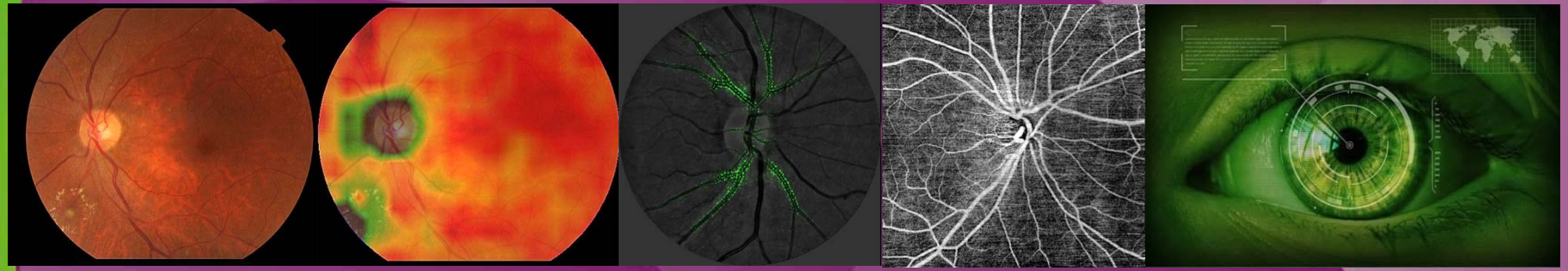
PRE – CONFERENCE AFTERNOON MASTER CLASSES

Retinal Biomarkers



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Alzheimer's Disease (AD) is associated with pathological changes in the brain that result from neurodegeneration and vascular disease processes

Early diagnosis *and* ***early intervention*** *for AD are considered important mechanisms to delay progression of disease for managing the worldwide impact of dementia.*

Difficult to identify early AD

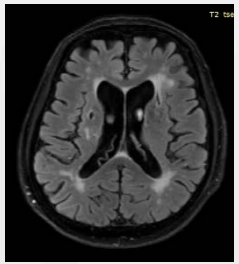
Sensitivity and specificity are relatively **LOW**

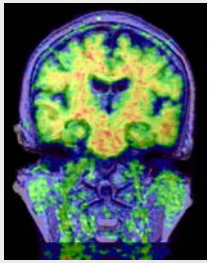
Traditional Brain scan (i.e. CT, MRI)

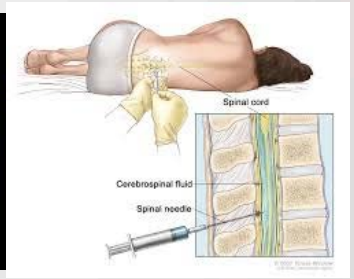
Amyloid- and Tau-PET scan

Cerebrospinal fluid (CSF) analysis via lumber puncture

Expensive
Invasive
Not widely available



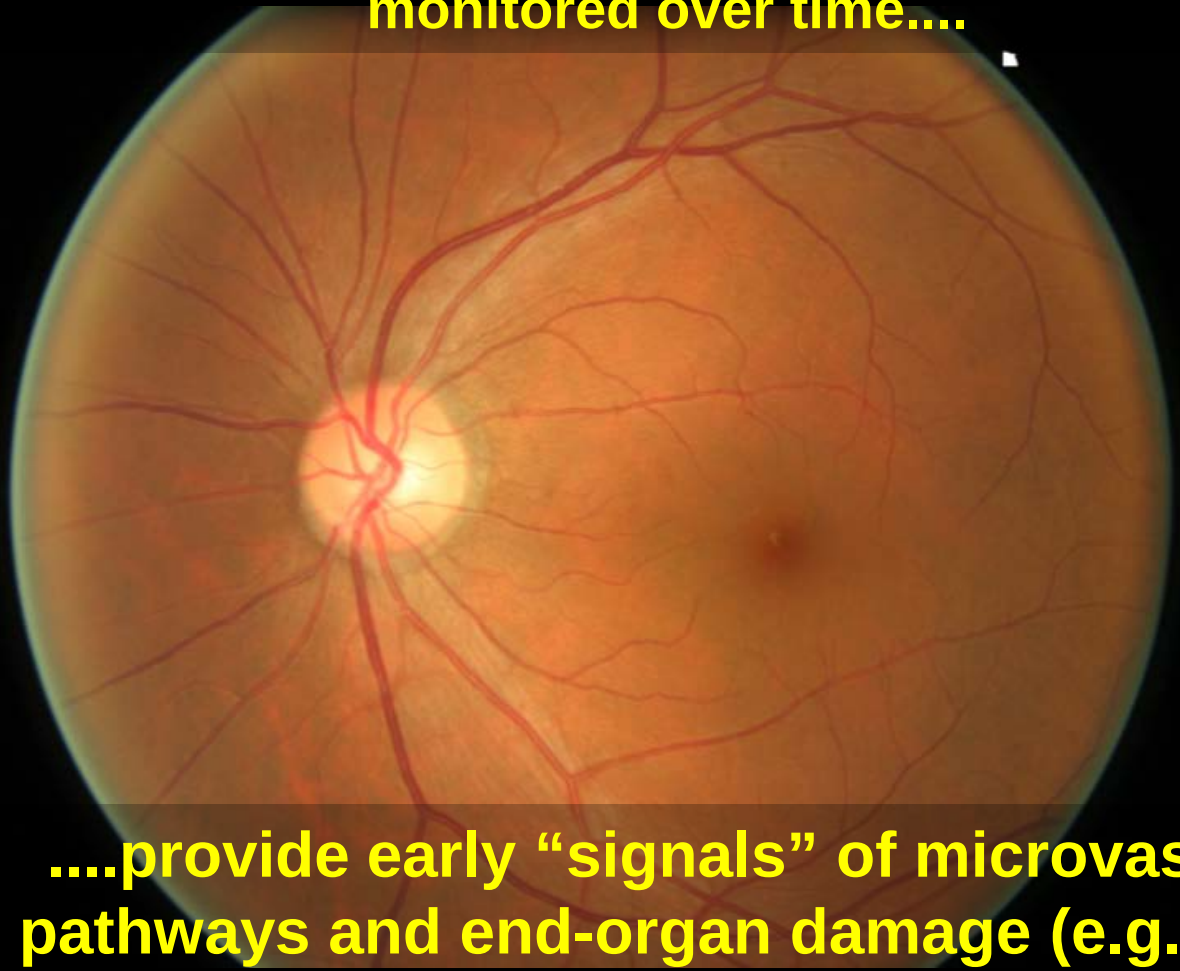




Biomarkers of amyloid-β & pathologic tau

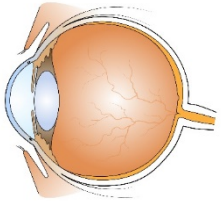
Olsson B, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol 2016;15:673-84.

Retinal vasculature can be imaged, measured and monitored over time....

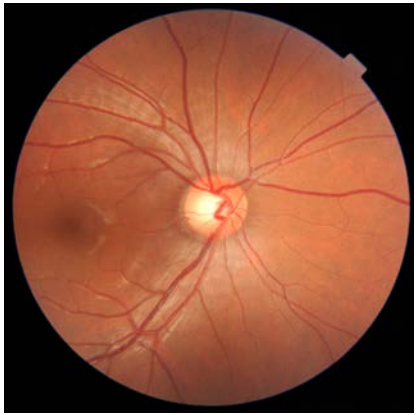


....provide early “signals” of microvascular pathways and end-organ damage (e.g. brain)

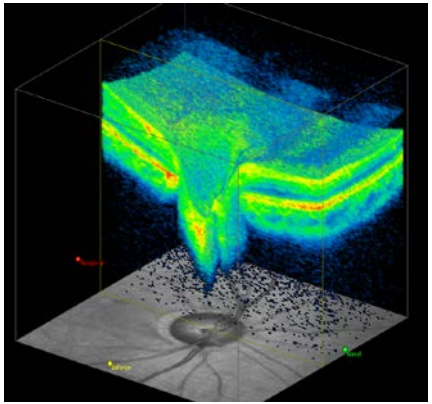
Ocular Imaging

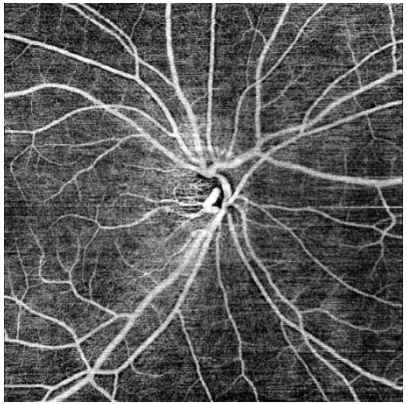


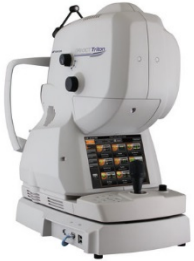
Fundus photography



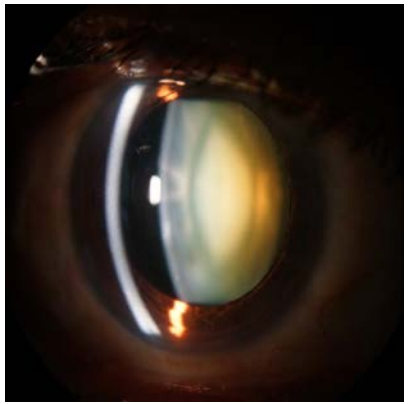
Optical Coherence Tomography (OCT)



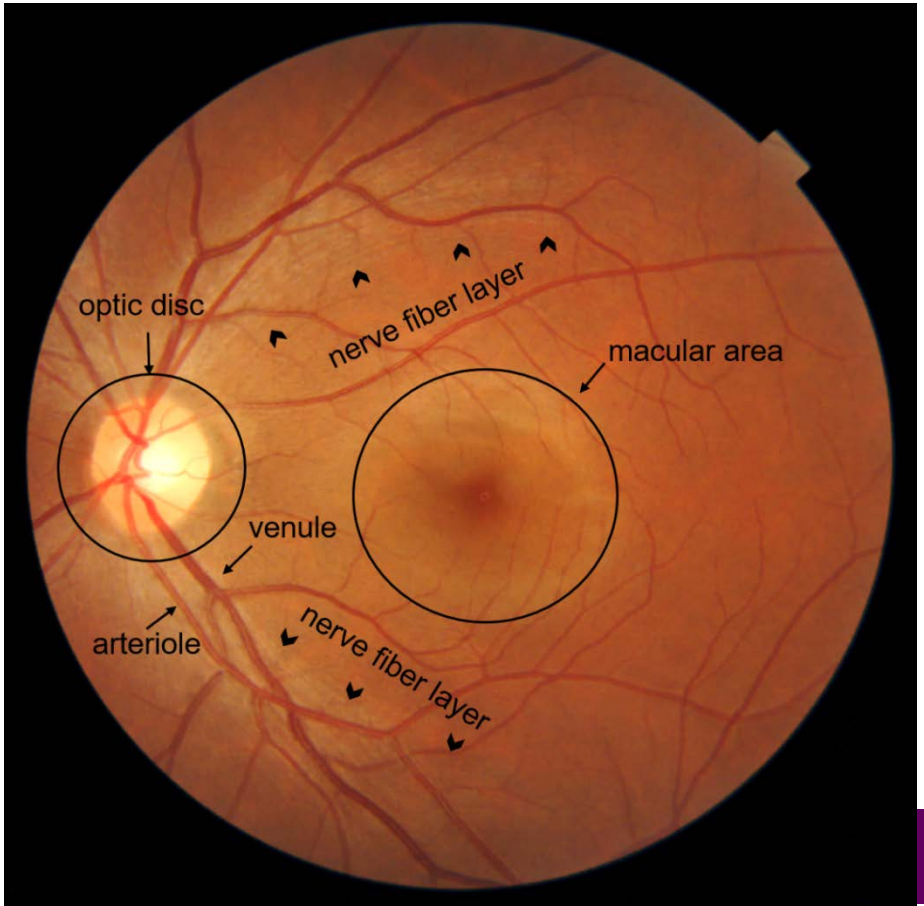


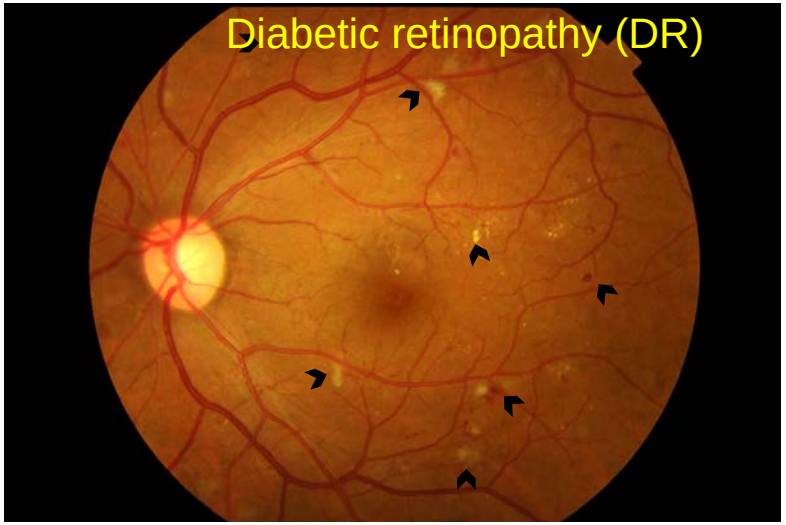


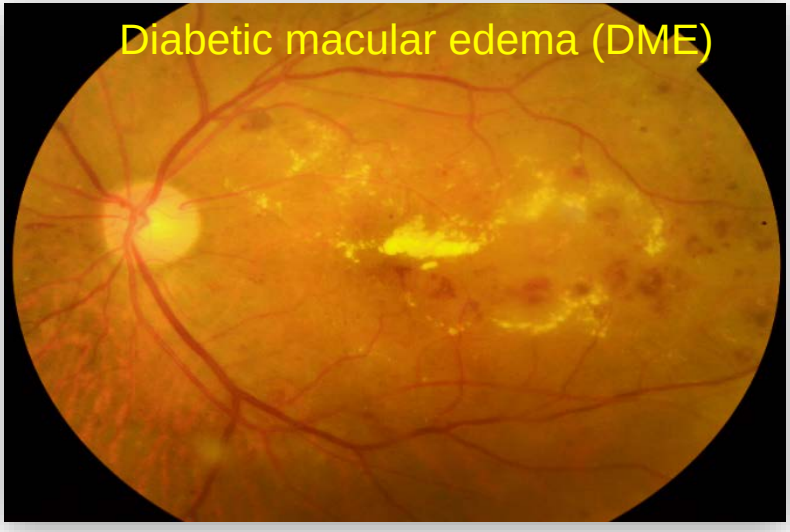
Slit-lamp photography

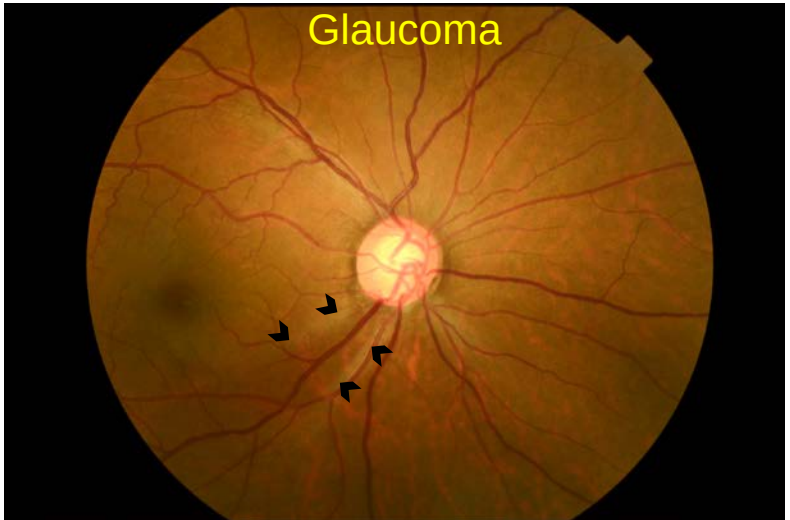


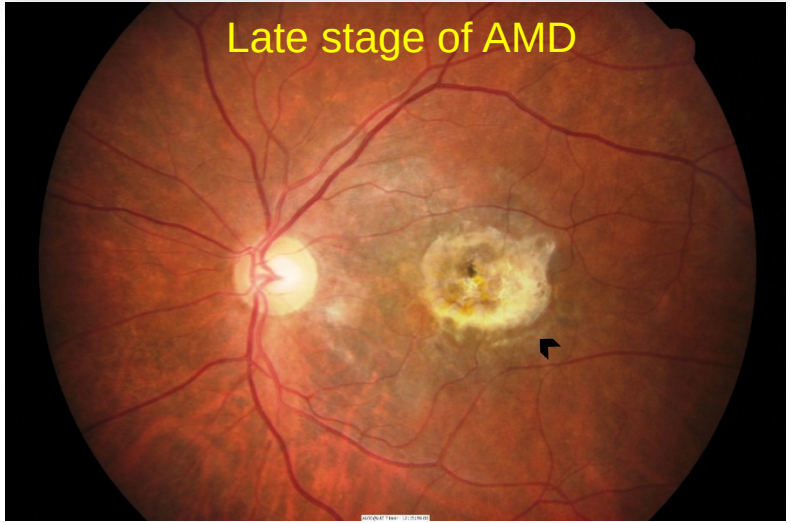
Retinal fundus photography



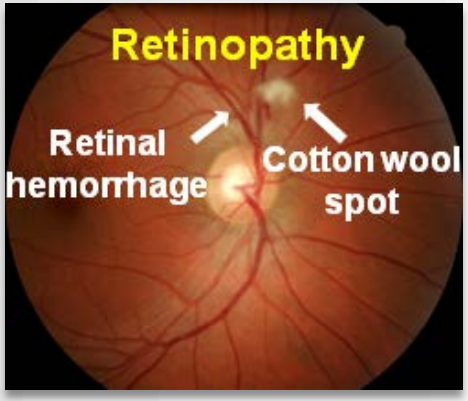

Diabetic retinopathy (DR)

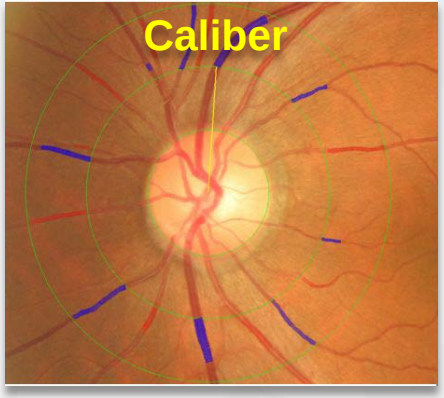

Diabetic macular edema (DME)

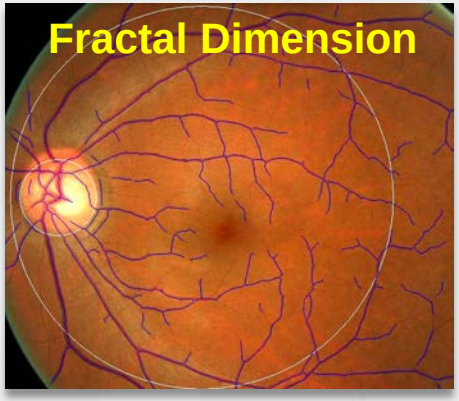

Glaucoma

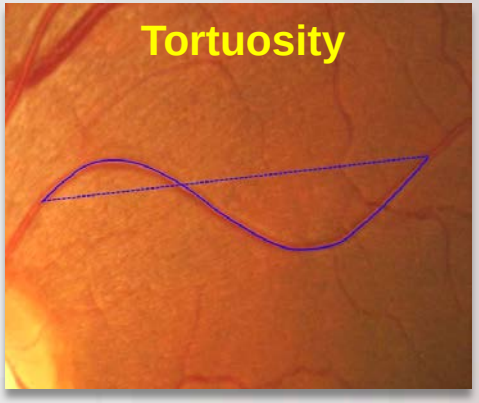

Late stage of AMD

Changes in the retinal vasculature are source of potential biomarkers for AD









Retinopathy and risk of dementia

The Rotterdam Study

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M. Kamran Ikram, MD, PhD
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Albert Hofman, MD, PhD
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ABSTRACT

Objective: To investigate the relation between retinopathy and the risk of dementia.

Methods: We investigated the associations between retinopathy and dementia and its subtypes Alzheimer disease (AD) and vascular dementia both cross-sectionally and prospectively in the Rotterdam Study, a large population-based cohort study. Digitized retinal images were available for 195 participants with prevalent dementia and 6,078 participants without dementia at baseline (1990–1993). Participants were reexamined in 1993–1994, 1997–1999, and 2002–2004 and were continuously monitored for development of dementia until January 1, 2007. Retinopathy was graded on fundus photographs and was defined as the presence of one or more dot/blot hemorrhages, microaneurysms, cotton wool spots, or evidence of laser treatment for retinopathy.

Results: Retinopathy was associated with prevalent dementia (age and sex-adjusted odds ratio 2.04, 95% confidence interval [CI] 1.34–3.09). Results were similar for AD and vascular dementia. During a mean follow-up of 11.4 years, 735 participants developed incident dementia, of whom 583 had AD and 80 had vascular dementia. There was no association of retinopathy at baseline with the risk of incident dementia during follow-up (age- and sex-adjusted hazard ratio 1.15, 95% CI 0.88–1.48) or the risk of incident AD or vascular dementia.

Con
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AD =
DSM-
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Dementia is a major cause of morbidity and mortality in elderly people. Many factors contribute to the development of dementia, and although the exact causes are still unclear, cerebrovascular disease is thought to be an important risk factor.[1] To study the role of cerebral microvascular disease in the pathogenesis of dementia, there is much interest in retinal microvascular signs, because embryologic, anatomic, and physiologic characteristics of the retinal vasculature are similar to those of the cerebral circulation, and the retina is easy to visualize noninvasively.[2,3] We have previously shown an association of larger retinal venular caliber and smaller arteriolar caliber with the risk of developing vascular dementia.[4] Another interesting retinal microvascular sign that has been associated with cognition and dementia is retinopathy.[5–9] In pro-

Table 3 ORs of retinopathy and prevalent dementia[a]

	Cases/ total no.	OR (95% CI) Model 1	Model 2	Model 3
All dementia				
No retinopathy	160/5,800	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Retinopathy	34/473	2.04 (1.34–3.09)	1.90 (1.25–2.91)	1.92 (1.24–2.98)
Alzheimer disease				
No retinopathy	124/5,764	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Retinopathy	25/463	1.80 (1.11–2.91)	1.81 (1.12–2.94)	1.89 (1.15–3.10)
Vascular dementia				
No retinopathy	22/5,662	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Retinopathy	7/445	3.01 (1.26–7.21)	2.12 (0.80–5.62)	2.00 (0.71–5.63)

Table 4 HRs of retinopathy and risk of incident dementia during follow-up

		HR (95% CI)		
				3
				Ref)
Retinopathy	63/438	1.15 (0.88–1.48)	1.13 (0.88–1.47)	1.15 (0.89–1.50)
Alzheimer disease				
No retinopathy	534/5,640	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Retinopathy	49/438	1.12 (0.83–1.50)	1.12 (0.83–1.50)	1.15 (0.86–1.55)
Vascular dementia				
No retinopathy	74/5,640	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Retinopathy	6/438	0.97 (0.42–2.23)	0.92 (0.40–2.12)	0.90 (0.39–2.11)

Retinopathy signs are associated with
prevalent dementia and prevalent Alzheimer's disease

ELSEVIER

Alzheimer's & Dementia 10 (2014) 135–142

Alzheimer's & Dementia

Featured Articles

Microvascular network alterations in the retina of patients with Alzheimer's disease

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Abstract

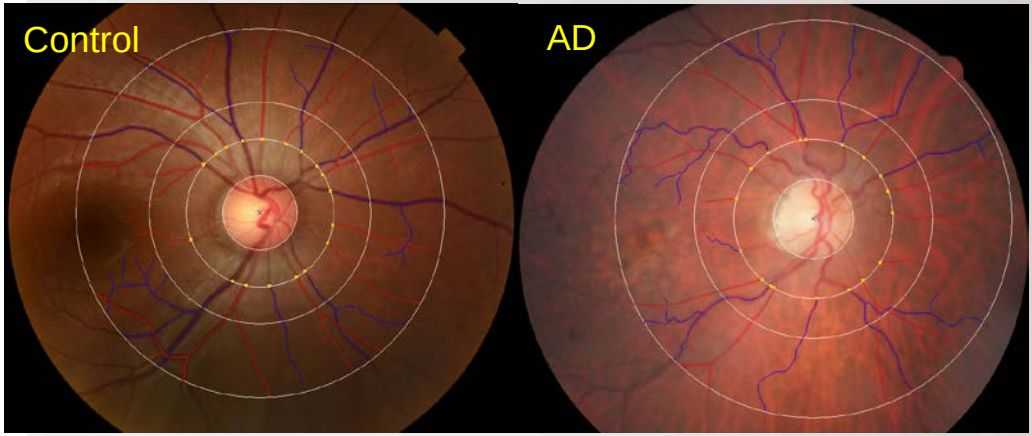
Background: Although cerebral small-vessel disease has been implicated in the development of Alzheimer's disease (AD), the cerebral microcirculation is difficult to visualize directly in vivo. Because the retina provides a noninvasive window to assess the microcirculation, we determined whether quantitatively measured retinal microvascular parameters are associated with AD.

Methods: We conducted a case-control study (case:control matching ≈ 1:2). Retinal photographs were analyzed using a computer program, and a spectrum of quantitative retinal microvascular parameters (caliber, fractal dimension, tortuosity, and bifurcation) were measured. Logistic regression models were used to compute the odds ratio (OR) and 95% confidence interval for AD adjusting for age, gender, ethnicity, smoking, hypertension, diabetes, hypercholesterolemia, and history of myocardial infarction.

Results: We included 136 demented patients with AD and 290 age-gender-race-matched controls. Persons with n
[1.27–3.19]), de
[1.08–1.68], 1.47
per SD increase
AD. These assoc
disease were included.

Conclusions: Patients with AD have altered microvascular network in the retina (narrower retinal venules and a sparser and more tortuous retinal vessels) compared with matched nondemented controls. These changes in retinal microvasculature may reflect similar pathophysiological processes in cerebral microvasculature in the brains of patients with AD.

Keywords: Retina; Retinal vasculature; Alzheimer's disease; Microcirculation; Small-vessel disease



Associations between AD and retinal vascular parameters

	Model 1			Model 2		
Retinal vascular parameter	OR	95% CI		OR	95% CI	
Caliber						
Central retinal artery equivalent, per SD decrease	2.02	1.59	2.58	1.22*	0.78	1.91
Central retinal vein equivalent, per SD decrease	2.17	1.69	2.79	2.01†	1.27	3.19
Fractals						
Total fractal dimension, per SD decrease	1.49	1.20	1.84	1.54	1.23	1.93
Arteriolar fractal dimension, per SD decrease	1.37	1.10	1.69	1.35	1.08	1.68
Venular fractal dimension, per SD	1.39	1.12	1.72	1.47	1.17	1.84
Venular tortuosity, per SD increase	1.87	1.46	2.41	1.94	1.48	2.53
Bifurcation						
Arteriolar branching angle, per SD increase	1.09	0.88	1.35	1.07	0.87	1.33
Venular branching angle, per SD increase	1.00	0.81	1.23	0.97	0.78	1.20

…AD have narrower, sparser & more tortuous vessels…

Neuroscience Letters 577 (2014) 95–100

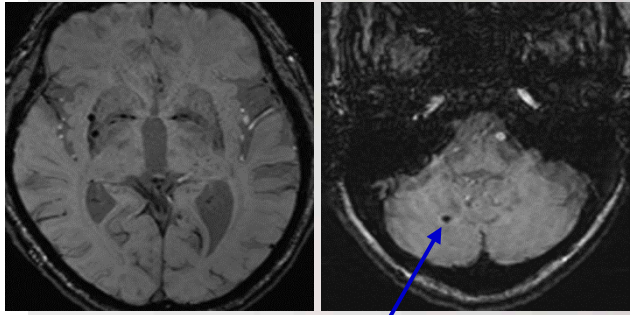
Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Retinal Parameter	ORs for presence of ≥2CMB: Model I‡ OR (95% CI)	ORs for presence of ≥2CMB: Model II§ OR (95% CI)	ORs for increase in CMB number: Model I‡ RR (95% CI)	ORs for increase in CMB number: Model II§ RR (95% CI)
Caliber, per SD				
Arteriolar	**2.17 (1.04-4.51)**	2.07 (0.98-4.38)	**1.48 (1.01-2.17)**	1.42 (0.98-2.05)
Venular	**2.40 (1.20-4.77)**	**2.23 (1.09-4.56)**	**1.39 (1.00-1.93)**	1.31 (0.93-1.84)
Fra				
Arte				
Ven				
Tortuosity, per SD				
Arteriolar	1.17 (0.80-1.38)	1.29 (0.87-1.93)	**1.25 (1.01-1.55)**	**1.29 (1.03-1.61)**
Venular	0.96 (0.64-1.45)	0.96 (0.64-1.44)	0.99 (0.76-1.29)	0.98 (0.76-1.27)

…patients with CMB and AD have ***narrower, sparser & more tortuous vessels***…



Cerebral microbleeds (CMB): preclinical MRI imaging markers of cognitive decline in AD

ARTICLE INFO

Article history:
Received 13 April 2014
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ABSTRACT

Novel retinal imaging techniques have enabled the assessment of quantitative vascular parameters, which provide information on the microvasculature before the appearance of retinopathy signs. Advances in neuroimaging have revealed that cerebral microbleeds (CMB) – besides lacunar infarcts and white matter

Evaluation of optical coherence tomography angiographic findings in Alzheimer's type dementia

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ABSTRACT

Background/Aims To identify the retinal vascular pathologies in patients with Alzheimer's type dementia (ATD) through optical coherence tomography angiography (OCTA) imaging.

Methods Our study included 26 patients in the patient group, and age-matched and sex-matched 26 subjects

smoking, depression, cognitive or physical inactivity and obesity increase the risk of ATD.[1]

ATD is a serious health problem that occurs at advanced age. The most important problem with this disease is related to diagnosis. Today, it can be diagnosed at the early stages of cognitive impairment. The diagnosis can be established after the by testing the nt.[2] Once it is at will lead to gnosis of ATD process starts. th is 4.6 years. established by

d biomarkers e the disease e disease will icacy of drugs treatment will

th the visual s while it was . The studies wever, demon-

creased blood n the cerebral chers focused ular vascular

Table 2 Relationship of vascular density, foveal avascular zone, outer and choroidal flow rate and choroidal thickness with ATD and control subjects

	Patients with ATD (n=26 eyes of 26 subjects)	Control subjects (n=26 eyes of 26 subjects)	p Value
Vascular density (%)			
Whole	45.50±3.85	48.67±3.29	0.002*
Fovea	29.04±7.17	34.80±6.76	0.004*
Parafovea	47.96±4.86	51.12±4.10	0.015*
Foveal avascular zone (mm²)	0.47±0.18	0.33±0.08	0.001*

and flow rate).
*Significant at p<0.05.
ATD, Alzheimer's type dementia.

INTRODUCTION

Alzheimer's type dementia (ATD) is a chronic, progressive neurodegenerative disease and results

structures as a biomarker in ATD.[6]

In ATD and other neurodegenerative diseases, retinal imaging with optical coherence tomography angiography (OCTA) may give us additional

JAMA Ophthalmology | Original Investigation

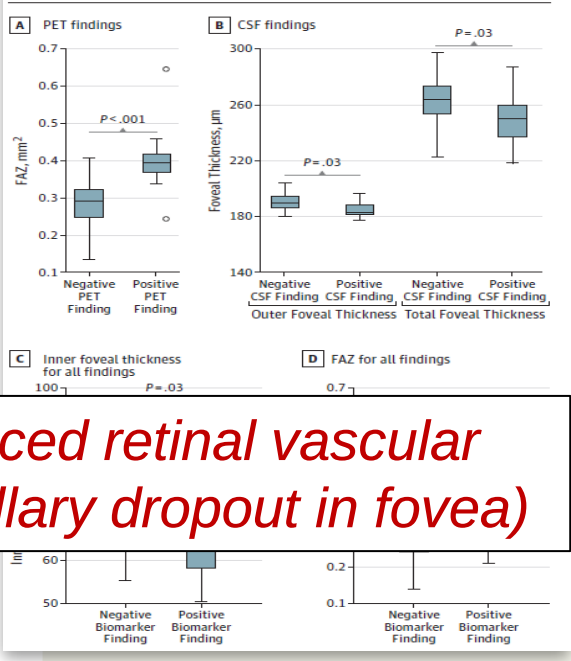
Association of Preclinical Alzheimer Disease With Optical Coherence Tomographic Angiography Findings

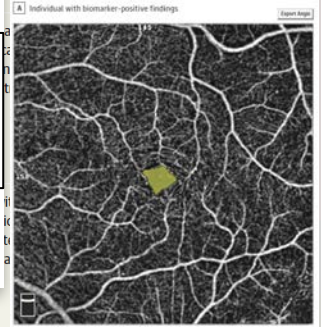
Bliss Elizabeth O'Bryhim, MD, PhD; Rajendra S. Apte, MD, PhD; Nathan Kung, MD; Dean Coble, PhD; Gregory P. Van Stavern, MD

IMPORTANCE Biomarker testing for asymptomatic, preclinical Alzheimer disease (AD) is invasive and expensive. Optical coherence tomographic angiography (OCTA) is a noninvasive

Invited Commentary
Author Audio Interview
Supplemental content

Figure 2. Foveal Thickness and Foveal Avascular Zone (FAZ) Measurements





Patients with AD have reduced retinal vascular density & enlarged FAZ (capillary dropout in fovea)

New Retinal Imaging Technologies & AD

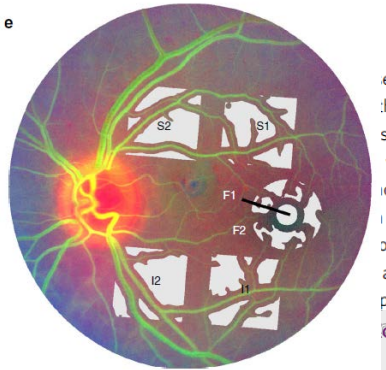
nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-12242-1 OPEN

Non-invasive in vivo hyperspectral imaging of t retina for potential biomarker use in Alzheimer' disease

Xavier Hadoux et al.#



ease (AD) and of human tissues suggest that the he accumulation of amyloid beta (Aβ), may serve s Aβ has a wavelength-dependent effect on light vivo retinal hyperspectral imaging to serve as a ces in the retinal reflectance spectra are found brain PET imaging and mild cognitive impairment ontrols ($n = 20$). Retinal imaging scores are cor- are validated in an independent cohort, using a pectral difference is found between control and

ong

Journal of Alzheimer's Disease 49 (2016) 79–83
DOI 10.3233/JAD-150457
IOS Press

Retinal Oximetry Imaging in Alzheimer's Disease

Anna Bryndis Einarsdottir[a,*], Sveinn Hakon Hardarson[b,d], Jona Valgerdur Kristjansdottir[b,d], David Thor Bragason[b], Jon Snaedal[c] and Einar Stefánsson[b,d]
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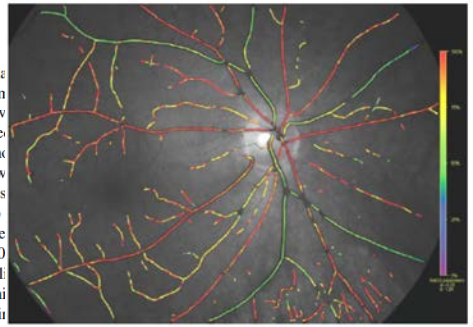
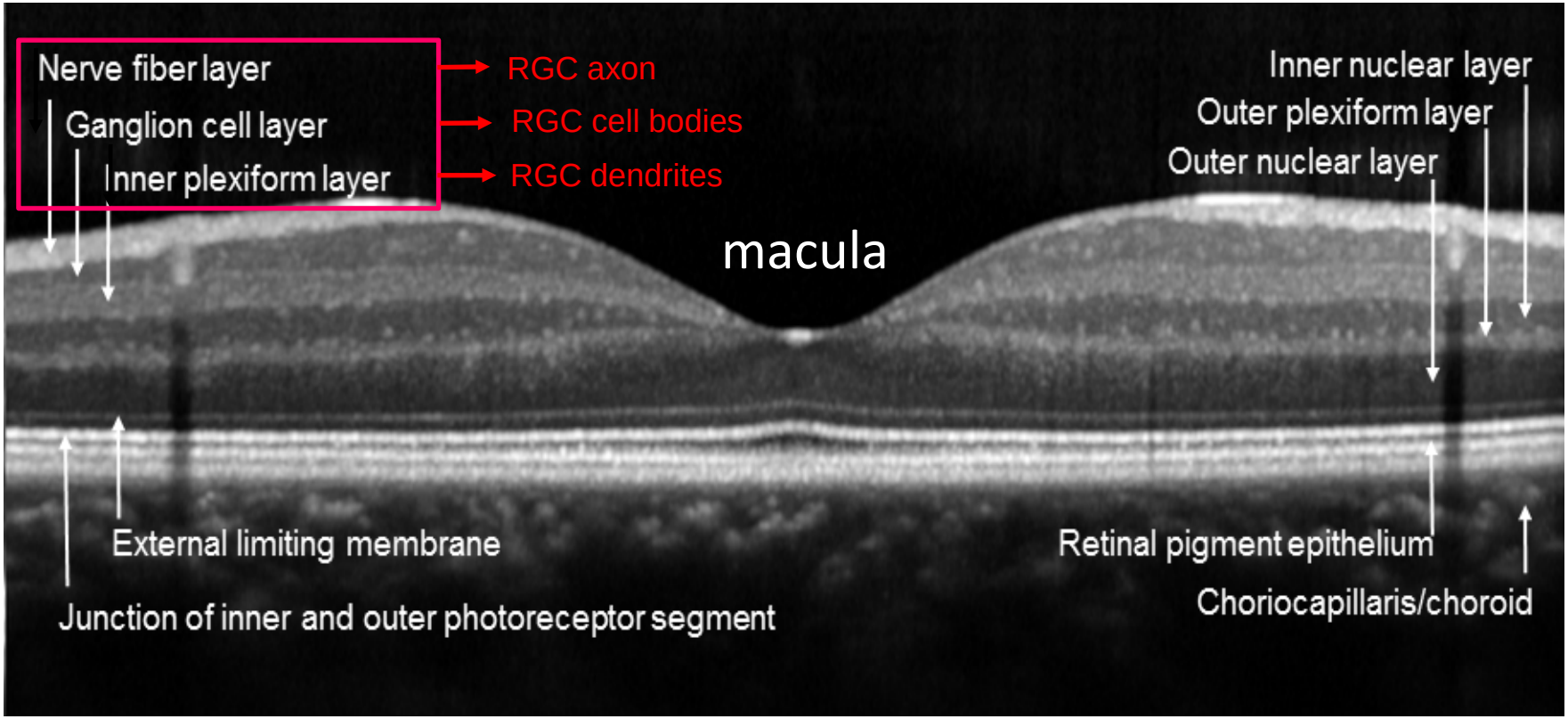
Accepted 27 July 2015



Abstract.
Background: Structural and physiological abnormalities ha
oximetry detects changes in retinal oxygen metabolism in n
Objective: To compare oxygen saturation in retinal blood v
Methods: Oxygen saturation of hemoglobin was measure
noninvasive retinal oximeter. 18 individuals with mild to m
Global Deterioration Scale) and 18 healthy subjects underw
Results: Retinal oxygen saturation in arterioles and venules
to healthy individuals. Retinal arterioles have $94.2 \pm 5.4\%$
healthy subjects (mean $\pm$ SD, $n = 10$, $p = 0.028$). Retinal ve
$49.7 \pm 7.0\%$ in healthy subjects (mean $\pm$ SD, $n = 10$, $p = 0.0$
Conclusion: This is the first study of retinal oxygen metaboli
in retinal oxygen metabolism in AD. The findings are simi
retinopathy. Noninvasive retinal oximetry may offer new i
confirm and expand these findings.

Keywords: Alzheimer's disease, blood vessels, diagnosis, hemoglobin, oxygen, retina, retinal oximetry, vessel diameter

Optical Coherence Tomography (OCT)

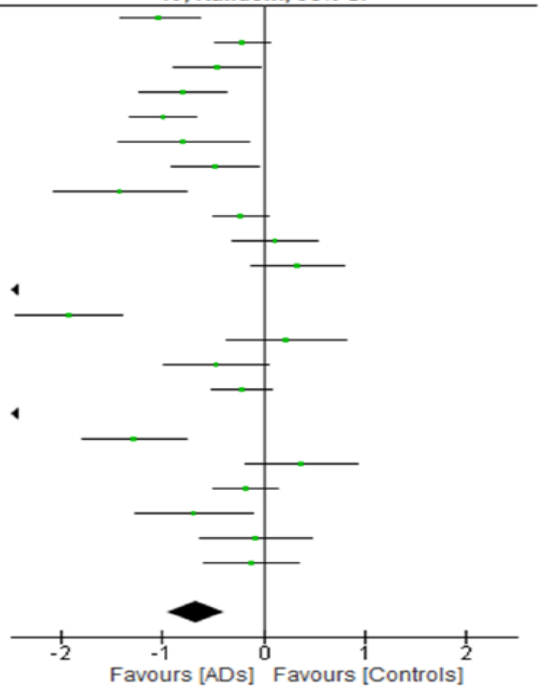


Meta-analysis: RNFL thinning in AD

Study or Subgroup	AD Subjects Mean	SD	Total	Controls Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bambo et al. 2015	89.4	10.4	56	100.9	11.7	56	4.7%	-1.03 [-1.43, -0.64]
Cheung et al. 2015	86.83	13.812	92	90.37	18.9648	123	4.9%	-0.21 [-0.48, 0.06]
Choi et al. 2016	88.9547	9.5264	30	93.47	9.91	66	4.6%	-0.46 [-0.89, -0.02]
Cunha et al. 2016	93.75	13.42	45	102.96	9.19	48	4.6%	-0.80 [-1.22, -0.38]
Cunha et al. 2017	85.72	14.42	50	96.51	9.36	152	4.8%	-0.99 [-1.33, -0.66]
Eraslan et al. 2015	98.3	10.3	20	110.7	19.1	20	4.1%	-0.79 [-1.44, -0.15]
Ferrari et al. 2017	93.0705	10.2132	37	97.49	8.52	49	4.6%	-0.47 [-0.90, -0.04]
Gao et al. 2015	85.99	9.5	25	98.6	7.6529	21	4.0%	-1.42 [-2.08, -0.77]
Garcia-Martin 2016	95.67	15.22	150	99.23	16.48	75	4.9%	-0.23 [-0.50, 0.05]
Gharbiya et al. 2014	96.8	6.9	42	95.9	8.5	42	4.6%	0.12 [-0.31, 0.54]
Golzan et al. 2017	99	17	28	93	18	50	4.5%	0.34 [-0.13, 0.80]
Gunes et al. 2014	84	7	40	107.1	6.3	40	3.9%	-3.44 [-4.14, -2.74]
Kirbas et al. 2013	65	6.2	40	75	3.8	40	4.4%	-1.93 [-2.46, -1.39]
Kromer et al. 2014	105	17.0133	22	101.8	10.7	22	4.2%	0.22 [-0.37, 0.81]
Kwon et al. 2017	42.75	4.53	30	44.83	4.24	30	4.4%	-0.47 [-0.98, 0.05]
Larrosa et al. 2014	97.55	14.12	151	100.55	12.99	61	4.9%	-0.22 [-0.51, 0.08]
Moreno-Ramos et al. 2013	94.5	2.2	10	108	2.2	10	1.3%	-5.88 [-8.09, -3.66]
Oktem et al. 2015	80.6	9.6	35	91.5	7.1	35	4.4%	-1.28 [-1.79, -0.76]
Pillai et al. 2016	88.9	9.6234	21	85.3	9.3295	34	4.3%	0.38 [-0.17, 0.92]
Polo et al. 2014	97.4	11.2	75	99.21	9.9	75	4.8%	-0.17 [-0.49, 0.15]
Polo et al. 2017	91	11.23	24	97.61	7.13	24	4.2%	-0.69 [-1.28, -0.11]
Salobrar-Garcia et al. 2015	87.5083	20.2557	23	89.0833	20.8664	28	4.3%	-0.08 [-0.63, 0.48]
Trebbastoni et al. 2016	96.7	6.3	36	97.6	8.3	36	4.5%	-0.12 [-0.58, 0.34]
Total (95% CI)			**1082**			**1137**	**100.0%**	**-0.67 [-0.95, -0.38]**

Heterogeneity: $Tau^2 = 0.42$; $Chi^2 = 208.62$, $df = 22$ ($P < 0.00001$); $I^2 = 89\%$

Test for overall effect: $Z = 4.56$ ($P < 0.00001$)



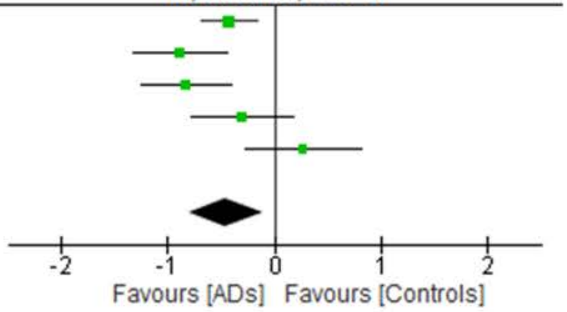
(Chan V et al. Ophthalmology 2018)

Meta-analysis: GC-IPL thinning in AD

A. Mean Macular GC-IPL Thickness

Study or Subgroup	AD Subjects Mean	SD	Total	Controls Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cheung et al. 2015	72.23	10.8454	99	77.79	14.5286	123	24.7%	-0.43 [-0.69, -0.16]
Choi et al. 2016	72.4957	9.1763	30	79.11	6.49	66	19.5%	-0.88 [-1.33, -0.43]
Cunha et al. 2016	63.24	7.6	45	69	6.09	48	20.2%	-0.83 [-1.26, -0.41]
Liu et al. 2016	78.41	5.85	27	80.19	5.89	47	18.7%	-0.30 [-0.78, 0.18]
Pillai et al. 2016	75.7	7.7904	21	73.5	8.1633	34	16.8%	0.27 [-0.28, 0.82]
Total (95% CI)			**222**			**318**	**100.0%**	**-0.46 [-0.80, -0.11]**

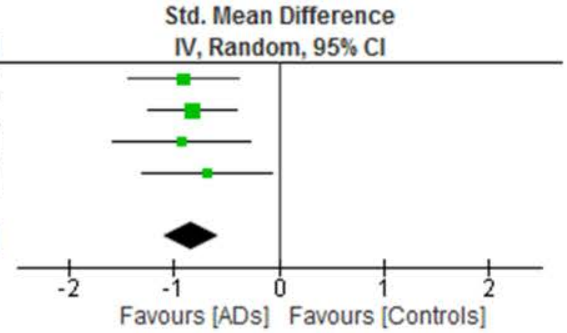
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 13.69$, df = 4 (P = 0.008); $I^2 = 71\%$
Test for overall effect: Z = 2.58 (P = 0.010)



B. Mean Macular GCC Thickness

Study or Subgroup	AD Subjects Mean	SD	Total	Controls Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bayhan et al. 2015	91.83	6.23	31	97.49	6.09	30	25.5%	-0.91 [-1.44, -0.38]
Cunha et al. 2016	95.66	11.69	45	103.85	7.73	48	39.6%	-0.82 [-1.25, -0.40]
Eraslan et al. 2015	89.8	10.3	20	97.6	5.5	20	16.6%	-0.93 [-1.58, -0.27]
Marziani et al. 2013	96.0111	14.9089	21	107.4444	17.549	21	18.3%	-0.69 [-1.31, -0.06]
Total (95% CI)			**117**			**119**	**100.0%**	**-0.84 [-1.10, -0.57]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.36$, df = 3 (P = 0.95); $I^2 = 0\%$
Test for overall effect: Z = 6.15 (P < 0.00001)



(Chan V et al. Ophthalmology 2018)

JAMA Neurology | Original Investigation

Association of Retinal Nerve Fiber Layer Thinning With Current and Future Cognitive Decline

A Study Using Optical Coherence Tomography

Fang Ko, MD; Zaynah A. Muthy, BSc; John Gallacher, PhD; Cathie Sudlow, DPhil; Geraint Rees, PhD; Qi Yang, PhD; Pearse A. Keane, MD; Axel Petzold, PhD; Peng T. Khaw, PhD; Charles Reisman, MSc; Nicholas G. Strouthidis, PhD; Paul J. Foster, PhD; Praveen J. Patel, FRCOphth; for the UK Biobank Eye & Vision Consortium

Author Audio Interview

Supplemental content

IMPORTANCE Identifing potential screening tests for future cognitive decline is a priority for developing treatments for and the prevention of dementia.

OBJECTIVE To examine the potential of retinal nerve fiber layer (RNFL) thickness measurement in identifying those at greater risk of cognitive decline in a large community cohort of healthy people.

DESIGN, SETTING, AND PARTICIPANTS UK Biobank is a prospective, multicenter, community-based study of UK residents aged 40 to 69 years at enrollment who underwent baseline retinal optical coherence tomography imaging, a physical examination, and a questionnaire. The pilot study phase was conducted from March 2006 to June 2006, and the main cohort underwent examination for baseline measures from April 2007 to October

fifth percentile in at least 2 of 4 cognitive tests at baseline, or worsening results on at least 1 cognitive test at follow-up. These analyses were adjusted for age, sex, race/ethnicity, height, refraction, intraocular pressure, education, and socioeconomic status.

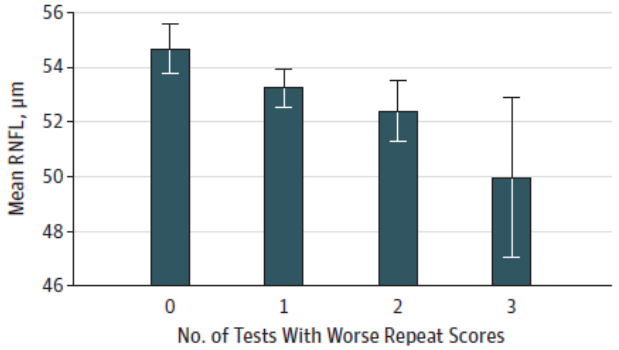
RESULTS A total of 32 038 people were included at baseline testing, for whom the mean age was 56.0 years and of whom 17 172 (53.6%) were women. A thinner RNFL was associated with worse cognitive performance on baseline assessment. A multivariable regression controlling for potential confounders showed that those in the thinnest quintile of RNFL were 11% more likely to fail at least 1 cognitive test (95% CI, 2.0%-2.1%; *P* = .01). Follow-up cognitive tests were performed for 1251 participants (3.9%). Participants with an RNFL thickness in the 2 thinnest quintiles were almost twice as likely to have at least 1 test score be worse at follow-up cognitive testing (quintile 1: OR, 1.92; 95% CI, 1.29-2.85; *P* < .001; quintile

*RNFL thinning is associated with future **cognitive decline***

Table 3. Multivariable Logistic Regression Modeling of the Association Between Retinal Nerve Fiber Layer (RNFL) Thickness and Risk of Worsening on 1 or More Follow-up Cognitive Function Tests (Compared With 0 Tests)[a]

Characteristic	Odds Ratio (95% CI)	*P* Value
RNFL quintile, µm		
≤45.9	1.92 (1.29-2.85)	<.001
45.9-50.4	2.08 (1.40-3.08)	<.001
50.4-54.6	1.48 (1.01-2.18)	.05
54.6-60.2	1.51 (1.05-2.19)	.03
≥60.2	1 [Reference]	NA
RNFL, µm		
Per quintile	1.18 (1.08-1.29)	.001

Figure 2. Proportion of UK Biobank Participants Exhibiting a Decline in Cognitive Function on Repeat Assessment



JAMA Neurology | Original Investigation

Association of Retinal Neurodegeneration on Optical Coherence Tomography With Dementia

A Population-Based Study

Unal Mutlu, MD, PhD; Johanna M. Colijn, MD; M. Arfan Ikram, MD, PhD; Pieter W. M. Bonnemaijer, MD; Silvan Licher, MD; Frank J. Wolters, MD; Henning Tiemeier, MD, PhD; Peter J. Koudstaal, MD, PhD; Caroline C. W. Klaver, MD, PhD; M. Kamran Ikram, MD, PhD

IMPORTANCE Retinal structures may serve as a biomarker for dementia, but longitudinal studies examining this link are lacking.

OBJECTIVE To investigate the association of inner retinal layer thickness with prevalent and incident dementia in a general population of Dutch adults.

DESIGN, SETTING, AND PARTICIPANTS From September 2007 to June 2012, participants from the prospective population-based Rotterdam Study who were 45 years and older and had gradable retinal optical coherence tomography images and at baseline were free from stroke, Parkinson disease, multiple sclerosis, glaucoma, macular degeneration, retinopathy, myopia, hyperopia, and optic disc pathology were included. They were followed up until January 1, 2015, for the onset of dementia.

EXPOSURES Inner retinal layer thicknesses (ie, retinal nerve fiber layer [RNFL]) and ganglion cell–inner plexiform layer (GC-IPL) thicknesses measured on optical coherence tomography images.

MAIN OUTCOMES AND MEASURES Odds ratios and hazard ratios for incident dementia per SD decrease in retinal layer thickness adjusted for age, sex, education, and cardiovascular risk factors.

RESULTS Of 5065 individuals eligible for optical coherence tomography scanning, 3289 (64.9%) (mean [SD] age 68.9 [9.9] years, 1879 [57%] women) were included in the analysis. Of these 3289 individuals, 41 (1.2%) already had dementia. Thinner GC-IPL was associated with prevalent dementia (odds ratio per SD decrease in GC-IPL, 1.37 [95% CI, 0.99-1.90]). No association was found of RNFL with prevalent dementia. During 14 674 person-years of follow-up (mean [SD], 4.5 [1.6] years), 86 individuals (2.6%) developed dementia of whom 68 (2.1%) had Alzheimer disease. Thinner RNFL at baseline was associated with an increased risk of developing dementia (hazard ratio per SD decrease in RNFL, 1.44 [95% CI, 1.19-1.75]), which was similar for Alzhein
was found between GC-IPL t
0.90-1.43]).

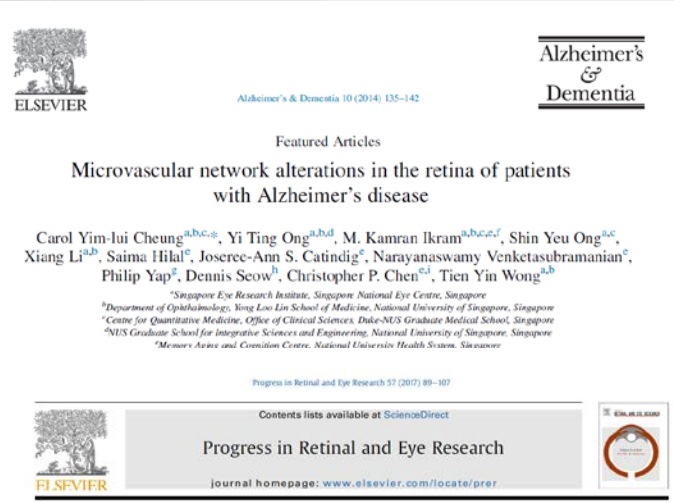
CONCLUSIONS AND RELEVAN
dementia, including Alzheim
as a preclinical biomarker for

Table 3. Association of Inner Retinal Layer Thickness With Incident Dementia

Variable	Model 1 Hazard Ratio (95% CI)[a]	Model 1 *P* Value	Model 2 Hazard Ratio (95% CI)[b]	Model 2 *P* Value
All dementia				
Retinal nerve fiber layer[c]				
Per SD decrease	1.51 (1.25-1.82)	<.001	1.44 (1.19-1.75)	<.001
Per 1-µm decrease	1.03 (1.01-1.04)	<.001	1.02 (1.01-1.04)	<.001
Ganglion cell-inner plexiform layer[d]				
Per SD decrease	1.13 (0.89-1.42)	.31	1.13 (0.90-1.43)	.29
Per 1-µm decrease	1.02 (0.99-1.05)	.33	1.02 (0.99-1.05)	.29
Alzheimer disease				
Retinal nerve fiber layer[e]				
Per SD decrease	1.49 (1.20-1.84)	<.001	1.43 (1.15-1.78)	.001
Per 1-µm decrease	1.03 (1.01-1.04)	<.001	1.02 (1.01-1.04)	.001
Ganglion cel-inner plexiform layer[f]				
Per SD decrease	1.15 (0.90-1.48)	.28	1.16 (0.90-1.48)	.25
Per 1-µm decrease	1.02 (0.99-1.05)	.28	1.02 (0.99-1.05)	.25

*RNFL thinning is associated with development of **dementia***

So is retinal Imaging a viable biomarker of AD?



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Alzheimer's & Dementia 10 (2014) 135–142

Featured Articles

Microvascular network alterations in the retina of patients with Alzheimer's disease

Carol Yim-lui Cheung[a,b,c,*], Yi Ting Ong[a,b,d], M. Kamran Ikram[a,b,c,e,f], Shin Yeu Ong[a,c], Xiang Li[a,b], Saima Hilal[g], Joseree-Ann S. Catindig[g], Narayanaswamy Venketasubramanian[g], Philip Yap[g], Dennis Seow[h], Christopher P. Chen[g,i], Tien Yin Wong[a,b]

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Progress in Retinal and Eye Research 57 (2017) 89–107

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Imaging retina to study dementia and stroke

Carol Yim-lui Cheung [a,*,1,2], M. Kamran Ikram [c,d,1,2], Christopher Chen [e,f,2], Tien Yin Wong [b,c,2]

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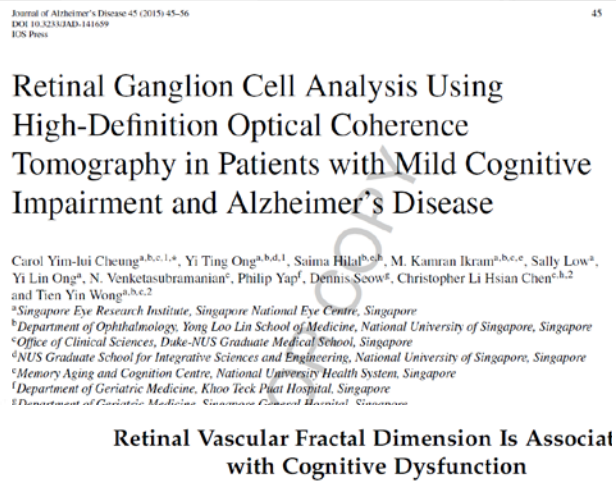
brain. Retinal components such as the microvasculature and retinal ganglion cell axons can now be visualized non-invasively using different retinal imaging techniques e.g., ocular fundus photography and optical coherence tomography. Advances in retinal imaging may provide new and potentially important insights into cerebrovascular neurodegenerative processes in addition to what is currently possible with neuro-imaging. In this review, we present an overview of the current literature on the application of



Journal of Alzheimer's Disease 45 (2015) 45–56
DOI 10.3233/JAD-141659
IOS Press

45

Retinal Ganglion Cell Analysis Using High-Definition Optical Coherence Tomography in Patients with Mild Cognitive Impairment and Alzheimer's Disease

Carol Yim-lui Cheung[a,b,c,1,*], Yi Ting Ong[a,b,d,1], Saima Hilal[b,e,2], M. Kamran Ikram[a,b,c,e], Sally Low[a], Yi Lin Ong[a], N. Venketasubramanian[e], Philip Yap[f], Dennis Seow[g], Christopher Li Hsian Chen[c,h,2] and Tien Yin Wong[a,b,c,2]

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[d]NUS Graduate School for Integrative Sciences and Engineering, National University of Singapore, Singapore
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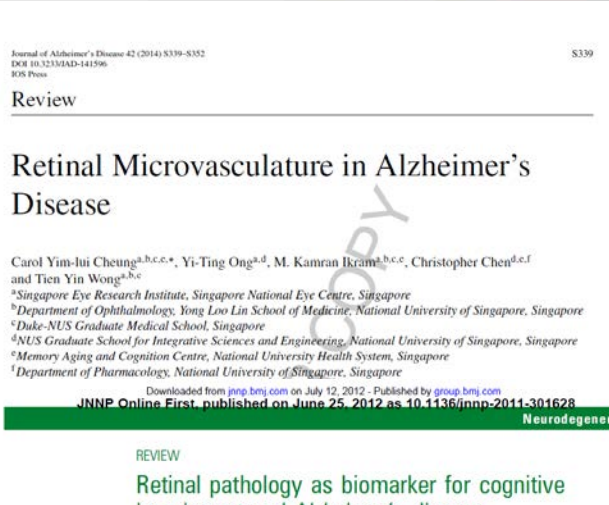
Retinal Vascular Fractal Dimension Is Associat with Cognitive Dysfunction

Carol Yim-lui Cheung, PhD,*†‡ ShinYeu Ong, MD,*‡ M. Kamran Ikram, Yi Ting Ong, BSc,†‖ Christopher P. Chen, FRCP,¶ N. Venketasubramanian, MBBS, MMd, FAMS, FRCP,# and Tien Yin Wong,

a locally validated Abbreviated Mental Test (AMT) score ≤6/10 in participants with 0-6 years of formal education and an AMT score ≤8/10 in those with more than 6 years of formal education. Cognitive dysfunction was identified in 262 of the 1202 participants (21.8%). Decreased retinal vascular D was significantly associ-



Journal of Alzheimer's Disease 42 (2014) S339–S352
DOI 10.3233/JAD-141596
IOS Press

S339

Review

Retinal Microvasculature in Alzheimer's Disease

Carol Yim-lui Cheung[a,b,c,e,*], Yi-Ting Ong[a,d], M. Kamran Ikram[a,b,c,e], Christopher Chen[d,e,f] and Tien Yin Wong[a,b,c]

[a]Singapore Eye Research Institute, Singapore National Eye Centre, Singapore
[b]Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[c]Duke-NUS Graduate Medical School, Singapore
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[e]Memory Aging and Cognition Centre, National University Health System, Singapore
[f]Department of Pharmacology, National University of Singapore, Singapore

JNNP Online First, published on June 25, 2012 as 10.1136/jnnp-2011-301628

Neurodegene

REVIEW

Retinal pathology as biomarker for cognitive impairment and Alzheimer's disease

Mohammad Kamran Ikram,[1,2,3,4,5] Carol Y Cheung,[1,2] Tien Y Wong,[1,2] Christopher P L H Chen[4,6]

[1]Department of Ophthalmology, Yong Loo Lin School of

ABSTRACT

Alzheimer's disease (AD) is the most common cause of

Singapore, Singapore

Correspondence to
Dr Mohammad Kamran Ikram, National University Health

many features with the brain, including embryological origin, anatomical (such as microvascular bed) and physiological characteristics (such as blood-tissue barrier), it has been suggested that the retina may

Although substantial progress has been m the past few decades in understanding A into clinical benefits d by the diagnosti present criteria to currently only symp le for clinically di t that improved me ction are essential to viduals who have a AD, so that inter y the progression o gies. Over the l major advances i for AD and MCI usi of-the-art neuroimaging and biochemical an the cerebrospinal fluid (CSF). Although symptoms of dementia become manifest la course of the disease, it has been shown

*AD has a unique "**Retinal Fingerprint**"*
that can be detected by retinal imaging

Biomarker

- A biomarker is defined as an ***objective*** substance, characteristic, or other parameter of ***a biological process*** that enables the assessment of a disease risk or prognosis and provides guidance for diagnosis or monitoring of treatment.

- Biomarkers may aid in risk profiling to identify those ***at greatest risk***, detection of pathology at the ***earliest possible stage***, and by providing ***end points for trials*** that identify benefit earlier in the natural history of the disease, thus accelerating the development of new treatments.

- For example, measures of amyloid-β and tau pathology using PET or CSF are biomarkers of AD

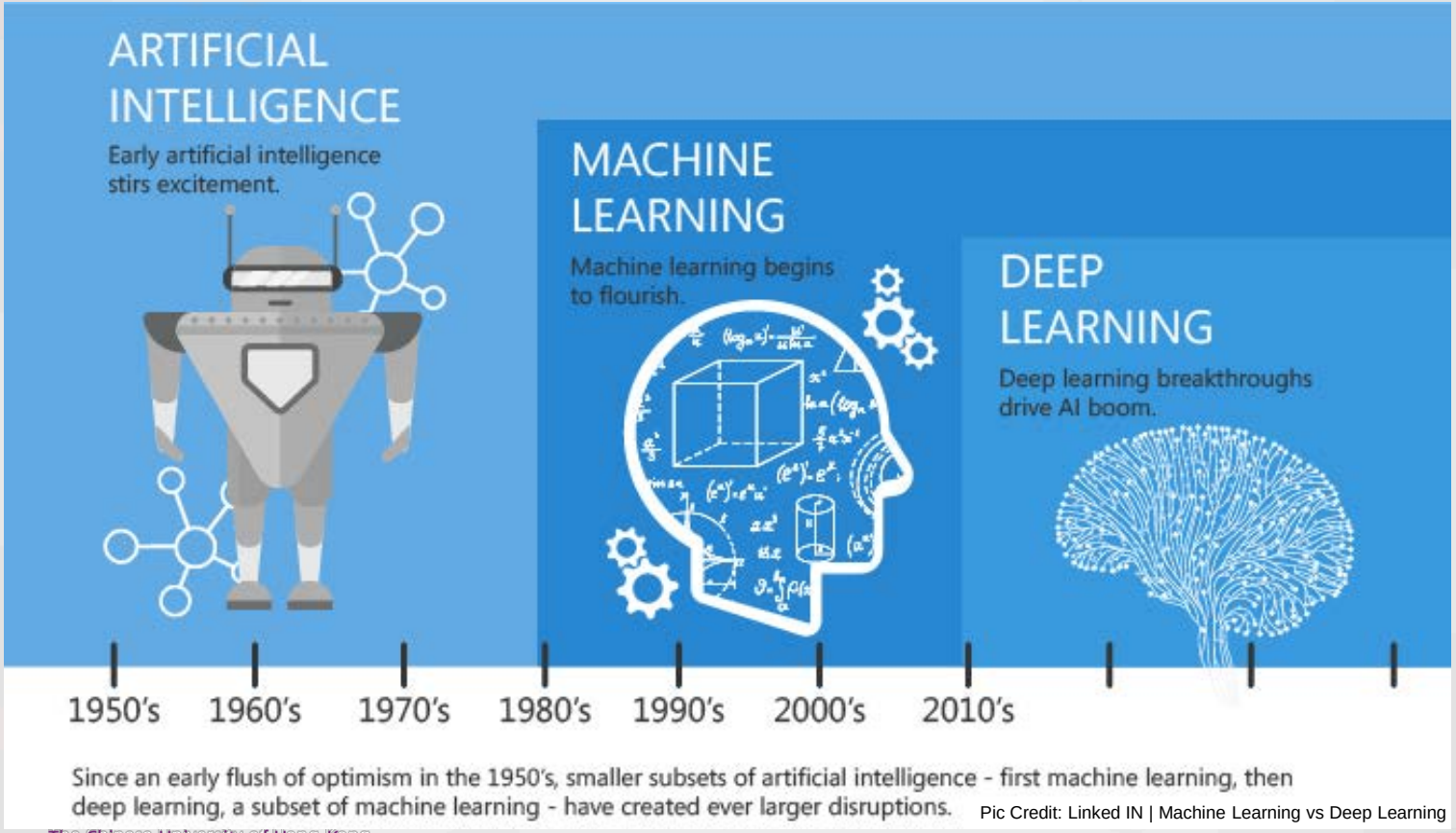
Yassine, H. N. Targeting prodromal Alzheimer's disease: too late for prevention? Lancet Neurol 16, 946-947, (2017).
Livingston, G. et al. Dementia prevention, intervention, and care. Lancet 390, 2673-2734, (2017).

So is retinal Imaging a viable biomarker of AD?

- Current retinal measures **not specific** to AD.
  - Associated with aging, vascular, neurological and systemic diseases
- **Strength of the associations** relatively modest.
  - Missing some ‘”retinal features”, not fully represented by currently defined parameters (e.g., retinal vessel caliber, RNFL, GC-IPL).
- Currently no good ways to incorporate retinal features related to AD, and identify who is at “high-risk”

Retinal imaging has not yet to meet the requirements to be considered a biomarker

Artificial Intelligence → Machine Learning → Deep Learning



Pic Credit: Linked IN | Machine Learning vs Deep Learning

Research

JAMA Ophthalmology | Original Investigation

Automated Grading of Age-Related Macular Degeneration From Color Fundus Images Using Deep Convolutional Neural Networks

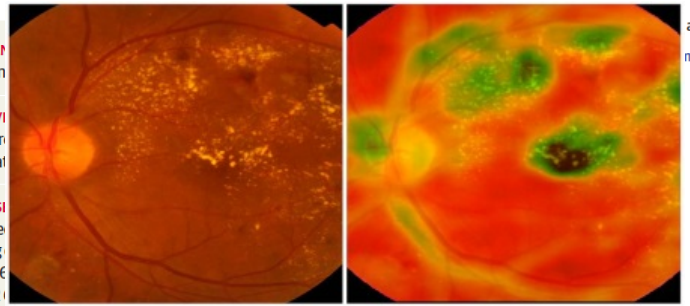
Philippe M. Burlina, PhD; Neil Joshi, BS; Michael Pekala, MS; Katia D. Pacheco, MD; David E. Freund, PhD; Neil M. Bressler, MD

Research

JAMA | Original Investigation

Development and Validation of a Deep Learning System for Diabetic Retinopathy and Related Eye Diseases Using Retinal Images From Multiethnic Populations With Diabetes

Daniel Shu Wei Ting, MD, PhD; Carol Yim-Lui Cheung, PhD; Gilbert Lim, PhD; Gavin Siew Wei Tan, FRCSEd; Nguyen D. Quang, BEng; Alfred Gan, MSc; Haslina Hamzah, BSc; Renata Garcia-Franco, MD; Ian Yew San Yeo, FRCSEd; Shu Yen Lee, FRCSEd; Edmund Yick Mun Wong, FRCSEd; Charumathi Sabanayagam, MD, PhD; Mani Baskaran, MD, PhD; Farah Ibrahim, MB, BCh, BAO; Ngiap Chuan Tan, MCI, FAMS; Eric A. Finkelstein, MHA, PhD; Ecosse L. Lamoureux, PhD; Ian Y. Wong, FRCOph; Neil M. Bressler, MD; Sobha Sivaprasad, FRCOph; Rohit Varma, MD, MPH; Jost B. Jonas, MD, PhD; Ming Guang He, MD, PhD; Ching-Yu Cheng, MD, PhD; Gemmy Chui Ming Cheung, FRCOph; Tin Aung, MD, PhD; Wynne Hsu, PhD; Mong Li Lee, PhD; Tien Yin Wong, MD, PhD



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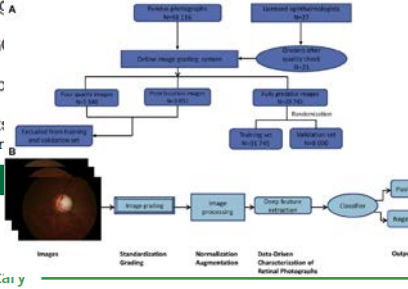
Efficacy of a Deep Learning System for Detecting Glaucomatous Optic Neuropathy Based on Color Fundus Photographs

Zhixi Li, MD,[1,*] Yifan He, BS,[2,*] Stuart Keel, PhD,[3,*] Wei Meng, BS,[2] Robert T. Chang, PhD,[4] Mingguang He, MD, PhD[1,3]

Purpose: To assess the performance of a deep learning alg
neuropathy (GON) based on color fundus photographs.
Design: A deep learning system for the classification of G
GON on color fundus photographs.
Participants: We retrospectively included 48 116 fundus p
a deep learning algorithm.
Methods: This study recruited 21 trained ophthalmologist
defined as vertical cup-to-disc ratio of 0.7 or more and other tyr



Finding Glaucoma in Color Fundus Photographs Using Deep Learning

Invited Commentary

Finding Glaucoma in Color Fundus Photographs Using Deep Learning

Karine D. Bojikian, MD, PhD; Cecilia S. Lee, MD, MS; Aaron Y. Lee, MD, MSCI

Advances in artificial intelligence (AI) and applications of deep learning in ophthalmic imaging analyses have created remarkable successes and enthusiasm.[1-3] In this issue of *JAMA Ophthalmology*, Liu and colleagues[4] report a deep learning system (DLS) for detecting glaucomatous optic neuropathy (GON) and its generalizability in various data sets of color fundus photographs. In addition to the local validation set, the authors assessed the model's performance in external validation data sets that varied in geographic location, population ethnicities, and camera systems. The area under the receiver operating characteristic curve for the local validation set was 0.996, whereas the areas under the precision-recall curve were 0.

Related article

ties, and specificities, the authors suggested that DLS could b
applied in current GON screening programs. However, refer
able glaucoma was noted to be imbalanced across the train
ing data set and all external validation data sets. The use of are
under the receiver operating characteristic curve is prevalen
in ophthalmic binary classification results, but the area un
der the precision-recall curve is noted to be a more accurat
measure of performance.[5] The inclusion of a balanced test se
accuracy or including the area under the precision-recal
curve in the reported metrics would greatly strengthen the un
derstanding of the performance of automated diagnosti
algorithms.

Better understanding of the strengths and limitations o

nature biomedical engineering

ARTICLES

https://doi.org/10.1038/s41551-018-0195-0

Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning

Ryan Poplin[1,4], Avinash V. Varadarajan[1,4], Katy Blumer[1], Yun Liu[1], Mich
Greg S. Corrado[1], Lily Peng[1,4]* and Dale R. Webster[1,4]

CVD risk factors

nature biomedical engineering

ARTICLES

https://doi.org/10.1038/s41551-021-00745-6

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Deep-learning models for the detection and incidence prediction of chronic kidney disease and type 2 diabetes from retinal fundus images

Kang Zhang[1,2,23] ✉, Xiaohong Liu[3,23], Jie Xu[4,5,23], Jin Yuan[6,23], Wenjia Cai[6,23], Ting Chen[3] ✉, Kai Wang[5], Yuanxu Gao[2], Sheng Nie[7], Xiaodong Xu[5], Xiaoqi Qin[5], Yuandong Su[1], Wenqin Xu[1], Andrea Olvera[1], Kanmin Xue[8], Zhihuan Li[1], Meixia Zhang[1], Xiaoxi Zeng[1,9], Charlotte L. Zhang[10], Oulan Li[10], Edward E. Zhang[10], Jie Zhu[11], Yiming Xu[3], Daniel
Shaoyun Li[13], Iat Fan Lai[14], Ying Chi[15], Changuang Wang[16], M
Johnson Lau[18], Dennis Lam[18,19], Xiaoguang Zou[20], Aizezi Wu
Fan Fan Hou[7], Ping Zhang[5], Tao Xu[10] ✉, Yong Zhou[22] ✉ and Guangyu Wang[5] ✉

CKD and diabetes

Prediction of systemic biomarkers from retinal photographs: development and validation of deep-learning algorithms

Tyler Hyungtaek Rim*, Geunyoung Lee*, Youngnam Kim*, Yih-Chung Tham*, Chan Joo Lee, Su Jung Baik, Young Ah Kim, Marco Yu, Mihir Deshmukh, Byoung Kwon Lee, Sungha Park, Hyeon Chang Kim, Charumathi Sabayanagam, Daniel S W Ting, Ya Xing Wang, Jost B Jonas, Sung Soo Kim†, Tien Yin Wong†, Ching-Yu Cheng†

Summary

Background
sex, blood
deep learni
remains unexplored.

body muscle mass and serum creatinine

Lancet Digital Health 2020; 2: e526–36

* Co-first authors

† Contributed equally

OPEN

Effects of Hypertension, Diabetes, and Smoking on Age and Sex Prediction from Retinal Fundus Images

Yong Dae Kim[1,2,7], Kyoung Jin Noh[1,7], Seong Jun Byun[1,7], Soochahn Lee[3], Tackeun Kim[4], Leonard Sunwoo[5], Kyong Joon Lee[5], Si-Hyuck Kang[6], Kyu Hyung Park[1] & Sang Jun Park[1*]

Retinal fundus images are used to detect organ damage from vasc
and hypertension) and screen ocular diseases. We aimed to assess
(CNN) models that predict age and sex from retinal fundus images
participants with underlying systemic vascular-altered status. In a
clues regarding differences between normal ageing and vascular pathologic changes using the CNN

Age and sex

SCIENTIFIC REPORTS

OPEN

Detection of smoking status from retinal images; a Convolutional Neural Network study

eceived: 3 January 2019
ccepted: 29 April 2019
ublished online: 09 May 2019

Ehsan Vaghefi[1,2], Song Yang[1], Sophie Hill[3], Gayl Humphrey[4], Nata
David Squirrell[3]

Cardiovascular diseases are directly linked to smoking habits, which has both physiological and anatomical effects on the systemic and retinal circulations, and these changes can be detected with fundus photographs. Here, we aimed to 1- design a Convolutional Neural Network (CNN), using retinal photographs, to differentiate between smokers and non-smokers; and 2- use the attention maps to

Smoking

Association of Cardiovascular Mortality and Deep Learning-Funduscopic Atherosclerosis Score derived from Retinal Fundus Images

JOOYOUNG CHANG, AHRYOUNG KO, SANG MIN PARK, SEULGGIE CHOI. KYUWOONG KIM. SUNG MIN KIM, JAE MOON YUN, UK KANG, IL HYUNG SHIN, JOO YOU
BAEK-LOK OH, AND KI HO PARK

CVD mortality

A deep learning model for detection of Alzheimer's disease based on retinal photographs: a retrospective, multicentre case-control study

Carol Y Cheung, An Ran Ran*, Shujun Wang*, Victor T T Chan, Kaiser Sham, Saima Hilal, Narayanaswamy Venketasubramanian, Ching-Yu Cheng, Charumathi Sabanayagam, Yih Chung Tham, Leopold Schmetterer, Gareth J McKay, Michael A Williams, Adrian Wong, Lisa W C Au, Zhihui Lu, Jason C Yam, Clement C Tham, John J Chen, Oana M Dumitrascu, Pheng-Ann Heng, Timothy C Y Kwok, Vincent C T Mok†, Dan Milea†, Christopher Li-Hsian Chen†, Tien Yin Wong†*

Summary

Background There is no simple model to screen for Alzheimer's disease, partly because the diagnosis of Alzheimer's disease itself is complex—typically involving expensive and sometimes invasive tests not commonly available outside highly specialised clinical settings. We aimed to develop a deep learning algorithm that could use retinal photographs alone, which is the most common method of non-invasive imaging the retina to detect Alzheimer's disease-dementia.

Methods In this retrospective, multicentre case-control study, we trained, validated, and tested a deep learning algorithm to detect Alzheimer's disease-dementia from retinal photographs using retrospectively collected data from 11 studies that recruited patients with Alzheimer's disease-dementia and people without disease from different countries. Our main aim was to develop a bilateral model to detect Alzheimer's disease-dementia from retinal photographs alone. We designed and internally validated the bilateral deep learning model using retinal photographs from six studies. We used the EfficientNet-b2 network as the backbone of the model to extract features from the images. Integrated features from four retinal photographs (optic nerve head-centred and macula-centred fields from both eyes) for each individual were used to develop supervised deep learning models and equip the network with unsupervised domain adaptation technique, to address dataset discrepancy between the different studies. We tested the trained model using five other studies, three of which used PET as a biomarker of significant amyloid β burden (testing the deep learning model between amyloid β positive *vs* amyloid β negative).

Findings 12 949 retinal photographs from 648 patients with Alzheimer's disease and 3240 people without the disease were used to train, validate, and test the deep learning model. In the internal validation dataset, the deep learning model had 83·6% (SD 2·5) accuracy, 93·2% (SD 2·2) sensitivity, 82·0% (SD 3·1) specificity, and an area under the receiver operating characteristic curve (AUROC) of 0·93 (0·01) for detecting Alzheimer's disease-dementia. In the testing datasets, the bilateral deep learning model had accuracies ranging from 79·6% (SD 15·5) to 92·1% (11·4) and AUROCs ranging from 0·73 (SD 0·24) to 0·91 (0·10). In the datasets with data on PET, the model was able to differentiate between participants who were amyloid β positive and those who were amyloid β negative: accuracies ranged from 80·6 (SD 13·4%) to 89·3 (13·7%) and AUROC ranged from 0·68 (SD 0·24) to 0·86 (0·16). In subgroup analyses, the discriminative performance of the model was improved in patients with eye disease (accuracy 89·6% [SD 12·5%]) versus those without eye disease (71·7% [11·6%]) and patients with diabetes (81·9% [SD 20·3%]) versus those without the disease (72·4% [11·7%]).

Interpretation A retinal photograph-based deep learning algorithm can detect Alzheimer's disease with good accuracy, showing its potential for screening Alzheimer's disease in a community setting.

Lancet Digit Health 2022

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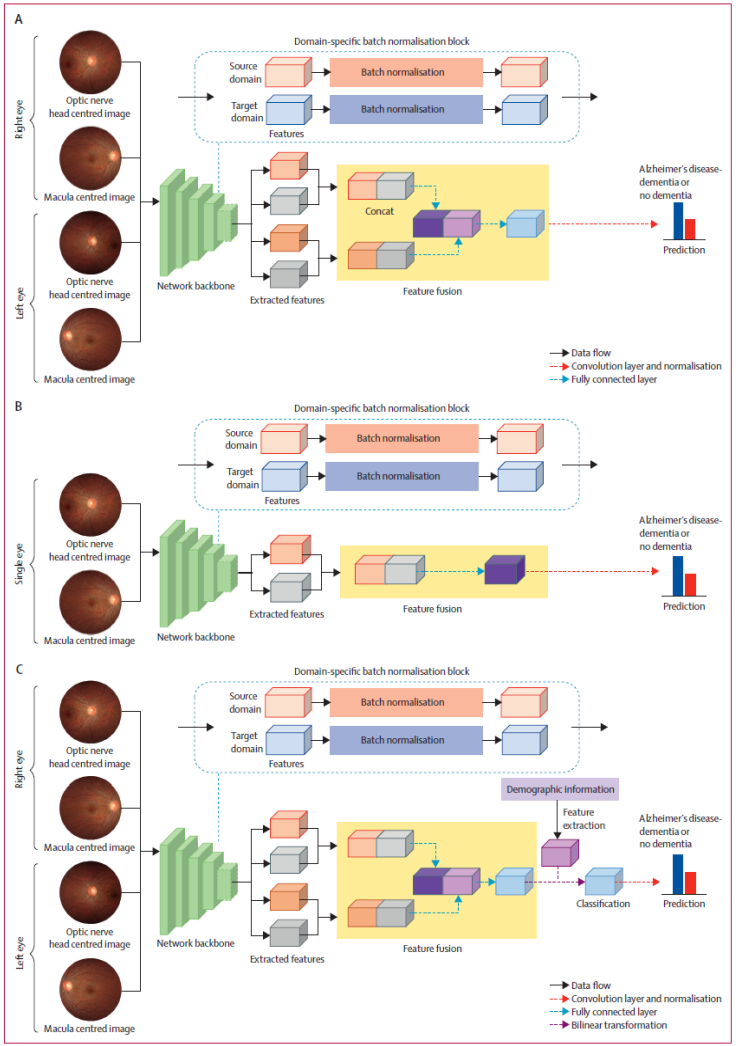
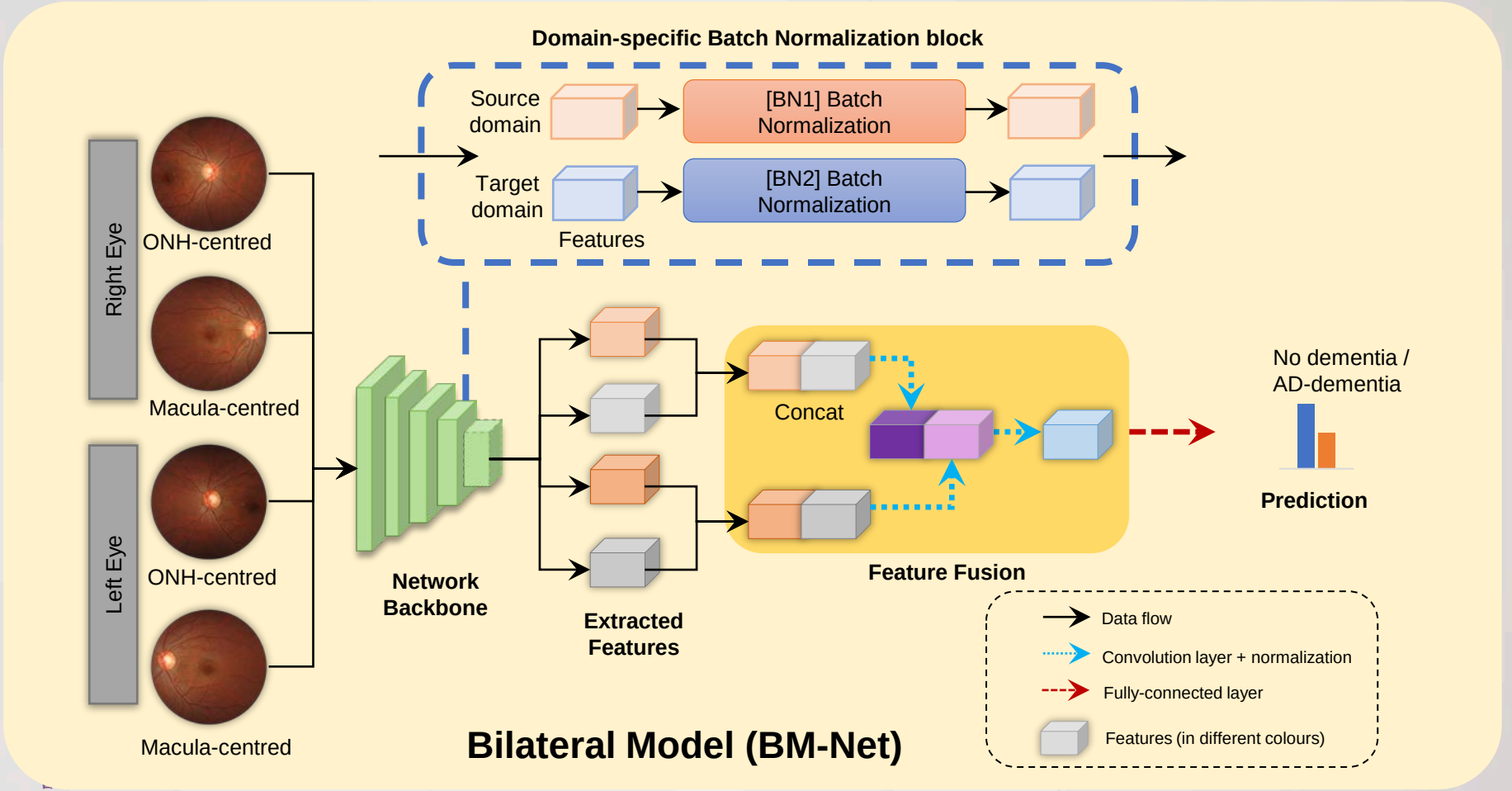


Figure: **Overview of the proposed deep learning models**
We used domain-specific batch normalisation block for unsupervised domain adaptation. All the remaining layers are shared through the network. (A) The bilateral model feeds four retinal photographs, including optic nerve head-centred and macula-centred photographs of right and left eye for the classification of Alzheimer's disease-dementia and no dementia. (B) The unilateral model fuses the information from both optic nerve head-centred and macula-centred images in each eye for the Alzheimer's disease-dementia prediction. (C) The hybrid model is based on our proposed bilateral model, by integrating demographic information into the deep models using bilinear transformation.



Cheung CY, Ran AR, Wang SJ, et al (The Lancet Digital Health 2022)

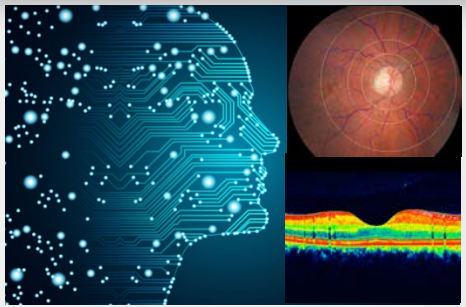
The performance of the deep-learning based model in the internal validation and the testing datasets

	Accuracy, %	Sensitivity, %	Specificity, %	AUROC
AD-dementia vs. no dementia				
Internal validation	83·6% ± 2·5%	93·2% ± 2·2%	82·0% ± 3·1%	0·93 ± 0·01
Testing-1	79·6% ± 15·5%	72·0% ± 19·8%	100·0% ± 0·0%	0·77 ± 0·21
Testing-2	89·3% ± 13·7%	91·7% ± 16·7%	90·0% ± 20·0%	0·73 ± 0·24
Testing-3	85·0% ± 9·1%	93·3% ± 14·9%	93·3% ± 14·9%	0·74 ± 0·16
Testing-4	92·1% ± 11·4%	95·0% ± 11·2%	93·3% ± 14·9%	0·88 ± 0·16
Testing-5	91·7% ± 8·4%	100·0% ± 0·0%	90·9% ± 9·1%	0·91 ± 0·10
Aβ-positive vs. Aβ-negative				
Testing-1	80·6% ± 13·4%	75·4% ± 22·5%	92·0% ± 11·5%	0·68 ± 0·24
Testing-2	89·3% ± 13·7%	90·0% ± 20·0%	93·8% ± 12·5%	0·86 ± 0·16
Testing-3	85·4% ± 10·5%	86·7% ± 16·3%	100·0% ± 0·0%	0·80 ± 0·14
Aβ-positive (clinically diagnosed AD-dementia cases only) vs. Aβ-negative (no cognitive impairment controls only)				
Testing-1	85·6% ± 10·9%	82·5% ± 23·6%	100·0% ± 0·0%	0·77 ± 0·21
Testing-2	90·8% ± 10·7%	91·7% ± 16·7%	93·8% ± 12·5%	0·85 ± 0·17
Testing-3	85·4% ± 17·2%	79·2% ± 25·0%	100·0% ± 0·0%	0·73 ± 0·21

Retinal imaging with deep learning → stratify AD

1. Screening tool in community.
2. Opportunistic screening tool in eye clinics.
3. Assessment for subjects with memory or cognitive symptom in general or specialized clinics.

Retinal imaging analysis using AI



High risk for AD

Moderate risk for AD

Low risk for AD

1. Confirmatory investigations (e.g. PET imaging, cerebrospinal fluid) at specialized clinics.
2. Implementation of potential preventive therapies (e.g. lifestyle modifications).
3. Recruitment into clinical trials.

Cheung CY, et al. J Neurol Neurosurg Psychiatry 2021;0:1–12.

nature biomedical engineering

ARTICLES

https://doi.org/10.1038/s41551-020-00626-4

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A deep-learning system for the assessment of cardiovascular disease risk via the measurement of retinal-vessel calibre

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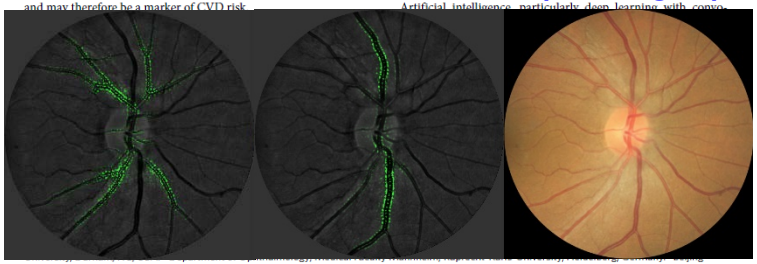
Retinal blood vessels provide information on the risk of cardiovascular disease (CVD). Here, we report the development and validation of deep-learning models for the automated measurement of retinal-vessel calibre in retinal photographs, using diverse multiethnic multicountry datasets that comprise more than 70,000 images. Retinal-vessel calibre measured by the models and by expert human graders showed high agreement, with overall intraclass correlation coefficients of between 0.82 and 0.95. The models performed comparably to or better than expert graders in associations between measurements of retinal-vessel calibre and CVD risk factors, including blood pressure, body-mass index, total cholesterol and glycated-haemoglobin levels. In retrospectively measured prospective datasets from a population-based study, baseline measurements performed by the deep-learning system were associated with incident CVD. Our findings motivate the development of clinically applicable explainable end-to-end deep-learning systems for the prediction of CVD on the basis of the features of retinal vessels in retinal photographs.

For more than a century, physicians have performed a fundus examination in patients with hypertension to detect hypertensive retinopathy (vascular damage as a means to estimate cardiovascular disease (CVD) risk[1–4]. This examination is based on the promise that changes observed in the retinal vascular ture, such as generalized retinal arteriolar narrowing, may reflect cular changes in cerebral and coronary blood vessels and may therefore be a marker of CVD risk.

risk factors (such as blood pressure and diabetes)[9,15–19] and the presence of clinical vascular diseases (such as carotid atherosclerosis and arterial stiffness)[20,21] and predictive of cardiovascular and cerebral CVD events (such as coronary heart disease, stroke and mortality)[22–35]. However, further validation of these highly promising findings in large clinical studies has been limited by the reliance on subjective grading or semi-automated software, which require human input. Artificial intelligence, particularly deep learning with convo-

Arteriolar caliber Venular caliber Original photograph



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Retinal vessel caliber, measured using SIVA-DLS, was associated with incident CVD events

			Model 1		Model 2	
	Number at risk (*n*)	Incident CVD event cases (*n* (%))	HR (95% CI)	*P*	HR (95% CI)	*P*
$CRAE_B$						
First quartile	2,221	246 (11.1)	1.27 (1.02–1.59)	0.035	1.23 (0.98–1.55)	0.079
Second quartile	2,244	189 (8.4)	0.94 (0.76–1.15)	0.534	0.93 (0.75–1.15)	0.491
Third quartile	2,256	202 (9.0)	1.03 (0.85–1.25)	0.792	1.02 (0.83–1.25)	0.854
Fourth quartile	2,259	214 (9.5)	Reference		Reference	
Per s.d. decrease	8,980	851 (9.5)	1.18 (1.08–1.30)	<0.001[a]	1.12 (1.02–1.24)	0.024[a]
$CRAE_C$						
First quartile	2,210	247 (11.2)	1.18 (0.94–1.47)	0.156	1.12 (0.89–1.42)	0.337
Second quartile	2,258	185 (8.2)	0.89 (0.73–1.10)	0.280	0.91 (0.74–1.13)	0.383
Third quartile	2,270	197 (8.7)	0.92 (0.75–1.11)	0.380	0.90 (0.74–1.10)	0.311
Fourth quartile	2,242	222 (9.9)	Reference		Reference	
Per s.d. decrease	8,980	851 (9.5)	1.24 (1.13–1.37)	<0.001[a]	1.13 (1.02–1.26)	0.017[a]
$CRVE_B$						
First quartile	2,190	212 (9.7)	Reference		Reference	
Second quartile	2,258	186 (8.2)	1.19 (0.97–1.47)	0.101	1.14 (0.91–1.41)	0.253
Third quartile	2,266	193 (8.5)	1.31 (1.05–1.64)	0.018	1.17 (0.92–1.47)	0.198
Fourth quartile	2,266	260 (11.5)	1.74 (1.37–2.21)	<0.001	1.30 (1.01–1.67)	0.039
Per s.d. increase	8,980	851 (9.5)	1.14 (1.04–1.25)	0.006[a]	1.08 (0.98–1.18)	0.130[a]
$CRVE_C$						
First quartile	2,209	206 (9.3)	Reference		Reference	
Second quartile	2,252	166 (7.4)	1.12 (0.90–1.40)	0.305	1.07 (0.85–1.34)	0.578
Third quartile	2,262	214 (9.5)	1.37 (1.09–1.71)	0.006	1.24 (0.98–1.57)	0.068
Fourth quartile	2,257	265 (11.7)	1.66 (1.31–2.12)	<0.001	1.23 (0.96–1.59)	0.108
Per s.d. increase	8,980	851 (9.5)	1.21 (1.09–1.33)	<0.001[a]	1.09 (0.99–1.21)	0.091[a]

https://doi.org/10.1093/braincomms/fcac212 BRAIN COMMUNICATIONS 2022: Page 1 of 9 | 1

BRAIN COMMUNICATIONS

Deep-learning retinal vessel calibre measurements and risk of cognitive decline and dementia

Carol Y. Cheung,[3,*] Win Lee Edwin Wong,[1,2,*] Saima Hilal,[1,2,6] Cheuk Ni Kan,[1,2] Bibek Gyanwali,[1,2,7] Yih Chung Tham,[4,5] Leopold Schmetterer,[4,8,9,10,11] Dejiang Xu,[12] Mong Li Lee,[12] Wynne Hsu,[12] Narayanaswamy Venketasubramanian,[13] Boon Yeow Tan,[14] Tien Yin Wong[4,5,†] and Christopher P. L. H. Chen[1,2,15,†]

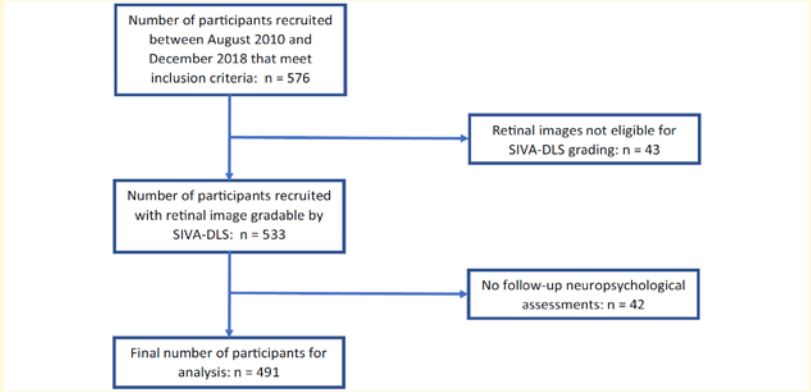

Figure 1 Flow chart with exclusions for study population.

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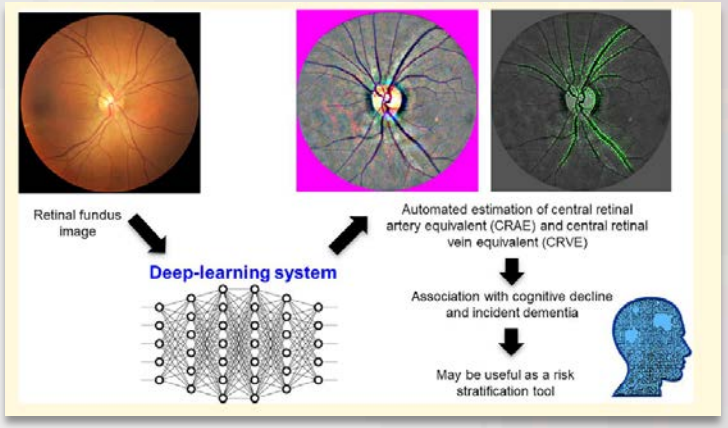

Table 2 Associations between retinal vessel calibres at baseline and risk of cognitive decline. Model 1 was unadjusted; Model 2 was adjusted for age, gender, ethnicity, and fellow calibre at baseline; Model 3 was additionally adjusted for education, cerebrovascular disease status, hypertension, hyperlipidemia, diabetes, and smoking at baseline

	Number of subjects, *n*	Developed cognitive decline, *n* (%)	Model 1 HR (95% CI)	Model 1 *P*-value	Model 2 HR (95% CI)	Model 2 *P*-value	Model 3 HR (95% CI)	Model 3 *P*-value
CRAE								
First tertile (67.35–104.18)	164	101 (61.6%)	1.377 (1.028–1.846)	0.032	1.496 (1.050–2.133)	0.026	1.479 (1.033–2.117)	0.043
Second tertile (104.18–113.85)	163	72 (44.2%)	0.877 (0.638–1.205)	0.417	0.900 (0.645–1.255)	0.533	0.893 (0.640–1.245)	0.504
Third tertile (113.85–148.30)	164	81 (49.4%)	*Reference category*	*NA*	*Reference category*	*NA*	*Reference category*	*NA*
Per SD decrease	491	254 (51.7%)	1.198 (1.058–1.356)	0.004	1.341 (1.133–1.588)	0.001	1.258 (1.062–1.490)	0.008
CRVE								
First tertile (110.52–155.05)	164	89 (54.3%)	*Reference category*	*NA*	*Reference category*	*NA*	*Reference category*	*NA*
Second tertile (155.05–166.87)	163	84 (51.5%)	0.958 (0.711–1.291)	0.778	1.242 (0.895–1.725)	0.195	1.190 (0.851–1.665)	0.310
Third tertile (166.87–230.49)	164	81 (50.3%)	0.913 (0.676–1.234)	0.554	1.364 (0.941–1.976)	0.101	1.213 (0.821–1.792)	0.333
Per SD increase	491	254 (51.7%)	0.989 (0.874–1.120)	0.865	1.281 (1.079–1.522)	0.005	1.204 (1.011–1.434)	0.037

CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent; CI, confidence interval; HR, hazard ratio; SD, standard deviation.

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IOS Press

Review

Deep Reinforcement Learning-Based Retinal Imaging in Alzheimer's Disease: Potential and Perspectives

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Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong, China

Handling Associate Editor: Defu Yang

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DRL: a learning strategy that constructs an "Optimal Policy" through trial-and-error to solve decision-making problems

BACKGROUND

Alzheimer's disease (AD), the most common cause of dementia, poses a significant clinical challenge worldwide amid today's aging population [1]. With evidence revealing the presence of pathophysiological markers before the manifestation of clinical symptoms [2, 3], the retina has been considered a "window" to study AD as an accessible extension of the brain in terms of embryology, anatomy, and physiology [4].

The advancement in retinal imaging modalities, such as optical coherence tomography (OCT), OCT angiography (OCT-A), and fundus photography (FP), has enabled detailed investigation into the neuronal and microvascular structures of the retina non-invasively [5–8]. Concomitantly, the development of cutting-edge artificial intelligence (AI) algorithms has the potential to facilitate retinal imaging analysis [5, 9–11], with deep learning (DL) showing promising results in detecting systemic diseases from retinal images, such as AD [10, 12, 13], cardiovascular disease [14, 15], kidney disease [16, 17], and

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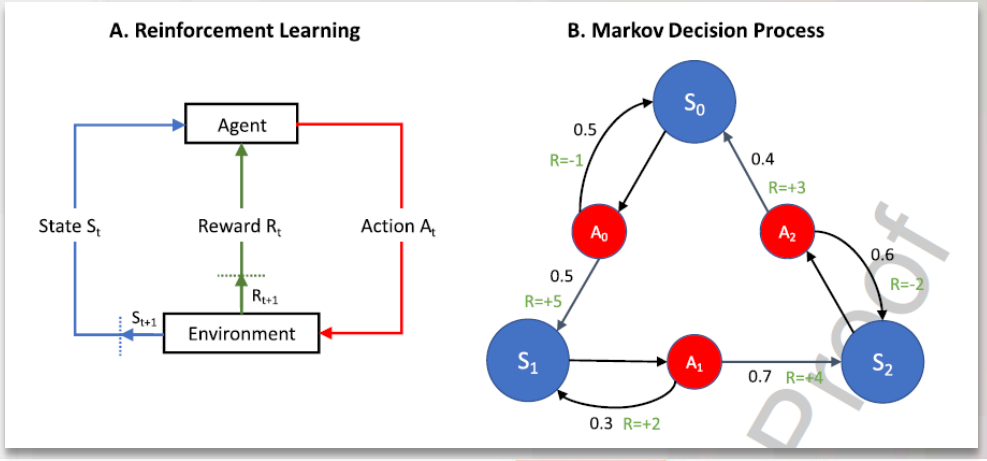

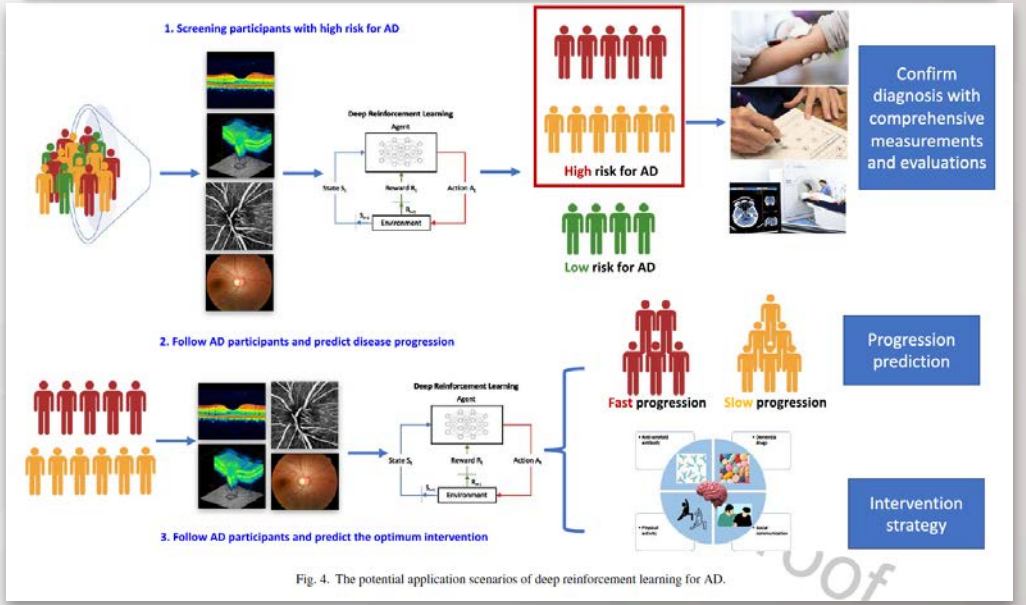

Fig. 4. The potential application scenarios of deep reinforcement learning for AD.

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Next → Large Language Models (LLMs)

Introducing ChatGPT

We've trained a model called ChatGPT which interacts in a conversational way. The dialogue format makes it possible for ChatGPT to answer followup questions, admit its mistakes, challenge incorrect premises, and reject inappropriate requests.

Try ChatGPT ↗ Read about ChatGPT Plus

"We believe the development of general-purpose artificial intelligence that benefits all of humanity must be carried out with a knowledge of and respect for the different perspectives and experiences that represent the full spectrum of humanity."

VIEWPOINT

AI-Generated Medical Advice—GPT and Beyond

Claudia E. Haupt, JSD, PhD
Northeastern University School of Law, Boston, Massachusetts; and

For years, experts have speculated about the future role of artificial intelligence (AI) in health care. Some AI tools can outperform physicians on specific tasks in radiology, dermatology, and other fields, which raised concerns that AI might render certain specialists obsolete. Some feared AI might expose patients and clinicians to

However, in its current form, GP omissions. It can fail at simple tasks, tic, or insidiously commit errors that scrutiny by subject matter experts. Sc when asked to provide references fo makes them up. Educators fear stu

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Research

JAMA Ophthalmology | Brief Report

Performance of an Artificial Intelligence Chatbot in Ophthalmic Knowledge Assessment

Andrew Mihalache, BMSc(C); Marko M. Popovic, MD, MPH(C); Rajeev H. Muni, MD, MSc

NCE ChatGPT is an artificial intelligence (AI) chatbot that has significant nplications. Training curricula using AI are being developed in medicine, erformance of chatbots in ophthalmology has not been characterized.

E To assess the performance of ChatGPT in answering practice questions certification in ophthalmology.

ETTING, AND PARTICIPANTS This cross-sectional study used a consecutive sample sed multiple-choice questions provided by the OphthoQuestions practice bank for board certification examination preparation. Of 166 available hoice questions, 125 (75%) were text-based.

ES ChatGPT answered questions from January 9 to 16, 2023, and on 17 2023

SPECIAL REPORT

Jeffrey M. Drazen, M.D., *Editor;*
Isaac S. Kohane, M.D., Ph.D., and Tze-Yun Leong, Ph.D., *Guest Editors*

AI IN MEDICINE

Benefits, Limits, and Risks of GPT-4 as an AI Chatbot for Medicine

Peter Lee, Ph.D., Sebastien Bubeck, Ph.D., and Joseph Petro, M.S

The uses of artificial intelligence (AI) in medicine have been growing in many areas, including in the analysis of medical images,[1] the detection of drug interactions,[2] the identification of high-risk patients,[3] and the coding of medical notes.[4] Several such uses of AI are the topics of the "AI in Medicine" review article series that debuts in

"prompt engineering," whi a science. Although future to be far less sensitive to used in a prompt, at presen developed and tested with duce the best results. At th a prompt is a question or re

EDITORIAL

What Artificial Intelligence Chatbots Mean for Editors, Authors, and Readers of Peer-Reviewed Ophthalmic Literature

Neil M. Bressler, MD

A new artificial intelligence (AI) chatbot debuted in November 2022. OpenAI's ChatGPT[1] lets an individual type a request and then almost immediately receive text designed to seem written by a human. The potential advantages of this

Specifically, the first criterion includes "substantial contributions to conception or design of the work or the acquisition, analysis, or interpretation of data for the work."[2] Asking a chatbot to design the methods of an original investigation is

Interview

‘We’ve discovered the secret of immortality. The bad news is it’s not for us’: why the godfather of AI fears for humanity

Alex Hern

Hinton: ‘Overreacting is a lot better than under-reacting.’ Photograph: Sarah Lee/The Guardian

Geoffrey Hinton recently quit Google warning of the dangers of artificial intelligence. Is AI really going to destroy us? And how long do we have to prevent it?

OpenAI CEO calls for laws to mitigate ‘risks of increasingly powerful’ AI

Sam Altman says before Senate judiciary committee that he supports guardrails for technology to minimize harms

ChatGPT CEO shares concern over AI being used to interfere with elections – video

The CEO of OpenAI, the company responsible for creating artificial intelligence chatbot ChatGPT and image generator Dall-E 2, said “regulation of AI is essential” as he testified in his first appearance in front of the US Congress.

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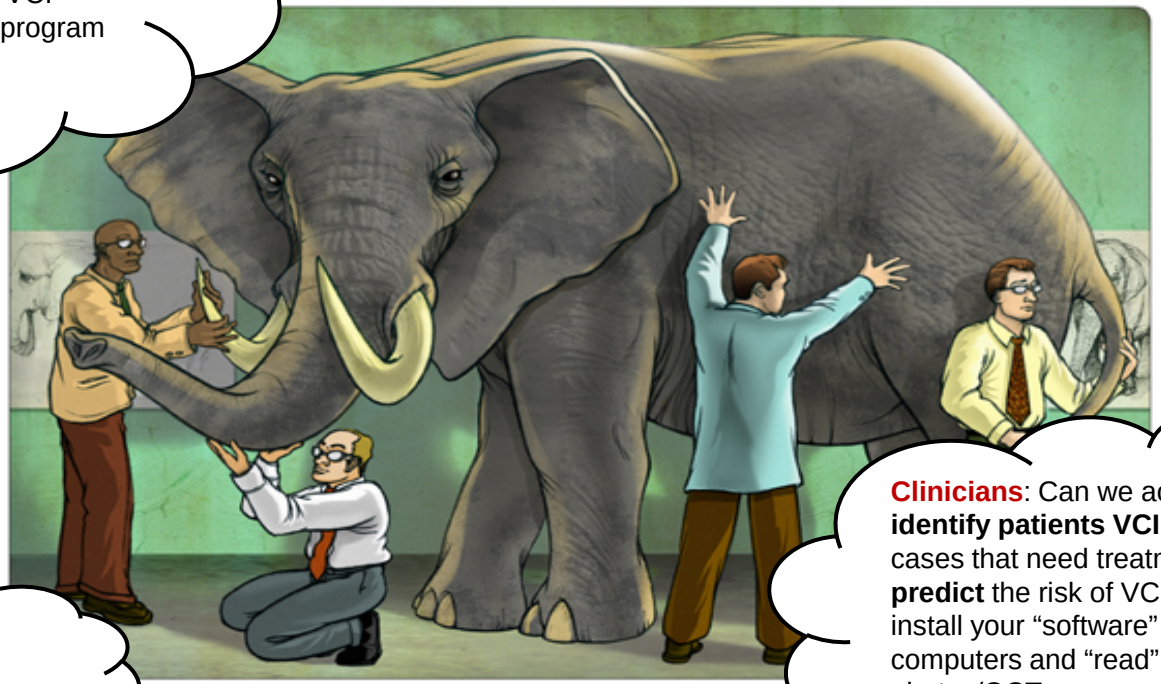
Different Perspectives

Computer Scientists: Just give us millions of images and tell us what is/is not “VCI” …we will give you a program in a few days



Clinicians: Can we accurately **identify patients VCI** and refer cases that need treatment? Can we **predict** the risk of VCI? …just install your “software” into our computers and “read” the fundus photos/OCT

Health payers: Help us save money, reduce manpower….

Take home messages

- Recent studies have demonstrated a link between retinal measures with dementia and AD.
- AI-deep learning has huge potential to automatically interpret retinal images for AD detection.
- Keep learning and being innovative to benefit our patients and improve our healthcare system

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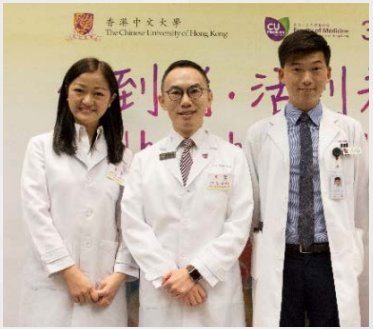
Mayo Clinic, US

BrightFocus Foundation

The Health and Medical Research Fund (HMRF), Hong Kong



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