The Prevalence of Age-Related Macular Degeneration and Associated Risk Factors

Ronald Klein, MD, MPH; Karen J. Cruickshanks, PhD; Scott D. Nash, MS; Elizabeth M. Krantz, MS; F. Javier Nieto, MD, PhD; Guan H. Huang, PhD; James S. Pankow, PhD, MPH; Barbara E. K. Klein, MD, MPH

Objectives: To determine the prevalence of age-related macular degeneration (AMD) and to examine how retinal drusen, retinal pigmentary abnormalities, and early AMD are related to age, sex, and other risk factors.

Participants: A total of 2810 people aged 21 to 84 years participating in the Beaver Dam Offspring Study.

Methods: The presence and severity of various characteristics of drusen and other lesions typical of AMD were determined by grading digital color fundus images using the Wisconsin Age-Related Maculopathy Grading System.

Results: Early AMD was present in 3.4% of the cohort and varied from 2.4% in those aged 21 to 34 years to 9.8% in those aged 65 years or older. In a multivariable model (expressed as odds ratio; 95% confidence interval), age (per 5 years of age, 1.22; 1.09-1.36), being male (1.65; 1.01-2.69), more pack-years of cigarettes smoked (1-10 vs 0, 1.31; 0.75-2.29; ≥11 vs 0, 1.67; 1.03-2.73), higher serum high-density lipoprotein cholesterol level (per 5 mg/dL, 0.91; 0.83-0.998), and hearing impairment (2.28; 1.41-3.71) were associated with early AMD. There were no associations of blood pressure level, body mass index, physical activity level, history of heavy drinking, white blood cell count, hematocrit level, platelet count, serum total cholesterol level, or carotid intimal-medial thickness with early AMD.

Conclusions: These data indicate that early AMD is infrequent before age 55 years but increases with age thereafter. Early AMD is related to modifiable risk factors, eg, smoking and serum high-density lipoprotein cholesterol level.

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Author Affiliations:
Departments of Ophthalmology and Visual Sciences (Drs R. Klein, Cruickshanks, and B. E. K. Klein and Ms Krantz) and Population Health Sciences (Drs Cruickshanks and Nieto and Mr Nash), School of Medicine and Public Health, University of Wisconsin, Madison; Institute of Statistics, National Chiao Tung University, Hsinchu, Taiwan, Republic of China (Dr Huang); and Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis (Dr Pankow).

ALTHOUGH A GROWING NUMBER of population-based studies have described the prevalence and severity of age-related macular degeneration (AMD), most have been limited to middle- and older-aged cohorts.[1-6] To our knowledge, accurate estimates of prevalence of AMD among adults younger than 40 years are lacking. Such information is important for understanding the relationships of risk factors to AMD across the age spectrum and for identifying factors that might affect this disease earlier in life. The purposes of this report are to describe the prevalence of AMD and its defining lesions and their relationship to age, sex, and other factors in the large Beaver Dam Offspring Study (BOSS) cohort.

METHODS

THE POPULATION

Methods used to identify the population and descriptions of it appear in previous reports.[7,8] Briefly, participants in the Epidemiology of Hearing Loss Study, a population-based study of hearing loss among Beaver Dam residents aged 48 to 92 years who participated in the baseline Beaver Dam Eye Study (BDES) from 1988 through 1990 and who were alive on March 1, 2003, who had previously reported having at least 1 living child were asked for permission to contact their adult children (1902 families).[1-9] Of the eligible families, 1671 (87.9%) gave permission to contact their children, 170 (8.9%) refused, and 61 (3.2%) were lost to follow-up. Of the 4965 offspring identified, 3285 (66.2%) participated in the study, 731 (14.7%) refused, 23 (0.5%) died, and 926 (18.7%) failed to complete an examination or a questionnaire despite multiple attempts to schedule them. Compared with nonparticipants, study participants were slightly older (48 vs 46 years, respectively; $P<.001$), more likely to be women (54.6% vs 44.4%; $P<.001$), and less likely to live out of state (17.7% vs 32.1%; $P<.001$). After adjusting for age and sex, there was no statistically significant difference between participants and nonparticipants in parental history of AMD (odds ratio [OR], 1.12; 95% confidence interval [CI], 0.99-1.27).

PROCEDURES

During the examination, informed consent was obtained. Pertinent parts of the examination

visit included an extensive questionnaire, including information on smoking, physical activity level, and alcohol consumption. Participants were asked to bring all of their medications with them to the examination. A standardized hearing evaluation, including pure-tone air-conduction (500-8000 Hz) and bone-conduction (500, 2000, and 4000 Hz) audiometry, was administered.[9,10] Blood pressure was measured using a Dinamap monitor (GE Medical Systems, Milwaukee, Wisconsin) after a 5-minute rest period; the average of the second and third readings was used in analyses. Height, weight, and waist circumference were measured. A B-mode carotid artery ultrasonogram (Biosound AU4; Biosound Esaote, Indianapolis, Indiana) was obtained and graded using modified Atherosclerosis Risk in Communities Study protocols.[11-13] Blood was drawn and analyzed for a complete blood count, glycosylated hemoglobin A_{1C} level, and serum total cholesterol and high-density lipoprotein (HDL) cholesterol levels.

DIGITAL FUNDUS PHOTOGRAPHY

Fundus photography using a 45° 8.2-megapixel digital nonmydriatic camera (Canon Inc, Paramus, New Jersey) was performed through a pharmacologically dilated pupil using a standardized protocol.[14] Two photographic fields were taken of each eye; the first centered on the optic disc (Early Treatment Diabetic Retinopathy Study field 1) and the second centered on the fovea (field 2).[15]

FUNDUS IMAGE GRADING

Capture and grading of digital images and quality control have been described in detail elsewhere.[14,15] Each image was graded twice (a preliminary and a detail grade) using a modification of the Wisconsin Age-Related Maculopathy Grading System.[15,16] For the purposes of this report, participants with gradable retinal images in at least 1 eye were included in these analyses. Of the 3285 participants, 2826 (86.0%) were examined and photographed, 20 (0.6%) were examined but refused imaging, and 439 (13.4%) completed only the questionnaire portions of the study. Of the 2826 participants photographed, 2810 (99.4%) had gradable retinal images (right eye, 27 [1.0%]; left eye, 20 [0.7%]; and both eyes, 2763 [97.8%]) and 16 (0.6%) had ungradable images. Among the 2810 participants included in these analyses, 102 (3.6%) were also participants in baseline BDES. They were eligible for the BOSS because their parents were also BDES participants.

Comparisons of parental characteristics for families contributing data to this study and those not included (nonparticipating or no available gradable images from any offspring) demonstrated no significant differences in parental history of AMD, history of cardiovascular disease, diabetes mellitus, and smoking or heavy drinking status (**Table 1**). There was a statistically significant difference in the distribution of the highest educational level among parents, consistent with the slightly older age of participants.

Table 1. Comparisons of Parental Characteristics of Families Included in Analyses and Excluded Families in the Beaver Dam Offspring Study

Parental History[a]	No. (%) of Participants: Families Included[b] (n=1315)	Families Excluded[c] (n=353)	*P* Value
Age-related macular degeneration	520 (39.5)	121 (34.3)	.07
History of cardiovascular disease	457 (34.8)	116 (32.9)	.49
Diabetes mellitus	296 (22.5)	66 (18.7)	.12
History of ever smoking	929 (70.7)	242 (68.6)	.40
History of heavy drinking	482 (36.7)	121 (34.3)	.39
Highest educational level, y[d]			
<12	221 (16.8)	50 (14.1)	.03
12	612 (46.5)	149 (42.2)	
13-15	248 (18.9)	72 (20.3)	
≥16	234 (17.8)	82 (23.2)	

[a] In these analyses, the authors considered a condition to be present if 1 Beaver Dam Eye Study parent had the condition.
[b] Participating families with gradable retinal images from at least 1 offspring.
[c] No gradable retinal images from any offspring; includes those who refused to participate.
[d] When data were available for both parents, the authors selected the highest educational level achieved for either parent.

DEFINITIONS OF VARIABLES

Among the AMD features evaluated were drusen size, type, and area; increased retinal pigment; retinal pigment epithelial (RPE) depigmentation; pure geographic atrophy; and signs of exudative macular degeneration (ie, subretinal hemorrhage, subretinal fibrous scar, RPE detachment, and/or serous detachment of the sensory retina or laser or photodynamic treatment for neovascular AMD). Hard drusen were small (usually <63 µm in diameter, although some may be larger), round, pale yellow–white spots. Soft distinct drusen were defined by size (≥250 µm in diameter) and appearance (sharp margins and a round nodular appearance with a uniform density [color] from center to periphery). Soft indistinct drusen were the same size as soft distinct drusen but had indistinct margins and a softer, less solid appearance. Increased retinal pigment appears as a deposition of granules or clumps of gray or black pigment in or beneath the retina; RPE depigmentation is characterized by faint gray-yellow or pink-yellow areas of varying density and configuration without sharply defined borders. Early AMD was defined by the presence of either soft indistinct drusen or the presence of RPE depigmentation or increased retinal pigment together with any type of drusen in the absence of signs of late AMD. Late AMD was defined by the presence of any of the following: geographic atrophy or pigment epithelial detachment, subretinal hemorrhage or visible subretinal new vessels, subretinal fibrous or laser treatment scar, or history of photodynamic or antivascular endothelial growth factor treatment for AMD.

When 2 eyes of a participant were discrepant for the severity of a lesion, the grade assigned for the participant was that of the more severely involved eye. When drusen or signs of AMD could not be graded in an eye, the participant was assigned a score equivalent to that in the other eye.

Eyes were considered gradable if field 2 was present and if the grader was able to assess whether drusen were present within the grid in 25% or more of the field. The degree of exact agreement achieved between the graders ranged from 66% to 73% for each of the drusen characteristics and 88% or more for the other AMD characteristics. The κ scores were generally in the moderate to substantial agreement categories.[16]

Current age was defined as the age at the time of the examination. Smoking status was defined as past smoking, current smoking, or never smoking, and pack-years smoked was calculated by dividing the number of cigarettes smoked per day by 20 and multiplying by the number of years smoked. For modeling, the median number of pack-years among those with any pack-years was used to categorize participants as no pack-years, 1 to fewer than 11 pack-years, or 11 or more pack-years

Table 2. Prevalence of Drusen Outcomes by Age and Sex in the Beaver Dam Offspring Study

		Outcome				
	No. of Participants at Risk	Any Drusen	Drusen ≥125 µm in Diameter	Any Soft Drusen	Any Soft Indistinct Drusen	Any Soft Distinct Drusen
Women, y						
21-34	98	49.0	1.0	4.1	0.0	4.1
35-44	453	58.7	0.2	1.6	0.0	1.6
45-54	560	68.0	2.0	5.0	0.0	5.0
55-64	319	64.6	5.0	9.7	2.2	8.8
65-84	97	73.2	7.2	21.7	4.1	19.6
All women	**1527**	63.7	2.4	6.0	0.7	5.6
Men, y						
21-34	70	41.4	0.0	0.0	0.0	0.0
35-44	369	53.9	2.7	4.6	0.8	4.1
45-54	487	67.6	4.1	8.8	1.9	7.2
55-64	280	67.9	6.4	13.9	3.2	11.4
65-84	77	76.6	11.7	26.0	5.2	24.7
All men	**1283**	62.8	4.4	9.3	2.0	7.9
Men and women, y						
21-34	168	45.8	0.6	2.4	0.0	2.4
35-44	822	56.6	1.3	2.9	0.4	2.7
45-54	1047	67.8	3.0	6.8	0.9	6.0
55-64	599	66.7	5.7	11.7	2.7	10.0
65-84	174	74.7	9.2	23.6	4.6	21.8
Total	**2810**	63.3	3.3	7.5	1.3	6.7

smoked. Heavy alcohol drinking was defined by report of consuming 4 or more alcoholic beverages daily. Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or currently taking blood pressure medication. Obesity was defined as having a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 30 or higher. Hearing impairment was defined as a pure-tone average of thresholds at 0.5, 1, 2, and 4 kHz greater than 25 dB hearing level in the worse ear. Carotid artery intimal-medial thickness (IMT) was categorized as more than 1.0 mm or 1.0 mm or thinner.

STATISTICAL METHODS

Confidence intervals for prevalence estimates were calculated using the normal approximation or exact binomial methods as appropriate. Logistic regression was used to estimate age and sex associations with drusen and early AMD outcomes. The following variables were considered in multivariable logistic regression models for early AMD: educational status, smoking status, number of pack-years smoked, history of heavy alcohol drinking, systolic and diastolic blood pressure, hypertension status, BMI, obesity, diabetes status, history of weekly exercise, hearing impairment, white blood cell count, hematocrit level, platelet count, serum total cholesterol level, serum HDL cholesterol level, and carotid IMT and plaque. First, age- and sex-adjusted models were constructed for each variable. Next, a multivariable model was developed by initially including variables that had a significance level of $P<.20$ in the age- and sex-adjusted models, then sequentially removing variables that were neither statistically significant nor affected the other covariate estimates by more than 20%. When multiple variables described highly correlated factors (eg, smoking and number of pack-years smoked, systolic/diastolic blood pressure, and hypertension), only 1 variable was selected for inclusion in the multivariable model to reduce problems of collinearity. Once the subset of variables retained in the multivariable model was identified, each of the variables originally excluded from the multivariable model was added one at a time to the model to confirm that none were significant or confounders. Interactions of each variable with age and sex were tested. Because sampling in our study was explicitly in family units and because AMD aggregates in families, we reran the models using generalized estimating equations to account for family relationships and test the robustness of the results to the independence assumption. Both SAS, version 9.1 (SAS Institute Inc, Cary, North Carolina), and Stata version 10.1 (Stata Corp, College Station, Texas), statistical software were used for analyses.

RESULTS

Drusen were present in the macula in 63.3% of the cohort (**Table 2**). There was an increase in the frequency of drusen with age (OR per 5 years of age, 1.16; 95% CI, 1.11-1.21) (Table 2). When controlling for age, the frequency of drusen was similar among men and women (OR men vs women, 0.95; 95% CI, 0.82-1.11).

There was an increase in the frequency of large drusen 125 µm or bigger in the macula with age (OR per 5 years of age, 1.38; 95% CI, 1.25-1.53) (Table 2). Drusen 125 µm or bigger were found as the largest drusen present in 0.6% of people aged 21 to 34 years and in 9.2% of those aged 65 years or older. When controlling for age, men had a significantly higher frequency of larger drusen than did women (OR, 1.90; 95% CI, 1.24-2.92).

Eight percent of the population had at least 1 soft drusen within the macula (Table 2). There was 1 person (0.04%) with reticular drusen present. Soft distinct drusen were more frequent than soft indistinct drusen (age-adjusted OR, 19.45; 95% CI, 2.48-152.60). The prevalence of soft distinct and indistinct drusen significantly increased with age (OR per 5 years of age, 1.42; 95% CI, 1.32-1.54; and 1.53; 1.30-1.79, respec-

Table 3. Drusen Area Distribution in the Worse Eye by Age and Sex in the Beaver Dam Offspring Study

	No. of Participants at Risk	% of Persons With Largest Drusen Area in the Worse Eye, μm²					
		0	1-62	63-124	125-249	250-499	≥500
Women, y							
21-34	98	51.0	33.7	11.2	2.0	1.0	1.0
35-44	453	41.3	37.1	18.5	2.7	0.4	0.0
45-54	560	32.0	37.7	22.1	5.7	2.1	0.4
55-64	319	35.4	26.3	24.8	9.1	3.8	0.6
65-84	97	26.8	21.7	18.6	18.6	8.3	6.2
All women	**1527**	36.4	33.9	20.7	6.1	2.3	0.7
Men, y							
21-34	70	58.6	28.6	11.4	1.4	0.0	0.0
35-44	369	46.1	29.0	16.8	5.4	1.6	1.1
45-54	487	32.4	30.0	24.6	8.2	3.7	1.0
55-64	280	32.1	27.1	21.4	12.1	5.0	2.1
65-84	77	23.4	18.2	28.6	15.6	11.7	2.6
All men	**1283**	37.2	28.3	21.2	8.3	3.7	1.3
Men and women, y							
21-34	168	54.2	31.6	11.3	1.8	0.6	0.6
35-44	822	43.4	33.5	17.8	3.9	1.0	0.5
45-54	1047	32.2	34.1	23.3	6.9	2.9	0.7
55-64	599	33.9	26.7	23.2	10.5	4.3	1.3
65-84	174	25.3	20.1	23.0	17.2	9.8	4.6
Total	**2810**	36.7	31.3	20.9	7.1	2.9	1.0

tively). When controlling for age, men had a significantly higher frequency of soft distinct and indistinct drusen than did women (OR, 1.42; 95% CI, 1.04-1.92; and 2.70; 1.32-5.54, respectively). There were no interactions of sex and age for soft distinct or indistinct drusen.

The area of the macula covered by drusen in the more severely involved eye increased with age (for drusen area ≥250 μm²: OR per 5 years of age, 1.42; 95% CI, 1.29-1.56) (**Table 3**). Adjusting for age, men were more likely to have larger areas of the macula covered by drusen than were women (OR, 1.67; 95% CI, 1.13-2.47). When only hard small drusen were present in the right eye as the most severe type of drusen, older persons were more likely to have a larger area of the macula covered by drusen than those who were younger (data not shown). Of right eyes with an area 250 μm² or greater covered by drusen, 29.0% had soft indistinct/reticular, 55.3% had soft distinct, and 15.8% had hard distinct drusen as the most severe type of drusen present. For left eyes, respective percentages were 28.1%, 63.2%, and 8.8%.

Retinal pigment epithelial depigmentation was present in 1.8%, increased retinal pigment in 2.7%, and pigmentary abnormalities in 2.9% of the sample (**Table 4**). The frequency of these lesions increased with age (for increased retinal pigment: OR per 5 years of age, 1.27; 95% CI, 1.13-1.42; and for RPE depigmentation: 1.25; 1.09-1.43) (Table 4). When controlling for age, men had a significantly higher frequency of increased retinal pigment and RPE depigmentation than did women (OR, 2.79; 95% CI, 1.70-4.58; and 2.87; 1.56-5.27, respectively). There were no interactions of sex and age for increased retinal pigment or RPE depigmentation.

The prevalence of AMD was 3.4% and increased with age in persons 55 years and older (OR per 5 years of age, 1.30; 95% CI, 1.18-1.44) (**Table 5**). When controlling for age, men had a significantly higher frequency of AMD than did women (OR, 2.39; 95% CI, 1.55-3.69). There was no interaction of sex and age for AMD. No

Table 4. Prevalence of Retinal Pigmentary Abnormalities by Age and Sex in the Beaver Dam Offspring Study

	No. of Participants at Risk (% With Outcome)		
	RPE Depigmentation	Increased Retinal Pigment	Any Pigmentary Abnormality
Women, y			
21-34	98 (2.0)	98 (1.0)	98 (3.1)
35-44	453 (0.4)	453 (0.9)	453 (0.9)
45-54	560 (0.4)	560 (0.7)	560 (0.9)
55-64	319 (1.6)	319 (2.2)	319 (2.5)
65-84	96 (4.2)	97 (7.2)	97 (7.2)
All women	**1526** (1.0)[a]	**1527** (1.5)	**1527** (1.8)
Men, y			
21-34	70 (0.0)	70 (1.4)	70 (1.4)
35-44	369 (2.4)	369 (3.3)	369 (3.3)
45-54	487 (3.1)	487 (3.9)	487 (4.1)
55-64	280 (2.1)	280 (5.4)	280 (5.4)
65-84	77 (7.8)	77 (7.8)	77 (9.1)
All men	**1283** (2.8)	**1283** (4.1)	**1283** (4.3)
Men and women, y			
21-34	168 (1.2)	168 (1.2)	168 (2.4)
35-44	822 (1.3)	822 (2.0)	822 (2.0)
45-54	1047 (1.6)	1047 (2.2)	1047 (2.4)
55-64	599 (1.8)	599 (3.7)	599 (3.8)
65-84	173 (5.8)	174 (7.5)	174 (8.1)
Total	**2809** (1.8)	**2810** (2.7)	**2810** (2.9)

Abbreviation: RPE, retinal pigment epithelium.
[a]There is 1 woman missing data for pigmentary abnormality.

Table 5. Prevalence of Early Age-Related Macular Degeneration by Age and Sex in the Beaver Dam Offspring Study

	No. of Participants at Risk	Prevalence, % (95% CI)
Women, y		
21-34	98	3.1 (0.6-8.7)
35-44	453	0.9 (0.2-2.2)
45-54	560	0.9 (0.3-2.1)
55-64	319	3.5 (1.4-5.5)
65-84	97	9.3 (4.3-16.9)
All women	**1527**	2.1 (1.4-2.8)
Men, y		
21-34	70	1.4 (0.0-7.7)
35-44	369	3.5 (1.6-5.4)
45-54	487	4.5 (2.7-6.4)
55-64	280	6.8 (3.8-9.7)
65-84	77	10.4 (4.6-19.4)
All men	**1283**	4.9 (3.7-6.1)
Men and women, y		
21-34	168	2.4 (0.7-6.0)
35-44	822	2.1 (1.1-3.0)
45-54	1047	2.6 (1.6-3.5)
55-64	599	5.0 (3.3-6.8)
65-84	174	9.8 (5.4-14.2)
Total	**2810**	3.4 (2.7-4.0)

Abbreviation: CI, confidence interval.

one in the cohort had signs of either pure geographic atrophy or exudative macular degeneration.

When controlling for age and sex, a history of current smoking, greater number of pack-years smoked, higher serum HDL cholesterol level, and hearing impairment were associated with early AMD (**Table 6**). There was a borderline association with history of heavy alcohol drinking. There were no statistically significant associations of educational status, blood pressure level, hypertension status, BMI, obesity, diabetes status, physical activity level, white blood cell count, hematocrit level, platelet count, serum total cholesterol level, or carotid IMT or plaque with AMD.

Many of the significant age- and sex-adjusted associations remained significant in multivariable analyses. The final model included age, sex, number of pack-years smoked, serum HDL cholesterol level, and hearing impairment (**Table 7**). When the multivariable model was rerun with never-smokers excluded, number of pack-years smoked was no longer statistically significant (data not shown). Rerunning the models using general estimating equation to adjust for familial correlations resulted in similar statistically significant associations (age, sex, number of pack-years smoked, serum HDL cholesterol level, and hearing impairment [data not shown]) with early AMD, although the relationship of HDL cholesterol level was of marginal statistical significance (OR, 0.91; 95% CI, 0.83-1.00).

When using a dichotomous age variable that split age at 55 years, a significant age–hearing impairment interaction for early AMD ($P=.03$) was present. Among participants younger than 55 years, 8.7% (15 of 172) with hearing impairment had early AMD, whereas 1.8% (33 of 1865) without hearing impairment had early AMD. Among those 55 years or older, 8.9% (20 of 224) of those with hearing impairment had early AMD, whereas 4.9% (27 of 547) without hearing impairment had early AMD. Incorporating this interaction into the multivariable model showed

Table 6. Age- and Sex-Adjusted Logistic Regression Estimates for Outcome Early Age-Related Macular Degeneration in the Worse Eye in the Beaver Dam Offspring Study

Characteristic	Overall No. of Participants in Model[a]	No. of Participants With the Characteristic	OR (95% CI)
Smoking status			
Never	2808	1509	1 [Reference]
Past		796	1.42 (0.88-2.30)
Current		503	1.83 (1.06-3.17)
Pack-years smoked			
0	2783	1536	1 [Reference]
1 to <11		614	1.35 (0.78-2.33)
≥11		633	1.80 (1.12-2.91)
Heavy drinking	2807	507	1.55 (0.97-2.49)
Systolic BP, 10 mm Hg	2804	2804	1.02 (0.90-1.14)
Diastolic BP, 10 mm Hg	2804	2804	0.93 (0.74-1.15)
Hypertension[b]	2807	1010	1.30 (0.84-2.03)
BMI, per 1 point	2781	2781	0.99 (0.96-1.03)
Obesity, BMI ≥30	2783	1243	0.84 (0.55-1.28)
Exercise[c]	2806	1708	1.25 (0.81-1.92)
Hearing loss	2808	396	2.34 (1.45-3.77)
White blood cell count, per 1000/μL	2745	2745	0.95 (0.85-1.07)
Hematocrit, per 5%	2745	2745	0.79 (0.58-1.09)
Platelet count, per 50 000/μL	2745	2745	0.96 (0.81-1.14)
Serum total cholesterol level, per 10 mg/dL	2748	2748	0.99 (0.94-1.04)
Serum total cholesterol, mg/dL			
<200	2748	1315	1 [Reference]
200-239		986	0.67 (0.41-1.09)
≥240		447	0.95 (0.52-1.71)
Serum HDL cholesterol level, per 5 mg/dL	2747	2747	0.90 (0.83-0.99)
Maximum IMT, per 0.1 mm	2769	2769	1.00 (0.96-1.04)
Maximum IMT, >1.0 mm	2769	854	1.14 (0.72-1.80)
Educational level, y			
≤12	2796	894	1.28 (0.76-2.18)
13-15		950	1.43 (0.85-2.43)
≥16		952	1 [Reference]
Annual income level, $			
<30 000	2723	339	1.56 (0.74-3.31)
30-50 000		556	1.53 (0.79-3.00)
<50 000-100 000		1269	1.17 (0.63-2.15)
>100 000		559	1 [Reference]

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CI, confidence interval; HDL, high-density lipoprotein; IMT, intimal-medial thickness; OR, odds ratio.

SI conversion factor: To convert total and HDL cholesterol to millimoles per liter, multiply by 0.0259.

[a] Numbers vary because of missing data.

[b] Defined as a systolic BP of 140 or higher, diastolic BP of 90 or higher, or currently taking BP medication.

[c] For this variable, 0 = those who report no weekly exercise, and 1 = those who report weekly exercise. Therefore, the reference group = no weekly exercise.

that among persons younger than 55 years, the OR for early AMD among those with hearing impairment compared with those without was 4.33 (95% CI, 2.26-8.29), whereas, among those 55 years and older, the OR was 1.57 (0.85-2.92).

COMMENT

The BOSS provides prevalence data on various signs of AMD in a well-defined large cohort of people over a wide age range beginning at age 21 years. Standardized detailed procedures were used for obtaining digital color fundus images of the macula, and an objective system was used for grading those images for AMD.[14-16] This allowed comparisons of the frequency of specific lesions associated with AMD to population-based studies that used similar grading systems.[1-6,16] The main findings of the study include the relatively low prevalence of early AMD, especially among those younger than 55 years, the higher prevalence of early AMD in men, and the association of early AMD with a history of current smoking and amount smoked, serum HDL cholesterol level, and hearing impairment.

The prevalence of AMD in the BOSS cohort was 3.4%. No one in the cohort had signs of late AMD. These low prevalence estimates, compared with previous studies, do not appear to be totally explained by the younger age of the cohort. Using definitions similar to those used in the BDES to define AMD in the BOSS, age-specific prevalence rates were lower among those in the BOSS compared with the BDES (43-54 years, 2.7% vs 8.6%; 55-64 years, 5.0% vs 15.6%; and 65-84 years, 9.8% vs 29.1%), and the overall direct age-sex adjusted (using the BDES as standard) prevalence rate of AMD was 6.3% compared with 19.1% in the BDES, suggesting that the prevalence of AMD may actually be decreasing over time. However, this finding may also reflect a birth period cohort effect and is consistent with the birth-period cohort effect found for early AMD in the BDES.[17,18] In that study, for most age groups, there was a lower 5-year incidence of early AMD in later birth cohorts or periods.[18] For example, the 5-year incidence rates of early AMD in people examined when they were 65 to 69 years was 13.5% among those born from 1918 through 1922, 10.0% among those born from 1923 through 1927, 6.0% among those born from 1928 through 1932, and 3.7% among those born from 1933 through 1937. It is thought that persons born at different times or seen in different periods may have differing exposures to factors (eg, smoking, uncontrolled blood pressure, sedentary lifestyle, and intake of multivitamins) and different patterns of care for systemic conditions (eg, inflammatory or infectious disease) that may affect the incidence of AMD.

A second possible reason for the decreased prevalence of early AMD in the BOSS might be owing, in part, to differences resulting from the grading of AMD from digital (BOSS) and film images (BDES). However, this is less likely in that it has been shown that detection of AMD resulting from high-resolution digital images, especially when the pupil is pharmacologically dilated, is comparable with those resulting from film-based images, with moderate to almost perfect agreement between the digital and film-based cameras for detecting AMD and its lesions.[14]

Table 7. Multivariable Logistic Regression Estimates for Age-Related Macular Degeneration in the Beaver Dam Offspring Study[a]

Covariate	OR (95% CI)
Age, per 5 y	1.22 (1.09-1.36)
Men vs women	1.65 (1.01-2.69)
Hearing loss	2.28 (1.41-3.71)
Serum HDL cholesterol, per 5 mg/dL	0.91 (0.83-0.998)
Pack-years smoked	
0	1 [Reference]
1 to <11	1.31 (0.75-2.29)
≥11	1.67 (1.03-2.73)

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio.
SI conversion factor: To convert HDL cholesterol to millimoles per liter, multiply by 0.0259.
[a] Model included 2718 participants.

The BOSS data show that early AMD and specific lesions defining early AMD are infrequent among persons younger than 55 years and increase markedly in people aged 65 years or older. There are few data to compare the frequencies of lesions characterizing early AMD in young adults with rates reported in the BOSS.[19-21] In a histopathological study of 182 unpaired postmortem human maculae from patients aged 8 to 100 years, van der Schaft et al[19] first found hard drusen beginning at age 34 years and soft drusen at age 54 years. In a twin study, at least 1 small hard drusen was found in the macular area in 18 of 220 participants (8.2%) ages 20 to 46 years.[20] Only 2 participants (0.9%) in that study had soft drusen present. In the population-based Colorado-Wisconsin Study of Age-Related Maculopathy, the prevalence of AMD among participants aged 20 to 42 years was 6.0% among non-Hispanic whites and 6.7% among Hispanics in the San Luis Valley.[21] The lower prevalence in the BOSS may reflect geographic differences or birth cohort effects because these photographic images were obtained in the 1980s.

The presence of larger areas of small hard drusen increases the risk of developing soft drusen and pigmentary abnormalities. During a 15-year follow-up period in the BDES, compared with eyes with approximately 1 to 3 small hard drusen, large areas of small hard retinal drusen (≥9087 μm^2, ≥8 with a mean diameter of 40 μm), in the absence of larger soft drusen or pigmentary abnormalities at baseline, were associated with a 3-fold increase in the risk of developing soft indistinct drusen and pigmentary abnormalities, signs of early AMD.[22] In the presence of soft drusen at baseline in the BDES, there was marked increase in the odds of developing late AMD (OR, 13.0). The findings from the BOSS indicate about 16% (74 of 470) of persons younger than 40 years had 8 or more small hard drusen based on estimates from total area of the macula involved with drusen, and were at higher risk of developing signs of early AMD during the next 15 years of follow-up. Further follow-up of the cohort will be informative regarding actual risk of developing signs of early AMD in these young to early middle-aged adults.

Although we found no significant age-sex interaction for early AMD, when we stratified by age group, we saw stronger associations between sex and early AMD among those younger than 55 years (age-adjusted men vs women OR, 3.68; 95% CI, 1.90-7.11) than we observed among those aged 55 years or older (1.61; 0.88-2.93). The reason for this is not clear. Our findings are consistent with a possible protective effect among younger women that is lost as they near menopause. It may reflect hormonal differences between men and women. We have previously shown that use of hormone replacement therapy in postmenopausal women was associated with a lower prevalence of RPE depigmentation compared with those not using hormone replacement therapy.[23] In an ancillary study to the Women's Health Initiative, a clinical trial of hormone replacement therapy among 4262 postmenopausal women, those randomized to conjugated equine estrogens combined with progestin had a reduced risk of soft drusen (OR, 0.83; 95% CI, 0.68-1.00) and of neovascular AMD (0.29; 0.09-0.92) compared with those randomized to placebo.[24]

A history of cigarette smoking was associated with early AMD in the BOSS, independent of age, sex, and other risk factors. This relationship was expected because smoking has consistently been found to be associated with AMD in epidemiological studies.[25] Smoking is thought to depress antioxidant levels, decrease luteal pigments in the retina, activate the immune system, reduce choroidal blood flow, reduce drug detoxification by the retinal pigment epithelium, and potentiate nicotine angiogenic activities, all of which have been hypothesized to be involved in the pathogenesis of AMD.[26-32] The relationship between heavy drinking and early AMD was of borderline statistical significance, and this variable was not retained in the multivariable model. A relationship with heavy drinking had been reported in the BDES and was attributed to the fact that heavy alcohol intake may reduce antioxidant nutrients, resulting in increased oxidant stress in the retina.[33,34] However, only a few studies have found a relationship between alcohol consumption and AMD.[35] Heavy drinking is often associated with heavier cigarette smoking, so it is possible that a small amount of the smoking effect seen in this study may be attributable to heavy drinking.

Higher serum HDL cholesterol level was associated with lower prevalence of early AMD in the BOSS. The protective effect of serum HDL cholesterol level in the BOSS, an approximate 10% reduction in the odds per 5 mg/dL increase in HDL level (to convert to millimoles per liter, multiply by 0.0259) while controlling for other factors, was consistent with data from the Blue Mountains Eye Study but not most epidemiological studies.[35,36] In the BDES and the Rotterdam Study, high serum HDL cholesterol level was associated with higher 5-year incidence of geographic atrophy.[37-39] The Multi-Ethnic Study of Atherosclerosis, the Pathologies Oculaires Liées à l'Age study, and a case-control study by Hyman et al also found a positive relationship between HDL cholesterol level and AMD.[40-42] The reasons for the inconsistencies among studies are not understood. Most studies of early AMD found either a protective association or no association, whereas most studies reporting an adverse association were studying late-stage AMD. Differences in the distribution of AMD end points (and definitions), sex, age of the cohorts, and serum HDL levels may contribute to the lack of consistency across studies. Given the younger age in the BOSS compared with these studies, it is likely that this is an important factor in explaining the discrepancies. It is possible that among younger adults (including premenopausal women), serum HDL level has a protective effect for the development of early lesions that is not detectable at older ages. The opposite (positive) association observed for late AMD in some older cohorts may reflect the effects of early mortality for people with lower serum HDL levels or differences in effects of factors that contribute to the development of early stages of AMD compared with those that contribute to the transition from early AMD to late AMD. Understanding the longitudinal relationships is further complicated by the impact of the changing patterns of medication usage, including antihypercholesterolemia agents and hormone replacement therapy, which have occurred during many of the older studies. Long-term follow-up studies from younger ages are needed to determine the impact of serum HDL level on the development and progression of early AMD.

Although atherosclerosis of the choroidal circulation and lipid deposition in the Bruch membrane have been thought to increase the risk of AMD, the BOSS data did not show a relationship between IMT or serum total cholesterol level and early AMD.

Few data are available regarding the relationship between hearing loss and AMD in large cohorts.[43] The finding in the BOSS of an increase in the odds of having early AMD in those with hearing loss compared with those without, after controlling for age and other risk factors, is consistent with the increased risk of late AMD (OR, 3.2) among persons with hearing loss in the BDES. The effect was more pronounced among younger persons in the BOSS cohort (age, <55 years), suggesting possible differences in the age-related processes affecting the retinal pigment epithelium and Bruch membrane that lead to development of signs of early AMD in the eye and changes in the cochlea or the auditory nerve that causes hearing loss. It is possible that this association reflects uncontrolled residual confounding from shared risk factors for these 2 age-related sensory disorders. Alternatively, given the strong sex difference in hearing loss,[9] some of the variability attributable to sex may be reflected in this point estimate.

There are many strengths to this study, including the use of standardized protocols to measure risk factors and AMD end points. It is the largest study including younger adults and provides important insights about the onset of AMD. Participation was unrelated to the health (AMD, cardiovascular disease, or diabetes) of the parent population and unrelated to patterns of parental smoking and drinking. Although less educated families were slightly more likely to be included in these analyses, neither this study nor the BDES have demonstrated an association between educational level and AMD. Therefore, it is unlikely that the prevalence estimates have been affected by participation bias. Although this population is predominantly non-Hispanic white, these data provide im-

portant estimates of the prevalence of AMD in baby boomers and younger generations not previously studied. Studying the offspring from a population-based cohort is a strong design for evaluating the impact of changing environmental and behavioral exposures in a genetically similar group. The consistency of the reported results when adjusting for familial correlations as well as their consistency with other published studies adds to the evidence that early AMD may be preventable at younger ages.

Any conclusions or explanations regarding associations or lack of them, described herein, must be made with caution for a number of reasons, including the cross-sectional design. In this middle-aged cohort, the concomitant low frequency of some risk factors (eg, maximum IMT >1.0 mm) and of the prevalence of early AMD limits our ability to detect or reject meaningful relationships. Some factors important in the development of late, vision-threatening stages might contribute to the progression of the disease but not to the development of early lesions, and, therefore, would be missed in this study of early stages of AMD. As in other studies of AMD, there may be misclassification of factors and uncontrolled confounding that might impact the effect size estimates. Direct comparisons with the BDES must also be made with caution in that 3.6% of the BOSS cohort with gradable photographs were also participants in the baseline BDES. However, removing these participants from the BOSS did not change any of the reported associations (R.K. and K.J.C., unpublished data, 2009).

In summary, the BOSS data provide precise estimates of the prevalence of various signs of AMD (soft drusen, pigmentary abnormalities) over a wide spectrum of ages from the third to the ninth decade of life. They demonstrate that early AMD onset may occur in midlife. Some modifiable factors (smoking status and serum HDL cholesterol level) associated with AMD in older cohorts were associated with early AMD in this cohort of middle-aged adults. The higher frequency of AMD in people aged 65 years or older in an aging American population makes this an important public health problem. Further information regarding the natural history of AMD and its risk factors, especially early in life, is important for developing preventive approaches to it.

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Correspondence: Ronald Klein, MD, MPH, Department of Ophthalmology and Visual Sciences, School of Medicine and Public Health, University of Wisconsin, 610 N Walnut St, Room 417 WARF, Madison, WI 53726 (kleinr@epi.ophth.wisc.edu).
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Since the author has maintained the view that in transplantation of the cornea, analogously with that of all other tissues, a gradual replacement of the transplanted flap takes place through the entrance of elements from the neighborhood and that this explains both the regular mishaps attendant on total keratoplasty in cases of total adherent leucomata and also the maintained clearness of the flaps in partial keratoplasty and in total in clear animal corneas, our knowledge concerning transplantation has become broader. But the overwhelming majority of successful transplantations of the thyroid, ovary, and breast, are cases of autoplasty, simple displacement in the same individual, while homoplasty is much less promising, and the possibility of a successful heteroplasty can be looked for only in the lower species of animals. Hence it is physiologically impossible that the cornea of a rabbit can be transplanted into the eye of a man and preserve its structure. According to the results of Fuchs and Zirm, the use of human cornea evidently affords better chances for the preservation of large portions of the flap.

Reference: Salzer F. Experimental contributions to the question of keratoplasty: presentation to the Heidelberg Ophthalmological Society, August 7, 1908. *Arch Ophthalmol*. 1909;38:70-71.

Note: Fritz Salzer (1867-1952), an ophthalmologist from Munich, Germany, was a pioneer in keratoplasty and keratoprosthesis.