5-16-2014

Age-related Macular Degeneration and Vascular and Renal Comorbidities in Adults Aged 40 Years or Older: NHANES 2005-2008

Qi Cheng

AGE-RELATED MACULAR DEGENERATION AND VASCULAR AND RENAL COMORBIDITIES IN THE ADULTS AGED 40 YEARS OR OLDER

NHANES 2005-2008

BY

QI CHENG

GEORGIA STATE UNIVERSITY

A Thesis Submitted to the Graduate Faculty

of Georgia State University

in Partial Fulfillment of the Requirements for the Degree

MASTER OF PUBLIC HEALTH

ATLANTA, GEORGIA

30302

APPROVE PAGE

Age-related Macular Degeneration and Vascular and Renal Comorbidities

NHANES 2005-2008

BY

QI CHENG

Approved :

Dr. Richard Rothenberg

_____

Committee Chair

Dr. Jinan Saaddine

_____

Committee Member

Dr. Dora Il'yasova

_____

Committee Member

_____

Date

AUTHOR'S STATEMENT

In presenting this thesis as a partial fulfillment of the requirements for an advanced degree from Georgia State University, I agree that the Library of the University shall make it available for inspection and circulation in accordance with its regulations governing materials of this type. I agree that permission to quote from, to copy from, or to publish this thesis may be granted by the author or, in his/her absence, by the professor under whose direction it was written, or in his/her absence, by the Associate Dean, College of Health and Human Sciences. Such quoting, copying, or publishing must be solely for scholarly purposes and will not involve potential financial gain. It is understood that any copying from or publication of this dissertation which involves potential financial gain will not be allowed without written permission of the author.

_____

Signature of Author

ABSTRACT

IMPORTANCE: Age-related macular degeneration (AMD) is a leading cause of low vision in elderly population. The association of vascular and renal conditions has been reported inconsistently. Unfolding the association may provide the insight to eye care providers to take account general health management into eye care.

OBJECTIVES: To investigate the prevalence of the vascular and renal comorbidities with AMD, examine the association of a single or combination of these comorbidities with AMD.

DSIGN AND PARTICIPANTS: Population-base cross-sectional study involved the adults aged 40 years or older (N=4596) who participated in the 2005 to 2008 National Health and Nutrition Examination Survey (NHANES), a national representative population-based survey of non-institutionalized US residents.

MAIN OUTCOMES AND MEASURES: AMD was defined by the presence of drusen and presence of pigmental abnormality. Angina pectoris (AP), coronary heart disease (CHD), congestive heart failure (CHF) and myocardial infarction (MI), and stroke, assessed by self-report by the questionnaire of medical conditions, Chronic kidney disease (CKD), assessed by self-report and estimation of glomerular filtration rate (GFR) and the level of urine albumin. Heart disease (HD) was defined as having AP or CHF or CHD or MI.

RESULTS: Among individuals with AMD, 6% had AP, 10% had CHD, 7% had CHF, 10% had MI, 13% had stroke, and 29% had CKD. The weighted prevalence of these conditions were significantly higher than those without AMD (All P-values <0.05). The

estimated crude odds ratios (ORs) for the association between a single comorbidity and AMD were the following: 1.96 (95%CI: 1.24-3.10) for AP; 2.46 (95%CI, 1.67-3.64) for CHD, 2.38 (95% CI, 1.64-3.45) for MI, 2.51 (95% CI, 1.60-3.95) CHF, 2.59 (95% CI, 1.95-3.43) HD, 3.91(95%CI, 2.72-4.36) for stroke, and 3.35 (95% CI, 2.57-4.36) for CKD. Adjusting for gender, age and other risk factors, ORs were attenuated but remained elevated and statistically significant; whereas, AP was no long significantly associated with AMD. One of three comorbidities (HD, Stroke and CKD) (Crude OR: 2.78 (95%CI: 2.00-3.78); adjusted OR: 2.60 (95% CI: 1.71-3.92)), combination of the comorbidities (Crude OR: 3.93 (95%CI: 2.69-5.73); adjusted OR: 2.33 (95%CI: 2.73-3.99)) were associated with AMD. The association of the combination of CKD and Stroke was the strongest (Crude OR: 7.43 (95%CI: 4.51-12.27); adjusted OR: 5.50 (95% CI: 2.74-12.02)).

CONCLUSION AND RELEVANCE: These findings from the nationally-representative sample of the US population highlight the prevalence of vascular and renal comorbidities associated with AMD, the modest evidence of relationship of each single comorbidity, and strong association of combination of stroke and CKD to AMD independent of age, gender, and other factors. Because of the cross-sectional design, the results of this study can not address a causal relationship between AMD and the examined comorbidities. It is unclear whether AMD and comorbidities arise from individual predisposition to vascular and renal diseases or whether complications from these morbidities increase the risk of AMD. However, the important caveat is that preventive and care management for the examined comorbidities may lessen the severity of symptoms or prevent AMD.

ACKNOWLEDGEMENTS

I would like to express my deep gratitude to my thesis committee chair Dr. Richard Rothenberg for his excellent guidance not only on this project, but also throughout studies on Master of Public Health Program. I would also give my thinks to my thesis committee member Dr. Saaddine, Jinan for generous supports through providing internship opportunity at her team to complete of this thesis study, as well as her direction on this study. I am extremely thankful to my thesis committee member, Dr. Dora Il'yasova, who always supported my interest and thoughts on the study of public health and directed the thesis study. She is always there when I needed her for assistance. I would like to express my gratitude to all my professors at the School of Public Health at Georgia State University who taught and supported for the completion of the program of public health.

I would like to convey my warm appreciation to my family, particularly to my parents for their everlasting love and support throughout my journey of academia. This thesis is dedicate to my son, Changyue, Yu. The path of the career has not been easy, but I made it worth because of my love to my son.

NOTICE OF BORROWER PAGE

All theses deposited in the Georgia State University Library must be used in accordance with stipulations prescribed by the author in the preceding statement.

The author of this thesis is:

Student's Name: Qi Cheng

Street Address: 3328 Marla Blvd

City, State, and Zip Code: Norcross, GA 30092

The Chair of the committee for this thesis is:

Professor's Name: Dr. Richard Rothenberg

Epidemiology & Biostatistics, School of Public Health

Georgia State University P.O. Box 3995, Atlanta, Georgia 30302-3395

Users of this thesis who not regularly enrolled as students at Georgia State University are required to attest acceptance of the preceding stipulation by signing below. Libraries borrowing this thesis for the use of their patrons are required to see that each user records here the information requested.

Name of User	Address	Date	Type of Use Examination only or Copying

TABLES AND CONTENTS

LIST OF TABLES

CHAPTER I

INSTRUCTION

Age-related macular degeneration (AMD) is one of most common ocular diseases in the elderly population. The prevalence of AMD is reported as 9.8% among people aged 65 years or older, while 6.5% in individuals aged 40 years or older in US population (Klein et al., 2011; Klein et al., 2010). Although the prevalence of AMD decreases from 9.4% to 6.5% in US population aged 40 years or older during the last decade (Klein, et al., 2011; Klein et al., 1999), it is still a contributable cause of visual impairment and blindness (Chou et al., 2013; Foran, Wang, & Mitchell, 2003), which significantly impact on individual health quality of life, and increase severity of public health concern. Gaining population-based evidence of AMD is significant for lowing the incidence of AMD and blindness since the effective treatment and clinical management of AMD remains challenge (van Lookeren Campagne, LeCouter, Yaspan, & Ye, 2014).

Concurrence of medical conditions is more prevalent with age, one of four Americans has two or more conditions age more than 40 years. AMD, a multifactoral disease, is more likely coexisting with the diseases which share common risk factors or biological plausible pathways. The substantial presence of the associated comorbidities of AMD could resulted in an increased frequency of disability of vision impairment and overall burden of diseases to our society. Study on the association between these comorbidities and AMD would predict the outcomes of AMD and provide the insight for eye care management so as to reduce the worse outcome.

Heart diseases, stroke and chronic kidney disease (CKD) are major vascular diseases, and each of them shares common risk factors of AMD. The linkage between these conditions and AMD has been reported, but the results were inconsistent. A study has reported that AMD may be the risk predictor of coronary heart disease (CHD) relating to high mortality (Tan, Wang, Liew, Rochtchina, & Mitchell, 2008), by contrast, another study has showed that AMD is not associated with CVD and CHD (Fernandez et al., 2012). The AMD was associated with stroke (Tan, et al., 2008), but not associated with cerebral infarction (Wieberdink et al., 2011), moreover, the early AMD is not a risk factor of stroke in people aged 69 to 97 years (Sun, Klein, & Wong, 2009). CKD patients are in a higher risk of early AMD (Liew, Mitchell, Wong, Iyengar, & Wang, 2008). With the inconsistency, there is a rationale for an investigation of the relationship between vascular and renal comorbidities and AMD because the substantial present of these associated comorbidities would increase overall health burden of AMD in both individual and society level. The measurement of concurrence between AMD and the comorbidities will unfold the association by using national representative population, it will lead to the better visual outcomes of AMD patients, if these comorbidities are taken account into eye care management.

We conducted a study to investigate whether there is an association between AMD and vascular and renal conditions including heart disease (HD) containing angina pectoris (AP), coronary heart disease (CHD), congestive heart failure (CHF) and myocardial infarction (MI), stroke and chronic kidney disease (CKD). We utilized the data of 2005 - 2008 National Health and Nutrition Examination Survey (NHANES), a national representative sample of US population. We compared the prevalence of these

vascular and renal diseases among individual with AMD to those without AMD. We analyzed the association between AMD and each vascular and renal medical condition. We explored the relationship between AMD and combination of three conditions (HD, Stroke and CKD). We hypothesized that the individuals with these vascular and renal medical conditions will have an association with AMD, the association with combined comorbidities may be stronger comparing to the single comorbidity.

CHAPTER II

REVIEW OF LITERATURE

II.I Age-related Macular Degeneration

Age-related macular degeneration (AMD) is a neurodegenerative ocular disease affecting the population aged 40 years or older. It is a leading cause of blindness accounting for up to 50% of all cases of legal blindness in the United States. The typical lesion of AMD occurs at the retinal macular area. The damage to the macula results in impairment of central acuity and eventually loss of vision. AMD is categorized in two stages based on clinical manifestations: early and late AMD. The early AMD is asymptomatic with the appearance of numerous large drusen in the retina identified by retinal image. The drusen develop from the slow progressive degeneration of the retinal pigment epithelium and retinal photoreceptors (Lengyel et al., 2004). Early AMD accounts for approximately 80% of the reported cases of all AMD. Late AMD is divided into two types: choroidal neovascularization (CNV, also known as wet AMD) and geographic atrophy (GA, also known as dry AMD) based on presence or absence of invasive new blood vessels in the retina (Zweifel, Imamura, Spaide, Fujiwara, & Spaide, 2010). Late AMD accounts for about 20% of all AMD; however, late AMD is responsible for majority of blindness (Bourne et al., 2013). Several novel treatments for late AMD have been identified. An intraocular injection of an anti-vascular endothelial growth factor (VEGF) agent (Akpek & Smith, 2013) is available for treatment of the CNV type of AMD. These agents have substantially gained the vision back and reduced the risk of blindness in some but not all patients. In contrast, there is no approved treatments for GA type of AMD. Effective management of AMD remains a significant challenge. Early

detection and prevention of AMD, therefore, is important to reduce the incidence of AMD and improve the quality of vision. Population-based epidemiological studies are capable of providing the evidence for the etiology of AMD in order to establish of prevention program of reduction of risk factors of AMD.

II.II Pathogenesis of AMD

AMD is generally considered as a complex genetic disorder influenced by environmental risk factors. Although biological mechanisms of AMD are largely unknown, major progress in understanding the pathogenesis of AMD have been made through the advances of molecular cell biology and genetics in the past decade implicating several pathogenetic pathways including oxidative damage, chronic inflammation, and excessive accumulation of lipofuscin, (Whitcup et al., 2013). Activation of immune cells in the retina, including microglia cells, Muller cells RPE cells and macrophages related to the pathway of GA type of AMD (Cherepanoff, McMenamin, Gillies, Kettle, & Sarks, 2010). Complement activation is reported to associated to the inflammation pathophysiological way of AMD. Molecular pathological evidence of oxidative damage in the retina linked to immune response has indicated the relevance of oxidative stress to initiate the development of AMD (Hollyfield et al., 2008). In addition, it is very accepted that genetic contribution is strongly correlated to the risk of AMD. Genetic analyses reveal that there is correlation between GA type of AMD risk and variations in genes encoding negative regulators in complement pathways, including complement factor H (*CFH*) and factor I (*CFI*), as well as additional

components of the AP such as complement factors B (*CFB*) and C3 (Fagerness et al., 2009; Heurich et al., 2011).

II.III The Epidemiology of AMD

The population of AMD patients bears the greatest burden of health due to disabilities in vision loss, complications and co-morbidities. Population-based studies on AMD are vital for understanding the etiology of AMD to reduce the burden of disease. There have been many epidemiological studies on the prevalence and incidence of AMD and decreased trend of prevalence of AMD is observed. The Framingham Eye Study reported the prevalence of AMD among people aged 52-85 years was 8.8% (Leibowitz et al., 1980). A fifteen year accumulative prevalence of ADM study has shown the prevalence of early stage of AMD was 24%, late state was 8% among people aged 75 and older (Klein et al., 2007). The Beaver Dam Offspring study estimated a 9.8% prevalence of AMD among people aged more than 65 years (Klein, et al., 2010). In the US population aged 40 years and older, the prevalence of any AMD was 6.5% and the prevalence of late AMD was 0.8% (Klein, et al., 2011). The disparity of prevalence of AMD among racial/ethnic groups has been observed and the prevalence of AMD is higher among the whites than any other racial groups. Dr. Klein et al's study has shown that blacks aged 60 years and older had a lower prevalence of AMD (OR = 0.37; 95% CI, 0.21-0.67) than non-Hispanic white persons in the same age groups (Klein, et al., 2011). It is thought that the prevalence of AMD does not differ from gender, although women have higher risk of CNVAMD (OR:1.2; 95% CI: 1.0-1.5) in one study (Owen et al., 2012). The population-based studies have led to major advances in

the understanding of the risk factors of AMD. A meta-analysis has reported that 73 risk factors of AMD are associated with AMD, and aging, cigarette smoking, previous cataract surgery and a family history of AMD are the risk factors consistently (Chakravarthy et al., 2010). In addition, factors of social economic status, oxidative stress (Hollyfield, et al., 2008), low level of antioxidants (Chew et al., 2013) and nutritional factors (Chew, et al., 2013; Wlodarek & Glabska, 2011) have been implicated as risk factors for the occurrence of AMD. Many of the etiological risk factors of AMD are commonly shared with medical conditions of different organ systems. Exploring the relationship between ADM and organ system diseases is ideal for understanding the etiology of AMD.

II.IV Vascular and Renal Comorbidities and AMD

Comorbidity is widely defined as the presence of more than 2 diseases in an individual. These conditions could be occurring synchronously or sequentially. For example, a patient with established depression is diagnosed with a glaucoma differs from a patient with depression and later is found to have a glaucoma. Comorbidity is usually associated with a worse outcome, consequently increasing health care cost. About 80% of health care expenditure in the United States is spent on patients who have 4 or more chronic diseases (Wolff, Starfield, & Anderson, 2002). Comorbidities often display either common etiological pathways or biological plausibility, hence the information of comorbidity predicts not only the disease pathogenesis, prognosis, and treatment, but also the burden of organ dysfunction. From the point view of

epidemiology and public health, understanding the comorbidity is very important as comorbidity is associated with a worse outcome.

Heart disease (HDs) share many common risk factors with AMD suggesting that HDs may be a comorbidity of AMD. CVDs generates the most health concerns because of high incidence and prevalence. The estimation from 2007-2010 NHANES (National Health and Nutrition Examination Survey), is that one of third deaths was attributable to CVDs in United States in 2009. One of six deaths is caused by CHD; one of nine deaths is from congestive heart failure; one of every nineteen deaths is attributable to stroke; one third of US adults aged 20 years and older have hypertension (Go et al., 2013). In s population based cohort study in middle-aged persons, participants with any AMD were at an increased risk of stroke with a stronger association for intracerebral hemorrhage than cerebral infarction after a mean follow-up 13 years (Ikram et al., 2012). Total serum cholesterol was associated directly with incident geographic atrophy (Tomany et al., 2004). AMD often coexists with CVD due to a shared pathogenesis. In this thesis study, common cardiovascular diseases listed in NHANES dataset are chosen to investigate the epidemiological linkage with AMD .

The association between Coronary heart disease (CHD) and AMD has long been postulated by epidemiological studies, but the results of the association vary. Several epidemiological studies have suggested the association between CHD and AMD. The linkage between the early AMD and an increased risk of CHD (HR1.57; 95% CI, 1.17-2.22) is described in the Cardiovascular Health Study in the Australian population aged 69-97 (Sun, et al., 2009), Another prospective cohort study has suggested an association between early AMD and CHD (RR: 1.08; 95% CI 0.82-1.42) in a middle

aged Australian population, but the individuals with late AMD had three times higher risk of incident CHD events (HR= 3.05, 95% CI, 1.14–8.17) (Wong et al., 2007). A case control study investigating a French population suggested a link between AMD and CHD (RR: 1.31, 95%CI: 1.02–1.68) (Chaine et al., 1998). Blue Mountains Eye Study has stated that early AMD had a 2-time increased risk of CHD mortality controls (HR= 2.32, 95% CI, 1.03 to 5.19) (Tan, et al., 2008). On the other hand, the most recent study has stated that AMD is a not risk indicator of CHD in the Multi-Ethics Study of Atherosclerosis (HR: 0.99; 95% CI, 0.74-1.33) in the population aged 45 to 84 years with an over 5.4 year follow-up (Fernandez, et al., 2012). The results implied the importance for further study of the association between CHD and AMD with a national representative population.

Heart attack (HA), also known as Myocardial infarction (MI), is one of the most common cardiovascular diseases and is a consequent of ischemic heart disease accounting for 12.2% of worldwide deaths based on the estimate of WHO in 2004. Many risk factors of MI have been postulated in epidemiological studies including age, smoking, abnormality of blood levels of certain lipids, diabetes, hypertension, and obesity. Previous cardiovascular disease is the most common risk factor of MI. Angina Pectoris commonly is thought to be related to myocardial ischemia. Angina also shares most of the same risk factors with MI. Heart failure also known as congestive heart failure (CHF) commonly results from cardiovascular diseases including MI. Heart failure affected 5.8 million people in the United States in 2011. The health care expenditure for heart failure exceeds $35 billion in the United States due to the hospitalization cost (Rosamond et al., 2008). The risk factors of CHF includes ischaemic heart disease,

hypertension, obesity, and diabetes which are major risk factors for MI and angina pectoris. Given these same risk factors of angina, MI and CHF with AMD, it is considerable that there is an association between AMD and angina, MI and CHF. However, there is no common agreement that this association exists. When reviewing the evidence from epidemiological studies. There is no association between angina, MI and AMD in Beaver Dam Eye Study (Klein et al., 2013). MI or angina RR was related with AMD (HR:1.57; 95% CI: 1.13-2.16) (Tan, et al., 2008), persons with MI was significantly more prevalent for early AMD (Liutkeviciene et al., 2012), furthermore, MI was associated with AMD, particularly in neovascular AMD (HR: 1.19; 95%CI: 1.16-1.22) (Duan et al., 2007). To the contrary, a study using a group of hospitalized cardiovascular disease patients reported that the rate ratio for MI with neovascular AMD was protective (HR: 0.58; 95% CI: 0.48-0.72) (Nguyen-Khoa et al., 2008) (Golan et al., 2011). It is important to investigate the epidemiological relationship between AMD and angina, MI and CHF with a national population.

Stroke was defined as a "neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours" World Health Organization, 1978 WHO's top ten causes of death list stroke as the second most cause of death worldwide in 2011, accounting for 6.2 million deaths. Risk factors for stroke that were identified include age, hypertension, previous stroke or transient ischemic attack (TIA), diabetes, and smoking (Donnan, Fisher, Macleod, & Davis, 2008). High blood pressure is the most important modifiable risk factor of stroke. As a result, stroke may be linked with AMD. There is no general agreement on this linkage based on the literature review.

The presence of early-stage AMD in persons aged 49 to 73 was associated with a higher adjusted risk for stroke (HR: 1.87 [95% CI, 1.21- 2.88]) over ten years follow up (Wong et al., 2006). In a Taiwanese population-based study, neovascular AMD in patients aged 65 and older was associated with a 2-fold increased incidence of stroke (Hu, Ho, & Lin, 2010). Moreover, AMD was an indicator of the risk of stroke (HR: 1.51; 95% CI: 1.11-2.06) with an association for both intracerebral hemorrhage (HR: 2.64; 95% CI: 1.18-5.87) and cerebral infarction (HR: 1.42; 95% CI: 1.01-1.99) in the Atherosclerosis Risk in Communities (ARIC) Study (Ikram, et al., 2012).

In contrary, a retrospective cohort study using hospitalized CVD database found contradictory results and the rate of cerebrovascular accidents (CVAs) was lower in neurovascular AMD (RR =0.56, 95% CI, 0.45–0.70) over a 3 year period (Nguyen-Khoa, et al., 2008). There is no relationship between AMD and Stroke in the Cardiovascular Health Study (Sun, et al., 2009) and the Beaver Dam Eye Study (Klein, et al., 2013). Late AMD was associated with an increased risk of any stroke (HR: 1.56; 95% CI: 1.08 - 2.26), and there was a strong association with intracerebral hemorrhage (HR: 6.11; 95% CI: 2.34-15.98), but no association with cerebral infarction in the Rotterdam Study (Wieberdink, et al., 2011). Future studies on AMD as an indicator of the risk of stroke is important.

Chronic kidney disease (CKD) shares common pathogenetic mechanisms of AMD including inflammation, oxidative stress, and microvascular dysfunction, suggesting that CKD may be linked with AMD. A few epidemiological studies of the link between AMD and CKD have been reported. CKD was associated with AMD (OR, 1.68; 95% CI, 1.04-2.72) (Choi, Moon, & Shin, 2011). Proteinuria and eGFR < 45 ml/min/1.73

m were positively associated with AMD only among men (OR2.06, 95% CI 1.05, 4.04) (Nitsch, Evans, Roderick, Smeeth, & Fletcher, 2009). Mild CKD was associated with the 15 year cumulative incidence of early AMD (OR: 1.36, 95% CI, 1.00-1.86]) in the Beaver Dam Eye Study (Klein, Knudtson, Lee, & Klein, 2009), the 5-yr incidence of early AMD with CKD was 4 times higher than those without CKD in the Australian population (Liew, et al., 2008), and had a higher prevalence of AMD (1.7% vs. 0.9%, P = 0.01) in a Chinese population-based study (Gao et al., 2011). However, little research of CKD and AMD with a national population of US has been reported.

This thesis study aims to investigate the association between AMD and vascular medical conditions including cardiovascular diseases (AP, CHD, MI and CHF), stroke and CKD.

CHAPER III

METHODS

III.I Study Population

NHANES is a national representative population-based survey of non-institutionalized US residents conducted by the National Center for Health Statistics, the Centers for Disease Control and Prevention (CDC). The subjects, collection and program description have been published at CDC website. NHANES utilized a complex, multistage cluster sampling design to achieve the generalizability of US population. In brief, subjects contain entire non-civilian population in the United States. Data collection was through a questionnaire survey, medical examination and laboratory tests. Retinal image photography was conducted 2005 to 2008 and limited to the participants aged 40 years old and older. Data from NHANES 2005 to 2008 were used for this study. Of the total 20,497 subjects, 6,874individuals were more than 40 years old, and 4,596 (66.9%) individuals has complete retinal image photography at the time of the completion. Among the individuals aged more than 40 years, 49.7% were male and 50.4% were female. To the distribution of racial/ethnicity, non-Hispanic white were 39.2%, non-Hispanic black were 24.0%, Mexican American were 24.4%, and other races/ethnicities were 12.3%. The education distribution shows 54.1% were high school graduate or low, 26.8% indicated some college, 19.1% were college graduate or above.

III.II Sociodemographic and clinical characteristics

Standardized the questionnaires were administered in the home. Physical and medical lab examinations were conducted in the NHANES examination center by

trained medical professionals. The demographic, social behavioral and clinical characteristics were defined for the analysis. Race/Ethnicity was categorized into four groups: Non-Hispanic Whites, Non-Hispanic Blacks, Mexican American and other race. Education was defined as high school graduate, College or Associate and College graduates or more. Family annual incomes were categorized as less than $25,000, $25,000 - $49,000, $50,000 - $74,999 and greater than $75,000. Smoking status and alcohol consumption were dichotomized as none current smoker and current smoker, none regular drinker and regular drinker, respectively. Body Mass Index (BMI) was determined as four categories: Less than 18.5, 18.5 to 24.99, 25-29.99 and greater than 30. Lipid profiles including total cholesterol (TLC), Triglycerides, Low density lipoprotein (LDL); High density lipoprotein (LDL) were categorized as the levels based on the American Heart Association (AHA) recommends. For the TCL levels: less than 200 mg/dL, 200-239 mg/dL, greater that 240 mg/dL; Level of Triglycerides levels: less than 150 mg/dL, 150-199 mg/dL, 200-500 mg/dL and greater than 500mg/dL. Level of LDL: less than 129 mg/dL, 130-159 mg/dL, 160-190 mg/dL and greater than 190 mg/dL. Level of HDL: less than 40 mg/dL, 40-60 mg/dL and greater than 60 mg/dL, respectively.

III.III Definition of Variables of the Comorbidities

The comorbidities of AMD for cardiovascular diseases were defined based on the questionnaire and medical laboratory examination. The self reported questions were used to define some of comorbidities, and the subjects were asked similar questions, including coronary heart disease (“Has a doctor or other health professional ever told

you that you had a coronary heart disease?"), congestive heart failure ("Has a doctor or other health professional ever told you that you had congestive heart failure?"), stroke ("Has a doctor or other health professional ever told you that you had a stroke?") and angina pectoris ("Has a doctor or other health professional ever told you that you had an angina pectoris?"), and heart attack ("Has a doctor or other health professional ever told you that you had Heart Attack?"). Chronic Kidney Disease (CKD) is defined by self report and estimation of glomerular filtration rate (GFR). All individuals with GFR <60 mL/min/1.73 m^2 are classified as CKD. GFR estimation was done according to Epidemiology Collaboration equation. Serum creatinine values were collected from the NHANES dataset. Persistent presence of more than 30 mg albumin per gram creatinine in the urine is diagnostic of chronic kidney disease. Microalbuminuria is a level of 30–299 mg/L (Bowling, Sharma, Fox, O'Hare, & Muntner, 2013).

III.IV Retinal Imaging Evaluation

Procedures for ophthalmological retinal imaging evaluation have been described previously (Klein, et al., 1999). The retinal imaging evaluation was adapted from the Wisconsin Age-Related Maculopathy Grading Scheme (Klein et al., 1991). The presence of any drusen, soft drusen, retinal pigment epithelial (RPE) depigmentation and increased retinal pigment were assessed. GA was determined by absence of the RPE in which choroidal vessels are visible. The signs of CNV contain subretinal hemorrhage and fibrous scar, and retinal pigment epithelium detachment. Early AMD was determined by the presence of either soft drusen consistent with Grade 3 drusen or any drusen type with areas of depigmentation or hypopigmentation of the retinal

pigment epithelium without any visibility of choroidal vessels or with increased retinal pigment in the macular area. Late AMD was determined by the presence of signs of CNV or GA. RPE depigmentation was graded as present or absent. Increased retinal pigment which is the presence of granules or clumps of gray or black pigment in or beneath the retina was graded as present or absent. Retinal photograph was taken under a dilated eye. Retinal image is the field centered horizontally and vertically.

III.V Statistical Analysis

All analyses were conducted by using SAS 9.3 (SAS Institute, Cary, NC). Frequency distributions, percentages and means, and standard deviation were used to describe the difference of sociodemographic characteristics of the NHANES study population relating to AMD. The significance of the differences among categorical variables were determined by Chi square statistics, and Wilcoxon Rank Sum were used to test the difference among continuous variables based on the sample distribution and equality of variance. Univariate and multiple logistic regression models were used to assess the association between AMD and potential confounders including age, gender, race/ethnicity, alcohol consumption, education level, smoking status, and annual family income. Full sample 2 year interview and MEC exam weight were used to weight all survey samples. All analysis used weighted and stratified sample.

CHAPETER IV

RESULTS

IV.I Prevalence of AMD Stratified by Age in NHANES Population 2005 - 2008

The total number of participants who were aged 40 years or older were 4596 with a completion of examination of retinal image. Among them, the number of people who had AMD were 441. The overall weighted prevalence of AMD was 7%. Compared to the individuals whose age were 40-49 years old, the weighted prevalence of AMD were 10% for those aged 70 years or older, 5% for those aged 60- 69 years, and 2% for those 50-59 years, respectively (Table1).

Table 1. Weighted prevalence of AMD stratified by age: Adults 40 years or older, 2005 -2008 NHANES

	Participation's age (Years) (OR, 95 %CI)			
Outcome	40 - 49	50 - 59	60 - 69	70 or older
AMD	1.00 (Reference)	1.90 (1.89-1.91)	4.53 (4.512 - 4.534)	9.85 (9.83 - 9.88)

IV.II Descriptive Analysis of Study Population with or without of AMD

The characteristics of 2005-2008 NHANES population with or without AMD was summarized in Table 2. Briefly, average of the age among individuals with AMD was 68 years old, and 87% of study population was whites, which were significantly higher than those among the individuals without AMD (Age: 56, Whites: 76%, P value <0.05). The gender did not differ between two groups. The proportion of annual family incomes among the individuals with AMD was significantly difference from those among the participants without AMD (P value <0.05). The proportion of annual family incomes greater than $75K in individuals with AMD was 10%, which was significantly lower than

those among the individuals without AMD (22%). Level of education did not differ between individuals without or with AMD. The proportion of current smokers with AMD (15%) was lower comparing to those without AMD (19%, P value <0.05) in this population. The proportion of AMD among the regular alcohol drinker (47%) was lower compared to those without AMD (60%, P-value<0.05). The level of HDL was significantly differ between AMD and non AMD participants (P<0.05); whereas, the levels of TCL, triglycerides and LDL were not statistically different (Table 2).

Table 2. Characteristics of participants with or without AMD: Adults aged 40 years or older, AMD defined by retinal photography, NHANES 2005-2008

Characteristics	No AMD [a] (N= 4596)	AMD [a] (N =441)	*P value* [c]
Demographic			
Age (year)[b]	55.6 (55.2-55.9)	68.0 (66.4-69.6)	<0.0001
Gender			0.8960
Male	47.4 (45.7-49.2)	47.0 (41.3-52.8)	
Female	52.6 (50.8-54.3)	53.0 (47.2-58.7)	
Race/ Ethnicity			<0.0001
Non-Hispanic Whites	76.4 (75.3-77.6)	86.6 (83.6-90.0)	
Non-Hispanic Blacks	8.1 (7.2-9.0)	3.76 (2.4-5.1)	
Mexican American	8.1 (7.2-9.0)	5.5 (3.2-7.8)	
The others	5.5 (5.1-5.9)	4.2 (2.9-5.5)	
Socioeconomic			
Education			0.0736
High school graduate	44.0 (42.2-45.7)	49.6 (43.9-55.3)	
College or Associate	28.3 (26.8-29.9)	28.8 (23.5-34.1)	
College graduate or above	27.7 (26.1-29.3)	21.6 (16.6-26.6)	
Family annual income			<0.0001

<$25,000	26.0 (24.6-27.5)	36.4 (30.8-42.0)	
$25,000-$4999	35.2 (34.4-38.0)	41.1(35.0-47.2)	
$50,000-$74999	16.5 (15.0-18.0)	12.2 (7.3-17.0)	
>$75,000	22.2 (20.6-23.9)	10.4 (6.3-14.5)	
Smoking status			0.0203
None current smoker	81.3 (80.0-90.0)	85.0 (80.7-89.4)	
Current smoker	18.7 (17.3-20.0)	15.0 (10.6-19.3)	
Alcohol consumption			0.0079
None regular drinker	39.6 (36.6-42.7)	53.1 (43.5-63.7)	
Regular drinker	60.4 (57.3-63.4)	46.9 (37.3-56.5)	
Medical examinational			
Body Mass Index (BMI)			0.0654
<18.5	2.0 (1.6-2.5)	1.1 (0.2-2.0)	
18.5 -24.99	26.0 (24.5-27.6)	29.9 (24.5-35.3)	
25-29.99	35.1 (33.4-36.7)	38.3 (32.7-43.8)	
>30	36.9 (35.2-38.5)	30.7 (25.4-36.0)	
Total Cholesterol (mg/dL)			0.7235
<200	50.3 (48.5-52.0)	50.7 (45.0-56.5)	
200-239	31.8 (30.2-33.5)	33.2 (27.6-38.8)	
>240	17.9 (16.5-19.2)	16.1 (11.9 -20.3)	
Triglycerides (mg/dL)			0.2465
<150	83.8 (82.5-85.1)	85.8 (82.1-90.0)	
150-199	7.9 (6.9-8.8)	6.2 (3.8-8.7)	
200-500	3.7 (3.1-4.4)	4.9 (2.6-7.3)	
> 500	4.6 (3.9-5.3)	3.0 (1.1-4.9)	
LDL (mg/dL)			0.8518
<129	82.6 (81.2 -83.9)	80.7 (75.7-85.7)	
130-159	11.8 (10.7-12.9)	13.5 (9.0-17.9)	
160-190	4.1 (3.4-4.8)	4.4 (1.9-7.0)	
>190	1.6 (1.1-2.0)	1.4 (0.2-2.6)	
HDL (mg/dL)			0.0288
<40	20.1 (18.7-21.5)	17.2 (12.9-21.5)	
40-60	49.8 (48.1-51.6)	45.2 (39.5-50.9)	
> 60	30.1 (28.5-31.8)	37.5 (31.9-43.2)	

Values for categorical variables presented weighted proportion and 95% CI , and P-values were generated by Chi square test. Values for continues variables were weighted mean and 95% CI and P-values were generated by F-test . [a] = % (95% CI); [b] = mean (95% CI). [c] = P value <0.05. LDL: Low density lipoprotein; HDL: High density lipoprotein; CI: Confidence interval.

We also compared these sociodemographic characteristics among the individuals with early or late AMD to those without AMD. These characteristics of early AMD results were similar to the participants without AMD, however, the mean of age (78 years) among the individuals with late AMD were significantly older than those with early AMD (67 years), and higher proportion of whites in late AMD participants (94%, P-value <0.05) were observed compared with early AMD (86%). Females with late AMD were more likely to have AMD (70% versus 52% early AMD) (Table 3).

Table 3. Characteristics of participants with early/late AMD: Adults aged 40 years or older, AMD defined by retinal photography, NHANES 2005-2008

Characteristics	Early AMD [a] (N=441)	Late AMD [a] (N =51)	*P value* [c]
Demographic			
Age (year)[b]	66.6(64.9-68.3)	78.0 (76.2-80.0)	<0.0001
Gender			0.0724
Male	49.4 (43.9-55.6)	30.1 (17.4-42.8)	
Female	52.2 (46.2-58.2)	69.7 (57.2-82.6)	
Race/ Ethnicity			<0.0001
Non-Hispanic Whites	86.0 (82.8-89.1)	94.4 (89.4-99.2)	
Non-Hispanic Blacks	5.6 (3.1-8.0)	2.2 (0-5.5)	
Mexican American	4.7 (3.2-6.2)	0.6 (0-1.8)	
The others	4.0 (2.5-5.5)	0.5 (0-6.2)	
Socioeconomic			

Education			0.1028
High school graduate	49.2 (43.0-55.5)	52.1 (37.8-66.5)	
College or Associate	27.6 (22.2-33.1)	37.8 (21.0-48.6)	
College graduate or above	22.4 (17.1-27.8)	13.1 (3.2-23.0)	
Family annual income			<0.0001
<$25,000	33.9 (29.5-41.1)	53.0 (37.5-68.5)	
$25,000-$4999	41.1 (34.5-47.7)	40.8 (25.2-56.3)	
$50,000-$74999	13.9 (8.5-19.4)	0	
>$75,000	11.0 (6.4-15.6)	6.2 (0-13.4)	
Smoking status			0.1596
None current smoker	85.0(80.3-90.0)	89.2 (80.3-98.0)	
Current smoker	15.0 (10.2-19.7)	10.9 (2.0-19.7)	
Alcohol consumption			0.0024
None regular drinker	49.0 (38.3-59.8)	73.2 (55.6-90.9)	
Regular drinker	51.0 (40.2-61.7)	26.8 (9.1-44.5)	
Medical examinational			
Body Mass Index (BMI)			0.0338
<18.5	0.9 (0-1.8)	2.4 (0-5.7)	
18.5 -24.99	28.9 (23.0-34.7)	37.3 (23.2-51.5)	
25-29.99	37.4 (31.4-43.3)	44.6 (30.3-58.8)	
>30	32.8 (27.0-38.6)	15.7 (6.2-25.1)	
Total Cholesterol (mg/dL)			0.5664
<200	50.6 (44.4-56.9)	51.3 (37.0-65.6)	
200-239	34.3 (8.2-40.4)	25.3 (13.1-37.4)	
>240	15.1(10.6-19.5)	23.4(11.3-35.5)	
Triglycerides (mg/dL)			0.5731
<150	86.2 (82.2-90.1)	83.5 (72.4-94.6)	

150-199	6.0 (3.4-8.5)	8.3 (0.1-16.5)	
200-500	4..8 (2.3-7.3)	5.9 (0-13.2)	
> 500	3.1 (1.0-5.1)	2.2 (0-6.6)	
LDL (mg/dL)			0.9134
<129	80.6 (75.1-86.0)	81.8 (70.6-92.9)	
130-159	13.9 (9.0-18.8)	10.1 (0.8-19.3)	
160-190	4.3 (1.6-7.1)	5.2 (0-11.0)	
>190	1.2 (0-2.4)	2.3 (0-7.5)	
HDL (mg/dL)			0.0411
<40	18.3 (13.5-23.0)	9.7 (1.3-18.1)	
40-60	45.1 (38.9-51.3)	46.2 (32.0-60.5)	
> 60	36.6 (30.5-42.7)	44.1 (30.0-58.4)	

See Table 1's footnote. P-values presented the comparisons of either early or late AMD to none-AMD (iiTable 2).

IV.III Prevalence of Vascular and Renal Comorbidities and AMD in the 2005-2008 NHANE

The proportions of these comorbidities were estimated in the individuals with or without AMD by using the NHANES data combining 2 surveys. Among the individuals with AMD, 6% had AP, 10% had CHD, 7% had CHF, 10% had MI, 13% had stroke, and 29% had CKD. The weighted prevalence were significantly higher than those among individuals without AMD (AP: 3%; CHD: 5%; CHF: 3%; MI: 5%; Stroke: 4%; CKD: 12%, P-value <0.05) (Table4).

Table 4. Weighted prevalence of vascular and renal comorbidities with or without AMD: Adults aged 40 years or older, AMD defined by retinal photography, 2005-2008 NHANES

	No AMD	AMD	
Medical conditions	Weighted %(95%CI)	Weighted %(95%CI)	*P value*
Angina Pectoris (AP)	3.2 (2.7-3.7)	6.1 (3.7-8.5)	0.0033
Coronary heart disease (CHD)	4.5 (3.8-5.1)	10.3 (7.0-13.6)	<0.0001
Congestive heart failure (CHF)	3.0 (2.6-3.5)	7.3 (4.5-10.2)	<0.0001
Myocardial Infarction (MI)	4.5(3.9-5.2)	10.1 (7.0-13.2)	<0.0001
Stroke	3.5 (3.0-4.1)	12.5 (9.0-16.1)	<0.0001
Chronic Kidney Disease (CKD)	10.8 (9.8-11.8)	28.8(23.8-33.8)	<0.0001

Values present weighted proportion (%) and 95% Confidence interval (CI). Rao-Scott Chi-Square statistics were used for the comparison between no AMD and AMD.

When we examined the weighted prevalence of these comorbidities among the individuals with early or late AMD, results were similar; however, the proportions of stroke (26%) and CKD (49%) in the participants with late AMD were significantly higher than those without AMD (P value<0.05) (Table 5).

Table 5.Weighted prevalence of the cormorbidites with early or late AMD or without AMD: Adults aged 40 years or older, AMD defined by retinal photography, 2005-2008 NHANES

	No AMD	Early AMD	Late AMD	
Medical conditions	Weighted % (95%CI)	Weighted %(95%CI)	Weighted %(95%CI)	*P value*
AP	3.2 (2.7-3.7)	6.6 (3.9-9.3)	2.1 (0-5.3)	0.009
CHD	4.5 (3.8-5.1)	10.2 (6.6-13.8)	10.6 (2.3-19.1)	<0.0001
CHF	3.3 (2.6-3.5)	6.5(3.5-9.4)	13.4 (3.5-23.3)	<0.0001
MI	4.5(3.9-5.2)	10.2 (6.8-13.6)	9.3 (2.0-16.6)	<0.0001
Stroke	3.5 (3.0-4.1)	10.7(7.2-14.3)	26.4(13.2-39.5)	<0.0001
CKD	10.8 (9.8-11.8)	26.0 (20.7-31.2)	49.4 (35.1-63.8)	<0.0001

Values present weighted proportion (%) and 95% Confidence interval (CI). Rao-Scott Chi-Square statistics were used for the comparison between no AMD and early/late AMD.

IV.IV Association Between Each Single Comorbidity and AMD in the 2005-2008 NHANE

To address the association of each single vascular and renal comorbidity with AMD, we, first, conducted univariate logistic regression analysis. ORs were estimated. The crude ORs for all AMD among the participants with these conditions (AP, CHD, MI, CHF, HD and stroke) were 2.0 (95% CI:1.2-3.1), 2.5 (95% CI: 1.7-3.6), 2.4 (95% CI: 1.6-3.5), 2.5 (95% CI: 1.6-4.0), 2.6 (95%CI: 2.0-3.4) and 3.9 (2.7-4.4), respectively. In addition, the crude OR for AMD was 3.4 (95%CI: 2.6-4.4) among the individuals with CKD. After controlling for gender, age, race/ethnicity, current smoke status, alcohol consumption, and annual family incomes, and level of serum HDL, the adjusted ORs for AMD were similar to the crude ORs among the individuals with CHD (2.3, 95% CI: 1.4-3.7), MI (2.2, 95% CI: 1.3-3.5), CHF (2.0, 95% CI: 1.1-3.8), HD (2.0, 95% CI: 1.4- 2.9), and stroke (3.0, 95%CI: 1.8-4.9) and CKD (2.4, 95%CI: 1.7-3.4), respectively; however, the adjusted OR for the AMD among the individuals with AP was no longer significant (1.5, 95% CI: 0.8-2.7). We also examined the crude and adjusted ORs for early AMD using the same logistic regression models, similar results were observed (Table 6).

Table 6. Association between a single comorbidity and AMD, respectively : Adults age 40 years or older, AMD defined by retinal photography, 2005-2008 NHANES

Medical conditions	AMD		Early AMD	
	Crude OR (95%CI)	Adjusted OR (95%CI)	Crude OR (95%CI)	Adjusted OR (95%CI)
AP	1.96 (1.24-3.10)	1.50 (0.83-2,71)	2.05 (1.29-3.27)	1.59 (0.88-2.87)
CHD	2.46 (1.67-3.64)	2.27 (1.35-3.67)	2.44 (1.63-3.66)	2.17 (1.30-3.62)
MI	2.38 (1.64-3.45)	2.20 (1.34-3.51)	2.34 (1.59-3.44)	2.12 (1.29-3.49)
CHF	2.51 (1.60-3.95)	1.98 (1.05-3.75)	2.44 (1.52-3.92)	2.09 (1.10-3.97)
HD	2.59 (1.95-3.43)	2.01 (1.38-2.93)	2.57 (1.91-3.45)	2.04 (1.39-3.00)
Stroke	3.91 (2.72-4.36)	2.99(1.82-4.92)	2.37 (2.55-5.44)	2.12 (0.57-7.80)
CKD	3.35 (2.57-4.36)	2.44 (1.73-3.43)	2.99 (2.26-3.96)	2.32 (1.63-3.31)

Adjusting factors: Gender, age race/ethnicity, smoking, alcohol consumption, and annual family incomes, and level of HDL Abbreviations: HD: either AP or CHD or CHF or MI. OR, odds ratio

IV.V Association of Combination of Comorbidities and AMD

To investigate whether there is a strong association of these comorbidities with AMD, we conducted the logistic regression analysis with. Without any condition was defines as a reference group. We found that crude ORs for AMD were 2.8 (95% CI: 2.9-3.9) among the individuals with any one condition, 3.9 (95% CI: 2.7-5.7) among the participants with any two conditions or more. The association was statistically significant (P-value <0.05). After controlling for age, gender, race/ethnicity, smoking status, alcohol consumption and annual family incomes, and the level of HDL, the association remained a significant level (P-value <0.05). We also examined whether the c association was presented in early AMD (P<0.05). The results were similar (Table 7).

Table 7. Association of combination of comorbidity with AMD: Adults aged 40 years or older, AMD defined by retinal photography, 2005-2008 NHANES

Medical conditions	AMD		Early AMD	
	Crude OR (95%CI)	Adjusted OR (95%CI)	Crude OR (95%CI)	Adjusted OR (95%CI)
None (Reference)	1.00	1.00	1.00	1.00
Any one	2.78 (2.00-3.87)	2.60 (1.71-3.92)	2.67 (1.89-3.77)	2.56 (1.68-3.92)
Any two or more	3.93 (2.69-5.73)	2.33 (2.73-3.99)	3.60 (2.42-5.36)	2.31 (1.33-4.01)

Adjusting factors: Gender, age race/ethnicity, smoking, alcohol consumption, and annual family incomes and level of HDL. Abbreviations: one condition, either HD or CKD or stroke; two conditions, any combination of two among HD, CKD and stroke; OR, odds ratio.

IV.VI Association of Specific Combination of Comorbidities with AMD in the 2005-2008 NHANES

To estimate whether there is an association among a specific combination of these comorbidities, we analyzed the ORs for AMD among three specific combinations of comorbidities (HD/Stroke, HD/CKD and Stroke/CKD) using the same logistic regression model designed above with same controlling factor. We found that the crude ORs for AMD were 4.0 (95%CI: 3.3-7.0), 3.9 (2.6-5.8) and 7.4 (4.5-12.2) among the individuals with HD/Stroke, HD/CKD and Stroke/CKD, respectively. With controlling for the adjusted factors, the associations remained same. In addition, we estimated these associations for early AMD, the results were similar (Table 8)

Table 8. Association of specific combination of co-morbidity with AMD: Adults aged 40 years or older, AMD defined by retinal photography, 2005 - 2008 NHANES

Medical conditions	AMD		Early AMD	
	Crude OR (95%CI)	Adjusted OR (95%CI)	Crude OR (95%CI)	Adjusted OR (95%CI)
HD/Stroke	404 (2.34-6.96)	2.25 (1.00-5.07)	4.16 (2.39-5.26)	2.37 (1.06-5.33)
HD/ CKD	3.88 (2.58-5.80)	2.43 (1.36-4.34)	3.40 (2.19-5.26)	2.39 (1.31-4.33)
Stroke/ CKD	7.43 (4.51-12.27)	5.50 (2.74-11.02)	6.92 (4.12-11.61)	5.87(2.94-11.74)

Adjusting factors: Gender, age race/ethnicity, smoking, alcohol consumption, and annual family incomes and level of HDL

CHAPTER V

DISCUSSION AND CONCLUSIONS

The association of vascular or renal comorbidities with AMD has been reported inconsistently with some studies showing a significant association, and others not showing the association. To our knowledge, this study is first to investigate a relationship of combination of these comorbidities with AMD by utilizing the large nationally representative sample of US. We found that the prevalence of six vascular and renal conditions (AP, CHD, CHF, MI, Stroke and CKD) among individuals with AMD was significantly higher than those without AMD. Each of six comorbidities was significantly associated with AMD by the analysis of univariate logistic regression, respectively; whereas, the association was no longer existing in individuals with AP, other conditions remained the association, after controlling for age, gender, race/ethnicity, family annual income, smoking status, alcohol consumption and the level of HDL. Comparing to individuals without three conditions (HD, Stroke and CKD), the crude ORs of AMD increased 2-fold with the presence of any one and 4-fold with any two conditions and more, respectively. The adjusted ORs were attenuated, but remained significantly difference. Furthermore, the individuals with both stroke and CKD were strongly associated with AMD. Correspondently, we found that the prevalence of both stroke and CKD among individuals with AMD were approximately 3 times higher than those among individuals without AMD. Similar results were observed in early AMD. The findings may provide insight for appropriate preventive measurement for health care management.

Our results indicate that there is an association of vascular and renal comorbidities with AMD. Several possible reasons that would explain it. AMD shares common risk factors with these comorbidities, for example, smoking (Erke et al., 2014; Snow & Seddon, 1999). The pathological regions for these three comorbidities are all involved with the abnormalities of blood vessels. The abnormalities are commonly correlated to atherosclerosis. AMD shares pathological similarities with atherosclerosis (Machalinska, Kawa, Marlicz, & Machalinski, 2012). According to the association seen in this study, a potential hypothesis is that atherosclerosis occurred at the choroidial circulation may contribute to the development of AMD. Dyslipidemia is well-known risk factor of vascular diseases. Reducing the level of HDL could lead to preventive outcomes (Schaefer, 2012). The high level of HDL seen in the AMD participants in this study reveals that the dyslipidemia may be a common risk factor of AMD and vascular and renal diseases. It shed the light that reducing the level of HDL would lead to the potential prevention of development of AMD. The most recent study revealed an association of cholesteryl ester transfer protein (CETP) gene with neovascular AMD (Liu et al., 2014), Out results might indicate a potential to investigate the gene-related relationship not only in neovascuar AMD, but in all type of AMD.

The most interesting finding of this study is a strong relationship of combination of stroke and CKD with AMD. Microvascular alteration in the retinal circulation and the retinal pigment epithelium play important roles in the pathology of AMD. Kidney damage generally is considered from burden of microvascular and systematic epithelium. Furthermore, genetic predisposition of kidney disease and AMD share similar involvement of alternative complement pathway (Ansari et al., 2013; Ma et al., 2014;

Zhan et al., 2013). Both common shared pathological pathways and genetic predisposition similarities, therefore, may explain the strong association of the combination of the comorbidities with AMD, particularly in the combination of stroke and CKD. .

There are important implications of our results. The estimates of prevalence in this study provide the probabilities of presence of these comorbidities, the presence of higher probabilities among individuals with AMD compared with those without AMD should trigger a further longitudinal study for the potential coexistence of these comorbidities. If there is temporal relationship between comorbidities and AMD, these vascular and renal comorbidities will need to be recognized as a potential risk factor of AMD. These comorbidities should be managed and measured in the AMD care management.

Management of AMD should take into account these vascular and renal diseases because coexisting these comorbidities and AMD will lead the worse health outcome. These comorbidities could be potential risk factor indicators for eye care management in order to early detect AMD. For example, increased frequency of regular eye examination among people who have these comorbidities would be ideal. Furthermore, the preventive strategies and managements for vascular and renal disease could be applied to AMD-risk population. For instance, change in the life style behavior, such as physical activity.

Strengths and limitation of this study deserve to be discussed. This study was using nationally representatively sample of US with a continuous 2 years surveys, therefore, the results more likely lead to generalizability of US population. Also,

standardized retinal image examination was conducted to our study, and individuals with a completion of the retinal image examination were include in the study population to determine the presence of drusen and pigment alteration, this minimized the misclassification of diagnosis of AMD, while the cross-sectional study design can not address a potential temporal relationship between these comorbidities and AMD. Further research for longitudinal studies would be desirable to investigate the plausible relationship. In order to minimize the misclassification from self-reported diagnosis for the comorbidities related to heart diseases, the variable of heart disease was defined by mutual exclusive of each heart condition. Thus, it is unlikely that misclassification of diagnosis would explain the strong association observed in this study.

In conclusion, these findings from a nationally representative US population highlight the remarkable association between vascular and renal comorbidities of AMD. Give the worse outcome of AMD associated with these comorbidities, these comorbidities should be take account into the eye care management for not only AMD patient, but also AMD-risk population. The preventive strategies for vascular and renal conditions should be preferred to be applied to AMD care management.

ABBREVIATIONS

AP: Angina Pectoris

AMD: Age-related macular degeneration

CHD: Coronary heart disease

CHF: Congestive heart failure

CI: Confidence Interval

HD: Heart disease

MI: Myocardial Infarction

CKD: Chronic kidney disease

REFERENCES

Akpek, E. K., & Smith, R. A. (2013). Current treatment strategies for age-related ocular conditions. *Am J Manag Care, 19*(5 Suppl), S76-84.

Ansari, M., McKeigue, P. M., Skerka, C., Hayward, C., Rudan, I., Vitart, V., et al. (2013). Genetic influences on plasma CFH and CFHR1 concentrations and their role in susceptibility to age-related macular degeneration. *Hum Mol Genet, 22*(23), 4857-4869.

Bourne, R., Price, H., Taylor, H., Leasher, J., Keeffe, J., Glanville, J., et al. (2013). New systematic review methodology for visual impairment and blindness for the 2010 Global Burden of Disease study. *Ophthalmic Epidemiol, 20*(1), 33-39.

Bowling, C. B., Sharma, P., Fox, C. S., O'Hare, A. M., & Muntner, P. (2013). Prevalence of reduced estimated glomerular filtration rate among the oldest old from 1988-1994 through 2005-2010. *JAMA, 310*(12), 1284-1286.

Chaine, G., Hullo, A., Sahel, J., Soubrane, G., Espinasse-Berrod, M. A., Schutz, D., et al. (1998). Case-control study of the risk factors for age related macular degeneration. France-DMLA Study Group. *Br J Ophthalmol, 82*(9), 996-1002.

Chakravarthy, U., Wong, T. Y., Fletcher, A., Piault, E., Evans, C., Zlateva, G., et al. (2010). Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. *BMC Ophthalmol, 10*, 31.

Cherepanoff, S., McMenamin, P., Gillies, M. C., Kettle, E., & Sarks, S. H. (2010). Bruch's membrane and choroidal macrophages in early and advanced age-related macular degeneration. *Br J Ophthalmol, 94*(7), 918-925.

Chew, E. Y., Clemons, T. E., Agron, E., Sperduto, R. D., Sangiovanni, J. P., Kurinij, N., et al. (2013). Long-term effects of vitamins C and E, beta-carotene, and zinc on age-related macular degeneration: AREDS report no. 35. *Ophthalmology, 120*(8), 1604-1611 e1604.

Choi, J., Moon, J. W., & Shin, H. J. (2011). Chronic kidney disease, early age-related macular degeneration, and peripheral retinal drusen. *Ophthalmic Epidemiol, 18*(6), 259-263.

Chou, C. F., Cotch, M. F., Vitale, S., Zhang, X., Klein, R., Friedman, D. S., et al. (2013). Age-related eye diseases and visual impairment among U.S. adults. *Am J Prev Med, 45*(1), 29-35.

Donnan, G. A., Fisher, M., Macleod, M., & Davis, S. M. (2008). Stroke. *Lancet, 371*(9624), 1612-1623.

Duan, Y., Mo, J., Klein, R., Scott, I. U., Lin, H. M., Caulfield, J., et al. (2007). Age-related macular degeneration is associated with incident myocardial infarction among elderly Americans. *Ophthalmology, 114*(4), 732-737.

Erke, M. G., Bertelsen, G., Peto, T., Sjolie, A. K., Lindekleiv, H., & Njolstad, I. (2014). Cardiovascular risk factors associated with age-related macular degeneration: the Tromso Study. *Acta Ophthalmol*.

Fagerness, J. A., Maller, J. B., Neale, B. M., Reynolds, R. C., Daly, M. J., & Seddon, J. M. (2009). Variation near complement factor I is associated with risk of advanced AMD. *Eur J Hum Genet, 17*(1), 100-104.

Fernandez, A. B., Wong, T. Y., Klein, R., Collins, D., Burke, G., Cotch, M. F., et al. (2012). Age-related macular degeneration and incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. *Ophthalmology, 119*(4), 765-770.

Foran, S., Wang, J. J., & Mitchell, P. (2003). Causes of visual impairment in two older population cross-sections: the Blue Mountains Eye Study. *Ophthalmic Epidemiol, 10*(4), 215-225.

Gao, B., Zhu, L., Pan, Y., Yang, S., Zhang, L., & Wang, H. (2011). Ocular fundus pathology and chronic kidney disease in a Chinese population. *BMC Nephrol, 12*, 62.

Go, A. S., Mozaffarian, D., Roger, V. L., Benjamin, E. J., Berry, J. D., Borden, W. B., et al. (2013). Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation, 127*(1), e6-e245.

Golan, S., Shalev, V., Goldstein, M., Treister, G., Chodick, G., & Loewenstein, A. (2011). The rate of myocardial infarction events among patients with age-related macular degeneration: a population-based study. *Graefes Arch Clin Exp Ophthalmol, 249*(2), 179-182.

Heurich, M., Martinez-Barricarte, R., Francis, N. J., Roberts, D. L., Rodriguez de Cordoba, S., Morgan, B. P., et al. (2011). Common polymorphisms in C3, factor B, and factor H collaborate to determine systemic complement activity and disease risk. *Proc Natl Acad Sci U S A, 108*(21), 8761-8766.

Hollyfield, J. G., Bonilha, V. L., Rayborn, M. E., Yang, X., Shadrach, K. G., Lu, L., et al. (2008). Oxidative damage-induced inflammation initiates age-related macular degeneration. *Nat Med, 14*(2), 194-198.

Hu, C. C., Ho, J. D., & Lin, H. C. (2010). Neovascular age-related macular degeneration and the risk of stroke: a 5-year population-based follow-up study. *Stroke, 41*(4), 613-617.

Ikram, M. K., Mitchell, P., Klein, R., Sharrett, A. R., Couper, D. J., & Wong, T. Y. (2012). Age-related macular degeneration and long-term risk of stroke subtypes. *Stroke, 43*(6), 1681-1683.

Klein, R., Chou, C. F., Klein, B. E., Zhang, X., Meuer, S. M., & Saaddine, J. B. (2011). Prevalence of age-related macular degeneration in the US population. *Arch Ophthalmol, 129*(1), 75-80.
Klein, R., Cruickshanks, K. J., Myers, C. E., Sivakumaran, T. A., Iyengar, S. K., Meuer, S. M., et al. (2013). The relationship of atherosclerosis to the 10-year cumulative incidence of age-related macular degeneration: the Beaver Dam studies. *Ophthalmology, 120*(5), 1012-1019.
Klein, R., Cruickshanks, K. J., Nash, S. D., Krantz, E. M., Nieto, F. J., Huang, G. H., et al. (2010). The prevalence of age-related macular degeneration and associated risk factors. *Arch Ophthalmol, 128*(6), 750-758.
Klein, R., Davis, M. D., Magli, Y. L., Segal, P., Klein, B. E., & Hubbard, L. (1991). The Wisconsin age-related maculopathy grading system. *Ophthalmology, 98*(7), 1128-1134.
Klein, R., Klein, B. E., Jensen, S. C., Mares-Perlman, J. A., Cruickshanks, K. J., & Palta, M. (1999). Age-related maculopathy in a multiracial United States population: the National Health and Nutrition Examination Survey III. *Ophthalmology, 106*(6), 1056-1065.
Klein, R., Klein, B. E., Knudtson, M. D., Meuer, S. M., Swift, M., & Gangnon, R. E. (2007). Fifteen-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study. *Ophthalmology, 114*(2), 253-262.
Klein, R., Knudtson, M. D., Lee, K. E., & Klein, B. E. (2009). Serum cystatin C level, kidney disease markers, and incidence of age-related macular degeneration: the Beaver Dam Eye Study. *Arch Ophthalmol, 127*(2), 193-199.
Leibowitz, H. M., Krueger, D. E., Maunder, L. R., Milton, R. C., Kini, M. M., Kahn, H. A., et al. (1980). The Framingham Eye Study monograph: An ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration, and visual acuity in a general population of 2631 adults, 1973-1975. *Surv Ophthalmol, 24*(Suppl), 335-610.
Lengyel, I., Tufail, A., Hosaini, H. A., Luthert, P., Bird, A. C., & Jeffery, G. (2004). Association of drusen deposition with choroidal intercapillary pillars in the aging human eye. *Invest Ophthalmol Vis Sci, 45*(9), 2886-2892.
Liew, G., Mitchell, P., Wong, T. Y., Iyengar, S. K., & Wang, J. J. (2008). CKD increases the risk of age-related macular degeneration. *J Am Soc Nephrol, 19*(4), 806-811.
Liu, K., Chen, L. J., Lai, T. Y., Tam, P. O., Ho, M., Chiang, S. W., et al. (2014). Genes in the High-Density Lipoprotein Metabolic Pathway in Age-related Macular Degeneration and Polypoidal Choroidal Vasculopathy. *Ophthalmology, 121*(4), 911-916.
Liutkeviciene, R., Lesauskaite, V., Zaliuniene, D., Zaliaduonyte-Peksiene, D., Cimbalas, A., Jasinskas, V., et al. (2012). Early age-related macular degeneration in patients with myocardial infarction. *Curr Eye Res, 37*(2), 94-100.
Ma, R., Cui, Z., Hu, S. Y., Jia, X. Y., Yang, R., Zheng, X., et al. (2014). The alternative pathway of complement activation may be involved in the renal damage of human anti-glomerular basement membrane disease. *PLoS One, 9*(3), e91250.
Machalinska, A., Kawa, M. P., Marlicz, W., & Machalinski, B. (2012). Complement system activation and endothelial dysfunction in patients with age-related macular degeneration (AMD): possible relationship between AMD and atherosclerosis. *Acta Ophthalmol, 90*(8), 695-703.
Nguyen-Khoa, B. A., Goehring, E. L., Jr., Werther, W., Gower, E. W., Do, D. V., & Jones, J. K. (2008). Hospitalized cardiovascular diseases in neovascular age-related macular degeneration. *Arch Ophthalmol, 126*(9), 1280-1286.
Nitsch, D., Evans, J., Roderick, P. J., Smeeth, L., & Fletcher, A. E. (2009). Associations between chronic kidney disease and age-related macular degeneration. *Ophthalmic Epidemiol, 16*(3), 181-186.
Owen, C. G., Jarrar, Z., Wormald, R., Cook, D. G., Fletcher, A. E., & Rudnicka, A. R. (2012). The estimated prevalence and incidence of late stage age related macular degeneration in the UK. *Br J Ophthalmol, 96*(5), 752-756.
Rosamond, W., Flegal, K., Furie, K., Go, A., Greenlund, K., Haase, N., et al. (2008). Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation, 117*(4), e25-146.
Schaefer, J. R. (2012). [HDL level or HDL function as the primary target in preventive cardiology]. *Herz, 37*(1), 51-55.
Snow, K. K., & Seddon, J. M. (1999). Do age-related macular degeneration and cardiovascular disease share common antecedents? *Ophthalmic Epidemiol, 6*(2), 125-143.
Sun, C., Klein, R., & Wong, T. Y. (2009). Age-related macular degeneration and risk of coronary heart disease and stroke: the Cardiovascular Health Study. *Ophthalmology, 116*(10), 1913-1919.

Tan, J. S., Wang, J. J., Liew, G., Rochtchina, E., & Mitchell, P. (2008). Age-related macular degeneration and mortality from cardiovascular disease or stroke. *Br J Ophthalmol, 92*(4), 509-512.
Tomany, S. C., Wang, J. J., Van Leeuwen, R., Klein, R., Mitchell, P., Vingerling, J. R., et al. (2004). Risk factors for incident age-related macular degeneration: pooled findings from 3 continents. *Ophthalmology, 111*(7), 1280-1287.
van Lookeren Campagne, M., LeCouter, J., Yaspan, B. L., & Ye, W. (2014). Mechanisms of age-related macular degeneration and therapeutic opportunities. *J Pathol, 232*(2), 151-164.
Whitcup, S. M., Sodhi, A., Atkinson, J. P., Holers, V. M., Sinha, D., Rohrer, B., et al. (2013). The role of the immune response in age-related macular degeneration. *Int J Inflam, 2013*, 348092.
Wieberdink, R. G., Ho, L., Ikram, M. K., Koudstaal, P. J., Hofman, A., de Jong, P. T., et al. (2011). Age-related macular degeneration and the risk of stroke: the Rotterdam study. *Stroke, 42*(8), 2138-2142.
Wlodarek, D., & Glabska, D. (2011). [Influence of the lutein-rich products consumption on its supply in diet of individuals with age-related macular degeneration (AMD)]. *Klin Oczna, 113*(1-3), 42-46.
Wolff, J. L., Starfield, B., & Anderson, G. (2002). Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med, 162*(20), 2269-2276.
Wong, T. Y., Klein, R., Sun, C., Mitchell, P., Couper, D. J., Lai, H., et al. (2006). Age-related macular degeneration and risk for stroke. *Ann Intern Med, 145*(2), 98-106.
Wong, T. Y., Tikellis, G., Sun, C., Klein, R., Couper, D. J., & Sharrett, A. R. (2007). Age-related macular degeneration and risk of coronary heart disease: the Atherosclerosis Risk in Communities Study. *Ophthalmology, 114*(1), 86-91.
Zhan, X., Larson, D. E., Wang, C., Koboldt, D. C., Sergeev, Y. V., Fulton, R. S., et al. (2013). Identification of a rare coding variant in complement 3 associated with age-related macular degeneration. *Nat Genet, 45*(11), 1375-1379.
Zweifel, S. A., Imamura, Y., Spaide, T. C., Fujiwara, T., & Spaide, R. F. (2010). Prevalence and significance of subretinal drusenoid deposits (reticular pseudodrusen) in age-related macular degeneration. *Ophthalmology, 117*(9), 1775-1781.