Continuing Medical Education:

Age-related macular degeneration and mortality: the Melbourne Collaborative Cohort Study

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Learning Objectives

Upon completion of this activity, participants will be able to:

1. Assess the risk for death associated with early age-related macular degeneration (AMD)
2. Identify retinal patterns associated with a higher risk for all-cause mortality among patients with late AMD
3. Determine retinal patterns associated with a higher risk for cardiovascular mortality among patients with late AMD
4. Identify retinal patterns associated with a higher risk for tobacco-related cancer mortality among patients with late AMD

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Age-related macular degeneration and mortality: the Melbourne Collaborative Cohort Study

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Abstract

Aims To assess associations between features of age-related macular degeneration (AMD) and mortality.

Methods A total of 21 129 participants from the Melbourne Collaborative Cohort Study aged 47–85 years (60% female) were assessed for AMD (2003–2007). Mortality data to December 31, 2012 were obtained through linkage with the National Death Index. Associations were assessed using Cox regression, adjusting for age, sex, smoking, region of birth, education, physical activity, diet and alcohol.

Results Late AMD was identified in 122 (0.6%) participants, including those with choroidal neovascularisation ($n = 55$, 0.3%), geographic atrophy ($n = 87$, 0.4%) and reticular pseudodrusen ($n = 87$, 0.4%). After a median follow-up period of 8.1 years, 1669 (8%) participants had died, including those from cardiovascular diseases (386), tobacco-related cancers (179), and neurodegenerative disease (157). There was evidence of an increased rate of all-cause mortality for those with choroidal neovascularisation (Hazard Ratio (HR) 1.71 95% CI 1.06–2.76) and geographic atrophy (HR 1.46 95% CI 0.99–2.16). Choroidal neovascularisation was also associated with an increased rate of cardiovascular mortality (HR 3.16 95% CI 1.62–6.15) and geographic atrophy was associated with an increased rate of death from tobacco-related cancer (HR 2.86 95% CI 1.15–7.09). Weak evidence was also present for an association between choroidal neovascularisation and death from neurodegenerative disease (HR 2.49 95% CI 0.79–7.85). Neither reticular pseudodrusen nor the earlier stages of AMD were associated with mortality.

Conclusions Late AMD is associated with an increased rate of all-cause mortality.

Choroidal neovascularisation and geographic atrophy were associated with death from cardiovascular disease and tobacco-related cancer, respectively.

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Introduction

Theories of shared mechanisms of development between age-related macular degeneration (AMD) and other age-related systemic diseases are gaining support through evidence of a positive association between AMD and mortality.^{1–5} As AMD is increasingly common in all aging populations in high-income countries, it is important to assess whether it is associated with an increased risk of death.^{6,7}

While several studies have investigated the association between AMD and cancer mortality, most have regarded cancer as a single entity rather than a group of heterogeneous conditions with varying risk factors and biological mechanisms.^{2,8–12} The Atherosclerosis Risk in Communities Study found some evidence of an increased risk of lung cancer mortality for those with early AMD, but to our knowledge no other studies have looked at the relationship between AMD and death from other tobacco-related cancers.⁸ Recent literature has explored theories that AMD and neurodegenerative diseases such as Parkinson's and Alzheimer's share etiological pathways, and the association between neurodegenerative disease and increased rates of mortality is well known.^{13–15} However, to our knowledge, the association between AMD and death due to neurological disease has not yet

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been investigated. It has also been suggested that poor vision stemming from the later stages of AMD is an additional risk factor for death; and given that there is evidence of increased rates of falls and hip fractures for those with AMD it is conceivable that accidents and trauma may lead to death for those with low vision.^{16,17}

Klein *et al*¹⁸ assessed the relationship between reticular pseudodrusen (RPD) and all-cause mortality, but, to our knowledge, no investigation of the association between RPD and cause-specific mortality has been published.¹⁸ Furthermore, only one study has investigated CNV and GA as separate clinical entities.⁴ In that study, only all-cause and cardiovascular mortality were analysed.

We hypothesized that participants with retinal features associated with late AMD have an increased risk of all-cause mortality, and mortality associated with cardiovascular disease (CVD), trauma, neurodegenerative disease and tobacco-related cancers.

Materials and methods

Participants

The Melbourne Collaborative Cohort Study is a prospective cohort study of 41 514 participants (24 469 females) living in Melbourne, Australia. Caucasian volunteers, 98% of whom were aged between 40 and 69 years of age, were recruited between 1990 and 1994 (wave 1).¹⁹ Fundus photography was performed at a single follow-up wave between 2003 and 2007 (wave 3). The study protocol was approved by the Human Research and Ethics Committees of The Cancer Council Victoria and the Royal Victorian Eye and Ear Hospital, and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants after explanation of the nature of the study.

Assessment of AMD and RPD

Non-mydriatic colour digital fundus photography, centred on the macula and optic disc, was performed at wave 3 and graded for retinal features of AMD using 'OptoLite/OptoMize Pro' software (Digital HealthCare Image Management Systems, Cambridge, UK), as previously described.²⁰ Photographs were assessed by examiners who were masked to participant characteristics. Participants were classified according to features in the area 6000 μm in diameter centred on the fovea in the worse affected eye. For this analysis, AMD was defined according to the Beckman classification.²¹ Those with CNV (retinal pigment epithelial detachments; sub-retinal or sub-retinal pigment epithelial neovascular membranes; fibrosis, atrophy and scar tissue indicative of previously active CNV; or sub-retinal haemorrhages)

and/or GA ($\geq 175 \mu\text{m}$ hypopigmentation with visible choroidal vessels) in either eye were classified as having late AMD. Individuals with both CNV and GA ($n = 20$) were included in both the CNV and GA exposure groups. Individuals with drusen 63 to 124 μm in size without pigmentary abnormalities in either eye were classified as having early AMD. Individuals with drusen 63 to 124 μm in size accompanied by pigmentary abnormalities, or drusen $\geq 125 \mu\text{m}$ with or without pigmentary abnormalities in the absence of late AMD in either eye were classified as having intermediate AMD. Participants with only one eye graded were omitted from the analysis unless late AMD was detected in the graded eye.

In recent years the sign of RPD has become of great interest as it appears to be a high risk sign for progression to late disease and has been associated with a reduced blood supply to the outer retina.¹⁸ Fundus photographs for which any abnormality was detected were therefore re-graded for presence of RPD in 2013–14 by two ophthalmologists (E.C. and R.H.G.). RPD was defined as confluent pale lesions forming an interlacing ribbon-like network (ribbons), and/or individual paler drusen-like round lesions, which are spaced equidistant from each other, usually more than 125 μm in diameter (dots) as described for this cohort previously.²²

Mortality data

Mortality data to December 31, 2012 were obtained through probabilistic matching with the National Death Index and the Victorian Cancer Registry. The *International Classification of Diseases*, 10th Revision (ICD-10, World Health Organization) was used to classify causes of death. Up to nine contributing causes of death were listed for each participant.

Cardiovascular deaths were defined as those from hypertension, hypertensive heart disease, ischemic heart disease, conduction disorders, dysrhythmias, heart failure, cerebrovascular diseases and diseases of the blood vessels with any of the following ICD-10 codes assigned as the underlying cause of death: I10; I11; I13; I20–I25; I44–I52; I60–I79. We restricted our definition of tobacco-related cancers to those involving the respiratory tract (pharynx, larynx, trachea, lung) and the upper gastrointestinal tract (lip, oral cavity, esophagus, stomach) with ICD-10 codes C00–C16 and C32–C34. A considerable proportion of cancers at these sites have been attributed to tobacco smoke in Australia.²³ Trauma was defined as any contributing cause of death from: injury; falls; exposure to hot substances, smoke, fire or flames; electrocution; transport accidents; or complications/sequelae from any of the above (ICD-10 codes S00–T14, T20–T29, T79, T90–T95, V01–W19, W21–W22, W25–W31, W45, W85–87, X00–X19, X58–X59).

Y85-Y86), excluding transport accidents where the participant was a passenger. Participants whose injuries resulted from intentional self-harm or assault were not categorized as traumatic (ICD-10 codes X60-Y09). Neurodegenerative causes of death were attributed to any contributing cause of death related to Parkinson or Alzheimer's disease or to dementia (ICD-10 codes F00, F02.3, F03, G20 and G30).

Covariates

Region of birth was dichotomized into as Southern European migrants (born in Italy, Greece or Malta) and all others (born in Australia, New Zealand, England, Ireland, Scotland, Wales or Latvia). The highest level of educational attainment at wave 1 was categorized as less than high or technical school, completed high or technical school or completed a trade, degree or diploma. We assumed that for this population educational attainment was unchanged between waves 1 and 3. Smoking status at wave 3 was classified as never-smokers, former-smokers, current moderate smoker (1–14 cigarettes per day) and current heavy smoker (≥ 15 cigarettes per day). Food intake at wave 3 was estimated using a self-administered food frequency questionnaire, specifically developed for the Melbourne Collaborative Cohort Study, and used to calculate the Mediterranean diet score, a sex-specific diet scale based on intakes of vegetables, fruit and nuts, legumes, cereal, fish, meat products, dairy products, olive oil and alcohol.^{24,25} Scores range from zero (indicating less compliance with the Mediterranean diet) to nine (indicating greater compliance with the Mediterranean diet). Weekly physical activity at wave 3 was calculated by assigning the following metabolic equivalent task (MET) values to each hour of activity: moderate or vigorous activity in the garden or yard (3.5); moderate activity inside the home (3.2); walking slowly (2.8), at a normal pace (3.3), briskly (4.3) or very briskly (5.0); and moderate (4.0) or vigorous (8.0) activity for leisure.²⁶ Walking and activities for leisure were each truncated at 21 h per week.²⁷

Statistical analysis

The retinal features and causes of mortality investigated were selected prior to any analysis of the data. Cox regression was used to estimate hazard ratios for mortality from all-causes, CVD, neurodegeneration and tobacco-related cancer in relation to early, intermediate and late AMD and for RPD, GA and CNV. Follow-up time commenced at the time of fundus photography (wave 3) and ended at the date of death or 31 December 2012, whichever came first. Potential confounders of the association between AMD and mortality were determined

a priori using a causal diagram. Participant age at wave 3 was used as the time scale with adjustment for sex, smoking status at wave 3, region of birth, educational attainment, physical activity at wave 3, and Mediterranean diet score at wave 3.²⁸ Effect modification by age ($<$ or ≥ 75 years) was investigated for the association between early and intermediate AMD and all-cause and cause-specific mortality by including time-varying coefficients in the models. A small number of events for late AMD and RPD in younger participants prevented exploration of effect modification by age for GA, CNV or RPD. Health outcomes such as body size and blood pressure, which are considered to stem from the included covariates, were not included in the models.²⁹ No hazard ratios were calculated for deaths related to trauma due to a small number of events. Participants who had missing data on cause of death were excluded from the cause-specific mortality analyses.

A total of 784 (3.7%) participants had missing data for the potential confounder, physical activity at wave 3, and 869 participants (4.1%) had missing data for Mediterranean diet score at wave 3. Multiple imputation was implemented to deal with these missing data. Missing values for Mediterranean diet score and weekly physical activity (log transformed) were multiply imputed (25 imputed datasets) using fully conditional specification (also known as chained equations) with univariate linear regression imputation models.³⁰ All variables included in the target analyses (ie Cox regression models) were included in the imputation models along with Mediterranean diet score and physical activity at wave 1 and an indicator of whether participants had reported having diabetes mellitus at any study wave. Post imputation, Mediterranean diet score was then categorized as 0–2, 3–4, 5 and 6–9, and physical activity was categorized into approximate quartile groupings for the target analysis. Complete case analyses were also conducted for comparison as a secondary analysis.

Statistical analyses were performed using Stata/IC version 13.1 (StataCorp LP, College Station, TX, USA).

Results

Participant characteristics

Of the 41 514 participants seen at wave 1, 32% did not attend wave 3 including 9% who had died before commencement of wave 3. Of the wave 3 sample, 79.3% had fundus photographs taken, of which 94% could be graded. After exclusions based on confounding macular pathology precluding AMD grading, poor quality or missing photographs, or missing covariates, 21 129 participants were included in the final analyses (see Supplementary eFigure 1 in the supplement).

Table 1 Participant Characteristics of the Melbourne Collaborative Cohort Study at the time of Fundus Photography (2003–2007)

	AMD				CNV ^a		GA ^a		RPD	
	Absent n = 14 016	Early n = 4297	Intermediate n = 2694	Late n = 122	Absent n = 21 074	Present n = 55	Absent n = 21 042	Present n = 87	Absent n = 21 042	Present n = 87
Age, (years) Median [IQR]	64 [57–72]	63 [56–69]	68 [60–75]	77 [73–79]	64 [57–72]	77 [73–79]	64 [57–72]	77 [74–79]	64 [57–72]	76 [74–79]
Sex, n (%)										
Male	5884 (42.0)	1424 (33.1)	1065 (39.5)	52 (42.6)	8401 (39.9)	24 (43.6)	8388 (39.9)	37 (42.5)	8400 (39.9)	25 (28.7)
Female	8132 (58.0)	2873 (66.9)	1629 (60.5)	70 (57.4)	12 673 (60.1)	31 (56.4)	12 654 (60.1)	50 (57.5)	12 642 (60.1)	62 (71.3)
Smoking status, n (%)										
Non-smoker	8329 (59.4)	2706 (63.0)	1569 (58.2)	63 (51.6)	12 642 (60.0)	25 (45.5)	12 620 (60.0)	47 (54.0)	12 618 (60.0)	49 (56.3)
Former-smoker	5013 (35.8)	1399 (32.6)	1006 (37.3)	49 (40.2)	7440 (35.3)	27 (49.1)	7435 (35.3)	32 (36.8)	7435 (35.3)	32 (36.8)
Smoker 1–14 cigarettes/day	316 (2.3)	96 (2.2)	64 (2.4)	4 (3.3)	478 (2.3)	2 (3.6)	478 (2.3)	2 (2.3)	478 (2.3)	2 (2.3)
Smoker ≥ 15 cigarettes/day	358 (2.6)	96 (2.2)	55 (2.0)	6 (4.9)	514 (2.4)	1 (1.8)	509 (2.4)	6 (6.9)	511 (2.4)	4 (4.6)
Region of birth, n (%)										
Australia, New Zealand, UK, Ireland or Latvia	12 310 (87.8)	3598 (83.7)	2254 (83.7)	107 (87.7)	18 222 (86.5)	47 (85.5)	18 193 (86.5)	76 (87.4)	18 198 (86.5)	71 (81.6)
Southern Europe	1706 (12.2)	699 (16.3)	440 (16.3)	15 (12.3)	2852 (13.5)	8 (14.5)	2849 (13.5)	11 (12.6)	2844 (13.5)	16 (18.4)
Educational attainment, n (%)										
Less than high/technical school	6448 (46.0)	2101 (48.9)	1404 (52.1)	77 (63.1)	9994 (47.4)	36 (65.5)	9974 (47.4)	56 (64.4)	9967 (47.4)	63 (72.4)
Completed high/technical school	2043 (14.6)	610 (14.2)	367 (13.6)	15 (12.3)	3028 (14.4)	7 (12.7)	3026 (14.4)	9 (10.3)	3023 (14.4)	12 (13.8)
Completed trade/degree/diploma	5525 (39.4)	1586 (36.9)	923 (34.3)	30 (24.6)	8052 (38.2)	12 (21.8)	8042 (38.2)	22 (25.3)	8052 (38.3)	12 (13.8)
Mediterranean diet score, n (%) ^b										
0 to 2 (less compliant)	1538 (11.4)	419 (10.2)	249 (9.7)	9 (7.8)	2209 (10.9)	6 (11.1)	2209 (10.9)	6 (7.4)	2204 (10.9)	11 (13.3)
3 to 4	4950 (36.8)	1494 (36.4)	936 (36.3)	52 (44.8)	7410 (36.7)	22 (40.7)	7394 (36.6)	38 (46.9)	7406 (36.7)	26 (31.3)
5	2907 (21.6)	930 (22.6)	602 (23.4)	28 (24.1)	4453 (22.0)	14 (25.9)	4448 (22.0)	19 (23.5)	4447 (22.0)	20 (24.1)
6 to 9 (more compliant)	4066 (30.2)	1264 (30.8)	790 (30.7)	27 (23.3)	6135 (30.4)	12 (22.2)	6129 (30.4)	18 (22.2)	6121 (30.3)	26 (31.3)
Physical activity, n (%) ^b										
Quartile 1 (Less active)	3206 (23.7)	873 (21.1)	614 (23.7)	28 (25.0)	4708 (23.2)	13 (24.5)	4698 (23.2)	23 (29.5)	4708 (23.2)	13 (16.7)
Quartile 2	3399 (25.2)	1048 (25.3)	641 (24.7)	30 (26.8)	5104 (25.2)	14 (26.4)	5096 (25.1)	22 (28.2)	5095 (25.1)	23 (29.5)
Quartile 3	3459 (25.6)	1127 (27.2)	658 (25.4)	33 (29.5)	5260 (25.9)	17 (32.1)	5259 (25.9)	18 (23.1)	5254 (25.9)	23 (29.5)
Quartile 4 (More active)	3439 (25.5)	1089 (26.3)	680 (26.2)	21 (18.8)	5220 (25.7)	9 (17.0)	5214 (25.7)	15 (19.2)	5210 (25.7)	19 (24.4)

Abbreviations: AMD, age-related macular degeneration; CNV, choroidal neovascularization; GA, geographic atrophy; IQR, interquartile range; RPD, reticular pseudodrusen. ^a20 participants had both choroidal neovascularization and geographic atrophy. ^bMissing values for Mediterranean diet score at follow up (*n* = 869) and physical activity at follow-up (*n* = 784).

Characteristics of included participants are provided in Table 1 and a comparison with those not included is given in Supplementary eTable 1 (in the supplement). The median age at the time of fundus photography was 64.9 years (interquartile range 57–72) and 12 704 participants (60%) were female. Early, intermediate and late AMD were detected for 4297 (20%), 2694 (13%), and 122 (0.6%) participants respectively. Of the participants with late AMD, 55 had CNV and 87 had GA including 20 with both. RPD was detected in 87 participants (0.4%).

Participants with missing values for Mediterranean diet score or weekly physical activity at wave 3 were similar to those without missing data when comparing age, sex, smoking status, wave 1 Mediterranean diet score, wave 1 physical activity score and vital status (see Supplementary eTable 2 in the supplement). Participants born in Southern Europe or who had not complete high school were more likely to have missing values for these measures than those born elsewhere or those who had attained higher levels of education.

Mortality

The 21 129 participants were followed for a median duration of 8.1 years (interquartile range 7.3–8.8 years, maximum 9.7 years). The mortality rate was 10 deaths per 1000 person years (95% CI 9.6–10.5).

Cause of death information was missing for 73 participants (20 with early, intermediate or late AMD; including one with GA and two with RPD), hence, these participants were included in analysis of all-cause mortality only. Of the 56 deaths observed for participants with late AMD, none had a contributory cause of trauma. Unadjusted incidence rates for death related to trauma are provided in Supplementary eTable 3 (in the supplement).

Cox regression revealed an increased risk of all-cause mortality for those with CNV and GA (adjusted hazard ratio (HR) 1.71, 95% CI 1.06–2.76 and 1.46, 95% CI 0.99–2.16 respectively, Table 2). CNV was also associated with cardiovascular mortality (HR 3.16, 95% CI 1.62–6.15; Table 3) and the associations remained evident in the complete case analyses despite a reduction in sample size. GA was associated with an increased risk of death from tobacco-related cancers (HR 2.86, 95% CI 1.15–7.09; Table 4). The results are suggestive of a positive association between CNV and neurodegenerative disease, however, these findings should be interpreted cautiously due to the wide confidence interval (HR 2.49, 95% CI 0.79–7.85, Table 5). Neurodegenerative mortality was not recorded for any participants with GA. RPD did not appear to be associated with any type of mortality.

There was no evidence of an association between early or intermediate AMD and all-cause, neurodegenerative and tobacco-related cancer mortality; overall (Tables 2, 4

and 5) and for the younger and older participants (75 years of age cut-off; see Supplementary eTable 4). There was, however, some evidence of higher rates of cardiovascular death for those with early AMD at ages less than 75 (HR 2.11, 95% CI 1.21–3.67) compared with more elderly participants (75 years and above HR 0.81, 95% CI 0.56–1.16, ratio of HRs 0.38, 95% CI 0.20–0.74).

Discussion

In this analysis, late AMD was associated with an increased risk of all-cause mortality, in keeping with a number of previous studies.^{1–4,10,31} We investigated associations with CNV and GA and found CNV to be associated with an increased risk of cardiovascular death and GA to be positively associated with death from tobacco-related cancers. Early AMD was also associated with increased rates of cardiovascular mortality for participants aged less than 75 years old.

Strengths and weaknesses

The major strength of this study is the large sample size ($n = 21\,129$) which provided sufficient statistical power to assess the associations of CNV and GA with mortality separately. Previously published studies have had fewer participants with sample sizes ranging from 1125 to 12 536.^{1–4,8,10,11,31–35} Other major strengths include the prospective design of the study and the quality of the death registry data.³⁶ Furthermore, as anti-vascular endothelial growth factor use only became available in the community during the final year of the AMD assessment period in this study, neovascular AMD would likely be obvious to graders because it was not masked by its treatment. Treatment for CNV via intravitreal injection became routine during the follow-up period of this study and has the potential to confound survival analyses if systemic adverse events ensue from their use.^{37–39} However, the intravitreal use of anti-VEGF agents has not convincingly been shown to be associated with a change in mortality.⁴⁰

AMD status was determined at a single visit during follow-up so no comment can be made about survival time from the onset of AMD. The true association between RPD and mortality is difficult to estimate as only fundus photography was used for its determination without the help of optical coherence tomography, autofluorescence or infrared photography, which are more sensitive to the presence of RPD.⁴¹ As a result we have underestimated the prevalence of RPD in our sample, which may have biased the estimated hazard ratios.²² Additionally, it is difficult to completely remove

Table 2 Cox Regression Analysis for All-cause Mortality^a in the Melbourne Collaborative Cohort Study until December 31, 2012

	Primary Analysis Multiple imputation for handling missing data				Secondary Analysis Complete-case analysis			
	<i>n</i>	<i>Deaths</i>	<i>HR</i>	<i>(95% CI)</i>	<i>n</i>	<i>Deaths</i>	<i>HR</i>	<i>(95% CI)</i>
Total	21 129	1669			19 879	1535		
<i>Age-related macular degeneration</i>								
Control	14 016	1111	1.00		13 211	1032	1.00	
Early	4297	257	1.02	(0.89,1.18)	4037	234	1.00	(0.87,1.16)
Intermediate	2694	266	0.97	(0.85,1.12)	2521	237	0.94	(0.82,1.16)
Late	122	35	1.44	(1.03,2.03)	110	32	1.54	(1.08,2.20)
<i>Choroidal neovascularization^b</i>								
Absent	21 074	1652	1.00		19 826	1520	1.00	
Present	55	17	1.71	(1.06,2.76)	53	15	1.58	(0.95,2.63)
<i>Geographic atrophy^b</i>								
Absent	21 042	1643	1.00		19 803	1511	1.00	
Present	87	26	1.46	(0.99,2.16)	76	24	1.68	(1.12,2.52)
<i>Reticular pseudodrusen</i>								
Absent	21 042	1650	1.00		19 803	1520	1.00	
Present	87	19	1.18	(0.75,1.86)	76	15	1.06	(0.63,1.77)

Abbreviations: CI, confidence interval; HR, hazard ratio; n, number at risk. ^aAdjusted for age, sex, region of birth, educational attainment and wave 3 assessment of smoking status, physical activity and Mediterranean diet score. ^b20 participants had both choroidal neovascularization and geographic atrophy.

Table 3 Cox Regression Analysis for Cardiovascular Mortality^a in the Melbourne Collaborative Cohort Study until December 31, 2012

	Primary Analysis Cardiovascular Mortality Multiple imputation for handling missing data				Secondary Analysis Cardiovascular Mortality Complete-case analysis			
	<i>n</i>	<i>Deaths</i>	<i>HR</i>	<i>(95% CI)</i>	<i>n</i>	<i>Deaths</i>	<i>HR</i>	<i>(95% CI)</i>
Total	21 056	386			19 812	351		
<i>Age-related macular degeneration</i>								
Control	13 963	257	1.00		13 159	235	1.00	
Early	4293	54	1.04	(0.77,1.39)	4033	49	1.02	(0.75,1.39)
Intermediate	2679	62	0.89	(0.67,1.17)	2511	54	0.86	(0.64,1.15)
Late	121	13	1.71	(0.97,3.02)	109	13	2.04	(1.15,3.60)
<i>Choroidal neovascularization^b</i>								
Absent	21 001	377	1.00		19 759	342	1.00	
Present	55	9	3.16	(1.62,6.15)	53	9	3.33	(1.71,6.49)
<i>Geographic atrophy^b</i>								
Absent	20 970	377	1.00		19 737	342	1.00	
Present	86	9	1.61	(0.82,3.16)	75	9	2.04	(1.05,4.00)
<i>Reticular pseudodrusen</i>								
Absent	20 971	383	1.00		19 738	349	1.00	
Present	85	3	0.63	(0.20,1.98)	74	2	0.49	(0.12,1.96)

Abbreviations: CI, confidence interval; HR, hazard ratio; n, number at risk. ^aCardiovascular disease underlying cause of death. Cause of death missing for 73/1669 (4%) participants included in the primary analysis (includes participants with missing data imputed for Mediterranean diet and physical activity), and for 58/1258 (5%) participants from the complete-case sample. Adjusted for age, sex, region of birth, educational attainment and wave 3 assessment of smoking status, physical activity and Mediterranean diet score. ^b20 participants had both choroidal neovascularization and geographic atrophy.

Table 4 Cox Regression Analysis for Mortality from Tobacco-related Cancer^a in the Melbourne Collaborative Cohort Study until December 31, 2012

	Primary Analysis Tobacco-related Cancer Multiple imputation for handling missing data				Secondary Analysis Tobacco-related Cancer Complete-case analysis			
	<i>n</i>	<i>Deaths</i>	<i>HR</i>	<i>(95% CI)</i>	<i>n</i>	<i>Deaths</i>	<i>HR</i>	<i>(95% CI)</i>
Total	21 056	179			19 812	170		
Age-related macular degeneration								
Control	13 963	122	1.00		13 159	117	1.00	
Early	4293	23	0.78	(0.50,1.22)	4033	21	0.74	(0.46,1.18)
Intermediate	2679	29	1.03	(0.69,1.56)	2511	29	1.06	(0.70,1.59)
Late	121	5	1.99	(0.80,4.94)	109	3	1.26	(0.40,4.03)
Choroidal neovascularization ^b								
Absent	21 001	178	1.00		19 759	170		
Present	55	1	0.93	(0.13,6.68)	53	0		
Geographic atrophy ^b								
Absent	20 970	174	1.00		19 737	167	1.00	
Present	86	5	2.86	(1.15,7.09)	75	3	1.91	(0.60,6.08)
Reticular pseudodrusen								
Absent	20 971	178	1.00		19 738	169	1.00	
Present	85	1	0.61	(0.09,4.41)	74	1	0.63	(0.09,4.51)

Abbreviations: CI, confidence interval; HR, hazard ratio; n, number at risk. ^aUnderlying cause of death cancer of the pharynx, larynx, trachea, lung, lip, oral cavity, esophagus or stomach. Cause of death missing for 73/1669 (4%) participants included in the primary analysis (includes participants with missing data imputed for Mediterranean diet and physical activity), and for 58/1258 (5%) participants from the complete-case sample. Adjusted for age, sex, region of birth, educational attainment and wave 3 assessment of smoking status, physical activity and Mediterranean diet score. ^b20 participants had both choroidal neovascularization and geographic atrophy.

Table 5 Cox Regression Analysis for Mortality from Neurodegenerative Disease^a in the Melbourne Collaborative Cohort Study until December 31, 2012

	Primary Analysis Neurodegenerative Mortality Multiple imputation for handling missing data				Secondary Analysis Neurodegenerative Mortality Complete-case analysis			
	<i>n</i>	<i>Deaths</i>	<i>HR</i>	<i>(95% CI)</i>	<i>n</i>	<i>Deaths</i>	<i>HR</i>	<i>(95% CI)</i>
Total	21 056	157			19 812	132		
Age-related macular degeneration								
Control	13 963	110	1.00		13 159	92	1.00	
Early	4293	23	1.07	(0.68,1.68)	4033	17	0.96	(0.57,1.63)
Intermediate	2679	21	0.66	(0.41,1.06)	2511	20	0.76	(0.47,1.23)
Late	121	3	0.97	(0.30,3.06)	109	3	1.25	(0.39,3.99)
Choroidal neovascularization ^b								
Absent	21 001	154	1.00		19 759	129	1.00	
Present	55	3	2.49	(0.79,7.85)	53	3	2.79	(0.88,8.80)
Reticular pseudodrusen								
Absent	20 971	156	1.00		19 738	132		
Present	85	1	0.56	(0.08,4.03)	74	0		

Abbreviations: CI, confidence interval; HR, hazard ratio; n, number at risk. ^aDementia, Alzheimer or Parkinson disease contributing cause of death. Cause of death missing for 73/1669 (4%) participants included in the primary analysis (includes participants with missing data imputed for Mediterranean diet and physical activity), and for 58/1258 (5%) participants from the complete-case sample. Adjusted for age, sex, region of birth, educational attainment and wave 3 assessment of smoking status, physical activity and Mediterranean diet score. No participants with geographic atrophy had a neurodegenerative cause of death.

all confounding related with smoking which varies greatly in exposure levels.

Participants with considerable morbidity such as neurodegenerative disease may have been less likely to

present for AMD assessment at wave 3, and this differential loss to follow-up may result in decreased precision and bias when estimating associations with mortality. There were an insufficient number of deaths

attributed to trauma to allow any inference regarding associations with AMD. It is possible that long term complications of accidents and falls may contribute to an individual's demise but would not necessarily be recorded as a contributing cause of death.⁴² Furthermore, the number of deaths due to cardiovascular disease and tobacco-related cancer was small in those with late AMD.

Possible mechanisms

AMD is a complex heterogeneous disease, which is multifactorial in nature and results from interactions between genetic, behavioural and environmental influences.⁴³ In this study, positive associations between late AMD and mortality remained after controlling for important confounders, supporting the theory that AMD shares similar mechanisms of development with CVD, neurodegeneration and tobacco-related cancer. By excluding covariates on the pathways of interest such as history of cancer or cardiovascular disease, we have estimated the total association between features of AMD and mortality. This includes an indirect effect via the disease of interest.⁴⁴ Adjustment for the past diagnosis of the disease of interest would have further obscured any relationships which exist between the potential mechanisms that underlie both AMD and fatal illnesses.

Inflammation is believed to play a prominent role in the development of AMD, cancer, CVD and neurodegenerative disease.^{45–49} In AMD, oxidative stress from chronic inflammation is hypothesized to damage the mitochondrial DNA of retinal pigment epithelial (RPE) cells, leading to cell death and the formation of drusen.⁵⁰ Further damage to the RPE leads to the death of photoreceptor cells which rely on the RPE to function.⁵⁰ Additional immune system responses can further increase atrophy leading to patches of GA or stimulation angiogenesis in individuals with CNV.^{45,51} Similarly, neurodegeneration will ensue when neuronal cells are subjected to mitochondrial dysfunction and permanent damage from oxidative stress.⁴⁸ Mutations of the respiratory epithelium DNA, an increase of growth factor production and angiogenesis in lung cancer are also thought to be partially attributable to oxidative stress.^{52,53} The upper aerodigestive tract is especially susceptible to these processes in the presence of cigarette smoke, which contains high levels of reactive oxygen species and comes into direct contact with the epithelial cells. The macula is also susceptible to these processes as it has a high metabolic rate.⁵⁴

Among the components of drusen are lipids and apolipoproteins.⁵⁵ The mechanism by which these deposits form is hypothesized to be similar to that of atherosclerotic plaques, with inflammatory processes playing a central role.^{56,57} Excessive plaque formation in the arteries can precipitate potentially fatal myocardial

infarction and cerebrovascular accidents. Extracellular accumulations of lipids and beta-amyloids which are seen in retinal drusen are also features of Alzheimer's disease.⁵⁸

Additionally, the complement factor H gene (*CFH*, chromosome 1q31) is a regulator of immune function; the Y402H polymorphism of this gene (rs1061170) is strongly associated with AMD and there is also some evidence of an association with increased mortality.^{59–64}

Interestingly, GA, which was found to be associated with death from tobacco-related cancer, was not detected in any of the participants who died from Alzheimer's or Parkinson's Disease. There was weak evidence of an inverse association between intermediate AMD and neurodegenerative disease, and smoking has previously been shown to have an inverse relationship with Parkinson's and Alzheimer's diseases.⁶⁵

Associations with mortality were strongest among participants with late AMD. Not all individuals with early AMD will progress to having late AMD; it is likely that progression to late AMD will be seen among those who are less healthy and have a higher risk of mortality, given they do not die first.⁶⁶

Conclusions

Both forms of late AMD, CNV and GA, are associated with an increased risk of all-cause mortality. Further laboratory and clinical studies are required to reveal the mechanisms by which CNV and GA develop concurrently with cardiovascular disease and tobacco-related cancer.

Summary

What was known before

- People with late age-related macular degeneration are thought to have an increased risk of all-cause mortality. For those with late age-related macular degeneration, there is stronger evidence for a positive association with cardiovascular mortality than with mortality due to cancer.

What this study adds

- In this large cohort, the two forms of late age-related macular degeneration, geographic atrophy and choroidal neovascularisation, were assessed separately. Choroidal neovascularisation was found to be associated with all-cause mortality and death from cardiovascular disease. Geographic atrophy was found to be associated with all-cause mortality and death from tobacco-related cancer.

Conflict of interest

The authors declare no conflict of interest.

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Age-related macular degeneration and mortality: the Melbourne Collaborative Cohort Study

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1. You are seeing a 65-year-old woman with a history of early age-related macular degeneration (AMD). She is worried about how AMD may affect her overall health. According to the current study by McGuinness and colleagues, early AMD among patients younger than 75 years was most associated with which of the following types of mortality?
 - A Cardiovascular mortality
 - B Tobacco-related cancer mortality
 - C Neurodegenerative mortality
 - D All-cause mortality only
2. The patient goes on to develop late AMD during the next 4 years. Which of the following retinal patterns was most associated with a higher risk for overall mortality among patients with late AMD in the current study?
 - A Geographic atrophy (GA) and choroidal neovascularization (CNV)
 - B GA and reticular pseudodrusen (RPD)
 - C CNV and RPD
 - D RPD, GA, and CNV
3. According to the current study, which of the following retinal patterns was most associated with a higher risk for cardiovascular mortality?
 - A GA only
 - B RPD only
 - C CNV only
 - D GA and RPD
4. According to the current study, which of the following retinal patterns was most associated with a higher risk for tobacco-related cancer mortality?
 - A GA only
 - B RPD only
 - C CNV only
 - D GA and RPD