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RESEARCH ARTICLE

# Association of corneal endothelial cell morphology with neurodegeneration in mild cognitive impairment and dementia

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## Abstract

**INTRODUCTION:** Corneal confocal microscopy (CCM) detects neurodegeneration in mild cognitive impairment (MCI) and dementia and identifies subjects with MCI who develop dementia. This study assessed whether abnormalities in corneal endothelial cell (CEC) morphology are related to corneal nerve morphology, brain volumetry, cerebral ischemia, and cognitive impairment in MCI and dementia.

**METHODS:** Participants with no cognitive impairment (NCI), MCI, and dementia underwent CCM to quantify corneal endothelial cell density (CECD) and area (CECA), corneal nerve fiber morphology, magnetic resonance imaging (MRI) brain volumetry, and severity of brain ischemia.

**RESULTS:** Of the 114 participants, 14 had NCI, 77 had MCI, and 23 had dementia. CECD (1971.3 ± 594.6 vs 2316.1 ± 499.5 cells/mm$^2$, $p < 0.05$) was significantly lower in the dementia compared to the NCI group. CECD and CECA were comparable between the MCI and NCI groups ($p = 0.13$–$0.65$). Corneal nerve fiber density (CNFD)

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(31.7 ± 5.6 vs 24.5 ± 9.2 and 17.3 ± 5.3 fibers/mm$^2$, $p < 0.01$), corneal nerve branch density (CNBD) (111.8 ± 58.1 vs 50.4 ± 36.4 and 52.7 ± 21.3 branches/mm$^2$, $p < 0.0001$), and corneal nerve fiber length (CNFL) (24.6 ± 6.6 vs 16.5 ± 6.8 and 16.2 ± 5.0 mm/mm$^2$, $p < 0.0001$) were lower in the MCI and dementia groups compared to the NCI group. Lower CECD partially mediated the impact of age and diabetes on CNFL reduction ($p < 0.05$), whereas CECA lost its significance after adjustment ($p = 0.20$). CEC morphology does not affect the association between corneal nerve fiber loss and MCI/dementia. CECD and CECA had no significant association with cerebral ischemic lesions ($p = 0.21$–$0.47$), dementia ($p = 0.11$–$0.35$), or cognitive decline ($p = 0.37$–$0.38$). However, lower CECD and higher CECA were associated with decreased cortical gray matter volume ($p < 0.05$–$0.01$).

**DISCUSSION:** CEC loss occurs in patients with dementia, and both endothelial cell loss and hypertrophy are associated with cortical gray matter atrophy. CNF loss occurs in individuals with MCI and dementia. Corneal nerve and endothelial cell abnormalities could act as biomarkers for neurovascular pathology in dementia.

KEYWORDS
brain volumetry, corneal confocal microscopy, dementia, endothelial cell density, mild cognitive impairment

### Highlights

- Corneal endothelial cell density is significantly reduced in patients with dementia.
- Corneal nerve fiber density, branch density, and length are lower in subjects with mild cognitive impairment (MCI) and dementia.
- Corneal endothelial cell loss and hypertrophy are associated with cortical gray matter atrophy.
- Corneal nerve and endothelial cell abnormalities could act as biomarkers for neurovascular pathology in dementia.
- Reduced corneal endothelial cell density partially mediates the effects of age and diabetes on corneal nerve fiber loss.

## 1 | INTRODUCTION

Dementia affects around 55 million people globally.[1] There is a need for reliable biomarkers to identify sub-clinical neurodegeneration, predict disability worsening, and to accurately monitor treatment response. Neuroimaging methods include magnetic resonance imaging (MRI), positron emission tomography (PET), and ocular imaging techniques such as optical coherence tomography and corneal confocal microscopy (CCM).[2] We and others have used CCM to identify neurodegeneration in many peripheral and central neurodegenerative diseases including multiple sclerosis, Parkinson's disease, and dementia.[3–5] However, although current CCM measures of neurodegeneration have good sensitivity, they are not disease specific and therefore may have limited diagnostic utility. Nevertheless, CCM identifies corneal nerve fiber (CNF) loss in individuals with mild cognitive impairment (MCI) and dementia,[3] which is associated with a decline in cognitive function and functional independence,[6] and also predicts progression of MCI to dementia.[7]

The corneal epithelium and stroma are avascular, but the corneal endothelial cell (CEC) layer, much like the vascular endothelium, regulates fluid and nutrient transport between the aqueous humor and corneal stroma.[8] We have shown previously that CEC morphology is abnormal in individuals with acute ischemic stroke (IS).[9] Furthermore, we have also shown that endothelial cell density is lower and endothelial cell area and perimeter are significantly higher in patients with transient ischemic attack (TIA) or minor IS and related to CNF loss.[10] However, recently we showed that corneal nerve loss, but not endothelial cell morphology, was related to the pial collateral status in patients with IS.[11] Indeed, stroke survivors show cognitive decline in multiple domains independent of stroke type or IS subtype.[12] A recent study has shown impaired spontaneous cerebrovascular reactivity in the parahippocampal gyrus in adults with MCI.[13] We have shown

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that individuals with MCI and dementia and subcortical and cortical ischemia have a lower hippocampal volume and corneal nerve fiber length (CNFL) compared to those with subcortical ischemia only.[14] We have also shown that the diagnostic accuracy of CCM was high and comparable to medial temporal lobe atrophy (MTA) rating for dementia and was superior for MCI.[15]

This study assessed whether abnormalities in CEC morphology are related to corneal nerve morphology, brain volumetry, cerebral ischemic lesions, and cognitive impairment in individuals with MCI and dementia.

**RESEARCH IN CONTEXT**

1. **Systematic review**: We searched PubMed and Google Scholar for studies on the relationship between corneal endothelial cell (CEC) morphology and neurodegenerative conditions, focusing on mild cognitive impairment (MCI) and dementia. Key terms included corneal confocal microscopy, endothelial cell morphology, neurodegeneration, MCI, and dementia.
2. **Interpretation**: Our study shows that corneal endothelial cell density (CECD) is reduced in patients with dementia compared to those without cognitive impairment, whereas corneal endothelial cell area (CECA) remains unchanged. Lower CECD partially mediates the effects of age and diabetes on corneal nerve fiber length (CNFL) reduction. Lower CECD and higher CECA correlate with decreased cortical gray matter volume, suggesting that CECD and CECA could be biomarkers for neurovascular pathology in dementia.
3. **Future directions**: Future longitudinal studies with larger, more diverse cohorts are needed to validate the utility of CECD and CECA as surrogate biomarkers to identify those at risk for neurodegeneration.

## 2 | METHODS

### 2.1 | Study design and participants

This cross-sectional study recruited individuals, 60 to 85 years of age, with no cognitive impairment (NCI), MCI, and dementia (including Alzheimer's disease [AD], vascular dementia [VaD], and mixed AD) from the geriatric and memory clinic at Rumailah Hospital, Qatar, from 2016 to 2020. Exclusion criteria included reversible cognitive impairment, complex and young-onset dementia, severe dementia, frontotemporal dementia, Lewy body dementia, Parkinson's disease, severe anxiety, severe depression, mood disorders, psychosis, hypomania, peripheral neuropathy (including severe vitamin $B_{12}$ deficiency), hypothyroidism, HIV infection, hepatitis C, and self-reported severe dry eye, ocular trauma, or surgery in the preceding 12 months and corneal dystrophies confirmed by ophthalmic examination. In addition, participants unable to cooperate during the CCM assessments were excluded. Diabetes was excluded only in the control group but not in the MCI and dementia groups due to its high prevalence in the study population.[3]

### 2.2 | Ethical approval

The study was approved by the institutional review board (IRB) of Weill Cornell Medicine in Qatar (WCM-Q) and Hamad Medical Corporation (HMC) (IRB#: NPRP12S-0213-190080). All participants provided written informed consent. The research adhered to the tenets of the Declaration of Helsinki.

### 2.3 | Demographic and metabolic measures

Age, gender, blood pressure, body weight, body mass index (BMI), hemoglobin A1c (HbA1c), lipid profile, vitamin $B_{12}$, thyroid function, and medical history were recorded from the electronic medical register (Cerner).

### 2.4 | Cognitive function assessment

Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) basic test version 7.1. A score of $\leq$ 26/30 indicates cognitive impairment.[16] An extra point was added for individuals who were illiterate or who had attended only primary school.

### 2.5 | Diagnosis

The diagnosis of MCI was based on International Classification of Diseases, Tenth Revision (ICD-10): F06.7 criteria version: 2019. A consensus diagnosis was reached by geriatricians, geriatric psychiatrists, and neurologists based on a comprehensive history and assessment of cognitive impairment using MoCA, psychiatric history, family and medical history, other medical comorbidities, medication and functional history of basic activities of daily living, and dementia screening labs, alongside MRI of the brain to exclude other causes of cognitive decline such as brain tumors, subdural hematoma, or normal pressure hydrocephalus.

The diagnosis of dementia, including AD, VaD, and mixed AD was based on ICD-10 criteria. The diagnosis of AD was based on typical symptoms and radiological features of AD, for example, atrophy in hippocampi, entorhinal cortex, and amygdala on MRI. Brain atrophy was assessed by neuroradiologists using the criteria of Dubois et al.[17] and blinded to the diagnosis and clinical data. The diagnosis of probable or possible VaD was based on the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et L'Enseignement en Neurosciences (NINDS-AIREN) criteria,[18] which includes multiple large vessel infarcts or a single strategically placed

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infarct in the angular gyrus, thalamus, basal forebrain, or posterior or anterior cerebral artery territories, and multiple lacunes in the basal ganglia and white matter, extensive periventricular white matter lesions, or combinations thereof. The diagnosis of mixed dementia was based on the presence of AD and significant vascular changes.

## 2.6 | CCM

CCM was performed on both eyes using the Heidelberg Retinal Tomograph 3 (HRT-3) device with the Rostock cornea module (RCM) (Heidelberg Engineering GmbH, Heidelberg, Germany). The cornea was locally anesthetized by instilling one drop of 0.4% benoxinate hydrochloride (Chauvin Pharmaceuticals, Chefaro, UK). Viscotears (Carbomer 980, 0.2%, Novartis, UK) was used as the coupling agent between the cornea and TomoCap, and between the TomoCap and objective lens. Patients were instructed to fixate on a target with the eye not being examined. High-resolution, 400 × 400 µm field of view images were generated using a 670 nm red wavelength diode laser. Several scans of the sub-basal nerve plexus in the central cornea were captured. To avoid bias, an investigator, blinded to diagnosis, cognitive function, and MRI brain volumetry, selected three high-clarity, nonoverlapping images of the sub-basal nerve plexus in the central cornea at 40–60 µm depth and three images of the endothelial layer at 550–600 µm depth per eye. The selection was based on focus, layer homogeneity, and clarity, as described previously.[19–21] CCMetrics was used to manually trace nerve fibers and quantify corneal nerve fiber density (CNFD) (main nerve fibers/mm$^2$), corneal nerve branch density (CNBD) (branches from the main nerve fibers/mm$^2$), and CNFL (length of the main fibers and branches mm/mm$^2$).[22] Sentizer, a fully automated software, was used to quantify corneal endothelial cell density (CECD) and corneal endothelial cell area (CECA)[23] (Figures 1A–D).

## 2.7 | MRI brain volume analysis

MRI was performed on a 3T MRI system (MAGNETOM Skyra, Siemens AG, Erlangen). A T1-weighted three-dimensional (3D) Magnetization Prepared Rapid Gradient Echo Imaging (MPRAGE) sequence was obtained in the sagittal plane with a 1 mm slice thickness, repetition time (TR) of 1900 ms, echo time (TE) of 2.67 ms and 2.46 ms, inversion time (TI) of 1100 ms and 900 ms, flip angle of 9° and 15°, and field of view (FOV) = 240 × 100. MRI brain volumetry was undertaken using NeuroQuant (NQ), U.S. Food and Drug Administration (FDA)–approved fully automated software.[24,25] The brain volume was adjusted for the percentage of intracranial volume (ICV%) to minimize the impact of head size as a confounding factor. Brain structures including the ICV% of cerebral white matter, cortical gray matter, hippocampus, ventricles, and whole brain were quantified.

## 2.8 | Ischemic lesion assessment

Ischemic lesions were defined as hyperintense foci on T2 and fluid-attenuated inversion recovery (FLAIR), including small vessel disease (SVD) and lacunes. SVD was assessed by the presence of white matter hyperintensities (WMHs) in cortical, subcortical, or both regions. Lacunes were identified as foci hyperintense on T2 with a central low signal and a peripheral hyperintense rim on FLAIR. Subcortical ischemia was identified by ischemic lesions in the subcortical white matter, deep gray nuclei (basal ganglia, thalami), and mesial temporal lobe. Cortical ischemia was identified by ischemic lesions in the cerebral convexity cortex. The cohort was stratified into three groups, those without ischemic lesions, those with subcortical ischemia, and those with both cortical and subcortical ischemia.

## 2.9 | Sample size calculation

The sample size calculation for detecting the association between CECD and CNFL was based on data from Khan et al. (2018),[9] which found significant differences in CECD between controls and patients with acute IS (3664.7 ± 43.9 cells/mm$^2$ vs 3342.9 ± 27.5 cells/mm$^2$, $p <$ 0.001). The effect size (Cohen's $d$) was calculated to be ≈8.79. Given this large effect size, the required sample size per group is minimal. However, to ensure robustness and account for potential variability, our study included 114 participants: 14 with NCI, 77 with MCI, and 23 with dementia.

## 2.10 | Statistical analysis

Descriptive statistics summarized clinical characteristics, cognitive function, CEC measures, CNF measures, and brain volume, with continuous variables as mean ± SD and categorical variables as frequencies and percentages. One-way analysis of variance (ANOVA) with post hoc least significant difference (LSD) tests was used to compare continuous variables across the NCI, MCI, and dementia groups, whereas chi-square tests were used for categorical variables. Cohen's $d$ was calculated to measure the effect sizes of the significant differences between groups. Pearson correlation coefficients ($r$) examined associations between CECD/CECA and variables such as age, diabetes, and HbA1c.

Multivariable linear regression models assessed the independent effects of CECD and CECA on CNF morphology, cognitive function, and brain volume measures, adjusting for age, diabetes, and other relevant variables. Regression unstandardized coefficients ($\beta$) and their 95% confidence intervals (CIs), and $p$ values were reported. Variables with $p \leq 0.05$ at the bivariate level were included in the multiple logistic regression to determine the best model using R-squared values. Mediation analysis evaluated how CECD mediated the effects of age and diabetes on CNFL.

Logistic regression analysis was used to examine the associations between CECD, CECA, and the dependent variables of dementia and cerebral ischemic lesions. Outputs included odds ratios (ORs), 95% CIs, and $p$ values.

All statistical analyses were conducted using SPSS software (version 26.0; IBM Corp., Armonk, NY, USA). A two-tailed $p$ value of $< 0.05$ was considered statistically significant.

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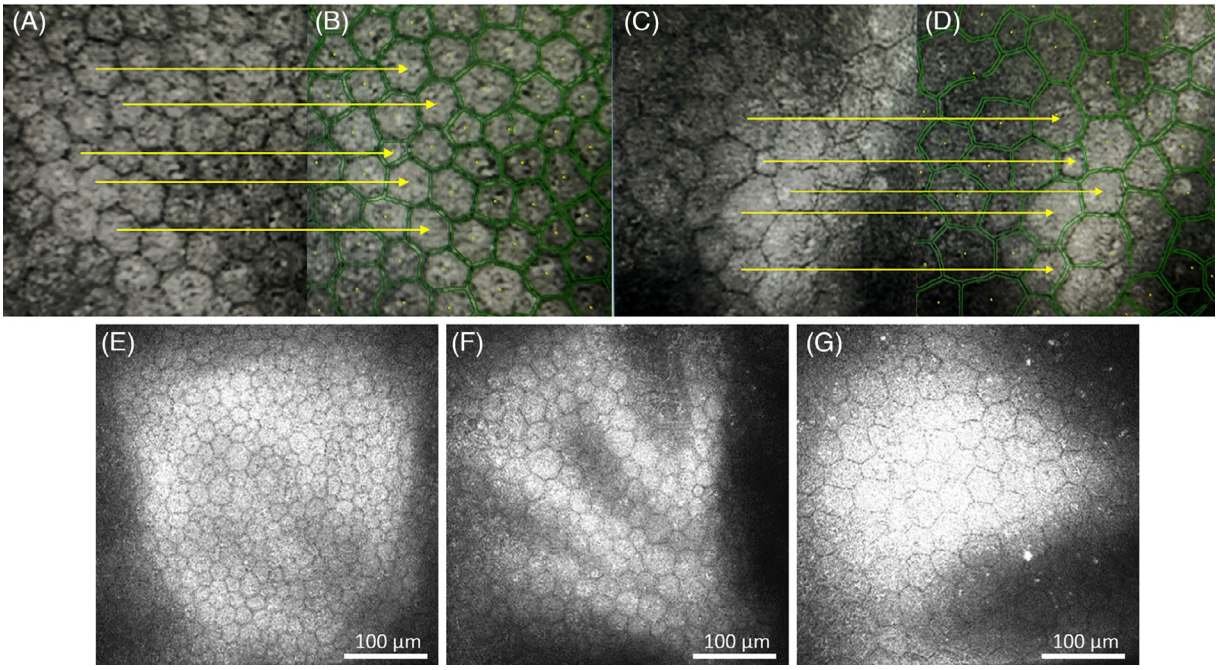



**FIGURE 1** Corneal endothelial cell layer imaging and representative corneal confocal microscopy images. Images A and C are the original images of the corneal endothelial cell layer. Images B and D are the analyzed images. The automated software accurately segments endothelial cells and quantifies their density (cells/mm$^2$) and average surface area (µm$^2$). Representative CCM images of corneal endothelial cells in a participant with (E) no cognitive impairment, (F) mild cognitive impairment, and (G) dementia. The endothelial cells appeared larger with disease severity, but the difference was not statistically significant. CCM, corneal confocal microscopy.

## 3 | RESULTS

### 3.1 | Clinical characteristics (Table 1)

Of the 114 participants enrolled, 14 had NCI, 77 had MCI, and 23 had dementia. Both the MCI and dementia groups had comparable ages but were older than the NCI group (70.5 ± 5.9 and 72.8 ± 7.2 vs 61.8 ± 8.9 years, $p < 0.0001$). Gender distribution was similar across the groups ($p = 0.40$). The prevalence of diabetes (55.8% vs 47.8%, $p = 0.50$) and HbA1c (6.5 ± 1.4 vs 6.5% ± 1.3%, $p = 0.96$) was comparable between the MCI and dementia groups, whereas no participants in the NCI group had diabetes and their HbA1c level was significantly lower 5.5% ± 0.2% ($p < 0.05$). Total cholesterol ($p = 0.27$), triglyceride ($p = 0.24$), high-density lipoprotein (HDL; $p = 0.33$), low-density lipoprotein (LDL; $p = 0.79$), systolic blood pressure (SBP) ($p = 0.92$), diastolic blood pressure (DBP) ($p = 0.26$), and body weight ($p = 0.97$) were comparable across the groups.

There was a decline in cognitive function from the NCI to the MCI groups (MoCA: 27.7 ± 2.7 vs 23.1 ± 5.4, $p < 0.01$) and from the MCI to the dementia group (MoCA: 23.1 ± 5.4 vs 15.3 ± 6.7, $p < 0.0001$).

### 3.2 | Corneal endothelial cell morphology (Table 1 and Figures 1 and 2)

CECD (1971.3 ± 594.6 vs 2316.1 ± 499.5 cells/mm$^2$, $p < 0.05$, Cohen's $d = 0.63$) was significantly lower in the dementia group compared to the NCI group, with no difference in CECA. Both CECD and CECA were comparable between the MCI and NCI groups ($p = 0.13$–$0.65$). There were no significant differences in CECD ($p = 0.20$–$0.78$) and CECA ($p = 0.43$–$0.76$) between individuals with no cerebral ischemic lesions, subcortical ischemia, and both cortical and subcortical ischemia.

CECD was negatively associated with age ($r = -0.27$, $p < 0.01$), diabetes ($r = -0.20$, $p < 0.05$), and HbA1c ($r = -0.22$, $p < 0.05$), whereas CECA was positively associated with age ($r = 0.19$, $p < 0.05$). Both CECD and CECA had no association with duration of diabetes ($p = 0.12$–$0.18$), SBP and DBP ($p = 0.18$–$0.39$), BMI ($p = 0.79$–$0.86$), cholesterol ($p = 0.38$–$0.87$), triglycerides ($p = 0.88$–$0.95$), HDL ($p = 0.31$–$0.70$), and LDL ($p = 0.64$–$0.71$).

### 3.3 | Corneal nerve fiber morphology (Table 1 and Figures 2 and 3)

Compared to the NCI group, CNFD was significantly lower in both the MCI group (31.7 ± 5.6 vs 24.5 ± 9.2 fibers/mm$^2$, Cohen's $d = 0.95$) and the dementia group (31.7 ± 5.6 vs 17.3 ± 5.3 fibers/mm$^2$, Cohen's $d = 2.64$, $p < 0.01$). CNBD was also significantly lower in the MCI group (111.8 ± 58.1 vs 50.4 ± 36.4 branches/mm$^2$, Cohen's $d = 1.27$) and the dementia group (111.8 ± 58.1 vs 52.7 ± 21.3 branches/mm$^2$, Cohen's $d = 1.35$, $p < 0.0001$). Similarly, CNFL was significantly reduced in the MCI group (24.6 ± 6.6 vs 16.5 ± 6.8 mm/mm$^2$, Cohen's $d = 1.21$) and the dementia group (24.6 ± 6.6 vs 16.2 ± 5.0 mm/mm$^2$, Cohen's

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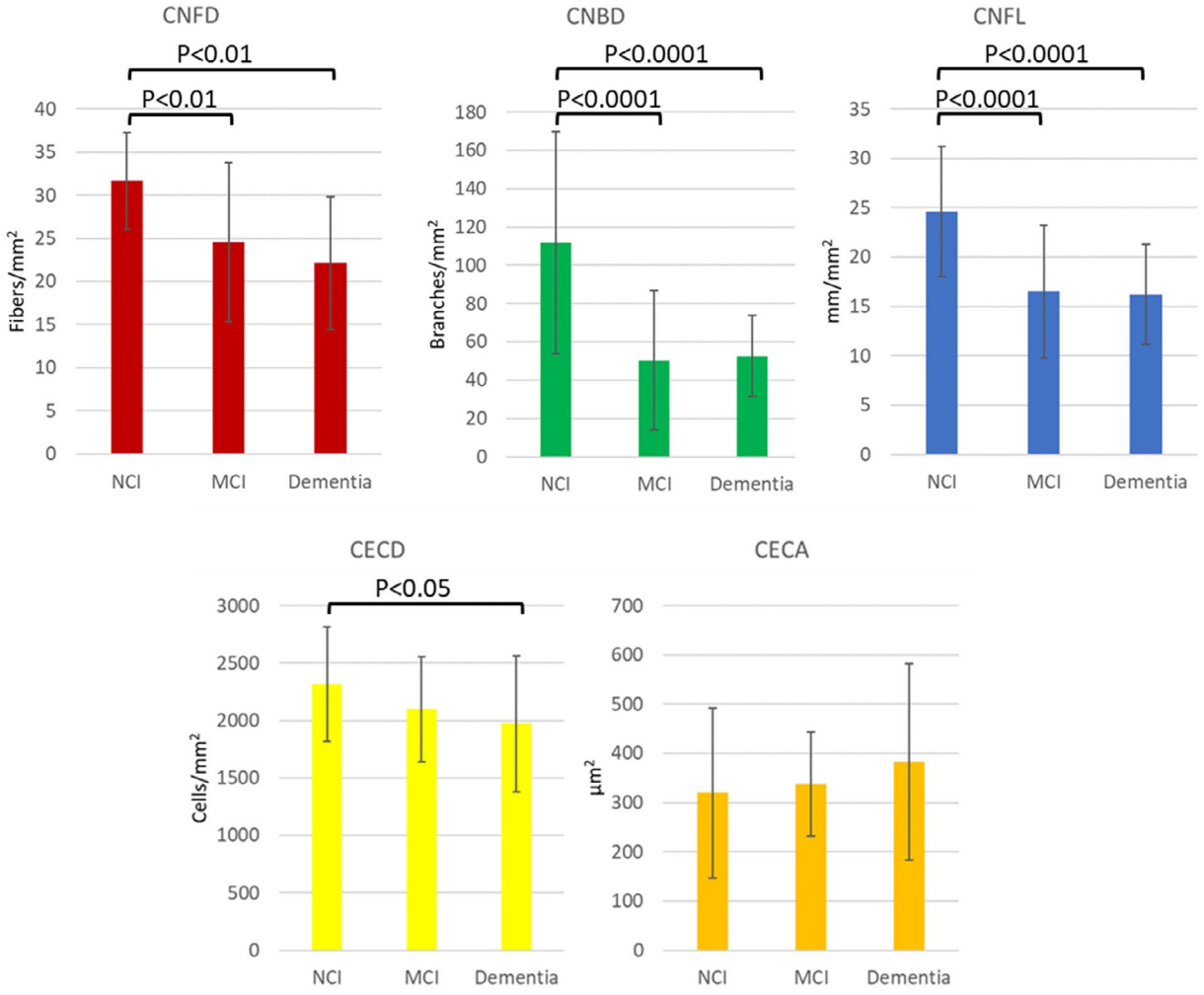



**FIGURE 2** Comparison of corneal nerve morphology and endothelial cell morphology between participants with no cognitive impairment, MCI, and dementia. CNFD, CNBD, and CNFL are significantly lower in both the MCI and dementia group ($p < 0.01$ to $p < 0.0001$) compared to the NCI group. CECD is lower in the dementia group compared to the NCI group ($p < 0.05$), with no significant differences in CECA between groups. Each bar represents the mean value with SD error bars. CECA, corneal endothelial cell area; CECD, corneal endothelial cell density; CNBD, corneal nerve branch density; CNFD, corneal nerve fiber density; CNFL, corneal nerve fiber length; MCI, mild cognitive impairment; NCI, no cognitive impairment.

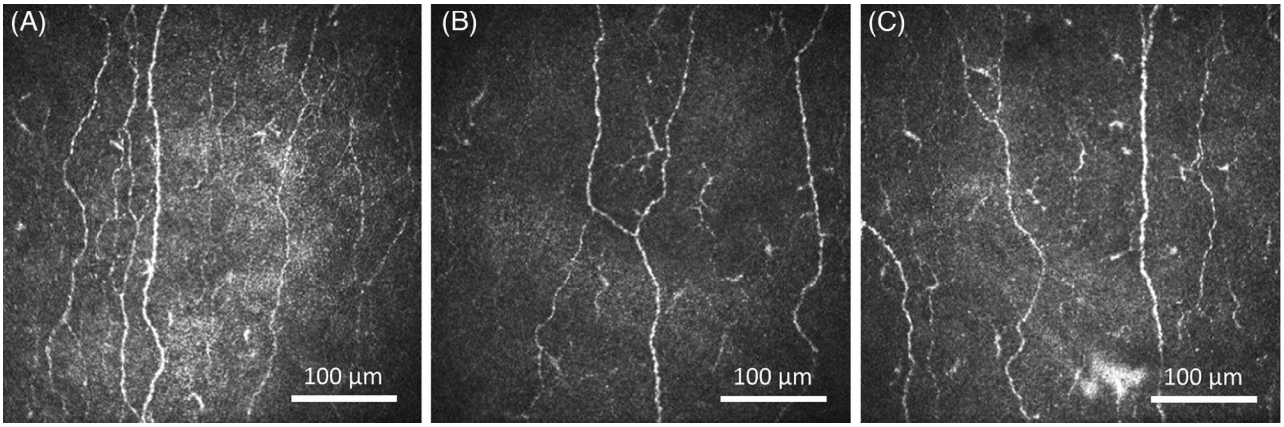



**FIGURE 3** Representative corneal confocal microscopy images of corneal nerve morphology. Corneal nerve fibers in (A) a participant without cognitive impairment (NCI), (B) a participant with MCI, and (C) a participant with dementia. Nerve fibers are visibly reduced in participants with MCI and dementia compared to the participant without cognitive impairment. MCI, mild cognitive impairment.

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**TABLE 1** Clinical characteristics, cognitive function, corneal endothelial cell morphology, nerve fiber morphology, and brain volume in subjects without cognitive impairment, mild cognitive impairment, and dementia.

| | NCI ($n = 14$) | MCI ($n = 77$) | Dementia ($n = 23$) | $p$ value |
|---|---|---|---|---|
| **Clinical characteristics** | | | | |
| Age, years | 61.8 ± 8.9 | 70.5 ± 5.9$^{\dagger\dagger\dagger}$ | 72.8 ± 7.2$^{\dagger\dagger\dagger}$ | 0.15 |
| Men, *n* (%) | 11/14 (78.6) | 49/77 (63.6) | 13/23 (56.5) | 0.40 |
| Women, *n* (%) | 3/14 (21.4) | 28/77 (36.4) | 10/23 (43.5) | |
| Diabetes, *n* (%) | 0/14 (0.0) | 43/77 (55.8)$^{\dagger\dagger}$ | 11/23 (47.8)$^{\dagger\dagger}$ | 0.50 |
| Hb1Ac, % | 5.5 ± 0.2 | 6.5 ± 1.4$^{\ddagger}$ | 6.5 ± 1.3$^{\ddagger}$ | 0.96 |
| Total cholesterol, mmol/L | 5.0 ± 0.9 | 4.5 ± 1.1 | 4.3 ± 1.1 | 0.57 |
| Triglyceride, mmol/L | 1.1 ± 0.5 | 1.5 ± 0.7 | 1.4 ± 0.6 | 0.75 |
| HDL, mmol/L | 1.4 ± 0.4 | 1.3 ± 0.5 | 1.2 ± 0.3 | 0.25 |
| LDL, mmol/L | 3.0 ± 0.7 | 8.5 ± 46.6 | 2.6 ± 1.0 | 0.56 |
| SBP, mmHg | 134.4 ± 12.5 | 135.7 ± 20.3 | 137.0 ± 20.1 | 0.78 |
| DBP, mmHg | 76.0 ± 10.6 | 72.1 ± 9.0 | 71.2 ± 8.0 | 0.70 |
| Body weight, kg | 76.0 ± 10.5 | 76.4 ± 14.1 | 77.2 ± 15.9 | 0.83 |
| **Cognitive function, MoCA score** | 27.7 ± 2.7 | 23.1 ± 5.4$^{\dagger}$ | 15.3 ± 6.7$^{\dagger\dagger\dagger}$ | **< 0.0001** |
| Corneal endothelial cell density, cells/mm$^2$ | 2316.1 ± 499.5 | 2098.1 ± 456.6 | 1971.3 ± 594.6$^{\ddagger}$ | 0.28 |
| Corneal endothelial cell area, μm$^2$ | 319.4 ± 172.3 | 337.9 ± 105.7 | 382.6 ± 200.1 | 0.18 |
| **Corneal nerve fiber morphology** | | | | |
| Corneal nerve fiber density, fibers/mm$^2$ | 31.7 ± 5.6 | 24.5 ± 9.2$^{\dagger}$ | 22.1 ± 7.7$^{\dagger}$ | 0.25 |
| Corneal nerve branch density, branches/mm$^2$ | 111.8 ± 58.1 | 50.4 ± 36.4$^{\dagger\dagger\dagger}$ | 52.7 ± 21.3$^{\dagger\dagger\dagger}$ | 0.80 |
| Corneal nerve fiber length, mm/mm$^2$ | 24.6 ± 6.6 | 16.5 ± 6.8$^{\dagger\dagger\dagger}$ | 16.2 ± 5.0$^{\dagger\dagger\dagger}$ | 0.86 |
| **Cerebral ischemic lesions** | | | | |
| No ischemic lesions, *n* (%) | 3/8 (37.5) | 12/58 (20.7) | 0/15 (0)$^{\ddagger}$ | |
| Subcortical ischemia, *n* (%) | 5/8 (62.5) | 31/58 (53.4) | 10/15 (66.7) | 0.12 |
| Cortical and subcortical ischemia, *n* (%) | 0/8 (0.0) | 15/58 (25.9) | 5/15 (33.3) | |
| **Brain volume measures** | | | | |
| Cerebral white matter, ICV% | 32.9 ± 2.1 | 29.5 ± 3.2$^{\dagger}$ | 30.4 ± 4.6 | 0.50 |
| **Cortical gray matter, ICV%** | 29.0 ± 2.7 | 29.2 ± 3.1 | 26.1 ± 4.8 | **< 0.05** |
| Hippocampus, ICV% | 0.51 ± 0.05 | 0.42 ± 0.08$^{\dagger}$ | 0.36 ± 0.05$^{\dagger\dagger\dagger}$ | 0.06 |
| Ventricle, ICV% | 1.9 ± 0.4 | 3.1 ± 1.4$^{\ddagger}$ | 3.5 ± 1.4$^{\ddagger}$ | 0.44 |
| **Whole brain, ICV%** | 75.1 ± 3.4 | 71.4 ± 3.4$^{\dagger}$ | 68.8 ± 3.0$^{\dagger\dagger}$ | **<0.01** |

*Note*: Numeric and categorical variables are summarized as means ± SD and *n* (%), respectively. Variables were compared using one-way analysis of variance (ANOVA) except for sex, diabetes, obesity, and cerebral ischemia, which were compared using $\chi^2$. Variables that were significantly different between the NCI group and MCI or dementia group are denoted as $^{\ddagger}p \le 0.05$, $^{\dagger}p \le 0.01$, $^{\dagger\dagger}p \le 0.001$, $^{\dagger\dagger\dagger}p \le 0.0001$.
Abbreviations: DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; ICV%, intracranial volume percentage; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; NCI, no cognitive impairment; SBP, systolic blood pressure.

$d = 1.44$, $p < 0.0001$). There were no significant differences between the MCI and dementia group ($p = 0.25$–$0.86$).

## 3.4 | Cerebral ischemic lesions (Table 1)

Cerebral ischemic lesions were present in 62.5% of the NCI group, 79.3% of the MCI group, and 100% of the dementia group. Subcortical ischemic lesions were present in 62.5% of the NCI group, 53.4% of the MCI group, and 66.7% of the dementia group. Both cortical and subcortical ischemia were present in 25.9% of the MCI group, 33.3% of the dementia group, and none of the NCI group.

## 3.5 | Brain volume measures (Table 1)

Compared to the NCI group, both the MCI and dementia groups had significantly lower percentage intracranial volumes (%ICVs) of the

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**TABLE 2** Risk factors and associations with corneal endothelial cell density and area.

| Associations of CNFL, brain volumes, ischemic lesions, and dementia with CECD and CECA | | | | |
|---|---|---|---|---|
| **Dependent variable** | **Independent variables** | **Adjusted β coefficient** | **95% CI** | ***p* value** |
| **CNFL, mm/mm²** | **CECD, cells/mm²** | 0.003 mm/mm²/cells/mm² | 0.001 to 0.01 | **< 0.05** |
| | **Age, years** | −0.21 mm/mm²/year | −0.38 to −0.03 | **< 0.05** |
| | **Diabetes** | −2.66 mm/mm² | −5.21 to −0.11 | **< 0.05** |
| **CNFL, mm/mm²** | CECA, μm² | −0.01 mm/mm²/μm² | −0.01 to 0.003 | 0.20 |
| | **Age, years** | −0.23 mm/mm²/year | −0.40 to −0.05 | **0.01** |
| | **Diabetes** | −2.99 mm/mm² | −5.54 to −0.45 | **< 0.05** |
| **Cortical gray matter, ICV%** | **CECD, cells/mm²** | 0.002 ICV%/cells/mm² | 0.0002 to 0.003 | **< 0.05** |
| | **CECA, μm²** | −0.007 ICV%/μm² | −0.01 to −0.002 | **< 0.01** |
| Hippocampus, ICV% | CECD, cells/mm² | < 0.001 ICV%/cells/mm² | −< 0.001 to < 0.001 | 0.21 |
| | CECA, μm² | −< 0.001 ICV%/μm² | −< 0.001 to < 0.001 | 0.26 |
| Ventricles, ICV% | CECD, cells/mm² | 0.001 ICV%/cells/mm² | −0.001 to 0.001 | 0.68 |
| | CECA, μm² | −0.001 ICV%/μm² | −0.003 to 0.002 | 0.58 |
| Whole brain, ICV% | CECD, cells/mm² | 0.001 ICV%/cells/mm² | −0.001 to 0.003 | 0.36 |
| | CECA, μm² | −0.001 ICV%/μm² | −0.007 to 0.005 | 0.66 |
| Cognitive function, MoCA | CECD, cells/mm² | 0.001 score/cells/mm² | −0.001 to 0.004 | 0.37 |
| score | CECA, μm² | −0.004 score/μm² | −0.013 to 0.005 | 0.38 |
| **Dependent variable** | **Independent variables** | **Odds ratio** | **95% CI** | ***p* value** |
| Dementia | CECD, cells/mm² | 0.99 | 0.99 to 1.00 | 0.11 |
| | CECA, μm² | 1.00 | 0.99 to 1.00 | 0.35 |
| Cerebral ischemic lesions | CECD, cells/mm² | 0.99 | 0.99 to 1.00 | 0.21 |
| | CECA, μm² | 1.00 | 0.99 to 1.00 | 0.47 |
| **Risk factors for corneal endothelial cell density (CECD) and area (CECA)** | | | | |
| **Dependent variable** | **Independent variables** | **Adjusted β coefficient** | **95% CI** | ***p* value** |
| **CECD, cells/mm²** | **Age, years** | −16.1 cells/mm²/year | −31.8 to −0.4 | **< 0.05** |
| | Diabetes | −188.6 cells/mm² | −308.6 to 5.4 | 0.06 |
| **CECA, μm²** | **Age, years** | 3.6 μm²/year | 0.1 to 7.2 | **< 0.05** |

Abbreviations: CECA, corneal endothelial cell area; CECD, corneal endothelial cell density; CNFL, corneal nerve fiber length; ICV%, intracranial volume percentage; MoCA, Montreal Cognitive Assessment.

hippocampi ($p < 0.01$–$0.0001$) and whole brain ($p < 0.01$–$0.001$), higher ICV% of ventricles ($p = 0.05$), but comparable ICV% of cortical gray matter ($p = 0.18$). Cerebral white matter ICV% was significantly lower in the MCI group ($p < 0.01$) compared to the NCI group. Compared to the MCI group, the dementia group had significantly lower ICV% of cortical gray matter ($p < 0.05$) and whole brain ($p < 0.01$).

## 3.6 | Association of corneal endothelial cell morphology with corneal nerve fiber morphology (Table 2)

Lower CECD was associated with a lower CNFL after adjusting for age and diabetes. For every decrease of 1000 endothelial cells/mm², CNFL decreased by 3 mm/mm² (95% CI: 1 to 10, $p < 0.05$). CECD also decreased as age increased (−16.1 cells/mm² per year, 95% CI: -31.8 to −0.4, $p < 0.05$) and with diabetes (−188.6 cells/mm², 95% CI: −308.6 to −5.4, $p < 0.05$). Because the direct effect of CECD after adjusting for age and diabetes on CNFL is lower compared to its total effect on CNFL ($\beta_3 = -3$ mm/mm²/1000 cells/mm² vs $\beta_1 = -4$ mm/mm²/1000 cells/mm²), CECD partially mediated the impact of age and diabetes on CNFL. The association between CECA and CNFL lost its significance ($p = 0.20$) after adjusting for age and diabetes, indicating that the impacts of age and diabetes were more dominant factors on CNFL.

## 3.7 | Association of corneal endothelial cell morphology with dementia, cognitive function, and cerebral ischemia (Table 2)

There was no significant association between dementia, cognitive function, and ischemic lesions with either CECD ($p = 0.35$, 0.37, and 0.47) or CECA ($p = 0.11$, 0.38 and 0.21) as indicated by an OR close to 1.

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### 3.8 | Association of corneal endothelial cell morphology with brain volume measures (Table 2)

Cortical gray matter was positively associated with CECD. For every decrease of 1000 endothelial cells/mm$^2$ in CECD, the volume of cortical gray matter decreased by 2 ICV% (95% CI: 0.2 to 3, $p < 0.05$). Conversely, cortical gray matter was negatively associated with CECA. For every increase of 1 mm$^2$ in CECA, the volume of cortical gray matter decreased by 7 ICV% (95% CI: −10 to −2, $p < 0.01$). The ICV% of the hippocampus, ventricle, and whole brain had no significant associations with either CECD ($p$'s = 0.21, 0.68, and 0.36) or CECA ($p$'s = 0.26, 0.58, and 0.66).

## 4 | DISCUSSION

This study shows moderate to large effect sizes for the differences in CECD between the NCI and dementia groups, and in corneal nerve measures between the NCI, MCI, and dementia groups, supporting the clinical relevance of these findings. Although CECD was lower in the dementia compared to the NCI groups, on logistic regression, CECD and CECA were not significant predictors of dementia, cognitive decline, or cerebral ischemic lesions. However, of note, the lower CECD and higher CECA were associated with cortical gray matter atrophy, a key finding in dementia.[26]

We have previously reported a significant association between CECD and CNF measures in individuals with acute IS.[9] In this study, CECD also partially mediated the adverse effects of age and diabetes on CNF morphology, which should caution us in relation to the specificity of this change in dementia. Thus, CEC abnormalities may impact on CNFs through metabolic alterations and dysregulated transport of nutrients between the aqueous humor and corneal stroma. Our findings align with previous studies showing that CECD is lower with increasing age[27] and type 2 diabetes.[28] Diabetes is highly prevalent in individuals with dementia affecting 13%–20%,[29] and indeed in our cohort about half had diabetes.

CEC and CNF morphology are abnormal in TIA and minor IS,[10] as well as in acute IS.[9] In stroke patients, CEC loss has been shown to be associated with corneal nerve loss independent of stroke and triglycerides, and CEC hypertrophy partially mediates the association between stroke and corneal nerve loss.[9] However, in our study on MCI and dementia, we found no association between CECD or CECA and cerebral ischemic lesions, dementia, or cognitive decline. This discrepancy could be due to the advanced age of our cohort, where age may be the primary factor affecting CEC morphology. In contrast, the stroke study cohort was younger, and elevated triglycerides were a significant confounder. Furthermore, amyloid beta (A$\beta$) has been shown to cause endothelial cell death in vitro,[30,31] which may affect the association between endothelial pathology and neurodegeneration. Our study suggests that altered CEC morphology does not mediate the association between CNF loss and dementia.

This study is the first to report that CEC loss and hypertrophy is associated with cortical gray matter atrophy. Vascular endothelial cells are crucial for regulating cerebral blood flow,[32] and any abnormality could lead to neuronal damage by increasing vulnerability to neurotoxic substances and contributing to neuroinflammation[33,34] and memory loss.[35] Cortical gray matter can be affected by hypertension, hyperlipidemia, diabetes, obesity, and smoking.[36,37] Monitoring of CECD and CECA as surrogate biomarkers of vascular endothelial pathology might help identify those at risk for neurodegeneration. The temporal relationship between the alterations in CECs and nerves with brain morphology merits further assessment in a longitudinal study.

Although CCM is not part of routine ophthalmology visits, it could be undertaken in patients already undergoing eye exams for age-related issues like cataracts, glaucoma, or macular degeneration, and for diabetic retinopathy screening. Thus CCM could identify subclinical corneal nerve abnormalities and prompt more detailed cognitive assessments to look for MCI or dementia.

We acknowledge that the small size of the NCI cohort may have biased our outcomes. However, the objective automated measurement of CECD and CECA has ensured high repeatability and accuracy of the measurements in relation to alterations in corneal nerves and brain volume in a large cohort of subjects with MCI and dementia.

In conclusion, our study shows that reduced CECD partially mediates the effects of age and diabetes on CNF loss. Furthermore, although abnormalities in CECs are not associated with dementia, cognitive decline, or cerebral ischemic lesions, they are associated with cortical grey matter atrophy, a key radiological feature of dementia. Longitudinal studies with larger, more diverse cohorts are needed to validate our results.

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### CONFLICT OF INTEREST STATEMENT

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship and are not listed. We confirm that the order of authors listed in the manuscript has been approved by all authors. None of the other authors have received or anticipate receiving income, goods, or benefit from a company that will influence the design, conduct, or reporting of the study. Author disclosures are available in the supporting information.

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## CONSENT STATEMENT

All human subjects provided written informed consent.

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