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RESEARCH



Are macular drusen in midlife a marker of accelerated biological ageing?

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ABSTRACT

Clinical relevance: Macular drusen are associated with age-related maculopathy but are not an ocular manifestation or biomarker of systemic ageing.

Background: Macular drusen are the first sign of age-related maculopathy, an eye disease for which age is the strongest risk factor. The aim of this cohort study was to investigate whether macular drusen in midlife – a sign of the earliest stages of age-related macular degeneration (AMD) – are associated with accelerated biological ageing more generally.

Methods: Members of the long-running Dunedin Multidisciplinary Health and Development Study (hereafter the Dunedin Study, $n = 1037$) underwent retinal photography at their most recent assessment at the age of 45 years. Images were graded for the presence of AMD using a simplified scale from the Age-Related Eye Disease Study (AREDS). Accelerated ageing was assessed by (i) a measure of Pace of Ageing defined from a combination of clinical and serum biomarkers obtained at ages 26, 32, 38, and 45 years and (ii) Facial Ageing, defined from photographs obtained at age 38 and 45 years.

Results: Of the 938 participants who participated at the age 45 assessments, 834 had gradable retinal photographs, and of these 165 (19.8%) had macular drusen. There was no significant difference in Pace of Ageing ($p = .743$) or Facial Ageing ($p = .945$) among participants with and without macular drusen.

Conclusions: In this representative general population sample, macular drusen in midlife were not associated with accelerated ageing. Future studies tracking longitudinal changes in drusen number and severity at older ages may reveal whether drusen are a biomarker of accelerated ageing.

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Introduction

For the first time in history, older people, aged 65 and above, outnumber people younger than 5¹ and the proportion of older people is predicted to increase further. By 2050, the world population aged 80 and over will approach 400 million people.^{2,3} Fries (1983) postulated that with increased longevity we should live healthier as well as longer lives (the 'compression of morbidity' hypothesis).⁴ However, evidence suggests that this is not the case: diseases are still striking at the same ages as previously, but advances in medicine and technology have increased the chance (and length) of survival.^{5,6} Thus, many people are spending more years than before with age-related chronic disease, creating an enormous health burden and a major public health challenge. To address this burden and meet these challenges, more information on the ageing process are required. However, most previous ageing research has been done on elderly people, with little known about biological ageing among younger humans.^{2,7}

The eye is a good model for studying ageing; not just because it can be imaged non-invasively, but because it allows non-invasive imaging of neurological and vascular tissue.⁸ Macular drusen are yellow deposits deep within the retina that are easily identifiable on clinical examination or

retinal photography. Drusen are accumulations of extracellular debris and come in a range of morphologies.⁹ While the initiation and growth of drusen and the mechanisms underlying drusen remain a key area of research, it is well established that drusen are the hallmark of age-related macular degeneration (AMD), a disease for which age is the strongest risk factor.^{10,11} Estimated 8.4 million people worldwide have moderate-to-severe vision loss caused by AMD.¹²

The significance of small hard drusen in younger subjects with normal visual function remains unknown. It is generally considered that individuals less than 55 years of age with drusen do not have AMD as it is defined clinically.¹³ There are two major differences in drusen due to normal ageing versus AMD: first, soft drusen are found only at the macula, and second, that hard and soft drusen have different molecular components.¹¹ So not only small drusen are associated with 'normal' ageing in the absence of AMD but also a range of diseases is strongly associated with ageing (e.g. Alzheimer's), independent of chronological age.^{10,11,14} Studies suggest that compared to age-matched controls, people with drusen are more likely to have higher rates of cognitive impairment and Alzheimer's disease (the drusen are usually peripheral) and to develop stroke, cardiovascular and renal disease.^{15–19}

However, whether macular drusen are a marker of accelerated biological ageing in younger, middle-aged people is unclear. The Dunedin study provides a unique opportunity to investigate this question. This study has followed a cohort of 1037 people from their birth in 1972–73 and has a proof of concept model to examine ageing and ageing trajectories by combining multiple measures obtained at four time points spanning the third to fifth decades of life.² It has shown that the biological age of the participants at the chronological age of 38 years ranged from 28 to 61, based on the way their bodies were functioning.² We hypothesised that macular drusen in midlife would serve as a simple and easily measured biomarker of pace of ageing.

Methods

Study design and population

Participants were members of the Dunedin Study, a longitudinal investigation of health and behaviour in a representative birth cohort.²⁰ Participants ($n = 1037$; 91% of the eligible births; 52% male) were all individuals born between April 1972 and March 1973 in Dunedin, New Zealand (NZ), who were eligible based on residence in the province, and who participated in the first assessment at age 3 years.²⁰ The cohort represented the full range of socioeconomic status (SES) in the general population of NZ's South Island and as adults matched the NZ National Health and Nutrition Survey on key adult health indicators (e.g., body mass index, smoking, GP visits) and the NZ Census of citizens of the same age on educational attainment. Participants are primarily white (93%, self-identified), matching South Island demographics.²⁰ Assessments were carried out at birth and ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, 38, and most recently (completed April 2019) 45 years, when 94.1% ($n = 938$) of the 997 participants still alive took part. At each assessment, participants were brought to the research unit for interviews and examinations. The relevant ethics committees approved each phase of the study and the informed consent was obtained from all participants.

Drusen detection and classification

Digital fundus photographs were taken at the Dunedin Study Research Unit after 5 min of dark adaptation. The same camera (Canon NMR-45 with a 20D single-lens reflex backing; Canon, Tokyo, Japan) was used for all photographs in order to avoid artefactual variation from different cameras. Both left and right eyes were photographed. Retinal photographs were graded at the Singapore National Eye Centre Ocular Reading Centre by trained graders who were blinded to participants' characteristics. A simplified AMD grading scale, broadly adapted from the AREDS, was used to grade the presence of drusen²¹ (see Table 1). Early AMD was defined as the presence of drusen within the macula and less than 125 microns, while intermediate AMD was classified as drusen within 2-disc diameter and bigger than 125 microns or

presence of significant pigmentary abnormalities. Advanced AMD is the presence of central geographic atrophy or neovascular lesions. No other quantitative grading was performed.

Measures of accelerated ageing

Accelerated ageing was assessed via two approaches: Pace of Ageing and Facial Ageing.² Pace of Ageing was measured for each participant with repeated assessments of a panel of 19 biomarkers obtained at ages 26, 32, 38, and 45 years using a method previously described.² The 19 biomarkers included were as follows: body mass index, waist–hip ratio, glycated haemoglobin (HbA1C), leptin, blood pressure (mean arterial pressure), cardiorespiratory fitness (VO2Max), forced expiratory volume in 1 s (FEV1), FEV1 to forced vital capacity ratio (FEV1/FVC), total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, apolipoprotein B100/A1 ratio, lipoprotein (a), creatinine clearance, urea nitrogen, C-reactive protein, white blood cell count, gum health, and caries-affected tooth surfaces. Change over time in each biomarker was modelled with mixed-effects growth models, and these rates of change were combined into a single index scaled (within sex) in years of physiological change occurring per one chronological year.² The Pace of Ageing has been validated as a measure of midlife individual differences in biological ageing, as it is correlated with other measures, such as tested cognitive decline and declining tested physical function.^{2,7,22–24}

Facial Ageing is the subjective perception of aged appearance based on a facial photograph. Measurement in the Dunedin study was based on ratings by an independent panel of eight raters of each participant's facial photograph.² Facial Ageing was based on two measurements of perceived age. First, age range was assessed by an independent panel of four raters, who were presented with standardised (non-smiling) facial photographs of participants and were kept blind to their actual age. Raters used a Likert scale to categorise each participant into a 5-year age range (i.e., from 20 to 24 years old up to 70+ years old) (interrater reliability = .77). Scores for each participant were averaged across all raters. Second, the relative age was assessed by a different panel of four raters, who were told that all photos were of people aged 45 years old. Raters then used a 7-item Likert scale to assign a 'relative age' to each participant (1 = 'young looking', 7 = 'old looking') (interrater reliability = .79). The measure of perceived age at 45 years, Facial Age, was derived by standardising and averaging Age Range and Relative Age scores.

Statistical analysis

Data were analysed by SPSS version 25 for Windows (SPSS Inc., Chicago, IL, USA). The data are reported as n (%) and median (interquartile range; IQR), as appropriate. Normality was assessed using a Kolmogorov–Smirnov test and revealed that Pace of Ageing was not normally distributed, but Facial Ageing was. Pace of Ageing and Facial Ageing of participants with and without drusen were compared using a Mann–Whitney U test and an independent-samples t-test, respectively. Linear regression was used to control for years of tobacco smoking and socioeconomic status at age 45. To test the possibility that associations with the Pace of Ageing

Table 1. Simplified AMD grading system.

Early AMD – drusen within the macula and less than 125 microns
Intermediate AMD – drusen within 2-disc diameter foveola and bigger than 125 microns, or presence of significant pigmentary abnormalities
Advanced AMD – central geographic atrophy or neovascularisation

were biased by the long right-hand tail of the Pace of Ageing distribution, we investigated associations after both Winsorising (± 2 s.d.) and log-transforming the Pace of Ageing. All the tests were two-tailed, and a value of $p < .05$ was considered significant.

Results

Of 1037 participants in the original cohort (91% of the eligible births; 535 [51.6%] male), 997 were still alive at age 45 years and 938 (94.1%) took part in the age 45 assessment between April 2017 and April 2019. Of these, 865 (92.2%) had both digital fundus photographs taken and a Pace of Ageing score calculated (435 [50.3%] male). The fundus photos of 31 participants were deemed unrateable for both eyes so were excluded, leaving 834 participants with rateable photographs in at least one eye.

While participants were graded using a simplified AMD grading scale, only two participants had drusen > 125 microns within the macula and only one had pigment abnormalities. No participant had geographic atrophy or neovascular AMD. This necessitated not using AMD as a variable but simply the presence or absence of drusen in any eye. One hundred and sixty-

five participants (19.8%) had drusen present (82 [49.7%] male) – 61 in one eye (22 right and 39 left) and 104 in both eyes. Example retinal photographs from participants with and without drusen are shown in Figure 1.

Participants ranged in their Pace of Ageing from 0.38 years of physiological change per chronological year to 2.64 years of physiological change per chronological year. The median Pace of Ageing score of the 834 participants from whom both a gradable fundus photograph and a Pace of Ageing score were obtained was 0.936 (IQR = 0.765–1.154). Pace of Ageing of participants with drusen was compared to those without drusen (Figure 2).

The median Pace of Ageing of participants with no drusen was 0.935 (IQR = 0.764–1.154). For participants that had drusen, the median Pace of Ageing was 0.943 (IQR = 0.789–1.154). A Mann–Whitney U test showed no significant difference between the Pace of Ageing of participants without drusen and participants with drusen ($U = 54284$, $p = .743$). Additionally, a Kruskal–Wallis H test showed no difference in Pace of Ageing between participants with no drusen, participants with drusen in one eye and participants with drusen in both eyes ($\chi^2(2) = 4.033$, $p = .133$; Figure 3).

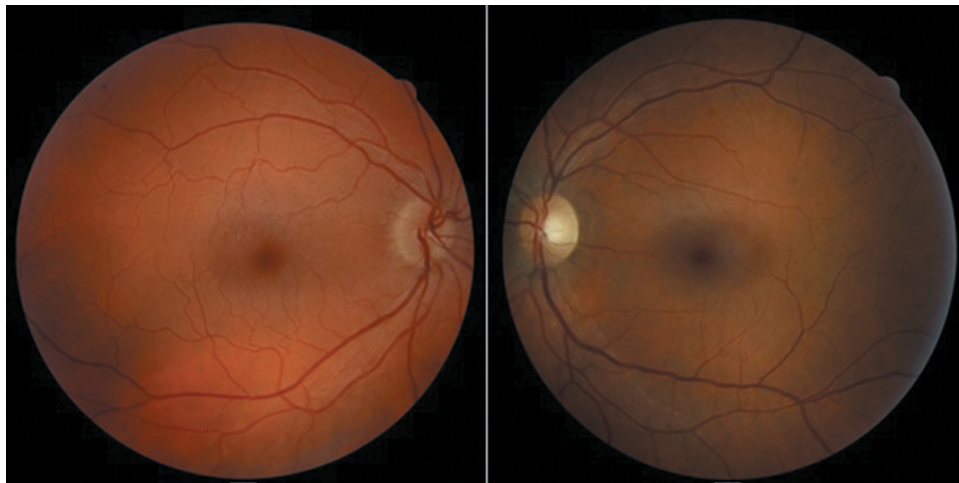


Figure 1. Fundus photographs showing macular drusen (right eye) and without drusen (left eye).

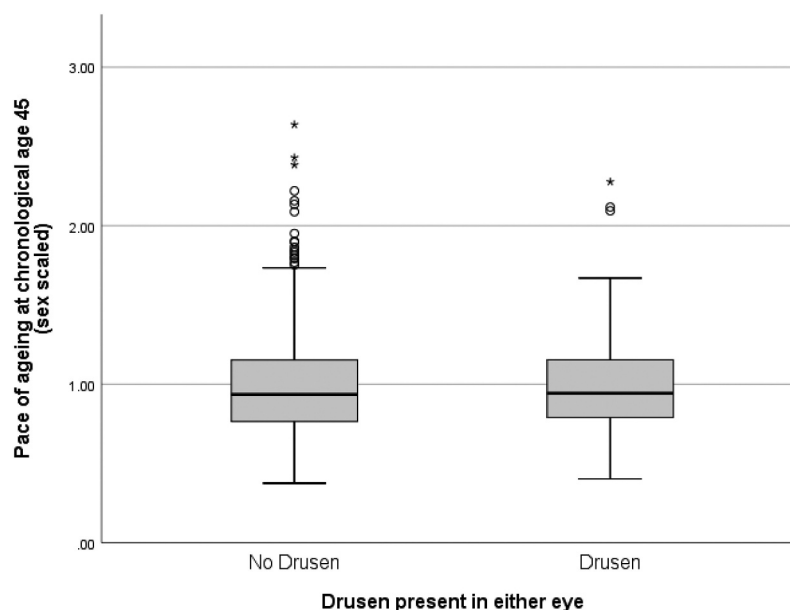


Figure 2. Pace of ageing of participants with drusen ($N = 165$) and without drusen ($N = 669$).

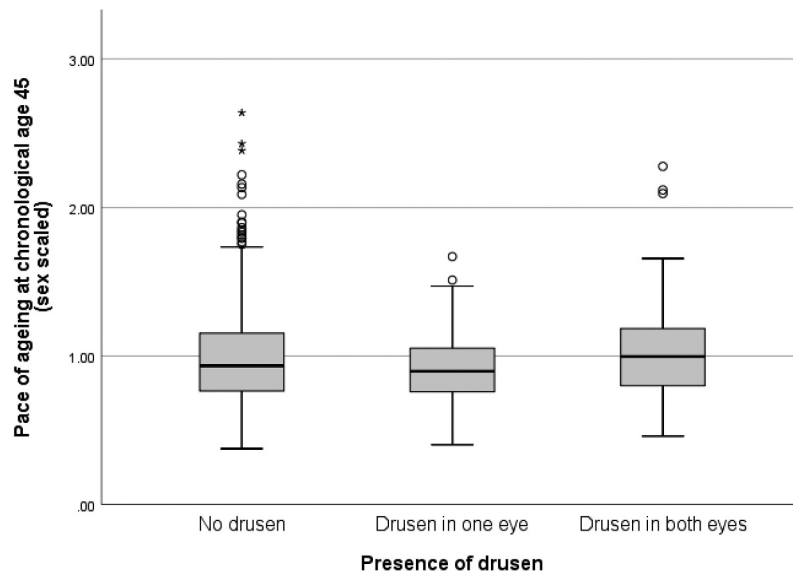


Figure 3. Pace of ageing of participants with no drusen ($N = 669$), with drusen in one eye ($N = 61$), and with drusen in both eyes ($N = 104$).

There was also no significant difference in Facial Age when comparing participants with and without drusen ($t(831) = 0.068$, $p = .945$) or when comparing participants with no drusen, participants with drusen in one eye, and participants with drusen in both eyes ($F(2,830) = 1.272$, $p = .281$).

Linear regression showed no difference in either Pace of Ageing or Facial Age between participants with and without drusen after controlling for smoking and socioeconomic status (Pace of Ageing: $B = -0.013$, 95% CI: -0.062 , 0.035 , $p = .587$; Facial Age: $B = -0.041$, 95% CI: -0.197 , 0.115 , $p = .609$). Winsorising (± 2 s.d.) and log-transforming the Pace of Ageing variable had no effect on this result.

Discussion

Drusen were prevalent within this mid-life cohort and were documented in 1 in 5 (19.8%) of participants in at least one eye. Whilst all participants assessed were of the same chronological age, there was marked variation in the Pace of Ageing. However, no significant association between macular drusen and increased Pace of Ageing or Facial Age was evident. This was an unexpected finding given that drusen are the hallmark of AMD, a disease for which ageing is the most important risk factor. Our finding suggests that drusen represent an ocular sign of eye disease associated with ageing (e.g., AMD), but not an ocular manifestation or biomarker of systemic ageing.

Measuring ageing remains complex, challenging, and controversial because ageing itself is highly variable.² Biological age reflects the health status of multiple organ systems in a person.²⁵ Common biomarkers utilised to assess biological ageing previously include DNA methylation, telomere length, and multiple-blood measurements of organ function.²⁵ The eye represents an ideal model for studying age-related processes.⁸ Proposed ocular parameters that can be readily measured and which may be of value in ageing research include: lens transparency, retinal blood vessel calibre, corneal endothelial cell counts, visual acuity, contrast sensitivity, amplitude of accommodation, and retinal thinning.⁸ Given that drusen are easily, commonly, and non-invasively detected by eye health professionals and are strongly associated with AMD,

it was hypothesised that drusen may be a potential biomarker of ageing. If so, drusen might be used to identify causes of ageing and evaluate prevention and rejuvenation therapies. Because the Dunedin study is a longitudinal cohort with a repeated and validated measure of Pace of Ageing, which is correlated with other measures of health-like cognitive loss and declining physical function, we considered the hypothesis a valid one to address in this cohort.²

Failure to find support for our hypothesis may be due to several factors. There is a wide spectrum of retinopathies with drusen or drusen-like phenotypes highlighting that not all drusen might be associated with AMD. Khan et al.¹⁴ have identified a cohort with early onset drusen with a suspected genetic aetiology. Perhaps this cohort, at age 45, is too young to detect an association of drusen with biological ageing, even though the Dunedin study has already reported that individuals who were ageing more rapidly were less physically able, showed cognitive decline and brain ageing, self-reported worse health, and looked older.² Or perhaps mechanisms other than ageing or confounding factors indicative of ageing may be at play, which were not measured. As both drusen and ageing are complex multifactorial diseases with some shared risk factors, our data may not have been sufficient to tease out an association.²⁶

The authors are not aware of any other study addressing the association between drusen and ageing, so it is not possible to compare our findings with other comparative studies. A 10-year meta-analysis in 2017 (participants over age 40 years) found that late AMD was associated with a 20% increase in all-cause mortality and 46% increase in cardiovascular mortality, but early AMD was not.²⁶ This suggests shared pathways (such as ageing) between late AMD and systemic disease. In addition, the NHANES (5603 participants aged 40 years or older) found late AMD was independently associated with all-cause mortality and mortality due to causes other than cardiovascular disease and cancer.²⁷ This suggests that late AMD may be a marker of biological ageing and frailty. But again, there is nothing in the literature to suggest that drusen alone are associated with ageing or mortality.

The population prevalence of drusen for younger persons varies from 8% in Denmark (age 20–46),²⁸ 13% in the USA (age 34–54),²⁹ to 31% in Europe (age 34–54).³⁰ Given that eye care

professionals will detect drusen in this age range, they can now inform the individual that while there are well-documented associations with future potential vision loss, the finding of drusen is unlikely to be associated with advanced biological ageing in midlife. In addition, drusen do not appear to be a biomarker of ageing or senescence by which the inevitable human condition of ageing and measures of anti-ageing therapies can be assessed and quantified. However, given the known links between drusen, AMD, cardiovascular disease, and ageing, and their likely shared (albeit complex) pathways, further research in this area is warranted.²⁶

The strengths of this study are that both eyes of participants were photographed and these were graded for drusen by a standardised technique/protocol at SERI. Ageing was studied by tracking multiple organ biomarkers at four time points spanning the third to fifth decades of life within a birth cohort with a retention rate of 94.1%. This investigation can be repeated when the participants return for their next assessment phase at age 52 and thereafter. Future studies on this cohort can address if drusen at age 45 are predictive of later AMD, the generalisability of these findings and the association with AMD genes and phenotype.

A limitation of this study is not classifying drusen into subtype or pathological phenotype by clinical or OCT morphology. Differing drusen subtypes (hard, soft, reticular pseudo-drusen, calcific) have different visual associations and outcomes and therefore possibly differing associations with ageing.¹⁴ Automated OCT-derived drusen volumes have recently been shown in population-based studies to correlate with colour fundus photography in many but not all participants.³¹ In addition, our grading system did not differentiate between participants with drusen and participants with small drusen (<63 µm), which are also termed drupelets and are considered a manifestation of normal ageing.¹³ The study population was 93% NZ European meaning generalisability to other population groups may be limited. Although socioeconomic status and tobacco consumption were controlled for, some potential confounding factors such as inflammation, arteriosclerosis, lipid metabolism, and oxidative stress were not adjusted for.

In conclusion, macular drusen were observed to be highly prevalent (1 in 5) within the current birth cohort study of individuals aged 45 years. Despite the previously known strong correlation of drusen with chronological age, no association was observed between macular drusen and accelerated Pace of Ageing or Facial Ageing, despite several overlapping risk factors for increased biological age and drusen. Failure to support our hypothesis highlights the limitations in our understanding about the aetiology of macular drusen. Birth cohort studies, such as the Dunedin Study offer a tantalising glimpse into the ageing process and should allow further examination of the natural history and pathogenesis of AMD through time.

Additional contributions

We thank the Dunedin Study participants, their families, and friends for their long-term involvement, the Dunedin Study research staff, and Study founder, Dr Phil A Silva.

Access to data and data analysis

Drs Cheyne, Niederer, and Wilson had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Role of the funder/Sponsor

The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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