The Relationship of Cardiovascular Disease and Its Risk Factors to Age-related Maculopathy

The Beaver Dam Eye Study

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Purpose: To examine the association between cardiovascular disease and its risk factors to age-related maculopathy in a population-based study of people between the ages of 43 and 86 years (n = 4926) between 1988 and 1990.

Methods: Population-based prevalence study using standardized protocols for physical examination, blood collection, administration of a questionnaire, and stereoscopic color fundus photography to determine age-related maculopathy. Standard univariate and multivariate analyses were performed.

Results: After controlling for age, early age-related maculopathy was related to low total serum cholesterol levels in women and a high high-density lipoprotein (HDL) cholesterol level and a low total cholesterol/HDL-cholesterol ratio in men. After controlling for age and sex, age-related exudative macular degeneration was associated with higher hematocrit values (odds ratio, 1.09; 95% confidence interval, 1.00, 1.19) and higher leukocyte count (odds ratio, 1.10; 95% confidence interval, 1.00, 1.19). There was no statistically significant relationship between blood pressure, hypertension, or history of cardiovascular disease and exudative macular degeneration or geographic atrophy.

Conclusion: With the exception of relationships between serum lipids and early age-related maculopathy, and hematocrit values, leukocyte counts, and exudative macular degeneration, these data suggest that most cardiovascular disease risk factors are not related to age-related maculopathy. Further longitudinal study is needed.
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Macular degeneration is an important cause of visual loss and blindness in people 75 years of age or older in the United States.[1] It is not amenable to medical intervention. Photocoagulation treatment is of benefit in preventing visual loss in only a small percentage of people with this condition.[2,3] Because of this, there is a need to identify characteristics associated with macular degeneration that can be modified.

Cardiovascular disease and increased blood pressure, by their effects on the choroidal circulation, and lipids, by deposition in Bruch's membrane, have been hypothesized as possible pathogenetic factors for the development of macular degeneration.[4–10] However, data from case–control and population-based studies regarding these re-

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lationships have been inconclusive.[11–17] Some studies have reported a relationship between history of cardiovascular disease and age-related macular degeneration[10–14] while others have not.[15,16] In the Health and Nutrition Examination Survey (HANES), age-specific mean systolic, but not diastolic, blood pressure tended to be slightly higher in persons with macular degeneration than in those without.[17] However, no relationship was found between a history of hypertension and macular degeneration. A positive association was reported between elevated diastolic blood pressure at the first examination in the Framingham Heart Study and macular degeneration in survivors of the cohort who participated in the Framingham Eye Study 20 years later.[16] However, most case–control studies have failed to find a relationship between blood pressure, history of hypertension, or use of antihypertensive medications and age-related macular degeneration.[11,13,15] In addition, epidemiologic data regarding a relationship between serum lipids and other cardiovascular disease risk factors and macular degeneration are inconsistent.[14,16,18–21] The relationship of age-related maculopathy to cardiovascular disease risk factors and history of cardiovascular disease was studied in the population-based Beaver Dam Eye Study.

Materials and Methods

The Population

Methods used to identify the population and descriptions of it appear in previous reports.[22–24] Briefly, a private census of the population of Beaver Dam, Wisconsin was performed from September 15, 1987, to May 4, 1988. Eligibility requirements for entry into the study included living in the city or township of Beaver Dam and being 43 to 84 years of age at the time of the census. In 3715 of the 6612 households identified by the census, there was at least one person satisfying the age criteria. In these households, there were a total of 5833 individuals between the ages of 43 and 84 years at the time of the census. After completion of the census, 76 additional households with a total of 92 eligible people were identified, and these people were included in the population. The population was evaluated during a 30-month period beginning March 1, 1988. Of the 5925 eligible people, 4926 (83.1%) participated in the study. Two hundred seventy-seven people (4.7%) permitted an interview only, 226 (3.8%) had died before the examination, 92 people (1.6%) moved out of the area, 23 people (0.4%) could not be located, and 381 (6.4%) refused to participate. Comparisons between participants and nonparticipants have been presented elsewhere.[24]

Procedures

Informed consent was obtained at the beginning of the examination. Pertinent parts of the physical examination included measuring weight, height, pulse rate, and blood pressure (using a random-zero sphygmomanometer following the Hypertension Detection and Follow-up Program protocol[25]). A standardized questionnaire was administered by the examiners. Questions pertinent to this report appear in the Appendix. Casual blood specimens were obtained from participants. Serum cholesterol, high-density lipoprotein cholesterol, and blood glucose levels were determined by enzymatic procedures.[26–28] Hematocrit values and leukocyte counts were determined by using a Coulter counter method. Blood glycosylated hemoglobin was determined using affinity chromatography.[29]

Stereoscopic 30° color fundus photographs centered on the disc (Diabetic Retinopathy Study [DRS] Standard Field 1), macula (DRS Standard Field 2), and a nonstereoscopic color fundus photograph temporal to but including the fovea of each eye were taken.[30,31] Grading for age-related maculopathy was performed in a masked fashion using a standardized protocol, The Wisconsin Age-Related Maculopathy Grading scheme.[32,33] This system permits the assessment of the presence and severity of up to 14 lesions associated with age-related maculopathy. More detailed descriptions of these lesions appear elsewhere.[32–34] In brief, retinal drusen-type (presence of soft indistinct drusen or reticular drusen) and area of involvement and confluence, retinal pigment epithelial degeneration, and increased retinal pigment were determined. Pigmentary abnormality was defined as the presence of either retinal pigment epithelial degeneration or increased retinal pigment in the macular area. For purposes of analyses, retinal pigment epithelial degeneration, increased retinal pigment, or pigmentary abnormality was divided into two categories: none or questionable, and present.

Early age-related maculopathy was defined as the presence in the macular area of either (1) soft indistinct or reticular drusen or (2) hard or soft distinct drusen plus pigmentary abnormalities (both in the absence of signs of late age-related maculopathy as defined below). Late age-related maculopathy was defined as the presence of signs of exudative age-related macular degeneration or pure geographic atrophy. Exudative macular degeneration was defined as the presence of a retinal pigment epithelial detachment or serous detachment of the sensory retina, subretinal, or subretinal pigment epithelial hemorrhage and/or subretinal fibrous scars. Pure geographic atrophy was defined as the presence of geographic atrophy and the absence of exudative macular degeneration. For purposes of analyses, two categories were used: absent or questionable, and present.

When two eyes of a participant were discrepant in the presence or severity of a lesion, the grade assigned for the participant was that of the more severely involved eye. For example, in assigning the presence of retinal pigment epithelial degeneration, if retinal pigment epithelial degeneration was present in one eye but not the other, the participant would be considered to have retinal pigment epithelial degeneration. When drusen or signs of age-related maculopathy could not be graded in one eye, the participant was assigned a score equivalent to that in the other eye.

For purposes of this report, only the 4771 people (96.9%) with gradable fundus photographs of at least one

eye and without a lesion unrelated to age-related maculopathy are included in the analyses. Comparisons between people included in the analyses and those who had neither eye included are presented elsewhere.[34]

Definitions

Current age was defined as the age at the time of the examination. The mean systolic blood pressure was the average of the two systolic blood pressure determinations, and the mean diastolic blood pressure was the average of the two diastolic blood pressures. Pulse pressure was defined as systolic blood pressure minus diastolic blood pressure. Hypertension was defined as a mean systolic blood pressure of 160 mmHg and/or a mean diastolic blood pressure of 95 mmhg and/or a history of hypertension using antihypertensive medication at the time of examination. The body mass index was defined as body weight (kg)/height (m^2). The ratio of serum total cholesterol to high-density lipoprotein (HDL) cholesterol was computed.

A person was defined as having a positive history of cardiovascular disease if he/she responded affirmatively to the questions regarding use of digoxin or medications for angina, or history of angina, heart attack, or stroke. A person was defined as having diabetes if he/she had a previous history of diabetes mellitus, treated with insulin, oral hypoglycemic agents, and/or diet, or was newly discovered to have diabetes at the time of examination. This was defined as no reported medical history of diabetes mellitus nor use of hypoglycemic medications for diabetes mellitus with a casual blood sugar of higher than 11.1 mmol/L and a glycosylated hemoglobin value that was greater than two standard deviations above the mean for a given age–sex group (for those 43–54 years of age, men >9.5% and women >9.6%; for those 55–64 years of age, men >9.4% and women >10.0%; for those 65–74 years of age, men >9.6% and women >9.6%; and for those 75 years of age or older, men >9.5% and women >9.6%).

Cigarette-smoking status at the time of the examination was determined as follows. A subject was classified as having never smoked if he/she had smoked less than 100 cigarettes in his/her lifetime, as being an ex-smoker if he/she had smoked at least this number of cigarettes in his/her lifetime but had stopped smoking before the examination, or as currently smoking if he/she had not stopped.

Statistical Methods

For the analyses, we examined the relationships of cardiovascular disease and its risk factors with the specific maculopathy lesions and with three dichotomous endpoints of severity: absent versus early age-related maculopathy; absent or early age-related maculopathy versus exudative macular degeneration; and absent or early age-related maculopathy versus geographic atrophy. The Statistical Analysis System was used for calculating the chi-square statistic.[35] Tests for trends in proportions were performed with the Mantel-Haenszel procedure.[36] Logistic regression was used to determine whether cardiovascular disease or its risk factors were associated with the prevalence of signs of age-related maculopathy while controlling for age and other risk factors for these lesions (e.g., diabetes status, smoking history, or history of alcohol use).[35] Tests for interaction were performed.

Results

The prevalences of specific maculopathy lesions, early age-related maculopathy, exudative macular degeneration, geographic atrophy, hypertension, heart attack, and stroke increased significantly ($P < 0.001$) with age in both sexes (Tables 1 and 2). Males had significantly ($P < 0.05$) higher frequencies of myocardial infarction than females after

Table 1. The Prevalence of Age-Related Maculopathy by Age and Sex in the Beaver Dam Eye Study (1988–1990)

	Soft Indistinct Drusen		Retinal Pigment Epithelial Degeneration		Increased Retinal Pigment		Pigmentary Abnormalities		Early Age-related Maculopathy		Exudative Macular Degeneration		Geographic Atrophy	
Age (yrs)	*No. at Risk*	*(%)*	*No. at Risk*	*(%)*	*No. at Risk*	*(%)*	*No. at Risk*	*(%)*	*No. at Risk*	*(%)*	*No. at Risk*	*(%)*	*No. at Risk*	*(%)*
Female														
43-54	789	(1.9)	789	(2.2)	789	(4.3)	789	(4.9)	788	(6.6)	789	(0.1)	788	(0.0)
55-64	678	(6.0)	687	(4.4)	687	(8.4)	687	(9.2)	684	(12.3)	686	(0.3)	685	(0.2)
65-74	722	(11.1)	722	(9.1)	722	(13.0)	722	(13.6)	711	(18.6)	719	(1.1)	714	(0.4)
75+	449	(21.8)	450	(23.3)	450	(26.7)	450	(29.1)	416	(32.2)	446	(6.7)	431	(3.5)
Total	2647	(8.8)	2648	(8.2)	2648	(11.6)	2648	(12.5)	2599	(15.5)	2640	(1.6)	2618	(0.7)
Male														
43-54	715	(2.2)	715	(5.3)	715	(9.7)	715	(9.9)	715	(10.5)	715	(0.0)	715	(0.0)
55-64	614	(5.7)	614	(8.1)	614	(12.7)	614	(14.2)	609	(15.8)	614	(0.8)	609	(0.0)
65-74	527	(10.3)	527	(8.7)	527	(13.9)	527	(14.4)	521	(17.7)	526	(1.0)	522	(0.2)
75+	264	(25.0)	264	(16.3)	264	(20.8)	264	(22.4)	250	(31.6)	257	(2.7)	259	(3.5)
Total	2120	(8.1)	2120	(8.4)	2120	(13.0)	2120	(13.8)	2095	(16.3)	2112	(0.8)	2105	(0.5)

Table 2. The Prevalence of Cardiovascular Disease by Age and Sex in the Beaver Dam Eye Study (1988–1990)

Age (yrs)	Hypertension No. at Risk	Hypertension (%)	Myocardial Infarction No. at Risk	Myocardial Infarction (%)	Stroke No. at Risk	Stroke (%)
Female						
43–54	789	(18.9)	788	(0.9)	783	(0.5)
55–64	684	(36.6)	685	(2.6)	681	(1.8)
65–74	721	(48.3)	710	(5.9)	715	(4.2)
75+	448	(58.9)	439	(8.4)	442	(7.5)
Total	2642	(38.3)	2622	(4.0)	2621	(3.0)
Male						
43–54	715	(26.0)	709	(2.7)	711	(0.8)
55–64	614	(36.6)	606	(8.9)	608	(2.8)
65–74	527	(42.7)	513	(15.2)	518	(5.2)
75+	262	(40.1)	260	(21.9)	258	(10.5)
Total	2118	(35.0)	2088	(10.0)	2095	(3.7)

65 years of age, whereas females had higher frequencies of hypertension and exudative macular degeneration.

Systolic blood pressure increased with increasing age, whereas diastolic blood pressure decreased with increasing age (Table 3). Total cholesterol/HDL cholesterol ratio increased with increasing age in females but decreased with increasing age in males. Body mass index decreased with increasing age only in males.

Pulse pressure increased with increasing age in both sexes (data not shown). Pulse and hematocrit levels decreased in males, whereas hematocrit levels increased in females with increasing age (data not shown). There was no relationship of leukocyte count to age (data not shown). Males had significantly ($P < 0.05$) higher age-specific hematocrit levels and leukocyte counts compared with females.

After controlling for age, systolic blood pressure was significantly ($P < 0.05$) related to the presence of retinal pigment epithelial degeneration, and pulse pressure was related to the presence of retinal pigment epithelial degeneration, increased retinal pigment, and pigmentary abnormalities in females, but not in males (Table 4). Diastolic blood pressure or hypertension, as defined in the study, was not related to drusen area, drusen confluence (data not shown), or other signs associated with early age-related maculopathy in either sex (Table 4).

After controlling for age, total serum cholesterol level was significantly and inversely related to retinal pigment epithelial degeneration, increased retinal pigment, and pigmentary abnormalities in males (Table 5). Total cholesterol level was inversely related to early age-related maculopathy in females and in males 75 years of age or older. In the latter group, there was a 34% decrease in the relative odds ratio for early age-related maculopathy for each 1 mmol/l increase in serum cholesterol. High-density lipoprotein cholesterol was significantly related to soft indistinct drusen ($P = 0.03$) and early age-related maculopathy ($P = 0.006$) in men only. This relationship remained after controlling for alcohol consumption during the year before the examination (data not shown). The total cholesterol/HDL cholesterol ratio was inversely related to soft

Table 3. Blood Pressure, Serum Total Cholesterol Level, High-density Lipoprotein Cholesterol, Total Cholesterol Level to High-density Lipoprotein Cholesterol Ratio and Body Mass Index by Age and Sex in the Beaver Dam Eye Study (1988–1990)

Age (yrs)	Systolic BP (mmHG) No.	Systolic BP (mmHG) Mean ± SD	Diastolic BP (mmHg) No.	Diastolic BP (mmHg) Mean ± SD	Total Cholesterol Level (mmol/L) No.	Total Cholesterol Level (mmol/L) Mean ± SD	HDL Cholesterol (mmol/L) No.	HDL Cholesterol (mmol/L) Mean ± SD	Total Cholesterol/ HDL Cholesterol No.	Total Cholesterol/ HDL Cholesterol Mean ± SD	Body Mass Index (kg/m²) No.	Body Mass Index (kg/m²) Mean ± SD
Female												
43–54	789	121.5 ± 17.4	789	77.7 ± 10.1	787	5.8 ± 1.1	787	1.5 ± 0.43	787	4.2 ± 1.6	786	27.6 ± 6.0
55–64	687	131.2 ± 20.8	687	77.8 ± 10.5	685	6.4 ± 1.1	685	1.5 ± 0.44	685	4.7 ± 1.6	686	28.6 ± 6.4
65–74	722	136.5 ± 21.3	722	75.2 ± 9.8	720	6.4 ± 1.1	720	1.5 ± 0.51	720	4.9 ± 2.2	720	27.8 ± 5.4
75+	450	142.5 ± 21.5	450	72.2 ± 11.2	450	6.4 ± 1.2	449	1.4 ± 0.45	449	4.9 ± 2.0	440	27.3 ± 5.1
Total	2648	131.7 ± 21.5	2648	76.1 ± 10.5	2642	6.2 ± 1.2	2641	1.5 ± 0.46	2641	4.6 ± 1.9	2632	27.9 ± 5.8
Male												
43–54	715	128.0 ± 16.0	715	82.4 ± 10.6	712	5.9 ± 1.1	709	1.2 ± 0.37	709	5.6 ± 2.3	713	28.7 ± 4.6
55–64	614	133.5 ± 18.8	614	80.1 ± 10.3	611	6.0 ± 1.1	611	1.2 ± 0.40	610	5.5 ± 1.9	611	28.8 ± 4.2
65–74	527	136.2 ± 20.6	527	77.4 ± 11.0	526	5.8 ± 1.0	526	1.2 ± 0.41	526	5.4 ± 1.8	524	28.4 ± 4.2
75+	265	135.6 ± 21.6	265	72.0 ± 11.7	266	5.6 ± 1.0	266	1.2 ± 0.39	266	5.2 ± 1.7	260	27.3 ± 4.3
Total	2121	132.6 ± 19.0	2121	79.2 ± 11.3	2115	5.9 ± 1.1	2112	1.2 ± 0.39	2111	5.4 ± 2.0	2108	28.5 ± 4.4

BP = blood pressure; HDL = high-density lipoprotein; SD = standard deviation.

Table 4. The Relationship of Blood Pressure and Hypertension to Signs of Age-related Maculopathy and Early Age-related Maculopathy after Controlling for Age in the Beaver Dam Eye Study (1988–1990)

Characteristics	Soft Indistinct Drusen		Retinal Pigment Epithelial Degeneration		Increased Retinal Pigment		Pigmentary Abnormalities		Early Age-related Maculopathy	
	Odds Ratio	*95% CI*	*Odds Ratio*	*95% CI*	*Odds Ratio*	*95% CI*	*Odds Ratio*	*95% CI*	*Odds Ratio*	*95% CI*
Female										
Systolic blood pressure (/10 mmHg)	0.98	0.92, 1.05	1.07	1.00, 1.14	1.05	0.99, 1.11	1.05	0.99, 1.11	1.02	0.97, 1.08
Diastolic blood pressure (/10 mmHg)	0.97	0.85, 1.11	1.01	0.88, 1.16	0.99	0.88, 1.11	0.99	0.89, 1.11	1.04	0.94, 1.15
Pulse pressure (/10 mmHg)	0.98	0.91, 1.06	1.10	1.01, 1.19	1.07	1.00, 1.15	1.08	1.01, 1.15	1.02	0.95, 1.08
History of hypertension	1.16	0.87, 1.55	0.98	0.73, 1.32	1.13	0.88, 1.46	1.10	0.86, 1.41	1.18	0.94, 1.48
Male										
Systolic blood pressure (/10 mmHg)	1.00	0.93, 1.09	1.04	0.96, 1.13	1.05	0.98, 1.12	1.05	0.98, 1.12	1.04	0.98, 1.10
Diastolic blood pressure (/10 mmHg)	1.01	0.87, 1.16	1.00	0.87, 1.16	1.00	0.89, 1.12	1.00	0.89, 1.12	1.02	0.92, 1.14
Pulse pressure (/10 mmHg)	1.00	0.92, 1.11	1.06	0.97, 1.17	1.08	0.99, 1.17	1.07	0.99, 1.16	1.05	0.97, 1.13
History of hypertension	1.00	0.72, 1.40	1.24	0.90, 1.70	1.07	0.82, 1.39	1.08	0.84, 1.40	0.97	0.76, 1.24

CI = confidence interval.

Table 5. The Relationship of Cardiovascular Disease Risk Factors to Specific Signs of Age-related Maculopathy and Early Age-related Maculopathy after Controlling for Age in the Beaver Dam Eye Study (1988–1990)

Characteristics	Soft Indistinct Drusen		Retinal Pigment Epithelial Degeneration		Increased Retinal Pigment		Pigmentary Abnormalities		Early Age-related Maculopathy	
	Odds Ratio	*95% CI*	*Odds Ratio*	*95% CI*	*Odds Ratio*	*95% CI*	*Odds Ratio*	*95% CI*	*Odds Ratio*	*95% CI*
Female										
Cholesterol (/mmol/L)	0.90	0.79, 1.02	0.89	0.78, 1.01	0.91	0.82, 1.02	0.91	0.82, 1.01	0.89	0.80, 0.98
HDL cholesterol (/mmol/L)	1.16	0.87, 1.55	0.75	0.56, 1.01	0.86	0.67, 1.10	0.87	0.67, 1.13	1.09	0.86, 1.37
Cholesterol/HDL cholesterol	0.94	0.87, 1.02	0.99	0.92, 1.06	0.98	0.92, 1.04	0.97	0.91, 1.04	0.95	0.89, 1.01
Body mass index (/kg/m^2)	1.00	0.97, 1.02	1.03	1.01, 1.06	1.03	1.01, 1.05	1.03	1.01, 1.05	1.01	0.99, 1.03
Male										
Cholesterol (/mmol/L)	0.93	0.80, 1.09	0.85	0.73, 0.99	0.87	0.77, 0.98	0.88	0.78, 0.99	Interaction*	
HDL cholesterol (/mmol/L)	1.53	1.05, 2.23	1.09	0.77, 1.55	1.15	0.87, 1.53	1.18	0.87, 1.61	1.48	1.12, 1.97
Cholesterol/HDL cholesterol	0.91	0.82, 0.99	0.92	0.84, 1.01	0.93	0.86, 0.99	0.92	0.86, 0.99	0.89	0.84, 0.96
Body mass index (/kg/m^2)	0.99	0.95, 1.02	0.99	0.95, 1.03	1.00	0.97, 1.03	1.00	0.97, 1.03	0.99	0.97, 1.02

CI = confidence interval; HDL = high-density lipoprotein.

* Interaction with age for males (odds ratio; 95% CI) for early age-related maculopathy and cholesterol: 43–54 yrs (odds ratio, 1.00; 95% CI 0.81, 1.25); 55–64 yrs (odds ratio, 0.92; 95% CI 0.75, 1.13); 65–74 yrs (odds ratio, 1.02; 95% CI 0.82, 1.27); 75+ yrs (odds ratio, 0.66; 95% CI 0.51, 0.88).

indistinct drusen, increased retinal pigment, pigmentary abnormalities, and early age-related maculopathy in males but not females (Table 5).

After controlling for age, body mass index was associated with increased frequency of retinal pigment epithelial degeneration, increased retinal pigment, and increased presence of pigmentary abnormalities in females only (Table 5). There was no relationship between hematocrit level, leukocyte count, or pulse rate and any of the signs of early age-related maculopathy (data not shown).

A history of stroke, myocardial infarction, or cardiovascular disease was not associated with drusen area or other signs of age-related maculopathy in either females or males (data not shown).

Exudative age-related macular degeneration was infrequent in people younger than 65 years of age. For this reason, we limited analyses to those who were 65 years of age or older. After controlling for age and sex, higher hematocrit level and higher leukocyte count were significantly related to exudative macular degeneration (Table 6). This relationship remained after controlling for diabetes status and smoking history. After controlling for age and sex in people 65 years or older, no relationship was found between any of the other cardiovascular disease risk factors, myocardial infarction, stroke, or cardiovascular disease and exudative macular degeneration (Table 6). Similarly, because most of the cases of geographic atrophy were in people 75 years of age or older, we limited analyses to this group. We found no relationship of any of the cardiovascular disease risk factors or cardiovascular disease to geographic atrophy in people this age (Table 6).

Discussion

In females, total serum cholesterol level was inversely related to early age-related maculopathy, whereas in males the total cholesterol/HDL cholesterol ratio was inversely related and HDL cholesterol was positively related to early age-related maculopathy. This has not been previously reported by others. The relationship between high HDL cholesterol levels and early age-related maculopathy remained after controlling for alcohol consumption. The reasons for these relationships are not clear. A possible explanation is selective survival. That is, because people

Table 6. The Relationship of Various Cardiovascular Disease Risk Factors and Cardiovascular Disease to Exudative Macular Degeneration in People 65 Years of Age or Older and Geographic Atrophy in People 75 Years of Age or Older after Controlling for Age and Sex in the Beaver Dam Eye Study (1988–1990)

	Exudative Macular Degeneration		Geographic Atrophy	
Characteristic	*Odds Ratio*	*95% CI*	*Odds Ratio*	*95% CI*
Systolic blood pressure (/10 mmHg)	1.07	0.94, 1.21	0.98	0.81, 1.18
Diastolic blood pressure (/10 mmHg)	0.88	0.67, 1.15	0.73	0.50, 1.06
Pulse pressure (/10 mmHg)	1.13	0.98, 1.31	1.08	0.87, 1.32
Hypertension	0.79	0.44, 1.42	1.07	0.46, 2.47
Diastolic hypertension (>95 mmHg)	0.74	0.10, 5.54	*	—
Using antihypertensive medication	0.82	0.45, 1.49	*	—
Pulse rate (beats/min)	1.04	0.99, 1.08	1.04	0.97, 1.11
Cholesterol (/mmol/l)	1.12	0.88, 1.44	1.00	0.69, 1.46
HDL cholesterol (/mmol/l)	0.75	0.39, 1.48	0.89	0.34, 2.34
Cholesterol/HDL cholesterol	1.03	0.90, 1.17	1.00	0.81, 1.23
Body mass index (/kg/m^2)	1.02	0.97, 1.08	1.06	0.98, 1.14
Hematocrit level (1)	1.09	1.00, 1.19†	1.07	0.95, 1.20
Leukocyte count (10^9/l)	1.10	1.00, 1.19‡	1.08	0.92, 1.26
History of myocardial infarction	0.51	0.15, 1.68	0.95	0.27, 3.35
History of stroke	0.96	0.33, 2.79	0.38	0.05, 2.91
History of cardiovascular disease	0.67	0.33, 1.37	0.74	0.28, 1.90

CI = confidence interval; HDL = high-density lipoprotein.

* Likelihood failed to converge due to small cell sizes.

† $P = 0.03$.

‡ $P = 0.043$.

with higher cholesterol levels or lower HDL-cholesterol levels are at higher risk of cardiovascular death than people with normal levels of cholesterol, a positive relationship would be obscured.[37] To date, there are no data available that link severity or type of age-related maculopathy, hypercholesterolemia, and the risk of cardiovascular death.

There was no association between serum total cholesterol level, HDL cholesterol level, and serum cholesterol/HDL-cholesterol ratio with exudative macular degeneration or geographic atrophy. This is different than the strong positive association (odds ratio, 3.0) between HDL cholesterol and exudative macular degeneration recently found in a large case–control study of white men and women 50 to 79 years of age (Hyman L, et al; presented as a paper at the Association for Research in Vision and Ophthalmology Annual Meeting, Sarasota, FL, May 4, 1992) and a protective effect of higher serum cholesterol level (odds ratio, 0.51) to age-related macular degeneration in the HANES.[14] The reasons for these differences among studies are not clear.

Others have speculated that neutral fat deposition in Bruch's membrane may decrease hydraulic conductivity, resulting in the development of detachments of the retinal pigment epithelium.[10] Serum fatty acids and triglycerides were not measured in our study.

With the exception of relationships of systolic blood pressure to the presence of retinal pigment epithelial degeneration and pulse pressure to the presence of increased retinal pigment in females, there were no relationships between blood pressure, presence and duration of hypertension, hypertension control, or use of antihypertensive medications and early or late age-related maculopathy in our study. No relationship was found between blood pressure and macular area covered by retinal drusen, as had been previously reported by Viadurri et al.[38] Earlier case–control studies also found no relationship of hypertension to macular degeneration, although Hyman et al have reported a significant association of diastolic blood pressure of greater than 95 mmHg and exudative macular degeneration (odds ratio, 3.2) (Hyman L, et al; presented as a paper at the Association for Research in Vision and Ophthalmology Annual Meeting, Sarasota, FL, May 4, 1992). The relationship of higher systolic blood pressure and macular degeneration reported in the population-based HANES may have been due, in part, to classification of retinal pigment epithelial degeneration as macular degeneration in that study.[17] Severe hypertension may result in alterations of the pigment epithelium resulting in areas of hyperpigmentation.[39] However, in the absence of macular edema or severe elevations of blood pressure, pigmentary changes in the macular area have not been reported as being associated with hypertension.

Both higher leukocyte count and hematocrit level were weakly associated with exudative macular degeneration in the Beaver Dam population. These relationships were independent of smoking history. In a case–control study, Blumenkranz et al[13] reported an association between exudative macular degeneration and leukocyte count but not erythrocyte count. No relationship was reported between hematocrit level and macular degeneration in the HANES.[14] The underlying relationship between higher leukocyte count and exudative macular degeneration is not known. Chronic inflammatory cells have been found on the outer surface of Bruch's membrane, in association with breaks in Bruch's membrane and subretinal new vessels in histopathologic studies of eyes with exudative macular degeneration.[40–42] It is not known whether these localized inflammatory reactions are associated with a secondary increase in the leukocyte count. In addition, higher leukocyte counts have been postulated to cause microvascular injury and atherogenesis via direct release of leukocyte products such as proteolytic enzymes, long-acting antioxidants, and toxic oxygen compounds.[43] These products may lead to further damage of Bruch's membrane.

People with a known history of cardiovascular disease were not at increased risk of having signs of age-related maculopathy present. This is consistent with findings from the Framingham Eye Study.[16] However, Hyman et al reported that patients with exudative macular degeneration had a higher risk of stroke and cardiovascular disease than controls without macular degeneration.[11] It is possible that the failure to find relationships between stroke or myocardial infarction and exudative macular degeneration or geographic atrophy may be due to the low frequencies of both conditions in the population. It is also possible that differences among observations from different studies are a result of genetic variations in the groups studied.[11–17] In addition, methods used to detect and define age-related maculopathy also differ between investigations. Study design also may affect the findings. Results of case–control studies are affected by selection of the control group, whereas prevalence studies may have limited power and may be more sensitive to those who survive to participate in the study.

Conclusions regarding associations described herein must be made with caution. When setting a level of significance at $P = 0.05$, the accepted possibility for chance findings occurs in 1 in 20 comparisons. Thus, with our large number of comparisons the chance of finding at least 1 in 20 relations to be spuriously correlated is accepted.

In summary, cross-sectional data from this study suggest an inverse relationship between serum cholesterol level and a positive relationship of HDL cholesterol with early age-related maculopathy, a direct relationship of hematocrit level and leukocyte count to exudative macular degeneration, and no relationship of cardiovascular disease or hypertension with either early or late age-related maculopathy. Additional longitudinal study of the cohort will be necessary to understand the nature of these relationships.

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Appendix

A standardized questionnaire was administered by the examiners. The following questions were pertinent to this report:

1. Has a doctor ever told you that you had high blood pressure?
2. Have you ever taken prescription medicine(s) for high blood pressure?
3. Are you currently taking any medication for this?
4. What are the names of the blood pressure pills you are taking (or last took)?
5. Have you ever had angina. . .that is pressure (or pain) in the chest on exertion due to heart disease?
6. Have you ever taken or are you still taking digitalis, digoxin, or lanoxin, for your heart?
7. Have you ever taken or are you still taking nitroglycerin (Nitro-Bid), isosorbide dinitrate (Isordil), etc., for angina?
8. Has a doctor ever said you had a heart attack (coronary, or myocardial infarction, or coronary thrombosis, or coronary occlusion?)
9. Did a doctor ever tell you that you had a stroke or a brain hemorrhage?
10. Has a doctor ever said you had diabetes, sugar in your urine, or high blood sugar?
11. Have you smoked more than 100 cigarettes in your lifetime?
12. Do you smoke cigarettes now?
13. How many months or years ago did you stop?
14. Have you had any beer (ale), wine, or liquor in the past year?

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