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Age-Related Macular Degeneration and Mortality in Older Women: The Study of Osteoporotic Fractures

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Abstract

OBJECTIVES—To examine the association of age-related macular degeneration (AMD) with all-cause and cause-specific mortality in a population of older women.

DESIGN—Prospective cohort study.

SETTING—Four U.S. clinical centers

PARTICIPANTS—A random sample of 1202 women with graded fundus photographs at year 10 visit of the Study of Osteoporotic Fractures (Mean age =79.5 years).

MEASUREMENTS—Forty-five degree stereoscopic fundus photographs were graded for presence and severity (early vs. late) of AMD. Vital status was adjudicated from death certificates. Cox proportional hazards models, adjusted for appropriate confounders, were used to estimate mortality hazards ratios.

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Author Contributions
Study concept and design: Pedula, Coleman, Ensrud, Hillier
Acquisition of subjects and/or data: Coleman, Yu, Cauley, Ensrud, Hochberg, Hillier
Data analysis and interpretation: Pedula, Coleman, Yu, Cauley, Ensrud, Hochberg, Fink, Hillier
Preparation of manuscript: Pedula, Coleman, Cauley, Ensrud, Hochberg, Fink, Hillier
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RESULTS—Prevalence of *any* AMD was 40.5% at baseline, with 441 (36.7%) having *early* AMD and 46 (3.8%) having *late* AMD. Cumulative mortality was 51.6% in over 15 years of follow-up. Overall, there was no significant association between AMD presence or severity with all-cause or cause-specific mortality. Because there was a significant interaction between AMD and age in predicting mortality ($p<0.05$ for each mortality type) analyses were stratified by age group. Among women younger than 80 years, after adjusting for covariates, *late* AMD was associated with CVD mortality (Hazard ratio[HR], 2.61; 95% confidence interval [CI], 1.05–6.46). Among women 80 years and older, *early* AMD was associated with all-cause (HR, 1.39; 95% CI, 1.11–1.75)and non-CVD/non-cancer (HR, 1.45; 95% CI, 1.05–2.00) mortality. Additionally, a*ny* AMD was associated with all-cause (HR, 1.42; 95% CI, 1.13–1.78) and CVD (HR, 1.45; 95% CI, 1.01–2.09) mortality in women ≥ 80 years.

CONCLUSION—AMD is a predictor of poorer survival among women, especially if 80 or older. Determination of shared risk factors may identify novel pathways for intervention that may reduce the risk of both conditions.

Keywords

age-related macular degeneration; mortality; older women

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of blindness in elderly persons in the developed world.[1–5] While a number of studies have shown an association between visual impairment and survival,[6–10] the findings relating AMD to survival are less consistent.[8,9,11–15] A common rationale is that AMD is associated with other systemic conditions that are risk factors for mortality. Yet, controlling for these risk factors has eliminated the AMD-mortality relationship in some,[9,11,14,15] but not all studies.[8,12,13]Differences in study design, study population, and length of follow-up may explain these differences. Studies that report an association between AMD and mortality, tended to have longer follow-up.[12,13] In fact, Buch et al suggested a follow-up of at least 15 years is necessary to adequately confirm their findings.[12] In addition, very few studies have examined mortality risk due to AMD in the very old, as average baseline ages in prior studies are less than 70 years. If AMD is indeed a predictor of mortality, this could allow for easy risk identification by eye examination when other co-morbidities are not well measured. The aims of this study were to evaluate the relationship of AMD to mortality in a cohort of older women with average age 79.5 years and over 15 years follow-up.

METHODS

Subjects

The Study of Osteoporotic Fractures (SOF) is a multicenter study of women recruited to identify risk factors for osteoporotic fractures and other health outcomes. In 1986–1988 a cohort of 9,704 community-dwelling, ambulatory White women age 65 years or older, irrespective of bone mineral density status, were recruited from four metropolitan areas of the United States. Women unable to walk without assistance and those with bilateral hip

replacements were excluded. Further details of the study have been previously published.[16] Black women were originally excluded from the SOF cohort due to their low incidence of hip fractures. At the year 10 visit in 1997–1998, the cohort was enhanced by the enrollment of 662 Black women. The institutional review boards at each site approved the study, and all women provided written informed consent.

Subjects were eligible for the present study if they had gradable fundus photographs at the year 10 visit. Figure 1 shows the study subject selection and reasons for exclusion. Of the 9,704 White subjects enrolled at baseline, 7008participated in the year 10 visit and 4638 had fundus photographs taken. Of the 662 Black subjects enrolled at this visit, 642 had fundus photographs. Women who did not have fundus photographs were older, less likely to have a clinic visit (visit took place in subject's home, at respite care, or in nursing home: n=548), or less likely to have a complete exam (986 had questionnaire only and 612 limited data collected). As part of a cost-efficient funded study design, arandom sample of 1274 (24%) was selected to be graded for AMD presence and severity. 72 women with ungradeable fundus photographs were excluded, resulting in a total of 1202 for the present study.

Definition of AMD

Two forty-five degree stereoscopic fundus photographs were taken for each eye per subject. They were double-graded for AMD by two independent trained graders in a masked fashion using a modification of the Wisconsin Age-Related Maculopathy Grading System (WARMGS).[17] AMD severity was evaluated using the 6-level severity scale of the Beaver Dam Eye Study[18] that was modified for use with 45-degree stereoscopic photographs. Details of the severity scale used for the SOF study have been previously published.[19] Briefly, early AMD was defined as the presence of soft drusen (≥95 microns (μm) in diameter) and either 1) drusen area < that of a circle with a diameter of 960 μm and retinal pigment epithelial depigmentation present; or 2) drusen area ≥ that of a circle with diameter 960 μm with or without pigmentary abnormalities in at least one eye and without late AMD in either eye. Late AMD was defined as the presence of sub-foveal geographic atrophy or choroidal neovascularization in at least one eye. In cases of a discrepancy in the categorization of presence or severity of AMD, photographs were evaluated by a retina specialist whose grading was taken as the final grade.

Assessment of Mortality

From the year 10 visit (1996–1998) to July 2013,participants were contacted by mail or telephone every 4 months for outcomes and to verify vital status. After more than 15 years of follow-up (median 9.5 years, range 0.1–15.5), these contacts remain over 95% complete. Death certificates, and when available, hospital discharge summaries were physician-adjudicated to determine the primary cause of death, using codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Cardiovascular (CVD) mortality was defined according to ICD-9-CM codes 401–404, 410–414, 425, 428, 429.2, 430–438, and 798. Cancer mortality was defined was defined to include deaths according to ICD-9-CM codes 140–239. Those who were not classified as CVD or cancer-related deaths were considered due to other causes.

Assessment of potential confounders

Demographic characteristics, self-reported health status, history of medical conditions, falls and smoking status were obtained via a questionnaire that was reviewed by trained interviewers. With the exception of clinic, education and ethnicity, all potential confounders were assessed at the same visit that fundus photographs were taken. Ethnicity was self-reported as either White or Black. For medical conditions (diabetes, stroke, hypertension, etc.), the subject was asked if a doctor ever told her that she had the condition. Medication used was determined by questionnaire and from the pill bottles that participants brought to the exam. For self-reported health status and self-reported frailty, subjects were asked to rate their overall health and frailty, compared to others their own age. Regarding walking for exercise, subjects were asked if they walk for exercise (yes/no), defined as walking one block or more without stopping. Functional limitations were assessed by self-report of difficulty performing any of 5 instrumental activities of daily living (IADL) that included walking 2–3 blocks, climbing up 10 steps, preparing meals, heavy housework, and shopping.[20,21]

Clinical characteristics were measured by personnel that were trained using standard protocols. We measured weight and height (by stadiometer) and knee height. Body mass index (BMI) in kilograms per meters squared was calculated with knee height substituted for total height as knee height is less likely to change with age. In addition to self-report, frailty was measured as whether or not the subject could rise up from a chair (without using her arms) five times.

Depression was assessed using the 26-point Geriatric Depression Scale[22] and evaluated on a continuous covariate as well as dichotomized into scores <6 vs. ≥ 6. Cognitive function was assessed using the 30-item mini-mental status exam (MMSE)[23] and evaluated on a continuous scale as well as dichotomized into scores <24 and ≥ 24.

Statistical Analysis

Baseline characteristics were compared using Chi-square, analysis of variance, and t-tests where appropriate. Cox Proportional Hazards models were used to estimate the multivariable-adjusted hazards ratios (HR) relating AMD presence and severity to mortality. Proportionality assumptions were verified prior to HR estimation. Covariates that were associated with mortality in bivariate analyses at the significance level of 0.10 or were clinically relevant in prior studies were initially entered into the full multivariable model. Final models included only those covariates that were significantly associated with mortality at level of $p<0.05$. Interactions between covariates were tested in the same manner. Because there was a significant interaction between age and AMD, we performed stratified analyses in the <80 and ≥ 80 year age groups.

All statistical analyses were performed using SAS version 9.2 statistical software (SAS institute, Cary, NC).

RESULTS

Of the 1202 women with graded photos, there were 487 (40.5%) with AMD, of whom 441(36.7%) had early AMD and 46(3.8%) had late AMD. Table 1 presents participant characteristics according to AMD status. In general, compared to women without AMD, women with early and late AMD were older, more likely to be White, currently unmarried, self-report more frailty, have lower BMI, have fallen in the past year, have worse average MMSE scores and worse GDS scores. There was no difference between women with and without AMD in their use of antihypertensive, anti-hyperlipidemic or anti-depressant medications. However, there was a trend toward less estrogen use among women with AMD. There were no differences among women with and without AMD in self-reported history of a variety of medical conditions including diabetes, hypertension, CHF, COPD, stroke, myocardial infarction, and depression.

Over a 15+ year follow-up period (median 9.5 years; range 0.1–15.5), 620 (51.6%) women died. Causes of death included: CVD (34.0%), Cancer (18.2%), and Other (47.7% which consists of cognitive death, including Alzheimer's and other dementia 11.6%; pulmonary 9.5%; unknown 9.4%; digestive 3.5%; trauma 3.2%; nervous system 2.7%; genitourinary 2.4%; infections 2.0%; other 3.4%). A number of characteristics were bivariately associated with mortality. In the multivariate-adjusted Cox proportional hazards model excluding AMD, participants who died were more likely to be older, White, have lower BMI, have slower walking speed, self-report a history of CHF, COPD, and myocardial infarction, self-report more frailty, self-report having used thiazide diuretics, and score worse on the mini-mental status scale ($p<0.05$ for all, data not shown). With the exception of history of CHF and history of COPD, the same covariates were significantly associated with non-cancer/non-CVD mortality. For CVD mortality, significant covariates included age, race, history of MI, history of CHF, and walking speed. History of MI was the only covariate associated with cancer mortality. Factors tested, that were not independently associated with mortality, include marital status, self-reported health status, need to use arms to rise from chair, number of IADL impairments, pulse, history of fracture after age 50, history of fall in past year, history of depression, history of antihypertensive use, and GDS score.

Cumulative 15-year mortality was 54.6% for women with AMD compared to 49.5% for women without AMD ($p=0.082$). There was not a consistent trend in mortality by AMD level. Overall, AMD presence and severity were not independently associated with survival in the Cox proportional hazards models. However, because there was a significant AMD*age interaction ($p=0.015$ for all-cause mortality), hazards ratios were calculated separately for the two age strata. The covariate-adjusted mortality curves by AMD status (*any* vs.*none*), for women <80 years and ≥80 years are shown in Figures 2a and 2b, respectively. There was no difference in all-cause mortality by AMD status in women younger than 80 years. However, women < 80 years with *late* AMD had 2.6 times increased risk of CVD-death compared to women without AMD (HR, 2.61; 95% CI, 1.05–6.46, Table 2). Among women 80 years and older, those with *any* AMD had a 42% greater risk of all-cause mortality (HR 1.42; 95% CI, 1.13–1.78). Further, *early* AMD was associated with all-cause (HR 1.39; 95% CI, 1.11–1.75) and *any* AMD was associated with CVD (HR 1.45; 95% CI, 1.01–2.09) mortality in women ≥80 years. Finally, in women ≥80 years, risk of

other (non-CVD, non-cancer) mortality was 45% greater in women with *early* AMD compared to none (HR 1.45; 95% CI, 1.05–2.00).

DISCUSSION

In this study of older women, we found that among women aged 80 and older, *any* AMD was related to all-cause and CVD mortality and *early* AMD was associated with all-cause and non-CVD/non-cancer mortality. In women younger than 80, *late* AMD was associated with CVD mortality. To our knowledge, this is the first study to report this relationship between AMD and mortality in the oldest old of women (mean age 79.5 years) with over 15 years subsequent follow-up for mortality. Our results suggest that AMD is a likely indicator of CVD disease severity and can be a useful prognostic marker in identifying women at increased risk of mortality.

Previous studies have shown inconsistent relationships between AMD and mortality. The Copenhagen Eye study[12] found that women with AMD had a 1.6 increased risk of 14-year mortality (HR 1.59, 95% CI 1.23–2.07) and the Blue Mountains Eye Study[13] found a similar risk (HR 1.59, 95% CI 1.04–2.43) in a combined gender analysis. The AREDS study showed that, compared to subjects with few drusen, participants with advanced AMD had increased risk of mortality during a 6.5 year follow-up (relative risk 1.41; 95% CI 1.08–1.86).[8] Associations of AMD with mortality were not statistically significant after covariate adjustment in the Beaver Dam Eye Study, the Beijing Eye Study and the Rotterdam Study.[9,11,15] However, the mean age of participants in these three studies was much younger (range 52–68) than our study, and only the Beaver Dam Eye Study reported follow-up greater than 10 years.

General consensus is that there is not a direct relationship between AMD and mortality, but that these two outcomes have other systemic conditions in common. It is possible that the associations that we found are due to unmeasured, or inadequately assessed, risks factors for AMD that also affect mortality. Second to age, smoking is the most consistently identified risk factor for AMD.[24,25] In this sample of women, smoking status - assessed as either a categorical variable (never, ex, current), as ever-smoked, or as pack-years smoked - was not a significant predictor of mortality. Further, inclusion of smoking status in the model did not affect the relationship of AMD with mortality. However the percentage of smokers was lower in this study compared to that in other studies[24,25](possibly due to a healthy survivor effect) and may have limited our ability to evaluate its impact. Cholesterol, also shown to be a risk factor for both AMD and mortality,[26] was measured in a small subsample of the SOF cohort and could not be sufficiently assessed in this study. The use of lipid-lowering agents was not associated with either AMD or mortality in these women. However, because comorbidities such as history of MI and CHF, consequences of poor control of cholesterol, were independently associated with mortality, we can not rule out the potential cholesterol-AMD-mortality relationship. Of importance, AMD remained a significant predictor of mortality after adjusting for these conditions. There is increasing evidence that genetics and inflammation are related to the development of AMD.[27,28] Determining whether inflammation initiates or advances AMD may help to explain the AMD/mortality relationship. Reasons for the association of *early* AMD with other (non-CVD, non-cancer)

death in the ≥80 group are unclear. Multiple co-morbidities are more common in this older group, suggesting that death may be due to multiple causes as well. It is possible that CVD contributed to but was not the primary cause of some of these deaths.

In addition to AMD and mortality having common risk factors, it is possible that AMD accelerates the aging process through decreased vision and increased frailty leading to more accidents, falls and fractures, all of which have been linked to higher mortality.[16,29–33] This may be most relevant in older women (where we found the strongest associations), as they may adapt less well to vision loss. We did not have sufficient trauma-related deaths to examine this hypothesis. There may be more falls, injuries and medication mistakes in the older group. It is also possible that the relationships of AMD to quality of life[34–36] and to depression[37,38] that, in turn, predict mortality[39–42], provide a causal pathway. In this sample, depression (either by measured GDS or self-report) did not remain significantly associated with mortality after adjustment for AMD. In addition, interaction terms of AMD with falls, fractures and depression were not significantly related to mortality, suggesting that there is no difference in the AMD-mortality relationship by these subgroups (data not shown). Further research is necessary to determine if these factors mediate the link between AMD and mortality.

A limitation of the study is that the results are not applicable to all older adults. The participants were women and represented a relatively healthy population. The White women included were those who had survived to the year 10 SOF visit and the Black women were those who enrolled during this same time frame. Thus, the Black women were somewhat younger and healthier than the White women. Further, women who did not have fundus photographs were older and less healthy than women selected for this study. A second limitation of this study, is that much of the information regarding potential confounding factors was self-reported and thus hinders our ability to capture disease severity. Importantly, as AMD shares many common risk factors with potential confounding conditions, our results suggest that AMD could serve as a more clinically relevant indicator of disease severity given many comorbid conditions are more difficult to measure and/or quantify. However, we recognize that assessment of AMD should not be the only measurement used to identify high-risk women. We should also note confounders were measured in the year 10 “baseline” exam. Thus, comorbidities that manifested during the follow-up period, that may have precipitated death were not considered. On the other hand, incident AMD cases that occurred after baseline, were not measured and could have biased our results toward the null. Spurious results due to multiple comparisons are possible, but the number of significant associations reported is greater than would be expected using a conservative Bonferroni approach. Finally, we can’t rule out the possibility of residual confounding or that the low frequency of late AMD in this sample may have limited our power.

This study also has several strengths. The population studied was considerably older than others to date, allowing for the estimation of mortality risk due to AMD in the oldest old. Both AMD and mortality were assessed using detailed and standardized procedures, thereby increasing the study’s precision and diminishing the likelihood of disease and/or mortality

misclassification. Finally, follow-up of over 15 years (with > 95% confirmed status) was among the longest reported to date, allowing for high cumulative mortality.

In summary, AMD is a predictor of poorer survival among women especially if 80 or older. Whether the AMD-mortality relationship is due to systemic factors affecting both outcomes or to mediating factors caused by AMD remains unknown. Importantly, AMD shares risk factors with many comorbid conditions including CVD; and AMD is also relatively easy to both identify and quantify. Thus, our results suggest that AMD may serve as a useful prognostic indicator for women who may benefit from risk factor modification, particularly women age 80 and older. Further research is necessary to determine if modification of these common risk factors can improve quality of life and decrease mortality among older women.

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Dr. Ensrud serves as a consultant on a Data Monitoring Committee for Merck Sharpe &Dohme.

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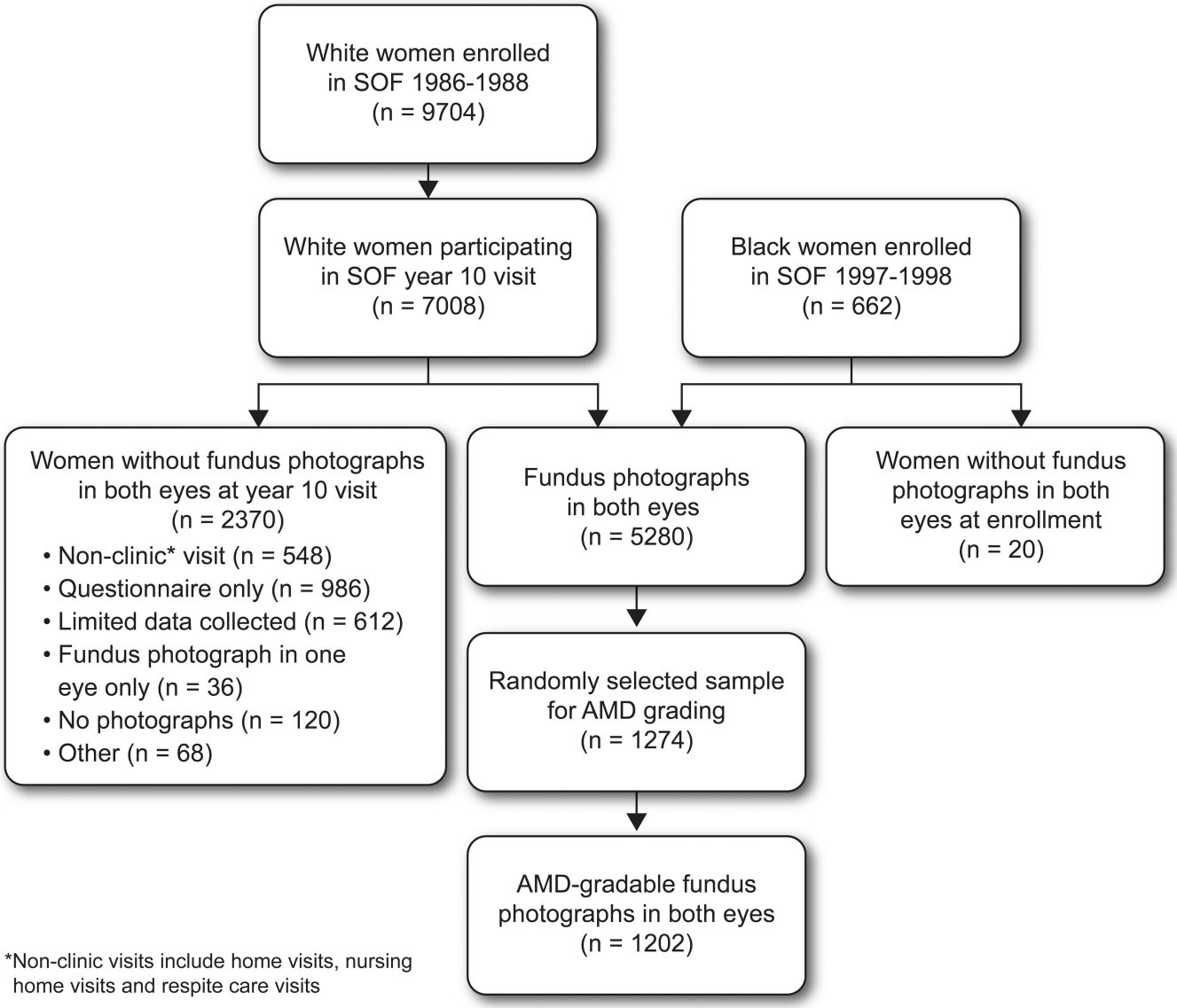
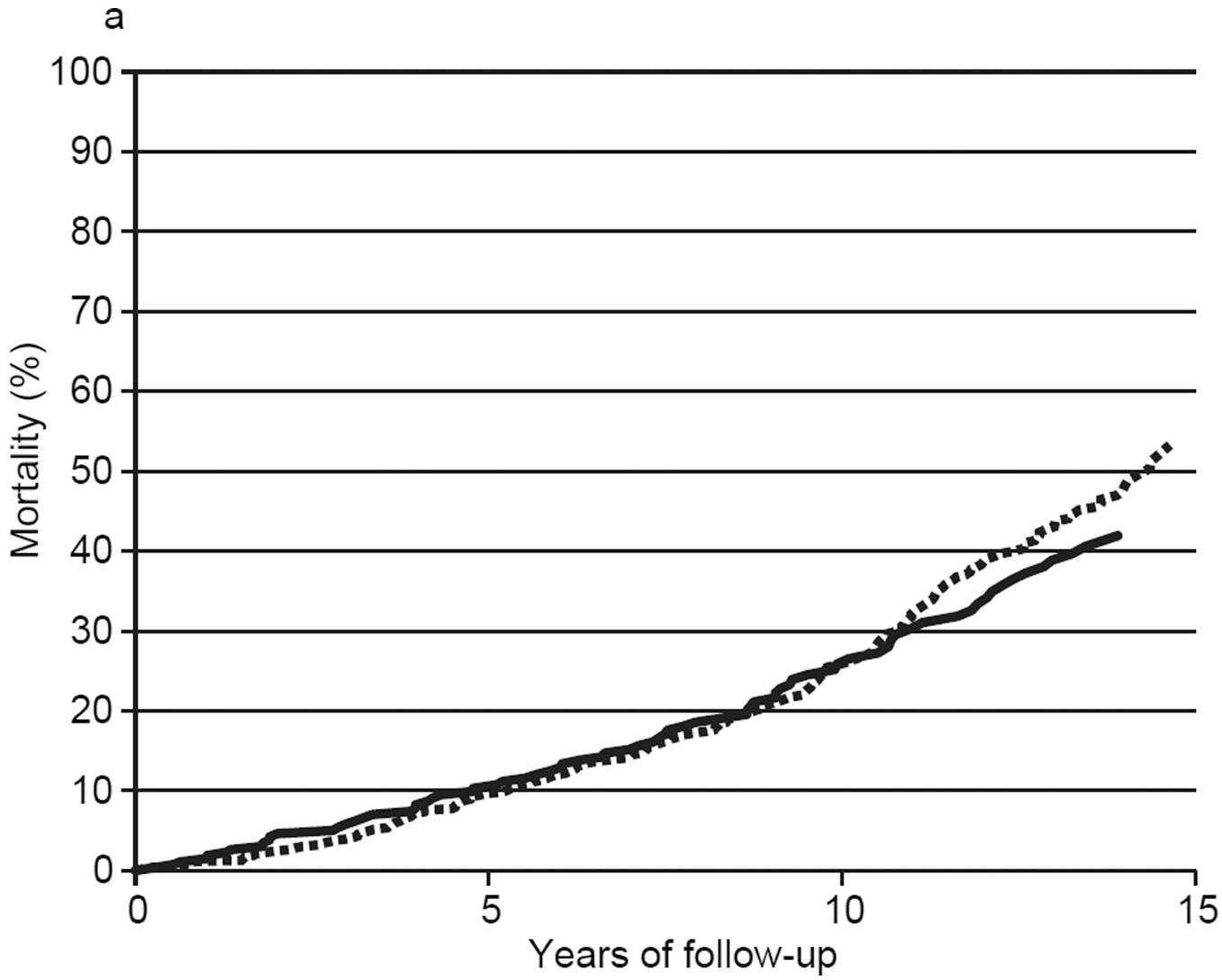


Figure 1.

Flow chart of study sample selection in the study of the relationship of age-related macular degeneration (AMD) to mortality for the Study of Osteoporotic Fractures (SOF).



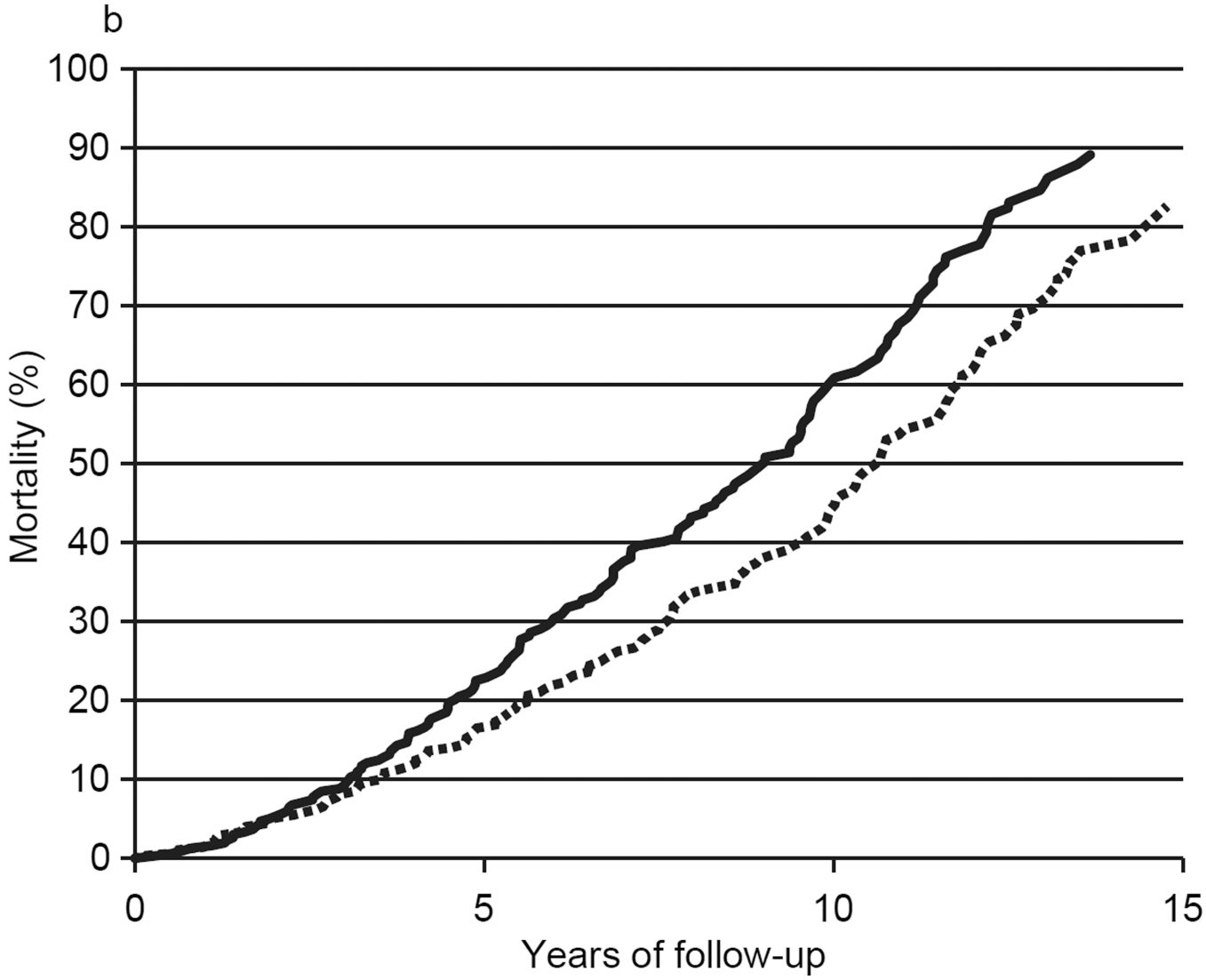


Figure 2.

A,B. Multivariate-adjusted all-cause mortality by age group and age-related macular degeneration (AMD) status. Mortality rates are adjusted for black ethnicity, self-reported frailty, body mass index, mini-mental state score, walking speed, history of congestive heart failure, history of myocardial infarction, history of chronic obstructive pulmonary disease, and history of thiazide diuretics. Mortality curves are shown for women younger than 80 years (A) and those 80 years and older (B) at baseline.

Legend:	**Solid line – any AMD**
	Dashed line – no AMD

Table 1

Participant Characteristics by Age-Related Macular Degeneration

	Age-Related Macular Degeneration			
Baseline Characteristic	**None (n=715)**	**Early (n=441)**	**Late (n=46)**	**p-value***
Clinic				
Baltimore (%)	22.4	24.9	32.6	0.2412
Minneapolis	32.5	33.1	39.1	
Pittsburgh	25.3	26.1	17.4	
Portland	19.9	15.9	10.9	
Black (%)	15.2	4.1	4.1	<0.0001
Age				
Years: mean (±SD)	78.7 (4.1)	80.7 (4.7)	81.0 (4.3)	<0.0001
<80 years (%)	63.5	46.0	45.7	<0.0001
≥80 years	36.5	54.0	54.3	
Education ≥12 years (%)	43.6	43.8	47.8	0.8521
Currently Married (%)	53.9	49.7	37.0	0.0481
Self-report Health Status				
Excellent/Good (%)	86.1	90.3	89.1	0.1139
Poor/Very Poor	13.9	9.7	10.9	
Self-report Frailty				
Not Frail (%)	82.7	77.9	76.1	0.0358
Somewhat/Very Frail	17.3	22.1	23.9	
Require Arms to Rise from Chair (%)	14.7	15.7	21.7	0.2912
Walks for Exercise (%)	39.8	39.9	54.4	0.1448
# IADL† impairments out of 5: mean(±SD)	0.9 (1.3)	0.8 (1.3)	1.0 (1.3)	0.6794
Body Mass Index (kg/m^2): mean(±SD)	27.1 (5.2)	26.1 (4.5)	26.5 (5.1)	0.0041
Walking Speed (meters/sec): mean (±SD)	0.90 (0.3)	0.89 (0.3)	0.92 (0.2)	0.6131
Pulse (per 30 sec): mean(±SD)	33.8 (4.8)	33.8 (5.0)	35.3 (6.3)	0.1247
Fracture after age 50 (%)	30.9	37.1	37.0	0.0890
Fall within last year (%)	29.0	32.7	41.3	0.0484
Ever Smoked (%)	39.6	36.5	53.3	0.0750
History of Diabetes (%)	6.4	5.7	0	0.1931
History of CHF‡ (%)	4.9	4.5	6.5	0.8283
History of COPD§ (%)	8.3	8.4	6.5	0.9080
History of Depression (%)	7.0	7.7	4.4	0.6790
History of Myocardial Infarction (%)	5.7	3.6	10.9	0.0589
History of Hypertension (%)	36.8	35.4	21.7	0.1321
History of Stroke (%)	4.3	5.0	4.4	0.6958
Current use of Antihyperlipidemics (%)	12.5	11.1	19.6	0.2403
Current use of Antihypertensives (%)	35.8	36.7	26.1	0.3577
Current use of Antidepressants (%)	9.5	8.4	8.7	0.8092

	Age-Related Macular Degeneration			
Baseline Characteristic	**None (n=715)**	**Early (n=441)**	**Late (n=46)**	**p-value***
History of Thiazide Diuretic Use (%)	30.6	31.8	34.8	0.5190
Estrogen Use				
Never (%)	48.5	51.8	56.5	0.0548
Ex	30.0	30.0	32.6	
Current	21.5	18.2	10.9	
Mini-mental State Score				
Mean(±SD)	27.8 (2.2)	27.6 (2.3)	28.2 (1.8)	0.0452
<24 (%)	4.4	5.8	2.5	0.5765
≥ 24	95.6	94.2	97.5	
Geriatric Depression Score				
< 6 (%)	91.7	89.3	82.6	0.0305
≥ 6	8.3	10.7	17.4	

*p-value comparing based on chi-square for proportions and analysis of variance for means

†IADL- Instrumental Activities of Daily Living

‡CHF – Congestive Heart Failure

§COPD – Chronic Obstructive Pulmonary Disease

Table 2

15-Year All-Cause and Cause-Specific Mortality Hazards Ratios by Age-Related Macular Degeneration (AMD) Status

		All-Cause Mortality*		CVD Mortality†		Cancer Mortality‡		Non-CVD/Non-cancer Mortality§	
Baseline AMD	**At Risk (n)**	**Affected (%)**	**Adjusted HR* (95% CI)**	**Affected (%)**	**Adjusted HR (95% CI)**	**Affected (%)**	**Adjusted HR (95% CI)**	**Affected (%)**	**Adjusted HR (95% CI)**
All Ages									
No AMD	715	49.5	Reference	16.5	Reference	9.2	Reference	23.8	Reference
Early AMD	441	54.7	1.08 (0.91 – 1.28)	18.6	1.09 (0.82 – 1.46)	10.0	1.24 (0.85 – 1.81)	26.1	1.05 (0.82 – 1.35)
Late AMD	46	51.4	1.04 (0.65 – 1.68)	23.9	1.66 (0.87 – 3.18)	6.5	0.81 (0.26 – 2.57)	23.9	0.75 (0.33 – 1.69)
Any (Early or Late) AMD	487	54.6	1.10 (0.93 – 1.30)	19.1	1.18 (0.89 – 1.56)	9.7	1.22 (0.84 – 1.78)	25.9	1.03 (0.80 – 1.32)
< 80 years									
No AMD	454	42.7	Reference	13.2	Reference	10.4	Reference	19.2	Reference
Early AMD	203	37.4	0.91 (0.69 – 1.20)	11.8	1.01 (0.63 – 1.62)	10.3	1.07 (0.64 – 1.79)	15.3	0.80 (0.52 – 1.23)
Late AMD	21	47.6	0.84 (0.36 – 1.93)	**23.8**	**2.61 (1.05 – 6.46)**	0.0	++	23.8	0.81 (0.19 – 3.43)
Any (Early or Late) AMD	224	38.4	0.91 (0.70 – 1.19)	13.0	1.18 (0.75 – 1.85)	9.4	0.96 (0.57 – 1.61)	16.1	0.75 (0.49 – 1.15)
≥ 80 years									
No AMD	261	61.3	Reference	22.2	Reference	7.3	Reference	31.8	Reference
Early AMD	238	**69.3**	**1.39 (1.11 – 1.75)**	24.8	1.37 (0.95 – 1.98)	9.7	1.44 (0.80 – 2.61)	35.3	**1.45 (1.05 – 2.00)**
Late AMD	25	60.0	1.36 (0.76 – 2.46)	24.0	1.68 (0.67 – 4.18)	12.0	2.04 (0.62 – 6.68)	24.0	0.95 (0.35 – 2.61)
Any (Early or Late) AMD	263	**68.4**	**1.42 (1.13 – 1.78)**	**24.3**	**1.45 (1.01 – 2.09)**	9.9	1.59 (0.87 – 2.87)	34.2	1.37 (0.98 – 1.90)

Abbreviations: AMD – age-related macular degeneration; HR – hazards ration; CVD – cardiovascular disease

*Adjusted for age, Black ethnicity, self-reported frailty, body mass index (BMI), mini-mental state (MMSE) score, walking speed, history of congestive heart failure (CHF), history of myocardial infarction (MI) and history of chronic obstructive pulmonary disease(COPD), and history of thiazide diuretics

†Adjusted for age, Black ethnicity, history of MI, history of CHF, and walking speed

‡Adjusted for history of MI

§Adjusted for age, Black ethnicity, self-reported frailty, BMI, MMSE, walking speed, history of MI, and history of thiazide diuretics

++Unestimable due to few events