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Association of Age-Related Macular Degeneration with Cholelithiasis

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Purpose: Dysregulated lipid metabolism likely contributes to the pathogenesis of age-related macular degeneration (AMD). There is an overlap in risk factors between AMD and diseases of lipid metabolism, such as cholelithiasis, suggesting that an association between these diseases could provide insight into AMD pathogenesis. This study sought to determine if there is an association between cholelithiasis and AMD.

Design: A cohort study was conducted using patients in the Optum deidentified Clinformatics Data Mart database from January 1, 2000, to June 30, 2022.

Participants: Patients over the age of 55 with ≥2 years of data and no prior history of AMD were included. The exposed cohort included patients who had a history of cholelithiasis, cholecystitis, or cholecystectomy. The control cohort included patients with gastroesophageal reflux disease (GERD), matched for age ±3 years, sex, race, and year of index date.

Methods: Propensity scores were created using multivariable logistic regression and applied to inverse probability of treatment weighting (IPTW). Cox proportional hazard regression modeling with IPTW was used to compare progression to AMD in each cohort.

Main Outcome Measures: Progression to AMD for patients with cholelithiasis, cholecystitis, or a history of cholecystectomy.

Results: A total of 332 536 patients with cholelithiasis and 776 591 matched GERD controls were analyzed. After IPTW, the mean age (±standard deviation) was 66.6 ± 9.4 years in the cholelithiasis cohort and 67.5 (±10.3) years in the GERD cohort. Women comprised 58% of the cholelithiasis cohort and 57% of the GERD cohort. In the cholelithiasis cohort, 3511.7 (1.14%) were diagnosed with AMD, compared with 23 367.1 (2.92%) in the GERD cohort and corresponding to a significantly decreased hazard of AMD (adjusted hazard ratio [aHR] = 0.72, 95% confidence interval [CI]: 0.69–0.75, $P < 0.0001$). In the subanalysis, before IPTW weighting, AMD developed in 3809 of 275 897 (1.4%) patients with only cholelithiasis (aHR = 0.76, 95% CI: 0.73–0.80, $P < 0.0001$), 335 of 47 166 (0.71%) patients with cholecystitis (aHR = 0.54, 95% CI: 0.47–0.61, $P < 0.0001$), and 114 of 9473 (1.20%) patients who underwent cholecystectomy (aHR = 0.50, 95% CI: 0.41–0.63, $P < 0.0001$).

Conclusions: Cholelithiasis was associated with a 28% hazard reduction in AMD. More severe gallbladder disease conferred greater protection.

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Supplemental material available at www.ophthalmologyscience.org.

Age-related macular degeneration (AMD) is the most common cause of blindness in the elderly, with a global prevalence of >8% in individuals between 45 and 85 years old.[1] The hallmarks of AMD are extracellular lipid deposits that form on the basal or apical side of the retinal pigment epithelium (RPE), categorized as drusen and subretinal drusenoid deposits, respectively.[2] Although many mechanisms have been proposed to explain AMD development, its pathogenesis is still unclear. The correlation of the size and number of extracellular lipid-containing deposits to disease severity suggests that aberrant RPE lipid homeostasis is a key contributing factor. Furthermore, several genes involved in lipid metabolism are associated with increased AMD risk, including *APOE*, *LIPC*, *LPL*, *CETP*, and *ABCA1*.[3]

Risk factors for AMD include smoking, a diet high in fat and low in minerals and antioxidants, obesity, and age.[4] These risk factors overlap significantly with diseases traditionally linked to dysregulation of lipid metabolism, making it unsurprising that AMD is also associated with atherosclerosis,[5] coronary artery disease,[6] ischemic stroke,[7] and diabetes.[8] Gallbladder disease also shares risk factors with AMD, including age, dyslipidemia, and female sex.[9] The abundance of cholesterol in AMD lipid deposits[2] and the supersaturation of cholesterol[10] in cholesterol gallstones suggest the possibility of a shared

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pathophysiologic pathway between AMD and cholelithiasis. However, no studies have examined the link between these 2 diseases. An association between AMD and cholelithiasis may facilitate earlier diagnosis of AMD and inspire investigation into novel prognostic or treatment modalities.

In this study, we performed a cohort study to investigate an association between AMD and cholelithiasis. In addition, we performed subgroup analysis to determine how AMD risk might change with cholelithiasis severity, using cholecystitis and cholecystectomy as proxies for more severe disease.

Methods

Database

Data were abstracted from the Optum deidentified Clinformatics Data Mart database. This database consists of all outpatient medical claims (office visits, procedures, and medications given), demographic data, and some laboratory values for all patients enrolled in commercial and Medicare Advantage insurance plans. The subset of data available for this study included all patients in the database from January 1, 2000, to June 30, 2022. Due to the deidentified nature of the data, the University of Pennsylvania Institutional Review Board deemed this study exempt from review and waived the need for informed consent. This study also adhered to the Declaration of Helsinki.

Cohorts

Two cohorts were created. The exposed cohort was comprised of all patients >55 years of age who were either diagnosed with cholelithiasis or cholecystitis or had a cholecystectomy. The index date was set to either the first date of diagnosis/procedure or the date the patient turned 55, whichever was later. Similarly, the unexposed cohort was created from all patients >55 years of age diagnosed with gastroesophageal reflux disease (GERD). The control cohort of GERD was chosen to be similar to cholelithiasis in that it is a disease of the gastrointestinal tract and likely to afflict a similar patient population, yet has no known associations with AMD. See Table S1 (available at www.ophthalmologyscience.org) for the full list of International Classification of Diseases-9/International Classification of Diseases-10 and Current Procedural Terminology codes used during this study. Exclusion occurred for having <2 years of data in the dataset or any history of AMD prior to the index date. The GERD cohort also excluded all patients with a history of gallbladder disease. The cholelithiasis cohort was then matched up at 1:3 to GERD patients on age (±3 years), sex, race, and year of index date.

Outcome of Interest, Covariates, and Statistical Analysis

The primary outcome of interest was the progression to AMD. Multivariable logistic regression was used to create propensity scores for application in inverse probability of treatment weighting (IPTW) to reduce confounding between cohorts due to potential differences in the baseline characteristics. Cox proportional hazard regression modeling with IPTW was performed to compare the cholelithiasis to the GERD cohort. Censoring occurred when a patient left the insurance plan. The covariates used in the analysis can be found in Table 2. A subanalysis was performed that divided the cholelithiasis cohort into groups of increasing severity of disease at the index date: cholelithiasis, cholecystitis, and cholecystectomy. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) software. All tests were considered statistically significant at a 2-tailed P value of 0.05.

Results

After inclusion and exclusion criteria were applied, 332 536 patients with cholelithiasis and 776 591 matched GERD controls were analyzed. See Table 2 for baseline characteristics of both cohorts before and after IPTW. After IPTW, the mean age (±standard deviation) in the cholelithiasis and GERD cohorts was 66.6 (±9.4) and 67.5 (±10.3) years old, respectively. Women comprised 58% and 57% of the cholelithiasis and GERD cohorts, respectively. By race, both cohorts were 73% White, 10% Black, 3% Asian, and 5% unknown; Hispanics were 10% of the cholelithiasis cohort and 9% of the GERD cohort. After IPTW, all variables were balanced except hypertension (cholelithiasis: 69% vs. GERD: 48%, standardized mean difference = 0.42), number of health care visits in the previous year (cholelithiasis: 7.5 vs. GERD: 3.5, standardized mean difference = 1.07), and statin use (cholelithiasis: 23% vs. GERD: 28%, standardized mean difference = −0.12).

In the cholelithiasis cohort, 3511.7 (1.14%) were diagnosed with AMD, compared with 23 367.1 (2.92%) in the GERD cohort. Using multivariable Cox proportional hazards regression analysis with IPTW and controlling for the unbalanced variables, being in the cholelithiasis cohort conferred a significantly decreased hazard of AMD (adjusted hazard ratio [aHR] = 0.72, 95% confidence interval [CI]: 0.69−0.75, $P < 0.0001$) compared with being in the GERD cohort (Fig 1).

Subanalysis of 275 897 patients with only cholelithiasis, 47 166 patients with cholecystitis, and 9473 patients who underwent cholecystectomy had 3809 (1.4%), 335 (0.71%), and 114 (1.20%) develop AMD, respectively. This conferred an increasingly reduced hazard for AMD corresponding to gallbladder disease severity (cholelithiasis aHR = 0.76, 95% CI: 0.73−0.80, $P < 0.0001$; cholecystitis aHR = 0.54, 95% CI: 0.47−0.61, $P < 0.0001$; cholecystectomy, aHR = 0.50, 95% CI: 0.41−0.63, $P < 0.0001$) (Fig 2).

Discussion

After analyzing 332 536 cholelithiasis patients and 776 591 GERD controls, we found that cholelithiasis conferred a 28% reduction in the hazard of AMD. Assuming that cholecystitis and cholecystectomy would be rough proxies for more severe disease, we also found a biological gradient where more severe gallbladder diseases offered greater protection from developing AMD. To our knowledge, this is the first study examining the relationship between cholelithiasis and AMD. Interestingly, although balanced by the IPTW, the cholelithiasis cohort had higher rates of risk factors associated with AMD (e.g., female sex, hypercholesterolemia, and hypertension). Despite this, the raw rate of conversion to AMD was ∼2.6 times less in this cohort (1.14% in cholelithiasis vs. 2.92% in GERD). Additional evidence for a gallbladder−AMD association can be found

Table 2. Demographics and Medical History in Patients with and without Cholelithiasis

Characteristic	Before IPTW Weighting			After IPTW Weighting		
	Controls (N = 776 591)	*Exposed (N = 332 536)*	*SMD*	*Controls (N = 800 367)*	*Exposed (N = 308 760)*	*SMD*
Age						
Mean (SD)	66.9 (9.8)	68.8 (10.1)	0.1937	67.5 (10.3)	66.6 (9.4)	−0.0798
Sex						
Female	58%	54%	0.0806	57%	58%	0.0202
Male	42%	46%		43%	42%	
Unknown	0%	0%		0%	0%	
Race						
White	73%	72%	0.0638	73%	73%	0.0572
Black	10%	9%		10%	10%	
Hispanic	9%	10%		9%	10%	
Asian	3%	3%		3%	3%	
Unknown	5%	5%		5%	5%	
Education level						
Less than 12th Grade	0%	1%	0.1544	0%	0%	0.0000
High School Diploma	26%	26%		26%	26%	
Less than a Bachelor's	54%	55%		54%	54%	
Bachelor's Degree Plus	16%	15%		16%	16%	
Unknown	4%	4%		4%	4%	
Household income						
<$40K	23%	24%	0.1014	23%	22%	0.0287
$40K–$49K	7%	8%		7%	7%	
$50K–$59K	8%	8%		8%	8%	
$60K–$74K	10%	11%		10%	10%	
$75K–$99K	15%	15%		15%	15%	
$100K+	25%	23%		25%	26%	
Unknown	11%	12%		11%	11%	
Geographic location						
Southern Midwest	19%	18%	0.1003	19%	19%	0.0286
South Atlantic	25%	22%		24%	24%	
Pacific	10%	13%		11%	11%	
Northeast	11%	11%		11%	11%	
Mountain	10%	10%		10%	10%	
Upper Midwest	25%	25%		25%	26%	
Smoking	19%	36%	0.3913	25%	28%	0.0676
Number of health care visits (mean [SD])	2.6 (5.1)	8.9 (7.5)	1.5531	3.5 (6.1)	7.6 (6.6)	1.0682
Statin use	29%	27%	−0.0487	28%	23%	−0.1166
Preexisting comorbidities						
Hypertension	36%	80%	0.9814	48%	69%	0.4219
Hypercholesterolemia	39%	80%	0.9116	53%	57%	0.0985
Diabetes mellitus	15%	39%	0.5651	24%	26%	0.0597
Peripheral arterial disease	7%	22%	0.4239	13%	14%	0.0363
Peripheral vascular disease	8%	25%	0.4514	14%	16%	0.0381
Ischemic heart disease	13%	37%	0.5551	22%	24%	0.0524
Heart failure	5%	19%	0.4322	11%	11%	0.0216
Congestive heart failure	6%	21%	0.4445	12%	12%	0.0246
Previous myocardial infarction	4%	14%	0.3300	8%	9%	0.0230
Coronary artery bypass graft	0%	2%	0.1369	1%	1%	0.0026
Arrhythmia	11%	30%	0.4910	18%	20%	0.0498
Atrial fibrillation/flutter	5%	17%	0.4048	9%	10%	0.0207
Ischemic stroke	7%	20%	0.3746	12%	13%	0.0389
Previous intracerebral hemorrhage	1%	2%	0.0995	1%	1%	0.0095
Chronic kidney disease	10%	31%	0.6527	17%	19%	0.0524
End-stage renal disease	2%	8%		4%	4%	
Chronic liver disease	1%	4%	0.2272	2%	2%	−0.0254
Chronic pulmonary disease	8%	21%	0.3587	13%	15%	0.0526

IPTW = inverse probability of treatment weighting; SD = standard deviation; SMD = standardized mean difference.

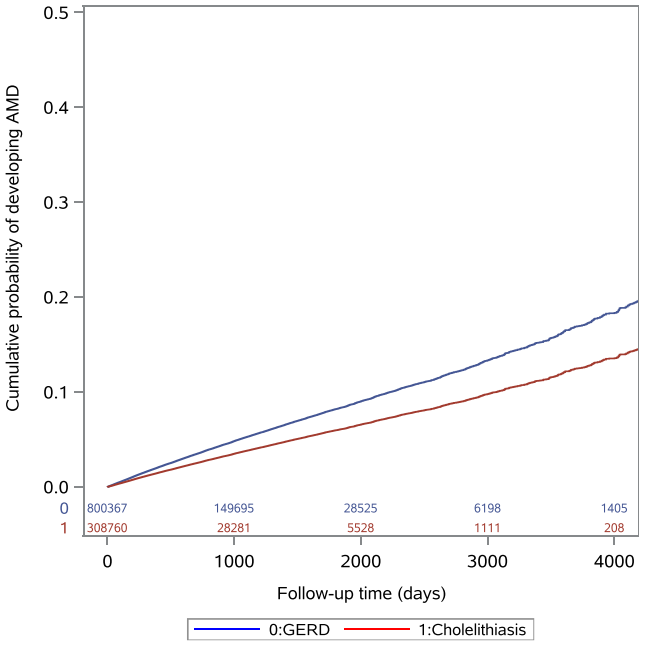

Figure 1. Probability of developing AMD for patients with and without cholelithiasis. Red and blue numbers at the bottom of the graph represent the number of patients at risk for developing AMD. AMD = age-related macular degeneration; GERD = gastroesophageal reflux disease.

in a recent publication that analyzed curcuma-based nutritional supplements that reported a protective association against AMD.[11] Curcuma-based nutritional supplements are a common nutritional supplement used as an anti-inflammatory and as a naturopathic treatment for gallbladder disease.

While the mechanism of this association between cholelithiasis and AMD is yet to be elucidated, lipid metabolism may play a role. High density lipoprotein is associated with AMD[12] but reduces the risk of cholelithiasis,[13] suggesting the converse is also true. Patients with gallstones may have had lower high density lipoprotein and subsequently a lower risk of AMD. Compared with cholesterol from other lipoproteins, high density lipoprotein-derived cholesterol is incorporated more quickly into biliary cholesterol and stimulates liver bile acid production.[14,15] While there is no consensus on the association of AMD with low density lipoprotein,[16] this may be due to the failure to account for low density lipoprotein subclasses,[17] which can vary in their relationship to disease. Low density lipoprotein cholesterol decreases for months after cholecystectomy,[18] suggesting that patients with cholelithiasis or postcholecystectomy may have alterations in low density lipoprotein composition that protect against AMD.

Genetic variants of lipid metabolism proteins may also influence this association. The ApoE4 isoform is associated with an increased risk of cholelithiasis[19] but a reduced risk of AMD.[20] Also, single nucleotide polymorphisms in *ABCG8*, the major transporter exporting cholesterol from hepatocytes into bile,[21] are associated with AMD, although their functional consequences on cholesterol transport have not been determined.[22] If *ABCG8* activity

A

	Total Patients	No. AMD (%)	Hazard ratio (95% CI)	P-value
Unexposed	776591	22588 (2.9%)	Reference	Reference
Cholelithiasis	275897	3809 (1.4%)	0.76 (0.73 - 0.80)	p < 0.0001
Cholecystitis	47166	335 (0.71%)	0.54 (0.47 - 0.61)	p < 0.0001
Cholecystectomy	9473	114 (1.2%)	0.50 (0.41 - 0.63)	p < 0.0001

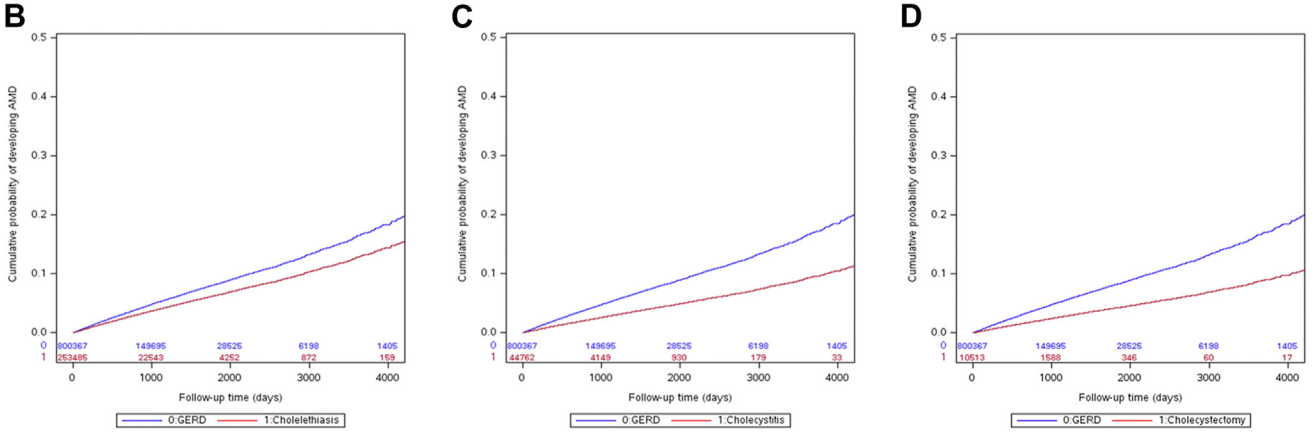

Figure 2. Probability of developing AMD by severity of cholelithiasis. **A,** Hazard of developing AMD by severity of gallbladder disease. **B–D,** Probability of developing AMD for patients with only cholelithiasis **(B)**, cholecystitis **(C)**, and a history of cholecystectomy **(D)**. Red and blue numbers at the bottom of **B–D** represent the number of patients at risk for developing AMD. AMD = age-related macular degeneration; CI = confidence interval; GERD = gastroesophageal reflux disease.

is elevated, patients may be more prone to developing gallstones while also being less likely to accumulate pathologic cholesterol in their RPE.

Since cholesterol gallstones form due to an abnormally high ratio of cholesterol to bile acids, it is also possible that the protective effect observed is due to the differences in serum or tissue bile acids. Bile acids, the major active constituents of bile, serve as lipid emulsifiers and play a crucial role as signaling molecules in the regulation of metabolic homeostasis.[23] Although the liver was long thought to be the only organ capable of bile acid synthesis, recent studies indicate that extrahepatic organs, including brain[24] and retina,[25] can also synthesize bile acids via the alternate biosynthetic pathway. Hydrophobic bile acids like deoxycholic acid are associated with gallstones, while hydrophilic bile acids like ursodeoxycholic acid and tauroursodeoxycholic acid can be used to treat gallstones[26] and have been shown to protect against retinal degeneration in cultured RPE cells and animal models.[27–32] Neuroprotective properties of bile acids have been demonstrated in animal models of photoreceptor degeneration,[33] retinitis pigmentosa,[34] diabetic retinopathy,[35] retinopathy of prematurity,[36] and choroidal neovascularization.[37] These bile acids act as antioxidants and antiapoptotic agents, thereby reducing cell death and improving retinal function. Cholelithiasis or its treatment may change the composition or quantity of serum bile acids, thereby enhancing cholesterol clearance from the RPE cells. Consistent with this, bile acid synthesis increases in patients with gallstones, which would also improve systemic cholesterol efflux.[38]

Bile acids undergo significant modification by the gut microbiome, suggesting that microbiome changes in cholelithiasis patients may also influence the risk of AMD. Many studies have found differences in the gut microbiome in patients with cholelithiasis, but these studies conflict on the specific phyla that are changed and suffer from small sample sizes.[39] Age-related macular degeneration may be associated with a distinct gut microbiome signature,[40] with enrichment of *Anaerotruncus*, *Oscillibacter*, *Ruminococcus torques*, and *Eubacterium ventriosum*.[41] Microbiome changes have similarly been identified in patients with GERD.[42] Unfortunately, the studies examining the role of the microbiome in these 3 diseases have largely identified no overlaps in taxa, making it impossible to determine whether microbiome changes in cholelithiasis explain the protection against AMD. Moreover, the microbiome is affected by other factors such as smoking, diet, and obesity,[43] which increases the complexity of determining whether microbiome changes underlie this protective effect. However, as the microbiome is responsible for the conjugation of primary bile acids into secondary bile acids, microbiome alterations in cholelithiasis patients could modulate bile acid composition and hence also AMD risk.

Strengths of this study included the cohort design, large patient population, long duration of follow-up, and accounting for numerous comorbidities that may be associated with AMD or altered lipid status, e.g., kidney disease, liver disease, coronary artery disease, diabetes, arrhythmias, and others.

Some potential limitations of our study should be noted. First, the database consists of claims from 1 insurance network and may not be generalizable to other patient populations. Second, administrative data do not contain information about diet, physical activity, or other environmental factors associated with AMD. Next, all data used within this study are retrospective in nature. Lastly, although some variables were matched exactly and others had IPTW used to balance them at baseline, hypertension and health care utilization were unable to be balanced. Of note, however, hypertension is a well-known risk factor for AMD, and the cholelithiasis cohort had more hypertension. This suggests that the exposed cohort should have had more AMD, and yet our results showed the opposite. Lastly, due to the nature of the database, we are unable to control the body mass index.

Our study demonstrates a protective association between gallbladder pathologies and AMD. The mechanisms behind this association are unknown but could involve differences in patient serum lipid profiles, lipid metabolism proteins, and bile acids. Better understanding of this association could lead to new cholesterol/lipid altering drugs that can slow AMD progression. Future research should look into whether ursodiol, used to treat cholelithiasis, has an impact on the incidence of AMD.

Footnotes and Disclosures

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All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s):

B.L.V.: Consultant – Eyepoint Pharmaceuticals; Honoraria – Real World Ophthalmology Data Summit.

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HUMAN SUBJECTS: No human subjects were included in this study. Due to the deidentified nature of the data, the University of Pennsylvania's Institutional Review Board deemed this study exempt from review and waived the need for informed consent. This study also adhered to the Declaration of Helsinki.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Jin, Dunaief, VanderBeek

Data collection: Chen, Jin, VanderBeek

Analysis and interpretation: Zhang, Nair, Chen, Jin, Dunaief, VanderBeek

Obtained funding: N/A

Overall responsibility: Zhang, Nair, Jin, Dunaief, VanderBeek

Abbreviations and Acronyms:

aHR = adjusted hazard ratio; **AMD** = age-related macular degeneration; **CI** = confidence interval; **GERD** = gastroesophageal reflux disease; **IPTW** = inverse probability of treatment weighting; **RPE** = retinal pigment epithelium.

Keywords:

AMD, Cholelithiasis, Gallstones, Cohort, Lipid.

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