

# Optical coherence tomography evaluation of retinal nerve fiber layer thickness in non-arteritic anterior ischemic optic neuropathy and primary open angle glaucoma: a systematic review and Meta-analysis

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## Abstract

• **AIM:** To assess the differences in average and sectoral peripapillary retinal nerve fiber layer (pRNFL) thickness using spectral domain optical coherence tomography (SD-OCT) in patients with non-arteritic anterior ischemic neuropathy (NAION) compared with those with primary open angle glaucoma (POAG).

• **METHODS:** A comprehensive literature search of the PubMed, Cochrane Library, and Embase databases were performed prior to October, 2021. Studies that compared the pRNFL thickness in NAION eyes with that in POAG eyes with matched mean deviation of the visual fields were included. The weighted mean difference (WMD) with 95% confidence interval (CI) was used to pool continuous outcomes.

• **RESULTS:** Ten cross-sectional studies (11 datasets) comprising a total of 625 eyes (278 NAION eyes, 347 POAG eyes) were included in the qualitative and quantitative analyses. The pooled results demonstrated that the superior pRNFL was significantly thinner in NAION eyes than in POAG eyes (WMD=-6.40, 95%CI: -12.22 to -0.58,  $P=0.031$ ), whereas the inferior pRNFL was significant thinner in POAG eyes than in NAION eyes (WMD=11.10, 95%CI: 7.06 to

15.14,  $P\leq 0.001$ ). No difference was noted concerning the average, nasal, and temporal pRNFL thickness (average: WMD=1.45, 95%CI: -0.75 to 3.66,  $P=0.196$ ; nasal: WMD=-2.12, 95%CI: -4.43 to 0.19,  $P=0.072$ ; temporal: WMD=-1.24, 95%CI: -3.96 to 1.47,  $P=0.370$ ).

• **CONCLUSION:** SD-OCT based evaluation of inferior and superior pRNFL thickness can be potentially utilized to differentiate NAION from POAG, and help to understand the different pathophysiological mechanisms between these two diseases. Further longitudinal studies and studies using eight-quadrant or clock-hour classification method are required to validate the obtained findings.

• **KEYWORDS:** non-arteritic anterior ischemic optic neuropathy; primary open angle glaucoma; optical coherence tomography; peripapillary retinal nerve fiber layer thickness

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## INTRODUCTION

Primary open angle glaucoma (POAG) is an age-related neurodegenerative optic neuropathy characterized by the progressive deterioration of retinal ganglion cells (RGCs) and their axons<sup>[1-3]</sup>, followed by the excavation of the optic nerve head (ONH) and impaired visual field (VF)<sup>[4-5]</sup>. Non-arteritic anterior ischemic optic neuropathy (NAION) is a non-glaucomatous optic neuropathy that presents with the sudden painless loss of vision, optic disc edema with resolution after several weeks and optic disc pallor at the atrophic stage<sup>[6-7]</sup>. Similar to POAG, NAION also results in the loss of RGCs and their axons. However, the pathophysiological mechanisms underlying the different ONH configuration changes in these two diseases are not completely understood<sup>[3,7]</sup>.

Evaluation of the peripapillary retinal nerve fiber layer (pRNFL) thickness enables clinicians to assess the degree and the pattern of the damage to the RGC axons coursing toward the ONH. Multiple quantitative retinal imaging techniques comprising scanning laser polarimetry, Heidelberg retinal tomography, as well as optical coherence tomography (OCT)<sup>[8-13]</sup>, have been utilized to measure RNFL thickness. Among them, spectral-domain optical coherence tomography (SD-OCT), which is the latest generation of OCT, provides a high-resolution and enhance-depth visualization of the retina and the ONH<sup>[14-16]</sup>.

With the utilization of SD-OCT in daily routine diagnosis, several studies have demonstrated that the attenuation of average pRNFL thickness is common in NAION and glaucoma<sup>[5,13,17-33]</sup>, where NAION may mimic with POAG<sup>[34]</sup>. However, the pattern and severity of sectoral pRNFL thickness thinning were inconsistent<sup>[18-20,22,24-26,28-29]</sup>, which may help reveal the different underlying mechanisms that induce optic damage in these two ophthalmic neuropathies and help differentiate NAION from POAG in a non-invasive manner.

Therefore, we performed this systematic review and Meta-analysis to compare the average and sectoral pRNFL thickness in patients with NAION and those with POAG with similar VF mean deviation (MD), facilitating a better understanding of the biomechanisms that lead to the different patterns of neurodegeneration.

## MATERIALS AND METHODS

The present systematic review and Meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines<sup>[35-36]</sup>. Three individual investigators (Tong YX, Zhang XY, and He Y) independently conducted the literature search, qualification, data extraction, quality evaluation by Agency for Healthcare Research and Quality (AHRQ) checklist, and risk of bias assessment. The present study was registered in PROSPERO (registration number: CRD42020220934).

**Search Strategy** Literature search was conducted from inception to October, 2021 in PubMed, Cochrane Library and Embase databases. The following search terms were used: “non-arteritic anterior ischemic optic neuropathy”, “NAION”, “glaucoma”, “retinal nerve fiber layer”, “RNFL”, “optical coherence tomography”, “OCT” with no restriction. The search strategies were modified by the requirements of the different databases. Potential eligible articles were included by detailed screening of full-text versions of the literature.

**Inclusion and Exclusion Criteria** We included cross-sectional studies if they met the following requirements: 1) original article; 2) inclusion of NAION at the atrophic stage where

optic disc swelling had to occur at least 3mo prior to the documentation and has resolved at the time of the study; 3) inclusion of both NAION and POAG with the same diagnostic standards; 4) inclusion of NAION and POAG with similar severities in terms of the MD of the VF; 5) inclusion of pRNFL thickness assessed by SD-OCT.

Exclusion criteria were: 1) conference abstracts, reviews, case reports and animal experiments; 2) enrollment of NAION at the acute stage; 3) different diagnostic standards; 4) non-inclusion of SD-OCT based evaluation of pRNFL thickness; 5) studies without extractable data.

**Data Extraction** The following information was extracted and summarized: title, first author, publication year, region, study type, number of patients and eyes, source of patients, time periods for identifying patients, mean age of patients, female/male ratios, types of OCT devices, episode of NAION, types of glaucoma, diagnostic criteria, average and quadrant pRNFL thickness, scan protocol and area of ONH, MD of the VF, severity of glaucoma, onset time of NAION. Disagreements were resolved by discussing among all the authors.

**Quality Assessment** Ten included cross-sectional studies were evaluated based on the AHRQ methodology checklist.

**Statistical Analysis** Stata version 12.0 (StataCorp, Texas, USA) and Review Manager version 5.4.1 (Cochrane Collaboration, London, UK) were used for the statistical analyses. We used weighted mean difference (WMD) with a 95% confidence interval (CI) to pool the mean differences in average and sectoral pRNFL thickness between the NAION and POAG groups. A *P* value <0.05 was regarded to be statistically significant. Statistical heterogeneities among different groups were measured using Cochrane’s *Q* test and quantified by *I*<sup>2</sup>. We used a fixed-effects model when *I*<sup>2</sup><50%<sup>[37]</sup>, indicating the heterogeneity was acceptable; otherwise, we employed a random-effects model when *I*<sup>2</sup>>50%. The stratified analyses were performed by the onset time of NAION and OCT device types. Egger *et al*’s<sup>[38]</sup> and Begg *et al*’s<sup>[39]</sup> tests were used to evaluate the potential publication bias. The “leave-one-out” sensitivity analysis concerning the average and quadrant pRNFL thickness was performed to explore the sources of heterogeneity.

In some studies, RNFL thickness was displayed by six-quadrant classification method, and in others the four-quadrants classification method was used. To transform the six-quadrant data to four-quadrant data (since the majority of the articles used four-quadrant classification method), we used a modified method as previously described<sup>[40]</sup>.

## RESULTS

**Literature Search** A total of 170 studies were initially identified, of which 37 duplicates were removed. Of the remaining 133 articles, 109 were excluded after screening

**Table 1 Characteristics of included studies**

Study Year	Region	Design	No. eye		Mean±SD age (y)		Gender (F/M)		Device (SD-OCT)	Scan area of ONH (mm <sup>2</sup> )	MD of the VF (dB)		Severity of glaucoma	Onset time of NAION
			NAION	POAG	NAION	POAG	NAION	POAG			NAION	POAG		
Shin 2021 <sup>[17]</sup>	Korea	CS, R	27	27	65.2±7.8	61.7±11.1	11/16	17/10	Cirrus	3.45 mm circle	-15.13±8.34	-15.11±7.57	Not indicated	>6mo
Hondur 2021 <sup>[18]</sup>	Turkey	CS	21	26	61±7	62±11	9/12	13/13	Spectralis	4.5×4.5	-18.79±6.13	-20.99±6.36	Severe	>6mo
Fard 2020 <sup>[19]</sup>	Iran	CS, P	19	37	57.4±12.2	63.6±0.4	N/A	N/A	Optovue	3.4 mm circle	-14.0±5.3	-12.7±5.5	Moderate to severe	>6mo
Robolleda 2019 <sup>[20]</sup>	Spain	CS	23	25	68.6±10.3	72.3±9.8	12/11	11/14	Spectralis	3.5 mm circle	-14.7±8.6	-12.9±8.32	Not indicated	>6mo
Resch 2018 <sup>[22]</sup>	Austria	CS	20	20	66.8±8.3	71.2±6.0	8/12	11/9	Spectralis & Cirrus	3.4 mm circle	-9.85±4.79	-10.24±4.71	Moderate to severe	>6mo
Fard 2018 <sup>[24]</sup>	Iran	CS	31	42	54.1±11	60.2±8	15/16	16/26	Spectralis	3.45 mm circle	-18.4±8.6	-17.2±8.6	Moderate to severe	>6mo
Liu 2017 <sup>[25]</sup>	Taiwan, China	CS, R	10	16	59.9±10.7	53.75±10.21	6/4	7/9	Optovue	3.45 mm circle	-12.78±6.34	-9.69±3.56	Moderate	>3mo
Lee 2017 <sup>[26]</sup>	Korea	CS, R	35	70	63.6±8.6	64.4±9.0	20/15	40/30	Cirrus	Optic disc cube 200×200	-17.7±8.7	-13.5±7.5	Moderate to severe	>3mo
Fard 2016 <sup>[29]</sup>	Iran	CS	30	32	58.4±10.5	65.6±13.1	17/13	10/22	Spectralis	3.4 mm circle	-16.47±9.05	-16.28±9.98	Moderate to severe	>3mo
Fard 2016 <sup>[28]</sup>	Iran	CS	42	32	58.02±8.83	64.59±9.79	22/20	10/22	Spectralis	3.4 mm circle	-16.47±9.05	-16.28±9.98	Moderate to severe	>3mo

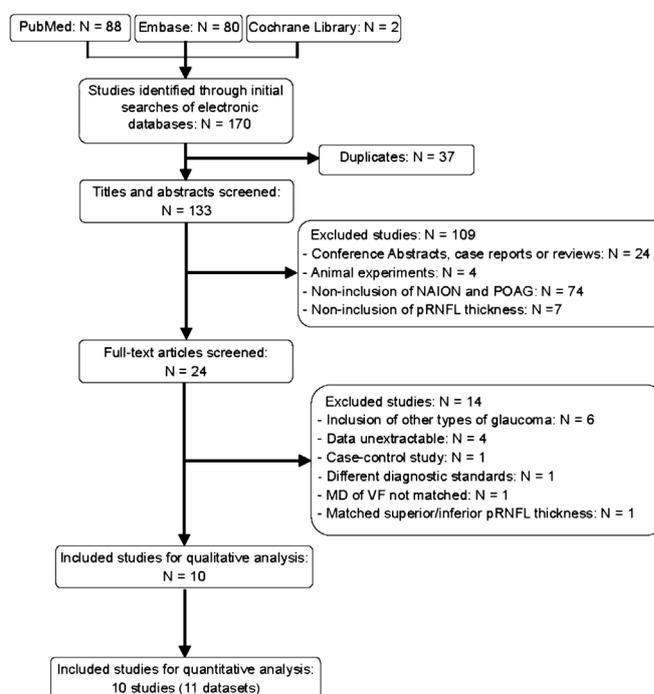
F/M: Female/male; SD-OCT: Spectral-domain optical coherence tomography; ONH: Optic nerve head; MD: Mean deviation; VF: Visual field; NAION: Non-arteritic anterior ischemic optic neuropathy; POAG: Primary open angle glaucoma; CS: Cross-sectional study; P: Prospective study; R: Retrospective study.

the titles and abstract: 74 did not include NAION and POAG patients; 24 were conference abstracts, case reports, or reviews; seven lacked SD-OCT-based pRNFL thickness data; and four performed animal experiments. With full-text screening, another 14 studies were removed: six included other types of glaucoma rather than POAG, four reported unextractable data, one was a case-control study, one used different diagnostic standards, one included NAION and POAG with un-matched MD of VF, and one included NAION and POAG with matched superior or inferior pRNFL thickness. Thus, 10 eligible articles were included in the qualitative analysis, and 10 studies (11 datasets) were integrated in the quantitative analysis. A flow diagram of the literature search is shown in Figure 1.

**Characteristics and Qualities of Included Studies** Ten included cross-sectional studies (11 datasets) comprising 625 eyes (278 NAION eyes, 347 POAG eyes) were published between 2016 and 2021 across different regions (Turkey, Iran, Spain, Austria, Korea, and Taiwan, China). The mean age varied from 54.1 to 68.6y in NAION patients and 53.75 to 72.3y in POAG patients. The pRNFL thickness was detected by using three types of SD-OCT devices: Spectralis, Cirrus, and Optovue. Most of the scan protocols were centered at the 3.4-3.5 mm circle around the ONH. Moreover, the MD of the VF was comparable between NAION and POAG eyes, and the majority of the included studies enrolled patients with moderate to severe POAG patients. The included studies recruited NAION patients with time from the onset of more than 3 or 6mo. The detailed characteristics are summarized in Table 1.

In terms of evaluating methodological quality, the AHRQ scores of all included studies were more than 3, indicating adequate quality (Table 2).

**RNFL Thickness in NAION and POAG Patients** Ten studies (11 datasets) assessing the average pRNFL thickness



**Figure 1 Flow diagram of studies identified, included and excluded.**

showed no heterogeneity ( $I^2=0$ ). The pooled results demonstrated that no difference in average pRNFL thickness between NAION and POAG eyes (WMD=1.45, 95%CI: -0.75 to 3.66,  $P=0.196$ ; Figure 2). However, eight studies (nine datasets) evaluating the sectoral pRNFL thickness demonstrated that the superior pRNFL thickness was significantly lower in NAION patients than in POAG patients (WMD=-6.40, 95%CI: -12.22 to -0.58,  $P=0.031$ ; Figure 3), whereas the inferior pRNFL was significantly thinner in POAG eyes (WMD=11.10, 95%CI: 7.06 to 15.14,  $P\leq 0.001$ ; Figure 4). No difference in the nasal and temporal quadrants was found between NAION and POAG patients (nasal: WMD=-2.12, 95%CI: -4.43 to 0.19,  $P=0.072$ ; Figure 5; temporal: WMD=-1.24, 95%CI: -3.96 to 1.47,  $P=0.370$ ; Figure 6).

**Table 2 Methodological quality of included studies**

Study	11-item check list recommended by AHRQ checklist											Score	Quality
	i	ii	iii	iv	v	vi	vii	viii	ix	x	xi		
Shin 2021 <sup>[17]</sup>	★	★	★			★	★	★				6	M
Hondur 2021 <sup>[18]</sup>		★			★	★		★				4	M
Fard 2020 <sup>[19]</sup>	★	★	★			★	★	★		★		7	M
Robolleda 2019 <sup>[20]</sup>	★	★				★	★	★				5	M
Resch 2018 <sup>[22]</sup>	★	★				★	★	★				5	M
Fard 2018 <sup>[24]</sup>	★	★	★				★	★		★		6	M
Liu 2017 <sup>[25]</sup>	★	★	★				★					4	M
Lee 2017 <sup>[26]</sup>	★	★	★					★		★		5	M
Fard 2016 <sup>[29]</sup>	★	★	★	★		★	★	★				7	M
Fard 2016 <sup>[28]</sup>	★	★	★				★	★		★		6	M

AHRQ: Agency for Healthcare Research and Quality; H: High quality; M: Moderate quality; L: Low quality; high quality (score: 8-11); moderate quality (score: 4-7); low quality (score: 0-3). i: Define the source of information; ii: List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications; iii: Indicate time period used for identifying patients; iv: Indicate whether or not subjects were consecutive if not population-based; v: Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants; vi: Describe any assessments undertaken for quality assurance purposes; vii: Explain any patient exclusions from analysis; viii: Describe how confounding was assessed and/or controlled; ix: If applicable, explain how missing data were handled in the analysis; x: Summarize patient response rates and completeness of data collection; xi: Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained.

**Table 3 Subgroup analysis of pRNFL thickness according to the onset time of NAION**

Subgroup	No.	Heterogeneity		WMD (95%CI)	Overall effect	
		I <sup>2</sup>	P		Z	P
Onset time >3mo						
Average	4	0	0.869	0.58 (-3.12, 4.28)	0.31	0.758
Superior	4	0	0.953	-5.65 (-11.87, 0.57)	1.78	0.075
Inferior	4	0	0.779	10.89 (3.97, 17.82)	3.08	0.002
Nasal	4	42.5%	0.157	-2.28 (-5.47, 0.91)	1.40	0.161
Temporal	4	0	0.996	0.53 (-3.46, 4.52)	0.26	0.795
Onset time >6mo						
Average	7	9.6%	0.355	1.93 (-0.81, 4.68)	1.38	0.167
Superior	5	76.6%	0.002	-6.55 (-16.58, 3.48)	1.28	0.201
Inferior	5	1.7%	0.397	11.20 (6.23, 16.18)	4.42	≤0.001
Nasal	5	0	0.623	-1.94 (-5.30, 1.41)	1.14	0.256
Temporal	5	0	0.845	-2.77 (-6.47, 0.94)	1.46	0.143

pRNFL: Peripapillary retinal nerve fiber layer; NAION: Non-arteritic anterior ischemic optic neuropathy; SD-OCT: Spectral-domain optical coherence tomography; WMD: Weighted mean difference; CI: Confidence interval; I<sup>2</sup>: I-square heterogeneity statistic; Z: Z-statistic.

**Subgroup Analysis** The subgroup analysis regarding the onset time of NAION (Table 3) also demonstrated that the inferior pRNFL thickness was significantly lower in POAG eyes than in NAION eyes (onset time >3mo: WMD=10.89, 95%CI: 3.97 to 17.82, P=0.002; onset time >6mo: WMD=11.20, 95%CI: 6.23 to 16.18, P≤0.001). However, in contrast to the combined pooled data, significant difference in the superior pRNFL thickness was not found between the NAION eyes and POAG eyes regardless of the onset time of NAION (onset time >3mo: WMD=-5.65, 95%CI: -11.87 to 0.57, P=0.075; onset time >6mo: WMD=-6.55, 95%CI: -16.58 to 3.48, P=0.201).

Similarly, no difference in the average, nasal, and temporal pRNFL thicknesses was noted.

Stratified analysis according to the different types of SD-OCT (Table 4) also revealed that the inferior pRNFL was significantly thinner in POAG eyes when different SD-OCT devices were utilized (Spectralis: WMD=10.11, 95%CI: 4.69 to 15.53, P≤0.001; Cirrus: WMD=10.57, 95%CI: 2.94 to 18.19, P=0.007; Optovue: WMD=15.33, 95%CI: 5.37 to 25.29, P=0.003). The pooled results showed that the superior pRNFL was significantly thinner in NAION eyes than in POAG eyes when the Spectralis SD-OCT was used (WMD=-10.20,

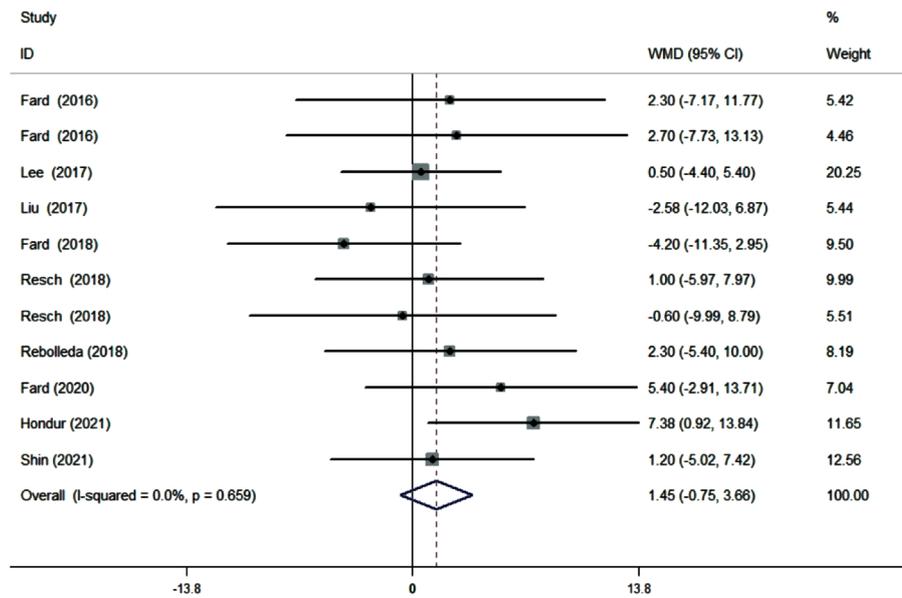


Figure 2 Forrest plot of average pRNFL thickness in patients with NAION and POAG.

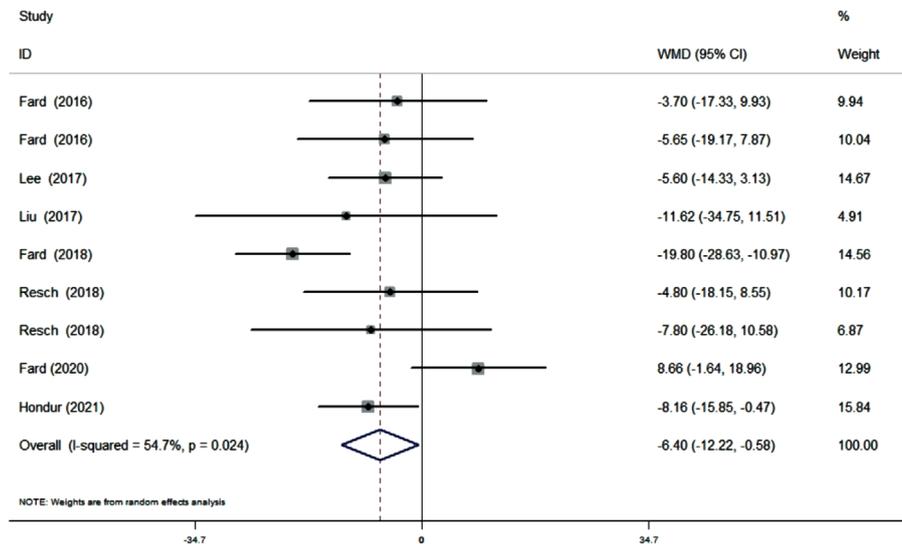


Figure 3 Forrest plot of superior pRNFL thickness in patients with NAION and POAG.

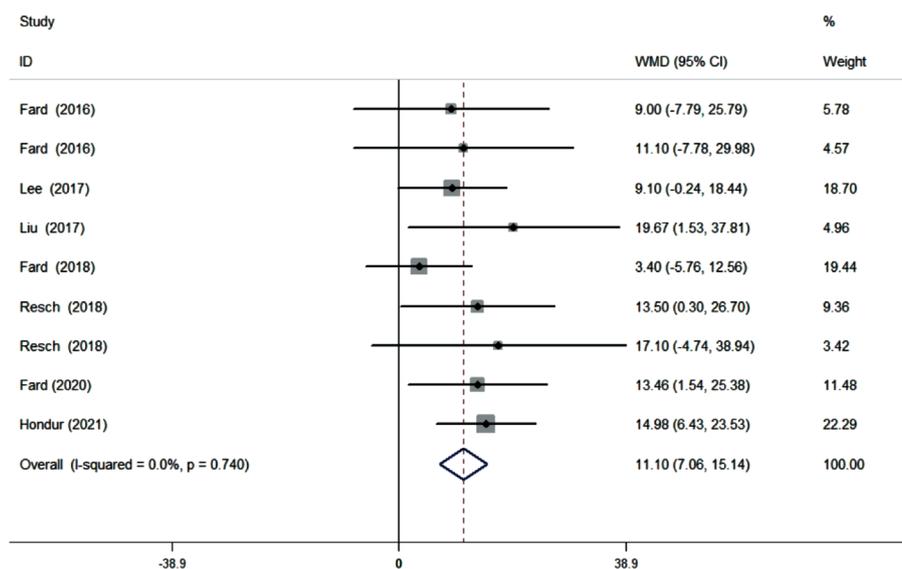


Figure 4 Forrest plot of inferior pRNFL thickness in patients with NAION and POAG.

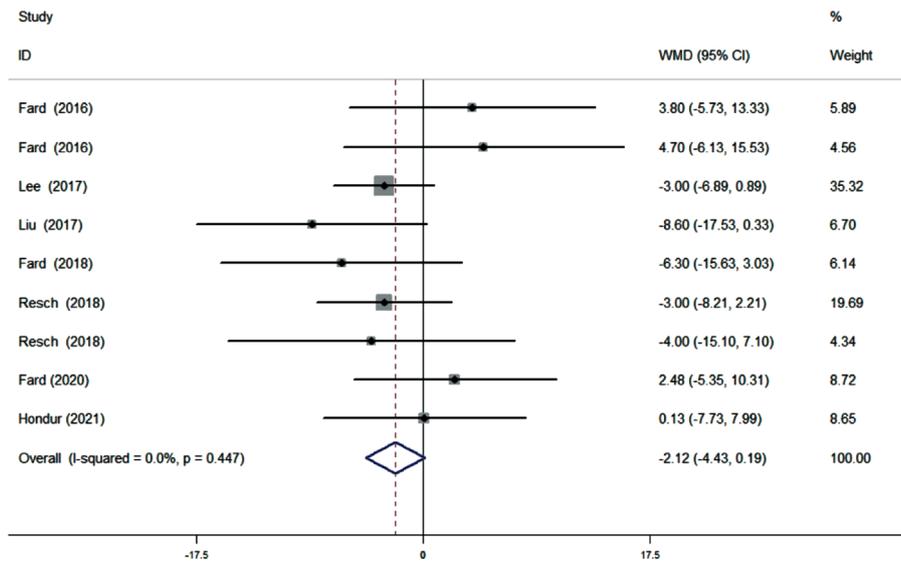


Figure 5 Forrest plot of nasal pRNFL thickness in patients with NAION and POAG.

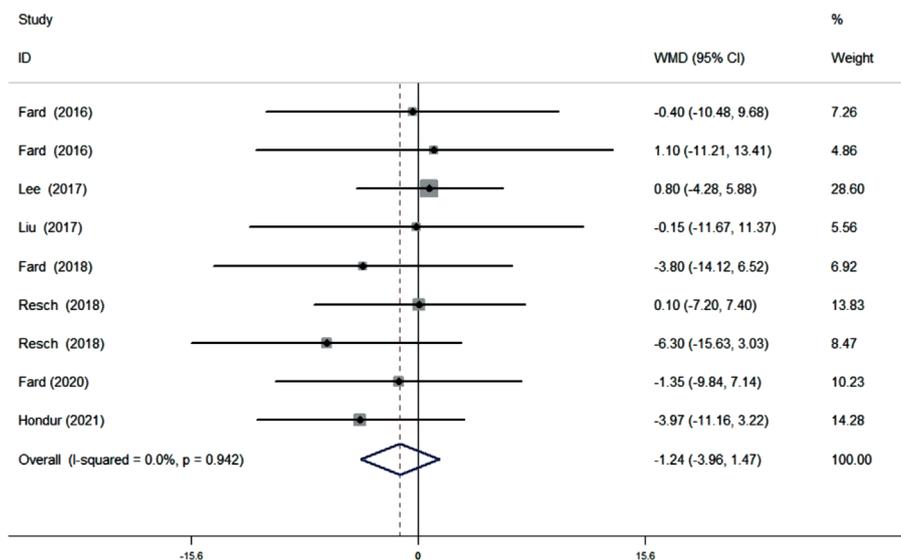


Figure 6 Forrest plot of temporal pRNFL thickness in patients with NAION and POAG.

95%CI: -16.51 to -3.90,  $P=0.002$ ), whereas no difference was demonstrated when Cirrus and Optovue SD-OCT were used (Cirrus: WMD=-5.36, 95%CI: -12.67 to 1.94,  $P=0.150$ ; Optovue: WMD=1.27, 95%CI: -17.85 to 20.40,  $P=0.896$ ). Similarly, no difference in the average, nasal, and temporal pRNFL thickness was indicated between NAION and POAG eyes regardless of SD-OCT type.

**Publication Bias** Results of Begg's test and Egger's test demonstrated no significant risk of publication bias in the average and sectoral pRNFL thickness ( $P>0.05$ ; Table 5).

**Sensitivity Analysis** No obvious change in the results was noted after excluding each study (Figure 7), demonstrating the stability and reliability of our results. Two studies by Fard *et al*<sup>[19,24]</sup> were found to contribute most to the heterogeneity of the superior pRNFL thickness (Table 6).

## DISCUSSION

In the present study, we pooled the average and quadrant

pRNFL thickness in NAION and POAG patients. Our data demonstrated no significant difference in the average pRNFL thickness between the NAION and POAG eyes ( $P=0.196$ ). This finding is consistent with those of previous studies<sup>[5,17-26,29-30,32-33,41]</sup>. Currently, POAG has been reported to be associated with multiple risk factors including race, age, elevated intraocular pressure, family history, myopia, and diastolic perfusion pressure, *etc*<sup>[3,42-47]</sup>. In glaucomatous neurodegeneration, the increase in intraocular pressure or imbalance of trans-laminar cribrosa pressure continuously stresses the RGCs and their supporting glia, leading to the progressive loss of RGCs and axons<sup>[48]</sup>. In contrast to glaucoma, NAION is presumed to be correlated with factors that can disrupt vascular autoregulation, such as nocturnal hypotension and other predisposed conditions such as small-to-disc ratio, *etc*<sup>[49-50]</sup>. Transient infarction of the anterior segment of the optic nerve nourished by the posterior ciliary

**Table 4 Subgroup analysis of pRNFL thickness according to the type of SD-OCT**

Subgroup	No.	Heterogeneity		WMD (95%CI)	Overall effect	
		I <sup>2</sup>	P		Z	P
<b>Spectralis</b>						
Average	6	14.9%	0.319	1.92 (-1.37, 5.22)	1.14	0.252
Superior	5	34.9%	0.189	-10.20 (-16.51, -3.90)	3.17	0.002
Inferior	5	0	0.444	10.11 (4.69, 15.53)	3.66	≤0.001
Nasal	5	0	0.469	-0.38 (-4.63, 3.87)	0.17	0.862
Temporal	5	0	0.870	-3.20 (-7.40, 1.00)	1.50	0.135
<b>Cirrus</b>						
Average	3	0	0.983	0.82 (-2.55, 4.19)	0.48	0.632
Superior	2	0	0.922	-5.36 (-12.67, 1.94)	1.44	0.150
Inferior	2	0	0.594	10.57 (2.94, 18.19)	2.72	0.007
Nasal	2	0	1.000	-3.00 (-6.12, 0.12)	1.89	0.059
Temporal	2	0	0.877	0.57 (-3.60, 4.74)	0.27	0.788
<b>Optovue</b>						
Average	2	35.3%	0.214	1.92 (-4.32, 8.16)	0.60	0.546
Superior	2	59.4%	0.116	1.27 (-17.85, 20.40)	0.13	0.896
Inferior	2	0	0.575	15.33 (5.37, 25.29)	3.02	0.003
Nasal	2	70.1%	0.067	-2.84 (-13.69, 8.01)	0.51	0.607
Temporal	2	0	0.869	-0.93 (-7.76, 5.91)	0.27	0.790

WMD: Weighted mean difference.

**Table 5 Begg’s test and Egger’s test results of average and sectoral pRNFL thickness**

pRNFL thickness	Begg’s test		Egger’s test	
	z	P> z	t	P> t
Average	0.16	0.876	-0.07	0.947
Superior	0.10	0.917	0.34	0.743
Inferior	0.52	0.602	1.06	0.323
Nasal	0.94	0.348	0.69	0.514
Temporal	-0.10	1.000	-0.89	0.404

pRNFL: Peripapillary retinal nerve fiber layer.

artery circulation also results in the deterioration of RGCs and axons<sup>[51]</sup>, where NAION may mimic POAG with regard to the average pRNFL thickness.

Despite no difference in average pRNFL thickness, the superior pRNFL was significantly thinner in NAION eyes (P=0.031), whereas the inferior sector was significantly thicker (P≤0.001) when the MD of the VF was similar between NAION and POAG. These findings could be explained in several aspects. First, studies have reported that the inferior altitudinal VF defect was more common in NAION patients, although the VF defects tended to be less diffuse compared to POAG, while the superior hemifield loss was more commonly seen in glaucoma patients<sup>[32,51-54]</sup>. Moreover, the superior altitudinal VF defects can result from the loss of inferior RNFL thickness since structural deterioration can precede VF defects in glaucoma<sup>[55-56]</sup>. These structure-function relationship findings are in line with our findings that the superior pRNFL is significantly thinner in NAION eyes, whereas the inferior

pRNFL thickness is significantly thinner in POAG eyes. Second, a longitudinal study revealed that RNFL thickness was lowest superiorly at 6mo from the onset of NAION, indicating that peripapillary structure attenuation was most severe in the superior quadrant in NAION during this period<sup>[57]</sup>. Third, the loss of the neuro-retinal rim of glaucoma is shown to start from the inferior temporal to superior nasal sector<sup>[58]</sup>, which may account for the different progression patterns between these two diseases. In addition, the diagnostic ability of inferior pRNFL thickness is highest in glaucoma<sup>[59-60]</sup>. Recently, with the use of OCT angiography, a study reported a stronger correlation between inferior peripapillary capillary density and inferior pRNFL thickness in POAG patients compared with NAION patients, suggesting a higher susceptibility of inferior peripapillary capillary density that may contribute to the attenuation of inferior pRNFL in POAG<sup>[24]</sup>. Another study revealed that the inferior parafoveal deep vasculature in POAG eyes was lower than that in NAION eyes, indicating that the vulnerable regions of POAG were more susceptible to optic damage<sup>[19]</sup>.

To clarify the sources of heterogeneity, we performed a “leave-one-out” sensitivity analysis. No obvious change in the average and sectoral pRNFL thickness was observed after excluding each study, demonstrating that our data were stable and reliable. However, the results indicated that the two studies by Fard *et al*<sup>[19,24]</sup> (more deviated from the estimate line; Figure 7B) contributed to the heterogeneity mostly of the superior pRNFL thickness (I<sup>2</sup>=54.7%). Nevertheless, heterogeneity was largely reduced after excluding these two studies separately

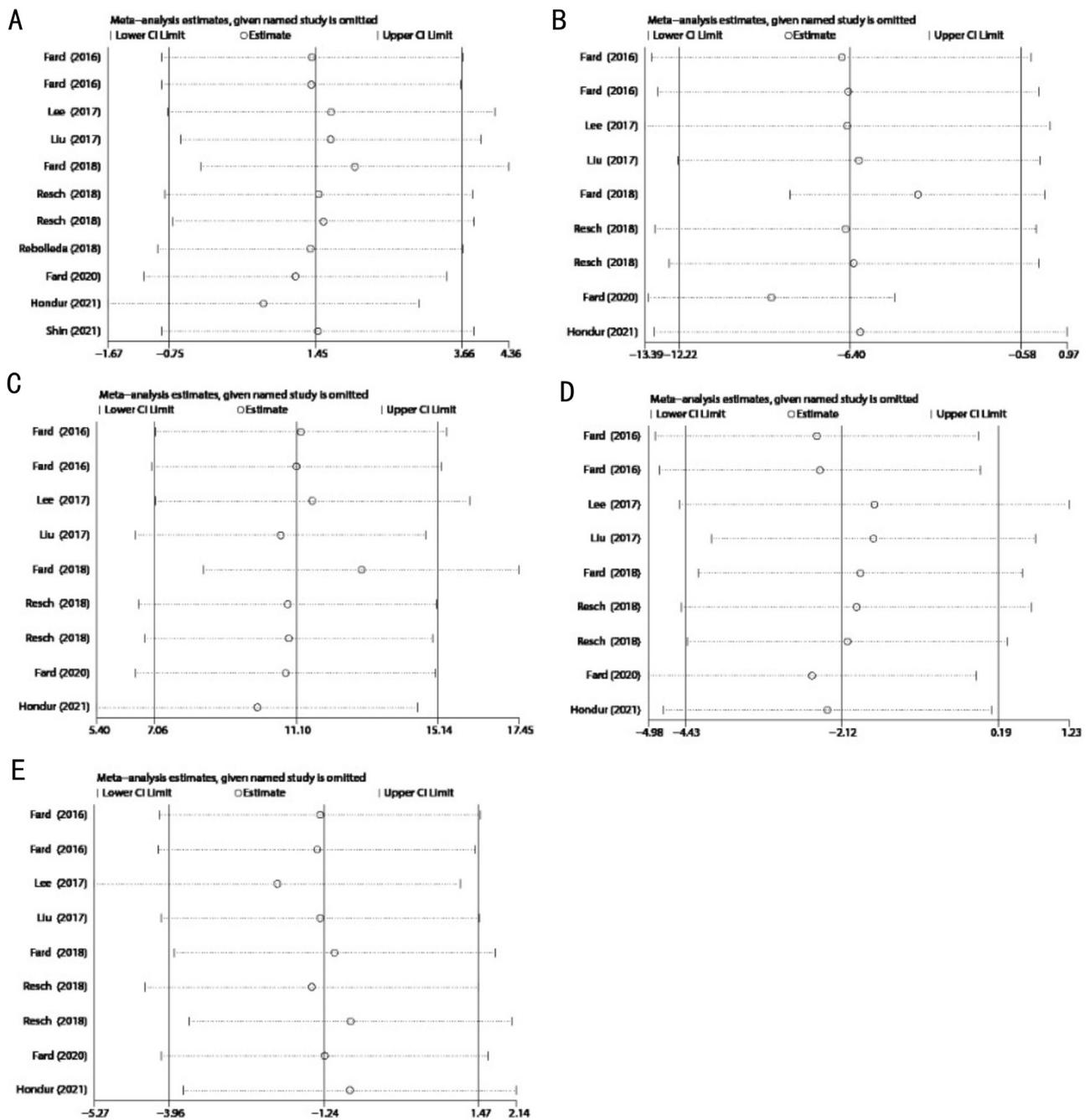


Figure 7 Sensitivity analyses of pRNFL thickness in patients with NAION and POAG A: Average pRNFL thickness; B: Superior pRNFL thickness; C: Inferior pRNFL thickness; D: Nasal pRNFL thickness; E: Temporal pRNFL thickness.

Table 6 Sensitivity analysis of superior pRNFL thickness

Study excluded	Fixed-effects model		Random-effects model		Heterogeneity $I^2$
	WMD (95%CI)	P	WMD (95%CI)	P	
Hondur 2021 <sup>[18]</sup>	-6.50 (-10.70, -2.30)	0.002	-6.05 (-13.08, 0.97)	0.09	60%
Fard 2020 <sup>[19]</sup>	-9.16 (-13.11, -5.22)	<0.00001	-9.09 (-13.29, -4.89)	<0.0001	8%
Resch 2018 <sup>[22]</sup>	-6.84 (-10.60, -3.08)	0.0004	-6.28 (-12.58, 0.03)	0.05	60%
Resch 2018 <sup>[22]</sup>	-7.05 (-10.89, -3.22)	0.0003	-6.56 (-13.06, -0.07)	0.05	60%
Fard 2018 <sup>[24]</sup>	-4.15 (-8.21, -0.10)	0.004	-4.09 (-8.44, 0.25)	0.06	9%
Liu 2017 <sup>[25]</sup>	-6.76 (-10.49, -3.02)	0.0004	-6.11 (-12.28, 0.07)	0.05	60%
Lee 2017 <sup>[26]</sup>	-7.16 (-11.22, -3.09)	0.0006	-6.50 (-13.39, 0.39)	0.06	60%
Fard 2016 <sup>[29]</sup>	-6.98 (-10.81, -3.15)	0.0004	-6.46 (-12.96, 0.03)	0.05	60%
Fard 2016 <sup>[28]</sup>	-7.13 (-10.96, -3.30)	0.0003	-6.69 (-13.14, -0.23)	0.04	60%

pRNFL: Peripapillary retinal nerve fiber layer.

(the heterogeneity dropped from 54.1% to 9% when we excluded Fard *et al*<sup>[24]</sup>; the heterogeneity dropped from 54.1% to 8% when we excluded Fard *et al*<sup>[19]</sup>).

The loss of pRNFL thickness is reported to reach a plateau at 6mo from the onset of NAION, and to be more correlated with VF at the atrophic stage<sup>[57]</sup>. Similarly, the pRNFL decreases rapidly in early-to-moderate glaucoma, showing a “floor effect” where the pRNFL decreases relatively slower in the advanced stage<sup>[30]</sup>. For this reason, we included most of the studies that enrolled POAG patients at moderate or more severe stages with comparable MD of the VF to ensure the similar severities in these diseases. However, pRNFL thickness is also shown to decrease slowly 3mo after NAION onset<sup>[27]</sup>. Based on these findings, we performed a subgroup analysis attributed by the time from the onset of NAION. Our pooled results indicated a significant decrease of inferior pRNFL thickness in POAG eyes compared with that in NAION eyes, regardless of the onset time (onset time >3mo:  $P=0.002$ ; onset time >6mo:  $P\leq 0.001$ ). Nevertheless, unlike the combined data of the superior pRNFL thickness ( $n=9$ ), there was no significant difference between NAION and POAG eyes (onset time >3mo,  $P=0.075$ ,  $n=4$ ; onset time >6mo,  $P=0.201$ ,  $n=5$ ). This may be due to the sources of heterogeneity introduced by Fard *et al*<sup>[19,24]</sup> when patients were enrolled at 6mo from the onset, and the relatively small sample size of this subgroup ( $n=5$ ).

In the subgroup analysis according to the SD-OCT type, the pooled results demonstrated that the inferior pRNFL thickness was significantly lower in the POAG eyes regardless of the SD-OCT type (Spectralis:  $P\leq 0.001$ ; Cirrus:  $P=0.007$ ; Optovue:  $P=0.003$ ). Interestingly, in the subgroup analysis regarding the superior pRNFL thickness, a significant decrease was found in patients compared to that in POAG patients when the Spectralis SD-OCT was used ( $P=0.002$ ). However, the superior pRNFL thickness was lower in NAION than in POAG, but no significant difference was observed when Cirrus and Optovue SD-OCT were used (Cirrus:  $P=0.150$ ; Optovue:  $P=0.896$ ). One reason may be the differences in the parameters, algorithms and software in different types of SD-OCT, although all types of SD-OCT devices can provide similar diagnostic abilities to detect the typical pattern of glaucomatous pRNFL deterioration<sup>[61]</sup>. In addition, since the relatively small sample size in Cirrus ( $n=2$ ) and Optovue ( $n=2$ ) groups, more studies are needed to fully assess the influence of SD-OCT types on measuring the sectoral pRNFL thickness.

This study has several limitations despite its strengths. First, the 10 included studies were cross-sectional studies. Further longitudinal studies and studies using eight-quadrant or clock-hour classification method are needed to verify our findings. Second, the sample size in the subgroup analyses was relatively small when Cirrus and Optovue SD-OCT were used.

This may have introduced difficulties in completely assessing heterogeneity due to inadequate data. Therefore, interpreting the results should be cautious. In addition, we did not perform subgroup analysis according to the severity of glaucoma because most of the studies recruited patients with moderate to severe glaucoma. Nevertheless, we only included studies that enrolled NAION and POAG patients with comparable MD of the VF, to ensure similar severities in these diseases.

In conclusion, SD-OCT-based evaluation of pRNFL thickness reveals that the superior pRNFL was significantly lower in NAION eyes, whereas the inferior pRNFL thickness was significantly lower in POAG eyes. In the future, the application of SD-OCT in evaluating pRNFL thickness may help us better understand the different pathophysiological mechanisms between NAION and POAG, and help in differentiating these two diseases in a non-invasive manner.

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