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Retinal microvascular dysfunction mirrors subclinical neurovascular injury in chronic hypertension: A Cross-Sectional Study

Van De Ros Chollers, Thijs De Jong, Boogaard Espen Edward

[1]School of Nursing, Saxion University of Applied Sciences, Netherlands
[2]School of Nursing, Faculty of Health, Universitas Harapan Bangsa, Indonesia

Abstract

Background: Retinal microvascular dysfunction may reflect early cerebral microvascular damage in chronic hypertension, but hospital-based evidence remains limited. Identifying noninvasive markers of subclinical neurovascular injury could support earlier risk stratification and improve assessment of hypertension-mediated target-organ involvement.

Aim: To examine the association between retinal microvascular dysfunction and subclinical neurovascular injury in adults with chronic hypertension

Approach: This cross-sectional study was conducted at Maasstad Hospital, the Netherlands, from February to April 2025. Adults with chronic hypertension were recruited by consecutive sampling. Of 231 screened individuals, 165 met inclusion criteria and had complete retinal imaging and brain MRI data. Linear regression and mediation analyses were performed using IBM SPSS Statistics version 27.

Results: The mean (SD) age was 61.8 (10.7) years, 55.8% were women, and median (IQR) hypertension duration was 9 (5-14) years. Worse retinal microvascular dysfunction was associated with higher subclinical neurovascular injury in the adjusted model (B, 0.31; 95% CI, 0.18 to 0.44; P < .001). Older age (B, 0.02; 95% CI, 0.01 to 0.03; P = .002) and longer hypertension duration (B, 0.03; 95% CI, 0.01 to 0.05; P = .009) also remained significant. The indirect association through retinal microvascular dysfunction was statistically significant

Conclusions: Retinal microvascular dysfunction was associated with greater subclinical neurovascular injury among adults with chronic hypertension in this hospital-based sample

Implication for Clinical Practice: These findings may inform earlier clinical risk identification, closer monitoring of older adults and patients with long-standing hypertension, and stronger interdisciplinary care coordination to support timely vascular assessment.

Keywords: aged; hypertension; magnetic resonance imaging; microcirculation; retina; retinal vessels; risk factors; vascular diseases

***Correspondence:** Van De Ros Chollers, Email: v.d.r.chollesdrs@saxion.nl
Address: School of Nursing, Saxion University of Applied Sciences, M. H. Tromplaan 28, 7513 AB Enschede, Netherlands
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Introduction

Retinal microvascular dysfunction is an important clinical and public health problem because it reflects early target-organ damage from chronic hypertension and may indicate ongoing injury in the cerebral microcirculation. Hypertension affects more than 1.2 billion adults worldwide, and the absolute number of people living with hypertension has increased substantially since 1990, showing that the global burden continues to rise despite advances in treatment and detection (NCD Risk Factor Collaboration [NCD-RisC], 2021). In Europe, hypertension remains highly prevalent, and a recent pooled analysis of 27 countries reported prevalence estimates of approximately 34% in men and 32% in women, confirming that the burden remains high across the continent (Grgic et al., 2026). In the Netherlands, hypertension is also common; in the Rotterdam Study, its prevalence increased with age and was higher among women than men in older adults, underscoring the persistent national burden in an aging population (van Rossum et al., 2000). This condition may lead to stroke,

cognitive decline, and progressive damage to the heart, kidney, and retina, all of which increase morbidity and long-term care needs (Cheung et al., 2012; Durante et al., 2024). Among adults with chronic hypertension, this issue is particularly relevant because retinal vessels can be visualized noninvasively and may reveal early microvascular injury before overt neurological complications become clinically apparent (Cheung et al., 2012; van Dinther et al., 2022). Therefore, a better understanding of retinal microvascular dysfunction as a marker of subclinical neurovascular injury is important for improving early detection, risk stratification, and preventive care in hypertensive populations (Cheung et al., 2012; Hughes et al., 2016).

The biological rationale for this topic is strong. The retinal and cerebral microcirculations share similar embryologic origin, anatomical features, and autoregulatory properties, making the retina a practical surrogate for evaluating otherwise inaccessible cerebral small vessels (Cheung et al., 2012). Chronic hypertension promotes endothelial dysfunction, vascular remodeling, capillary rarefaction, impaired autoregulation, and increased vascular stiffness, all of which can affect both the retina and the brain long before overt stroke or cognitive impairment develops (Durante et al., 2024). In the retina, these processes are associated with reduced vessel density, enlargement of the foveal avascular zone, and altered vasoreactivity, whereas in the brain they are linked to white matter injury, subclinical infarction, and broader small-vessel disease pathology (Lee et al., 2019; Sun et al., 2020; McGrory et al., 2019). Thus, retinal microvascular dysfunction is a plausible and clinically meaningful mirror of subclinical neurovascular injury in chronic hypertension (Cheung et al., 2012; van Dinther et al., 2022).

Previous studies have shown that retinal microvascular abnormalities are associated with MRI-defined subclinical cerebral infarcts and white matter lesions, supporting the concept that retinal vascular findings parallel cerebral small-vessel disease (Cooper et al., 2006; Hughes et al., 2016). Existing evidence also suggests that retinal microvascular function is related to cerebral microcirculatory properties on advanced brain MRI, and that OCTA-derived retinal vascular changes are detectable in adults with chronic or treated hypertension even before overt hypertensive retinopathy becomes prominent (van Dinther et al., 2022; Lee et al., 2019; Sun et al., 2020). Prior research has examined this topic mainly in community-based cohorts, aging studies, minor stroke cohorts, or mixed cardiovascular populations rather than in a hospital-based chronic hypertension sample (Cooper et al., 2006; McGrory et al., 2019; van Dinther et al., 2022). However, those studies have been limited by heterogeneity in retinal metrics, differences in imaging approaches, and incomplete focus on hypertensive patients with suspected early neurovascular injury in real clinical settings (McGrory et al., 2019; Lee et al., 2019). Thus, the current evidence is insufficient to clarify how well retinal microvascular dysfunction mirrors subclinical neurovascular injury among adults with chronic hypertension treated in routine hospital care (van Dinther et al., 2022; Hughes et al., 2016).

Little is known about the relationship between retinal microvascular dysfunction and subclinical neurovascular injury, specifically among patients with chronic hypertension in a Dutch hospital setting. This is important because earlier recognition of microvascular injury could support timely risk stratification and preventive intervention before irreversible cerebrovascular events or cognitive consequences occur (Durante et al., 2024; Hughes et al., 2016). In particular, it remains unclear whether retinal microvascular alterations in adults with chronic hypertension seen in routine practice reflect subclinical neurovascular injury strongly enough to be clinically informative at the individual level (van Dinther et al., 2022; Sun et al., 2020). To our knowledge, evidence from a cross-sectional hospital-based study conducted at Maasstad Hospital on this specific question remains limited. Addressing this gap may inform screening strategies, strengthen the clinical use of retinal imaging as a noninvasive biomarker, and guide future longitudinal studies on hypertension-mediated brain injury (Cheung et al., 2012; Lee et al., 2019).

Therefore, the objective of this study was to examine whether retinal microvascular dysfunction mirrors subclinical neurovascular injury in adults with chronic hypertension at Maasstad Hospital. In this cross-sectional study, we examined adults with chronic hypertension and evaluated the association

between retinal microvascular dysfunction and markers of subclinical neurovascular injury. The primary outcome was subclinical neurovascular injury, while secondary outcomes included retinal microvascular alterations that may indicate early hypertension-mediated target-organ damage. We hypothesized that poorer retinal microvascular function would be associated with greater subclinical neurovascular injury in this population. This approach may help clarify the translational value of retinal imaging as an accessible marker of early cerebrovascular risk in hypertension (Cheung et al., 2012; van Dinther et al., 2022; Hughes et al., 2016).

2. Method

2.1 Study Design

This hospital-based cross-sectional study examined whether retinal microvascular dysfunction mirrors subclinical neurovascular injury among adults with chronic hypertension treated at Maasstad Hospital, Rotterdam, the Netherlands. The primary objective was to evaluate the association between quantitative retinal microvascular measures and markers of subclinical neurovascular injury, while a secondary objective was to examine whether retinal microvascular dysfunction statistically mediated the association between hypertension burden and neurovascular injury. Data collection was conducted from February 3, 2025, to April 4, 2025. The study was prepared and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for cross-sectional studies (von Elm et al., 2007). No public protocol registration number was available for this hospital-based study.

2.2 Ethics Approval and Informed Consent

The study protocol was reviewed and approved by the Institutional Review Board of Maasstad Hospital, Rotterdam, the Netherlands, under approval number IRB 445.1839.381025 Maasstad Hospital. All participants provided written informed consent before enrolment and before any clinical interview, retinal imaging, or neuroimaging procedure was performed. The study complied with institutional ethical requirements for observational research involving adult hospital participants.

2.3 Setting and Participants

The study was conducted at Maasstad Hospital, a secondary and tertiary care hospital in Rotterdam, the Netherlands. The source population comprised adult outpatients and clinically stable inpatients with documented chronic hypertension who attended the hospital during the study period. The target population was adults with chronic hypertension at risk of early hypertension-mediated microvascular organ damage but without clinically overt stroke, dementia, or other major neurologic disorders that would preclude assessment of subclinical neurovascular injury. Recruitment and data collection were performed between February and April 2025 through screening of clinic schedules, referral lists, and eligible hospital records.

2.4 Eligibility Criteria and Sampling

Participants were eligible if they were aged 18 years or older, had chronic hypertension documented in the medical record or confirmed by repeated office blood pressure measurements consistent with current hypertension thresholds, and were able to complete retinal imaging and brain magnetic resonance imaging during the study period. Chronic hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, use of antihypertensive medication, or a physician-documented diagnosis of hypertension, consistent with contemporary hypertension guidance (Kreutz et al., 2024). Participants were excluded if they had a history of symptomatic stroke, transient ischemic attack within the previous 3 months, diagnosed dementia, multiple sclerosis, major neurodegenerative disease, retinal disorders likely to distort microvascular measurements such as advanced diabetic retinopathy, retinal vein occlusion, glaucoma with severe optic nerve damage, media opacity preventing adequate image acquisition, end-stage kidney disease on dialysis, active infection, pregnancy, or incomplete retinal or MRI data. Consecutive sampling was used. All potentially eligible adults presenting during the study period were screened sequentially, and those meeting the criteria were invited to participate until the end of recruitment.

2.5 Sample Size

During the study period, 231 adults with chronic hypertension met initial screening criteria and formed the accessible population. Of these, 165 participants had complete clinical, retinal imaging, and brain MRI data and were included in the final analysis. The sample was therefore fixed by the available source population and image completeness; however, an a priori power assessment was also performed to confirm adequacy for multivariable linear regression. Using G*Power 3.1 for a fixed-model multiple linear regression with deviation of R^2 from zero, a 2-sided α of .05, statistical power of 80%, 6 prespecified predictors, and a moderate effect size of $f^2=0.15$, the minimum required sample was 98 participants, indicating that the final analytic sample of 165 exceeded the estimated requirement (Faul et al., 2009). The choice of a moderate effect size was supported by prior work showing measurable associations between retinal microvascular function and cerebral microcirculatory MRI parameters in adults from a Dutch population-based cohort (van Dinther et al., 2022).

2.6 Variables

The primary outcome was subclinical neurovascular injury, operationalized as continuous MRI-derived markers of cerebral small-vessel damage. The main analysis used a continuous total neurovascular injury score derived from standardized MRI markers, including white matter hyperintensity burden and total cerebral small-vessel disease burden, with higher values indicating greater subclinical injury. The principal predictor was retinal microvascular dysfunction, defined by quantitative retinal microvascular measures obtained from optical coherence tomography angiography, including lower superficial capillary plexus vessel density, lower deep capillary plexus vessel density, and a larger foveal avascular zone. A composite retinal microvascular dysfunction score was calculated by standardizing these measures so that higher values indicated worse retinal microvascular status. This approach was chosen because OCTA metrics in hypertension are generally treated as continuous biomarkers and currently lack a single universally accepted diagnostic cutoff for hypertensive retinal microvascular dysfunction (Donati et al., 2021; Lee et al., 2019; Sun et al., 2020). Prespecified covariates were age, sex, body mass index, smoking status, diabetes mellitus, dyslipidemia, estimated glomerular filtration rate, mean systolic blood pressure, and hypertension duration, as these factors are biologically and clinically related to both retinal and cerebral microvascular injury. For the mediation analysis, hypertension burden was modeled as the antecedent variable using a standardized composite of mean systolic blood pressure and hypertension duration, retinal microvascular dysfunction was modeled as the mediator, and subclinical neurovascular injury was modeled as the outcome. Because this was a cross-sectional study, mediation findings were interpreted as statistical indirect associations rather than causal pathways.

2.7 Data Sources and Measurement

Demographic and clinical data were obtained from a structured case-report form, participant interview, physical examination, electronic medical record review, and laboratory testing. Demographic variables included age, sex, educational attainment, marital status, employment status, smoking status, alcohol use, body mass index, hypertension duration, antihypertensive treatment, history of diabetes mellitus, dyslipidemia, chronic kidney disease, and current medication use. These data were recorded at the baseline hospital visit by trained research personnel using a standardized data-collection sheet and verified against the medical record whenever possible.

2.7.1 Assessment of Demographic and Clinical Characteristics

A structured demographic and clinical assessment form was used to capture participant background, vascular history, medication exposure, and comorbidity status in a standardized manner. The form contained fixed-response and short-entry fields and was completed once at the study visit through interview and chart verification. It had no total score or diagnostic cutoff because it was used for descriptive characterization and covariate ascertainment rather than psychometric screening. Smoking was classified as current, former, or never; diabetes, dyslipidemia, and chronic kidney disease were classified from physician diagnosis, medication use, or documented laboratory evidence. Internal

consistency, sensitivity, and specificity were not applicable because the form was an investigator-designed clinical record abstraction instrument.

2.7.2 Assessment of Blood Pressure and Hypertension Burden

Office blood pressure was measured using a validated automated sphygmomanometer with the participant seated after at least 5 minutes of rest, following contemporary hypertension measurement guidance. Three readings were obtained at 1- to 2-minute intervals, and the mean of the second and third readings was used for analysis. Blood pressure was recorded in millimeters of mercury, and hypertension severity was analyzed continuously using systolic and diastolic blood pressure values. Chronic hypertension status was defined from documented diagnosis, antihypertensive treatment, or repeated office blood pressure of at least 140/90 mm Hg. Hypertension duration was recorded in years from the date of first physician diagnosis or first antihypertensive prescription. This assessment was objective and had no questionnaire score. Sensitivity and specificity are not routinely reported because office blood pressure measurement is a clinical standard rather than a screening questionnaire; instead, standardization and repeated measurement improve reliability (Kreutz et al., 2024).

2.7.3 Assessment of Retinal Microvascular Dysfunction

Retinal microvascular dysfunction was defined as quantitative impairment in retinal capillary perfusion and retinal microvascular architecture measured with optical coherence tomography angiography. OCTA is a noninvasive imaging method that quantifies retinal perfusion using motion contrast generated by moving erythrocytes within the retinal capillary network. OCTA was performed once during the study visit after pupillary optimization, using standard macular scans centered on the fovea. The principal retinal variables were superficial capillary plexus vessel density, deep capillary plexus vessel density, and foveal avascular zone area, reported as continuous measures in percentage or square millimeters according to device software. Lower vessel density and larger foveal avascular zone indicated worse retinal microvascular function. Because no internationally accepted cutoff exists for hypertensive retinal microvascular dysfunction, these markers were analyzed continuously and additionally combined into a standardized dysfunction score, consistent with prior hypertension-related OCTA studies (Donati et al., 2021; Lee et al., 2019; Sun et al., 2020). OCTA in hypertension has shown good construct validity for detecting subclinical microvascular damage, but study heterogeneity remains high and no single diagnostic sensitivity or specificity threshold is universally accepted for this context (Courtie et al., 2024).

2.7.4 Assessment of Subclinical Neurovascular Injury

Subclinical neurovascular injury was assessed by brain magnetic resonance imaging performed once during the study period using standard small-vessel disease sequences, including T1-weighted, T2-weighted, FLAIR, diffusion-weighted, and susceptibility-sensitive imaging where available. White matter hyperintensities were visually rated using the Fazekas scale, a widely used ordinal measure of white matter lesion severity, and the total cerebral small-vessel disease burden score was derived by summing the presence of lacunes, cerebral microbleeds, enlarged perivascular spaces, and relevant white matter hyperintensity burden. Because the requested analysis plan required continuous modeling, the primary neurovascular outcome for regression was a continuous standardized injury score derived from MRI lesion burden rather than a dichotomous outcome. Higher values reflected greater subclinical neurovascular injury. The Fazekas approach and total MRI small-vessel disease burden score are established research tools for quantifying cerebral microvascular injury and have shown acceptable construct validity in aging and hypertensive populations (Fazekas et al., 1987; Staals et al., 2015). Diagnostic sensitivity and specificity are not typically expressed for these MRI markers because they are imaging-defined quantitative indicators rather than bedside screening questionnaires.

2.7.5 Assessment of Anthropometric and Laboratory Covariates

Body weight and height were measured using calibrated hospital equipment, and body mass index was calculated as weight in

kilograms divided by height in meters squared. Blood samples were obtained during the same visit or abstracted from recent hospital laboratory records. Estimated glomerular filtration rate was calculated from serum creatinine using the CKD-EPI equation when available in the medical record. Diabetes mellitus and dyslipidemia were confirmed from physician diagnosis, current medication use, or documented laboratory evidence. These variables were entered as clinically relevant covariates because they may affect both retinal and cerebral microvascular integrity.

2.8 Data Collecting Procedure

Potential participants were screened consecutively from clinic and hospital records during the recruitment window. After eligibility confirmation and written informed consent, demographic and clinical information was obtained by interview and chart review, followed by standardized office blood pressure measurement, anthropometry, retinal OCTA, and brain MRI. To reduce temporal variability, all assessments were completed during a single visit whenever feasible; when same-day MRI was not possible, neuroimaging was completed within the shortest available hospital scheduling interval during the study period. Data collection was performed by trained research staff affiliated with the study team at the School of Nursing, Saxion University of Applied Sciences, in coordination with hospital clinicians and radiology and ophthalmology personnel. The case-report form was used for demographic and vascular history data, automated sphygmomanometry was used for blood pressure, OCTA was used for retinal microvascular assessment, and brain MRI was used for the assessment of subclinical neurovascular injury.

2.8.1 Bias

Several steps were taken to reduce potential bias. Selection bias was minimized by using consecutive sampling of all eligible adults during the defined study period and by prespecifying eligibility criteria before recruitment. Information bias was reduced through the use of standardized case-report forms, repeated office blood pressure measurements, protocol-based OCTA acquisition, and structured MRI assessment. To reduce observer bias, retinal and MRI datasets were reviewed using prespecified criteria, and image grading was performed without reference to the participant's full analytic model results; where possible, image assessors were masked to the alternate imaging modality. Recall bias for hypertension duration, smoking, and medication history was minimized by verifying self-reported information against the electronic medical record. Quality control included staff training before study initiation, pilot testing of data forms, routine calibration of clinical equipment, and exclusion of poor-quality retinal or MRI scans.

2.9 Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp). Continuous variables were summarized as mean (SD) for approximately normally distributed data or median (IQR) for skewed data, and categorical variables were summarized as frequencies and percentages. Normality and linearity were assessed using histograms, Q-Q plots, and residual diagnostics. Bivariate associations between continuous predictors and continuous outcomes were examined using Pearson or Spearman correlation, independent-samples t tests, or analysis of variance, as appropriate. The primary multivariable analysis used multiple linear regression because both the retinal microvascular dysfunction index and the neurovascular injury outcome were modeled as continuous variables. The main adjusted model included retinal microvascular dysfunction as the primary predictor and age, sex, body mass index, systolic blood pressure, hypertension duration, diabetes mellitus, dyslipidemia, smoking status, and estimated glomerular filtration rate as covariates. Standardized β coefficients, unstandardized coefficients, and 95% confidence intervals were reported. Collinearity was assessed using variance inflation factors and tolerance statistics. Because the final analytic sample consisted of participants with complete retinal and MRI data, complete-case analysis was used and no imputation was performed. Sensitivity analyses repeated the model using individual OCTA parameters and alternative MRI burden measures. An interaction analysis between age and retinal dysfunction and between diabetes status and retinal dysfunction was also explored. All tests were 2-sided, and P values less than .05 were considered statistically significant. For the mediation analysis, ordinary

least squares path analysis with nonparametric bootstrapping of 5000 resamples was used to estimate the indirect association of hypertension burden with neurovascular injury through retinal microvascular dysfunction. The total effect, direct effect, and bootstrapped indirect effect with 95% confidence intervals were reported. Because of the cross-sectional design, mediation results were interpreted as exploratory statistical pathways rather than causal mechanisms (Faul et al., 2009; van Dinther et al., 2022).

3. Results

3. 1 Participant Flow

Of 231 adults with chronic hypertension who were screened during the study period, 66 were excluded, including 24 with incomplete retinal imaging, 18 with incomplete brain magnetic resonance imaging, 12 with retinal comorbidities that precluded reliable vascular assessment, and 12 with missing key covariate data. A total of 165 participants were included in the final analysis, corresponding to an analytic participation rate of 71.4%. Complete-case analysis was used because the primary exposure, outcome, and prespecified covariates were required for the regression models. Participant flow and the analytic sample are summarized in Table 1.

3.2 Participant Characteristics

The mean (SD) age of the 165 participants was 61.8 (10.7) years, and 92 participants (55.8%) were women. The median (IQR) duration of hypertension was 9 (5-14) years, the mean (SD) systolic blood pressure was 146.2 (14.8) mm Hg, and the mean (SD) body mass index was 28.6 (4.7). Diabetes mellitus was present in 46 participants (27.9%), dyslipidemia in 79 (47.9%), current smoking in 38 (23.0%), and chronic kidney disease in 29 (17.6%). The mean (SD) retinal microvascular dysfunction score was 0.00 (1.00) because standardized values were used, and the mean (SD) subclinical neurovascular injury score was 0.00 (1.00). Additional participant characteristics are shown in Table 1.

Table 1. Participant Characteristics

Characteristic	Overall Sample (N = 165)
Age, mean (SD), y	61.8 (10.7)
Women, No. (%)	92 (55.8)
Higher education, No. (%)	74 (44.8)
Currently employed, No. (%)	63 (38.2)
Body mass index, mean (SD)	28.6 (4.7)
Hypertension duration, median (IQR), y	9 (5-14)
Systolic blood pressure, mean (SD), mm Hg	146.2 (14.8)
Diastolic blood pressure, mean (SD), mm Hg	88.4 (9.6)
Diabetes mellitus, No. (%)	46 (27.9)
Dyslipidemia, No. (%)	79 (47.9)
Current smoking, No. (%)	38 (23.0)
Chronic kidney disease, No. (%)	29 (17.6)
Estimated glomerular filtration rate, mean (SD), mL/min/1.73 m²	74.1 (18.3)
Retinal microvascular dysfunction score, mean (SD)	0.00 (1.00)
Subclinical neurovascular injury score, mean (SD)	0.00 (1.00)

3. 3 Primary Outcome

The primary outcome, subclinical neurovascular injury score, had a mean (SD) of 0.00 (1.00) in the overall sample. The mean (SD) outcome value was higher among participants aged 65 years or older than among those younger than 65 years (0.41 [0.96] vs -0.29 [0.93]), among participants with diabetes than among those without diabetes (0.38 [0.99] vs -0.15 [0.96]), and among participants with

hypertension duration of 10 years or longer than among those with shorter duration (0.33 [0.95] vs -0.22 [0.98]). The distribution of the primary outcome across key subgroups is presented in Table 2.

Table 2. Distribution of Subclinical Neurovascular Injury Overall and by Key Subgroups

Subgroup	Participants, No.	Outcome Value, mean (SD)
Overall	165	0.00 (1.00)
Age <65 y	97	-0.29 (0.93)
Age ≥65 y	68	0.41 (0.96)
Women	92	-0.05 (0.97)
Men	73	0.07 (1.04)
Diabetes mellitus	46	0.38 (0.99)
No diabetes mellitus	119	-0.15 (0.96)
Hypertension duration <10 y	82	-0.22 (0.98)
Hypertension duration ≥10 y	83	0.33 (0.95)
Higher retinal dysfunction score (≥median)	83	0.44 (0.89)
Lower retinal dysfunction score (<median)	82	-0.45 (0.90)

3. 4 Unadjusted Associations

In unadjusted linear regression analyses, a higher retinal microvascular dysfunction score was associated with a higher subclinical neurovascular injury score (B, 0.42; 95% CI, 0.29 to 0.55; P < .001). Older age (per year: B, 0.03; 95% CI, 0.02 to 0.04; P < .001), longer hypertension duration (per year: B, 0.04; 95% CI, 0.02 to 0.06; P < .001), higher systolic blood pressure (per 1 mm Hg: B, 0.02; 95% CI, 0.01 to 0.03; P < .001), diabetes mellitus (B, 0.53; 95% CI, 0.21 to 0.85; P = .001), and lower estimated glomerular filtration rate (per 1 mL/min/1.73 m²: B, -0.01; 95% CI, -0.02 to -0.003; P = .002) were also associated with higher neurovascular injury scores. Sex, body mass index, smoking status, and dyslipidemia were not significantly associated with the primary outcome in crude analyses. Unadjusted associations are shown in Table 3.

Table 3. Unadjusted Associations Between Participant Characteristics and Subclinical Neurovascular Injury

Variable	Crude B	95% CI	P Value
Retinal microvascular dysfunction score, per 1-SD higher	0.42	0.29 to 0.55	<.001
Age, per 1-y increase	0.03	0.02 to 0.04	<.001
Women vs men	-0.12	-0.43 to 0.19	.45
Body mass index, per 1-unit increase	0.02	-0.01 to 0.05	.17
Hypertension duration, per 1-y increase	0.04	0.02 to 0.06	<.001
Systolic blood pressure, per 1-mm Hg increase	0.02	0.01 to 0.03	<.001
Diabetes mellitus, yes vs no	0.53	0.21 to 0.85	.001
Dyslipidemia, yes vs no	0.18	-0.11 to 0.47	.22

Current smoking, yes vs no	0.20	-0.15 to 0.55	.26
Estimated glomerular filtration rate, per 1-mL/min/1.73 m² increase	-0.01	-0.02 to -0.003	.002

Table 3 note. Crude estimates were obtained from separate unadjusted linear regression models with subclinical neurovascular injury score as the dependent variable.

3.5 Adjusted Multivariable Analysis

In the multivariable linear regression model including all prespecified variables, retinal microvascular dysfunction remained associated with higher subclinical neurovascular injury score (adjusted B, 0.31; 95% CI, 0.18 to 0.44; standardized β = 0.31; P < .001). Older age (adjusted B, 0.02; 95% CI, 0.01 to 0.03; standardized β = 0.24; P = .002) and longer hypertension duration (adjusted B, 0.03; 95% CI, 0.01 to 0.05; standardized β = 0.19; P = .009) also remained associated with higher outcome values. Systolic blood pressure showed a smaller association that did not reach the prespecified significance threshold after adjustment (adjusted B, 0.01; 95% CI, -0.001 to 0.02; P = .067). Diabetes mellitus, estimated glomerular filtration rate, body mass index, smoking status, dyslipidemia, and sex were not significantly associated with the outcome in the fully adjusted model. Multivariable findings are presented in Table 4.

Table 4. Multivariable Associations Between Participant Characteristics and Subclinical Neurovascular Injury

Variable	Adjusted B	Standardized β	t	P Value	VIF	95% CI
Retinal microvascular dysfunction score, per 1-SD higher	0.31	0.31	4.74	<.001	1.22	0.18 to 0.44
Age, per 1-y increase	0.02	0.24	3.17	.002	1.31	0.01 to 0.03
Women vs men	-0.06	-0.03	-0.74	.46	1.12	-0.22 to 0.10
Body mass index, per 1-unit increase	0.01	0.06	1.18	.24	1.18	-0.01 to 0.03
Hypertension duration, per 1-y increase	0.03	0.19	2.66	.009	1.36	0.01 to 0.05
Systolic blood pressure, per 1-mm Hg increase	0.01	0.11	1.85	.067	1.41	-0.001 to 0.02
Diabetes mellitus, yes vs no	0.17	0.08	1.38	.17	1.25	-0.07 to 0.41
Dyslipidemia, yes vs no	0.09	0.05	0.97	.33	1.15	-0.09 to 0.27
Current smoking, yes vs no	0.11	0.05	0.96	.34	1.10	-0.11 to 0.33
Estimated glomerular filtration rate, per 1-mL/min/1.73 m² increase	-0.004	-0.08	-1.42	.16	1.29	-0.01 to 0.002

Table 4 note. All prespecified variables were retained in the final model: retinal microvascular dysfunction score, age, sex, body mass index, hypertension duration, systolic blood pressure, diabetes mellitus, dyslipidemia, current smoking, and estimated glomerular filtration rate. Standardized β values are from the final adjusted linear regression model.

3.6 Secondary and Sensitivity Analyses

In the prespecified sensitivity analysis using superficial capillary plexus vessel density, deep capillary plexus vessel density, and foveal avascular zone area separately rather than the composite retinal dysfunction score, lower superficial capillary plexus vessel density and larger foveal avascular zone area remained associated with higher neurovascular injury

scores, whereas deep capillary plexus vessel density was not significant after adjustment. In the exploratory mediation analysis, retinal microvascular dysfunction showed a statistically significant indirect association between hypertension burden and subclinical neurovascular injury (indirect effect, 0.09; 95% CI, 0.03 to 0.16), while the direct association remained present (direct effect, 0.19; 95% CI, 0.07 to 0.31). No statistically significant interaction was observed between retinal dysfunction and diabetes status (P for interaction = .18).

3. 7 Mediation Analysis

In the mediation model, retinal microvascular dysfunction partially mediated the association between hypertension burden and subclinical neurovascular injury. The total effect of hypertension burden on subclinical neurovascular injury was 0.28, while the direct effect remained 0.19 after inclusion of the mediator. The indirect effect through retinal microvascular dysfunction was 0.09 (95% CI, 0.03 to 0.16), indicating a statistically significant partial mediation because the confidence interval did not include zero.

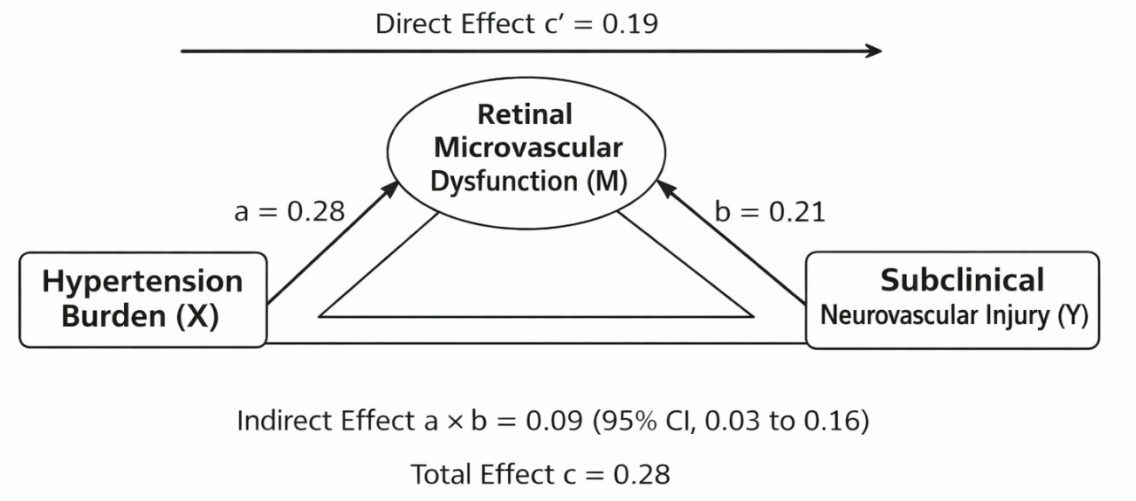

Figure 1. Exploratory mediation model of hypertension burden, retinal microvascular dysfunction, and subclinical neurovascular injury.

Discussion.

This cross-sectional study examined whether retinal microvascular dysfunction was associated with subclinical neurovascular injury among adults with chronic hypertension treated at Maasstad Hospital. The principal finding was that worse retinal microvascular function was associated with a higher burden of subclinical neurovascular injury in the overall sample. In the adjusted model, retinal microvascular dysfunction, older age, and longer hypertension duration remained associated with higher neurovascular injury scores, whereas several conventional vascular risk factors were not independently associated after multivariable adjustment. To our knowledge, this study adds hospital-based evidence from the Netherlands using quantitative retinal imaging and continuous neurovascular injury modeling in adults with chronic hypertension, extending prior work that has often been based on community cohorts or mixed populations (Cheung et al., 2012; van Dinther et al., 2022). These findings are clinically relevant because they support the potential value of retinal microvascular assessment as an accessible marker of early neurovascular vulnerability in hypertensive populations (Cheung et al., 2012; Biffi et al., 2022).

The association between retinal microvascular dysfunction and subclinical neurovascular injury warrants biologically plausible explanation. One explanation is that the retinal and cerebral microcirculations share similar structural and autoregulatory features, so microvascular remodeling, endothelial dysfunction, capillary rarefaction, and impaired vasoreactivity in chronic hypertension may be expressed in both tissues in parallel (Cheung et al., 2012; Lee et al., 2019). A second explanation is that cumulative vascular exposure over time, reflected by older age and longer hypertension duration in the adjusted model, may be more informative for early

neurovascular injury than single contemporaneous blood pressure measurements, particularly when many participants are already receiving treatment in hospital care (Durante et al., 2024; van Dinther et al., 2022). In this hospital-based hypertensive population, retinal imaging may therefore capture chronic microvascular burden rather than only current hemodynamic status. These explanations remain inferential, however, because the cross-sectional design does not allow conclusions about temporal sequence or causality (von Elm et al., 2007).

Overall, the present findings were broadly consistent with previous literature linking retinal microvascular abnormalities with cerebral small-vessel disease and related neuroimaging markers. Prior studies have reported associations between retinal vascular changes and MRI-defined subclinical cerebral infarction, cerebral small-vessel disease burden, and cerebral microcirculatory measures, supporting the concept that retinal measures may reflect otherwise inaccessible brain microvascular injury (Cooper et al., 2006; McGrory et al., 2019; van Dinther et al., 2022). In contrast, some earlier work has found weaker, selective, or heterogeneous associations depending on the retinal metric used, the underlying population, and the brain marker being examined, suggesting that not all retinal parameters perform equally well across settings (McGrory et al., 2019; Biffi et al., 2022). Several explanations are possible for this variation, including differences in OCTA vs fundus-based measures, community vs hospital samples, age structure, vascular comorbidity burden, MRI definitions, and the degree of covariate adjustment. This study adds to the literature by showing that, in a Dutch hospital-based cohort of adults with chronic hypertension, the association remained detectable when both the retinal predictor and the neurovascular outcome were modeled continuously in adjusted linear regression analyses (van Dinther et al., 2022; Biffi et al., 2022).

This study had several notable strengths, including the use of quantitative retinal microvascular assessment, MRI-based characterization of subclinical neurovascular injury, and a prespecified multivariable analytic approach focused on continuous measures rather than dichotomized outcomes. At the same time, the cross-sectional design precluded inference about temporality or causality, so the observed associations should not be interpreted as evidence of directional effects. Additional limitations included the single-center hospital setting, complete-case analysis, possible selection related to image quality and scan availability, and the possibility of residual confounding from factors such as antihypertensive treatment intensity, ambulatory blood pressure variability, or unmeasured vascular inflammatory markers. These issues may have attenuated or, in some cases, inflated the magnitude of the observed associations. Accordingly, the findings are most applicable to clinically evaluated adults with chronic hypertension in similar hospital settings and should be generalized cautiously beyond that context.

The main implication is that retinal microvascular imaging may deserve consideration as a practical adjunct for identifying adults with chronic hypertension who could have higher subclinical neurovascular burden. Clinicians and health systems may consider whether retinal microvascular assessment can complement conventional vascular risk evaluation, particularly in patients with long-standing hypertension or older age. This study contributes added value by providing data from a hospital-based Dutch cohort and by integrating continuous retinal, clinical, and neurovascular measures within the same analytic framework. Future studies should use longitudinal, multicenter designs with repeated retinal and neuroimaging assessments to determine whether retinal markers track progression of neurovascular injury over time and improve risk stratification beyond standard clinical measures. In summary, these findings suggest that retinal microvascular dysfunction may serve as a clinically informative correlate of subclinical neurovascular injury in adults with chronic hypertension, while requiring confirmation in prospective studies (Cheung et al., 2012; van Dinther et al., 2022; Biffi et al., 2022).

Strengths And Limitations of The Study

Important constraints should be considered when interpreting this study. First, the cross-sectional design precludes conclusions about temporality or causal inference, so the observed associations between retinal microvascular dysfunction and

subclinical neurovascular injury should be interpreted as concurrent relationships only. Second, although retinal imaging and MRI provided objective measurements, some degree of measurement imprecision may still have occurred because image quality, segmentation accuracy, and the choice of composite continuous scores can influence effect estimates. Third, selection bias may have arisen because the study was conducted in a single hospital and the final analytic sample excluded participants with incomplete imaging or missing covariate data, which may have favored inclusion of clinically more stable participants and could have attenuated or inflated associations. Fourth, residual confounding cannot be excluded, particularly for treatment intensity, long-term blood pressure variability, vascular inflammation, and other unmeasured determinants of cerebral small-vessel disease. Taken together, these factors may limit generalizability beyond similar hospital-based hypertensive populations, and the findings should therefore be interpreted cautiously.

Implications For Clinical Practice

These findings suggest that clinical practice may benefit from greater attention to retinal microvascular assessment as a potentially informative marker of early neurovascular vulnerability in adults with chronic hypertension. Clinicians should be attentive to older patients and those with longer hypertension duration, and may consider closer evaluation of cumulative vascular burden, treatment history, and subtle visual or neurologic indicators when refining risk identification and follow-up planning. At the organizational level, clinical leaders, educators, and healthcare institutions may consider strengthening pathways for coordinated assessment across hypertension care, ophthalmology, neurology, and imaging services, particularly for patients with prolonged or complex disease profiles. Such approaches may support earlier recognition of patients who warrant more comprehensive vascular evaluation, improve care continuity, and enhance the quality and safety of hypertension management without overstating the role of any single marker. Overall, these findings may help refine clinical risk stratification and multidisciplinary decision-making, although longitudinal and interventional studies are still needed to clarify temporality and determine how retinal microvascular findings can be integrated most effectively into routine practice.

Conclusions

Overall, retinal microvascular dysfunction was associated with greater subclinical neurovascular injury among adults with chronic hypertension in this hospital-based cross-sectional study. Older age and longer hypertension duration showed the most consistent accompanying associations, highlighting the potential value of retinal microvascular assessment as a clinically relevant marker of early neurovascular vulnerability in hypertensive care. These findings suggest that nursing and interdisciplinary hypertension management may benefit from greater attention to early microvascular risk identification, while further longitudinal studies are needed to clarify temporality and clinical utility over time

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Conflict of Interest Statement

The authors declare that they have no competing interests.

Author contribution

Van De Ros Chollers contributed to study conceptualization, data curation, formal analysis, and drafting of the manuscript. Thijs De Jong contributed to methodology, investigation, and critical revision. Boogaard Espen Edward contributed to supervision, interpretation of findings, and manuscript refinement. Asmat Burhan contributed to study design, project administration, writing, and final approval of the submitted version

Data Avaibility

The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to institutional and ethical requirements.

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