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ORIGINAL RESEARCH

Association Between Age-Related Macular Degeneration and Risk of Heart Failure: A Population-Based Nested Case-Control Study

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BACKGROUND: Heart failure (HF) is a major health problem worldwide because of its high morbidity and mortality. Recently, the role of the microvasculature in HF has gained more attention. Age-related macular degeneration (AMD) is manifested through geographic atrophy or the development of neovascularization. However, there are limited data on investigations about the association between AMD and HF. The purpose of this study was to examine the association of AMD with the risk of HF in a large population-based cohort of men and women.

METHODS AND RESULTS: A nested case-control study using Taiwan's National Health Insurance Research Database was conducted between 2000 and 2012. Newly diagnosed heart failure cases (n=13 721) and matched controls (n=54 884) in the database were recruited. Patients who had ≥2 clinical visits with a diagnosis of AMD at least 1 year before the diagnosis of HF were identified as patients with AMD. Conditional logistic regressions were performed to calculate odds ratios and 95% CIs to assess the association between AMD and risk of HF. AMD was associated with a 1.58-fold increased risk of HF (95% CI, 1.16–1.87) (P<0.001) after adjustment for potential confounders. This significant association was evident in both nonexudative and exudative AMD subgroups.

CONCLUSIONS: Our study provides evidence that AMD was associated with an increased risk of HF. Further molecular and pathophysiological studies are needed to clarify the underlying pathophysiological mechanisms behind the association of AMD with HF.

Key Words: age-related macular degeneration ■ heart failure ■ National Health Insurance Research Database ■ nested case-control study

Age-related macular degeneration (AMD) is a leading cause of visual impairment and severe vision loss. It accounts for 8.7% of all blindness worldwide and is the most common cause of blindness in developed countries, particularly in people aged >60 years.[1–3] There are 2 types of AMD: nonexudative (dry) and exudative (wet).[1,2] The prevalence rate of AMD is likely to increase as a consequence of exponential population aging. Although the precise cause of AMD remains unknown, increasing evidence suggests that there are multiple similarities in the risk factors and pathogenic mechanisms of both AMD and cardiovascular disease (CVD).[4–6] The overlap of risk factors between AMD and CVD is remarkable because AMD may then be regarded as a predictor of CVD, and modifiable risk factors for CVD can be controlled to reduce the risk for both AMD and CVD. However, the association between AMD and CVD has been scarcely defined,[7–13] despite the identification of risk factors common to both diseases.

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CLINICAL PERSPECTIVE

What Is New?

- In this real-world prospective study, patients with both nonexudative and exudative age-related macular degeneration were associated with an increased risk of heart failure.

What Are the Clinical Implications?

- For patients with age-related macular degeneration, early detection is beneficial because of the availability of treatments that can decrease the progression of age-related macular degeneration to the late stages.
- Thus, screening for age-related macular degeneration is potentially useful for prevention of heart failure.

Nonstandard Abbreviations and Acronyms

AMD	age-related macular disease
ATC	Anatomic Therapeutic Chemical
NHIRD	National Health Insurance Research Database

Heart failure (HF) is a major health problem in Western societies because of its high prevalence, morbidity, and mortality, comparable to neoplasia. Given its chronic characteristic, with frequent acute events often requiring hospitalization, HF consumes a huge amount of technical and economic resources.[14] In 2012, it was responsible for an estimated health expenditure of around $31 billion, equivalent to >10% of the total health expenditure for cardiovascular diseases in the United States. Projections are even more alarming, however, with total costs expected to increase by 127% between 2012 and 2030.[15] Endothelial dysfunction is a hallmark feature of CVD, including HF, and is considered an early marker of elevated CVD risk.[16] Most studies on endothelial dysfunction in HF focused on evaluation of larger vessels such as brachial artery measurement of flow-mediated vasodilation.[17] Recently, the role of the microvasculature in HF gained more attention.[18,19] Retinal circulation offers an opportunity to noninvasively explore the relationship of systemic microvascular disease to HF. However, there are limited studies that have investigated whether AMD is an independent predictor of HF. The purpose of the current study was to examine the association of AMD with the risk of HF in a large population-based cohort of men and women.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure by reasons of ethical and data-protective legislation. However, the study group welcomes initiatives for cooperation, and data access may be granted upon application.

Study Design and Data Source

In this nested case-control study, we enrolled patients aged >50 years who were registered in the Taiwan's National Health Insurance Research Database (NHIRD). The NHIRD is a nationwide medical claims database containing comprehensive healthcare information of all beneficiaries enrolled in the National Health Insurance program, which covers ≈99% of the population in Taiwan. This healthcare information includes insurant sex and date of birth, inpatient and outpatient care facilities, disease diagnostic codes in the format of the *International Classification of Disease, Ninth Revision, Clinical Modification* (*ICD-9-CM*), procedures, surgeries, drug prescriptions, dates of visits or hospitalization, and expenditures.[20] The data used in this study were obtained from the Longitudinal Health Insurance Database 2000, a subset of the NHIRD. The Longitudinal Health Insurance Database 2000 data set contains all the original claims data of 1 million beneficiaries randomly sampled in year 2000 from the NHIRD. There were no significant differences in the distributions of age, sex, and healthcare costs between the individuals in the Longitudinal Health Insurance Database and NHIRD.[21] These databases have been used for high-quality epidemiological studies,[22,23] and information on diagnoses, prescriptions, and hospitalizations have been shown to be of good validity.[24,25] Because the database was released for research purposes and included only scrambled information on patient identification, the study was exempt from informed consent from the subjects. The study protocol was approved by the institutional review board of Cathay General Hospital in Taipei City (CGH-P107074).

Identification of Cases and Controls

We identified cases as patients who were diagnosed with HF (*ICD-9-CM* 428) during the study period between January 1, 2000 and December 31, 2012 (n=13 721). To identify patients with HF with sufficient accuracy, the diagnosis for HF was required on at least 2 outpatient claims or 1 inpatient claim during the study period. Only patients with HF symptoms requiring hospitalization for further management were treated as HF cases. The diagnostic date of HF was defined as the index date. We excluded those who had

been diagnosed with HF before January 1, 2000 to increase the likelihood of recruiting patients with incident HF. Through risk-set sampling, we randomly selected 4 controls for each case who did not have any history of HF before or at the index date in the Longitudinal Health Insurance Database and were matched by a propensity score (n=54 884) (Figure). In this study, the propensity score was calculated for each patient by using a logistic regression with covariates of age; sex; monthly income; comorbidities including hypertension (*ICD-9-CM* codes 401-405), diabetes mellitus (*ICD-9-CM* code 250), hyperlipidemia (*ICD-9-CM* code 272), coronary artery disease (*ICD-9-CM* codes 410-414), and chronic kidney disease (*ICD-9-CM* code 585); as well as use of multiple medications including low-dose aspirins (Anatomic Therapeutic Chemical [ATC] code B01AC06), nonsteroidal anti-inflammatory drugs (ATC codes M01AB, M01AC, M01AE, M01AG, and M01AH), antihypertensive drugs (ATC codes C02, C03, C07, C08, and C09), hypoglycemic agents (ATC codes A10A, A10B, and A10X), statins (ATC codes C10AA01, C10AA02, C10AA03, C10AA04, C10AA05, and C10AA07), and nonstatin lipid-lowering drugs (ATC codes C10AB, C10AC, and C10AD).

Identification of AMD

The exposure of interest in this study was AMD. The definition of AMD used in the present study was based on the *ICD-9-CM* codes (362.50 and 362.51 for nonexudative AMD and 362.52 for exudative AMD) plus at least 1 of the following 4 procedures: color photo picture for the fundus (procedure code 23502), optical coherence tomography exam (procedure code 23506), fluorescein angiography (procedure code 23505), or intravitreal injection (procedure code 86201).[26] When both eyes of a patient had lesions of different severities, the grade assigned for the patient was that of the

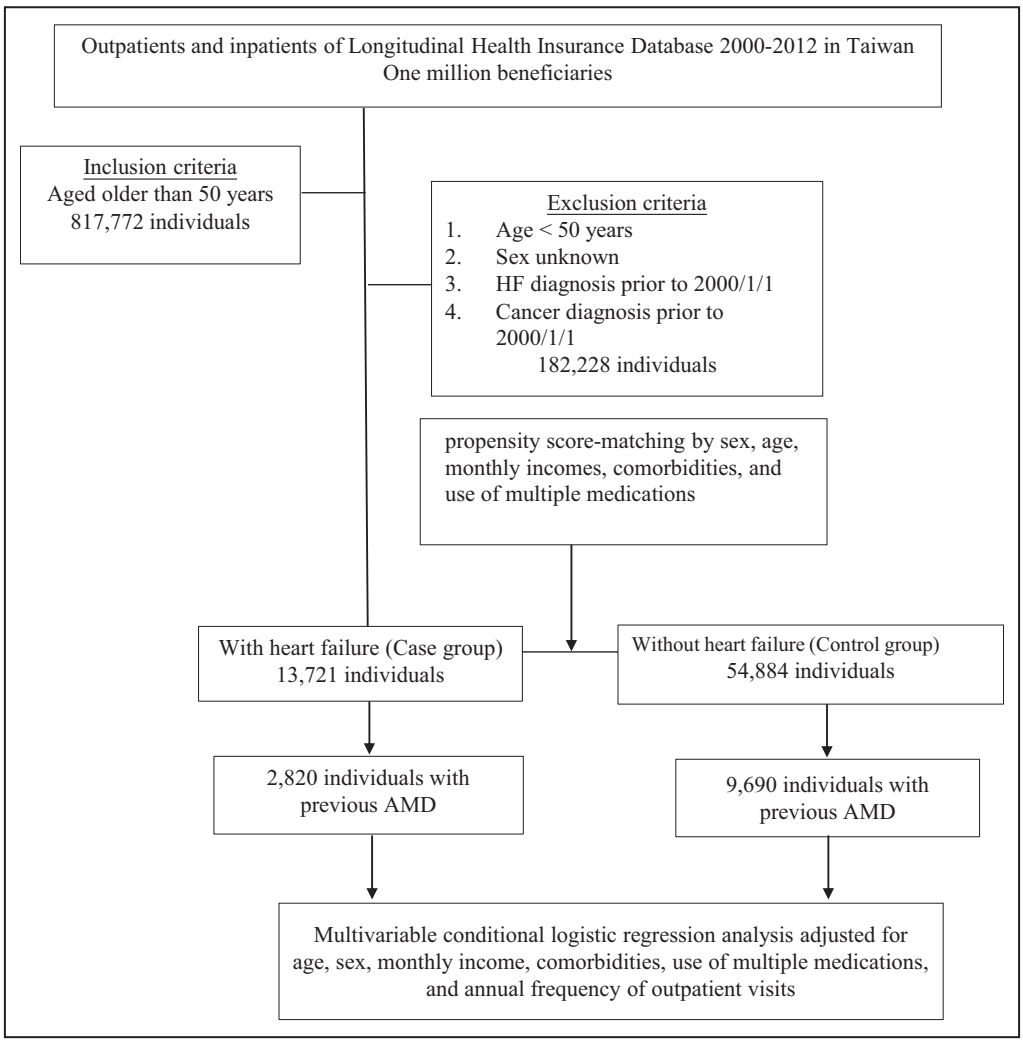

Figure. The flowchart of the nested case-control study based on the National Health Insurance Research Database in Taiwan.
AMD indicates age-related macular degeneration; and HF, heart failure.

more severely involved eye. In this study, we identified patients who had ≥2 clinical visits with a diagnosis of AMD at least 1 year before the index date as patients with AMD.

Statistical Analysis

Paired *t* tests were used to compare continuous variables between cases and controls, and the McNemar test was used for categorical variables. We used conditional logistic regression models to estimate odds ratios (ORs) and their 95% CIs for the association between AMD and risk of HF. To further control for potential confounders, all models were adjusted for the propensity score. To enhance the comparability between cases and controls, adjustment for numbers of outpatient visits were also made in all models. Given that diabetes mellitus, hypertension, and coronary artery disease were associated with both AMD and HF,[27,28] we also performed subgroup analyses by status of diabetes mellitus, hypertension, and coronary artery disease to examine the effects of cardiometabolic diseases on the association between AMD and risk of HF. Finally, multivariable conditional logistic regressions based on age and sex matching were conducted to estimate independent predictors of HF. Data analysis was performed using SAS software version 9.3 (SAS Institute, Cary, NC). All *P* values were 2-sided, and $P<0.05$ was considered statistically significant.

Table 1. Baseline Characteristics of Cases With HF and the Propensity Score–Matched Control Group

Variable	Cases With HF, n=13 721	Controls, n=54 884	*P* Value
Age, y, mean±SD	63.1±8.1	63.1±8.1	0.965
Sex, %			1.000
Men	51.0	51.0	
Women	49.0	49.0	
Monthly income, NT$, %			0.882
≤15 840	38.0	39.3	
15 841–25 000	52.9	51.2	
>25 000	9.1	9.5	
Annual frequency of outpatient visits, mean±SD	6.9±8.9	6.2±7.2	0.071
Comorbidities, %			
Hypertension	83.4	82.4	0.782
Diabetes mellitus	43.1	42.9	0.608
Hyperlipidemia	47.2	46.7	0.679
CAD	50.4	49.5	0.682
CKD	27.3	26.5	0.624
Use of comedications, %			
Aspirin	32.8	31.4	0.648
NSAIDs	76.6	76.4	0.535
Antihypertensive medications	31.8	30.2	0.568
Hypoglycemic agents	68.6	67.7	0.442
Lipid-lowering drugs	63.9	62.1	0.658

CAD indicates coronary artery disease; CKD, chronic kidney disease; HF, heart failure; and NSAIDs, nonsteroidal anti-inflammatory drugs.

RESULTS

The study cohort consisted of 817 772 individuals aged >50 years. During the study period, we identified 13 721 cases with HF and 54 884 control subjects matched by age, sex, comorbidities, and use of polypharmacy. The mean age (±SD) was 63.15 years (±8.10 years) for cases and controls, and 50.98% of the subjects were men. The distributions of comorbidities and use of polypharmacy were comparable between cases and controls because of the propensity score–matched scheme (Table 1).

As shown in Table 2, there were 20.55% (2820/13 721) of cases with HF and 17.66% (9690/54 884) of matched controls diagnosed as AMD. AMD was associated with a 1.58-fold increased risk of HF (adjusted OR, 1.56; 95% CI, 1.16–1.87; $P<0.001$) after adjustment for potential confounders. The association between AMD and increased risk of HF was evident in both nonexudative and exudative AMD subgroups. The adjusted OR (95% CI) for nonexudative and exudative AMD subgroups was 1.43 (1.15–1.64) ($P<0.001$) and 1.62 (1.28–1.86) ($P<0.001$), respectively.

Table 3 shows the adjusted ORs of HF from further analyses of the association of AMD with the risk of HF stratified by the status of diabetes mellitus, hypertension, and coronary artery disease. There was a significant association between AMD and risk of HF among patients with diabetes mellitus, hypertension, or coronary artery disease. The adjusted ORs among patients with diabetes mellitus, hypertension, or coronary artery disease were 1.56 (95% CI, 1.18–1.84) ($P<0.001$), 1.48 (95% CI, 1.12–1.68) ($P<0.001$), and 1.28 (95% CI, 1.08–1.53) ($P=0.002$), respectively. By contrast, no significant associations between AMD and HF were observed among patients without diabetes mellitus, hypertension, or coronary artery disease.

Table 4 shows the results of multivariable analysis of risk determinants of HF. As expected, diabetes mellitus, hypertension, hyperlipidemia, and coronary artery disease were independent predictors of HF with adjusted ORs ranging from 1.09 (95% CI, 1.05–1.13) to 2.87 (95% CI, 2.74–3.01) ($P<0.001$). Likewise, AMD was associated with an increased risk of HF (adjusted OR, 1.29; 95% CI, 1.14–1.34) ($P<0.001$). However, the use of aspirins or nonsteroidal anti-inflammatory drugs was related to a reduced risk of HF (adjusted OR, 0.83; 95% CI, 0.78–0.87) ($P<0.001$).

Table 2. Association Between AMD and Risk of HF

Variable	Cases With HF, n=13 721	Controls, n=54 884	Adjusted OR (95% CI)	*P* Value
AMD				<0.0001
Present	2820	9690	1.58 (1.16–1.87)	
Absent	10 901	45 194	1.00	
Nonexudative AMD				<0.0001
Present	2495	8852	1.43 (1.15–1.64)	
Absent	10 824	44 669	1.00	
Exudative AMD				<0.0001
Present	325	838	1.62 (1.28–1.86)	
Absent	77	525	1.00	

ORs were adjusted for age; sex; monthly income; comorbidities including hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, and chronic kidney disease; and use of multiple medications including aspirin, nonsteroidal anti-inflammatory drugs, hypoglycemic agents, antihypertensive medications, and lipid-lowering drugs; as well as annual frequency of outpatient visits. AMD indicates age-related macular degeneration; HF, heart failure; and OR, odds ratio.

DISCUSSION

In this population-based, nested case-control study, our results show that AMD was significantly associated with the risk of HF. This association was evident in both nonexudative and exudative AMD subgroups. The association was independent of age, sex, socioeconomic status, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, and chronic kidney disease.

AMD phenotypes have been associated with a variety of CVD outcomes, including coronary artery disease, myocardial infarction, or a pooled composite CVD category.[29] However, the relationship between AMD and HF has not been well studied. The present study, therefore, addresses an important gap in the

Table 3. Association Between AMD and Risk of HF Stratified by Status of DM, Hypertension, and CAD

Variable	Cases With HF, n=13 721	Controls, n=54 884	Adjusted OR (95% CI)	*P* Value
Non-DM				0.153
No. of subjects	7803	31 345	1.02 (0.84–1.76)	
No. of AMD (%)	962 (12.3%)	3484 (11.1%)		
DM				<0.0001
No. of subjects	5918	23 539	1.56 (1.18–1.84)	
No. of AMD (%)	1858 (31.4%)	6206 (26.4%)		
Nonhypertension				0.221
No. of subjects	2147	8361	1.18 (0.61–1.87)	
No. of AMD (%)	358 (16.7%)	1207 (14.4%)		
Hypertension				<0.0001
No. of subjects	8754	36 833	1.48 (1.12–1.68)	
No. of AMD (%)	2462 (28.1%)	8483 (23.0 %)		
Non-CAD			1.04 (0.85–1.62)	0.158
No. of subjects	5759	23 508		
No. of AMD (%)	1178 (17.0%)	4201 (15.2%)		
CAD				0.002
No. of subjects	5142	21 686	1.28 (1.08–1.53)	
No. of AMD (%)	1642 (24.2%)	5489 (20.2%)		

ORs for DM were adjusted for age; sex; monthly income; comorbidities including hypertension, hyperlipidemia, CAD, and chronic kidney disease; and use of multiple medications including aspirin, nonsteroidal anti-inflammatory drugs, antihypertensive medications, and lipid-lowering drugs; as well as annual frequency of outpatient visits. ORs for hypertension were adjusted for age; sex; monthly income; comorbidities including DM, hyperlipidemia, CAD, and chronic kidney disease; and use of multiple medications including aspirin, nonsteroidal anti-inflammatory drugs, hypoglycemic agents, and lipid-lowering drugs; as well as annual frequency of outpatient visits. ORs for CAD were adjusted for age; sex; monthly income; comorbidities including DM, hypertension, hyperlipidemia, and chronic kidney disease; and use of multiple medications including aspirin, nonsteroidal anti-inflammatory drugs, hypoglycemic agents, antihypertensive medications, and lipid-lowering drugs; as well as annual frequency of outpatient visits. AMD indicates age-related macular degeneration; CAD, coronary artery disease; DM, diabetes mellitus; HF, heart failure; and OR, odds ratio.

Table 4. Multivariable Analysis of Risk Determinants of Heart Failure

Variable	Adjusted OR (95% CI)	*P* Value
Hypertension		<0.0001
No	1.00 (referent)	
Yes	2.87 (2.74–3.01)	
Diabetes mellitus		<0.0001
No	1.00 (referent)	
Yes	1.26 (1.22–1.31)	
Hyperlipidemia		<0.0001
No	1.00 (referent)	
Yes	1.09 (1.05–1.13)	
CAD		<0.0001
No	1.00 (referent)	
Yes	1.45 (1.41–1.50)	
AMD		<0.0001
No	1.00 (referent)	
Yes	1.29 (1.14–1.34)	
Use of aspirin or NSAIDS		<0.0001
No	1.00 (referent)	
Yes	0.83 (0.78–0.87)	

AMD indicates age-related macular degeneration; CAD, coronary artery disease; and NSAIDs, nonsteroidal anti-inflammatory drugs.

published data. In the current study, a significantly increased risk of HF was observed in both nonexudative and exudative AMD. In addition, AMD was a significant risk determinant of HF in patients with diabetes mellitus, hypertension, or coronary artery disease. Conversely, reports from cross-sectional studies demonstrate null findings of the association.[30] Such inconsistent results may result partially from different study designs and study subjects as well as potential confounders controlled for in the main analyses. Of note, previous work has shown that AMD was associated with cardiovascular and all-cause mortality.[31,32] Accordingly, such null findings in previous cross-sectional studies could be explained by selective mortality bias in that the removal of susceptible people results in null associations in cross-sectional settings. In any event, our study involving a large number of patients with AMD has illuminated the longitudinal association between AMD and HF.

Extensive data support roles for local inflammation, complement activation, oxidative stress, and lipid homeostasis in the pathogenesis of AMD.[33,34] Furthermore, inflammation and oxidative stress have been associated with the development of HF.[35–37] Given that inflammation and oxidative stress are implicated in both AMD and HF, it is biologically plausible that these conditions could share underlying risk factors and pathophysiological mechanisms. On another note, microvascular disease has been linked with precursors of heart failure, including peripheral vascular dysfunction and cardiac and left ventricular remodeling.[38,39] It is suggested that microvascular abnormalities might be involved in the pathogenesis of HF. Previous studies have indicated that retinopathy is an independent predictor of HF.[40] The retinal vessels share similar anatomical and physiological properties with coronary and cerebral microcirculation and have been suggested as biomarkers of vascular health.[41] This suggests that microvascular disease may play an important role in the development of HF. Thus, small-vessel damage seen in the retina might represent widespread systemic microcirculatory disease that places an increased impedance burden on the heart, in part through reflected waves.[42] This in turn can lead to an increased load to the heart and compromise cardiac performance (eg, impair ventricular emptying and contractility), predisposing the development and manifestation of clinical HF. Thus, screening for AMD is potentially useful for prevention of HF.[43] More research is needed to understand the possible use of AMD screening among patients with HF.

The main strength of the present study is that this nested case-control study is based on a national cohort of Taiwan's NHIRD, which contains data from Taiwan's compulsory and universal healthcare system. This allowed us to perform our analyses in a real-life setting in an unselected patient population, thus minimizing the possibilities of patient dropout and selection bias. In addition, the large size of the database provided considerable statistical power to detect differences between case and control groups more effectively. However, the findings of this study need to be interpreted mindful of the following methodological limitations. First, the diagnoses of AMD, HF, or other comorbid medical conditions that are totally dependent on the *ICD-9-CM* codes may be less accurate than those obtained through a standardized procedure.[44] This is a major limitation of this study compared with studies that use standardized examinations of patients. However, the National Health Insurance Bureau of Taiwan randomly samples a fixed percentage of claims from every hospital and randomly interviews patients and reviews charts each year to verify the diagnosis validity and quality of care.[20] On another note, major advances in identifying the genetic variants associated with AMD have revealed a strong connection between the complement cascade, importantly the regulation of innate immunity and disease susceptibility.[45,46] Independent effects of complement factor H and age-related maculopathy susceptibility 2/high-temperature requirement factor A1 genes with the risk of neovascular AMD were identified in a Chinese population.[47] In addition, AMD-associated variants were related to the risk of coronary artery disease.[48] However, the information on genetic variants of AMD is not available in

the NHIRD. Moreover, given that HF has been singled out as an epidemic and is a staggering clinical and public health problem, the nested case-control approach we adopted in this study might have a statistical type 2 error. Furthermore, multiple testing resulting from analyzing the association between AMD and HF among different subsets of patients was not taken into account in this study. Moreover, although we adjusted for several potential confounders in the statistical analyses, other important covariates, such as smoking habits and visual acuity, could not be integrated into the analysis because the claims data set lacks these parameters. It is likely that our findings could subject to residual confounding. Finally, most of our study subjects were ethnically Chinese people from Taiwan, and the generalizability of our results to other ethnic groups needs to be further confirmed.

In conclusion, our nationwide population-based nested case-control study provides evidence that AMD was associated with an increased risk of HF. The results remain consistent across a set of subgroup analyses. The epidemiological data presented herein must be validated with molecular and pathophysiological studies to understand the complex pathophysiology and molecular mechanisms underlying the association between AMD and HF. Such studies are critical for taking current understanding beyond observing disease associations to determine cause and effect relationships.

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

1. Gottlieb JL. Age-related macular degeneration. *JAMA*. 2002;288:2233–2236. DOI: 10.1001/jama.288.18.2233.
2. Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. *Lancet*. 2018;392:1147–1159. DOI: 10.1016/S0140-6736(18)31550-2.
3. Wong WL, Su X, Li X, Cheung CMG, Klein R, Cheng CY, Wong TY. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014;2:e106–e116. DOI: 10.1016/S2214-109X(13)70145-1.
4. Smith W, Mitchell P, Leeder SR, Wang JJ. Plasma fibrinogen levels, other cardiovascular risk factors, and age-related maculopathy: the Blue Mountains Eye Study. *Arch Ophthalmol*. 1998;116:583–587. DOI: 10.1001/archopht.116.5.583.
5. Snow KK, Seddon JM. Do age-related macular degeneration and cardiovascular disease share common antecedents? *Ophthalmic Epidemiol*. 1999;6:125–143. DOI: 10.1076/opep.6.2.125.1558.
6. Klein R, Peto T, Bird A, Vannewkirk MR. The epidemiology of age-related macular degeneration. *Am J Ophthalmol*. 2004;137:486–495. DOI: 10.1016/j.ajo.2003.11.069.
7. Duan Y, Mo J, Klein R, Scott IU, Lin HM, Caulfield J, Patel M, Liao D. Age-related macular degeneration is associated with incident myocardial infarction among elderly Americans. *Ophthalmology*. 2007;114:732–737. DOI: 10.1016/j.ophtha.2006.07.045.
8. Wong TY, Tikellis G, Sun C, Klein R, Couper DJ, Sharrett AR. Age-related macular degeneration and risk of coronary heart disease: the Atherosclerosis Risk in Communities Study. *Ophthalmology*. 2007;114:86–91. DOI: 10.1016/j.ophtha.2006.06.039.
9. Sun C, Klein R, Wong TY. Age-related macular degeneration and risk of coronary heart disease and stroke: the Cardiovascular Health Study. *Ophthalmology*. 2009;116:1913–1919. DOI: 10.1016/j.ophtha.2009.03.046.
10. Golan S, Shalev V, Goldstein M, Treister G, Chodick G, Loewenstein A. The rate of myocardial infarction events among patients with age-related macular degeneration: a population-based study. *Graefes Arch Clin Exp Ophthalmol*. 2011;249:179–182. DOI: 10.1007/s00417-010-1489-4.
11. Fernandez AB, Wong TY, Klein R, Collins D, Burke G, Cotch MF, Klein B, Sadeghi MM, Chen J. Age-related macular degeneration and incident cardiovascular disease: the Multi- Ethnic Study of Atherosclerosis. *Ophthalmology*. 2012;119:765–770. DOI: 10.1016/j.ophtha.2011.09.044.
12. Wu J, Uchino M, Sastry SM, Schaumberg DA. Age-related macular degeneration and the incidence of cardiovascular disease: a systematic review and meta- analysis. *PLoS One*. 2014;9:e89600. DOI: 10.1371/journal.pone.0089600.
13. Wang J, Xue Y, Thapa S, Wang L, Tang J, Ji K. Relation between age-related macular degeneration and cardiovascular events and mortality: a systematic review and meta-analysis. *Biomed Res Int*. 2016;2016:8212063. DOI: 10.1155/2016/8212063.
14. Dunlay SM, Roger VL. Understanding the epidemic of heart failure: past, present, and future. *Curr Heart Fail Rep*. 2014;11:404–415. DOI: 10.1007/s11897-014-0220-x.
15. Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev*. 2017;3:7–11. DOI: 10.15420/cfr.2016:25:2.
16. Flammer AJ, Anderson T, Celermajer DS, Creager MA, Deanfield J, Ganz P, Hamburg N, Luscher TF, Shechter M, Taddei S, et al. The assessment of endothelial function: from research into clinical practice. *Circulation*. 2012;126:753–767. DOI: 10.1161/CIRCULATIONAHA.112.093245.
17. Poelzl G, Frick M, Huegel H, Lackner B, Alber HF, Mair J, Herold M, Schwarzacher S, Pachinger O, Weidinger F. Chronic heart failure is associated with vascular remodeling of the brachial artery. *Eur J Heart Fail*. 2005;7:43–48. DOI: 10.1016/j.ejheart.2004.04.008.
18. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med*. 2007;356:830–840. DOI: 10.1056/NEJMra061889.
19. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol*. 2013;62:263–271. DOI: 10.1016/j.jacc.2013.02.092.
20. Lin LY, Warren-Gash C, Smeeth L, Chen PC. Data resource profile: the National Health Insurance Research Database (NHIRD). *Epidemiol Health*. 2018;40:e2018062. DOI: 10.4178/epih.e2018062.
21. Hsiao FY, Yang CL, Huang YT, Huang WF. Using Taiwan's national health insurance research databases for pharmacoepidemiology research. *J Food Drug Anal*. 2007;15:99–108. DOI: 10.38212/2224-6614.2426.

22. Wu CY, Chen YJ, Ho HJ, Hsu YC, Kuo KN, Wu MS, Lin JT. Association between nucleoside analogues and risk of hepatitis B virus-related hepatocellular carcinoma recurrence following liver resection. *JAMA*. 2012;308:1906–1913. DOI: 10.1001/2012.jama.11975.
23. Chang SH, Chou IJ, Yeh YH, Chiou MJ, Wen MS, Kuo CT, See LC, Kuo CF. Association between use of non-vitamin K oral anticoagulants with and without concurrent medications and risk of major bleeding in nonvalvular atrial fibrillation. *JAMA*. 2017;318:1250–1259. DOI: 10.1001/jama.2017.13883.
24. Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the national health insurance research database with ischemic stroke cases in Taiwan. *Pharmacoepidemiol Drug Saf*. 2011;20:236–242. DOI: 10.1002/pds.2087.
25. Kao WH, Hong JH, See LC, Yu HP, Hsu JT, Chou IJ, Chou WC, Chiou MJ, Wang CC, Kuo CF. Validity of cancer diagnosis in the National Health Insurance database compared with the linked National Cancer Registry in Taiwan. *Pharmacoepidemiol Drug Saf*. 2018;27:1060–1066. DOI: 10.1002/pds.4267.
26. Chang KH, Hsu PY, Lin CJ, Lin CL, Juo SHH, Liang CL. Traffic-related air pollutants increase the risk for age-related macular degeneration. *J Invest Med*. 2019;67:1076–1081. DOI: 10.1136/jim-2019-001007.
27. Chen X, Rong SS, Xu Q, Tang FY, Liu Y, Gu H, Tam POS, Chen LJ, Brelén ME, Pang CP, et al. Diabetes mellitus and risk of age-related macular degeneration: a systematic review and meta-analysis. *PLoS One*. 2014;9:e108196. DOI: 10.1371/journal.pone.0108196.
28. Greenberg BH, Abraham WT, Albert NM, Chiswell K, Clare R, Stough WG, Gheorghiade M, O'Connor CM, Sun JL, Yancy CW, et al. Influence of diabetes on characteristics and outcomes in patients hospitalized with heart failure: a report from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J*. 2007;154:e1–e8. DOI: 10.1016/j.ahj.2007.05.001.
29. Rastogi N, Smith RT. Association of age-related macular degeneration and reticular macular disease with cardiovascular disease. *Surv Ophthalmol*. 2016;61:422–433. DOI: 10.1016/j.survophthal.2015.10.003.
30. Phan K, Mitchell P, Liew G, Plant AJ, Wang SB, Chiha J, Thiagalingam A, Burlutsky G, Gopinath B. Relationship between macular degeneration with prevalent heart failure: a cross-sectional population study. *Int J Cardiol*. 2015;182:213–215. DOI: 10.1016/j.ijcard.2014.12.146.
31. Tan JSL, Wang JJ, Lie WG, Rochtchina E, Mitchell P. Age-related macular degeneration and mortality from cardiovascular disease or stroke. *Br J Ophthalmol*. 2008;92:509–512. DOI: 10.1136/bjo.2007.131706.
32. Fisher DE, Jonasson F, Eiriksdottir G, Sigurdsson S, Klein R, Launer LL, Gudnason V, Cotch MF. Age-related macular degeneration and mortality in community-dwelling elders: the age, gene/environment susceptibility Reykjavik study. *Ophthalmology*. 2015;122:382–390. DOI: 10.1016/j.ophtha.2014.08.006.
33. Beatty S, Koh H, Phil M, Henson D, Boulton M. The role of oxidative stress in the pathogenesis of age-related macular degeneration. *Surv Ophthalmol*. 2000;45:115–134. DOI: 10.1016/S0039-6257(00)00140-5.
34. Tan W, Zou J, Yoshida S, Jiang B, Zhou Y. The role of inflammation in age-related macular degeneration. *Int J Biol Sci*. 2020;16:2989–3001. DOI: 10.7150/ijbs.49890.
35. Murphy SP, Kakkar R, McCarthy CP, Januzzi JL Jr. Inflammation in heart failure: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;75:1324–1340. DOI: 10.1016/j.jacc.2020.01.014.
36. Tsutsui H, Kinugawa S, Matsushima S. Oxidative stress and heart failure. *Am J Physiol Heart Circ Physiol*. 2011;301:H2181–H2190. DOI: 10.1152/ajpheart.00554.2011.
37. van der Pol A, van Gilst WH, Voors AA, van der Meer P. Treating oxidative stress in heart failure: past, present and future. *Eur J Heart Fail*. 2019;21:425–435. DOI: 10.1002/ejhf.1320.
38. Cheung N, Bluemke DA, Klein R, Sharrett AR, Islam FMA, Cotch MF, Klein BEK, Criqui MH, Wong TY. Retinal arteriolar narrowing and left ventricular remodeling: the multi-ethnic study of atherosclerosis. *J Am Coll Cardiol*. 2007;50:48–55. DOI: 10.1016/j.jacc.2007.03.029.
39. Lee JF, Barrett-O'Keefe Z, Garten RS, Nelson AD, Ryan JJ, Nativi JN, Richardson RS, Wray DW. Evidence of microvascular dysfunction in heart failure with preserved ejection fraction. *Heart*. 2016;102:278–284. DOI: 10.1136/heartjnl-2015-308403.
40. Wong TY, Rosamond W, Chang PP, Couper DJ, Sharrett AR, Hubbard LD, Folsom AR, Klein R. Retinopathy and risk of congestive heart failure. *JAMA*. 2005;293:63–69. DOI: 10.1001/jama.293.1.63.
41. de Jong FJ, Ikram MK, Witteman JC, Hofman A, de Jong PT, Breteler MM. Retinal vessel diameters and the role of inflammation in cerebrovascular disease. *Ann Neurol*. 2007;61:491–495. DOI: 10.1002/ana.21129.
42. Nagele MP, Barthelmes J, Ludovici V, Cantatore S, von Eckardstein A, Enseleit F, Luscher TF, Ruschitzka F, Sudano I, Flammer A. Retinal microvascular dysfunction in heart failure. *Eur Heart J*. 2018;39:47–56. DOI: 10.1093/eurheartj/ehx565.
43. Chan CK, Gangwani RA, McGhee SM, Lian J, Wong DSH. Cost-effectiveness of screening for intermediate age-related macular degeneration during diabetic retinopathy screening. *Ophthalmology*. 2015;122:2278–2285. DOI: 10.1016/j.ophtha.2015.06.050.
44. Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI. New York Heart Association Criteria Committee. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, MA: Lippincott Williams and Wilkins; 1994.
45. Haines JL, Hauser MA, Schmidt S, Scott WK, Olson LM, Gallins P, Spencer KL, Kwan SY, Noureddine M, Gilbert JR, et al. Complement factor H variant increases the risk of age-related macular degeneration. *Science*. 2005;308:419–421. DOI: 10.1126/science.1110359.
46. Rivera A, Fisher SA, Fritsche LG, Keilhauer CN, Lichtner P, Meitinger T, Weber BH. Hypothetical LOC387715 is a second major susceptibility gene for age- related macular degeneration, contributing independently of complement factor H to disease risk. *Hum Mol Genet*. 2005;14:3227–3236. DOI: 10.1093/hmg/ddi353.
47. Fang K, Gao P, Tian J, Qin X, Yu W, Li J, Chen Q, Huang L, Chen D, Hu Y, et al. Joint effect of CFH and ARMS2/HTRA1 polymorphisms on neovascular age- related macular degeneration in Chinese population. *J Ophthalmol*. 2015;9:1–8. DOI: 10.1155/2015/821918.
48. Pulido JS, McConnell JP, Lennon RJ, Bryant SC, Peterson LM, Berger PB, Somers V, Highsmith E. Relationship between age-related macular degeneration- associated variants of complement factor H and LOC387715 with coronary artery disease. *Mayo Clin Proc*. 2007;82:301–307. DOI: 10.1016/S0025-6196(11)61026-4.