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CLINICAL STUDY

The prevalence and analysis of risk factors for age-related macular degeneration: 18-year follow-up data from the Speedwell eye study, United Kingdom

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Abstract

Aims/Purpose **To determine the prevalence of age-related maculopathy (ARM) and age-related macular degeneration (AMD) in men aged 65–83 years living in the Speedwell region of Bristol, United Kingdom and identify modifiable risk factors.**

Methods **A total of 2348 men recruited to the Speedwell prospective cohort study in 1979 were followed up in 1997 with an eye questionnaire and had retinal photographs that were assessed using the International Classification System for ARM.**

Results **In all, 934 men (66.8% response rate) attended with a mean of 17.9 years (15.3–20.6 years) follow-up. Early ARM (grades 2–3) was found in 9.2% (95% confidence interval (CI) 7.4%, 11.4%) and late age-related maculopathy (grade 4, AMD) in 0.5% (95% CI 0.2%, 1.2%). The risk of ARM (grades 2–4) was increased with raised C-reactive protein and consumption of lard and solid fats, whereas triglyceride levels were associated with a lower risk. The latter were confirmed in multivariable analyses and in addition, haemodynamic measures also predicted risk (eg mean arterial pressure odds ratio (OR) per z-score 1.37, 95% CI 1.04, 1.79).**

Conclusions **In a representative cohort of men aged 65–83 from Bristol, United Kingdom, many had macular changes that put them at higher risk of developing AMD. Various modifiable exposures were associated with an increased risk ARM/AMD. Opportunities for screening and undertaking secondary prevention interventions need to be explored to prevent progression of the disease and blindness.**

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Introduction

Age-related macular degeneration (AMD) is a progressive, late onset degenerative eye disease, and the most severe form of the group of abnormalities termed age-related maculopathy (ARM). It is the leading cause of permanent blindness in the elderly in the Western world.[1] In the United Kingdom, it accounts for almost 42% of blindness occurring in those aged between 65–74 years, rising to 66% in those aged 75–84 years and 74% in those aged over 85 years.[2] AMD is associated with a significant reduction in quality of life and functional independence in the elderly.[3] As life expectancy in the developed world increases, the prevalence and incidence of blindness from this disease will undoubtedly rise unless preventive strategies or treatments are found. Several studies have examined the prevalence of ARM/AMD in the United Kingdom,[4–12] but only two community-based studies have had a sample size of more than a thousand participants,[13] and one was restricted to general practice patients

over 75 years.[14] Identifying those at high-risk of developing AMD is crucial in preventing irreversible visual impairment and blindness from this disease, and may lead to secondary/tertiary prevention strategies.

A number of epidemiological studies have reported a host of risk factors for ARM/AMD, the most consistent of which is smoking behaviour.[15] Most of these associations are inconsistent and this may be in part due to chance, selection and recall bias, and different confounding structures. Prospective studies have the advantage of measuring risk factors before the development of the disease. These have shown positive associations with smoking,[15,16] atherosclerosis,[17] systemic hypertension,[18,19] increased white cell count, gout and emphysema,[20] increased dietary fat and lipid levels[16] and an inverse association with a diet rich in fish.[21–24] All these studies examined risk factors within a relatively short latency period, which raises the concern that some associations may be because of reverse causation. In this study we have examined the prevalence of ARM and AMD in a population-based cohort of men from the United Kingdom who have been followed up for around 18 years as part of a cardiovascular cohort study. Our aim was to test whether previously observed associations, as well as novel risk factors were predictive of disease risk after a long latency period.

Methods

Study population

The Speedwell study invited all men aged 45–59 registered with the 16 general practitioners at two health centres in Speedwell, Bristol, England in 1979 to participate in a cohort study to examine cardiovascular risk factors. Full details of its design and aims have been published previously.[25] During phase I (1979–1982), 2348 men (representing 92% of the target sample of 2550) underwent a clinical examination and data collection on general health, medical history, life-style and potential risk factors. Blood samples were taken in a fasting state between 5 and 9 hours. Following this, the surviving men were seen at intervals of $\sim$4 years comprising phases II, III, and IV. These subsequent phases collected data on new ischaemic heart disease and stroke events, repeated some baseline tests and added others. Data on dietary factors, including major food nutrients and individual food items were collected in phase II on a 25% random subsample of men ($n = 231$). In 1997, 1420 men were sent questionnaires about their eye health and asked to participate in a study examining risk factors for ARM/AMD and cataract,[26] which took place between June 1997 and December 1999.

Procedures for eye examination

Details of the eye examination have been published previously.[26] Participants underwent a clinical examination including a brief history, visual acuity measurements and slit lamp examination. Eyes were then dilated with tropicamide 1% and phenylephrine 2.5%, unless contraindicated. Two 32° stereoscopic colour slide photographs centred on the macula were taken for each eye. Photography was followed by clinical examination of the posterior pole by indirect ophthalmoscopy using a Volk 78D lens.

Photographic grading

The International Classification System for ARM grading was used,[27] which is based on the Wisconsin Age-related Maculopathy Grading system.[28] We used the same stratification of ARM described by Klaver *et al*,[29] whereby: 0—No ARM, 1a—Soft distinct drusen, 1b—Pigmentary irregularities, 2a—Soft, indistinct, or reticular drusen, 2b—Soft, distinct drusen with pigmentary irregularities, 3—Soft, indistinct, or reticular drusen with pigmentary irregularities, 4—Presence of atrophic or neovascular macular degeneration. Grade 4 is defined as AMD. Grading was carried out independently at the Rotterdam ARM grading centre by two trained graders. To minimise criterion shifts and inter-observer differences, images were regularly double-graded and disagreements were resolved by discussion to reach a consensus between graders. Using a grid system and grading tools, the graders were able to estimate drusen size and the area involved by drusen or retinal pigmentary changes. The number of drusen of each size both inside the grid and outside the grid, the size of the largest drusen, the most frequent size of drusen, and the percentage of confluence were recorded, as were the type of drusen: hard, soft, soft distinct, soft indistinct, reticular, and the percentage of area occupied by drusen in each of the three zones: central, inner, outer. Details of the participants' visual acuity, refractive error and previous retinal diseases were sent to the graders with the transparencies to allow attribution of the causes of lesions.

Pre-existing risk factor data

All risk factor data were taken from phase I (1979–1982) except for the dietary data, C-reactive protein (CRP) and D-dimer measures, which were taken from phase II (1985–1988) samples. Smoking habit was measured from a questionnaire and stratified into four groups: never smoked, ex-smoker, moderate smoking (including cigar/pipe and smoking between 1–14 cigarettes per day), and

heavy smoking (>15 cigarettes per day). Total alcohol consumption (including weekly beer, wine, and sherry intake in units of ethyl alcohol) was estimated from a self-administered questionnaire given to every man for completion at home. Full details of this questionnaire have been published.[30] A semi-quantitative food frequency questionnaire was used to acquire data on a wide variety of foodstuffs such as breads, meat, fruit, vegetables, snacks, dairy products, and cooking fats. This was carried out on a 25% random subsample (231 participants).

Resting blood pressures (BPs) were measured with a random zero sphygmomanonmeter. Cholesterol and triglyceride concentrations were measured with enzymatic procedures. The high density lipoprotein (HDL) fraction was isolated by precipitation of the low and very low-density lipoproteins (LDL, VLDL) with heparin and manganese chloride. LDL Cholesterol was estimated using the Friedewald formula whereby (LDL cholesterol) = (Total cholesterol) − (HDL cholesterol) − ((Triglycerides)/2.2), where all concentrations are in mmol/l.[31] Haemostatic factors, fibrinogen and white cell count were measured at baseline and methods for estimation have been published previously.[32] Fibrinogen was measured by heat precipitation nephelometry. CRP was measured by a sensitive nephelometric assay (Behring, Siemens Healthcare, Camberley, UK) and D-dimer, with an ELISA (Biopool International Inc., Ventura, CA, USA).

Statistical methods

To provide greater statistical power, we have defined any subject with ARM grades 2–4 as cases as they either have AMD (grade 4) or are at a high risk of developing future AMD (2-year risk between 3–9%).[29] We used ANOVA and χ^2 tests to compare the means and proportions for the baseline descriptive data by AMD/case status. Data were log transformed were necessary and appropriate. All continuous variables were standardised (by subtracting the mean value and then dividing by the standard deviation) to create *z*-scores, which allows direct comparison of effect estimates. We used logistic regression analysis to estimate the odds ratio (95% confidence intervals (CIs) and *P*-values) as a proxy for the risk ratio, initially adjusting for age. A test for trend, as well as a heterogeneity test was carried out for ordinal variables. A *P*-value <0.05 was considered as providing evidence against the null hypothesis. Further multivariable analyses considered four models: (1) adjusting for age and social class as a non-specific confounder, (2) adjusting for age and the lifestyle variables of smoking and alcohol intake, (3) adjusting for age, metabolic and inflammatory factors: systolic blood pressure (SBP), total cholesterol, total triglycerides, BMI, blood glucose, and CRP. We examined the dietary variables from the food frequency questionnaire separately owing to the reduced sample size, and any positive associations were then adjusted for covariates that predicted in the univariable analyses but were not thought to be on the causal pathway.

Results

Of the 1420 men who were still part of the Speedwell Study in 1999 (see Table 1), 51 could not be reached and 26 died during the data collection phase resulting in 1343 eligible participants. Of these, 212 (15.8%) returned questionnaires only, 24 (1.8%) were seen in the eye clinic only and 925 (68.9%) were seen in the eye clinic and returned questionnaires.

Of the 949 men who attended the clinic, 14 (1.4%) had no retinal photographs taken, 6 (0.6%) had contraindications for example, shallow anterior chamber or iris clip lenses, 7 (0.7%) refused dilation and 1 (0.1%) was dilated but his photographs were lost. Eight (0.8%) had photographs of one eye only, 927 (97.6%) had retinal photographs of both eyes. Reasons for only one eye being photographed were significant corneal scaring, enucleation, iris clip lens, contraindication for dilatation, and cataract. Gradable retinal photographs of at least one eye were available for 934 (98.5%) clinic participants. The mean age of the subjects was 71.1 years (SD 4.2 years, inter-quartile range 67–74 years, range 64–79 years).

Prevalence data

Late ARM—grade 4 (classified as AMD using the Wisconsin Age-related Maculopathy Grading System[28]) was seen in five participants that is, 0.5% (95% CI 0.2%, 1.2%), all of whom had the condition unilaterally (three in the right eye and two in the left) with signs of early ARM in the other eye (Table 1). Three men aged 72, 76, and 79 in 1999 (who were not examined in the eye study, but had agreed to further follow up) were identified as having AMD from an electronic search of medical

Table 1 Stratification of ARM (0–4), worse eye, by age group in men with a gradable retinal photograph ($n = 934$)

Age group	*ARM 0*	*ARM 1*	*ARM 2*	*ARM 3*	*ARM 4*	*Total*
65–69	189 (53.6%)	140 (39.8%)	20 (5.7%)	3 (0.9%)	0 (0.0%)	352
70–74	143 (41.9%)	164 (48.1%)	29 (8.5%)	4 (1.2%)	1 (0.3%)	341
75+	111 (46.1%)	96 (39.8%)	23 (9.5%)	7 (2.9%)	4 (1.7%)	241
Total	443 (47.4%)	400 (42.8%)	72 (7.7%)	14 (1.5%)	5 (0.5%)	934

Abbreviation: ARM, age-related maculopathy.

records increasing the rate of AMD to 0.9% (95% CI 0.4%, 1.7%). Early ARM (grade 2 and 3) was graded in 86 participants that is, 9.2% (95% CI 7.4%, 11.4%), and the prevalence of any maculopathy (ie ARM grades 1–4) was 52.6% (95% CI 48.0%, 57.4%).

Features of ARM

The worst eye was used in the analysis. Retinal pigment epithelium degeneration was found in 9.6% and hyperpigmentation in 10.4% of subjects. Overall 105 (11.3%) individuals had pigmentary abnormalities in at least one eye. The levels of hyperpigmentation and hypopigmentation were similar for each age group. Hard drusen and soft drusen less than 125 μm (C1), were the most frequent morphological types of drusen seen in all age groups. The largest drusen size gradually increased with age. For 'large' drusen, that is, those greater than 125 μm (C1) in diameter, the prevalence was 5.1% for those aged 64–70, 7.0% for those 70–74, and 12.0% for those 75–80 (OR per unit age-group 1.09; 95% CI 1.03, 1.15, $P = 0.005$). Confluent drusen (>50%) were found in 87 (9.3%), soft indistinct drusen in 23 (2.5%), reticular drusen in one (0.1%), and drusen occupying greater than 50% of central zone 5 (0.5%).

Risk factor data

The crude baseline characteristics of participants by case status (ARM grades 2–4) are shown in Table 2 and the age-adjusted odds ratios are in Table 3. At baseline, older men, lower total and VLDL triglycerides, CRP, increased use of lard and solid vegetable oil, or eating fried foods with solid fats all predicted an increased risk of maculopathy (Table 2), which was unlikely to be due to chance. The age-adjusted analysis revealed the same risk factors with the exception of VLDL triglycerides (Table 3). Surprisingly, heavy smokers in phase I had only a modestly elevated risk, which was consistent with chance. This result was not changed when we repeated the analysis using smoking data at phases II and III (results not shown). Associations for social class, alcohol intake, BP, BMI, blood glucose, white cell count, fibrinogen, and D-dimer levels were also consistent with chance variation.

Further multivariable logistic regression analyses showed that adjustment for social class (model 1) or for smoking and alcohol (model 2) made little difference to the results (table of data not shown). Mutual adjustment for the metabolic and inflammatory measures was performed to adjust for further potential confounders and/or intermediaries that may contribute to the development of AMD. When lifestyle measures

Table 2 Baseline characteristics of participants according to AMD status[a]

Characteristics	*Controls grades 0–1 (n = 843)*	*Cases grades 2–4 (n = 91)*	P-*value*
Age in years (mean, SD)	71.0 (4.2)	72.2 (4.1)	**0.02**
Social class[b]			0.90
Non-manual	337 (40.0)	37 (40.7)	
Manual	506 (60.0)	54 (59.3)	
BMI in kg/m^2 (mean, SD)	25.6 (3.0)	25.9 (2.6)	0.37
Smoking habit			0.90
Never smoked	174 (20.7)	17 (18.7)	
Ex smoker	329 (39.1)	39 (42.9)	
Cigar/pipe/1–14 cigarettes per day	171 (20.3)	17 (18.7)	
>15 cigarettes per day	168 (20.0)	18 (19.8)	
Alcohol consumption			0.63
<1 unit per week	211 (25.0)	28 (30.8)	
≥1 unit to ≤18 units per week	208 (24.7)	21 (23.1)	
>18 units to ≤60 units per week	222 (26.3)	24 (26.4)	
>60 units per week	202 (24.0)	18 (19.8)	
Haemodynamic measures in mm Hg (mean, SD)			
Systolic	135.2 (20.8)	137.9 (20.8)	0.24
Diastolic	85.4 (12.8)	87.9 (11.6)	0.08
Pulse pressure	49.9 (13.4)	50.1 (14.3)	0.89
Mean arterial pressure	102.0 (14.6)	104.6 (13.8)	0.11
Blood lipids in mmol/l (mean, SD)			
Total cholesterol	5.8 (1.2)	5.9 (1.1)	0.78
LDL cholesterol	4.0 (1.1)	4.1 (1.1)	0.48
HDL cholesterol	1.1 (0.4)	1.2 (0.4)	0.32
VLDL cholesterol	0.9 (0.6)	0.9 (0.8)	0.55
Total triglycerides	1.6 (1.0)	1.4 (0.7)	**0.04**
VLDL triglyceride	0.9 (0.7)	0.7 (0.6)	**0.05**
Glucose in mmol/l (mean, SD)	5.0 (0.9)	4.8 (0.5)	0.11
Inflammatory markers (mean, SD)			
White cell count (10^9 cells/l)	6.7 (1.8)	6.8 (1.7)	0.89
Fibrinogen (g/l)	1.4 (0.3)	1.4 (0.2)	0.68
CRP (mg/l)	2.3 (3.3)	3.2 (4.4)	**0.03**
D-dimer (ng/ml)	49.7 (57.9)	43.7 (23.2)	0.37
Dietary intake[c]			
Average family use of lard or solid vegetable oil			**0.04**
None	70 (35.4)	4 (15.4)	
1–200 oz per week	128 (64.6)	22 (84.6)	
Frequency of eating home fried food using solid fats			**<0.001**
<1 time a week	115 (56.1)	4 (15.4)	
1–7 times a week	90 (43.9)	22 (84.6)	

Abbreviations: SD, standard deviation; BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; VLDL, very low density lipoprotein; CRP, C-reactive protein.
Statistically significant data are highlighted in bold.
[a]Data are given in no (%) unless otherwise indicated.
[b]Social classes I, II, and III (non-manual); manual includes social classes III (manual), IV, V.
[c]Dietary data were only collected on a random subset of 231 (25%) subjects in phase II (1984–1988).

Table 3 Univariable age-adjusted analysis of risk factors for cases (ARM grades 2–4)

Risk factor	*Odds ratio*	*Confidence interval*	P-*value*
Age group			
45.6–50.9	1		
51–54.9	1.58	0.84–2.97	0.15
55–58.5	2.57	1.38–4.79	**0.003**
58.6–63.6	2.23	1.14–4.34	**0.02**
P-value for trend	1.34	1.10–1.63	**0.004**
Social class			
Non-manual	1		
Manual	0.97	0.62–1.50	0.88
Smoking habit			
Never smoked	1		
Ex smoker	1.12	0.61–2.04	0.72
Cigar/pipe/1–14 cigarettes per day	0.95	0.47–1.94	0.90
>15 cigarettes per day	1.12	0.56–2.26	0.75
P-value for trend	1.01	0.82–1.26	0.91
Alcohol consumption			
<1 unit per week	1		
≥1 unit to ≤18 units per week	0.81	0.44–1.49	0.50
>18 units to ≤60 units per week	0.82	0.46–1.47	0.51
>60 units per week	0.68	0.36–1.27	0.22
P-value for trend	0.89	0.73–1.08	0.25
Haemodynamic measures			
Systolic blood pressure[a]	1.09	0.86–1.38	0.47
Diastolic blood pressure[a]	1.22	0.97–1.53	0.08
Pulse pressure[a]	0.93	0.72–1.21	0.61
Mean arterial pressure[a]	1.17	0.93–1.47	0.18
BMI[a]	1.10	0.86–1.40	0.45
Blood lipids			
Total cholesterol[a]	1.04	0.83–1.31	0.74
LDL cholesterol[a]	1.10	0.87–1.38	0.43
HDL cholesterol[a]	1.08	0.88–1.33	0.44
VLDL cholesterol[a]	1.09	0.89–1.33	0.41
Total triglycerides[a]	0.73	0.54–1.00	**0.05**
VLDL triglyceride[a]	0.76	0.57–1.02	0.07
Glucose[a]	0.62	0.37–1.06	0.08
Inflammatory markers			
White cell count[a]	1.01	0.84–1.23	0.89
Fibrinogen levels[a]	1.03	0.81–1.30	0.82
CRP[a]	1.33	1.00–1.77	**0.05**
D-dimer[a]	0.74	0.42–1.31	0.31
Dietary intake			
Average family use of lard or solid vegetable oil			
None	1		
1–200 oz per week	3.27	1.07–10.01	**0.04**
Frequency of eating home fried food using solid fats			
<1 time a week	1		
1–7 times a week	6.85	2.26–20.77	**0.001**

P-values less than 0.05 are highlighted in bold.
[a]Values are standardised and *z*-scored.

(model 2: age, smoking, and alcohol) were adjusted in the analysis the associations of AMD with lower levels of triglycerides and raised CRP were attenuated

Table 4 Multivariable analysis of risk factors for AMD cases (ARM grades 2–4), adjusting for systolic BP, CRP, total cholesterol, total triglyceride, BMI and blood glucose

Risk factor	*Odds ratio*	*Confidence interval*	P-*value*
Age group			
45.6–50.9	1		
51–54.9	1.65	0.78–3.49	0.19
55–58.5	2.36	1.11–5.01	**0.03**
58.6–63.6	2.63	1.22–5.67	**0.01**
P-value for trend	1.37	1.09–1.73	**0.007**
Social class			
Non-manual	1		
Manual	0.82	0.50–1.36	0.45
BMI[a]	1.24	0.93–1.64	0.14
Smoking habit			
Never smoked	1		
Ex smoker	1.17	0.60–2.26	0.65
Cigar/pipe/1–14 cigarettes per day	0.75	0.33–1.72	0.49
>15 cigarettes per day	1.02	0.46–2.22	0.97
Alcohol consumption			
<1 unit per week	1		
≥1 unit to ≤18 units per week	0.76	0.39–1.48	0.42
>18 units to ≤60 units per week	0.56	0.28–1.11	0.10
>60 units per week	0.59	0.29–1.19	0.14
P-value for trend	0.82	0.66–1.03	0.09
Haemodynamic measures			
Systolic blood pressure[a]	1.34	1.01–1.76	**0.04**
Diastolic blood pressure[a,b]	1.35	1.03–1.77	**0.03**
Pulse pressure[a,b]	1.18	0.89–1.57	0.26
Mean arterial pressure[a,b]	1.37	1.04–1.79	**0.02**
Blood lipids			
Total cholesterol[a]	1.08	0.82–1.42	0.57
LDL cholesterol[a]	0.89	0.43–1.87	0.77
HDL cholesterol[a]	1.04	0.81–1.32	0.77
VLDL cholesterol[a]	1.25	0.86–1.82	0.24
Total triglycerides[a]	0.68	0.47–0.99	**0.04**
VLDL triglyceride[a]	0.70	0.44–1.11	0.13
Glucose[a]	0.60	0.32–1.11	0.11
Inflammatory markers			
White cell count[a]	0.94	0.71–1.25	0.67
Fibrinogen[a]	1.00	0.76–1.32	1.00
CRP[a]	1.28	0.93–1.75	0.13
D-dimer[a]	0.72	0.39–1.34	0.30

P-values <0.05 are highlighted in bold.
[a]Values are standardised and *z*-scored.
[b]Blood pressure variables were not adjusted by systolic BP due to co-linearity.

(OR CRP: 1.33, 95% CI 0.99, 1.77, $P=0.05$; OR triglycerides: 0.73 95% CI 0.54, 1.00, $P=0.05$). Older age was predictably associated with AMD (OR for trend: 1.33, 95% CI 1.09, 1.62, $P=0.006$). When anthropometric and metabolic factors were adjusted together (model 3), the association of AMD and age was maintained (see Table 4). Higher baseline systolic, diastolic, and mean arterial BPs were shown to

be associated with AMD with modest evidence against the null hypothesis. Again, higher serum total triglycerides were shown to be protective in the development of AMD.

Dietary data was analysed separately from the main analysis (because of the limited sample number). Lower concentrations of serum total triglycerides and VLDL triglyceride, as well as higher CRP remained predictive in this subgroup analysis. Consistent with the univariable analysis, a higher use of lard or solid fats and increased frequency of eating home fried food using solid fats were the only dietary variables shown to be associated with an increased prevalence of AMD in this model of multivariate analysis (OR lard: 3.19, 95% CI 1.04, 9.80, $P = 0.04$; OR fried food: 8.35, 95% CI 1.96, 35.66, $P = 0.004$).

Discussion

This is the second large population-based screening study of AMD in the United Kingdom. The prevalence of AMD in this study was lower than that reported in the Beaver Dam (BDES, 1.2%, males), Rotterdam (RS, 1.4%, males), Blue Mountains Eye Study (BMES) (1%, males), Chesapeake Bay Watermen (1.3%), the European eye study (EUREYE, 2.5%, males), the Eye diseases prevalence research group (Eye diseases PRG, 0.63–3.97%, white males), Cardiovascular health study (CHS, 1.4%, white males), and Melton Mowbray (1.9% exudative AMD, 1.9% GA),[1,4,33–38] but it is comparable to the Visual Impairment Project[39] (VIP, 0.58%, males) and the Colorado-Wisconsin Study[40] (0.53%, age-standardised to VIP study). In part this may be due to differences in grading between studies; however, the grading system used in our study was almost identical to that used in the RS. Although the average age in the Speedwell study was greater than several of the other studies (BDES 61.8 years, RS 69.0 years, BMES 66.1 years), we had an upper age limit of 83 years while in some of the other studies this was unrestricted. This might account for some of the difference, as the risk for AMD rises with age. A third possible issue is selection bias; men who did not attend may be more likely to have AMD (due to inability/disability to attend) or equally more willing to participate, if they have AMD (to seek medical attention), though our response rate of 86.4% for any clinical information and 70.7% for the eye examination is similar to other studies.[35,36] Virtually all the non-responders were contacted by phone or their medical records were checked. If we add the three men identified as having AMD from their clinical records to our estimate, the prevalence of 0.9% (95% CI 0.4%, 1.7%), although lower, is consistent with other estimates in the literature.

Hypopigmentation was seen in 9.6% of participants and hyperpigmentation in 10.4%. These figures are slightly higher than those found in the RS,[35] VIP,[41] or Colorado–Wisconsin[40] studies but less than the BDES,[34] BMES,[33] and Melton Mowbray[4] studies. Several studies have shown a greater risk of developing future AMD given the presence of these milder abnormalities.[29,42–44] Considering the increase in life expectancy due to age-specific reductions in cardiovascular mortality, more men will survive to develop AMD in the future with inevitable health consequences.

Potential risk factors for AMD

We found that age, higher blood levels of CRP and lower blood levels of triglycerides were associated with a higher risk of developing ARM/AMD. Following multivariable adjustment for metabolic factors, subjects with ARM/AMD also had higher baseline systolic, diastolic, and mean arterial BPs. The only dietary variables that potentially predicted the risk for developing ARM/AMD were higher intakes of lard or solid fats and fried food using solid fats.

In this study, socioeconomic status was not associated with ARM/AMD, similar to other studies[21,45–47] that have used educational level as a surrogate indicator of socioeconomic status.[48–50] In contrast to previously published reports, this study showed no evidence that smoking at baseline was associated with ARM/AMD,[15,45,51–56] although this is not seen consistently across studies.[19,41,57,58] Pooled analysis of BDES, BMES and the Rotterdam study showed a threefold association of current smoking at baseline with the development of AMD,[16] whereas the Nurses' health[59] and the Physicians' health[56] studies both observed positive dose-related associations between smoking and AMD. Analysis of data in later phases showed an age-related decline in smoking prevalence, however, this did not change our findings. We suspect that our negative findings most likely reflect a type II error or a healthy survivor effect, which will differ between populations because of variations in competing causes of death.

We found that baseline serum levels of CRP (measured in Phase II), a marker of systemic inflammation, was associated with ARM/AMD. This result strengthens the previously reported findings from prospective[60–62] and cross-sectional studies[63–66] and supports the hypothesis that the pathogenesis of AMD may be inflammatory or immune-related. Drusen, one of the pathological hallmarks of AMD, contain inflammatory proteins such as fibrinogen, vitronectin, complement, and CRP.[67,68] This association, however, may reflect reverse causation despite the relatively long latency between exposure and outcome measures. Recent epidemiological work has

failed to find associations between functional genetic variants associated with elevated CRP levels and coronary heart disease.[69] Furthermore, adjustment for other metabolic factors attenuated this association, which is in agreement with another study,[70] suggesting that either these factors may mediate the association or they both share a common antecedent.

Surprisingly, there was an inverse relationship between fasting serum triglyceride lipid levels and the VLDL subfraction with AMD risk, which is counterintuitive to the hypothesis that the pathogenesis of AMD is related to atherosclerosis.[20] Other epidemiological studies have found either no,[46,71–74] a positive association[21] or an inverse association between serum lipids and ARM/AMD.[16,22,38,75,76] More recent studies are difficult to interpret because of the widespread use of lipid-lowering medication, which may have a pharmacological effect independent of their effects on lipids. However, this cannot account for our findings as in the 1980s, few men would have been on lipid-lowering therapies and this predates the statin era. The reasons for these discrepancies are unclear. Furthermore, our study reports that an increased dietary intake of solid fats (lard, solid vegetable oils) and food fried in solid fats were independent risk factors in the development of AMD, despite no change in serum cholesterol levels or BMI. Other studies have shown similar results.[23,77,78] This would be consistent with the idea that AMD, cardiovascular disease and atherosclerosis may share a similar pathogenesis, however, one must be cautious with such associations because of the possibility of residual confounding, as dietary intakes are strongly associated with other lifestyle and sociodemographic factors.

In this study, higher systolic, diastolic and mean arterial BPs were associated with an increased risk of ARM/AMD. Hypertension has been postulated as a risk factor for AMD through its deleterious functions on the choroidal circulation.[20,79] Similar associations have been found by others.[38,46,47,80,81] However, other studies have failed to find an association,[16,45,72–74,81–83] and to our knowledge there are no reports of a reduction in risk of AMD in those being treated for hypertension.[20,45,84]

Strengths and limitations

This study has prospective risk factor data on a longer period than any other studies to the best of our knowledge. This greatly reduces the chance that any associations are secondary to reverse causation or ascertainment bias, whereby subjects with co-morbidity are more like to have ARM/AMD detected due to greater clinical surveillance. The generalisability of our findings are limited to Caucasian men though, as we note above many of our associations have been seen in other studies including women. Another major limitation is the relatively small number of cases that we had available for analysis. At 80% power and 5% significance, we could detect a doubling of the odds ratios or more but not more modest effects.

Conclusions

We have found that AMD and ARM are moderately common in an unselected sample of elderly white men living in South West England. Long-term risk factor data suggest associations with several cardiovascular risk factors and poor diet, yet there may be a paradoxical association with triglyceride levels, which remains unexplained. Improvements in cardiovascular health may result in an increasing burden of AMD in the community due to longer survival, unless this is counterbalanced by any beneficial effects from better risk-factor control. Long-term trend data on incidence rate will help confirm or refute a shared cardiovascular mechanism.

Summary

What was known before

- Prevalence of ARM/AMD in the United Kingdom: Accurate figures are unknown using the International classification system for AMD. Other studies worldwide report the prevalance of AMD at 0.53–2.5%. Risk factors for AMD: Smoking, atherosclerosis, inflammation, hypertension, lipid levels and dietary fats but limited to short follow-up and potential for reverse causation; also inconsistent findings because of selection/recall bias and confounding.

What this study adds

- Prevalence of ARM/AMD in the United Kingdom: Early age-related maculopathy (grades 2–3) was found in 9.2% and late age-related maculopathy (grade 4, age-related macular degeneration) in 0.5%. In an unselected, representative cohort of men aged 65–83 from Bristol, United Kingdom, many had macular changes that put them at higher risk of developing age-related macular degeneration. Opportunities for screening and undertaking secondary prevention interventions need to be explored to prevent progression of the disease and blindness. Risk factors for AMD: Long-term risk factor data (~18-years follow up) suggest associations with several cardiovascular risk factors (systolic, diastolic, mean arterial blood pressures, and CRP) and poor diet, yet there may be a paradoxical association with triglyceride levels, the significance of which remains unclear. Improvements in cardiovascular health may result in an increasing burden of AMD in the community due to longer survival, unless this is counterbalanced by any beneficial effects from better risk-factor control.

Conflict of interest

The authors declare no conflict of interest.

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Ethics approval

The study was approved by the following research ethic committees: Frenchay Health Care Trust, United Bristol Health Care Trust and South and West Local Research Ethics committee.

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