, in making the corneal flap, the laser will damage the sub-basal corneal nerve.[27] In contrast, a lenticule is made in SMILE and removed through a small incision.[28] However, the corneal incision in SMILE is only 30° to 40° wide, whereas the incision in FS-LASIK is nearly 300°, which may explain why the corneal nerve density is much better after SMILE in the early stage postoperatively. Cai et al[20] reached a similar conclusion in their meta-analysis that the damage to the sub-basal corneal nerves was less in the first 3 months after SMILE than after FS-LASIK, and there was no significant difference at 6 months postoperatively between these two procedures.

The number of corneal nerve trunks is an index reflecting the residual nerves and nerve regeneration postoperatively. Although there was no significant difference between FS-LASIK and SMILE at 1 month postoperatively in the network meta-analysis, the mean number of corneal nerve trunks of the SMILE group was higher than that of the FS-LASIK group. After FS-LASIK, less than 10% of the sub-basal nerve in the cornea was preserved. The regenerated nerve from the stroma below the surgery interface cannot cross and connect with the remaining nerve in the flap.[7,26,29] In contrast, SMILE involves a smaller incision and no corneal flap. With only a small area of stromal nerves and sub-basal nerves cut off, the nerve fibers that do not penetrate the Bowman's layer, and are located outside the lenticule and incision area, remain unchanged. Sekundo et al[28] suggested less nerve damage is associated with SMILE than FS-LASIK, so there is a significant difference in the nerve number between the two groups immediately after surgery. Rabbit experiments[29,30] suggested that residual corneal nerves send out branches for repair, and neurogenesis is not the primary repair method after FS-LASIK. The condition may be different after SMILE. Immediately after surgery, more nerve trunks were preserved in the SMILE group. As time goes by, corneal nerves began to regenerate in the SMILE group more than in the FS-LASIK group, so the gap between the two groups became larger, resulting in a significant difference at 6 months postoperatively.

The number of corneal nerve branches over time reflects nerve reinnervation from residual nerves postoperatively. In the network meta-analysis, no significant difference was observed between the two groups at 1 and 6 months postoperatively. The results of some other studies[9,16,31] conflict with ours, and suggest that the number of corneal nerve branches is significantly greater after SMILE than FS-LASIK. As mentioned before, FS-LASIK causes more nerve damage than SMILE. In addition, in the early postoperative stage, the remaining sub-basal nerve in the flap may undergo degeneration.[32] It is evident that, in the early postoperative period, the

number of branches in FS-LASIK is fewer. Although there was no significant difference between the two groups in the network meta-analysis, the mean number of nerve branches in SMILE was higher than that in FS-LASIK. After FS-LASIK surgery, the remaining fibers begin to sprout and show short sub-basal branches. After 3 months, the branches continue to grow and become longer. Moreover, in contrast to SMILE, sprouting is the primary repair method after FS-LASIK,[29,32] so the difference in the number of corneal nerve branches becomes smaller as time goes by postoperatively.

Several limitations of this meta-analysis should be considered. First, the measurement of the corneal nerves still lacks a unified standard, and different researchers may have inevitable observation biases. Second, there are only limited indicators to evaluate the corneal nerve, which cannot comprehensively evaluate the corneal nerve. Finally, the number of eligible studies is limited. Therefore, more high-quality studies are needed to compare the differences in corneal nerve injury caused by different surgical methods.

In this meta-analysis, there was a slight difference in the results of the network and traditional meta-analyses, which may have resulted from the small sample size of the existing studies. In addition, because the distribution of corneal nerves on the cornea is uneven, the size of the flap and incision and ablation depth and time will affect the degree of corneal nerve injury.[19,33] The surgical methods and specific parameters adopted by surgeons in included studies are different, which may also be a reason for the differences between the network and traditional meta-analyses. Nevertheless, the results still suggest that the degree of corneal nerve damage in the SMILE group is lower than that in the FS-LASIK group immediately postoperatively. Six months postoperatively, there was no statistical difference between the two groups, but the mean value of the SMILE group was still higher than the FS-LASIK group.

AUTHOR CONTRIBUTIONS

Study concept and design (XJ, YW, HY, YL, HW, ZA, XL); data extraction (XJ, YW, HY, YL, HW, ZA, XL); analysis and interpretation (XJ, YW, HY, YL, HW, ZA, XL); writing the manuscript (XJ, YW, HY, YL, HW, ZA, XL); critical reversion of the manuscript (XJ, HW, HY, YL, HW, ZA, XL); supervision (XJ, HW, XL).

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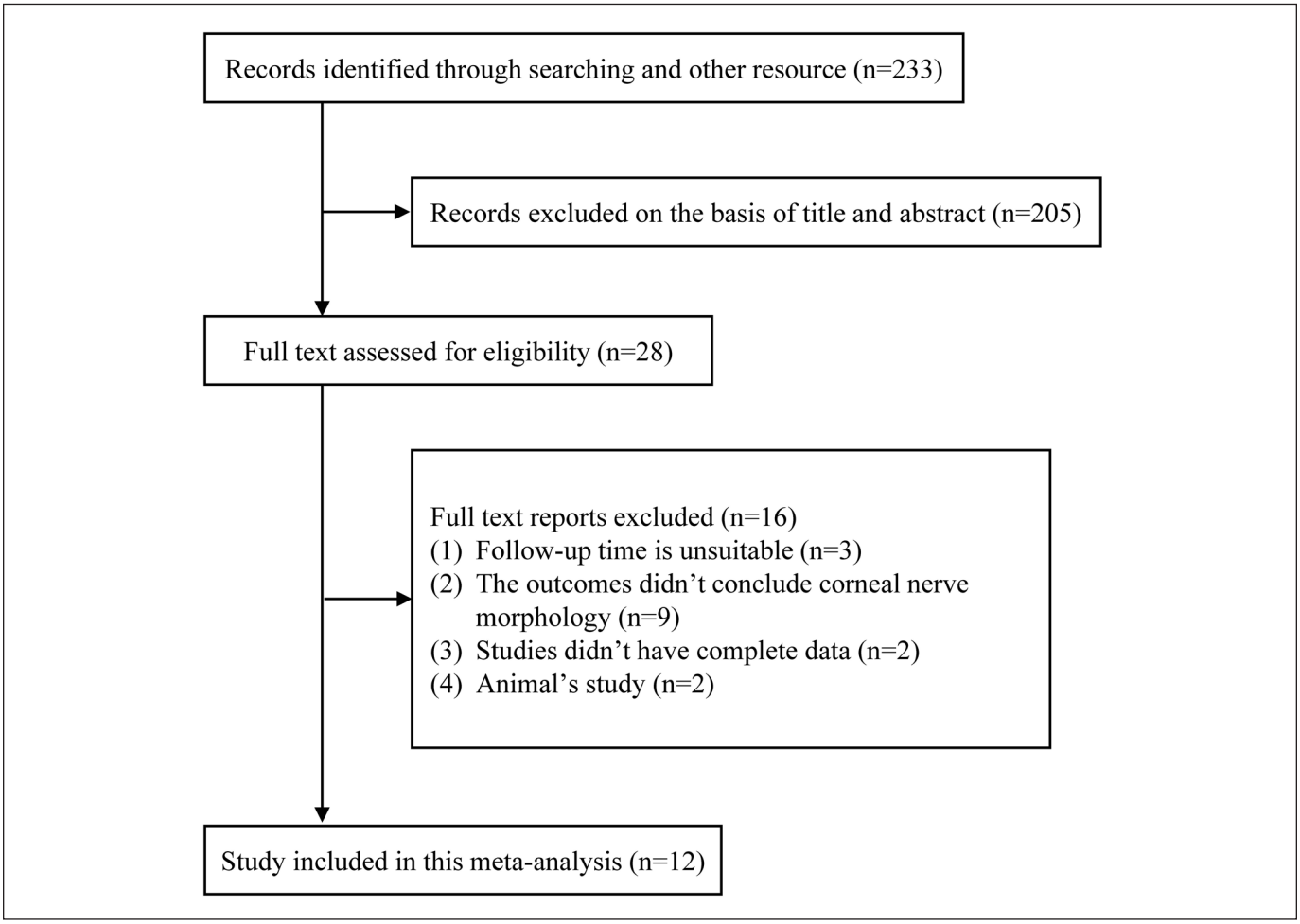

Figure A. Flow diagram of the identification and inclusion of eligible studies.

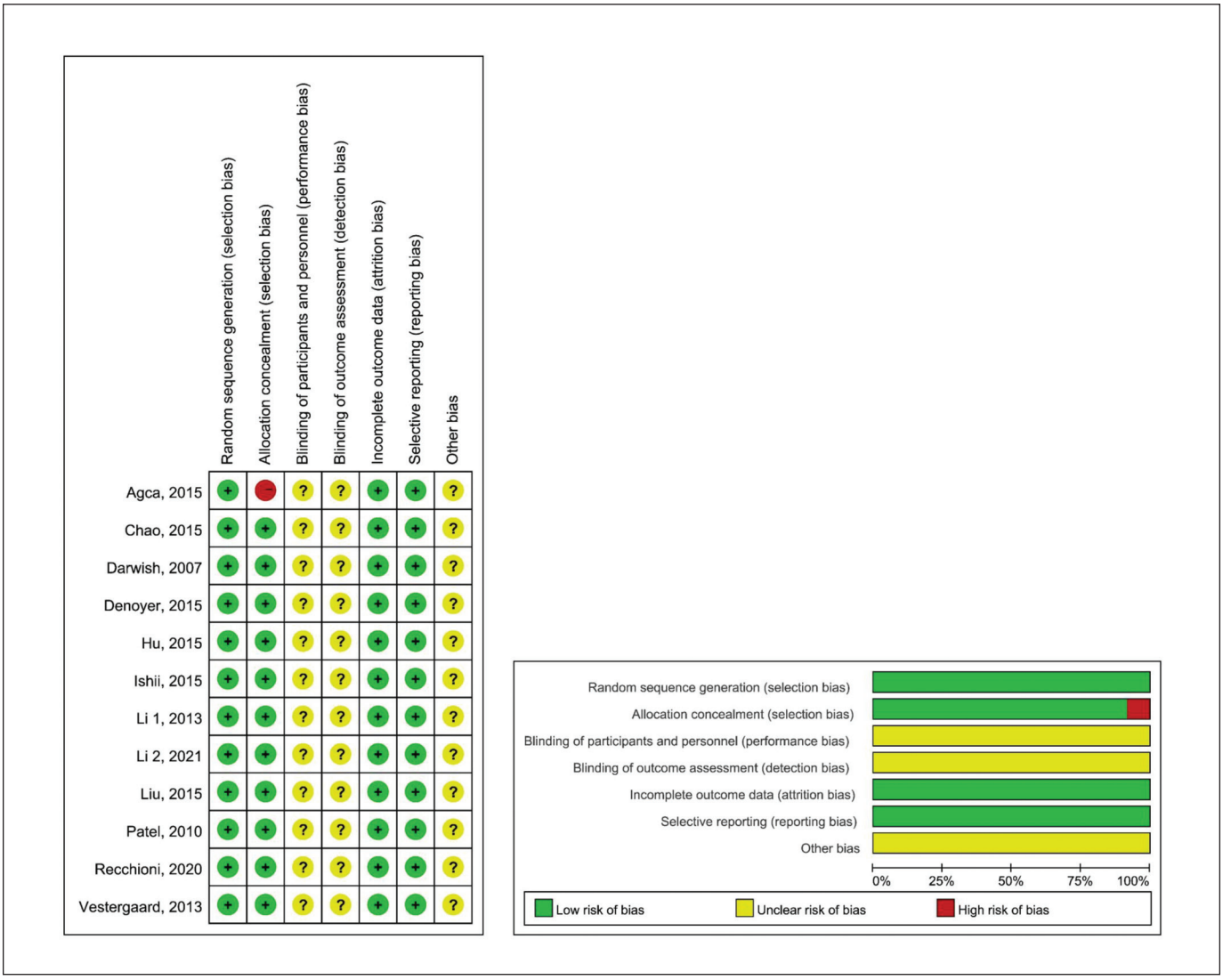

Figure B. Risk of bias summary.

TABLE A

NOS Score of the Studies in the Meta-analysis

	Selection		Comparability		Outcomes			
Study	Representativeness of the Exposed Cohort	Ascertainment of Exposure	Demonstration That Outcomes of Interest Were Not Present at the Start of Study	Comparability of Cohorts Based on the Design or Analysis	Assessment of the Outcomes	Was Follow-up Long Enough for Outcomes to Occur	Adequacy of Follow-up of Cohorts	NOS Score
Recchioni et al, 2020[16]	*	*	*	**	*	*	*	8
Agca et al, 2014[23]	*	–	*	**	*	*	*	7
Li et al, 2013[13]	*	*	*	**	*	*	*	8
Denoyer et al, 2015[9]	*	*	*	**	*	*	*	8
Chao et al, 2015[7]	*	*	*	**	*	*	*	8
Hu et al, 2015[10]	*	*	*	**	*	*	*	8
Patel et al, 2010[15]	*	*	*	**	*	*	*	8
Darwish et al, 2007[8]	*	*	*	**	*	*	*	8
Vestergaard et al, 2013[17]	*	*	*	**	*	*	*	8
Li et al, 2021[12]	*	*	*	**	*	*	*	8
Ishii et al, 2015[11]	*	*	*	**	*	*	*	8
Liu et al, 2015[14]	*	*	*	**	*	*	*	8

*NOS = Newcastle-Ottawa Scale; * = 1 score; ** = 2 scores; – = 0 score*