



## Retinal Imaging

 The application of retinal fundus camera imaging in dementia:  
A systematic review

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<sup>a</sup>Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK<sup>b</sup>Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, Edinburgh, UK<sup>c</sup>College of Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh, UK<sup>d</sup>Department of Psychology, University of Edinburgh, Edinburgh, UK<sup>e</sup>Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK<sup>f</sup>Scottish Imaging Network: A Platform for Scientific Excellence (SINAPSE) Collaboration, Edinburgh, UK<sup>g</sup>VAMPIRE Project and Computer Vision and Image Processing Group School of Science and Engineering (Computing), University of Dundee, Dundee, UK<sup>h</sup>VAMPIRE Project and Edinburgh Clinical Research Facility, University of Edinburgh, Edinburgh, UK**Abstract**

**Introduction:** The ease of imaging the retinal vasculature, and the evolving evidence suggesting this microvascular bed might reflect the cerebral microvasculature, presents an opportunity to investigate cerebrovascular disease and the contribution of microvascular disease to dementia with fundus camera imaging.

**Methods:** A systematic review and meta-analysis was carried out to assess the measurement of retinal properties in dementia using fundus imaging.

**Results:** Ten studies assessing retinal properties in dementia were included. Quantitative measurement revealed significant yet inconsistent pathologic changes in vessel caliber, tortuosity, and fractal dimension. Retinopathy was more prevalent in dementia. No association of age-related macular degeneration with dementia was reported.

**Discussion:** Inconsistent findings across studies provide tentative support for the application of fundus camera imaging as a means of identifying changes associated with dementia. The potential of fundus image analysis in differentiating between dementia subtypes should be investigated using larger well-characterized samples. Future work should focus on refining and standardizing methods and measurements.

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**Q3 Keywords:**

Fundus; Dementia; Alzheimer's disease; Retinal imaging

**1. Introduction**

Dementia poses a major global medical, economic, and public health challenge [1–3]. Given this worldwide burden there is currently great interest in finding early and easily accessible biomarkers of dementia to ultimately aid prevention. An ideal biomarker for dementia screening

should be reliable, predictive, reproducible, noninvasive, simple to perform, and inexpensive [4]. Novel biomarkers, including structural and functional neuroimaging, genetic factors, and biochemical analysis of blood and cerebrospinal fluid, have been examined. Despite this research focus, there remains an ongoing need for sensitive biomarkers for dementia. Increasingly, studies have found evidence that cerebrovascular disease and systemic vascular factors such as type 2 diabetes and hypertension are associated with increased risk of dementia [5,6]. Alzheimer's disease (AD), the most common form of dementia, is known to

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have a vascular component with small-vessel disease, micro-infarction, and cerebral amyloid angiopathy contributing to the pathogenesis [6,7]. Despite the evidence of a vascular component, difficulties in directly visualizing the cerebral microvasculature in vivo have hindered efforts to demonstrate the involvement of cerebral vessels in dementia.

Anatomically and developmentally, the retina is an extension of the brain [8]. Because of the homology between the retinal and cerebral microvasculature [9], the retinal vasculature has potential to be used as a proxy measure whereby the condition of retinal vessels may reflect the condition of the cerebral vasculature. This has distinct advantages because of the ease with which the retina can be noninvasively visualized and photographed, offering a “window” to study brain microvascular and neuronal pathology [10,11]. Different retinal imaging modalities, such as fundus camera imaging and optical coherence tomography (OCT), to measure changes in retinal nerve fiber layer and retinal ganglion cell loss, and fluorescein angiography have been applied in the management and research of systemic diseases. Advancements in retinal imaging technology have led to promising findings, particularly OCT where a recent review demonstrated that the measurement of retinal nerve fiber layer thickness, as a reflection of axonal loss, provides a promising method to aid in the diagnosis of various neurodegenerative diseases, including AD [12]. Although all imaging modalities merit further study, this review chose to focus on the use of fundus camera imaging.

Retinal microvascular abnormalities in relation to cognitive dysfunction and dementia have been described in review articles previously [13–15]. These reviews found evidence to support the hypothesis that retinal microvascular abnormalities are associated with dementia [14,15] or cognitive impairment/dementia both in diabetic patients and the general population [13]. Retinal abnormalities were most consistently associated with poorer verbal memory, information processing speed, and executive function in population-based samples of middle age and older people [13]. Heringa et al. [14] reported stronger associations between retinal microvascular changes and dementia in cross-sectional studies (odds ratio [OR] range, 1.17–5.57) than in longitudinal studies where no consistent associations between retinal morphology and dementia or cognitive impairment were found (OR and hazard ratio [HR] range, 0.77–1.55). Cheung et al. [15] noted that although various studies have found an association between retinal vascular changes and dementia, the results across these studies were variable. The findings were inconclusive because of heterogeneity of study design in terms of retinal parameters, imaging methods, and outcomes. These previous reviews have examined the extent to which retinal properties relate to cognitive ability and dementia [13–15]. To our knowledge, no comprehensive review has been published on the specific utility of *fundus camera imaging* as a

method of identifying and measuring a wide range of retinal changes, specific to dementia and its various subtypes. For the purposes of this review, we define fundus imaging as the use of fundus camera photography to measure, observe, and quantify microvascular retinal features and abnormalities.

The direct visualization of the retina using fundus imaging offers an opportunity to assess the potential for abnormalities and changes in retinal microvasculature to serve as biomarkers of microvascular pathology in subtypes of dementia. Fundus photography, with high sensitivity, specificity, and interexamination and intraexamination agreement [16], is typically used to determine three different types of retinal properties: retinopathy, variation in vessel caliber, and changes in the global geometric branching network [17]. Furthermore, the digital output from modern camera systems lends itself to image processing methods for computer-assisted programs to objectively quantify important features of the retina and its vasculature with increasing accuracy and reliability [18]. We aimed to conduct a systematic review of the literature to examine the application of fundus camera imaging and analysis in dementia, including AD, vascular dementia (VaD), frontotemporal dementia, and dementia with Lewy bodies.

## 2. Methods

### 2.1. Search strategy

Published studies were identified through systematic searches of the Medical Literature Analysis and Retrieval System Online (MEDLINE, including work in progress from 1946), PubMed (from 1950), and the Excerpta Medica Database (EMBASE, from 1980) for all human studies published until March 2016, in all languages. Search filters included were keyword, title, and abstract information. The Medical Subject Heading search terms were “retina,” or “fundus,” or “retinal vasculature,” or “retinal microvasculature,” or “retinal vascular,” or “retinal vessel,” or “retinopathy” and in combination with “dementia,” or “Alzheimer,” or “Lewy bodies,” or “cognition,” or “cognitive”. Articles with any combination of any of the retinal terms and any dementia or cognition term were reviewed. We also searched Google Scholar for all studies published before and including March 2016. References of relevant articles were hand-searched and a forward citation search was performed to identify further studies.

### 2.2. Inclusion and exclusion criteria

This review aimed to include all published studies applying fundus camera imaging to examine the association between retinal vasculature/retinopathy and any form of dementia. Inclusion criteria were (1) original study; (2) written in English; (3) assessment of retinal parameters using fundus imaging; (4) diagnosis of AD, frontotemporal dementia, dementia with Lewy bodies, or VaD; and (5) diagnosis of

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