Age-Related Macular Degeneration Is Associated with Incident Myocardial Infarction among Elderly Americans

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Objective: To investigate whether age-related macular degeneration (AMD) is associated with the development of myocardial infarction (MI) among elderly Americans.

Design: Population-based cross-sectional and cohort study.

Participants: Five percent random sample of 2000 to 2003 Medicare enrollees.

Methods: The cross-sectional study included the first 2-year (2000 and 2001) enrollees who were aged ≥65 years (n = 1 519 086). The cohort study included only baseline MI-free enrollees (n = 1 445 677).

Main Outcome Measures: Chronic conditions (AMD and type, history of MI, hypertension, and diabetes) were defined based on any occurrence of relevant International Classification of Diseases 9 codes in relevant diagnosis fields of the baseline Medicare claim files. A total of 56 611 incident MI cases were identified from the follow-up data (2002 and 2003).

Results: Baseline mean age was 76 years, with 60% women and 88% whites. The prevalence of neovascular AMD was 2.2% (2.3% in women vs. 1.7% in men and 2.3% in whites vs. 1.2% in blacks; $P<0.01$ for both gender and race differences). The prevalence of nonneovascular AMD was 8.8% (9.9% in women vs. 7.3% in men and 9.5% in whites vs. 4.3% in blacks; $P<0.01$ for both gender and race differences). Baseline age-, gender-, and race-adjusted prevalences of hypertension, diabetes, and history of MI were 75%, 33%, and 5.00%, respectively, in the neovascular AMD group. In contrast, they were 73%, 27%, and 4.68% in the nonneovascular AMD group, and 65%, 25%, and 4.54% in the non-AMD group ($P<0.01$ for comparing the prevalence in neovascular and nonneovascular AMD vs. non-AMD groups). Prospectively, baseline age-, gender-, race-, hypertension-, and diabetes-adjusted 2-year incident odds ratios and 95% confidence intervals of MI associated with AMD are 1.19 (1.16–1.22) for all persons with AMD, 1.26 (1.20–1.33) for neovascular AMD, and 1.18 (1.14–1.21) for nonneovascular AMD.

Conclusions: AMD is associated with older age, female gender, being white, and having a history of MI, hypertension, and diabetes. Furthermore, presence of AMD, especially neovascular AMD, is prospectively associated with a higher risk of incident MI. These findings, if confirmed by other studies that control for smoking and other lifestyle covariables, suggest the possibility of shared common antecedents between MI and AMD.
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Age-related macular degeneration (AMD) is a disease characterized by progressive degenerative abnormalities in the macula. Age-related macular degeneration is classified into 1 of 2 general subgroups—the nonneovascular (nonexudative) form of the disease and the neovascular (exudative) form of the disease. The nonneovascular form of AMD is more prevalent, accounting for approximately 90% of all AMD cases, and is often characterized by a slow degeneration of the macula resulting in atrophy of the central retina with gradual vision loss over a period of years. By contrast, neovascular AMD, although less prevalent, more commonly causes sudden, often substantial, loss of central vision and is responsible for most cases of severe loss of visual acuity in this disease.[1] However, the etiology of AMD is poorly understood. Genetic factors[2,3]; smoking[4,5]; and, less consistently, oxidative stress, long-term exposure to sunlight, or low levels of antioxidants[6,7]; nutritional factors[8]; obesity[9,10]; and lipid levels[11,12] have been implicated as possible etiological factors for the development of AMD. Many of these factors are traditional risk factors for cardiovascular disease, the leading cause of death in the United States and other developed countries. The current study was conducted in 2 phases: phase I as a cross-sectional investigation of associations between AMD and risk factors and comorbidity, and phase II to investigate whether baseline AMD (espe-

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Table 1. Demographic Characteristics and Adjusted* Prevalence and 95% Confidence Intervals of Comorbidity at Baseline (2000–2001)

	Non-AMD (n = 1 352 052)	Neovascular AMD (n = 32 788)	Nonneovascular AMD (n = 134 246)
Age (yrs) (standard deviation)	75 (7.7)	80 (7.2)	80 (7.5)
Women (%)	59	65	67
White (%)	87	93	94
Hypertension*	65 (64.9–65.0)	75 (74.7–75.7)	73 (72.4–72.9)
Diabetes*	25 (24.6–24.7)	33 (32.0–33.1)	27 (26.4–26.9)
MI*	4.54 (4.51–4.58)	5.00 (4.78–5.22)	4.68 (4.57–4.79)

AMD = age-related macular degeneration; MI = myocardial infarction. *Adjusted for age, gender, and race.

cially neovascular AMD) is related to the development of incident MI among elderly Americans.

Population and Methods

Study Population

The official 5% random sample of 2000 to 2003 Medicare beneficiaries data and medical reimbursement claims data (including the research identifiable Carrier files, inpatient and outpatient files, and enrollment demographic files) obtained from Center for Medicare and Medicaid Services were employed for this study. Specifically, all enrollees from this sample during the first 2 years (January 1, 2000, to December 31, 2001) formed a cohort of persons aged ≥65 years (n = 1 519 086), after excluding persons enrolled in Medicare before 65 years of age and persons with conflicting demographic information (date of birth, race, or gender) in the Center for Medicare and Medicaid Services demographic databases from different years. These data were used for the phase I cross-sectional investigation of the associations with AMD. From the baseline cohort, we excluded 73 409 persons who had a documented MI during the baseline period, and derived our follow-up cohort (n = 1 445 677). This baseline MI-free cohort is the study population for the phase II follow-up study (January 1, 2002, to December 31, 2003) of the prospective relationship between baseline AMD and the incident MI.

Definitions of Key Variables

Baseline demographic variables and the history of medical conditions (AMD, MI, hypertension, and diabetes) during the 2-year baseline period of January 1, 2000, to December 31, 2001 were extracted from the Medicare Claims database based on any occurrence of relevant International Classification of Diseases 9 (ICD9) codes in either the "Claim Diagnosis Code" or the "Line Diagnosis Code" field of the Medicare claim files.

Neovascular Age-Related Macular Degeneration. A person was identified as having neovascular AMD if there was any occurrence of the following ICD9 codes: 362.42–362.43, serous or hemorrhagic detachment of retinal pigment epithelium; 362.52, exudative senile macular degeneration of retina; or 362.53, cystoid macular degeneration of retina.[13,14]

Nonneovascular Age-Related Macular Degeneration. A person was identified as having nonneovascular AMD if the person did not have neovascular AMD, but had any occurrence of the following ICD9 codes: 362.5, degeneration of macula and posterior pole; 362.50, unspecified macular degeneration (senile) of retina; 362.51, nonexudative senile macular degeneration of retina; or 362.57, drusen (degenerative) of retina.[13,14]

Hypertension. A person was identified as having hypertension if there was any occurrence of the following ICD9 codes: 401.0–401.9, essential hypertension; 402.00–402.91, hypertensive heart disease; 403.00–403.91, hypertensive renal disease; or 404.00–404.93, hypertensive heart and renal disease.

Diabetes. A person was identified as having diabetes if there was any occurrence of the following ICD9 codes: 250.00–250.93, diabetes; 357.2, polyneuropathy in diabetes; 362.01, background diabetic retinopathy; 362.02, proliferative diabetic retinopathy; or 366.41, diabetic cataract.

History of Myocardial Infarction. A person was identified as having a history of MI if there was any occurrence of the following ICD9 codes: 410.00–410.92, acute MI.

Incident Myocardial Infarction. Among baseline MI-free persons, a person was identified as having had an incident MI if there was any occurrence of the following ICD9 codes during the 2-year follow-up period (January 1, 2002, to December 31, 2003): 410.00–410.92, acute MI.

Analysis Methods

Cross-sectional and prospective cohort designs were used for phase I and phase II investigations, respectively. In the phase I investigation, the means (standard deviations [SDs]) or proportions of demographic variables and comorbidity were calculated. Logistic regression models were used to obtain multivariable adjusted prevalence and 95% confidence intervals (CI) of comorbidity. In the phase II investigation, logistic regression models were also used to estimate the multivariable adjusted, as well as stratified, incident odds ratio and 95% CI of MI associated with baseline AMD. To eliminate confounding by age, we stratified all major analysis by 5-year age groups and adjusted for age within each age stratum. All analyses were performed using SAS software (version 9.13, SAS Institute, Cary, NC).

Results

From the 5% Medicare random sample of 2000 to 2001 data, we identified 1 519 086 individuals as the cross-sectional study population. Among them, 11% (n = 167 034) were classified as having AMD. The overall prevalence of neovascular AMD was 2.2%, with 2.3% in women versus 1.7% in men and 2.3% in whites versus 1.2% in blacks ($P<0.01$ for gender and race differences). The prevalence of nonneovascular AMD was 8.8%, with 9.9% in women versus 7.3% in men and 9.5% in whites versus 4.3% in blacks ($P<0.01$ for gender and race differences). The descriptive characteristics of the study population at baseline are summarized in Table 1. Briefly, the average age of the baseline cohort was 76 years (SD = 7.8), with 60% women and 88% whites. Among the non-AMD group, the average age was 75 years, with 59% women and 87% whites. In contrast, among the neovascular AMD group, the average age was 80 years, with 65% women and 93% whites; and among the nonneovascular AMD group, the mean age was 80 years, with 67% women and 94% whites. The prevalence of MI was higher among persons with AMD than among persons without AMD after adjusting for age, gender, race, prevalence of hypertension, and prevalence of diabetes. The similarly adjusted odds ratio (95% CI) of history of MI associated with neovascular AMD is 1.09 (1.04–1.14); nonneovascular AMD, 1.01 (0.98–1.03); and both types of AMD combined, 1.03 (1.00–10.4).

Table 2. Age-Adjusted* Prevalence (%) and 95% Confidence Intervals of Selected Demographic

	Non-AMD				Neovascular	
	65–69 (359 644)	*70–74 (328 519)*	*75–79 (282 807)*	*≥80 (381 082)*	*65–69 (2868)*	*70–74 (5200)*
Gender (% women)	55 (54.5–54.9)	56 (55.7–56.1)	59 (58.4–58.8)	67 (66.8–67.1)	58 (55.9–59.5)	59 (57.4–60.1)
Race (% White)	87 (86.6–86.8)	86 (86.3–86.6)	87 (87.0–87.3)	88 (87.5–87.7)	88 (87.2–89.6)	90 (89.2–90.8)
Hypertension (%)	57 (57.1–57.4)	64 (64.1–64.4)	68 (68.2–68.6)	69 (68.6–68.9)	70 (67.9–71.3)	74 (72.4–74.8)
Diabetes (%)	23 (23.3–23.6)	26 (25.8–26.1)	27 (26.8–27.2)	24 (23.9–24.2)	43 (41.1–44.7)	38 (36.2–38.8)
Myocardial infarction (%)	3.0 (3.0–3.1)	4.1 (4.0–4.2)	5.1 (5.0–5.2)	6.7 (6.6–6.8)	4.0 (3.4–4.8)	5.2 (4.6–5.8)

AMD = age-related macular degeneration.
*Also adjusted to the mean age of each age group.

The distributions of demographic characteristics and comorbidity by age groups are presented in Table 2. These data show a consistent pattern of association between AMD and gender, race, hypertension, diabetes, and MI, cross-sectionally in each of the age strata, and the pattern remains unchanged even after adjusting for age within each age stratum.

For the prospective investigation (phase II), we excluded 73 409 persons who were identified as having a history of MI during the baseline period, resulting in a baseline MI-free population of 1 445 677 individuals for the phase II investigation. During the 2-year follow-up period (2002–2003), a total of 56 611 cases of incident MI were identified, with a 2-year cumulative incidence of 3.9%. In this baseline MI-free population, 89.1% were non-AMD and 10.9% had AMD (with 19.6% neovascular AMD and 80.4% nonneovascular AMD). As shown in Table 3, the age-, race-, and gender-adjusted 2-year cumulative incidences (95% CI) of MI were 4.38% (4.18–4.59), 4.09% (3.99–4.20), and 3.50% (3.47–3.54) among persons with neovascular AMD, nonneovascular AMD, and without AMD, respectively. Table 4 presents the age-, gender-, race-, hypertension-, and diabetes-adjusted 2-year incident odds ratios and 95% CI of MI associated with AMD, in all-age combined and stratified by age group. In the all-age group, the odds ratios (95% CI) of incident MI were 1.26 (1.20–1.33), 1.18 (1.14–1.21), and 1.19 (1.16–1.22) comparing neovascular AMD, nonneovascular AMD, and all AMD to the group without AMD (referent group), respectively. These prospective data showed a consistent pattern of significant associations between baseline AMD and the development of MI, across all age strata, and the associations remain statistically significant after adjusting for demographic variables, comorbid chronic conditions, and age within each age stratum. Stratification by AMD type demonstrated that the magnitude of association was stronger for neovascular AMD than for nonneovascular AMD, in all age combined and every age stratum (Table 4).

Discussion

Age-related macular degeneration is highly prevalent among persons ≥ 65 years of age. An earlier study (1980) estimated that 6% of the U.S. population aged 65 to 74 years and 20% of those > 75 years are affected by AMD,[15] which causes 54% of legal blindness in persons ≥ 65 years of age.[15] Because of the increasing life expectancy in developed and developing countries, the elderly sector of the general population is expected to increase at the greatest rate in the coming decades. It was recently estimated that 1.56 million U.S. citizens aged ≥65 years are affected by neovascular AMD, and this number is estimated to increase to almost 3 million by 2020.[16] Data from 1 study suggested that the 5-year incidence of neovascular AMD, which has been reported to be responsible for 90% of severe vision loss associated with AMD in Medicare beneficiaries, was 18.7 per 1000.[14] Several epidemiologic studies have provided data concerning risk factors associated with AMD. The most consistently identified risk factors include older age, female gender, white ethnicity, cigarette smoking, as well as long-term exposure to light, nutritional factors, obesity, and elevated cholesterol levels.[1–12] However, the pathologic processes through which these factors may contribute to AMD remain poorly understood.

Findings from our cross-sectional investigation show that AMD is associated with older age, female gender, and white race, and that AMD, especially neovascular AMD, is associated with the presence of systemic hypertension, diabetes mellitus, and a history of MI, independent of age, gender, and race. Others have reported that women and whites are at higher risk of AMD.[13–16] The associations between AMD and hypertension and diabetes mellitus have been found to be inconsistent,[17–29] with some studies showing significant associations and others showing no association.

In the current study, AMD is cross-sectionally associated with a history of MI when compared with non-AMD patients. Most important, in the prospective analysis, baseline AMD is significantly associated with the development of incident MI. The AMD and MI relation was stronger for neovascular AMD. These findings remained statistically significant after adjusting for potential confounding factors, including age, race, gender, and comorbidities, such as diabetes and hypertension status. The association between AMD and incident MI was consistent across different age strata, even after adjusting for age within each age stratum. Furthermore, the age group stratified results consistently show that the association between AMD and incident MI is slightly more pronounced among the older age group than among the younger age group. For example, baseline AMD (both types combined) is associated with a 10% higher risk (odds ratio 1.10) of incident MI among those <70 years of age, in contrast to a 22% higher risk (odds ratio 1.22) among persons ≥ 80 years. The stratified results also show that both neovascular AMD and nonneovascular AMD were associated with incident MI, but the former was a stronger predictor than the latter. For example, baseline neovascular AMD is associated with a 26% higher risk of incident MI compared to the group without AMD, in contrast to an 18%

Characteristics and Comorbidity, Stratified by Age Group at Baseline (2000–2001)

AMD		Nonneovascular AMD			
75–79 (7736)	*≥80 (16 984)*	*65–69 (11 653)*	*70–74 (21 573)*	*75–79 (30 197)*	*≥80 (70 823)*
62 (61.1–63.2)	69 (68.6–69.9)	63 (61.7–63.4)	62 (61.7–63.0)	64 (63.5–64.5)	71 (70.8–71.4)
93 (92.6–93.7)	95 (95.1–95.7)	91 (90.3–91.4)	92 (91.6–92.3)	93 (92.7–93.3)	95 (94.5–94.9)
75 (74.5–76.4)	78 (77.5–78.8)	63 (62.2–64.0)	70 (69.1–70.3)	74 (73.6–74.6)	77 (76.6–77.2)
34 (32.5–34.6)	27 (25.9–27.3)	26 (25.6–27.2)	27 (26.7–27.8)	28 (27.3–28.4)	24 (23.8–24.5)
5.6 (5.1–6.1)	6.7 (6.3–7.1)	3.1 (2.8–3.5)	4.0 (3.8–4.3)	5.0 (4.8–5.3)	6.7 (6.5–6.9)

higher risk among persons with nonneovascular AMD when compared to the group without AMD. The magnitude of association between AMD and MI is stronger from the prospective analysis than from the cross-sectional analysis. This may be due to the methodologic differences of 2 analytical approaches. In summary, to our knowledge, this is the first large-scale population-based study to demonstrate a significant prospective association between AMD and MI. These data suggest that AMD and MI may share some common antecedents. We speculate that the presence of AMD is a risk indicator of higher levels of various factors such as cigarette smoking, inflammation,[30] and arthrosclerosis,[22,31] which were not assessed in this study. Although not adjusted for these "not measured" confounding factors, these weak associations (all odds ratios < 2.00) suggest that AMD is a "minor" predictor of acute MI under an etiologic model. By contrast, a public health perspective argues that estimates of the magnitude observed in this study would have a significant impact on the population's health, because of the high prevalence of AMD among elderly individuals.

Medicare claims data from Medicare beneficiaries have been used for various research projects. The enrollment rate in the Medicare system among American elderly population remains extremely high; for example, there are currently about 40 million Americans age ≥65 years enrolled in Medicare, which accounts for approximately 98% of elderly Americans. Thus, medical claims data from these Medicare beneficiaries provide a very large sample size, which would be unmatchable by any other population-based studies. Additionally, Medicare data are the greatest representative sample of the U.S. population aged ≥65 years. However, there are limitations of using Medicare claims data. First, the sensitivity and specificity for the diagnosis of chronic conditions vary in the Medicare claims data. For example, in a study comparing claims-based ICD9 codes with hospital chart review, it was shown that the sensitivity and specificity for claim-based diagnosis of hypertension were 0.61 and 0.95, respectively.[32] In the same study, the sensitivity and specificity for claims-based diagnosis were 0.75 and 0.99 for diabetes, 0.57 and 0.96 for coronary heart diseases, and 0.35 and 0.99 for stroke.[32] In another similar study, the sensitivity and specificity were 0.69 and 0.83 for hypertension, 0.90 and 0.93 for diabetes, 0.58 and 0.93 for heart failure, and 0.68 and 0.95 for glaucoma.[33] We anticipate that our findings would be biased toward the null hypothesis if the misclassification due to limited sensitivity, and to a lesser degree limited specificity, were nondifferential, or if there were similar misclassifications among AMD and non-AMD, and among incident MI and non-MI persons. Similarly, our classifications of AMD and incident MI, the key predictor and outcome variables, were solely based on the claims diagnostic codes, without the ability to obtain results from medical charts pertaining to eye examinations, retinal photographs, blood enzyme assays, regular electrocardiograph, or any other laboratory tests. Therefore, we cannot confirm the diagnosis of various medical conditions analyzed in this study, nor can we provide direct assessment of the sensitivity and specificity of the major variables included in this study. In addition, in this report, ICD9 code 362.53 was used in the algorithm to identify persons with neovascular AMD (to be consistent with the report by Lee et al[14]). In practice, this code is used to code other non-AMD conditions also. We performed 2 additional sensitivity analyses by classifying ICD9 code 362.53 either as nonneovascular or as non-AMD, and the pattern of association did not change meaningfully (data not shown). Second, because the data are claims based, we did not have

Table 3. Multivariable Adjusted* 2-Year Incidence (%) and 95% Confidence Intervals of Myocardial Infarction, Stratified by Age-Related Macular Degeneration (AMD) and Age Group

	All Age Groups (n = 1 445 677)	Age Group (yrs)			
		65–69	*70–74*	*75–79*	*≥80*
Non-AMD	3.50 (3.47–3.54)	2.60 (2.54–2.65)	3.05 (2.99–3.12)	3.76 (3.68–3.83)	4.51 (4.44–4.58)
Neovascular AMD	4.38 (4.18–4.59)	3.48 (2.92–4.14)	3.58 (3.14–4.08)	4.39 (3.97–4.85)	5.68 (5.34–6.04)
Nonneovascular AMD	4.09 (3.99–4.20)	2.68 (2.41–2.98)	3.30 (3.07–3.54)	4.32 (4.09–4.55)	5.39 (5.22–5.56)

*Adjusted for gender, race, hypertension, diabetes, and mean age of each group.

Table 4. Multivariable Adjusted* 2-Year Incident Odds Ratios and 95% Confidence Intervals of Myocardial Infarction, Stratified by Type of Age-Related Macular Degeneration (AMD) and Age Group

	All Age Groups (n = 1 445 677)	Age Group (yrs)			
		65–69	*70–74*	*75–79*	*≥80*
Without AMD (referent)	1.00	1.00	1.00	1.00	1.00
All AMD	1.19 (1.16–1.22)	1.10 (1.00–1.21)	1.11 (1.04–1.19)	1.17 (1.11–1.23)	1.22 (1.18–1.26)
Neovascular AMD	1.26 (1.20–1.33)	1.39 (1.16–1.66)	1.20 (1.04–1.37)	1.18 (1.06–1.32)	1.27 (1.19–1.36)
Nonneovascular AMD	1.18 (1.14–1.21)	1.03 (0.92–1.14)	1.09 (1.01–1.17)	1.16 (1.10–1.23)	1.21 (1.17–1.26)

*Adjusted for age within each age group, gender, race, hypertension, and diabetes. Persons without AMD during baseline period were the referent group.

the ability to ascertain the chronic conditions before the study period. Therefore, we can analyze the chronic conditions only within the study period and assume that the absence of a condition during the baseline period represents a negative history of such condition. For example, when we excluded persons with MI at the baseline period to derive a baseline "MI-free" cohort, we may have misclassified some individuals as "MI-free" because we assumed they did not have a history of MI before 2000. However, it is possible that some individuals in this cohort had an MI before 2000 but did not seek medical services for their past MI during the 2-year baseline period. As a result he/she would be classified as an MI-free person at baseline. Third, we cannot ascertain that a claim for MI diagnosis during the follow-up period is indeed an MI incidence during that period. It is possible that the Medicare service was provided for an MI that occurred before the follow-up period or even before 2000. However, given the clinical characteristics of acute MI and its poor prognosis without medical intervention, we believe that we have a high capture rate for all true MI cases which occurred during this 2-year follow-up period.

Another potential limitation of this study is the unavailability of some established cardiovascular disease risk factors from the claims databases. For example, data on cigarette smoking (both history and intensity), cholesterol level, obesity, physical activity, and alcohol consumption cannot be derived from the Center for Medicare and Medicaid Services database. Therefore, we cannot control for potential confounding by these cardiovascular disease risk factors. Last, reimbursement factors may affect the recording of ICD codes for certain medical conditions; for example, a clinical diagnosis of "rule-out acute MI" may have occurred as an MI code in the claim form for reimbursement purposes. However, there is no evidence suggesting that such reimbursement purpose–oriented "up-coding" is differential by AMD status.

Despite the inherited limitations of using Medicare claims data discussed, our findings suggest that, cross-sectionally, AMD is associated with older age, female gender, and white race. Multiple studies have identified these factors as risk factors for AMD, which supports the validity of our findings from claims-based data. Our findings also indicate that AMD, especially neovascular AMD, is associated with the prevalence of hypertension, diabetes, and a history of MI, independent of age, gender, and race. Most important, our prospective findings indicate that baseline AMD, especially neovascular AMD, is associated with higher risk of incident MI, independent of baseline demographic factors and comorbidity. These findings, if confirmed by other studies that control for smoking and other lifestyle covariables not measured in this study, suggest the possibility of shared common antecedents between MI and AMD.

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