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REVIEW ARTICLE

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Optical coherence tomography angiography in Parkinson's disease: a systematic review and meta-analysis

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BACKGROUND: To examine the association between optical coherence tomography angiography (OCTA) retinal measurements and Parkinson's disease (PD).

METHODS: We searched MEDLINE and EMBASE from inception up to November 5th, 2021 for studies examining the differences between OCTA retinal measurements in PD patients and healthy controls. We used the Hartung–Knapp–Sidik–Jonkman random-effects method to combine study-specific standardized mean differences (SMD) in pooled effect estimates and a meta-analytic extension of the E-value metric to quantify the confounding bias capable of nullifying the pooled estimates.

RESULTS: Nine eligible studies for our systematic review were identified through our search strategy. The pooled SMD between the retinal vessel density of PD patients and healthy participants in the whole superficial vascular plexus (SVP), foveal SVP, parafoveal SVP and foveal avascular zone (FAZ) was −0.68 (95% CI: −1.18 to −0.17, p value = 0.02, $n = 7$ studies), −0.14 (95% CI: −0.88 to 0.59, p value = 0.62, $n = 5$ studies), −0.59 (95% CI: −1.41 to 0.23, p value = 0.12, $n = 5$ studies) and −0.20 (95% CI: −0.79 to 0.38, p value = 0.39, $n = 5$ studies), respectively. An unmeasured confounder would need to be associated with a 3.01-fold, 1.54-fold, 2.81-fold and 1.70-fold increase in the risk of PD and OCTA retinal measurements, in order for the pooled SMD estimate of vessel density in whole SVP, parafoveal SVP and FAZ, respectively, to be nullified.

CONCLUSIONS: Our results provide evidence on an inverse association between whole SVP vessel density and PD.

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INTRODUCTION

Neurological disorders are the leading causes of disability worldwide, with Parkinson's disease (PD), the second most common neurodegenerative disease after Alzheimer's disease, having the fastest increase not only in disability, but also in prevalence and mortality [1]. PD is a progressive disorder which affects predominantly dopaminergic neurons and subsequently leads to a variety of symptoms ranging from motor impairment to non-motor neurological symptoms [2], including visual impairment and cognitive deficits, which may have a detrimental impact on the quality of life of patients with PD [3].

The histopathological hallmark of PD is the intracellular accumulation of misfolded alpha-synuclein mainly in the dopaminergic neurons of the substantia nigra, with subsequent dopaminergic neurodegeneration [4]. Since, the central nervous system shares anatomical and histological similarities with the retina due to their common embryological origin, neurodegenerative changes in the brain disorders like Alzheimer's disease and multiple sclerosis, have been associated with structural alterations of retinal tissue [5, 6]. Similarly, structural and functional retinal changes have been linked to PD in observational [7], as well as postmortem studies [8], and visual symptoms sometimes precede motor symptoms in PD patients.

In recent years, apart from neurodegeneration, brain microvasculature changes have also been deemed a contributing factor to the incidence and progression of neurodegenerative disorders [9]. The advent of optical coherence tomography angiography (OCTA) has given us the opportunity to assess noninvasively whether microvascular retinal changes can serve as potential surrogate biomarkers for neurodegenerative diseases, including PD. Additionally, since noninvasive objective tests for early diagnosis of PD remain an unmet need, several studies in the last years have examined the association of OCTA metrics, such as retinal vascular density and foveal avascular zone (FAZ), with PD occurrence [10–12].

Therefore, our aim in this study was to perform a systematic review and meta-analysis of the literature on the differences of OCTA retinal measurements between PD patients and healthy controls, as well as to assess the robustness of these meta-analytic associations to unobserved confounding by bias analysis.

MATERIALS

Eligibility criteria

To conduct the respective systematic review and meta-analysis, we adhered to the guideline of "Meta-analysis of Observational

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Studies in Epidemiology" (Supplementary Table 1) [13]. We attempted to discern if there was truly a connection between OCTA measurements and PD, and thus, our search algorithm was structured accordingly. The inclusion criteria that studies needed to fulfill in order to be considered eligible for inclusion in our systematic review and meta-analysis were: 1) cross-sectional, case–control, or prospective design; 2) data of OCTA measurements as mean or mean difference and standard deviation between PD patients and healthy controls was reported; 3) PD diagnosis in participants was based on established diagnostic systems (e.g. UK Brain Bank Criteria, International Parkinson and Movement Disorder Society clinical criteria (MDS-PD) diagnostic criteria); 4) PD patients were recruited in addition to controls; 5) sample size of the study was >10. Moreover, studies in which the data provided could be used to calculate the association estimates indirectly were considered eligible for inclusion in our meta-analysis. We excluded case-report studies, letters to the editor, non-English studies, non-human studies, and low-quality studies using the Newcastle-Ottawa Scale (NOS) [14].

Literature search

A literature search was performed independently by two authors (AK, IP), utilizing the databases MEDLINE and EMBASE (OvidSP) from database inception up to November 5th, 2021. The search strategy employed was tailored to the research question and the respective inclusion and exclusion criteria considered in our review. Keywords from the hierarchically organized terminology for indexing and cataloging were used and synonyms of these terms. We also used free-text words in order to retrieve "In Process" and "publisher-supplied citations" as they are not indexed with structured terminology. Finally, in order not to omit relevant articles, a manual search was performed of the reference lists of all the eligible studies ("snowball" procedure). The exact combination of search terms that were put in the search query of the OvidSP databases is provided in Supplementary Table 2. Additionally, other sources of gray literature were searched, such as Google Scholar and suggested citations.

Study selection and study quality assessment

Upon discarding duplicate articles, eligible studies were identified using a selection process involving two steps. Initially, two authors (AK, IP) independently screened the titles and abstracts of the studies yielded from the computerized literature search. Secondly, the authors fully assessed the texts of the remaining studies in order to identify relevant articles. Studies that did not meet the aforementioned eligibility criteria were not considered and any discrepancies were resolved by consensus.

The methodologic quality of the studies included was assessed by the same two investigators through a modified version of NOS for cross-sectional studies, which has been previously described [15]. They independently reviewed and graded the eligible articles obtained from the literature search to assess their quality. The main domains assessed with the modified NOS are representativeness of the sample, whether the sample size is justified and satisfactory, description of respondents and non-respondents, characteristics and response rate, ascertainment of the exposure, comparability of the subjects in different outcome groups, assessment of the outcome, and adequacy of statistical analysis. Only studies including subjects diagnosed with PD according to established diagnostic systems were considered representative of the average exposed cohort in the target population and were allotted a star in the "Selection" section of the NOS. In the "Comparability" section, age was set as the most important factor for controlling confounding and can be awarded a maximum of 2 stars. Similarly, the "Ascertainment of the exposure" and "Assessment of the outcome" sections can be awarded a maximum of 2 stars respectively, while the remaining sections can be awarded a maximum of 1 star. A study can be given a maximum score of 10. Studies with scores of less than 6 were deemed low quality and were excluded from this meta-analysis, while studies with scores of 6 or higher were considered of moderate to high quality.

Data extraction

The data of the studies deemed eligible were independently checked by two authors (AK, IP) and were entered in a customized extraction form. The information which was extracted from each selected study included: first author's name, publication year, the country in which the study was conducted, sample size, number of male and female participants, mean age, mean disease severity score, mean PD duration, mean Unified Parkinson's Disease Rating Scale (UPDRS) score, OCTA machine type used, the OCTA parameters that each study assessed on each outcome group and control covariates. All reported data were extracted from published articles. Furthermore, the authors were contacted for additional information.

Statistical analysis

We used means and standard deviations from each outcome group to calculate standardized mean differences (SMDs) of each OCTA measurement between different outcome groups, with corresponding 95% confidence intervals (95% CI). In case the OCTA measurements weren't directly available, the values where indirectly calculated by combining means and standard deviations. The Hartung–Knapp/Sidik–Jonkman random-effects method was employed in order to combine study-specific SMDs in pooled effect estimates with respective 95% confidence intervals and to estimate variance between studies (τ^2). The Hartung–Knapp/Sidik–Jonkman method boasts several advantages which were mentioned previously [16, 17]. This becomes evident especially in the case of high heterogeneity among studies and when the number of studies in the meta-analysis is small. Furthermore, the percentage of total variation due to heterogeneity was calculated (I^2) and the Cochran Q was used to test for heterogeneity between the studies. We conducted a meta-analysis on the association between OCTA retinal measurements and PD only in the case where 5 or more studies were eligible for a particular OCTA parameter.

At the same time sensitivity analyses were performed to assess unmeasured confounding since random-effect meta-analyses can incur biased estimates when the included studies are subject to unmeasured confounding [18]. More specifically, we calculated the minimum magnitude of unmeasured confounding on the risk ratio scale required to nullify the SDM between the outcome groups. This approach is a meta-analytic extension of the *E* value metric [19] that estimates the confounding bias capable of bringing the effect estimate, of single studies, to a specific threshold. Due to the relatively low number of eligible studies, no tests for the assessment of publication bias nor meta-regression to identify sources of heterogeneity were conducted [20]. *P* values less than 0.05 were considered statistically significant, and all statistical tests were two-sided. All analyses were performed using the statistical software R (version 3.5.1, Foundation for Statistical Computing, Vienna, Austria; package) [21].

RESULTS

Systematic review

Through our literature search, we identified 745 articles in total and upon removing duplicates, 540 articles were selected for the title and abstract screening and 529 of them were excluded (Fig. 1). The remaining 11 articles were considered for full-text review. One article was excluded since it included retinal microvasculature measurements derived from fluorescein angiography [22] and another one was due to overlapping study populations with a larger study [23]. Ultimately, nine articles

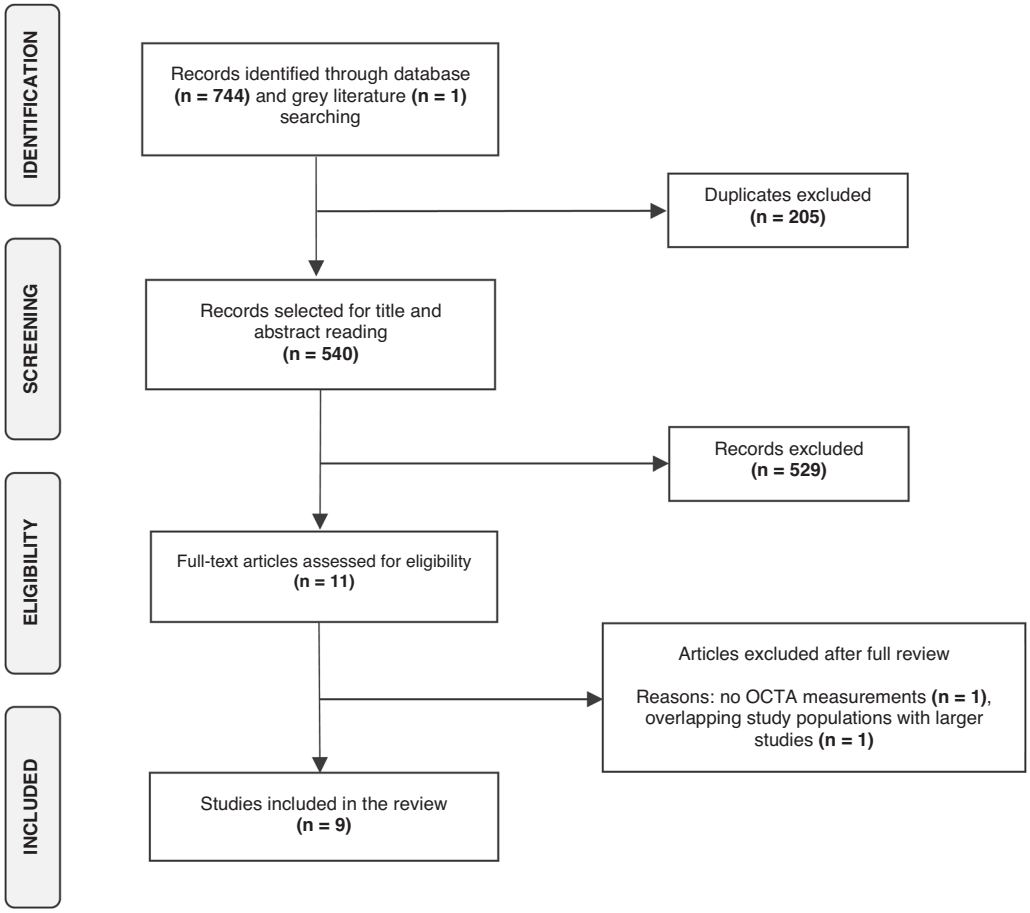


Fig. 1 Flowchart of the selection strategy of eligible studies. A two-step screening process was adopted for the identification of eligible articles for our systematic review and meta-analysis.

[10, 11, 24–30] were included in our systematic review and were eligible for meta-analysis. All eligible studies were of moderate or high quality with the NOS score ranging from 7/10 to 9/10 with a median score of 9/10 (Supplementary Table 3).

The main characteristics of the eligible studies are summarized in Tables 1 and 2. Among the nine included articles, five were conducted in Asia [25, 27–30], two in Europe [10, 26], and two in the U.S.A. [11, 24]. All studies were cross-sectional and the total number of participants' eyes was 1280 (499 eyes from PD patients and 781 eyes from healthy participants), ranging from 47 to 372 participants in individual studies. Moreover, the mean age of participants ranged from 55.92 to 71.7 years and from 54.68 to 70.9 years in PD patients and healthy participants, respectively. The mean disease severity score of PD patients was reported from seven out of nine eligible studies [10, 11, 26–30]. More specifically, the UK Brain Bank Criteria and the International Parkinson and MDS-PD clinical criteria were utilized for PD diagnosis in six [25–30] and two studies [10, 11], respectively. In order to assess the retinal microvasculature the AngioVue software of Optovue spectral domain-OCT [31], was utilized in four studies [10, 24, 25, 27], three studies [11, 29, 30] used the AngioPlex software of Carl Zeiss spectral domain-OCT, one study [28] utilized the SVision commercial SSOCT system and one study [26] used the Spectralis spectral-domain OCT system.

The methodology of participants' eye selection varied among studies; in seven studies [10, 11, 24–28] values from both eyes of every participant were used, unless only one suitable image was available, in one study [29] the eye with the highest signal quality score was selected for each participant and in one study [30] one eye of each participant was included in the analysis without reporting the reasoning behind the selection. Finally, two studies [25, 27] recruited controls from the working staff at the hospitals where the studies were conducted, one study [11] included community-dwelling volunteers as healthy subjects, in one study [29] controls were recruited from the patients' non-consanguineous families or friends and five studies [10, 24, 26, 28, 30] did not report the way that their controls were recruited.

Meta-analysis

Considering the fact that several OCTA parameters exist, which assess the vessel density of retinal microvasculature and may differ among different OCTA machines (Table 2), use of the SMD was made as a summary statistic in our meta-analyses. This method is particularly useful when studies assess the same outcome but measure it in various ways [32]. OCTA data on the vessel density of the whole superficial vascular plexus (SVP), foveal SVP, parafoveal SVP, and foveal avascular zone (FAZ), were obtained in more than five studies and thus, these were the OCTA metrics that were meta-analyzed. Regarding the whole SVP vessel density, foveal SVP vessel density, and FAZ, estimates were obtained from seven studies [10, 11, 25, 27–30], five studies [10, 26, 28–30] and five studies [11, 24, 26, 29, 30], respectively. Since Murueta-Goyena et al. [26] provided two estimates for FAZ (FAZ of SVP and DVP) we included the average of them in our meta-analysis. More specifically, we meta-analyzed seven estimates of the whole SVP vessel density measured over the 3×3 mm circle centered on the fovea. [10, 11, 25, 27–30]. Of these seven estimates, three of them [10, 25, 27] were directly obtained from the data of each study, while the rest four were indirectly

Table 1. Main characteristics of eligible studies[a].

Author, country, year	Study design	No. of participants/ no. of eyes	Males/ females	Mean age ± SD	Mean disease severity score ± SD	Mean PD duration	Mean UPDRS score ± SD	Adjustments	NOS
Kwapong et al., China, 2018	Cross- sectional	38/49 PD 28/34 controls	NR NR	62.95 ± 7.97 61.18 ± 5.74	NR NR	3.84 ± 2.80 NA	NR NR	Age and IOP	9/10
Berkowitz et al., USA, 2020	Cross- sectional	7/14 PD NR/135 controls	NR NR	NR NR	NR NR	NR NR	NR NR	Age matching	8/10
Rascunà et al., Italy, 2020	Cross- sectional	21/41 PD 17/33 controls	12/9 9/8	61.5 ± 6.5 65.1 ± 10.7	HY: 1.9 ± 0.4 NA	2.28 ± 1.19 NA	25.0 ± 6.9 3.2 ± 2.7	None	7/10
Shi et al., China, 2020	Cross- sectional	25/50 PD 25/50 controls	13/12 13/12	61.9 ± 7.6 59.0 ± 5.8	HY: 2.2 ± 1.0 NA	3.7 ± 2.4 NA	NR NR	Age and sex matching	9/10
Zou et al., China, 2020	Cross- sectional	35/35 PD 35/35 controls	16/19 20/15	61.86 ± 5.46 60.20 ± 6.75	HY: 1.7 ± 0.7 NA	3.2 ± 2.0 NA	NR NR	Age matching	8/10
Robbins et al., USA, 2020	Cross- sectional	69/124 PD 137/248 controls	15/14 10/16	71.7 ± 7.0 70.9 ± 6.7	MMSE: 28.4 ± 2.4 MMSE: 29.0 ± 2.8	NR NA	30.9 ± 6.7 NA	Age and sex matching	9/10
Zhang et al., China, 2021	Cross- sectional	42/75 PD 75/150 controls	NR 32/43	55.92 ± 7.53 54.68 ± 6.66	HY: 1.42 ± 0.55 NA	3.2 ± 2.0 NA	16.92 ± 7.6 NA	Age, sex, IOP, inter-eye correlation	9/10
Murueta-Goyena et al., Spain, 2021	Cross- sectional	49/87 PD 40/73 controls	33/16 13/27	64.6 ± 7.9 62.1 ± 8.0	MoCA: 24.4 ± 4.1 MoCA: 25.7 ± 2.5	7.1 ± 4.1 NA	16.92 ± 7.6 NA	Age, sex, and hypertension	9/10
Zhou et al., China, 2021	Cross- sectional	24/24 PD 23/23 controls	18/6 11/12	65.88 ± 6.50 63.43 ± 7.11	HY: 2.0 ± 0.3 MMSE: 28.5 ± 1.6 NA	5.3 ± 4.2 NA	26.5 ± 12.3 NA	Age, sex, and hypertension	9/10

[a]*PD* Parkinson's disease, *HY* Hoehn and Yahr, *MMSE* Mini-Mental State Exam, *MoCA* Montreal Cognitive Assessment, *NOS* Newcastle-Ottawa Scale, *NR* not reported, *NA* not applicable, *SD* standard deviation.

calculated [11, 28–30]. We were not able to meta-analyze the estimates of the whole SVP vessel density of 6 × 6 mm scans since only four of them could be obtained [11, 28–30]. Regarding the meta-analysis of parafoveal SVP, in four studies [11, 24, 26, 30] the effect estimates were obtained directly from the data provided by each study, while in the remaining study [29] the estimate was indirectly calculated. When more than one type of vessel density metrics was provided by a study for a specific vascular plexus, we selected the one that was used by most of the remaining studies for the meta-analyses.

The pooled SMD between the retinal vessel density of PD patients and healthy participants in the whole SVP, foveal SVP, parafoveal SVP and FAZ was -0.68 (95% CI: −1.18 to −0.17, p value = 0.02, $I^2 = 90\%$, $n = 7$ studies), −0.14 (95% CI: −0.88 to 0.59, p value = 0.62, $I^2 = 88\%$, $n = 5$ studies), −0.59 (95% CI: −1.41 to 0.23, p value = 0.12, $I^2 = 93\%$, $n = 5$ studies) and −0.20 (95% CI: −0.79 to 0.38, p value = 0.39, $I^2 = 76\%$, $n = 5$ studies), respectively (Fig. 2). High and statistically significant heterogeneity was observed among the studies examining all the meta-analyzed associations, which justifies our use of the Hartung–Knapp/Sidik–Jonkman method. In order for the pooled SMD estimate of vessel density in whole SVP, foveal SVP parafoveal SVP, and FAZ to be nullified, an unmeasured confounder would have to be associated with a risk ratio of 3.01, 1.54, 2.81, and 1.70, respectively, with the risk of PD and the corresponding OCTA metrics.

DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis to assess the associations between OCTA retinal measurements and PD. In our study, a statistically significant inverse association was found, of whole SVP vessel density with PD.

Changes in the brain microvasculature in PD as well as in its variants, like multiple system atrophy and progressive supranuclear palsy, have been identified by several studies [33, 34]. Additionally, dopamine is a crucial retinal neuromodulator, which regulates several aspects of visual function, including circadian nature of light-adapted vision and contrast acuity [35]. Even though the exact pathophysiological mechanism of reduced vessel density in PD patients remains unclear, it has been suggested that degeneration of dopamine neurons could lead to vessel fragmentation and loss of capillary connections due to the interactions of endothelial cells, neurons and glial cells, which together form a functional and structural unit [33]. Moreover, several postmortem studies have found structural and physiological changes, like abnormal capillaries and string vessel formation with no functional blood flow, in retinal vessels of PD patients [33, 36]. Finally, in a recent systematic review assessing the use of OCTA in Parkinson's disease [37], the authors have also shown that alterations of the macular capillary plexus may comprise useful biomarkers for PD diagnosis. Since it is difficult to identify the exact mechanism of retinal microvascular changes in PD patients through observational studies, further experimental and histopathology studies are required.

As it has also been highlighted in a previous meta-analysis conducted by us [36], which examined the associations between OCTA metrics and Alzheimer's disease, the variation in the way that vessel density is assessed among different OCTA machines is a significant concern. A specific OCTA machine can utilize various OCTA metrics to quantify retinal vessel density. We addressed this concern by using SMD as the summary statistic in our meta-analyses, giving us the possibility to summarize OCTA metrics that assess the same outcome (vessel density) on a different scale. In most of our included studies, vessel density was defined either as the percentage of perfused retinal area (unit of measurement was %) or as the ratio of total retinal vessels' length per unit area in the

Table 2. OCTA machine and parameters of included studies[a].

Author, Country, Year	OCTA machine	OCTA parameters assessed within macula	Macular scan diameter (mm)
Kwapong et al., China, 2018	Optovue	**Vessel density (%)** of SVP, DVP and whole retinal capillary plexus (Ø 0.6–2.5 mm) and **FAZ (mm^2)**	2.5
Berkowitz et al., USA, 2020	Optovue	FAZ (mm^2)	6
Rascunà et al., Italy, 2020	Optovue	**Vessel density (%)** of SVP, DVP, outer retinal layer (whole [3 mm diameter circle], fovea [1 mm diameter circle] and parafovea [Ø 1-3 mm])	3 and 4.5
Shi et al., China, 2020	Optovue	**Vessel density (%)** and skeleton density (%) of SVP and DVP (Ø 0.6–2.5 mm)	2.5
Zou et al., China, 2020	Zeiss	**Perfusion density (%)** and vessel length density (mm) of SVP (1 mm, 3 mm and 6 mm diameter circles, Ø 1-3 mm and Ø 3-6 mm) and **FAZ (mm^2)**	6
Robbins et al., USA, 2020	Zeiss	**Perfusion density (%)** and vessel density (/mm) of SVP (whole [6 mm diameter circle], parafovea [Ø 1-3 mm] and perifovea [Ø 3-6 mm]) and **FAZ (mm^2)**	6
Zhang et al., China, 2021	SVision	Flow density (mm^2) and **flow ratio (%)** of SVP and DVP (whole [3 mm and 6 mm diameter circles] and fovea [1 mm diameter circle])	6
Murueta-Goyena et al., Spain, 2021	Heidelberg Engineering	**Perfusion density (%)**, skeleton density (1/mm) and fractal dimension (Dbox) of SVP and DVP (whole [2.5 mm diameter circle], fovea [1 mm circle diameter] and parafovea [Ø 1-2.5 mm]) and **FAZ (mm^2)**	2.5
Zhou et al., China, 2021	Zeiss	**Vessel density (/mm)** of SVP (whole [6 mm diameter circle], fovea [1 mm circle diameter], parafovea [Ø 1-3 mm] and perifovea [Ø 3-6 mm]) and **FAZ (mm^2)**	6 and 3

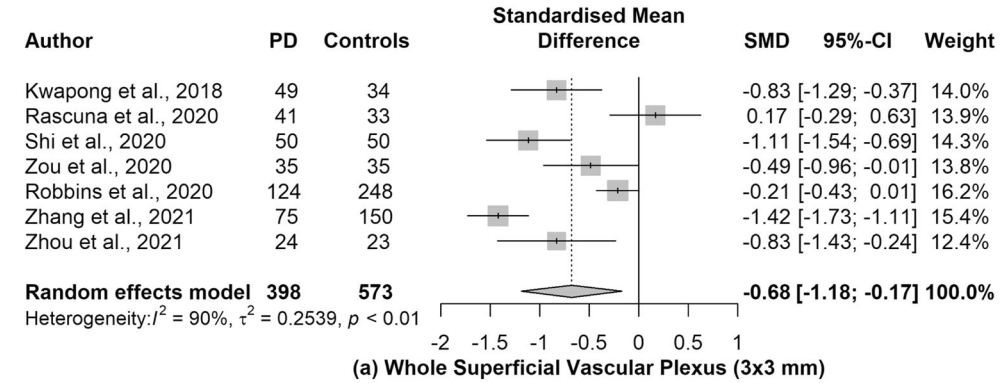
Meta-analyzed metrics of each study appear in bold.
[a]*DVP* deep vascular plexus, *FAZ* Foveal Avascular Zone (mm^2), *SVP* superficial vascular plexus, *Ø* ring around fovea.

region of measurement (unit of measurement was /mm). Apart from these two common OCTA metrics, several OCTA parameters of retinal vessel density were additionally included in some studies, like flow density (mm^2) [28], fractal dimension (Dbox) [26], flow ratio (%) [28], skeleton density (%) [28] and vessel length density (mm) [30].

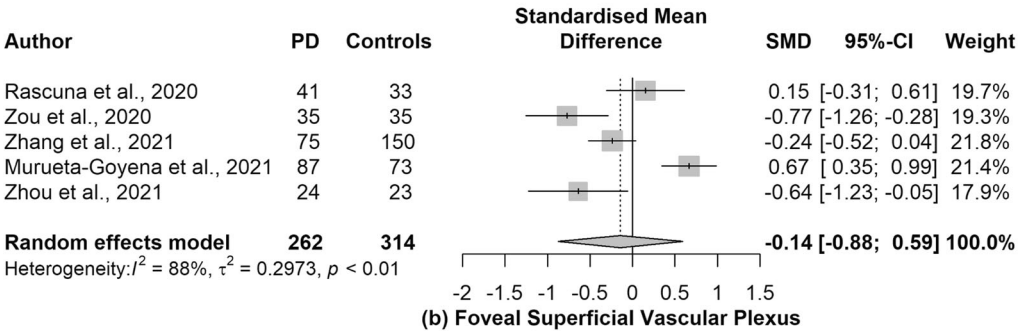
Our findings have important clinical implications as far as PD screening and diagnosis is concerned. Current diagnostic methods for PD are based on clinical assessment using the UPDRS (scale), which despite having been identified as a reliable, and valid tool for PD diagnosis, it has several drawbacks, including ambiguities in the written text, metric flaws, and a tangible lack of screening questions for several non-motor symptoms of PD [38]. Moreover, by the time that a PD diagnosis has been made, a substantial amount of dopaminergic neuronal loss has already taken place [39]. Consequently, faster, more patient-friendly, reliable, and objective diagnostic techniques, which could detect PD before a considerable neuronal loss has occurred, constitute a large unmet need for efficient screening of those at risk. In this context, quantitative OCTA metrics may represent promising biomarkers for monitoring the progression of pathological neural degeneration associated with PD, considering also that OCT metrics of retinal structure have already been identified as potential surrogate biomarkers of PD [7]. However, our results need also to be interpreted with caution, since the differences in vessel density between patients with PD and controls for several vascular plexuses are small and below the repeatability levels of vessel density assessed by OCTA. In particular, Pappelis et al. [40] found the coefficient of repeatability (standard deviation) of the parafoveal perfused capillary density to be 2.7% (1.8%), corresponding to an SMD of 1.5, larger than all of our meta-analyzed SMDs. Thus, it is unlikely that the reported differences could become clinically relevant, at least not until inherent OCTA limitations are overcome.

Although considering exclusively moderate to high-quality studies in accordance to the NOS score in our meta-analyses, several potential limitations should be simultaneously taken into consideration. First of all, several factors may have influenced the pooled estimates of our meta-analyses such as the methodological heterogeneity among studies with regard to the OCTA machine and the metrics utilized, the reasoning behind the selection of the eyes of participants and the covariates included in analysis. Second, although most studies made use of official disease severity scales which reflect the severity of disease with accuracy, there was heterogeneity in the types of disease severity scales utilized, as well as, in the disease severity scores. This variability in disease severity in individual studies could have resulted in over- or underestimation of the true effect sizes. Third, despite the majority of the studies having been controlled in the analysis for the age of the participants
(a strong potential confounder on the association estimates), other potential confounding variables such as socioeconomic status, were not considered. The small sample size of most studies could be the culprit for this, which at the same time restricts the number of covariates in the analysis and constitutes an additional limitation of our meta-analysis. Fourth, several of the considered studies which evaluated both eyes of the participants, failed to adjust for the inter-eye correlation in their analyses, consequently increasing the likelihood of overestimating the correlation between retinal microvascular measurements and PD. Lastly, considering that all meta-analyzed studies are cross-sectional, no temporal ordering of the OCTA metrics and PD can be established.

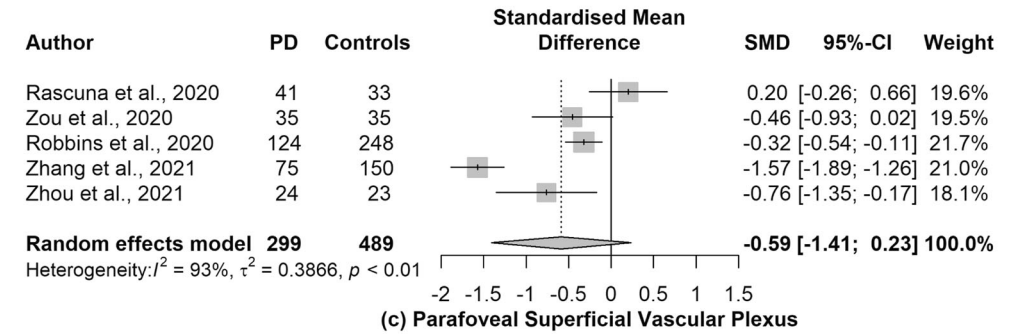
In conclusion, this systematic review and meta-analysis provides evidence of an inverse association of whole SVP vessel density with PD. Due to several limitations, causal associations cannot be



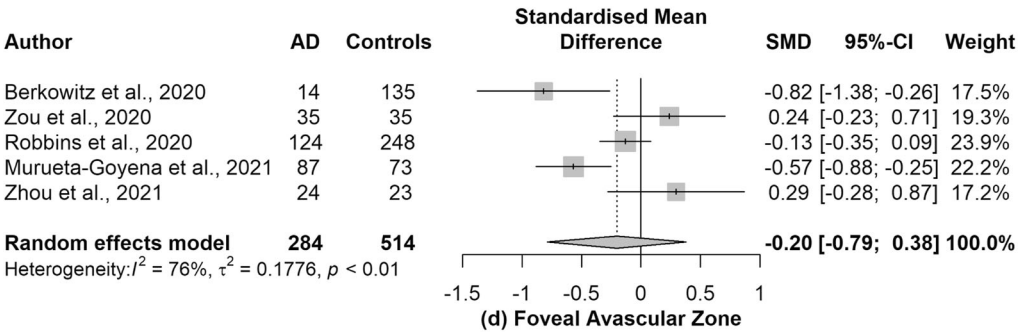
(a) Whole Superficial Vascular Plexus (3x3 mm)



(b) Foveal Superficial Vascular Plexus



(c) Parafoveal Superficial Vascular Plexus



(d) Foveal Avascular Zone

Fig. 2 Forest plots of the pooled standardized mean differences (SMDs) on patients with Parkinson's disease (PD) and healthy participants. Association estimates between PD and **a** the whole superficial vascular plexus, **b** the foveal superficial vascular plexus, **c** the parafoveal superficial vascular plexus and **d** the foveal avascular zone.

established and thus, future longitudinal studies, with more robust design and analysis are warranted to support our results.

Summary

What is known about this topic

- It has been shown that an association exists between OCTA retinal measurements and PD.

What this study adds

- This study underlines that OCTA metrics may constitute promising biomarkers for PD.

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AUTHOR CONTRIBUTIONS

AK conceived and designed the presented study and performed the analysis. All authors wrote and critically reviewed the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

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