Original Investigation

Incidence, Progression, and Associated Risk Factors of Medium Drusen in Age-Related Macular Degeneration
Findings From the 15-Year Follow-up of an Australian Cohort

Nichole D. L. Joachim, BSc(Hons); Paul Mitchell, MD, PhD; Annette Kifley, MAppStats, PhD; Jie Jin Wang, MMed, PhD

IMPORTANCE The natural course and prognosis of medium drusen and risk factors associated with the incidence and progression of this lesion type in age-related macular degeneration (AMD) are not well understood.

OBJECTIVE To assess the 15-year incidence and progression of medium drusen and associated risk factors.

DESIGN, SETTING, AND PARTICIPANTS Population-based cohort in the Blue Mountains region, west of Sydney, Australia. Included in the study were 3654 participants 49 years or older who attended baseline examinations of the Blue Mountains Eye Study (1992-1994), and 75.8%, 76.7%, and 56.1% of survivors who attended the 5-year, 10-year, and 15-year follow-up examinations, respectively.

MAIN OUTCOMES AND MEASURES Color retinal fundus photographs were obtained at each examination. The incidence and progression of medium drusen (maximum diameter, 63 to <125 μm) were assessed using Kaplan-Meier product-limit survival methods, controlling for competing risk of death. Factors associated with a 15-year incidence of medium drusen were assessed using discrete logistic regression models after adjusting for age, sex, smoking status, serum lipid levels, systemic and dietary factors, and *CFH* rs1061170 and *ARMS2* rs10490924 polymorphisms. Associations between lesion characteristics and the progression to late AMD were assessed using generalized estimating equation models and eye-specific data.

RESULTS Among 1317 participants at risk, the 15-year cumulative incidence of medium drusen was 13.9% (n = 281). Increasing age (per decade older) (odds ratio [OR], 1.4; 95% CI, 1.2-1.8) and the presence of at least 3 risk alleles of the *CFH* rs1061170 or *ARMS2* rs10490924 genes (OR, 2.1; 95% CI, 1.1-4.1) were associated with a higher incidence. There was no association between past smoking (OR, 0.8; 95% CI, 0.6-1.1) or current smoking (OR, 0.6; 95% CI, 0.4-1.1) and the development of medium drusen. The progression rate to late AMD in eyes with both medium drusen and retinal pigmentary abnormalities was 4-fold higher than that in eyes with medium drusen alone. Larger total area and central location of medium drusen were associated with a greater likelihood of the progression to worse stages of AMD.

CONCLUSIONS AND RELEVANCE Older age and the presence of *CFH* and *ARMS2* risk alleles are 2 main risk factors associated with the development of medium drusen. The copresence of medium drusen plus retinal pigment epithelium abnormalities signals a greater risk of the progression to late AMD than the presence of medium drusen alone.

JAMA Ophthalmol. doi:10.1001/jamaophthalmol.2015.0498
Published online April 2, 2015.

Author Affiliations: Centre for Vision Research, Department of Ophthalmology, University of Sydney, Sydney, Australia (Joachim, Mitchell, Kifley, Wang); Westmead Millennium Institute, Westmead Hospital, Westmead, Australia (Joachim, Mitchell, Kifley, Wang).

Corresponding Author: Jie Jin Wang, MMed, PhD, Centre for Vision Research, Department of Ophthalmology, University of Sydney, C24, Westmead, New South Wales, Australia 2145 (jiejin.wang@sydney.edu.au).

Early age-related macular degeneration (AMD) is characterized by the presence of drusen and retinal pigmentary abnormalities.[1,2] Drusen vary in size (diameter range, ≤63 to ≥250 µm) and type (hard, soft, distinct, and indistinct). Pigmentary abnormalities include clusters of pigment granules within the sensory retina (increased pigmentation) and sharply demarcated areas of retinal pigment epithelium (RPE) depigmentation.

The international classification and grading system for AMD categorizes medium drusen as intermediate soft drusen, defined as drusen with a maximum diameter of 63 to less than 125 µm, larger than the maximum diameter of hard drusen (<63 µm) but smaller than the minimum diameter of large soft drusen (≥ 125 µm).[1] A similar definition of this drusen type was used by the Age-Related Eye Disease Study[2] and clinical classification system,[3] categorized as medium drusen. Furthermore, the Wisconsin Age-Related Maculopathy Grading System[4] defines medium drusen by the maximum diameter, although the categorization of medium drusen is not used. In this study, we describe this type of drusen as medium drusen.

Despite recent interest in medium drusen and their inclusion in AMD incidence studies,[5,6] knowledge of the associated risk factors and the progression of medium drusen is limited. Medium drusen have been underrepresented in studies[3,7-9] compared with large drusen, soft drusen, and pigmentary lesions. In this study, we aimed to assess the 15-year incidence and progression of medium drusen in an older Australian cohort, as well as associations between common AMD risk factors and the development and progression of medium drusen.

Methods

Population

The Blue Mountains Eye Study (BMES) is a population-based cohort study of vision and eye disease in Australians 49 years or older residing in the Blue Mountains region, west of Sydney. The survey methods and the BMES baseline population have been previously described.[10,11] Briefly, 3654 residents (82.4% of those eligible) participated in baseline examinations from 1992 to 1994 (BMES I). Of these, 2334 (75.8% of survivors) were reexamined from 1997 to 1999 (BMES II), 1952 (76.7% of survivors) were reexamined from 2002 to 2004 (BMES III), and 1149 (56.1% of survivors) were reexamined from 2007 to 2009 (BMES IV). Baseline and all follow-up examinations were approved by human research ethics committees of the Western Sydney Area Health Service and the University of Sydney and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants at each visit.

Procedures

At each visit, a comprehensive interview with questionnaires on demographic and lifestyle factors and medical histories was conducted. A validated Food Frequency Questionnaire was self-administered by participants before each visit. Comprehensive eye examinations were performed as described previously.[10] Briefly, 30° stereoscopic retinal photographs of the macula and other retinal fields of both eyes were obtained using a fundus camera (FF3; Carl Zeiss) at the BMES I, II, and III examinations, and 40° photographs were obtained using a digital camera (CF-60 DSi with Ds Mark III body; Canon) at the BMES IV examination.

Photographic Grading

Retinal photographic grading of both eyes of each participant was conducted by 2 senior graders using a modified Wisconsin Age-Related Maculopathy Grading System protocol.[10] The Wisconsin Age-Related Maculopathy Grading System grid consists of 3 concentric circles that subdivide the macula from the foveal center, with radii of 500, 1500, and 3000 µm that demarcate the central, inner, and outer subfields of the macula, respectively. The grid was superimposed on the macula during the grading. The grading procedures and intergrader and intragrader agreements have been previously described,[10] with quadratic weighted κ values ranging from 0.64 to 0.93 and 0.54 to 0.94, respectively. Adjudication was provided by a senior retinal specialist (P.M.) if needed.

Late AMD was defined per an international age-related maculopathy classification[1] as the presence of neovascular AMD (indicated by RPE or neurosensory subretinal detachment, retinal or subretinal hemorrhage, subretinal fibrosis or old atrophic disciform scars, or photocoagulation scars) or the presence of geographic atrophy. Early AMD was defined as the presence of large (diameter, ≥125 µm) indistinct soft drusen or reticular drusen or the presence of large distinct soft drusen and retinal pigmentary abnormalities (hyperpigmentation and depigmentation of RPE cells) within the macula, in the absence of any late AMD lesions. The maximum diameters of individual drusen and collective macular areas involved by drusen and pigmentary abnormalities within the eye were estimated as specified in the Wisconsin Age-Related Maculopathy Grading System[4] using circles with diameters of 63, 125, 250, 350, and 644 µm, 0.5 disc area, and 1 disc area.

Definition of Medium Drusen Incidence and Progression

The incidence of medium drusen was defined as its presence at the 5-year, 10-year, or 15-year follow-up visit in persons who had no drusen or hard drusen only in any eye at baseline visits. The progression of medium drusen was defined as a progression to worse AMD lesions, including large soft drusen, retinal pigmentary abnormalities, or late AMD at follow-up visits, in eyes with medium drusen as the most severe lesion at baseline visits.

Genotyping

Genotyping data were available in 2761 participants of the BMES cross-section II examinations, which included the original cohort and BMES extension survey (1999-2000) samples. A custom array (Human 670-Quad, version 1; Illumina Inc) was used, with stringent quality control testing using a whole-genome association analysis tool set (PLINK, version 1.07; http://pngu.mgh.harvard.edu/purcell/plink/). After quality control checking, 2534 participants with genome-wide association study data

Table 1. Fifteen-Year Incidence of Medium Drusen by Age and Sex[a]

	Women		Men		Both	
Age, y	No. of Cases/No. at Risk	% (95% CI)	No. of Cases/No. at Risk	% (95% CI)	No. of Cases/No. at Risk	% (95% CI)
15-Year Kaplan-Meier Incidence of Medium Drusen						
49-54	32/145	28.5 (20.8-38.3)	17/110	19.9 (12.7-30.3)	49/255	24.7 (19.1-31.6)
55-64	68/319	28.9 (23.3-35.4)	49/257	27.0 (20.8-34.6)	117/576	28.1 (23.8-32.9)
65-74	59/219	41.1 (31.3-52.7)	43/167	43.9 (32.8-57.0)	102/386	42.7 (35.1-51.3)
≥75	8/51	15.7 (8.2-28.9)	5/49	15.8 (5.5-40.5)	13/100	16.2 (8.6-29.4)
Total	**167/734**	32.2 (28.0-36.9)	**114/583**	29.0 (24.5-34.3)	**281/1317**	30.8 (27.7-34.3)
15-Year Cumulative Incidence of Medium Drusen After Controlling for Competing Risk of Death						
49-54	13/145	24.1 (17.0-31.2)	8/110	16.8 (9.7-23.9)	21/255	20.9 (15.8-25.9)
55-64	37/319	22.2 (17.6-26.7)	48/257	17.6 (13.3-21.9)	85/576	20.0 (16.9-23.2)
65-74	63/219	17.8 (13.9-21.8)	79/167	13.0 (9.7-16.4)	142/386	15.5 (13.0-18.1)
≥75	40/51	2.5 (0.8-4.1)	39/49	1.8 (0.3-3.3)	79/100	2.2 (1.0-3.3)
Total	**153**/734	15.8 (13.7-17.9)	**174/583**	11.8 (9.9-13.7)	**327/1317**	13.9 (12.5-15.3)

[a] The definition of medium drusen herein excludes larger soft drusen, retinal pigmentary abnormalities, and late age-related macular degeneration.

were imputed with a genetic variation catalog (1000 Genomes, version 1; http://www.1000genomes.org/) using a software program (IMPUTE, version 2.0; https://mathgen.stats.ox.ac.uk/impute/impute_v2.html).[12] The imputation r^2 coefficients were 0.968 for *CFH* (OMIM 134370) rs1061170 and 0.996 for *ARMS2* (OMIM 611313) rs10490924.

The *CFH* single-nucleotide polymorphism rs1061170 was also genotyped in 1928 participants using an assay (TaqMan; Applied Biosystems),[13] and the *ARMS2* single-nucleotide polymorphism rs10490924 was genotyped in 638 participants using restriction fragment length polymorphism analysis.[14] Imputed single-nucleotide polymorphisms of these 2 genes were used for the remaining participants. Of the 1544 and 547 participants who had both typed and imputed rs1061170 and rs10490924, respectively, the concordance rates between typed and imputed single-nucleotide polymorphisms were 99.6% for rs1061170 and 99.2% for rs10490924.

Other Risk Factors

Participants were classified as nonsmokers if they answered no to the question of whether they smoke regularly. Past smoking was recorded if participants had smoked regularly but quit smoking at least 1 year before the examination. Current smoking was recorded if participants were current smokers or had stopped smoking less than 1 year before the examination. Alcohol consumption (including beer, wine, or spirits) was categorized as none, 1 to 2, or more than 2 standard drinks per day. These categories were based on Australian National Health and Medical Research Council[15] recommendations of no more than 2 standard drinks per day.

Systolic and diastolic blood pressure measurements were recorded from the first and fifth Korotkoff sounds using a mercury sphygmomanometer after participants had been seated for at least 5 minutes.[16] Dietary consumption and supplement use were extracted from the self-administered Food Frequency Questionnaire.[17] The Australian tables of food composition[18,19] and the US Department of Agriculture carotenoid food composition database[20] were used to estimate the intake of nutrients, including lutein and zeaxanthin intake in micrograms. Regular fish consumption was defined as consuming at least 1 serving of fish per week.

Fasting blood samples were collected from 3222 baseline participants to assess white blood cell count and cholesterol levels as previously described.[21-23] Briefly, white blood cell count was determined using cell counting methods (Coulter Counter; Beckman Coulter, Inc).[21] Total cholesterol, high-density lipoprotein cholesterol, and triglycerides concentrations were measured on a reflectance photometric analyzer (Reflotron; Roche Diagnostics).[22]

Statistical Analysis

A software package (SAS, version 9.3; SAS Institute Inc) was used for statistical analyses. The 15-year incidence of medium drusen was estimated using Kaplan-Meier product-limit survival estimates and competing risk analyses that control for competing risk of death among persons at risk of medium drusen, after excluding participants with any worse stage of early or late AMD lesions at baseline. Associations between common AMD risk factors (age, sex, smoking status, blood pressure, white blood cell count, fish consumption, alcohol consumption, antioxidant and zinc supplementation intake, *CFH* rs1061170 and *ARMS2* rs10490924 risk alleles, and total cholesterol, high-density lipoprotein cholesterol, and triglycerides concentrations) and the 15-year incidence of medium drusen were assessed using age- and sex-adjusted discrete logistic regression models. If these risk factors reached $P \leq .09$ in the age- and sex-adjusted regression models, they were included in the multivariable-adjusted logistic regression model. The final multivariable-adjusted logistic regression model included age, sex, past and current smoking, zinc supplementation, and the combined *CFH* rs1061170 and *ARMS2* rs10490924 risk alleles as covariables. The combined *CFH* rs1061170 and *ARMS2* rs10490924 risk alleles were categorized as none, 1, 2, or 3 or more.

Frequencies of the progression from medium drusen alone, as well as from medium drusen plus RPE abnormalities, to worsening stages of AMD were reported. Generalized estimating equation models using the GENMOD procedure

Table 2. Comparison of Baseline Characteristics of Participants With vs Without Incident Medium Drusen

Baseline Characteristic	Without Incident Medium Drusen	With Incident Medium Drusen	*P* Value
Age, mean (SD), y	62.1 (8.1)	62.3 (7.5)	.65
Female sex, %	54.7	59.4	.16
Smoking status, %			<.001[a]
Never smoker	47.8	61.8	
Past smoker	37.3	28.7	
Current smoker	14.8	9.5	
CFH rs1061170, %			.40[a]
TT	42.3	38.2	
CT	47.0	49.0	
CC	10.6	12.9	
ARMS2 rs10490924, %			.09[a]
GG	65.6	57.9	
GT	30.4	37.8	
TT	4.0	4.3	
CFH and *ARMS2* combined risk, %			.15[a]
No risk alleles	28.7	21.3	
1 Risk allele	40.6	44.0	
2 Risk alleles	25.5	27.6	
≥3 Risk alleles	5.2	7.1	
Blood pressure, mean (SD), mm Hg			
Systolic	143.4 (19.9)	144.6 (21.1)	.39
Diastolic	83.2 (10.0)	83.8 (9.1)	.38
White blood cell count, mean (SD), /μL	6371.8 (1760.9)	6175.4 (1409.6)	.06
Total cholesterol concentration, mean (SD), mg/dL	232.4 (40.7)	233.9 (42.2)	.60
High-density lipoprotein cholesterol concentration, mean (SD), mg/dL	55.3 (17.4)	56.4 (14.7)	.29
Triglycerides concentration, mean (SD), mg/dL	155.3 (90.8)	147.7 (97.9)	.23
Fish consumption of ≥1 serving per wk, %	60.3	60.2	.98
Alcohol consumption, standard drinks per d, %			.65[a]
None	29.6	31.6	
1-2	58.6	55.5	
>2	11.8	12.9	
Any antioxidant supplementation, %	36.1	35.2	.79
Any zinc supplementation, %	16.9	11.6	.04
Dietary lutein and zeaxanthin intake, mean (SD), μg	0.8 (0.5)	0.8 (0.4)	.55

SI conversion factors: To convert white blood cell count to $\times 10^9$/L, multiply by 0.001; to convert total and high-density lipoprotein cholesterol concentrations to millimoles per liter, multiply by 0.0259; to convert triglycerides level to millimoles per liter, multiply by 0.0113.

[a] Unadjusted tests for heterogeneity were used to calculate these *P* values.

(SAS, version 9.3; SAS Institute Inc)[24] were applied to eye-specific data to assess associations between medium drusen area and location characteristics and the progression to early or late AMD. Association estimates are presented as age- and sex-adjusted or multivariable-adjusted odds ratios (ORs) and 95% CIs.

Results

Prevalence of Medium Drusen

Of 3654 baseline participants, we excluded persons with late AMD (n = 75), early AMD (n = 185), or large soft distinct drusen (n = 113), and we included 3281 for the assessment of medium drusen. The status of medium drusen could be clearly defined in 2959 participants, among whom 534 (18.0%) had medium drusen, including 445 (83.3%) with medium drusen alone and 89 (16.7%) with medium drusen plus RPE abnormalities. Medium drusen was bilateral in 16.6% (74 of 445).

Incidence of Medium Drusen

Among 1317 persons without any AMD lesions at baseline who had been followed up, the 5-year, 10-year, and 15-year cumulative incidences of medium drusen were 10.1% (95% CI, 8.6%-11.9%), 17.7% (95% CI, 15.6%-20.1%), and 30.8% (95% CI, 27.7%-34.3%), respectively. After controlling for competing risk of death, the 5-year, 10-year, and 15-year cumulative incidences of medium drusen were 5.7% (95% CI, 4.8%-6.6%), 9.2% (95% CI, 9.1%-9.3%), and 13.9% (95% CI, 12.5%-15.3%). The 15-year incidences of medium drusen by age and sex are listed in **Table 1**. The incidence rates across all age groups were comparable, except for those 75 years or older. The incidence of medium drusen was slightly lower in men compared with women.

Table 3. Associations Between Known Age-Related Macular Degeneration Risk Factors and the 15-Year Incidence of Medium Drusen

Risk Factor	15-Year Incidence of Medium Drusen, Odds Ratio (95% CI)	
	Age and Sex Adjusted, Where Appropriate	Multivariable Adjusted[a]
Age, per decade older, y	1.4 (1.2-1.7)	1.4 (1.2-1.8)
Male sex	0.8 (0.6-1.0)	0.9 (0.6-1.2)
Smoking status		
Never smoker	1 [Reference]	1 [Reference]
Past smoker	0.7 (0.5-0.9)	0.8 (0.6-1.1)
Current smoker	0.6 (0.4-1.0)	0.6 (0.4-1.1)
CFH and *ARMS2* combined risk[b]		
No risk alleles	1 [Reference]	1 [Reference]
1 Risk allele	1.4 (1.0-2.0)	1.6 (1.1-2.4)
2 Risk alleles	1.4 (0.9-2.1)	1.5 (0.9-2.2)
≥3 Risk alleles	2.1 (1.1-3.9)	2.1 (1.1-4.1)
Zinc supplementation	0.7 (0.5-1.1)	0.7 (0.4-1.0)

[a] Adjusted for age, sex, past and current smoking, any zinc supplementation, and the combined *CFH* and *ARMS2* risk alleles.

[b] Single-nucleotide polymorphisms *CFH* rs1061170 and *ARMS2* rs10490924.

Baseline characteristics of participants with and without incident medium drusen are listed in **Table 2**. There were no significant differences in the mean age or the frequency of female sex between participants with and without incident medium drusen. However, participants with incident medium drusen were marginally more likely to have at least 1 risk allele of *ARMS2* rs10490924 and have a lower mean white blood cell count and were less likely to be past or current smokers or to take zinc supplementation.

Table 3 lists associations between known AMD risk factors and the incidence of medium drusen. Each decade increase in age was significantly associated with a 15-year incidence of medium drusen after adjusting for sex. The presence of at least 3 risk alleles of *CFH* rs1061170 and *ARMS2* rs10490924 combined was significantly associated with an increased risk of developing medium drusen (OR, 2.1; 95% CI, 1.1-3.9) after adjusting for age and sex. These associations remained similar after additional adjustment for past and current smoking and for zinc supplementation. The 15-year incidence of medium drusen was inversely associated with a higher intake of zinc; however, this association was marginally nonsignificant in both age- and sex-adjusted and multivariable-adjusted models. Risk factors, including smoking status, blood pressure, white blood cell count, serum lipid levels, fish and alcohol consumption, antioxidant supplementation, and lutein and zeaxanthin intake, were not significantly associated with the 15-year incidence of medium drusen in the age- and sex-adjusted models.

Progression of Medium Drusen

The frequency of the progression to large soft drusen in eyes with medium drusen alone was similar to that in eyes with medium drusen plus RPE abnormalities (41.8% and 50.0%, respectively; $P = .20$). However, the progression to late-stage AMD or late AMD lesions (geographic atrophy or neovascular AMD) was 4-fold higher in eyes with medium drusen plus RPE abnormalities compared with eyes with medium drusen alone (23.0% vs 5.0%). An example of medium drusen progression is shown in the **Figure**.

Table 4 summarizes the 15-year progression of medium drusen to early and late AMD in relation to total area and location of medium drusen. Eyes with medium drusen plus RPE abnormalities were excluded. After adjusting for age and sex, a large total area (≥375 µm) compared with a small total area (<375 µm) of medium drusen was significantly associated with high risk of developing early AMD (OR, 2.9; 95% CI, 1.5-5.4) and any (early or late) AMD (OR, 3.0; 95% CI, 1.6-5.5). However, it was not significantly associated with risk of late AMD (OR, 2.3; 95% CI, 0.8-6.8). After further adjusting for smoking status, fish consumption, and the presence of the *CFH* and *ARMS2* risk alleles, these associations remained. Similarly, the association between a central location of medium drusen and the development of early AMD (OR, 2.6; 95% CI, 1.4-4.8) and any AMD (OR, 2.4; 95% CI, 1.3-4.5) was significant after adjusting for these covariables.

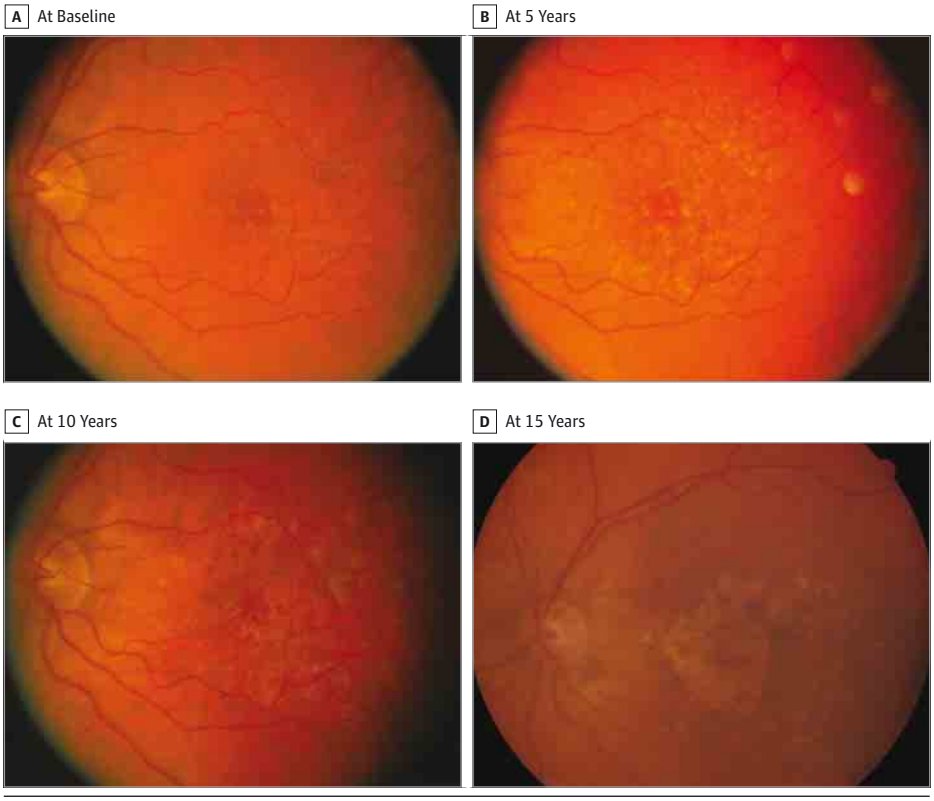
Discussion

We found that 13.9% of at-risk persons 49 years or older developed medium drusen over 15 years. The incidence of medium drusen did not appear to differ across the 3 age groups from 49 to 74 years, but it was slightly higher in women compared with men. The lower incidence of medium drusen observed in participants 75 years or older at baseline is likely because most persons in this age group had died or passed this early stage of AMD, and few participants in this age group were considered at risk of developing medium drusen.

A per decade increase in age and the presence of at least 3 risk alleles of *CFH* rs1061170 and *ARMS2* rs10490924 combined were independently associated with an increased risk of developing medium drusen. No other known AMD risk factors were found to be associated with the incidence.

Few population-based reports on the incidence of medium drusen are available in the literature. The 5-year, 10-year, and 15-year incidence rates of medium drusen in the BMES were 5.7%, 9.2%, and 13.9%, respectively. In the Reykjavik Eye Study,[25] a population-based study of residents in Iceland, the 5-year incidence of medium drusen increased with older age, ranging from 5.0% in individuals 50 to 59 years old to 22.7% in individuals 70 to 79 years old. In comparison, the overall 5-year incidence of medium drusen was 10.1% in the BMES (using the Kaplan-Meier method), or 5.7% after accounting for competing risk of death. The Copenhagen City Eye Study[26] reported a 27.4% 14-year incidence of medium drusen among persons 60 to 80 years old at baseline. The Beaver Dam Eye Study[27,28] found 14.0% and 23.9%, respectively, 10-year and 15-year cumulative incidences of medium drusen after adjusting for competing risk of death, higher than the 9.2% and 13.9% incidences at 10 years and 15 years, respectively, in our cohort study. Sources of disparity between our findings and the results of the Reykjavik Eye Study[25] and Copenhagen City Eye Study[26] likely include variations in defining medium drusen

Figure. An Example of the Progression of Medium Drusen



A, Left eye with medium drusen plus retinal pigment epithelium abnormalities at baseline. B, Large soft drusen at 5 years. C, More apparent retinal pigmentary abnormality at 10 years. D, Geographic atrophy at 15 years.

Table 4. Fifteen-Year Progression of Medium Drusen to Worse Age-Related Macular Degeneration (AMD) Stages by Medium Drusen Area and Location at Baseline[a]

Medium Drusen Characteristic	15-Year Progression to Worse AMD Stage								
	Early AMD			Any Late AMD			Any Early or Late AMD		
	No. of Cases/ No. at Risk	aOR (95% CI)		No. of Cases/ No. at Risk	aOR (95% CI)		No. of Cases/ No. at Risk	aOR (95% CI)	
		Age and Sex Adjusted	Multivariable Adjusted		Age and Sex Adjusted	Multivariable Adjusted		Age and Sex Adjusted	Multivariable Adjusted
Area									
Diameter <375 µm	73/308	1.0	1.0	13/327	1.0	1.0	76/311	1.0	1.0
Diameter ≥375 µm	41/68	2.9 (1.5-5.4)	3.2 (1.4-7.2)	9/71	2.3 (0.8-6.8)	1.6 (0.4-6.6)	44/71	3.0 (1.6-5.5)	3.3 (1.5-7.4)
P value	<.001	NA	NA	.03	NA	NA	<.001	NA	NA
Location									
Radius of the foveal center ≥500 µm	30/150	1.0	1.0	5/160	1.0	1.0	32/152	1.0	1.0
Radius of the foveal center <500 µm	82/222	2.6 (1.5-4.3)	2.6 (1.4-4.8)	17/235	3.1 (0.8-11.4)	3.5 (0.6-20.4)	86/226	2.5 (1.5-4.2)	2.4 (1.3-4.5)
P value	<.001	NA	NA	.06	NA	NA	<.001	NA	NA

Abbreviations: aOR, adjusted odds ratio; NA, not applicable.

[a] As defined in the Blue Mountains Eye Study, early AMD includes large indistinct soft or reticular drusen or large distinct soft drusen with retinal pigmentary abnormalities. Odds ratios are adjusted for age, sex, past and current smoking, fish consumption, and increasing numbers of *CFH* and *ARMS2* gene risk alleles (0, 1, or 2). *P* values are for differences in the number of cases between small vs large areas or between farther vs closer locations of intermediate drusen by AMD stage.

and different methods used to calculate the incidence estimates (eg, the competing risk approach was not used in the Reykjavik Eye Study or the Copenhagen City Eye Study). While the Beaver Dam Eye Study had a lower age limit (43 years at baseline) for their study sample, variations in other environmental exposures, as well as grading variations in defining medium drusen, could also explain the difference in incidence between our study and the BDES.[27,28]

The age-related increase in medium drusen incidence before adjusting for competing risk of death found herein is consistent with other AMD stages and lesions.[7,29,30] Past or current smoking was not associated herein with the 15-year

incidence of medium drusen as in previous BMES observations.[31,32] Although current smoking was previously strongly associated with the prevalence and incidence of late AMD, the association between smoking and early AMD was much weaker than that between smoking and late AMD.[31,32] Smoking may likely be a promoter, having a greater role in the progression from early to late AMD than in the initiation of early AMD.

We demonstrated that risk of the progression of medium drusen to late AMD was substantially higher for medium drusen plus RPE abnormalities. This parallels previous findings of faster progression from early to late AMD in eyes with large drusen plus RPE abnormalities compared with eyes with large drusen alone.[27,30,33] This observation supports the use of severity scales that incorporate multiple lesion types to better classify risk of the progression to late AMD.[2,3,34]

We also found that eyes with medium drusen located closer to the fovea or eyes with large total macular areas involved by medium drusen were more likely to progress to early AMD. The nonsignificant association of these characteristics with the progression to late AMD was likely due to the few incident late AMD cases in this cohort. These findings are consistent with the Beaver Dam Eye Study[28] in that the 15-year incidences of both early and late AMD were higher in eyes with a large total area of medium drusen at baseline compared with a small total area of medium drusen at baseline.

The strengths of this study include its long-term follow-up of an older Australian cohort, the use of retinal photographs, and the availability of a validated AMD grading system to assess the size and location of AMD lesions. Its limitations include the low follow-up rate at the 15-year examination, which could have led to an overestimation or underestimation of the incidence. Because only color fundus photographs rather than high-resolution imaging (eg, spectral-domain optical coherence tomography) were available during baseline and follow-up examinations, this may have led to an underestimation of the prevalence and incidence. However, we used only color photographs among the entire BMES cohort to ensure that the comparisons were valid. Although the medium drusen category has been included in retinal photographic grading since the 5-year follow-up examinations, side-by-side grading of baseline and follow-up retinal images provided precise classification of this drusen type.

Conclusions

In summary, the 15-year cumulative incidence of medium drusen was 13.9% in this at-risk older Australian cohort. The proportion of eyes that progressed to late AMD was significantly higher in eyes with medium drusen plus RPE abnormalities compared with eyes with medium drusen alone. Larger total area and central location of medium drusen were associated with a greater likelihood of the progression to worse stages of AMD. These findings are informative for the monitoring and management of patients at risk of early and late AMD.

ARTICLE INFORMATION

Submitted for Publication: November 27, 2014; final revision received January 16, 2015; accepted January 29, 2015.

Published Online: April 2, 2015. doi:10.1001/jamaophthalmol.2015.0498.

Author Contributions: Ms Joachim and Dr Wang had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Mitchell, Wang.
Acquisition, analysis, or interpretation of data: Joachim, Kifley, Wang.
Drafting of the manuscript: All authors.
Administrative, technical, or material support: All authors.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Mitchell reported being paid by Bayer Inc and Novartis Inc for consultancy, lectures (including service on speakers bureaus and travel), accommodation, and meeting expenses. No other disclosures were reported.

Funding/Support: This work was supported by grants 974159, 211069, and 457349 from the National Health and Medical Research Council of Australia.

Role of the Funder/Sponsor: The National Health and Medical Research Council of Australia had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Bird AC, Bressler NM, Bressler SB, et al; International ARM Epidemiological Study Group. An international classification and grading system for age-related maculopathy and age-related macular degeneration. *Surv Ophthalmol*. 1995;39(5):367-374.

2. Ferris FL, Davis MD, Clemons TE, et al; Age-Related Eye Disease Study (AREDS) Research Group. A simplified severity scale for age-related macular degeneration: AREDS report No. 18. *Arch Ophthalmol*. 2005;123(11):1570-1574.

3. Ferris FL III, Wilkinson CP, Bird A, et al; Beckman Initiative for Macular Research Classification Committee. Clinical classification of age-related macular degeneration. *Ophthalmology*. 2013;120(4):844-851.

4. Klein R, Davis MD, Magli YL, Segal P, Klein BE, Hubbard L. The Wisconsin Age-Related Maculopathy Grading System. *Ophthalmology*. 1991;98(7):1128-1134.

5. Jonasson F, Arnarsson A, Sasaki H, Peto T, Sasaki K, Bird AC. The prevalence of age-related maculopathy in Iceland: Reykjavik Eye Study. *Arch Ophthalmol*. 2003;121(3):379-385.

6. Chew EY, Clemons TE, Agrón E, et al; Age-Related Eye Disease Study Research Group. Ten-year follow-up of age-related macular degeneration in the age-related eye disease study: AREDS report no. 36. *JAMA Ophthalmol*. 2014;132(3):272-277.

7. Mitchell P, Wang JJ, Foran S, Smith W. Five-year incidence of age-related maculopathy lesions: the Blue Mountains Eye Study. *Ophthalmology*. 2002;109(6):1092-1097.

8. Klein R, Klein BE, Jensen SC, Meuer SM. The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 1997;104(1):7-21.

9. VanNewkirk MR, Nanjan MB, Wang JJ, Mitchell P, Taylor HR, McCarty CA. The prevalence of age-related maculopathy: the Visual Impairment Project. *Ophthalmology*. 2000;107(8):1593-1600.

10. Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia: the Blue Mountains Eye Study. *Ophthalmology*. 1995;102(10):1450-1460.

11. Attebo K, Mitchell P, Smith W. Visual acuity and the causes of visual loss in Australia: the Blue Mountains Eye Study. *Ophthalmology*. 1996;103(3):357-364.

12. Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet*. 2009;5(6):e1000529. doi:10.1371/journal.pgen.1000529.

13. Wang JJ, Rochtchina E, Smith W, et al. Combined effects of complement factor H genotypes, fish consumption, and inflammatory markers on long-term risk for age-related macular degeneration in a cohort. *Am J Epidemiol*. 2009;169(5):633-641.

14. Wang JJ, Ross RJ, Tuo J, et al. The *LOC387715* polymorphism, inflammatory markers, smoking, and age-related macular degeneration: a population-based case-control study. *Ophthalmology*. 2008;115(4):693-699.

15. National Health and Medical Research Council. *Australian Guidelines to Reduce Health Risks From Drinking Alcohol.* Canberra, Australia: National Health and Medical Research Council; 2009.

16. Wang JJ, Mitchell P, Rochtchina E, Tan AG, Wong TY, Klein R. Retinal vessel wall signs and the 5 year incidence of age related maculopathy: the Blue Mountains Eye Study. *Br J Ophthalmol*. 2004;88 (1):104-109.

17. Tan JS, Wang JJ, Flood V, Rochtchina E, Smith W, Mitchell P. Dietary antioxidants and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. *Ophthalmology*. 2008;115(2):334-341.

18. Department of Community Services and Health. *NUTTAB 90 Nutrient Data Table for Use in Australia.* Canberra: Australian Government Publishing Service; 1990.

19. Food Standards Australia New Zealand. *NUTTAB 2010.* Canberra: Food Standards Australia New Zealand; 2010.

20. Chug-Ahuja JK, Holden JM, Forman MR, Mangels AR, Beecher GR, Lanza E. The development and application of a carotenoid database for fruits, vegetables, and selected multicomponent foods. *J Am Diet Assoc*. 1993;93 (3):318-323.

21. Shankar A, Mitchell P, Rochtchina E, Tan J, Wang JJ. Association between circulating white blood cell count and long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. *Am J Epidemiol*. 2007;165(4):375-382.

22. Shankar A, Mitchell P, Rochtchina E, Wang JJ. The association between circulating white blood cell count, triglyceride level and cardiovascular and all-cause mortality: population-based cohort study. *Atherosclerosis*. 2007;192(1):177-183.

23. Tan JS, Mitchell P, Smith W, Wang JJ. Cardiovascular risk factors and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. *Ophthalmology*. 2007; 114(6):1143-1150.

24. *SAS/STAT 9.1 User's Guide: The GENMOD Procedure*. Version 3. Cary, NC: SAS Institute Inc; 2004:chap 31.

25. Jonasson F, Arnarsson A, Peto T, Sasaki H, Sasaki K, Bird AC. 5-year incidence of age-related maculopathy in the Reykjavik Eye Study. *Ophthalmology*. 2005;112(1):132-138.

26. Buch H, Nielsen NV, Vinding T, Jensen GB, Prause JU, la Cour M. 14-Year incidence, progression, and visual morbidity of age-related maculopathy: the Copenhagen City Eye Study. *Ophthalmology*. 2005;112(5):787-798.

27. Klein R, Klein BE, Tomany SC, Meuer SM, Huang GH. Ten-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 2002;109(10):1767-1779.

28. Klein R, Klein BE, Knudtson MD, Meuer SM, Swift M, Gangnon RE. Fifteen-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study. *Ophthalmology*. 2007;114 (2):253-262.

29. Joachim N, Mitchell P, Rochtchina E, Tan AG, Wang JJ. Incidence and progression of reticular drusen in age-related macular degeneration: findings from an older Australian cohort. *Ophthalmology*. 2014;121(4):917-925.

30. Wang JJ, Rochtchina E, Lee AJ, et al. Ten-year incidence and progression of age-related maculopathy: the Blue Mountains Eye Study. *Ophthalmology*. 2007;114(1):92-98.

31. Tan JS, Mitchell P, Kifley A, Flood V, Smith W, Wang JJ. Smoking and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. *Arch Ophthalmol*. 2007;125 (8):1089-1095.

32. Tomany SC, Wang JJ, van Leeuwen R, et al. Risk factors for incident age-related macular degeneration: pooled findings from 3 continents. *Ophthalmology*. 2004;111(7):1280-1287.

33. Klaver CC, Assink JJ, van Leeuwen R, et al. Incidence and progression rates of age-related maculopathy: the Rotterdam Study. *Invest Ophthalmol Vis Sci*. 2001;42(10):2237-2241.

34. Klein R, Meuer SM, Myers CE, et al. Harmonizing the classification of age-related macular degeneration in the Three-Continent AMD Consortium [published correction appears in *Ophthalmic Epidemiol*. 2014;21(3):204-205]. *Ophthalmic Epidemiol*. 2014;21(1):14-23.