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Cross-sectional study of the association between age-related macular degeneration and arthritis in the National Health and Nutrition Examination Survey 2005–2008

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ABSTRACT

Objective To explore the association between age-related macular degeneration (AMD) and arthritis in a representative sample of the US population.

Design Population-based, cross-sectional study.

Setting The National Health and Nutrition Examination Survey (NHANES) 2005–2008.

Participants A total of 4813 participants aged 40 years and older with available information on AMD and arthritis in the 2005–2008 NHANES.

Methods The status and types of arthritis were obtained from questionnaires. Non-mydriatic fundus photographs were collected. The types of AMD were assessed using the modified Wisconsin Age-Related Maculopathy Grading Classification Scheme. The association between arthritis and AMD was evaluated using logistic regression models.

Results After adjusting for covariates, participants with any or early AMD had significantly lower odds of having any type of arthritis (any AMD: OR=0.56, 95% CI: 0.36–0.86; early AMD: OR=0.55, 95% CI: 0.34–0.88) or osteoarthritis (OA) (any AMD: OR=0.43, 95% CI: 0.26–0.71; early AMD: OR=0.44, 95% CI: 0.25–0.76) compared with those without AMD. When considering AMD as the outcome, significant negative associations were also found between any arthritis or OA and any (any arthritis: OR=0.64, 95% CI: 0.43–0.94; OA: OR=0.52, 95% CI: 0.33–0.82) or early AMD (any arthritis: OR=0.61, 95% CI: 0.40–0.93; OA: OR=0.51, 95% CI: 0.31–0.86) in the multivariable logistic models. There was no significant association between different types of arthritis and late AMD.

Conclusions People with arthritis, especially those with OA, were less likely to have AMD compared with those without arthritis and vice versa. Further studies are needed to confirm this potential protective effect of arthritis and/or arthritis treatment on AMD and to explore the underlying mechanisms.

Strengths and limitations of this study

- This study pooled data from a nationally representative sample of the US adult population.
- Age-related macular degeneration status was determined by assessing fundus images using a standardised protocol.
- This study controlled for a range of confounding factors.
- This study was limited by the cross-sectional design and the definition of arthritis.
- The imbalance of baseline characteristics between included and excluded participants might cause bias.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness in developed countries,[1] and is associated with considerable economic burden, reduced quality of life and premature death.[2 3] It has been estimated that approximately 6.5% of adults aged 40 years and older in USA suffered from AMD in 2011.[4] Given an ageing population and the lack of effective treatments, the prevalence of AMD is expected to increase in the coming decades. By 2040, an estimated total of 288 million adults worldwide will have AMD.[1]

Arthritis affects 54.4 million adults in USA and is the most common cause of disability.[5] It causes chronic pain and limitations to daily activities and productivity, adversely affecting both individuals and society.[6] In 2013, the estimated healthcare expenditure and earning losses attributable to arthritis added up to US$303.5 billion in USA.[7] As the population ages, the number of cases of physician-diagnosed arthritis in USA is predicted to increase from 54.4 million in 2013–2015 to 78.4 million in 2040.[8]

Concerning the pathophysiology, there are some well-documented similarities between AMD and arthritis, including the involvement of inflammatory reactions and the extracellular matrix. However, studies exploring the potential association between these two

conditions have produced mixed results.[9–14] Two case-control studies reported a significantly increased risk of arthritis in people with early or neovascular AMD.[15 16] Whereas a cross-sectional study found no significant association between arthritis and either early or late AMD.[17] Of note, neither of these studies made a distinction between osteoarthritis (OA) and rheumatoid arthritis (RA), which are the two main types of arthritis with different pathophysiology.[18] Although a potential association between OA or RA and AMD has been reported in three studies, their results were inconsistent.[19–21] Furthermore, these studies are subject to selection bias, verification bias of AMD, and residual confounding. Understanding the relationships between AMD and different types of arthritis is important as it could provide insights into the shared risk factors between these two diseases, their pathogenesis and treatments.

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative survey of a non-institutionalised civilian population in USA. It provides an opportunity to explore the association between eye diseases and different types of arthritis. Interestingly, our previous analysis based on the NHANES found that patients with OA were less likely to have retinopathy when compared with those without.[22] The arthritis physiology and/or its therapies might explain the unorthodox results. In the present analysis, we investigated the association between AMD and different types of arthritis based on the NHANES, a large population-based study that used a standardised AMD grading protocol and collected comprehensive data on confounding factors.

METHODS

Sample and population

The NHANES was conducted by the National Center for Health Statistics (NCHS). It employed a stratified multistage sampling methodology and purposely oversampled participants who were older than 60 years of age and those from ethnic minority groups. Extensive health-related interviews and examinations, including blood and urine tests, were conducted at mobile exam centres. The sampling and testing methodologies have been described in detail elsewhere.[22 23] This study used NHANES data collected from 2005/2006 and 2007/2008 study cycles. A total of 6797 participants aged 40 years and older were identified. In total, 969 participants were excluded due to missing information on the retinal photographs for both eyes, and 224 participants were excluded due to missing information on the severity classification of AMD in at least one eye. Additionally, 791 participants who had missing information on the status and/or types of arthritis were excluded leading to a final sample of 4813 participants (figure 1). Excluded participants tended to be older, female, from ethnic groups other than the non-hispanic white ethnicity, less educated, unmarried, have a lower socioeconomic status and be less healthy (all $p<0.05$). The demographic characteristics and health-related behaviours of excluded and included subjects are shown in online supplemental table 1.

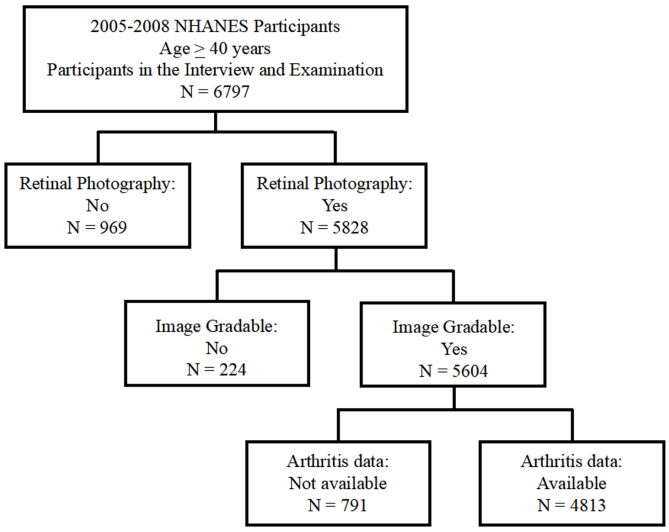

Figure 1 Schematic showing study participants included for the present analysis from the 2005–2008 NHANES. A total of 4813 participants aged 40 years and older with valid fundus photographs and available information on arthritis status were included. NHANES, National Health and Nutrition Examination Survey.

Participants provided written informed consent before being enrolled in the surveys.

Patient and public involvement

Data used in this analysis were publicly available and de-identified NHANES data. No patient and/or public were involved in the design and conception of our study.

Retinal photography and AMD grading

Retinal photographs were collected for participants aged 40 years and over in the 2005–2008 NHANES cycles. Canon CR6-45NM Ophthalmic Digital Imaging System and Canon EOS 10D digital camera (Canon USA, One Canon Park, Melville, New York, USA) were used to take retinal photographs. All retinal photographs were graded at the University of Wisconsin, Madison, according to the modified Wisconsin Age-Related Maculopathy Grading Classification Scheme.[24] All retinal images were graded by at least two experienced graders. Any discrepancies in the results were determined by a third senior grader. Early AMD was defined as signs of drusen with a grid area of greater than a 500 µm circle and/or pigmentary abnormalities, while the presence of exudative or geographic atrophy signs was defined as late AMD. If retinal images were available for both eyes, we used the status of the eye with more severe AMD in our analyses.

Arthritis status

Consistent with the previous analysis,[22] information on the arthritis status was collected by questionnaire and self-reported by participants. All participants aged 20 years and older were asked about whether they had ever been diagnosed with arthritis ('Has a doctor or

other health professionals ever told you that you had arthritis?'). If participants gave an affirmative answer, they were then asked, 'Which type of arthritis was it?' to identify the specific type. Possible answers included RA, OA, other, unknown type or declined to answer. Individuals who reported receiving a diagnosis of arthritis, but did not know the type or declined to answer to the type of arthritis were excluded from the current analysis. The consistency between self-reported and clinically confirmed diagnosis of arthritis has been previously demonstrated.[25]

Covariates

Information on demographic characteristics, health-related behaviours and comorbidities was obtained through comprehensive in-person interviews and examinations. Ethnicity was categorised as non-hispanic white or other. Education level was divided into less than a high school degree and a high school diploma or more. Two categories were used for marital status, unmarried and other or married/with a partner. The indicator for family income was the poverty income ratio and was classified as below poverty (<1.00) or at or above the poverty line (≥1.00). Smoking status was categorised into never or former/current smokers. Self-reported alcohol consumption was categorised into lifetime abstainer/former drinker, current drinker with less than four drinks per week, and current drinkers with more than three drinks per week.

Diabetes mellitus was defined as self-reported physician diagnosis, the use of antidiabetic medications or insulin, or glycosylated haemoglobin level (%) ≥6.5%. Hypertension was defined as having a self-reported history of hypertension, a prescription of antihypertensive agents or a systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg. Dyslipidaemia was defined as total cholesterol ≥240 mg/dL or the use of a cholesterol-lowering agent. Body mass index was calculated as weight in kilograms divided by height in metres squared and categorised as three groups: <18.5, 18.5–24.9 and ≥25 kg/m^2. C-reactive protein (CRP) level was analysed as a two-level categorical variable (≥1 mg/dL or not). Self-rated health status was dichotomised as poor/fair or good/excellent. The 2008 Physical Activity Guideline for Americans suggests at least 2.5 hours of moderate-intensity or 75 min of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate and vigorous-intensity aerobic activity for substantial health benefits. We categorised participants into two groups based on whether the 2008 Physical Activity Guideline was met or not. The presence of chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2. Self-reported history of cardiovascular disease (CVD) was defined as having a previous physician diagnosis of congestive heart failure, coronary heart disease, angina, heart attack or stroke.

Statistical analysis

Based on the NHANES Analytic and Reporting Guidelines, all analysis accounted for the complex and stratified design and used appropriate sample weights according to the NHANES Analytic and Reporting Guidelines. The baseline characteristics of study participants were reported by using means and SEs for continuous variables, and numbers and weighted percentages for categorical variables. The t-test for the comparison of continuous variables and design-adjusted Rao-Scott Pearson χ^2 for the comparison of categorical data were used to compare baseline characteristics by AMD or arthritis status. Logistic regression models were used to estimate ORs and 95% CIs for the association between AMD and arthritis status. All data analysis was performed using Stata (V. 14.0; StataCorp, College Station, Texas, USA). Two-sided p values <0.05 were considered significant for statistical inferences.

RESULTS

The mean age of the study population was 55.8 years (SE=0.36), 48.0% of participants were male and 76.6% were non-hispanic white. The overall prevalence of any arthritis was 26.6%, including 6.5% RA, 14.8% OA and 5.4% other types of arthritis. Compared with participants without arthritis, participants with arthritis were more likely to be older, female, of non-hispanic white, less educated, unmarried, living with poorer socioeconomic status, former/current smoker and lifetime abstainer/former drinker. Participants with arthritis were also less healthy, they were more likely to have diabetes mellitus, hypertension, dyslipidaemia, overweight/obesity, high level of CRP, poor/fair self-rated health status, less physical activity, chronic kidney disease and CVD. Demographic characteristics, health-related behaviours, and comorbidities of participants by arthritis status are presented in table 1.

The overall prevalence of AMD was 6.5%, of which 5.7% had early AMD and 0.8% had late AMD. Participants with any AMD were more likely to be older, non-hispanic white, unmarried or in other marital status, former/current smoker, less healthy in terms of diabetes mellitus, hypertension, chronic kidney disease and CVD. There was no significant difference in other characteristics between the AMD group and the no AMD group (table 2).

Tables 3 and 4 show the results of the multivariable logistic regression models of arthritis and AMD. Considering any arthritis as the outcome, participants who had any AMD had a significantly lower odds of having any arthritis (OR=0.56, 95% CI: 0.36–0.86, p=0.011) compared with participants without AMD, after adjusting for covariates. Additionally, participants with early AMD were 45% less likely to have any arthritis compared with participants with no AMD (OR=0.55, 95% CI: 0.34–0.88, p=0.014). The participants with any AMD and those with early patients with AMD had similarly reduced risk of OA when compared with those with no AMD, respectively

Table 1 Demographic characteristics, health-related behaviours and comorbidities of participants with and without arthritis

Characteristics	Overall, N=4813	No arthritis, n=3441 (%)	Any arthritis, n=1372 (%)	Unadjusted p value*
Age (SE), years	55.8±0.36	53.9±0.34	60.8±0.49	**<0.001**
Gender				
Male	2443 (48.0)	1878 (51.4)	565 (38.5)	**<0.001**
Female	2370 (52.0)	1563 (48.6)	807 (61.5)	
Ethnicity				
Non-hispanic white	2551 (76.6)	1707 (74.5)	844 (82.4)	**<0.001**
Other	2262 (23.4)	1734 (25.5)	528 (17.6)	
Education				
Less than high school	1357 (17.0)	976 (16.2)	381 (19.1)	**0.04**
High school and over	3456 (83.0)	2465 (83.8)	991 (80.9)	
Marital status				
Unmarried and other	1719 (30.8)	1153 (29.2)	566 (35.0)	**0.02**
Married/with a partner	3092 (69.3)	2286 (70.8)	806 (65.0)	
Poverty income ratio				
Below poverty (<1)	695 (8.9)	473 (8.1)	222 (11.0)	**0.006**
At or above poverty (≥1)	3800 (91.1)	2749 (91.9)	1051 (89.0)	
Smoking status				
Never	2313 (49.4)	1724 (51.6)	589 (43.4)	**<0.001**
Former/current	2499 (50.6)	1716 (48.4)	783 (56.6)	
Alcohol consumption				
Lifetime abstainer/former drinker	1152 (20.4)	778 (18.9)	374 (24.7)	**<0.001**
Current drinker (≤3 drinks/w)	2538 (55.0)	1805 (54.9)	733 (55.0)	
Current drinker (>3 drinks/w)	1011 (24.6)	776 (26.2)	235 (20.3)	
DM				
No	3833 (87.2)	2797 (88.9)	1036 (82.5)	**<0.001**
Yes	858 (12.8)	553 (11.1)	305 (17.5)	
HBP				
No	2446 (58.1)	1932 (62.9)	514 (45.1)	**<0.001**
Yes	2289 (41.9)	1455 (37.1)	834 (54.9)	
High cholesterol				
No	2895 (63.2)	2156 (65.5)	739 (56.6)	**<0.001**
Yes	1789 (36.8)	1189 (34.5)	600 (43.4)	
BMI				
<18.5 kg/m^2	72 (1.4)	55 (1.5)	17 (1.2)	**0.007**
18.5–25 kg/m^2	1188 (27.2)	888 (28.7)	300 (23.0)	
≥25 kg/m^2	3516 (71.4)	2470 (69.8)	1046 (75.8)	
High C-reactive protein				
No	4133 (89.7)	3027 (91.2)	1106 (85.8)	**<0.001**
Yes	523 (10.3)	305 (8.8)	218 (14.2)	
Self-rated health				
Poor/fair	1174 (17.9)	708 (14.2)	466 (28.0)	**<0.001**
Good/excellent	3540 (82.1)	2659 (85.8)	881 (72.0)	
Physical activity (meeting recommendation)				

Continued

Table 1 Continued

Characteristics	Overall, N=4813	No arthritis, n=3441 (%)	Any arthritis, n=1372 (%)	Unadjusted p value*
No	1474 (30.9)	974 (28.5)	500 (38.1)	**<0.001**
Yes	2451 (69.1)	1861 (71.5)	590 (61.9)	
Chronic kidney disease				
No	4046 (90.2)	2966 (92.1)	1080 (84.9)	**<0.001**
Yes	579 (9.8)	349 (7.9)	230 (15.1)	
Cardiovascular disease history				
No	4138 (89.1)	3082 (92.1)	1056 (80.6)	**<0.001**
Yes	675 (10.9)	359 (7.9)	316 (19.4)	

All proportions are weighted estimates of the US population characteristics, taking into account the complex sampling design of the National Health and Nutrition Examination Survey. Boldface indicates statistical significance.
*All p values were calculated using t-test for continuous variables and the design-adjusted Rao-Scott Pearson χ^2 test for categorical variables.
BMI, body mass index; DM, diabetes mellitus; HBP, high blood pressure.

(any: OR=0.43, 95% CI: 0.26–0.71, p=0.002; early: OR=0.44, 95% CI: 0.25–0.76, p=0.005). However, the risks of RA and other types of arthritis were not significantly different between participants who had any or early AMD and those without AMD. We did not find any significant association between late AMD and either any arthritis or the specific types of arthritis.

When considering AMD as the outcome, significant negative associations were found between any arthritis (OR=0.64, 95% CI: 0.43–0.94, p=0.025) or OA (OR=0.52, 95% CI: 0.33–0.82, p=0.006) and any AMD in the multivariable logistic models. We found no statistically significant association between RA or other types of arthritis and any AMD. Similarly, using early AMD as an outcome, participants who self-reported any arthritis or OA had 39% and 49% reduced odds of having early AMD, respectively (any arthritis: OR=0.61, 95% CI: 0.40–0.93, p=0.024; OA: OR=0.51, 95% CI: 0.31–0.86, p=0.012) after adjusting for multiple covariates. There was no significant association between different types of arthritis and the late AMD status.

DISCUSSION

In this pooled analysis of a nationally representative sample with a total of 4813 participants aged 40 years and older, we found that any arthritis and OA were negatively associated with any or early AMD after adjusting for confounding factors. No significant association was found between RA and AMD.

Considerable controversies exist in the relationship between arthritis and AMD. A retrospective case–control study reported a significantly increased risk of arthritis in patients with neovascular AMD compared with those without.[15] This claims-based data may be subject to inaccurate coding, referral and ascertainment biases, and potential residual confounding. The Age-Related Eye Disease Study (AREDS), a clinic-based case–control study, reported an increased risk of arthritis in subjects with one or more large drusen or substantial intermediate drusen when compared with those with less than 15 small drusen.[16] However, limitations, including chance finding, selection bias and residual confounding, should be considered when interpreting the AREDS results. A record linkage study suggested that AMD was not significantly associated with arthritis when considering RA or OA as the outcome, although patients with OA or RA had a modestly increased risk of developing AMD.[19] The definitions of AMD and arthritis in that study were based on hospital admissions datasets. Therefore, the prevalence of AMD may have been underestimated and the AMD identified by this method may be likely to be the severe types (eg, neovascular AMD). In a previous prospective cohort study, McGeer and Sibley compared the prevalence of AMD in a large sample of patients with RA to that in four general populations. They found that patients with RA were significantly less likely to develop AMD compared with the general population, but this study failed to account for confounders and failed to identify the majority of AMD cases.[20] In the Melbourne Collaborative Cohort Study,[21] the presence of intermediate AMD predicted an increased 10-year incidence of total hip replacement due to OA. However, total hip replacement as a surrogate for severe OA might underestimate the incidence of OA. A previous cross-sectional study reported that there was no significant association between arthritis and either early or late AMD.[17] This previous study and our study differ in study population (hospital-based vs population-based), study design (cohort vs cross-sectional), identification of arthritis (self-report vs medicare coding) and AMD (medicare coding, ophthalmoscopic screening vs fundus grading), and the confounding factors adjusted for. These may account for the differences observed in our results.

Table 2 Demographic characteristics, health-related behaviours and comorbidities of participants with and without AMD

Characteristics	No AMD, n=4441 (%)	Any AMD, n=372 (%)	Unadjusted p value*
Age (SE), years	55.0±0.32	67.3±0.99	**<0.001**
Gender			
Male	2245 (48.0)	198 (47.8)	0.95
Female	2196 (52.0)	174 (52.2)	
Ethnicity			
Non-hispanic white	2287 (76.0)	264 (86.2)	**<0.001**
Other	2154 (24.0)	108 (13.8)	
Education			
Less than high school	1253 (16.7)	104 (21.2)	0.14
High school and over	3188 (83.3)	268 (78.8)	
Marital status			
Unmarried and other	1548 (30.2)	171 (39.1)	**0.006**
Married/with a partner	2891 (69.8)	201 (60.9)	
Poverty income ratio			
Below poverty (<1)	649 (8.9)	46 (8.7)	0.93
At or above poverty (≥1)	3510 (91.1)	290 (91.3)	
Smoking status			
Never	2149 (49.8)	164 (43.1)	**0.04**
Former/current	2291 (50.2)	208 (56.9)	
Alcohol consumption			
Lifetime abstainer/former drinker	1047 (20.0)	105 (26.8)	0.05
Current drinker (≤3 drinks/week)	2352 (55.1)	186 (52.5)	
Current drinker (>3 drinks/week)	938 (24.9)	73 (20.7)	
DM			
No	3537 (87.4)	296 (84.1)	**0.05**
Yes	789 (12.6)	69 (15.9)	
HBP			
No	2315 (59.2)	131 (42.8)	**<0.001**
Yes	2057 (40.8)	232 (57.2)	
High cholesterol			
No	2665 (63.3)	230 (61.3)	0.56
Yes	1655 (36.7)	134 (38.7)	
BMI (kg/m^2)			
<18.5	68 (1.5)	4 (0.5)	0.09
18.5–25	1088 (26.9)	100 (30.9)	
≥25	3251 (71.6)	265 (68.6)	
High C-reactive protein			
No	3820 (89.9)	313 (87.1)	0.24
Yes	474 (10.1)	49 (12.9)	
Self-rated health			
Poor/fair	1074 (17.6)	100 (22.0)	0.08
Good/excellent	3276 (82.4)	264 (78.0)	
Physical activity (meeting recommendation)			
No	1350 (30.7)	124 (34.4)	0.29
Yes	2285 (69.3)	166 (65.6)	
Chronic kidney disease			
No	3796 (91.4)	250 (71.8)	**<0.001**
Yes	469 (8.6)	110 (28.2)	
Cardiovascular disease history			
No	3868 (90.0)	270 (75.5)	**<0.001**
Yes	573 (10.0)	102 (24.5)	

All proportions are weighted estimates of the US population characteristics, taking into account the complex sampling design of the National Health and Nutrition Examination Survey. Boldface indicates statistical significance.
*All p values were calculated using t-test for continuous variables and the design-adjusted Rao-Scott Pearson χ^2 test for categorical variables.
AMD, age-related macular degeneration; BMI, body mass index; DM, diabetes mellitus; HBP, high blood pressure.

The negative association between arthritis and AMD observed in our study may be explained by genetic, environmental, therapeutic or physiological factors. Genetically, the loci most strongly associated with AMD were found at the 1q32 (complement factor H [CFH]/complement factor H related [CFHR]) and 10q26 (pleckstrin homology domain containing A1 [PLEKHA1]/age-related maculopathy susceptibility 2 [ARMS2]/high temperature requirement A1 [HTRA1]).[26] However, neither loci have been strongly associated with the risk of developing RA or OA.[27 28] With respect to environmental risk factors, the association between cigarette smoking and AMD has been confirmed[29] but is not implicated in the risk of OA.[30]

Alternatively, treatments for arthritis may prevent AMD from developing and progressing. Of note, the risk of developing AMD is highly age-dependent, with a low prevalence of AMD before the age of 65.[31] However, both OA and RA are chronic progressive diseases that can present at any age.[32 33] We infer that patients with RA or OA might have received treatments for a long time before becoming susceptible to the development of AMD. Inflammatory

Table 3 Logistic regression models of AMD for arthritis status

	AMD status			
	No (n=4441)	Any (n=372)	Early (n=326)	Late (n=46)
Any arthritis				
Event	1239	133	112	21
Age-adjusted and sex-adjusted rates*	27.00%	22.40%	22.20%	23.70%
Multiple-adjusted models†	1	0.56 (0.36–0.86)‡	0.55 (0.34–0.88)‡	0.60 (0.24–1.52)
RA				
Event	371	44	35	9
Age-adjusted and sex-adjusted rates*	8.10%	8.30%	7.80%	11.20%
Multiple-adjusted models†	1	0.70 (0.35–1.37)	0.72 (0.35–1.48)	0.52 (0.12–2.27)
OA				
Event	616	66	58	8
Age-adjusted and sex-adjusted rates*	17.20%	12.2%‡	12.9%‡	7.9%§
Multiple-adjusted models†	1	0.43 (0.26–0.71)§	0.44 (0.25–0.76)§	0.40 (0.15–1.07)
Other arthritis				
Event	252	23	19	4
Age-adjusted and sex-adjusted rates*	6.90%	6.10%	5.20%	11.80%
Multiple-adjusted models†	1	0.87 (0.42–1.80)	0.69 (0.33–1.44)	2.26 (0.46–11.2)

Values are number of HR (95% CI).
*Adjusted for age and gender; Comparisons were between each AMD group and the no AMD group.
†Multiple-adjusted Model: Adjusted for age, gender, ethnicity, education level, marital status, income status, body mass index, smoking status, drinking status, hypertension, diabetes mellitus, cholesterol level, C-reactive protein, self-rated health status, physical activity, chronic kidney disease and cardiovascular disease history.
‡P<0.05.
§P<0.01.
AMD, age-related macular degeneration; OA, osteoarthritis; RA, rheumatoid arthritis.

processes, especially the complement system, are involved in the pathogenesis of both AMD and arthritis.[9–14] The anti-inflammatory treatments for arthritis might also be effective in preventing the onset of AMD and delaying its progression. A large number of studies have examined the relationship between AMD and aspirin use; but, controversy remains.[34 35] Two randomised controlled trials found that the use of low-dose aspirin did not have a significant impact on the risk of developing AMD.[36 37] When data from these two trials were combined, a non-significant 18% reduction in the risk of AMD was observed in aspirin group compared with the placebo group.[37] However, few studies have focused on the role of non-steroidal anti-inflammatory drugs (NSAIDs) other than aspirin in the risk of AMD. A recent large-scale prospective cohort study reported a negative association between longer-term use of any NSAIDs and exudative AMD. They also found that shorter-term use of any NSAIDs or aspirin reduced the risk of nonexudative AMD.[38] In the AREDS, Sen *et al* reported a non-significant association between NSAIDs and any AMD, geographic atrophy or neovascular AMD.[39]

Other key etiologic factors of AMD include oxidative stress, angiogenesis, and abnormal extracellular matrix.[40] Analgesic agents (eg, acetaminophen), chloroquine and penicillamine have been widely used for treating arthritis. In animal experiments,[41] acetaminophen has been shown to have substantial anti-oxidative effects, with a beneficial effect on the prevention of AMD. Anti-rheumatic drugs, including chloroquine and penicillamine might protect tissue inhibitor of metalloproteinase from inactivation by oxidative stress, thus preventing degenerative changes which could lead to AMD.[42]

Strengths of our study include the large sample size, the population-based design, the standardised grading of AMD, and multiple confounder adjustments. Nevertheless, this present analysis has some limitations. First, the cross-sectional study design did not allow investigation of the causal relationship between arthritis and AMD. Second, the accuracy of self-reported arthritis diagnoses may be limited, although the consistency between self-reported and clinically confirmed diagnoses of arthritis has been previously demonstrated.[25] Thirdly, the

Table 4 Logistic regression models of arthritis for AMD status

	Arthritis status				
	No (n=3441)	Any (n=1372)	Rheumatoid (n=415)	OA (n=682)	Other (n=275)
Any AMD					
Event	239	133	44	66	23
Age-adjusted and sex-adjusted rates*	6.80%	5.90%	7.30%	5.20%	6.40%
Multiple-adjusted models†	1	0.64 (0.43–0.94)‡	0.80 (0.43–1.47)	0.52 (0.33–0.82)§	0.99 (0.48–2.07)
Early AMD					
Event	214	112	35	58	19
Age-adjusted and sex-adjusted rates*	6.10%	5.10%	6.20%	4.80%	4.80%
Multiple-adjusted models†	1	0.61 (0.40–0.93)‡	0.82 (0.43–1.56)	0.51 (0.31–0.86)‡	0.77 (0.37–1.59)
Late AMD					
Event	25	21	9	8	4
Age-adjusted and sex-adjusted rates*	0.80%	0.90%	1.40%	0.50%	1.70%
Multiple-adjusted models†	1	0.86 (0.33–2.20)	0.80 (0.18–3.56)	0.53 (0.21–1.33)	4.33 (0.48–39.4)

Values are number of HR (95% CI).
*Adjusted for age and gender; Comparisons were between each AMD group and the no AMD group.
†Multiple-adjusted Model: Adjusted for age, gender, ethnicity, education level, marital status, income status, body mass index, smoking status, drinking status, hypertension, diabetes mellitus, cholesterol level, C-reactive protein, self-rated health status, physical activity, chronic kidney disease and cardiovascular disease history.
‡P<0.05.
§P<0.01.
AMD, age-related macular degeneration; OA, osteoarthritis.

imbalance of characteristics between the included and excluded participants might bias the relationship between arthritis and AMD. Lastly, despite adjusting for a number of confounding factors, it was not possible to exclude all risks of bias, and the potential for chance findings.

CONCLUSIONS

In conclusion, our study showed that any arthritis and OA were both negatively associated with any or early AMD. In addition, no significant association was found between RA and AMD. Further studies investigating the relationship between arthritis and AMD in a large-scale population-based cohort study with longitudinal design are needed to confirm our findings and explore causal factors.

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