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Changes in choroidal thickness quantified by Optical Coherence Tomography across cognitive impairment: data from the NORFACE cohort

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Abstract

Background Optical coherence tomography (OCT) enables high-resolution imaging of ocular structures in health and disease. Choroid thickness (CT) is a key vascular retinal parameter that can be assessed by OCT and might be relevant in the evaluation of the vascular component of cognitive decline. We aimed to investigate CT changes in a large cohort of individuals cognitive unimpaired (CU), with mild cognitive impairment due to Alzheimer's (MCI-AD), mild cognitive impairment due to cerebrovascular disease (MCI-Va), Alzheimer's disease dementia (ADD), and vascular dementia (VaD).

Methods Clinical, demographical, ophthalmological and OCT data from the Neuro-ophthalmological Research at Fundació ACE (NORFACE) project were analyzed. CT was assessed in the macula across nine Early Treatment Diabetic Retinopathy Study (ETDRS) quadrants, average thickness, total volume, and subfoveal choroidal thickness. Differences of CT among the five diagnostic groups were assessed in a multivariate regression model, adjusting for demographic and cardiovascular risk factors and OCT image quality. A comparison between manual and automatic CT measurements in a subset of participants was also performed.

Results The study cohort comprised 1,280 participants: 301 CU, 196 MCI-AD, 112 MCI-Va, 578 ADD, and 93 VaD. CT was significantly increased in individuals with cognitive impairment compared to those CU, particularly in the VaD and MCI-Va groups and in the peripheral ETDRS regions. No significant differences were found in inner superior, center and subfoveal choroidal thickness. The interaction of sex and diagnosis had no effect in differentiating CT. Mini-Mental State Examination (MMSE) scores were not correlated to CT. Manual and automated CT measurements showed good reliability.

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Discussion Our findings indicated that peripheral choroidal thickening, especially in patients with cerebrovascular disease, may serve as a potential choroidal biomarker for cognitive decline and suggest different pathogenic pathways in AD and VaD. Further research is required to explore CT as a reliable ocular biomarker for cognitive impairment.

Keywords Choroidal thickness, Optical coherence tomography, Alzheimer's disease, Vascular dementia, Biomarkers, NORFACE cohort

Introduction

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 60% to 80% of cases, followed by cerebrovascular (CV) disease [1]. Neuropathological studies suggest that "mixed dementia," characterized by the coexistence of AD pathology and CV damage, may be a prevalent but underrecognized cause of cognitive impairment in older adults [2, 3]. Traditionally, the diagnosis of cognitive impairment relies on clinical criteria [4–6] supported by neuroimaging [7] and fluid biomarkers [8]. These methods are often costly, invasive, and not widely accessible, underscoring the urgent need for new, non-invasive and cost-effective biomarkers.

The retina, often described as a "window to the brain" [9], is directly connected to the central nervous system through the optic nerve. Given the embryological, functional and pathophysiological similarities between the retina and brain [9], it is plausible that AD and CV disease may impact the eye in a manner similar to how they affect the brain. Moreover, in contrast to the brain, the eye can be examined non-invasively using optical coherence tomography (OCT) imaging, enabling detailed analysis of early retinal alterations. Thus, the retina is considered a potential source to study brain changes in cognitive decline.

OCT is currently a crucial tool in the field of ophthalmology, widely used to diagnose various pathologies related to the retina and optic nerve, including glaucoma, and to assess the choroid [10]. The increasing role of ocular biomarkers in detecting systemic diseases has led to the emergence of oculomics [11, 12], an innovative field focused on using ocular data to identify systemic conditions, particularly neurodegenerative and cardiovascular diseases. An example is the Alz Eye project [13], an ambitious initiative leveraging artificial intelligence to analyze over 6 million OCT images from more than 250,000 NHS patients.

Several studies have explored the use of OCT to identify biomarkers of neurodegenerative diseases, focusing particularly on the retinal nerve fiber layer (RNFL) [14], ganglion cells complex [15, 16], and macular thickness [17, 18] or the presence of retinopathy [19] in AD. However, findings have often been inconsistent [20]. With increasing recognition of the vascular component in dementias [21, 22], choroidal thickness (CT), a critical vascular layer of the retina, has emerged as a key area of interest. Manual OCT-based choroidal measurements have suggested a relationship between CT changes and cognitive impairment [23, 24]. Nevertheless, the findings are mixed: while some OCT studies report a reduction in CT in patients with cognitive decline compared to cognitively normal individuals [25–27], others using histopathology data suggest a choroidal thickening [23, 24]. These discrepancies may be attributed to several limitations in earlier studies, including small sample sizes, reliance on manual measurements, and inadequate participant stratification. Despite these challenges, CT remains a promising area for investigating the connections between ocular microvasculature and brain alterations in dementia.

In this study, we aimed to analyze CT changes across the Early Treatment Diabetic Retinopathy Study (ETDRS) grid using swept source OCT (SS-OCT) technology in a large, well-characterized and single-site cohort of cognitively unimpaired individuals (CU), with mild cognitive impairment due to Alzheimer's disease (MCI-AD), MCI due to CV pathology (MCI-Va), Alzheimer's disease dementia (ADD), and vascular dementia (VaD), all of them evaluated in a memory clinic. We also examined the influence of sex, the correlation between CT and cognitive measures and the reliability between manual and automated measurements of CT.

Methods

Study participants

This study derives from the NORFACE project, established in 2014 at Ace Alzheimer Center Barcelona (Ace) with the goal to investigate retinal biomarkers in AD using OCT imaging [28–30]. The current work was designed as a cross-sectional observational study using data from a large cohort of consecutive patients evaluated due to cognitive decline at Ace between June 2016 and March 2019. Participants were recruited through various sources, including the 1) Ace´s memory unit [31], 2) the Open House Initiative [32], 3) the FACEHBI study [33], and 4) the BIOFACE study [34].

The current study inclusion criteria were: age 50–95 years, fluency in Spanish or Catalan, presence of a consensus-based clinical diagnosis about the participant's cognitive status, ability to complete a full

ophthalmological examination and OCT scan and signed informed consent. Exclusion criteria included advanced dementia, defined as a Global Deterioration Scale (GDS) [35] score > 6.

Clinical diagnostic groups

Study participants underwent neurological, neuropsychological, and social evaluations at Ace. A multidisciplinary team of neurologists, neuropsychologists, and social workers reached a consensus diagnosis on each participant's cognitive status [31]. Cognitive evaluations included the Spanish version of the Mini-Mental State Examination (MMSE) [36, 37], the memory section of the 7-Minute Test [38], the Neuropsychiatric Inventory Questionnaire (NPI-Q) [39], the GDS [35], the Clinical Dementia Rating (CDR) [40], the Blessed Dementia Scale [41], and the neuropsychological battery of Fundació ACE (NBACE) [42, 43]. Demographic and medical history data, including age, sex, years of formal education, smoking, hypertension, diabetes mellitus, dyslipidemia, heart disease, stroke, and chronic obstructive pulmonary disease (COPD), were collected. Neuroimaging, either brain magnetic resonance imaging (MRI) or head computed tomography (CT scan), was performed on all patients in order to assess brain atrophy patterns, cerebrovascular disease (including brain infarctions and white matter vascular burden) or other brain lesions.

Alzheimer's disease dementia (ADD) was defined using NIA-AA criteria [4]. Vascular dementia (VaD) was diagnosed based on NINDS-AIREN International Workshop Criteria [6]. The two dementia groups included patients in the GDS stages 4–6. Mild cognitive impairment (MCI) was defined using Petersen's criteria [44] and the Cardiovascular Health and Cognition Study [45]. In particular, the MCI-AD group was characterized by memory impairment and the absence of other comorbidities that could explain the cognitive decline (probable amnestic MCI) with suspected underlying AD [46]. The MCI-Va group was defined based on the suspected underlying etiology of CV pathology. The cognitively unimpaired (CU) group included cognitively healthy individuals and those with subjective cognitive decline (SCD), defined by self-reported cognitive problems without impairment on standardized cognitive tests [47, 48]. All CU participants had a CDR of 0, MMSE ≥ 27 and strictly normal performance on the NBACE.

Neuro-ophthalmological evaluation

Study participants underwent a comprehensive neuro-ophthalmological evaluation alongside their neurological assessment. Conducted by an optometrist, the evaluation lasted approximately 20 min and included: 1) a review of ophthalmological history, including previous treatments and surgeries; 2) monocular visual acuity assessment in the right eye using the participant's usual optical correction and a pinhole occluder, evaluated with the Early Treatment Diabetic Retinopathy Study (ETDRS) chart [49, 50]; 3) intraocular pressure (IOP) measurement with a rebound tonometer (iCare model) [51]; and 4) retinal examination using SS-OCT.

Visual acuity was assessed uniformly, regardless of cognitive status. All evaluations were performed by a single optometrist, who received training from an ophthalmologist. The ophthalmologist reviewed the history, examination results, and OCT images if abnormalities were detected, and confirmed diagnoses as needed. Both the ophthalmologist and neurologist were blinded to cognitive diagnoses. Only OCT data from the right eye were analyzed.

Ophthalmological exclusion criteria were the following: 1) conditions affecting retinal and/or choroidal measurements, such as glaucoma, age-related macular degeneration (AMD), and amblyopia; 2) IOP (intraocular pressure) ≥ 24 mmHg; 3) history of retinal surgery; 4) presence of OCT image artifacts; 5) refractive errors: patients with high myopia (< -6D) or high hyperopia (> + 6D) (as these extreme refractive errors are associated with significant variations in axial length, which can influence choroidal thickness measurements); [52, 53] 6) other causes, including non-glaucomatous optic neuropathy, inability to complete the ophthalmological exam, or absence of right eye OCT data.

OCT measurements of choroidal thickness

Retinal and choroidal images were captured using the DRI Triton—Swept Source (SS) OCT (Topcon Co., Tokyo, Japan), focusing on the right eye without using pupil dilation. The DRI Triton SS-OCT automatically measures the thickness of retinal and choroidal layers, producing a detailed map. Additionally, the integrated non-mydriatic color fundus camera allowed simultaneous acquisition of fundus photographs during the OCT scan. The CSI protocol, which measures CT from Bruch's membrane to the choroid-scleral interface (CSI) with a focus on this latter boundary, was used. The SMART TRACK feature was enabled to minimize motion artifacts, and the follow-up and enhanced depth imaging (EDI) modes were deactivated. An optometrist trained in OCT image interpretation evaluated the quality of the images, and only those rated with good or very good quality (scores 3 or 4) were included in the analysis. The optometrist did not perform fundoscopy but thoroughly recorded the ophthalmic history of each participant. Any abnormal OCT images were reviewed by an ophthalmologist, and patients with suspected retinal pathologies

were referred for further examination. Both the ophthalmologist and neurologist were blinded to diagnoses.

For data analysis, the TRITON DRI-OCT software (Capture Software v.1.1.4.45475, Analysis Software v.10.1.3.43469) was used. The software's automatic segmentation method calculated CT in the 9 ETDRS quadrants, centered on the fovea (Fig. 1). The subfoveal choroidal thickness (SFCT), which refers to the thickness of the choroid directly beneath the fovea and is typically measured at the thinnest point of the retina using OCT, was used as the central reference point for aligning the grid. CT was measured within a 1 mm central radius (Center) and two concentric circles representing the Inner ring (3 mm) and Outer ring (6 mm), covering a 6×6 mm area. Measurements were classified into Nasal (N), Temporal (T), Inferior (I), and Superior (S), and further divided into Inner (In) and Outer (Out) regions, resulting in 12 total measurements, including the average thickness, total volume, and SFCT. Average thickness refers to the average CT measured across the entire region of interest, calculated from multiple points within the ETDRS grid, which is divided into nine subfields covering the inner and outer rings. The average thickness reflects the mean choroidal thickness across all these regions [54]. Total volume represents the cumulative choroidal volume across the ETDRS grid, derived from

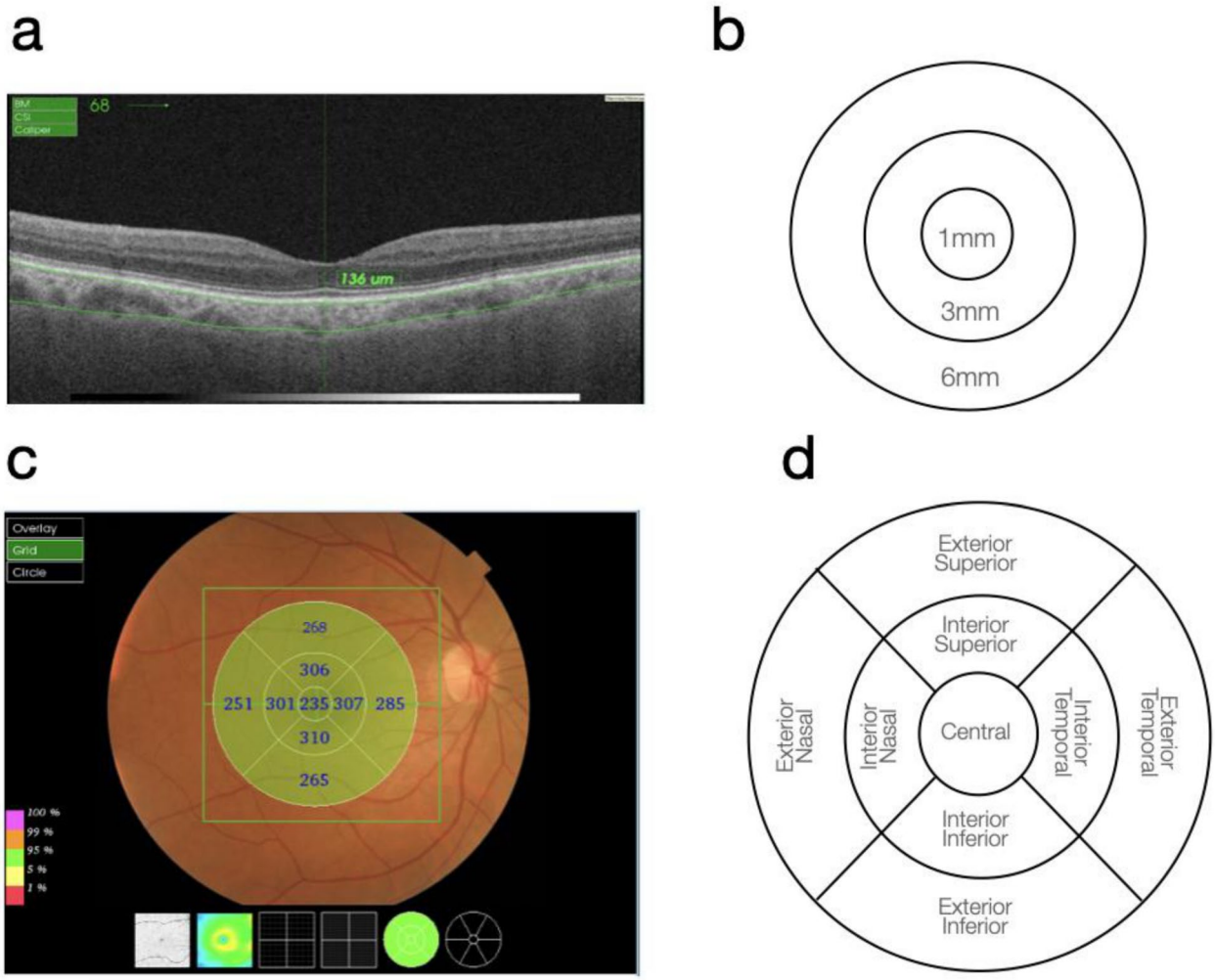

Fig. 1 OCT imaging protocol. **a** Limits of automated CT measurements focused on SFCT, which refers to the thickness of the choroid directly beneath the fovea. The measurement of SFCT is obtained from Bruch's membrane (upper boundary) to the choroid-scleral interface (CSI) (lower boundary). **b** The 3 measurement radii are shown: a 1 mm radius corresponding to the central region, a 3 mm radius corresponding to the inner measurements, and a 6 mm radius corresponding to the outer measurements. **c** The ETDRS grid in the macular region of the right eye represents the 9 ETDRS quadrants with the respective CT measurements. The scan range is 6×6 mm. **d** along with the assigned names and their respective ETDRS quadrants. Abbreviations: CT = choroidal thickness; CSI = choroid-scleral interface; ETDRS = Early Treatment Diabetic Retinopathy Study quadrants; OCT = optical coherence tomography; SFCT = subfoveal choroidal thickness

the average thickness and the area being analyzed. This volume measurement provides a global assessment of choroidal structure and is calculated for the full 6×6 mm area of the ETDRS grid [54]. Additionally, the numeric parameter "OCT image quality" was obtained from the software and used as a covariate in the analysis.

Manual CT measurements

From an initial sample of 1280 individuals, 140 manual measurements from the right eye were randomly selected using specialized software. The CT measurement technique used was based on Trebbastoni et al. [55], employing the "caliper tool" of the Triton-OCT software. Unlike Trebbastoni et al., we performed five measurements in the subfoveal area, 500 µm, and 1500 µm in the superior and inferior zones, omitting nasal and temporal measurements (Fig. 2). This modification aimed to better assess the correlation between manual and automated measurements by evaluating more individuals with fewer measurement points. The choroid was defined as the layer between the base of the retinal pigment epithelium and the hyperreflective boundary corresponding to the CSI. Measurements were taken at five specific points: the subfoveal choroid, and at 500 µm (±10 µm) and 1500 µm (±10 µm) along the vertical axis, in the superior and inferior zones. Manual measurements by a single blinded examiner were compared with the CSI protocol automatic tool of the OCT DRI-OCT software (Topcon Co., Tokyo, Japan).

Statistical analysis

Data processing and analysis were performed using R software version 4.1.2 [56]. Normality, skewness, and range restriction were evaluated, confirming that all quantitative variables followed an approximately normal distribution.

Demographic (age, sex, education), clinical (hypertension, diabetes mellitus, dyslipidemia, heart disease, COPD, stroke, smoking), and OCT image quality variables were described using frequency analyses, measures of central tendency, and dispersion across the five diagnostic groups (CU, MCI-AD, MCI-Va, ADD, and VaD). Bivariate analyses (ANOVA) and Pearson's Chi-square

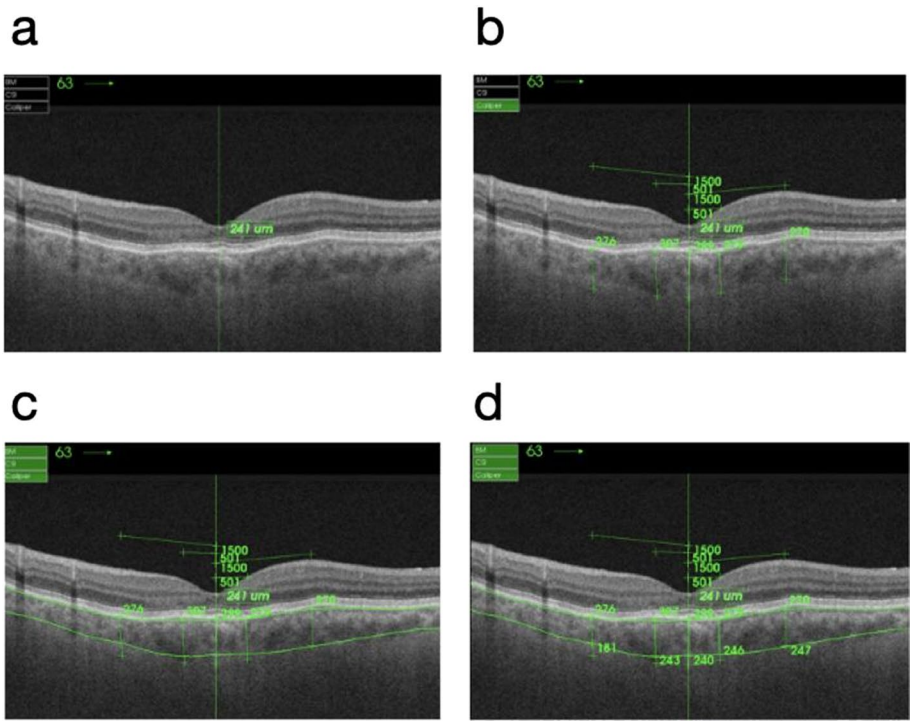

Fig. 2 Protocol for comparison of manual and automated CT measurements. **a** SFCT, which represents the thickness of the choroid directly beneath the fovea, was the first measurement performed. **b** Four additional CT measurement points were performed: two at 500 µm (Superior and Inferior) and two at 1500 µm (Superior and Inferior). These are measured manually using the "caliper tool," visible at the top of the image. **c** Activation of the automated measurement software on the Triton DRI-OCT, using the CSI protocol, which measures CT from Bruch's membrane (upper boundary) to the choroid-scleral interface (CSI) (lower boundary) highlighting its defined boundaries. **d** Use of the "caliper tool" to perform automated measurements, facilitating comparison between manual and automated methods, detailed at the bottom of the image. Abbreviations: CT = choroidal thickness; CSI = choroid-scleral interface; DRI-OCT = Deep Range Image Optical Coherence Tomography; SFCT = subfoveal choroidal thickness

tests were employed to characterize the distribution of these variables among the groups.

Three multinomial regression analyses were conducted to identify adjustment variables for the final multivariate model. The first examined demographic factors (age, sex, education); the second, clinical factors (hypertension, diabetes mellitus, dyslipidemia, heart disease, COPD, stroke, smoking); and the third, OCT image quality. The CU group served as the reference category in each of the analyses, and the significance level was set at 0.05.

The main analysis consisted of twelve multivariate regression analyses, one for each CT measure: subfoveal choroidal thickness, average thickness, total volume, and the nine ETDRS regions (center, inner temporal, inner superior, inner nasal, inner inferior, outer temporal, outer superior, outer nasal, outer inferior). The five diagnostic groups (CU, MCI-AD, MCI-Va, ADD, VaD) were used as discriminant factors, with adjustment for those factors that showed any significant effect in the former multinomial regression analysis. The CU group was considered the reference category. The following data were reported: regression coefficients, representing the average change in the outcome variable for each unit change in the predictor variable, holding other predictors in the model constant; beta coefficients, indicating the degree of change in the outcome variable for each unit change in the predictor variable; t-values, used to determine if the beta coefficient differs significantly from zero; and significance, expressed as the *p*-value, which indicates the probability of obtaining the observed results. A Bonferroni correction was applied to account for multiple comparisons performed in the twelve measurements, setting a corrected alpha level of $p < 0.0042$ to consider results as significant.

To avoid collider bias, all regression analyses were repeated without including the CVRF variables as adjustments, due to their stronger association with cognitive impairment in the MCI-Va and VaD groups.

A sensitivity analysis was conducted to assess the influence of extreme cases (defined as CT values ± 3 standard deviations from the mean) in the twelve multivariate regressions, using the CU group as the reference.

To examine the potential differential effects of sex in the relationship between CT and cognitive diagnosis, the twelve regressions were repeated considering the "diagnostic group x sex" interaction as the main factor.

Partial correlations between MMSE scores and each of the twelve CT measurements were also performed, adjusting for the same covariates, both in the total sample and by diagnostic group.

To assess the association between manual and automated CT measurements, the intraclass correlation coefficient (ICC) was calculated using a two-way mixed-effects model, where a single evaluator rated each target. This model estimates the ICC and its 95% confidence intervals using a single rating and consistency [57, 58]. The model was chosen because it is suited for studies where the selected raters are the only ones of interest. However, the results are specific to the raters involved and cannot be generalized to others, even with similar characteristics. ICC values below 0.5 indicate poor reliability, between 0.5 and 0.75 indicate moderate reliability, between 0.75 and 0.90 suggest good reliability, and values above 0.90 are considered excellent. These thresholds provide a framework for interpreting the level of agreement between manual and automated CT measurements based on the ICC value obtained.

Results

Demographic and Clinical Characteristics of the Cohort

Initially, 3,977 cases from Ace with available clinical information and OCT measurements were reviewed. A total of 2,134 patients were excluded for not meeting neurological and general inclusion criteria (62 were outside the age range, 61 lacked a clinical diagnosis, 1,102 had a diagnosis of MCI of non-AD or non-Va etiologies, and 629 had non-AD/VaD dementias). For patients with multiple OCT scans, one measurement was selected, removing 280 repeated scans. Of the remaining 1,843 patients, 563 were excluded due to ophthalmological criteria: 87 had glaucoma, 42 had age-related macular degeneration (AMD), 39 had amblyopia, 46 had intraocular pressure > 24mmHg, 27 had a history of retinal surgery, 37 had OCT artifacts, 106 for other reasons (including non-glaucomatous optic neuropathy, such as ischemic optic neuropathy or optic neuritis; high myopia (< -6D) or high hyperopia (> + 6D); inability to complete the ophthalmological exam due to poor cooperation or cognitive impairment), and 179 had no right eye CT measurements (see Fig. 3 for selection algorithm flowchart).

The final sample included 1,280 patients categorized as follows: 301 cognitively unimpaired (CU) individuals, 196 with MCI-AD, 112 with MCI-Va, 578 with ADD, and 93 with VaD (see Table 1 for cohort demographics and medical history).

Multinomial regression analysis of demographic, clinical, and OCT image quality variables across diagnostic groups

The first multinomial regression analysis, exploring age, sex, and education across diagnostic groups, revealed that all demographic variables had a significant effect, except for sex in the comparison between CU and ADD. Therefore, these three variables were included as adjustment factors in the final analysis (Additional file 1).

The second multinomial regression analysis, assessing cardiovascular risk factors (CVRFs) among diagnostic

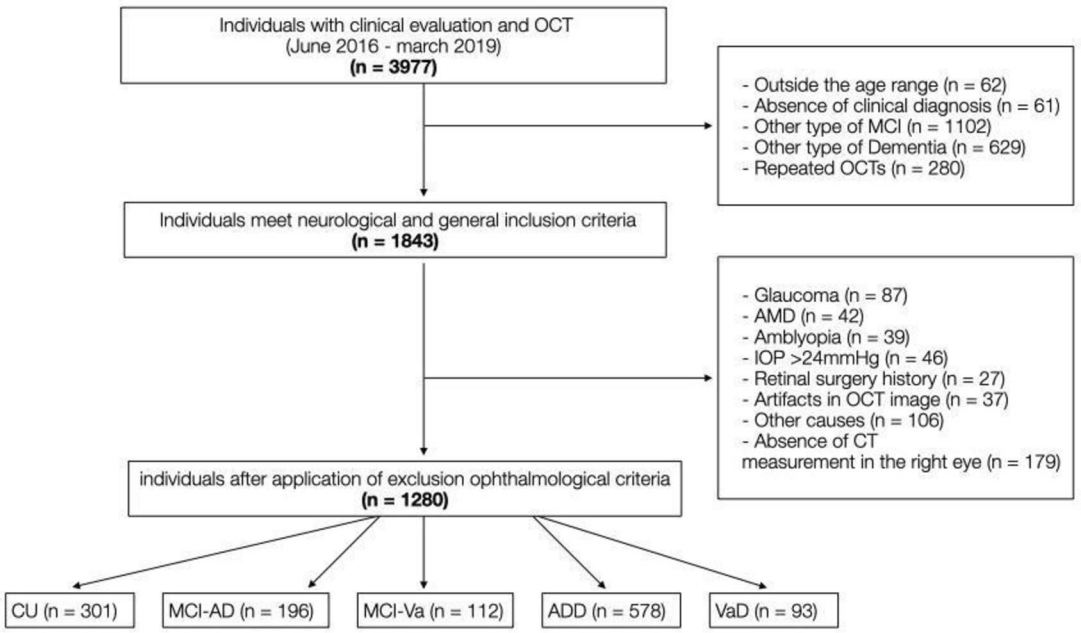

Fig. 3 Selection algorithm flowchart. Abbreviations: ADD = Alzheimer´s disease dementia; AMD = age-related macular degeneration; CT = choroidal thickness; CU = cognitively unimpaired; CV = cerebrovascular; IOP = intraocular pressure; MCI-AD = mild cognitive impairment due to Alzheimer´s disease; MCI-Va = mild cognitive impairment due to CV pathology; MMSE = Mini Mental State Examination; VaD = vascular dementia

groups, showed that hypertension, diabetes mellitus, heart disease, stroke, smoking, and COPD significantly differed among diagnostic groups. Hypertension and heart disease were significant across all cognitive impairment groups compared to CU individuals, while dyslipidemia was not. Stroke was more prevalent in MCI-AD, MCI-Va, and VaD groups compared to CU individuals. MCI-Va and VaD groups exhibited a higher number of significant CVRFs differences (Additional file 2).

In the third analysis, OCT image quality showed significant differences across all diagnostic groups, leading to its inclusion as an adjustment factor in the final analysis (Additional file 3).

Multivariate regression analysis of CT differences among diagnostic groups

Results of the multivariate regression analysis have been separated into two tables: Table 2 depicts the contribution of diagnosis to the variance in CT measurements, while Additional file 4 shows the contributions of each adjusting factor (sex, age, education, hypertension, diabetes mellitus, heart disease, COPD, stroke, smoking and OCT image quality) to the variance in CT measurements.

Regression analysis showed that, regarding the adjusting factors included in the model (Additional file 4), female sex had a positive effect (increased CT) only in the Out Temporal region ($p = 0.008$), but this association became non-significant after the Bonferroni correction. Age had a statistically significant negative relationship with CT in all regions ($p < 0.001$*, coefficients ranging from -4.40 to -0.11), indicating that as age increases, CT decreases across all areas. Presence of diabetes mellitus was also associated with decreased CT in the In Superior ($p = 0.040$), Out Temporal ($p = 0.016$), Out Superior ($p = 0.025$), Out Nasal ($p = 0.047$), average thickness ($p = 0.045$), and total volume ($p = 0.042$) (coefficients ranging from -12.52 to -0.28), but these associations became not significant after the Bonferroni correction. Better OCT image quality was associated to lower CT in several regions, including Center ($p = 0.045$), In Temporal ($p = 0.029$), In Nasal ($p = 0.010$), In Inferior ($p = 0.021$), and Out Temporal ($p = 0.014$), as well as average thickness ($p = 0.033$), Subfoveal choroidal thickness ($p = 0.043$), and total volume ($p = 0.024$) (coefficients ranging from -0.65 to -0.01), but again these associations became non-significant after the Bonferroni correction. Hypertension, heart disease, COPD, stroke, and smoking did not significantly affect CT measurements.

Regression analysis revealed a significant effect of diagnosis on adjusted CT measures. Overall, CT was significantly increased in all groups with cognitive impairment compared to CU individuals (Table 2 and Fig. 4), particularly in patients with CV disease. In the VaD group, CT measurements were significantly higher in the following regions: In Temporal ($p = 0.003$*), In Nasal ($p \leq 0.001$*), In Inferior ($p \leq 0.001$*), Out

Table 1 Demographic and clinical characteristics of the cohort

	Diagnostic group	Mean	SD	Intergroup significance
Age (years)	CU (*n* = 301)	66.56	7.37	< 0.001[a]
	MCI-AD (*n* = 196)	75.88	6.85	
	MCI-Va (*n* = 112)	77.06	7.57	
	ADD (*n* = 578)	81.13	6.82	
	VaD (*n* = 93)	82.01	6.45	
	Total (*n* = 1280)	76.61	9.17	
Sex (n, % women)	CU (*n* = 301)	193, 64.12%	n/a	< 0.001[b]
	MCI-AD (*n* = 196)	99, 50.51%	n/a	
	MCI-Va (*n* = 112)	56, 50.00%	n/a	
	ADD (*n* = 578)	417, 72.15%	n/a	
	VaD (*n* = 93)	52, 55.91%	n/a	
	Total (*n* = 1280)	817, 63.83%	n/a	
Education (years)	CU (*n* = 301)	12.29	4.53	< 0.001[a]
	MCI-AD (*n* = 196)	8.29	4.26	
	MCI-Va (*n* = 112)	7.04	3.94	
	ADD (*n* = 578)	6.16	4.05	
	VaD (*n* = 93)	6.46	4.37	
	Total (*n* = 1280)	8.03	4.88	
MMSE (score)	CU (*n* = 301)	29.31	0.91	< 0.001[a]
	MCI-AD (*n* = 196)	24.63	3.54	
	MCI-Va (*n* = 112)	26.22	2.58	
	ADD (*n* = 578)	18.78	4.43	
	VaD (*n* = 93)	21.54	4.25	
	Total (*n* = 1280)	23.01	5.63	
Hypertension	CU (*n* = 301)	102, 33.89%	n/a	< 0.001[b]
	MCI-AD (*n* = 196)	94, 47.96%	n/a	
	MCI-Va (*n* = 112)	82, 73.21%	n/a	
	ADD (*n* = 578)	377, 65.22%	n/a	
	VaD (*n* = 93)	73, 78.49%	n/a	
	Total (*n* = 1280)	728, 56.88%	n/a	
Diabetes mellitus	CU (*n* = 301)	22, 7.31%	n/a	< 0.001[b]
	MCI-AD (*n* = 196)	26, 13.27%	n/a	
	MCI-Va (*n* = 112)	30, 26.79%	n/a	
	ADD (*n* = 578)	92, 15.92%	n/a	
	VaD (*n* = 93)	32, 34.41%	n/a	
	Total (*n* = 1280)	202, 15.78%	n/a	
Dyslipidemia	CU (*n* = 301)	132, 43.85%	n/a	0.047[b]
	MCI-AD (*n* = 196)	85, 43.37%	n/a	
	MCI-Va (*n* = 112)	62, 55.36%	n/a	
	ADD (*n* = 578)	286, 49.48%	n/a	
	VaD (*n* = 93)	53, 56.99%	n/a	
	Total (*n* = 1280)	618, 48.28%	n/a	
Heart disease	CU (*n* = 301)	23, 7.64%	n/a	< 0.001[b]
	MCI-AD (*n* = 196)	40, 20.41%	n/a	
	MCI-Va (*n* = 112)	45, 40.18%	n/a	
	ADD (*n* = 578)	146, 25.26%	n/a	
	VaD (*n* = 93)	38, 40.86%	n/a	
	Total (*n* = 1280)	292, 22.81%	n/a	
COPD	CU (*n* = 301)	15, 4.98%	n/a	< 0.001[b]
	MCI-AD (*n* = 196)	19, 9.69%	n/a	
	MCI-Va (*n* = 112)	26, 23.21%	n/a	
	ADD (*n* = 578)	54, 9.34%	n/a	
	VaD (*n* = 93)	20, 21.51%	n/a	
	Total (*n* = 1280)	134, 10.47%	n/a	
Stroke	CU (*n* = 301)	7, 2.33%	n/a	< 0.001[b]
	MCI-AD (*n* = 196)	13, 6.63%	n/a	
	MCI-Va (*n* = 112)	31, 27.68%	n/a	
	ADD (*n* = 578)	38, 6.57%	n/a	
	VaD (*n* = 93)	35, 37.63%	n/a	
	Total (*n* = 1280)	124, 9.69%	n/a	
Smoking	CU (*n* = 301)	30, 9.97%	n/a	< 0.001[b]
	MCI-AD (*n* = 196)	3, 1.53%	n/a	
	MCI-Va (*n* = 112)	12, 10.71%	n/a	
	ADD (*n* = 578)	26, 4.50%	n/a	
	VaD (*n* = 93)	7, 7.53%	n/a	
	Total (*n* = 1280)	78, 6.09%	n/a	
OCT image quality	CU (*n* = 301)	66.32	6.57	< 0.001[a]
	MCI-AD (*n* = 196)	64.14	7.70	
	MCI-Va (*n* = 112)	63.25	8.51	
	ADD (*n* = 578)	61.50	9.62	
	VaD (*n* = 93)	63.80	8.66	
	Total (*n* = 1280)	63.36	8.74	

Demographic and medical conditions among groups are summarized

[a] 1-factor ANOVA [b]Pearson's Chi2 test. Significance was set up at $p < 0.05$

Abbreviations: *ADD* Alzheimer's disease dementia, *COPD* Chronic obstructive pulmonary disease, *CU* Cognitively unimpaired, *CV* Cerebrovascular, *MCI-AD* Mild cognitive impairment due to Alzheimer's disease, *MCI-Va* Mild cognitive impairment due to CV pathology, *MMSE* Mini Mental State Examination, *OCT* Optical coherence tomography, *SD* Standard deviation, *VaD* Vascular dementia

Temporal ($p = 0.003$*), Out Nasal ($p \leq 0.001$*), Out Inferior ($p \leq 0.001$*), Average thickness ($p \leq 0.001$*) and total volume ($p \leq 0.001$*) (coefficients ranging from 23.29 to 37.85). The MCI-Va group had significant CT increases compared to CU individuals in the following regions: Out Superior ($p = 0.003$*), Out Nasal ($p = 0.004$*), Out Inferior ($p = 0.003$*) and in average thickness ($p = 0.002$*) (coefficients ranging from 23.29 to 37.85). The MCI-AD group showed significant increases compared to CU individuals in the following regions: In Nasal ($p \leq 0.001$*), In Inferior ($p = 0.005$), Out Temporal ($p = 0.003$*), Out Nasal ($p \leq 0.001$*), Out Inferior ($p \leq 0.001$*), average thickness ($p \leq 0.001$*) and total volume ($p = 0.001$*) (coefficients ranging from 15.75 to 27.18). The ADD group

Table 2 Multivariate regression analysis of CT measurements by diagnostic group

Covariates	Dependent variables	Coefficient	t	Significance	Beta
Diagnostic groups: CU vs MCI-AD	Center	16.44	2.13	**0.034**	0.07
	In Temporal	20.05	2.81	**0.005**	0.09
	In Superior	17.88	2.40	**0.017**	0.08
	In Nasal	27.18	3.48	**0.001***	0.12
	In Inferior	20.75	2.83	**0.005**	0.09
	Out Temporal	19.63	2.97	**0.003***	0.10
	Out Superior	18.18	2.70	**0.007**	0.09
	Out Nasal	26.08	3.83	**< 0.001***	0.13
	Out Inferior	22.39	3.40	**0.001***	0.11
	Average thickness	21.54	3.44	**0.001***	0.11
	Subfoveal choroidal thickness	15.75	1.96	0.051	0.07
	Total volume	0.61	3.41	**0.001***	0.11
Diagnostic groups: CU vs MCI-Va	Center	17.69	1.85	0.065	0.06
	In Temporal	22.00	2.49	**0.013**	0.08
	In Superior	21.57	2.34	**0.020**	0.08
	In Nasal	24.92	2.57	**0.010**	0.08
	In Inferior	21.02	2.31	**0.021**	0.07
	Out Temporal	21.27	2.60	**0.009**	0.08
	Out Superior	24.94	2.99	**0.003***	0.09
	Out Nasal	24.40	2.90	**0.004***	0.09
	Out Inferior	24.69	3.03	**0.003***	0.10
	Average thickness	23.52	3.03	**0.002***	0.10
	Subfoveal choroidal thickness	17.85	1.79	0.074	0.06
	Total volume	0.66	3.00	**0.003***	0.09
Diagnostic groups: CU vs ADD	Center	9.75	1.32	0.187	0.06
	In Temporal	17.49	2.57	**0.010**	0.11
	In Superior	10.33	1.45	0.147	0.06
	In Nasal	15.32	2.05	**0.040**	0.09
	In Inferior	14.54	2.08	**0.038**	0.09
	Out Temporal	13.95	2.21	**0.027**	0.10
	Out Superior	9.99	1.55	0.121	0.07
	Out Nasal	15.60	2.40	**0.016**	0.11
	Out Inferior	19.27	3.06	**0.002***	0.13
	Average thickness	14.54	2.43	**0.015**	0.10
	Subfoveal choroidal thickness	9.92	1.29	0.197	0.06
	Total volume	0.41	2.42	**0.016**	0.10
Diagnostic groups: CU vs VaD	Center	27.79	2.57	**0.010**	0.09
	In Temporal	29.51	2.96	**0.003***	0.10
	In Superior	25.17	2.42	**0.016**	0.08
	In Nasal	37.85	3.47	**0.001***	0.12
	In Inferior	35.20	3.43	**0.001***	0.11
	Out Temporal	27.74	3.01	**0.003***	0.10
	Out Superior	23.29	2.47	**0.014**	0.08
	Out Nasal	37.17	3.91	**< 0.001***	0.13
	Out Inferior	35.43	3.85	**< 0.001***	0.13
	Average thickness	31.08	3.55	**< 0.001***	0.12
	Subfoveal choroidal thickness	28.13	2.50	**0.013**	0.08
	Total volume	0.88	3.55	**< 0.001***	0.12

Multivariate regression analysis showing the contribution of diagnosis (CU, MCI-AD, MCI-Va, ADD, and VaD) to variance in CT measurements. The analysis included the following adjusting factors: age, sex, years of education, hypertension, diabetes mellitus, heart disease, COPD, stroke, smoking, and OCT image quality (data showed in Additional file 4). In bold, $p < 0.05$. (*) Significance was corrected with Bonferroni for multiple comparisons ($p < 0.004$)

Table 2 (continued)

Abbreviations: *ADD* Alzheimer´s disease dementia, *CT* Choroidal thickness, *CU* Cognitively unimpaired, *CV* Cerebrovascular, *MCI-AD* Mild cognitive impairment due to Alzheimer´s disease, *MCI-Va* Mild cognitive impairment due to CV pathology, *VaD* Vascular dementia

Regions in the ETDRS grid are divided into "Inner" and "Outer" zones, with "Inner" representing CT measurements within a 3 mm radius and "Outer" representing CT measurements within a 6 mm radius, corresponding to specific areas used for CT measurements in the study. The abbreviations used in the table are as follows: In Temporal = Inner Temporal, In Superior = Inner Superior, In Nasal = Inner Nasal, In Inferior = Inner Inferior. Similarly, Out Temporal = Outer Temporal, Out Superior = Outer Superior, Out Nasal = Outer Nasal, and Out Inferior = Outer Inferior

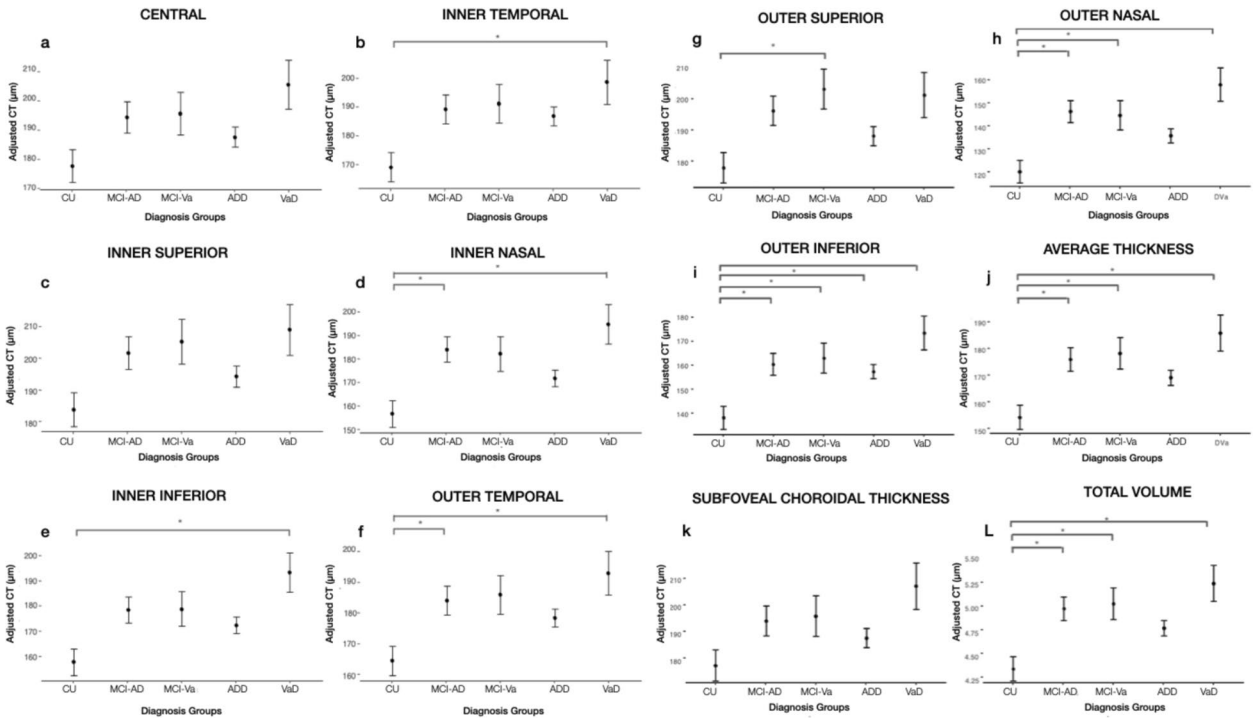

Fig. 4 Differences in CT between diagnostic groups. The Y-axis represents adjusted CT (µm), while the X-axis denotes diagnostic groups. The names of each ETDRS region are displayed at the top of each panel: **a** Central; **b** Inner Temporal; **c** Inner Superior; **d** Inner Nasal; **e** Inner Inferior; **f** Outer Temporal; **g** Outer Superior; **h** Outer Nasal; **i** Outer Inferior; **j** Average thickness; **k** Subfoveal choroidal thickness; **l** Total volume. (*) Significance was corrected with Bonferroni for multiple comparisons ($p < 0.004$). Abbreviations: ADD = Alzheimer´s disease dementia; CT = choroidal thickness; CU = cognitively unimpaired; CV = cerebrovascular; MCI-AD = mild cognitive impairment due to Alzheimer´s disease; MCI-Va = mild cognitive impairment due to CV pathology; VaD = vascular dementia

exhibited a smaller, non-significant increase in several CT measurements compared to CU individuals, including center ($p = 0.187$), In Superior ($p = 0.147$), Out Superior ($p = 0.121$), and Subfoveal choroidal thickness ($p = 0.197$) (coefficients ranging from 9.75 to 19.27). On the other hand, no statistically significant differences in CT were observed between any cognitive impairment group and CU individuals in the Center, Inner Superior, or Subfoveal choroidal thickness regions.

Regarding the number of regions with significant CT changes across diagnostic groups (Table 2 and Fig. 4), the VaD group showed the highest number of regions ($n = 8$) compared to CU individuals, followed by MCI-AD ($n = 6$), MCI-Va ($n = 5$), and ADD ($n = 1$).

Raw and adjusted CT measurements across diagnostic groups are displayed in Table 3.

Regression models excluding CVRFs as adjusting factors (Additional file 5) showed that, compared to the previous models including them (Additional file 4 and Table 2), the regression coefficients for adjusted CT differences between diagnostic groups were generally lower, especially between the VaD and CU groups. Moreover, the ADD and MCI-Va groups showed non-significant differences in CT measures compared to CU individuals without the CVRFs adjustment, but significant differences with it.

Additionally, a multivariate regression analysis was performed to compare CT measures between groups

Table 3 Raw and adjusted CT measurements differences across diagnostic groups

Group (n)	Mean	SD	Mean[aa]	SEM[aa]
Center				
CU (*n* = 301)	222.58	84.04	177.25	5.63
MCI-AD (*n* = 196)	196.52	78.01	193.69	5.45
MCI-Va (*n* = 112)	189.68	84.63	194.94	7.37
ADD (*n* = 578)	168.03	79.00	187.00	3.51
VaD (*n* = 93)	176.61	82.26	205.04	8.35
In Temporal				
CU (*n* = 301)	214.28	80.46	169.03	5.19
MCI-AD (*n* = 196)	191.38	68.00	189.08	5.02
MCI-Va (*n* = 112)	185.91	80.54	191.02	6.80
ADD (*n* = 578)	167.59	74.58	186.51	3.23
VaD (*n* = 93)	170.97	71.26	198.53	7.70
In Superior				
CU (*n* = 301)	228.44	78.72	184.09	5.42
MCI-AD (*n* = 196)	204.80	75.79	201.98	5.25
MCI-Va (*n* = 112)	199.94	79.06	205.67	7.10
ADD (*n* = 578)	176.12	78.81	194.42	3.38
VaD (*n* = 93)	180.41	77.03	209.27	8.04
In Nasal				
CU (*n* = 301)	202.75	83.72	156.91	5.69
MCI-AD (*n* = 196)	186.79	84.62	184.08	5.51
MCI-Va (*n* = 112)	175.98	78.14	181.83	7.45
ADD (*n* = 578)	153.26	79.02	172.23	3.54
VaD (*n* = 93)	165.60	88.73	194.76	8.44
In Inferior				
CU (*n* = 301)	205.74	81.29	157.96	5.34
MCI-AD (*n* = 196)	181.82	75.47	178.71	5.17
MCI-Va (*n* = 112)	173.94	83.35	178.98	6.99
ADD (*n* = 578)	152.10	74.46	172.50	3.33
VaD (*n* = 93)	164.76	80.76	193.15	7.92
Out Temporal				
CU (*n* = 301)	205.26	72.99	164.57	4.81
MCI-AD (*n* = 196)	185.64	64.57	184.21	4.65
MCI-Va (*n* = 112)	180.83	74.24	185.84	6.29
ADD (*n* = 578)	161.83	68.93	178.52	3.00
VaD (*n* = 93)	167.38	66.01	192.32	7.13
Out Superior				
CU (*n* = 301)	220.49	71.63	178.24	4.91
MCI-AD (*n* = 196)	199.18	67.16	196.42	4.75
MCI-Va (*n* = 112)	197.66	72.93	203.18	6.43
ADD (*n* = 578)	170.77	73.34	188.23	3.06
VaD (*n* = 93)	174.11	66.43	201.53	7.28
Out Nasal				
CU (*n* = 301)	160.35	75.39	120.99	4.95
MCI-AD (*n* = 196)	149.85	74.53	147.08	4.79
MCI-Va (*n* = 112)	141.16	70.36	145.39	6.48
ADD (*n* = 578)	119.88	67.00	136.59	3.09
VaD (*n* = 93)	133.88	74.12	158.16	7.34
Out Inferior				
CU (*n* = 301)	184.21	72.08	138.14	4.80
MCI-AD (*n* = 196)	163.63	70.09	160.53	4.64
MCI-Va (*n* = 112)	158.76	77.65	162.84	6.28
ADD (*n* = 578)	137.36	67.67	157.41	2.99
VaD (*n* = 93)	147.47	71.72	173.58	7.11
Average thicknesss				
CU (*n* = 301)	197.91	69.70	154.81	4.56
MCI-AD (*n* = 196)	178.92	65.18	176.35	4.41
MCI-Va (*n* = 112)	173.39	70.92	178.34	5.97
ADD (*n* = 578)	151.24	65.60	169.35	2.84
VaD (*n* = 93)	159.53	65.88	185.90	6.76
Subfoveal choroidal thickness				
CU (*n* = 301)	224.56	87.90	178.64	5.86
MCI-AD (*n* = 196)	197.20	80.67	194.38	5.68
MCI-Va (*n* = 112)	191.11	88.43	196.49	7.68
ADD (*n* = 578)	169.36	81.27	188.56	3.65
VaD (*n* = 93)	178.00	86.95	206.77	8.70
Total volume				
CU (*n* = 301)	5.60	1.97	4.38	0.13
MCI-AD (*n* = 196)	5.06	1.84	4.98	0.12
MCI-Va (*n* = 112)	4.90	2.01	5.04	0.17
ADD (*n* = 578)	4.28	1.86	4.79	0.08
VaD (*n* = 93)	4.51	1.86	5.26	0.19

Raw and adjusted CT, standard deviation (SD) and standard error of the mean (SEM) are shown. Dispersion is shown as SEM

[aa] = after adjustment for the following factors: age, sex, years of education, hypertension, diabetes mellitus, heart disease, COPD, stroke, smoking and OCT image quality, using multivariate regression analysis

Abbreviations: *ADD* Alzheimer's disease dementia, *CT* Choroidal thickness, *CU* Cognitively unimpaired, *CV* Cerebrovascular, *MCI-AD* Mild cognitive impairment due to Alzheimer´s disease, *MCI-Va* Mild cognitive impairment due to CV pathology, *SD* Standard deviation, *SEM* Standard error of the mean, *VaD* Vascular dementia

Regions in the ETDRS grid are divided into "Inner" and "Outer" zones, with "Inner" representing CT measurements within a 3 mm radius and "Outer" representing CT measurements within a 6 mm radius, corresponding to specific areas used for CT measurements in the study. The abbreviations used in the table are as follows: In Temporal = Inner Temporal, In Superior = Inner Superior, In Nasal = Inner Nasal, In Inferior = Inner Inferior. Similarly, Out Temporal = Outer Temporal, Out Superior = Outer Superior, Out Nasal = Outer Nasal, and Out Inferior = Outer Inferior

with cognitive impairment vs CU individuals excluding extreme cases or outliers (Additional file 6) and compared with the analyses including all cases (Additional file 4 and Table 2). The number of outliers detected and excluded varied across regions: Center (*n* = 2), In Temporal (*n* = 3), In Superior (*n* = 1), In Nasal (*n* = 2), In Inferior (*n* = 2), Out Temporal (*n* = 8), Out Nasal (*n* = 8), Out Superior (*n* = 1), and Out Inferior (*n* = 5). The exclusion of outlier cases did not have a significant effect on CT measures across diagnostic groups. Excluding outliers

though had a notable impact on certain adjusting variables, particularly diabetes mellitus and OCT image quality. In diabetes mellitus, the significance of the association with CT decreased after excluding outliers. For OCT image quality, the effect of excluding outliers was mixed, with significance decreasing in some regions and increasing in others. The association of other adjustment factors such as hypertension, age, education, heart disease, COPD, stroke, and smoking with CT measures remained unchanged after exclusion of outlier cases.

Effect of sex on CT measures across diagnostic groups

The interaction of sex and diagnosis overall had no effect in differentiating CT measures, adjusted for demographic factors, CVRFs, and OCT image quality (Additional file 7). Although statistically significant differences were observed in specific regions when comparing the CU with the MCI-AD group, these differences were not consistent across other groups, suggesting that sex does not substantially affect CT variability among diagnostic groups.

Association of CT measures with MMSE scores

No significant correlations were found between Mini-Mental State Examination (MMSE) scores and any of the 12 CT measurements, either across the entire sample or within diagnostic groups. Correlation coefficients (r) were below 0.17, and *p*-values exceeded 0.07 (Table 4).

Reliability between manual and automated CT Measurements

Five manual CT measurements were performed in selected ETDRS regions (subfoveal, inner superior, inner inferior, outer superior, and outer inferior) on 140 randomly selected cases from the initial sample of 1,280 participants. Comparing the manual measurements with the automated OCT measurements, the intraclass correlation coefficient (ICC) values ranged from 0.76 to 0.79 (Additional file 8), indicating good reliability ($p < 0.001$) [57]. The 95% confidence interval ranged from 0.67 to 0.84. Based on these results, the reliability of manual CT measurements is considered moderate to good. The "Bland–Altman plot of manual and automated measurements" (Additional file 9) visually depicts the agreement between the two methods.

Discussion

This study evaluated CT changes quantified by OCT in a large cohort from the NORFACE study including 1280 individuals with varying degrees of cognitive impairment (CU, MCI-AD, MCI-Va, AD, and VaD) assessed in a memory clinic. Our results showed a significant increase in CT, adjusted by demographic and CVRFs and OCT image quality, particularly in the peripheral macular regions (nasal, inferior and temporal quadrants) and in the groups with CV cognitive impairment (VaD and MCI-Va) compared to CU individuals. While MCI-AD and ADD also exhibited significant CT increases in some regions, these were minimal compared to the more pronounced changes in MCI-Va and VaD, highlighting the greater retinal vascular involvement in CV disease. Our results suggest that CT may differentiate between AD and CV-related pathogenic pathways in the late stages of cognitive decline.

In recent decades, there has been growing interest in identifying biomarkers for the early diagnosis of AD and VaD [11–13]. Many studies have highlighted that modifying CVRFs and engaging in early cognitive stimulation are among the most important strategies for prevention and slowing disease progression [22]. To further investigate retinal biomarkers, the NORFACE project was launched in 2014 at Ace Alzheimer Center Barcelona [14]. This study focuses on using OCT to explore structural and vascular changes in the retina, aiming to better understand the underlying pathophysiology of AD and CV diseases.

Several studies from the NORFACE cohort have explored several ocular structures in individuals with different degrees of cognitive decline. For example, Sánchez et al. [14, 18] detected no significant differences in retinal nerve fiber layer (RNFL) and macular thickness in a large cohort of cognitively unimpaired individuals and patients with MCI and ADD. Marquié et al. [28] examined associations between retinal thickness and cerebral β-amyloid (Aβ) accumulation in individuals with SCD, showing nasal macular thickening in early AD stages that did not correlate to future conversion to MCI. Regarding the retinal vascular component, measures of macular vessel density (VD) have also been explored in NORFACE. Marquié et al. [29] showed that the MCI-AD and MCI-Va groups had significant differences in opposite directions in macular VD compared to CU individuals, suggesting that this biomarker could differentiate two pathogenic pathways. Marquié et al. [59] highlighted that macular VD was not associated to the AT(N) classification measured by CSF in patients with MCI, and neither showed a correlation with CSF measures of Aβ and tau. García-Sánchez et al. [30] revealed that macular VD was not associated with CV pathology assessed by brain MRI in non-demented individuals. Despite the promise shown in these studies, results were variable, and no definitive conclusions were drawn regarding retinal microvascular structures as robust biomarkers for AD or VaD.

Given the inconclusive results of previous works centered on retinal structural measures and macular VD, our present NORFACE study focused on CT, a key ocular

Table 4 Partial correlation of CT measured with MMSE scores

Diagnostic groups	Variable	R	Significance
Whole sample (n = 1280)	Center	0.04	0.184
	In Temporal	0.03	0.310
	In Superior	0.03	0.375
	In Nasal	0.03	0.318
	In Inferior	0.03	0.254
	Out Temporal	0.03	0.299
	Out Superior	0.03	0.277
	Out Nasal	0.03	0.294
	Out Inferior	0.03	0.315
	Average thickness	-0.04	0.209
	Subfoveal choroidal thickness	-0.02	0.575
	Total volume	-0.03	0.339
CU (n = 301)	Center	0.02	0.764
	In Temporal	0.02	0.699
	In Superior	0.02	0.741
	In Nasal	0.03	0.665
	In Inferior	0.01	0.806
	Out Temporal	0.02	0.712
	Out Superior	0.02	0.714
	Out Nasal	0.02	0.743
	Out Inferior	0.02	0.712
	Average thickness	-0.01	0.928
	Subfoveal choroidal thickness	-0.01	0.918
	Total volume	-0.03	0.584
MCI-AD (n = 196)	Center	-0.07	0.365
	In Temporal	0.01	0.978
	In Superior	0.01	0.889
	In Nasal	-0.01	0.947
	In Inferior	0.04	0.624
	Out Temporal	0.01	0.988
	Out Superior	0.01	1.000
	Out Nasal	0.01	0.972
	Out Inferior	-0.01	0.971
	Average thickness	0.12	0.126
	Subfoveal choroidal thickness	0.10	0.208
	Total volume	-0.04	0.625
MCI-Va (n = 112)	Center	-0.02	0.846
	In Temporal	-0.02	0.886
	In Superior	-0.01	0.982
	In Nasal	-0.02	0.856
	In Inferior	-0.02	0.863
	Out Temporal	-0.02	0.849
	Out Superior	-0.02	0.868
	Out Nasal	-0.02	0.874
	Out Inferior	-0.02	0.859
	Average thickness	0.17	0.105
	Subfoveal choroidal thickness	0.01	0.921
	Total volume	-0.02	0.830

Table 4 (continued)

Diagnostic groups	Variable	R	Significance
ADD (n = 578)	Center	0.03	0.531
	In Temporal	0.03	0.496
	In Superior	0.02	0.646
	In Nasal	0.02	0.570
	In Inferior	0.01	0.778
	Out Temporal	0.02	0.646
	Out Superior	0.02	0.638
	Out Nasal	0.02	0.623
	Out Inferior	0.02	0.610
	Average thickness	-0.08	0.077
	Subfoveal choroidal thickness	-0.01	0.863
	Total volume	-0.02	0.692
VaD (n = 93)	Center	0.04	0.768
	In Temporal	0.01	0.921
	In Superior	-0.01	0.960
	In Nasal	0.01	0.929
	In Inferior	0.01	0.999
	Out Temporal	0.01	0.945
	Out Superior	0.01	0.906
	Out Nasal	0.01	0.931
	Out Inferior	0.01	0.929
	Average thickness	-0.01	0.948
	Subfoveal choroidal thickness	-0.03	0.809
	Total volume	-0.01	0.949

The model included the following adjusting factors: age, sex, years of education, hypertension, diabetes mellitus, heart disease, COPD, stroke, smoking and image quality. Significance was set up at $p < 0.05$

Abbreviations: *ADD* Alzheimer´s disease dementia, *CT* Choroidal thickness, *CU* Cognitively unimpaired, *CV* Cerebrovascular, *MCI-AD* Mild cognitive impairment due to Alzheimer´s disease, *MCI-Va* Mild cognitive impairment due to CV pathology, *OCT* Optical coherence tomography, *VaD* Vascular dementia

Regions in the ETDRS grid are divided into "Inner" and "Outer" zones, with "Inner" representing CT measurements within a 3 mm radius and "Outer" representing CT measurements within a 6 mm radius, corresponding to specific areas used for CT measurements in the study. The abbreviations used in the table are as follows: In Temporal = Inner Temporal, In Superior = Inner Superior, In Nasal = Inner Nasal, In Inferior = Inner Inferior. Similarly, Out Temporal = Outer Temporal, Out Superior = Outer Superior, Out Nasal = Outer Nasal, and Out Inferior = Outer Inferior

vascular component, as the primary variable. OCT technology with automated software was employed to provide a non-invasive, accessible, and reproducible method for quantifying CT across the 9 ETDRS quadrants. The study aimed to capture comprehensive measurements of average thickness, subfoveal choroidal thickness, and total volume in a well-defined and large cohort of individuals with CU, MCI-AD, MCI-Va, AD, and VaD, reflecting the continuum of cognitive impairment and its primary underlying causes. The primary finding of this study was a significant increase in CT in patients with cognitive impairment compared to CU individuals, especially in peripheral ETDRS regions, after adjusting for demographic factors, CVRFs and OCT image quality. This increase was more pronounced in patients with CV cognitive impairment (especially in the VaD stage), particularly in the external inferior, external nasal, external temporal, and internal nasal regions.

In contrast to our results, several prior studies have reported decreased CT evaluated by OCT in patients with cognitive impairment. Cunha et al. [27] conducted a study with a sample of 252 individuals, comparing CT in patients with MCI-AD *vs* CU individuals, and observed reductions in CT across 13 locations, notably in the fovea and temporal regions. Similarly, Trebbastoni et al. [55] analyzed 78 participants (39 with MCI-AD and 39 CU) and found significant CT reductions in the subfoveal region in those with MCI-AD after a 12-month follow-up.

Gharbiya et al. [60], with a sample of 42 individuals (21 AD and 21 CU), reported decreased CT in all macular regions except the most peripheral temporal region. Mo Li et al. [26] studied 37 AD patients and 34 CU individuals, finding that the choroid was significantly thinner in AD patients, with the subfoveal region identified as a strong predictor of the disease. Likewise, Salobrar-Garcia et al. [61] evaluated 32 patients with MCI-AD disease and 15 CU, concluding that choroidal thinning could serve as an early biomarker for AD. López-de-Eguileta et al. [62] also supported this, analyzing CT in 34 AD patients and CU individuals, with findings indicating decreased CT in the former in specific areas such as the fovea and temporal regions. However, our findings align more closely with those of Asanad et al. [23, 24], who utilized post-mortem histopathological evidence from 19 individuals (11 CU and 8 with AD) and demonstrated thickening in macular, temporal, and choroidal regions in those with AD. Our study expands these findings, showing a more pronounced increase in CT in the peripheral ETDRS regions in patients with MCI-AD, MCI-Va, and VaD compared to CU individuals, emphasizing a divergence from the previously established notion of choroidal thinning in cognitive impairment.

Importantly, our study highlights the peripheral areas of the ETDRS grid as key regions of choroidal thickening, extending the analysis to a radius of 6 mm at the limit of the outer ring. This may account for discrepancies with previous publications that primarily focused on the central regions within the 1 mm ring or up to a maximum of 1.5 mm [55, 61, 62], or up to the inner ring defined by a radius of 3 mm [26, 63]. To the best of our knowledge, no studies have addressed CT measures in the outer ring of the ETDRS in cognitive decline. Notably, our data showed no significant differences in central macular regions among patients with cognitive decline and CU individuals, indicating these areas may not be as sensitive to cognitive impairment-related retinal alterations.

The role of CVRFs in our study was significant. The presence of hypertension and diabetes mellitus was associated with lower CT in several regions, consistent with their known impact on vascular health, while dyslipidemia showed no significant effect. Importantly, our study included multiple CVRFs as adjustment factors, whereas many other studies have excluded patients with CVRFs from analysis or have not included them in the models, potentially overlooking their influence on CT measures [25, 26, 60, 62]. The results of the analysis excluding CVRFs as adjusting variables also supported their important role.

OCT image quality also significantly affected CT measures, reinforcing the importance of controlling for this variable in future research. Additionally, the comparison between automated and manual CT measurements demonstrated good reliability, with an ICC between 0.75 and 0.79, supporting the use of automated OCT measurements in clinical practice and research.

Several methodological differences could explain the discrepancies of our study with previous OCT literature, including our larger sample size ($n=1280$), the inclusion of peripheral measurements up to 6000 µm (outer ring), and adjustments for demographic and cardiovascular factors and OCT image quality. Additionally, our use of automated measurements, compared to manual ones, likely enhances reproducibility and accuracy, particularly in peripheral regions. Moreover, by using automated measurements without the enhanced depth imaging (EDI) mode, which can obscure choroidal boundaries, we were able to obtain more reliable readings [25, 64]. This methodological difference likely contributed to our findings of increased CT in patients with cognitive decline, as compared to studies that reported thinning, highlighting the importance of measurement techniques in interpreting results.

Despite significant increases in CT across diagnostic groups, we found no correlation between CT measurements and MMSE scores in the whole cohort or in each diagnostic group separately. To the best of our knowledge, no previous literature has assessed this potential association. This suggests that while CT may serve as a biomarker for distinguishing between types of cognitive impairment, it may not reflect cognitive performance directly.

Our results provide insights into the differing choroidal microvascular changes between AD and CV diseases. In our study we detected increased CT in the early stages of both pathologies (MCI-AD and MCI-Va) with further thickening only in VaD (but no in ADD), suggesting distinct progression patterns in their angiopathy components. Early compensatory vasculogenesis, driven by ischemia and oxidative stress, may explain the initial CT thickening observed in the MCI stage. In AD, however, beta-amyloid deposition triggers an inflammatory cascade that deteriorates the vascular structure [65, 66], potentially disrupting this compensation mechanism and leading to plateauing or thinning of CT in advanced stages (ADD). In contrast, the persisting vascular alterations in CV disease may sustain CT thickening throughout disease progression (VaD stage). The significant increase in CT observed in MCI-Va and VaD, compared to the minimal changes in MCI-AD and the plateauing in ADD, further supports this differentiation in pathogenic pathways, reflecting the potentially distinct impacts of amyloid pathology and vascular angiopathy on the retina and choroid [67].

This study has several strengths. First, the sample size ($n=1,280$) is the largest to date in studies of CT, derived from an initial cohort of 3,977 individuals. All participants were evaluated using the NBACE neuropsychological battery, ensuring comprehensive cognitive assessment. Moreover, the inclusion of two groups with vascular cognitive impairment (MCI-Va and VaD) adds a novel element, as these are often omitted in similar studies focused mostly on AD. Additionally, the study accounted for various CVRFs as adjustment factors in the analyses, enhancing the robustness of the findings. Another strength is the consistency of the methodology, with measurements limited to the right eye and a single blinded examiner using automated OCT measurements. This ensured data reliability and allowed exploration of peripheral areas in the ETDRS grid, which are often underexplored.

We acknowledge that our study also presents several limitations. First, the diagnosis of cognitive impairment was based on clinical criteria, without the use of AD-specific biomarkers, which may have reduced etiological precision, particularly in the MCI-AD group. Thus, given the lack of AD biomarkers and detailed MRI measures of cerebrovascular pathology in most of the sample, we acknowledge that the accurate assessment of the underlying neuropathological changes related to the clinical diagnosis in this cohort is limited, and our results need validation in future studies. Second, the sample size reduction from 3,977 to 1,280 participants, and particularly in the VaD group, may limit generalizability. Third, the cross-sectional design does not allow for the observation of temporal changes in CT, which would be crucial for understanding disease progression. Additionally, we did not track the cardiovascular medication use of participants, which may have influenced CT measurements, thus future studies should include this variable to better understand its impact. Furthermore, although we excluded patients with extreme refractive errors (+6 and -6 diopters) to reduce the impact of axial length on CT measurements, the absence of a biometer to directly measure axial length is a limitation. Axial length is a key factor influencing CT, and future studies should incorporate this measurement to improve precision and reduce variability [52, 53].

In summary, our study detected significant increases in CT in the MCI-Va and VaD groups compared to CU individuals, suggesting that CT assessed by OCT may help in understanding vascular contributions to cognitive impairment. Additionally, we detected no clear correlation between CT measures and cognitive scores, indicating that CT changes likely reflect underlying vascular physiopathology rather than cognitive decline. The inclusion of CVRFs and the use of automated OCT measurements in peripheral regions likely enhanced the accuracy of our findings. Future longitudinal studies of CT in cognitive decline incorporating additional biomarkers such as brain magnetic resonance imaging, cerebrospinal fluid and plasma p-tau and amyloid will be essential to validate these findings and clarify CT measurements' utility in clinical practice. The relationship between vascular changes in the eye and the brain could offer new research avenues, not only for dementia but also for cardiovascular diseases.

Abbreviations

Aβ	β-Amyloid
Ace	Ace Alzheimer Center Barcelona
AD	Alzheimer's disease
ADD	Alzheimer's disease dementia
AMD	Age-related macular degeneration
COPD	Chronic obstructive pulmonary disease
CSI	Choroid-scleral interface
CT	Choroidal thickness
CU	Cognitively unimpaired
CV	Cerebrovascular
CVRF	Cardiovascular risk factors
EDI	Enhanced Depth Imaging
ETDRS	Early Treatment Diabetic Retinopathy Study
GDS	Global Deterioration Scale
ICC	Intraclass correlation coefficient
I	Inferior
IOP	Intraocular pressure
MCI	Mild cognitive impairment
MCI-AD	Mild cognitive impairment due to Alzheimer's disease
MCI-Va	Mild cognitive impairment due to vascular pathology
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
N	Nasal
NBACE	Fundació ACE neuropsychological battery
NIA-AA	National Institute on Aging and Alzheimer's Association
NPI-Q	Neuropsychiatric Inventory Questionnaire
OCT	Optical coherence tomography
Out Inferior	Outer Inferior
Out Nasal	Outer Nasal
Out Superior	Outer Superior
Out Temporal	Outer Temporal
RNFL	Retinal nerve fiber layer
S	Superior
SCD	Subjective cognitive decline
SFCT	Subfoveal choroidal thickness
SS-OCT	Swept-source optical coherence tomography
T	Temporal
VaD	Vascular dementia
In Inferior	Inner Inferior
In Nasal	Inner Nasal
In Superior	Inner Superior
In Temporal	Inner Temporal

Supplementary Information

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Additional file 1. Multinomial regression analysis of the distribution of age, sex and education among diagnostic groups. Description: (*) Significance was set up at $p<0.05$. Abbreviations: ADD = Alzheimer´s disease dementia; CU = cognitively unimpaired; CV = cerebrovascular; MCI-AD = mild cognitive impairment due to Alzheimer´s disease; MCI-Va = mild cognitive impairment due to CV pathology; VaD = vascular dementia.

Additional file 2. Multinomial regression analysis of the distribution of CVRF among diagnostic groups. Description: (*) Significance was set up at $p < 0.05$. Abbreviations: ADD = Alzheimer´s disease dementia; COPD = chronic obstructive pulmonary disease; CU = cognitively unimpaired; CV = cerebrovascular; CVRF = cardiovascular risk factors; MCI-AD = mild cognitive impairment due to Alzheimer´s disease; MCI-Va = mild cognitive impairment due to CV pathology; VaD = vascular dementia.

Additional file 3. Multinomial regression analysis of the distribution of OCT image quality among diagnostic groups. Description: (*) Significance was set up at $p < 0.05$. Abbreviations: ADD = Alzheimer´s disease dementia; CV = cerebrovascular; MCI-AD = mild cognitive impairment due to Alzheimer´s disease; MCI-Va = mild cognitive impairment due to CV pathology; OCT = optical coherence tomography; VaD = vascular dementia.

Additional file 4. Multivariate regression analysis of CT measurements by adjusting factors. Description: Multivariate regression analysis showing the contribution of adjusting factors (age, sex, years of education, hypertension, diabetes mellitus, heart disease, COPD, stroke, smoking, and OCT image quality) to variance in CT measurements. This table is part of the analysis shown in Table 2 . In bold, $p < 0.05$. (*) Significance was corrected with Bonferroni for multiple comparisons ($p < 0.004$). Abbreviations: COPD = chronic obstructive pulmonary disease; CT = choroid thickness; OCT = optical coherence tomography. Regions in the ETDRS grid are divided into "Inner" and "Outer" zones, with "Inner" representing CT measurements within a 3 mm radius and "Outer" representing CT measurements within a 6 mm radius, corresponding to specific areas used for CT measurements in the study. The abbreviations used in the table are as follows: In Temporal = Inner Temporal, In Superior = Inner Superior, In Nasal = Inner Nasal, In Inferior = Inner Inferior. Similarly, Out Temporal = Outer Temporal, Out Superior = Outer Superior, Out Nasal = Outer Nasal, and Out Inferior = Outer Inferior.

Additional file 5. Multivariate regression analysis of CT measurements without CVRF as adjusting variables. Description: Including the following adjusting factors: age, sex, years of education and OCT image quality. In bold, $p < 0.05$. (*) Significance was corrected with Bonferroni for multiple comparisons ($p < 0.004$). Abbreviations: ADD = Alzheimer´s dementia; CT = choroidal thickness; CU = cognitively unimpaired; CVRF = cardiovascular risk factors; CV = cerebrovascular; MCI-AD = mild cognitive impairment due to Alzheimer´s disease; MCI-Va = mild cognitive impairment due to CV pathology; OCT = optical coherence tomography; VaD = vascular dementia. Regions in the ETDRS grid are divided into "Inner" and "Outer" zones, with "Inner" representing CT measurements within a 3 mm radius and "Outer" representing CT measurements within a 6 mm radius, corresponding to specific areas used for CT measurements in the study. The abbreviations used in the table are as follows: In Temporal = Inner Temporal, In Superior = Inner Superior, In Nasal = Inner Nasal, In Inferior = Inner Inferior. Similarly, Out Temporal = Outer Temporal, Out Superior = Outer Superior, Out Nasal = Outer Nasal, and Out Inferior = Outer Inferior.

Additional file 6. Multivariate regression analysis of CT measurements without outliers. Description: The multivariate regression analysis included the following adjusting factors: age, sex, years of education, hypertension, diabetes mellitus, heart disease, COPD, stroke, smoking and OCT image quality. In bold, $p < 0.05$. (*) Significance was corrected with Bonferroni for multiple comparisons ($p < 0.004$). Abbreviations: ADD = Alzheimer´s disease dementia; CT = choroidal thickness; CU = cognitively unimpaired; CV = cerebrovascular; MCI-AD = mild cognitive impairment due to Alzheimer´s disease; MCI-Va = mild cognitive impairment due to CV pathology; OCT = optical coherence tomography; VaD = vascular dementia. Regions in the ETDRS grid are divided into "Inner" and "Outer" zones, with "Inner" representing CT measurements within a 3 mm radius and "Outer" representing CT measurements within a 6 mm radius, corresponding to specific areas used for CT measurements in the study. The abbreviations used in the table are as follows: In Temporal = Inner Temporal, In Superior = Inner Superior, In Nasal = Inner Nasal, In Inferior = Inner Inferior. Similarly, Out Temporal = Outer Temporal, Out Superior = Outer Superior, Out Nasal = Outer Nasal, and Out Inferior = Outer Inferior.

Additional file 7. Multivariate regression analysis: interaction of sex and diagnosis in predicting CT measurements. Description: The multivariate regression analysis included the following adjusting factors: age, sex, years of education, hypertension, diabetes mellitus, heart disease, COPD, stroke, smoking and OCT image quality. (*) Significance was set up at $p < 0.05$. Abbreviations: ADD = Alzheimer´s disease dementia; COPD = chronic obstructive pulmonary disease; CT = choroidal thickness; CU = cognitively unimpaired; CV = cerebrovascular; MCI-AD = mild cognitive impairment due to Alzheimer´s disease; MCI-Va = mild cognitive impairment due to CV pathology; OCT = optical coherence tomography; VaD = vascular dementia.

Additional file 8. Comparison of manual and automated CT measurements. Description: Significance was set at $p < 0.05$. Abbreviations: CI = confidence interval; CT = choroidal thickness; ICC = intraclass correlation coefficient.

Additional file 9. Representation of the degree of dispersion and reliability in the Bland–Altman plot of manual and automated measurements. Description: This plot provides a visual representation of the degree of agreement between the two measurement techniques for CT. The X-axis represents the average of the manual and automated measurements, while the Y-axis indicates the difference between the two methods (manual minus automated). Measurements are defined as follows: Measurement 1 = subfoveal; Measurement 2 = 500 µm Superior; Measurement 3 = 500 µm Temporal; Measurement 4 = 1500 µm Superior; Measurement 5 = 1500 µm Temporal. Abbreviations: CT = choroidal thickness.

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Authors' contributions
LC-M, LT, AR, MB, MC-M and MM designed and conducted the study. LC-M and MM drafted the manuscript. AG-S and SV conducted the statistical analysis. LC-M and AG-S prepared the databases. JM, MR-R, LV, JPT, MA, GO, AE, AS, AP-C, NM, FG-G, JB-F, AM, IdR, PG-G, RP, CO, MC, AM-M, PB-B, AC, VF and MM acquired the data. All authors interpreted the study results, critically reviewed the manuscript, approved the final manuscript, and agreed to be responsible for all aspects of the work.

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Data availability
The dataset generated and analyzed for this study will be made available by the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study and its informed consent were approved by the Ethics Committee of the Hospital Clínic i Provincial de Barcelona in accordance with Spanish

biomedical laws (Law 14/2007, of July 3, on biomedical research; Royal Decree 1716/2011, of November 18) and followed the recommendations of the declaration of Helsinki. All participants signed an informed consent form (in the case of individuals with moderate stages of dementia, informed consent was signed by their legal representative or family member).

Consent for publication
Not applicable.

Competing interests
MB has consulted for Araclon, Avid, Grifols, Lilly, Nutricia, Roche, Eisai and Servier. She received fees from lectures and funds for research from Araclon, Biogen, Grifols, Nutricia, Roche and Servier. She reports grants/research funding from Abbvie, Araclon, Biogen Research Limited, Bioiberica, Grifols, Lilly, S.A, Merck Sharp & Dohme, Kyowa Hakko Kirin, Laboratorios Servier, Nutricia SRL, Oryzon Genomics, Piramal Imaging Limited, Roche Pharma SA, and Schwabe Farma Iberica SLU, all outside the submitted work. She has not received personal compensations from these organizations. AR is member of scientific advisory board of Landsteiner Genmed and Grifols SA. AR has stocks of Landsteiner Genmed. MM has consulted for F. Hoffmann-La Roche Ltd. The rest of authors declare that they have no competing interests.

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