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Cardiovascular Disease, its Risk Factors and Treatment, and Age-related Macular Degeneration: Women's Health Initiative Sight Exam Ancillary Study

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Abstract

Purpose—To examine the association of cardiovascular disease (CVD), CVD risk factors, and CVD treatment with age-related macular degeneration (AMD).

Design—Observational analysis of a randomized clinical trial.

Setting: The Women's Health Initiative Sight Examination (WHISE), an ancillary study to the Women's Health Initiative's (WHI) clinical trial of hormone replacement therapy.

Study Population: 4,288 women aged 63 years and older.

Observation Procedures: Information on CVD and its risk factors were obtained from a standardized questionnaire and examination.

Main Outcome Measure: AMD as determined by standardized grading of fundus photographs.

Results—Prevalence of any AMD was 21.4% (n=919). Of those with AMD, 5.8% (n=53) had signs of exudative AMD (n=39) or pure geographic atrophy (n=14), limiting the power to examine associations. Significant associations between late AMD and CVD risk factors were (odds ratio [OR], 95% confidence interval [CI]) older age (1.19, 1.13, 1.27, $p < 0.0001$), more pack years smoked (1.02 per pack-year smoked, 1.003, 1.03, $p = 0.01$), systolic blood pressure (0.84 per 10 mmHg, 0.71, 0.995, $p = 0.04$), report of taking calcium channel blockers (CCB) (2.49, 1.21, 5.12, $p = 0.04$), self-reported history of diabetes (2.00, 1.01, 3.96, $p = 0.05$), and greater body mass index (1.05 per 1 kg/m^2, 1.001, 1.10, $p = 0.05$). History of myocardial infarction, stroke, use of statins, or white blood cell were not associated with AMD.

Conclusions—Results suggest that smoking, use of CCBs, diabetes, and obesity are risk factors for late AMD in women. However, the association of late AMD with systolic blood pressure and the effects of other CVD risk factors on early AMD need to be further explored.

Introduction

Age-related macular degeneration (AMD) remains an important cause of visual impairment.[1] The influences of cardiovascular disease (CVD) (e.g., hypertension, coronary artery disease), CVD risk factors (e.g., total serum cholesterol, body mass index), and CVD treatment (e.g., statins, antihypertensive agents) on AMD are inconsistent across different studies.[2,3] The purpose of this report is to examine the association of these factors with AMD in a large cohort of women participating in the Women's Health Initiative Sight Examination (WHISE) study.

Methods

Description of the Population

The WHISE was designed to examine the effects of treatment with conjugated equine estrogen alone (CEE [Premarin,® Wyeth Ayerst, St. David's, PA]) or in combination with progestin (CEE/MPA [Prempro® Wyeth Ayerst, St. David's, PA]) on age-related macular degeneration (Haan MN, Klein R, Klein BEK, et al. Treatment with Conjugated Equine Estrogen Hormone Therapy (CEE) and CEE with Progestin in Relation to Age-related Macular Degeneration in the Women's Health Initiative Sight Examination Study, In Press). WHISE was an ancillary study to the Women's Health Initiative's (WHI) Clinical Trial of Hormone Replacement Therapy. Twenty one of the 39 WHI clinical centers participated in WHISE. Women were enrolled beginning September 1993. Details of the study design and baseline characteristics of the WHI have been described in detail previously.[4,5] In brief, women aged 50–79 years were excluded from the WHI Hormone Trial if they had any medical condition with a predicted survival of < 5 years, had prior breast or other cancer except non-melanoma skin cancer < 10 years, had an acute myocardial infarction or stroke in the past 6 months, and had severe

hypertension (systolic blood pressure > 299 mmHg or diastolic blood pressure > 105 mmHg). Women in the CEE/MPA trial were randomized to either 0.625 mg/day of CEE with 2.5 mg/day of MPA or a placebo as a continuous regimen in one tablet. Women in the Premarin® trial who had had a previous hysterectomy were randomized to 0.625 mg/day of CEE or placebo as a continuous regimen in one tablet. This study was approved by the institutional review committee at each site. All participants gave written informed consent prior to enrollment into the study.

Women were recruited into WHISE from those enrolled in the WHI commencing in April 2000; the last eye exam was completed in March, 2002. Women were only eligible for inclusion in WHISE if they were a participant in the WHI Hormone Trial at the time of enrollment into WHISE, had pupils that could be pharmacologically dilated, would sign a consent form, and agreed to have fundus photography. The 21 WHI clinics participated and obtained a separate informed consent from 4,688 women aged 63 years and older for the WHISE study. This represented 104% of the enrollment goal of 4,500 women. Of these, 4,347 eligible participants completed WHISE enrollment by having at least one fundus photograph set sent to the University of Wisconsin Ocular Epidemiology Reading Center (OERC) for grading. Of the 341 subjects without fundus photographs, 310 (91.4%) withdrew from the study prior to having eye photographs taken, 296 were deemed ineligible for the study after consent was received, and 5 died prior to having their photographs taken. Overall, AMD status was established for at least one eye in 4,288 (98.6% of participants, or 91.5% of those who originally consented).

Procedures

Fundus photography was done following the Beaver Dam Eye Study protocol.[6] Stereoscopic 30° color fundus photographs of DRS fields 1, 2, and a nonstereoscopic photograph of F3 were taken in each eye and graded at the OERC for AMD and other retinal diseases using the Wisconsin Age-related Maculopathy Grading Scheme in 4,347 women.[6,7]

AMD severity was defined as:

Level		
1	No AMD	No signs of any AMD lesions listed below.
2		Minimal Early AMD Soft drusen ≥125 μm in diameter with an area of drusen < 196,350 μm^2 (a circle with a radius of 250 μm) and no pigmentary abnormalities OR hard drusen and pigmentary abnormalities only. No signs of late AMD.
3	Moderate Early AMD·	Soft drusen ≥ 125 μm in diameter with an area of drusen ≥ 196,350 μm^2 and no pigmentary abnormalities OR soft drusen ≥ 125 μm^2 in diameter and an area of drusen <196,350 μm^2 with pigmentary abnormalities. No signs of late AMD.
4	Severe Early AMD	Soft drusen ≥ 125 μm in diameter with an area of drusen ≥ 196,350 μm^2 with pigmentary abnormalities present. No signs of late AMD.
5	Late: Pure geographic atrophy	Signs of geographic atrophy.
6	Late: Exudative AMD	Signs of exudative macular degeneration.

Further description of the lesions are found elsewhere.[8]

There were seven dichotomized outcomes: early AMD (defined as minimal, moderate, severe early AMD, compared with no AMD); the presence versus absence of soft drusen (defined as drusen having a diameter larger than 63 μm); increased retinal pigment; depigmentation of retinal pigment epithelium (RPE); exudative macular degeneration; geographic atrophy; and late AMD (defined as the presence of signs of exudative macular degeneration or pure geographic atrophy).[6,7]

Self-administered questionnaires were given to each participant to complete at the time of the WHISE enrollment. The form included questions about diabetes status, lipid lowering medications, antihypertensive medications, and medications taken for diabetes. All questionnaires were returned to the WHISE Data Coordinating Center at the University of Michigan for data entry.

Information on history of myocardial infarction, stroke, and antihypertensive medication use were collected at the first screening visit (SV1) of WHI as were measurements of systolic and diastolic blood pressure, waist and hip circumferences, and weight and height. Waist hip ratio (WHR) and body mass index (BMI) were calculated based on the information collected above. BMI categories were defined according to the clinical guideline published by the National Heart, Lung, and Blood Institute.[9] We divided BMI into four categories: < 18.5 kg/m^2 was defined as underweight, 18.5 to 24.9 kg/m^2 as normal weight, 25.0 to 29.9 kg/m^2 as overweight, and ≥ 30.0 kg/m^2 as obesity. Hypertension status was determined by self-report.

Statistical Analysis

Descriptive analyses about demographics, CVD related medical history, physical measurements, and vitamin with supplement use were conducted to examine the characteristics of the WHISE population at the time of WHI baseline examination. Logistic regression was used for the data analysis (SAS, version 9; SAS institute, Cary, North Carolina, USA).[10] Major CVD risk factors that were evaluated in the current analysis include systolic and diastolic blood pressure, history of antihypertensive medication use, history of CVD, history of statin use, diabetes status, and obesity. For the seven dichotomized AMD outcomes defined in this paper, their associations with these CVD conditions or risk factors were first tested by both univariate and age-adjusted logistic analysis individually. CVD conditions or risk factors that were statistically significantly related to ($p<0.05$) or previously reported to have association with a specific AMD outcome were further tested in multivariate logistic models by adding related variables singly to the age-adjusted models. Seven possible interactions (i.e., self-reported hypertension history and measured systolic and diastolic blood pressure, hormone replacement therapy and hypertension history, diabetes history and body mass index, and diabetes treatment status and body mass index, waist to hip ratio, and hormone replacement therapy) were also tested separately in the multivariate models for each outcome. Biologically plausible confounders such as age, race, and behavioral risk factors including smoking, alcohol drinking, and education levels were also tested separately for every outcome by multivariate modeling. Adjusted odds ratios (OR) and 95% confidence intervals (CI) for all variables in the final model were calculated for each AMD outcome.

Results

The mean age of WHISE participants at the time of WHI enrollment was 66.7 years. They had a mean age of 71.8 years at the time of the WHISE examination; 88% (n=3,784) were white; 7.4% (n=315) were African American, 2.6% (n=110) were Hispanic, and the 2% (n=79) were Asian, American Indian, and other (Table 1). The prevalence of AMD (severity levels 2 to 6) was 21.4% (n=919). Of those with AMD, 5.8% (n=53) had signs of exudative AMD (n=39) or pure geographic atrophy (n=14). Soft drusen were present in 30.1% (n=1292), increased retinal pigment in 7.3% (n=314), and retinal pigment epithelial (RPE) depigmentation in 3.6% (n=154) of the cohort. Thirty-five percent of the cohort had a history of hypertension, 11% diabetes, 2% myocardial infarction, and 0.6% stroke. These and other characteristics of the cohort by severity of AMD are found in Table 1. Age, systolic blood pressure, mean arterial blood pressure, pulse pressure, weight, waist circumference, BMI, education level, use of calcium channel blockers (CCB), and history of taking vitamin supplements were associated with AMD severity.

Age-adjusted associations of covariates with early AMD (Levels 2–4), late AMD (levels 5, 6), exudative AMD (level 6), and pure geographic atrophy (level 5) are presented in Table 2. While controlling for age, diastolic blood pressure and mean arterial blood pressure were associated with an increased risk of early AMD; and systolic blood pressure (OR per 10 mmHg increase 1.05, 95% CI 1.01, 1.09), diastolic blood pressure (OR per 10 mmHg increase 1.09, 95% CI 1.01, 1.17), and mean arterial blood pressure (OR per mmHg increase 1.09, 95% CI 1.02, 1.16) was associated with the presence of soft drusen. History of hypertension was not related to AMD nor was a history of taking ACE inhibitors, β-blockers, or diuretics (Table 2). A history of CCB use was associated with geographic atrophy (Table 2) and RPE depigmentation (OR 1.68 95% CI 1.10, 2.55).

There were no associations between BMI and AMD in age-adjusted analysis. Waist and hip measurements and the WHR ratio were associated with pure geographic atrophy and late AMD but not with exudative AMD or early AMD (Table 2). A larger WHR was inversely associated with soft drusen (OR 0.34, 95% CI 0.14, 0.80) but was not with pigmentary abnormalities (data not shown). A higher white blood cell count was associated with exudative and late AMD (Table 2).

A history of diabetes was associated with exudative and late AMD but not early AMD or geographic atrophy (Table 2). Diabetic persons on oral hypoglycemic agents were more likely to have RPE depigmentation than those without diabetes (OR 1.87, 95% CI 1.08, 3.25). There were no associations with diabetes treatment status and the presence of soft drusen or increased retinal pigment (data not shown). People without diabetes had a higher odds (OR 1.06, 95% CI 1.00, 1.12) of having exudative AMD for every kg/m^2 increase in body mass index, while persons with diabetes had a lower odds that was not statistically significant (OR 0.82, 95% CI 0.65, 1.04) of having exudative AMD. There were no other interactions found.

History of myocardial infarction, congestive heart failure, or stroke was not associated with early AMD (Table 2). More than twenty percent (861/4288) of the participants were using statins at the time of eye exam. A history of use of statins was associated inversely with soft drusen (OR 0.81, 95% CI 0.68, 0.96) but not with early AMD, geographic atrophy, and exudative AMD (Table 2) or with pigmentary abnormalities (data not shown).

We examined each of the risk factors of interest in multivariate models (Table 3). Few consistent relationships of risk factors with specific AMD endpoints were found. While controlling for age and other factors, use of CCBs was associated, independent of systolic blood pressure, with RPE depigmentation, geographic atrophy, and late AMD (levels 5 and 6). Systolic blood pressure was positively associated with soft drusen and inversely with RPE depigmentation and exudative AMD. Multivariable models in which antihypertensive medications and blood pressure levels were excluded showed no association between a history of hypertension and AMD (data not shown). Adjustment for hormone replacement did not influence these results and was not included in the models.

Discussion

The Women's Health Initiative Sight Exam provided an opportunity to examine the associations of various cardiovascular risk factors with AMD in a large cohort of women using standardized protocols to grade fundus photographs for AMD. Data from the study suggest that age, smoking, increased systolic blood pressure and a history of diabetes were independently associated with late AMD. While controlling for age, none of these factors was found to be associated with early AMD.

In our study, increased systolic blood pressure was found to be associated with soft drusen and inversely associated with RPE depigmentation, lesions defining the presence of early AMD;

it was also inversely associated with exudative AMD. There was no relationship of hypertension history to AMD. It has been hypothesized that increased blood pressure damages the choroidal circulation affecting the RPE.[11–13] However, epidemiologic data regarding this relationship have been inconsistent, with some studies showing a significant association[14–18] while others have not.[19–21] In the Age-Related Eye Disease Study (AREDS), persons with hypertension were 1.5 times as likely to have neovascular AMD compared to persons without hypertension.[17] In the Beaver Dam Eye Study, persons with treated and controlled hypertension at baseline were approximately twice as likely, and persons with treated and uncontrolled hypertension were about thrice as likely to develop neovascular macular degeneration after 10 years of follow-up than persons who were normotensive.22 In that study, an increase in systolic blood pressure between baseline and the 5-year follow-up was associated with an increase of late AMD at the 10-year follow-up compared with persons in whom the systolic blood pressure decreased. There are no randomized clinical trial data demonstrating the efficacy of lowering of blood pressure in reducing the progression of AMD. The reason for finding inverse relations of systolic blood pressure to RPE depigmentation and exudative AMD in our study is not understood.

In the WHISE, we found a statistically significant association of use of CCBs with prevalent pigmentary abnormalities and geographic atrophy and a borderline relationship with increased retinal pigment. An earlier study reported that CCBs verapamil and diltiazem induced cellular fluorescence indicating the presence of lipofuscin-like material in cultured human RPE cells (Abstract by Ellis SJ, Balasubramaniam B, Davies S, Boulton. Specific antihypertensive drugs induce lipofucsin-like pigment within cultured retinal pigment epithelial cells. Invest Ophthalmol Vis Sci 40 [suppl]:224, 1999.). However, no other cross-sectional or prospective associations of CCBs with AMD have been found in other large epidemiological studies.[22, 23] Given the large number of variables examined in the current study, care must be taken in interpreting this finding. We found no evidence of a protective effect of other antihypertensive agents such as ACE inhibitors.

While controlling for age and other risk factors, there was a weak association between larger BMI and late AMD in our study. This is consistent with data from a study that showed that those who were obese (a BMI of at least 30 kg/m^2) were at increased risk of developing late AMD (RR 2.35, 95% CI 1.27, 4.34) compared with those with a BMI of <25 kg/m^2.[3,24] Larger waist-hip circumference was also found to be associated with incident AMD in that study. Others have speculated that excessive caloric intake might increase the risk of AMD because of an increased risk of oxidative damage, a hypothesized pathogenetic factor, in obese persons.[25] Increased waist circumference is also associated with inflammation; another hypothesized pathogenetic mechanism in the development of AMD. However, data from other studies have not found an association between obesity and the incidence of early or late AMD.[18]

We found no association of history of myocardial infarction or stroke and AMD. This is consistent with the findings from most other population-based studies and suggests that atherosclerosis may not be associated with AMD.[26–34] However, data from the Rotterdam Study suggested that subclinical atherosclerotic disease of the carotid artery, as measured by ultrasonography was related to AMD.[35] In that study, Vingerling et al. reported that persons younger than 85 years of age with plaques at the carotid bifurcation were 4.7 times as likely to have late AMD (95% CI 1.8–12.2) as those without these plaques. Carotid artery plaque was also associated with an 1.8 times increase in risk of RPE depigmentation compared to people without plaque in the Atherosclerosis Risk in Communities (ARIC) study.[36] Furthermore, in the ARIC study, early AMD was found to be associated with increased risk of incident stroke.[37] It is possible that persons with manifestations of clinical cardiovascular disease at risk for AMD in the WHISE may have decreased survival leading to not finding the association in our and other studies.

Statin use was inversely related to presence of soft drusen and increased retinal pigment in the WHISE. This is consistent with findings from case-control studies in which persons without AMD were more likely to take statins than those with AMD.[38–41] It has been speculated that statins through an anti-inflammatory, anti-oxidative, and lipid lowering effect may have a protective effect on the incidence and progression of AMD.[41] However, these case-control studies suffer from a number of limitations, including lack of objective detection of AMD by fundus photography and, in some cases, the appropriateness of the control group selected.[42,43] No associations have been found in other large cohorts between statins and AMD.[23,33,44,45] The power to examine these associations has been limited in these studies as well as our own.

A history of diabetes was found to be associated with RPE depigmentation and exudative AMD in the WHISE. Histopathological studies in eyes of persons with diabetes of long duration have shown thickening of the basement membrane of the choriocapillaris walls, luminal narrowing, and dropout of the choriocapillaris, and thickening of Bruch's membrane which has been attributed to hyperglycemia.[46,47] While these findings of a relationship of diabetes with exudative AMD are consistent with cross-sectional findings in the Beaver Dam Eye Study and the Age-Related Eye Disease Study, few other studies have found this relationship.[16,18,26,31,32,48–50]

The WHISE has a number of strengths including the use of standardized protocols to grade fundus photographs for the presence of AMD. However, any conclusions or explanations regarding associations or lack of them, described herein, must be made with caution for a number of reasons. First, in this relatively healthy cohort, the concomitant low frequency of some risk factors (e.g., stroke) and the low prevalence of some lesions (e.g., exudative AMD or geographic atrophy) limits our ability to detect meaningful relations. Second, as is the case in all studies, some statistically significant associations may be type I errors (i.e., may be due to chance when, in fact, no association exists). Third, it is possible that no relationship was found for some characteristics because persons with these risk factors and AMD may have not been chosen, were not eligible to participate in the WHISE, or did not participate. Fourth, data related to some of the risk factors for AMD were collected at the WHI baseline, which may not precisely reflect the cross-sectional association between disease and exposure at the time of the eye examination. Lack of information about the status of AMD or duration of exposure to some risk factors at the WHI baseline among WHISE participants would further limit finding associations. Fifth, it is possible that the generalizability of the findings might be affected because participants in the WHISE were from the WHI, a clinical trial with its inherent selection biases.

In summary, the data, taken as a whole, do not suggest consistent associations of any of the factors studied with all the AMD end points under observation in women. This is possibly due to differences in the pathogenesis of early AMD and its characteristic lesions, soft drusen and pigmentary abnormalities, and late AMD and its characteristic lesions, exudative AMD and geographic atrophy. Nevertheless, the associations of obesity, diabetes history, and the use of CCBs and statins with AMD deserve further exploration.

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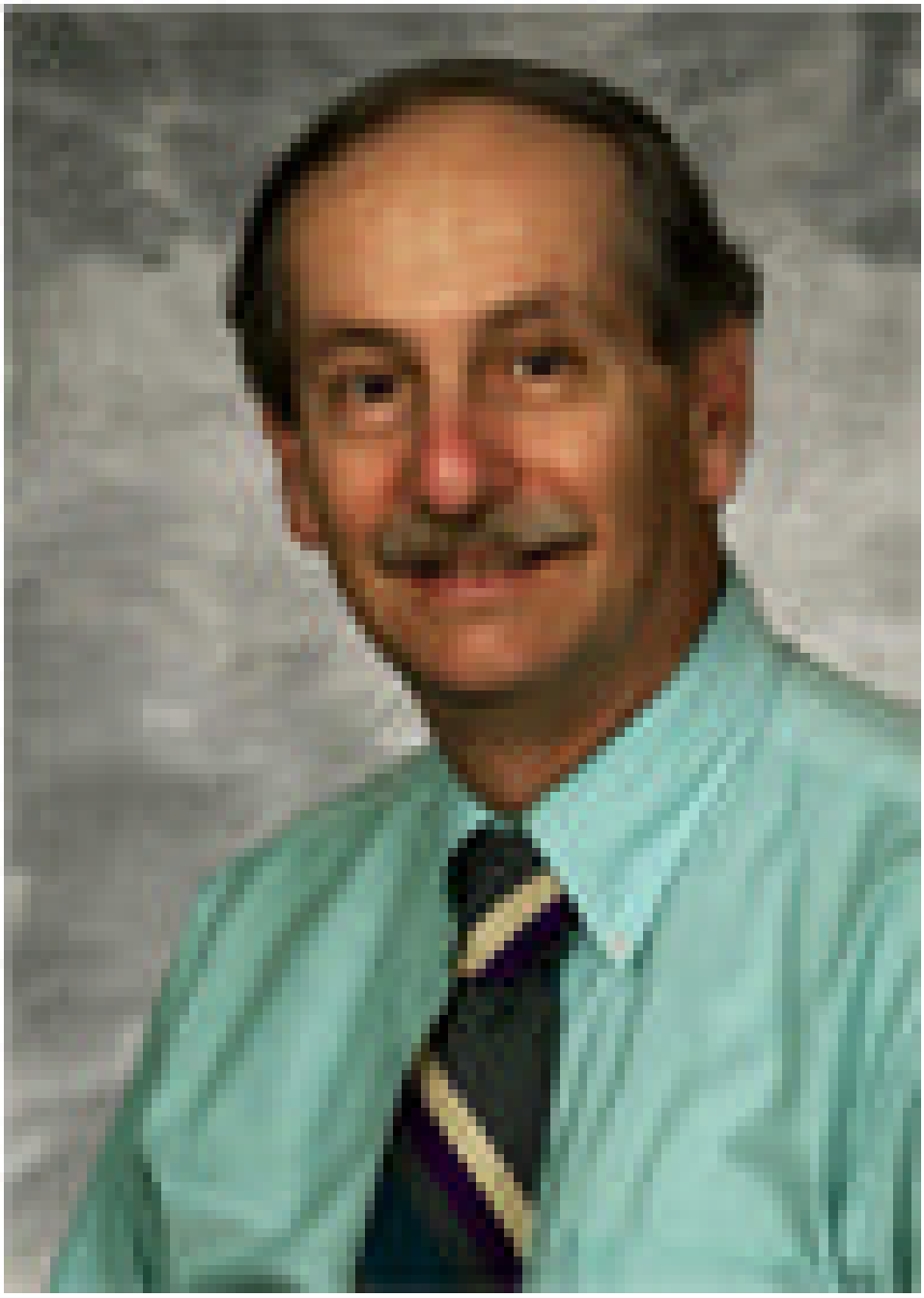
Biographies



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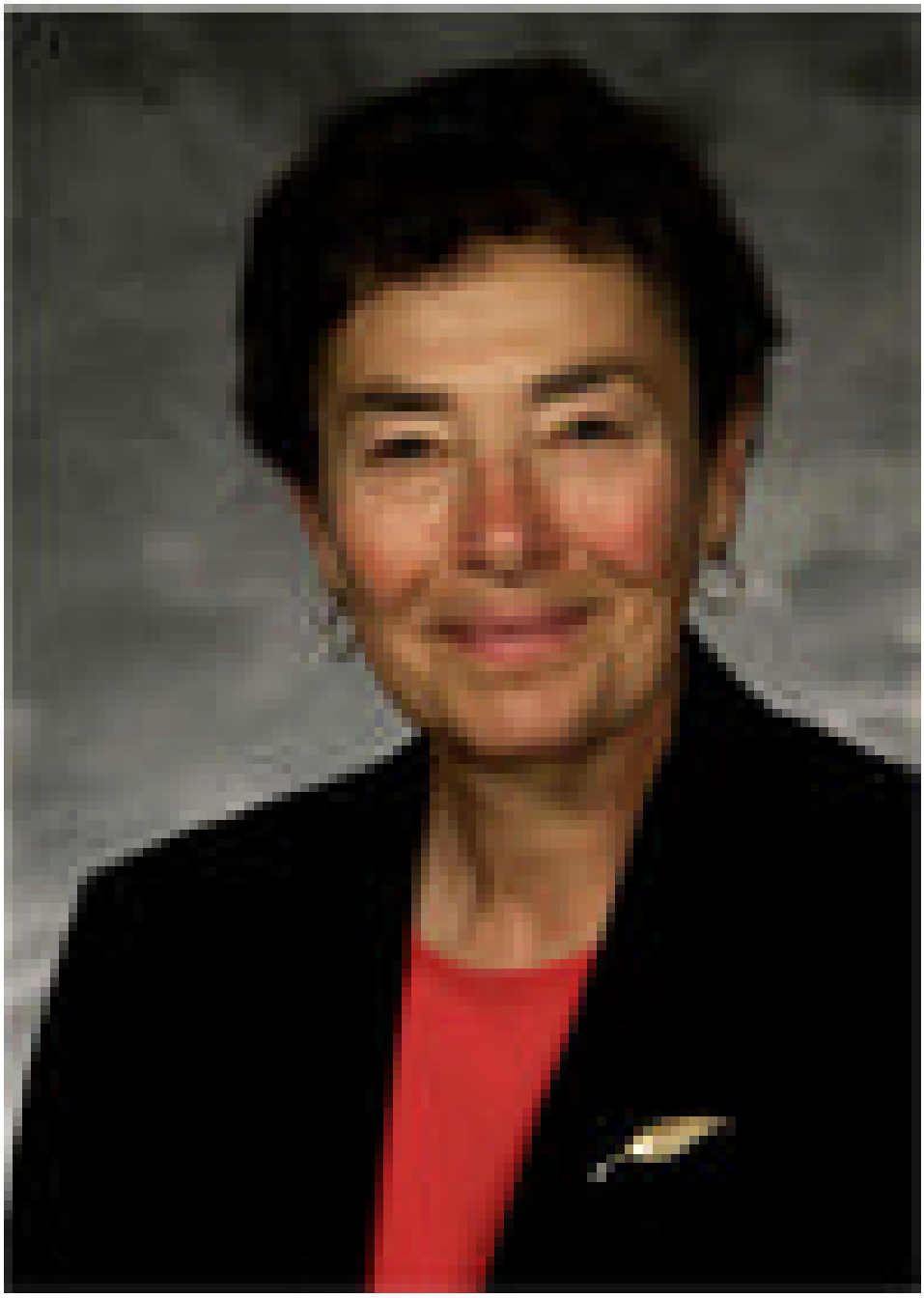

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Table 1

Distribution of Covariates at Women's Health Initiative Baseline (N=4288).

Covariate	Total % (n)	No AMD % (n)	Early AMD % (n)	Late AMD % (n)	P-value*
Race					NA
White	88.3 (3784)	88.2 (2972)	88.0 (762)	94.3 (50)	
Black or African American	7.4 (315)	7.6 (256)	6.7 (58)	1.89 (1)	
Hispanic	2.6 (110)	2.6 (87)	2.5 (22)	1.9 (1)	
Asian/Pacific Islander	0.7 (29)	0.6 (19)	1.2 (10)	0 (0)	
American Indian/Other/UNK	1.2 (50)	1.0 (35)	1.6 (14)	1.9 (1)	
Education					0.002
< High school	6.0 (258)	5.5 (184)	8.5 (73)	1.9 (1)	
High school	23.1 (986)	23.5 (789)	21.1 (182)	28.3 (15)	
Some college	39.2 (1671)	39.4 (1319)	37.5 (324)	52.8 (28)	
College +	31.7 (1353)	31.6 (1060)	32.9 (284)	17.0 (9)	
Income, in thousands					0.83
<$10	5.2 (212)	5.2 (165)	5.5 (45)	4.0 (2)	
$10 to $19	17.2 (699)	17.0 (545)	17.9 (145)	18.0 (9)	
$20 to $34	31.6 (1283)	31.4 (1005)	31.8 (258)	40.0 (20)	
$35 +	46.0 (1870)	46.4 (1487)	44.8 (364)	38.0 (19)	
Smoking status					0.15
Never	54.0 (2295)	53.8 (1797)	55.4 (475)	44.3 (23)	
Past	38.9 (1654)	38.7 (1293)	39.3 (337)	46.2 (24)	
Current	7.1 (301)	7.5 (250)	5.4 (46)	9.6 (5)	
History of drinking alcohol					0.40
Nondrinker	11.7 (498)	11.6 (388)	12.1 (104)	11.3 (6)	
Past drinker	18.1 (768)	17.8 (595)	18.9 (162)	20.8 (11)	
<1 drink per month	14.5 (617)	15.3 (512)	11.2 (96)	17.0 (9)	
<1 drink per week	19.7 (838)	19.5 (651)	20.5 (176)	20.8 (11)	
1 to <7 drinks per week	24.1 (1024)	23.9 (799)	25.1 (215)	18.9 (10)	
7+ drinks per week	11.9 (505)	11.8 (395)	12.1 (104)	11.3 (6)	
History of myocardial infarction	2.2 (92)	2.1 (70)	2.4 (21)	1.9 (1)	0.81

Covariate	Total % (n)	No AMD % (n)	Early AMD % (n)	Late AMD % (n)	P-value*
History of stroke	0.6 (25)	0.6 (21)	0.5 (4)	0 (0)	0.73
History of cardiovascular disease	15.8 (606)	15.6 (469)	15.9 (124)	27.7 (13)	0.08
History of congestive heart failure	0.7 (281)	0.5 (18)	1.0 (9)	1.9 (1)	0.08
History of diabetes at WHISE exam	10.5 (448)	10.6 (356)	9.3 (80)	22.6 (12)	0.008
History of hypertension	35.5 (1508)	35.1 (1174)	36.3 (310)	45.3 (24)	0.27
History of taking antihypertensive medications					
Calcium channel blockers	11.4 (488)	10.9 (366)	12.6 (109)	24.5 (13)	0.004
ACE inhibitor	8.6 (369)	8.5 (285)	9.4 (81)	5.7 (3)	0.52
β-blocker	8.8 (378)	8.9 (298)	8.3 (72)	15.1 (8)	0.24
Diuretic	15.0 (643)	14.8 (500)	15.1 (131)	22.6 (12)	0.29
History of taking lipid-lowering medications†					0.21
Statins	20.1 (861)	20.7 (697)	17.8(154)	18.9 (10)	
Other lipid lowering drugs	4.1 (175)	3.9 (131)	4.6(40)	7.6 (4)	
History of taking vitamin and supplement†	80.6 (3421)	79.8 (2663)	82.7(711)	88.7 (47)	0.04
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
Age at WHI exam	66.7 (4.9)	66.3 (4.8)	68.1 (5.1)	70.3 (4.9)	<0.0001
Age at WHISE exam†	71.8 (4.8)	71.4 (4.7)	73.1 (5.0)	75.6 (5.0)	<0.0001
Systolic blood pressure, mmHg	130.7 (17.5)	130.3 (17.2)	132.4 (18.4)	130.1 (16.2)	0.008
Diastolic blood pressure, mmHg	76.1 (9.1)	76.0 (9.1)	76.5 (9.2)	73.7 (8.7)	0.06
Mean arterial blood pressure, mmHg	94.3 (10.5)	94.1 (10.4)	95.1 (10.9)	92.5 (9.8)	0.02
Pulse-pressure, mmHg	54.6 (14.6)	54.3 (14.5)	55.9 (15.3)	56.4 (13.9)	0.01
Weight, kg	75.4 (16.1)	75.7 (16.4)	74.0 (15.1)	77.3 (14.0)	0.01
Body mass index, kg/m^2	28.9 (5.8)	29.0 (5.8)	28.5 (5.7)	30.5 (5.9)	0.01
Waist circumference, cm	89.2 (13.5)	89.5 (13.6)	88.2 (13.1)	93.2 (13.0)	0.005
Hip circumference, cm	108.0 (12.1)	108.2 (12.1)	107.3 (12.0)	110.0 (12.6)	0.06
Height, cm	161.2 (6.4)	161.2 (6.4)	161.0 (6.3)	159.6 (5.5)	0.09
Hemoglobin, g/L	13.6 (1.0)	13.6 (1.1)	13.6 (1.0)	13.7 (1.2)	0.96
WBC count, k/mL	5.9 (1.7)	5.9 (1.7)	5.9 (1.5)	6.8 (1.9)	0.01
Platelet count, k/mL	246.1 (56.1)	246.5 (55.7)	244.3 (57.7)	255.1 (55.3)	0.30

*P-values were generated from Chi-square tests for categorical variable distributions among three AMD groups; ANOVA test was used to test the difference in means of the three AMD groups;

[†]Measured at WHISE examination

AMD was categorized into three severity groups according to the AMD grading, no AMD=1; early AMD=2, 3 and 4; late AMD=5 and 6. CVD was defined as a positive response to the question “Has a doctor ever told you that you had heart problems, problems with your blood circulation, or blood clots?” WBC=white blood cells ACE=angiotensin-converting enzyme

Table 2

Age-adjusted Associations of Risk Factors with Early Age-Related Macular Degeneration, Exudative Macular Degeneration, Geographic Atrophy, and Late Age-Related Macular Degeneration in the Women's Health Initiative Sight Examination.

	Early AMD		Exudative AMD		Geographic Atrophy		Late AMD	
Characteristic	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Systolic blood pressure (/10 mmHg)	1.03	0.99,1.08	0.87	0.72,1.05	1.08	0.81,1.44	0.92	0.79,1.08
Diastolic blood pressure (/10 mmHg)	1.11	1.03,1.21*	0.79	0.56,1.12	1.19	0.67,2.12	0.88	0.65,1.19
Mean arterial blood pressure (/10 mmHg)	1.09	1.01,1.17*	0.78	0.57,1.06	1.18	0.72,1.93	0.87	0.67,1.13
Pulse pressure (/10 mmHg)	1.00	0.95,1.06	0.90	0.71,1.13	1.05	0.74,1.48	0.94	0.77,1.14
History of hypertension	0.99	0.85,1.17	1.14	0.60,2.18	2.03	0.70,5.93	1.33	0.77,2.31
History of taking calcium channel blocker	1.09	0.86,1.37	1.52	0.66,3.50	4.82	1.64,14.14*	2.20	1.16,4.20*
History of taking an ACE inhibitor	1.06	0.81,1.38	0.25	0.03,1.85	1.48	0.33,6.74	0.56	0.17,1.83
History of taking a β-blocker	0.90	0.68,1.18	1.72	0.71,4.16	1.49	0.33,6.73	1.66	0.77,3.57
History of taking a diuretic	0.93	0.75,1.15	1.46	0.68,3.11	1.19	0.33,4.33	1.39	0.72,2.68
History of taking a statin†	0.83	0.68,1.01	0.99	0.45,2.18	0.73	0.16,3.34	0.92	0.46,1.86
History of lipid lowering medications†	0.88	0.73,1.05	1.04	0.50,2.14	1.22	0.38,3.92	1.08	0.58,2.01
History of diabetes†	0.87	0.67,1.12	2.49	1.17,5.31*	2.28	0.63,8.28	2.43	1.26,4.70*
Body mass index								
Low (< 18.5 kg/m^2)	0.16	0.02,1.20	NA		NA	NA		
Overweight (25-29-9 kg/m^2)	1.07	0.88,1.30	1.16	0.51,2.64	1.75	0.32,9.65	1.26	0.60,2.65
Obese (≥ 30.0 kg/m^2)	0.90	0.74,1.10	1.21	0.54,2.74	3.73	0.78,17.90	1.60	0.79,3.27
Waist circumference (/cm)	1.00	0.99,1.00	1.02	0.99,1.04	1.05	1.02,1.09*	1.03	1.01,1.05*
Hip circumference (/cm)	1.00	0.99,1.00	1.02	0.99,1.04	1.04	1.00,1.09*	1.02	1.00,1.05*
Waist/hip ratio	0.55	0.21,1.44	NA	NA	NA	NA	NA	NA
Hemoglobin g/L	1.00	0.93,1.07	0.96	0.71,1.30	1.21	0.91,1.60	1.05	0.82,1.34
White blood count, k/mL	0.97	0.92,1.01	1.09	1.01,1.18*	1.08	0.98,1.20	1.10	1.02,1.19*
Platelet count, k/mL	1.00	1.00,1.00	1.00	1.00,1.01	1.01	1.00,1.02	1.00	0.99,1.02
History of myocardial infarction	1.05	0.63,1.73	0.87	0.12,6.55	NA	NA	NA	NA
History of stroke	0.66	0.22,1.97	NA	NA	NA	NA	NA	NA
History of congestive heart failure	1.83	0.80,4.23	1.94	0.22,16.75	NA	NA	1.35	0.16,11.60

Abbreviations: AMD=age-related macular degeneration, OR=odds ratio; CI=confidence interval; NA=not applicable Early AMD: AMD grade of 20, 30 and 40 compared with No AMD (10), Exudative AMD and geographic atrophy were set as missing; Exudative AMD: cases with AMD grade of 60 compared with no AMD. GA: geographic atrophy (AMD=50) compared with no AMD. Late AMD: combination of exudative late and geographic atrophy (AMD: 50, 60) compared with no AMD (10).

* *p*-value <0.05;

† Measured at WHISE examination

Table 3

Multivariate Model of Risk Factors for Various Age-Related Macular Degeneration Outcomes.

Early AMD				Soft Drusen				Increased Retinal Pigment			
Variables in the Final Model	**OR**	**95% CI**	**P**	**Variables in the Final Model**	**OR**	**95% CI**	**P**	**Variables in the Final Model**	**OR**	**95% CI**	**P**
Age, per year	1.07	1.06,1.09	<0.0001	Age, per year	1.07	1.06,1.09	<0.0001	Age, per year	1.08	1.05,1.10	<0.0001
Education			0.01	Education			0.05	Pack year smoked per year	1.01	1.00,1.01	0.015
<High school	1			<High school	1			History of antihypertensive agents			0.098
High school	0.68	0.51,0.92		High school	0.68	0.51,0.92		None	1		
Some college	0.62	0.46,0.85		Some college	0.67	0.50,0.89		Taking Ca channel blocker	1.47	1.03,2.08	
College +	0.68	0.50,0.93		College +	0.71	0.53,0.95		Taking other	1.11	0.82,1.49	
				Systolic BP /10 mmHg	1.06	1.02,1.10	0.007	History of taking statins (yes vs no)	0.70	0.51,0.97	0.03
				Body mass index per 1 kg/m^2	0.99	0.98,1.00	0.043				
				History of taking statins (yes vs no)	0.82	0.69,0.97	0.02				

RPE Depigmentation				Late AMD				Exudative AMD			
Variables in the Final Model	**OR**	**95% CI**	**P**	**Variables in the Final Model**	**OR**	**95% CI**	**P**	**Variables in the Final Model**	**OR**	**95% CI**	**P**
Age, per year	1.09	1.05,1.13	<0.0001	Age, per year	1.19	1.13,1.27	<0.0001	Age, per year	1.17	1.09,1.25	<0.001
Pack year smoked per year	1.01	1.00,1.02	0.019	Pack year smoked per year	1.02	1.00,1.03	0.01	Pack year smoked per year	1.02	1.00,1.03	0.02
History of antihypertensive agents				History of antihypertensive agents				Systolic blood pressure per 10	0.84	0.69,1.02	0.08
			0.02				0.04	mmHg			
None	1			None	1			History of diabetes*	2.62	1.21,5.67	0.01

RPE Depigmentation				Late AMD				Exudative AMD			
Variables in the Final Model	**OR**	**95% CI**	**P**	**Variables in the Final Model**	**OR**	**95% CI**	**P**	**Variables in the Final Model**	**OR**	**95% CI**	**P**
Taking Ca channel blocker	1.89	1.20,2.99		Taking Ca channel blocker	2.49	1.21,5.12					
Taking other	1.34	0.88,2.21		Taking other	1.64	0.83,3.25					
Systolic blood pressure per 10 mmHg	0.86	0.78,0.95	0.004	Systolic blood pressure per 10 mmHg	0.84	0.71,1.00	0.04				
History of diabetes	1.69	1.07,2.66	0.02	Body mass index per 1kg/m^2	1.05	1.00,1.10	0.05				
				History of diabetes*	2.00	1.01,3.96	0.05				

Geographic Atrophy			
Variables in the Final Model	**OR**	**95% CI**	**P**
Age, per year	1.26	1.12,1.41	0.0002
History of antihypertensive agents			0.03
None	1		
Taking Ca channel blocker	4.64	1.38,15.66	
Taking other	1.27	0.29,5.53	
Body mass index per 1 kg/m^2	1.09	1.01,1.19	0.03

Abbreviations: AMD=age-related macular degeneration, OR=odds ratio, CI=confidence interval, RPE=retinal pigment epithelial, Ca= calcium, BP=blood pressure

Age is at WHISE examination, otherwise characteristics from WHI baseline examination.