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# Lipids, Lipid Genes and Incident Age-Related Macular Degeneration: The Three Continent Age-Related Macular Degeneration Consortium

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## Abstract

**Purpose—**To describe associations of serum lipid levels and lipid pathway genes to the incidence of age-related macular degeneration (AMD).

**Design—**Meta-analysis.

**Setting—**Three population-based cohorts.

**Population—**6950 participants from the Beaver Dam Eye Study (BDES), Blue Mountains Eye Study (BMES) and Rotterdam Study (RS).

**Observation Procedures—**Participants were followed over 20 years and examined at 5-year intervals. Hazard ratios (HRs) associated with lipid levels per standard deviation above the mean or associated with each additional risk allele for each lipid pathway gene were calculated using random-effects inverse-weighted meta-analysis models, adjusting for known AMD risk factors.

**Main Outcome Measures—**Incidence of AMD.

**Results—**The average 5-year incidences of early AMD were 8.1%, 15.1%, and 13.0% in the BDES, BMES, and RS, respectively. Substantial heterogeneity in the effect of cholesterol and lipid pathway genes on the incidence and progression of AMD was evident when the data from the three studies were combined in meta-analysis. After correction for multiple comparisons, we did not find a statistically significant association between any of the cholesterol measures, statin use, or serum lipid genes and any of the AMD outcomes in the meta-analysis.

**Conclusion—**In a meta-analysis, there were no associations of cholesterol measures, history of statin use, or lipid pathway genes to the incidence and progression of AMD. These findings add to inconsistencies in earlier reports from our studies and others showing weak associations, no associations, or inverse associations of high-density lipoprotein cholesterol and total cholesterol with AMD.


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One of the functions of the retinal pigment epithelium (RPE) is to digest the lipid-rich photoreceptors outer segments shed each day.[1] Some residual lipids deposit in Bruch's membrane as lipoproteins. These deposits increase with age and have been hypothesized to increase the risk of age-related macular degeneration (AMD), an important cause of severe visual impairment in older people. [2–7] The lipoprotein particles in Bruch's membrane contain free and esterfied cholesterol thought not to be derived from the plasma.[1–7] The finding of lipids in retinal drusen and the associations of a number of candidate genes involving lipid metabolism (e.g., hepatic lipase gene [*LIPC*], cholesteryl ester transfer protein [*CETP*], apolipoprotein E [*APOE*], and lipoprotein lipase [*LPL*]) with AMD provide further support of a role of lipids in the pathogenesis of AMD.[8–10]

However, epidemiological data have been inconsistent regarding the associations of serum lipid levels and AMD.[11–22] Few of these studies have examined the associations of both serum lipids and candidate lipid pathway genes for AMD and their interactions with the incidence and progression of AMD. The purpose of this report is to examine the associations of serum high density lipoprotein cholesterol (HDL-C) and total cholesterol levels, lipid pathway genes, and history of statin use with the incidence and progression of AMD in



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meta-analyses of findings from three large population-based cohort studies within the Three Continent AMD Consortium, the Beaver Dam Eye Study (BDES), the Blue Mountains Eye Study (BMES), and the Rotterdam Study (RS).

## METHODS

### Populations

The current study extends previous pooled data analyses or meta-analyses of baseline and 5-year follow-up data from the three population-based studies to assess risk factors associated with prevalent and incident AMD.[13,17,18] Methods used in the BDES, the BMES, and the RS, and descriptions of the three populations have been previously reported.[23–36] The second RS examination occurred approximately 2 years after baseline and 3 years before the third follow-up examination. To correspond with the 5-year spacing in the BDES and BMES, data from the second RS examination were not included in analyses and future RS examinations 3–5 were renumbered as 2–4 for these analyses. Approvals for each study and for the Three Continent AMD Consortium projects were granted by the Institutional Review Boards at all three study sites. Informed consent was obtained from each participant before every examination of each study. The tenets of the Declaration of Helsinki were observed.

Serum lipid levels were measured at the first three examination phases of each study. The incidence of AMD and AMD lesions was examined over the first three examination intervals. The timing of each examination phase, the number of participants at risk for AMD, and the median follow-up time to the next examination is presented for each study in Table 1.

Of the 4926 participants at the BDES baseline examination, the following were excluded: 162 because photographs of both eyes were not gradable for AMD, 62 because cholesterol was not measured, 1250 because the individual died or was lost to follow-up, 3 because data on statin use was not available, and 1222 because genotype data was not available. This left 2227 individuals eligible for analyses.

Of the 3654 participants at the BMES baseline examination, the following were excluded: 175 because photographs of both eyes were not gradable for AMD, 360 because cholesterol was not measured, 1042 because the individual died or was lost to follow up, and 482 because genotype data was not available. This left 1595 individuals eligible for analyses.

Of the 5232 participants in the RS baseline examination, the following were excluded: 47 because photographs of both eyes were not gradable for AMD, 1589 because the individual died or was lost to follow up, and 468 because genotype data was not available. This left 3128 individuals eligible for analyses.

In total, there were 14778 person-visits from 6950 individuals over a 23-year period (approximately 15 years of follow-up for each study). More than 99% of the participants in the three studies were white. In general, individuals who participated in follow-up examinations were more likely to be younger than nonparticipants who were alive or individuals who died and, while adjusting for age, were less likely to have AMD.[24–35]



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## Procedures

Similar procedures were used at baseline and follow-up examinations.[23] A standardized interview and examination were administered at each visit. Information on demographic characteristics, history of diabetes, myocardial infarction (MI), stroke and angina, a current history of hypertension, physical activity, smoking, and use of lipid-lowering drugs by type were obtained from the questionnaire. Body weight, height, and blood pressure were measured in all studies.

Casual blood specimens were obtained at the time of each examination in the BDES and at the RS baseline examination while fasting blood specimens were obtained at all BMES and the RS follow-up examinations. In the BDES, serum was used to measure total and HDL-C levels. Serum total cholesterol and HDL-C levels at each of the four visits were measured by reflectance spectrophotometry.[37,38] In the BMES, fasting blood specimens were drawn, centrifuged on site, and then sent by courier within the same day to the Westmead Hospital, Sydney, for hematological analysis and clinical biochemistry assessment. Serum total cholesterol and HDL-C were measured on a Reflotron reflectance photometric analyzer (Boehringer Mannheim Diagnostics, currently Roche Diagnostics). In the RS, blood was drawn directly into Vacutainer tubes (BD Biosciences, Heidelberg, Germany) and nonfasting serum total cholesterol and HDL-C concentrations were measured according to the CHOD-PAP method (Monotest Cholesterol kit, Boehringer Mannheim Diagnostics). Fasting serum total cholesterol and HDL-C concentrations were measured with a Roche Hitachi 917 (Roche Diagnostics) until April 2007. From April 2007 onward, parameters were measured with a Roche Modular P800 (Roche Diagnostics).

## Definitions

In all three studies, body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Presence of hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg and/or use of anti-hypertensive medication use. Smoking status was categorized as current (defined as having smoked 100 cigarettes in one’s lifetime and still smoking at the time of the examination) or not current. A current history of cardiovascular disease was defined as a current history of MI, stroke or angina.

In each analysis, the risk allele for each single nucleotide polymorphism (SNP) was defined as the minor allele. The minor allele was the same for all three studies for all of the SNPs assessed. The risk alleles for *CETP* (16q21) rs3764261 and rs1864163, *ABCA1* (9q31.1) rs1883025, *LIPC* (15q21-q23) rs7163555, and *LPL* (8p22) rs281 were “A”, “A”, “T”, “G” and “T”, respectively.

In the BDES, participants were asked to bring all current medications to the examination and medication names were recorded by a trained examiner. Statin use was defined as currently taking a medication with an active ingredient identified as a statin. Information on dosing and duration of use were not recorded. In the BMES, participants were asked to bring their medications when they attended the study examinations and the interviewer recorded names of the medications during the face-to-face interview. Some participants brought a list of their

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medications instead of actual medications. Statin use was defined as currently taking a medication with an active ingredient identified as a statin. In the RS, a home interview took place before every examination at which all medication names were recorded by a trained examiner. Statin use was defined as currently taking a medication with an active ingredient identified as a statin.

Analysts for each of the three studies were in regular contact to ensure common definitions of risk factors and covariates were used. In some cases, covariates could not be harmonized because of differences in the questions asked by each study at each examination phase. When this occurred, we did not adjust for these variables when modeling but presented data for these factors in Table 2. For example, in the BDES, a participant was considered physically active if he or she worked up a sweat at least once a week; in the BMES, if he or she did vigorous exercise in the past two weeks; and in the RS, if he or she participated in sports (this was only asked at the third RS examination). All three studies asked participants about a history of MI at every visit. Both the BDES and BMES asked questions about history of stroke and angina at each examination phase. The RS asked about a history of stroke at the baseline examination but only about a history of transient ischemic attack or "mini-stroke" at the follow-up visits and did not ask a question about a history of angina.

## Genetic Measurements

All eligible BDES study participants were genotyped using Taqman assays (Applied Biosystems, Foster City, CA) and/or a custom Illumina Infinium Panel (Illumina Inc., San Diego, CA). In addition to the custom Illumina genotyping, we also genotyped 10 SNPs that are reported to be associated with AMD in two recent meta-analyses[10,39] using the KASP assay (LCG Genomics, Teddington, Middlesex, UK). To maximize the number of markers, we imputed the untyped genotypes at 12 known AMD loci using the MACH program version 1[40] with HapMap CEU haplotypes (release #22) as the reference. Hardy-Weinberg equilibrium (HWE) tests were carried out for each SNP using PLINK[41] and SNPs with HWE test P value less than $1\times10^{-5}$ among the controls were excluded from the study.

In the BMES, all eligible study participants were genotyped using Illumina Human670-Quad v1 custom array at the Wellcome Trust Centre for Human Genetics, Sanger Institute, Cambridge as part of the Wellcome Trust Case Control Consortium 2. A smaller subset of participants (N=1356) was also independently genotyped using the Illumina 610-Quad genotyping array at the Hunter Medical Research Institute, Newcastle, Australia. Following quality control, the genotyped data were imputed from the 1000 Genomes (Version 1) reference using IMPUTE software. Genomic DNA was extracted from peripheral blood leukocytes. HWE tests were carried out and SNPs with P value less than $1\times10^{-6}$ were excluded.

All eligible study participants in the RS were genotyped with the Illumina Infinium II HumanHap550 array. HapMap CEU data (release #22) was used for imputation. During quality control the genotypes were checked twice for HWE: once after genotyping (HWE > $1\times10^{-7}$) and after imputation (HWE > $1\times10^{-6}$).

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## Fundus Photography and Grading

Details regarding fundus photography, grading and harmonization of the phenotype are described elsewhere.[13,17,18,23] The severity of AMD was determined using the Three Continent AMD severity scale (a modification of the 5-step BDES AMD Severity Scale.[23]

Analyses were performed using data from the worse eye. When one eye was not gradable, it was assumed to have the same AMD level/lesions as the fellow eye. Eyes with late AMD were excluded from analyses of incident early AMD lesions. Early AMD was defined as the presence of small to intermediate sized drusen (<125 μm in diameter), regardless of area of involvement, with any pigmentary abnormality; or large drusen ( 125 μm in diameter) with drusen area <331,820 $\mu m^2$ (equivalent to O-2 circle, defined as a circle with diameter of 650 μm) and with or without pigmentary abnormalities in the absence of late AMD. Large soft indistinct (SI) drusen were defined as the presence of SI drusen 125 μm in diameter. Large drusen area was defined as the presence of a total area of drusen in the macula 650 μm in diameter. A pigmentary abnormality was defined as the presence of increased retinal pigment or RPE depigmentation. Late AMD was defined as pure geographic atrophy in the absence of exudative macular degeneration; or exudative macular degeneration with or without geographic atrophy present. Exudative AMD was defined as the presence of exudative macular degeneration with or without geographic atrophy (GA) present.

The incidence of a specific AMD lesion or level was defined by its presence at follow-up when it was absent at all previous examinations.

## Statistical Methods

We first examined the incidence of each AMD outcome and the association of serum lipids, statin use, and lipid pathway genes to the incidence of AMD in each cohort separately adjusting for age, sex, BMI, history of smoking habits, diabetes and hypertension. We further adjusted for statin use in the serum lipids models and adjusted for HDL-C in the statin use models. Serum lipid levels were standardized for each study by subtracting the population-specific mean and dividing by the standard deviation. Each AMD candidate gene SNP was examined using an additive model.

Incidence was modeled in each 5-year interval conditional upon being free of disease at all previous examinations. Serum lipids, statin use, AMD status, and other risk factors were updated at each examination. Associations of study factors with AMD outcomes were assessed using discrete-time hazard models using the complementary log-log link function. Heterogeneity was measured using the $I^2$ statistic. The results from each study were combined in a meta-analysis.[42] Heterogeneity (>50%) was present in several meta-analysis models; therefore, we computed an overall hazard ratio (HR) using a random-effect inverse-weighted meta-analysis with the study indicator as the random effect variable. This model incorporates information about the sample size and variability in each study to more accurately reflect the amount of variability between the studies when calculating the overall hazard ratio and confidence interval for the meta-analysis. The same terms entered in the models for each individual study (cholesterol measure/statin use/genotype and covariates) were included in each meta-analysis model. Multiplicative interactions were tested for each

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SNP and serum lipid measure using product terms in models adjusting for age, sex, and other covariates. SAS software version 9.3 (SAS Institute, Cary, North Carolina, USA) was used for all analyses.

To be included in analyses, a participant must have had information on AMD level, serum lipids, statin use, and lipid genes available at baseline and at all consecutive follow-up examinations until the individual developed AMD or was censored.

## RESULTS

Characteristics of those included and excluded from the analyses are presented in Table 3. Compared to those included, participants excluded due to missing genotype data were younger and, after adjusting for age and sex, were more likely to have lower serum HDL-C, greater BMI, and were less likely to be physically active.

Compared to those included, individuals excluded due to reasons other than missing genotype data (i.e., ungradable AMD lesions in both eyes, missing data on cholesterol or statin use, death, or loss to follow-up) were older and, after adjusting for age and sex, had lower serum HDL-C, higher total/HDL-C ratio, higher frequencies of hypertension, diabetes, current smoking, MI, angina, and stroke, a higher frequency of prevalent large SI drusen and a lower frequency of current physical activity. No other differences in the prevalence of early AMD or early AMD lesions were found between those included and those excluded.

Baseline characteristics of individuals included in analyses from each of the three studies are presented in Table 2. There were statistically significant differences in age, sex, serum lipid measures, pulse pressure, BMI, and *LPL* genotype as well as percentage of participants with hypertension, history of MI, diabetes, and percentage of participants who were current smokers, using statins, and physically active among the three studies. Genotype distributions for the other AMD candidate gene SNPs were similar among the three studies.

### Results from Individual Studies

The average incidence within each 5-year interval for early and late AMD and AMD lesions for each cohort are presented in Table 4. While adjusting for age, there were statistically significant differences in the incidence of all AMD outcomes except for late AMD and exudative AMD across the three study populations.

The associations of lipids, lipid pathway genes, and statins and the incidence of early and late AMD, SI drusen, large drusen area in the macula, pure GA and exudative AMD, adjusting for age, sex, BMI, smoking status, hypertension, diabetes, history of MI, and history of statin use in each cohort, are presented in Table 5. There were few associations among total cholesterol, HDL-C, total cholesterol/HDL-C ratio, and non-HDL-C and incident early AMD, SI drusen, large area of drusen, pigmentary abnormalities, late AMD, and exudative AMD. Associations of lipids with AMD outcomes were most frequent in the RS cohort (10 significant associations in the RS compared with 2 in the BDES and 0 in the BMES). Direct associations of HDL-C with incident pure GA were present in the BDES and

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RS cohorts but not the BMES cohort. Use of statins was not associated with any incident AMD outcome in any of the cohorts.

In the BDES, *CETP* rs1864163 and *LPL* rs281 were protective against the development of large drusen area in the macula and *CETP* rs3764261 was protective against the development of pure GA (Table 5). In the RS, *CETP* rs3764261 was associated with an increased risk of late AMD, pure GA, and exudative AMD (Table 5). *CETP* rs1864163 was associated with a decreased risk of incident early AMD and large drusen area. *ABCA1* rs1883025 was associated with a decreased risk of large SI drusen. *LPL* rs281 was associated with a decreased risk of large drusen area in the macula. In the BMES, none of these SNPs were found to be significantly associated with any the AMD outcomes, although marginally non-significant associations were found between *ABCA1* rs1883025/T and pure GA, and between *LIPC* rs7163555/G and exudative AMD (Table 5).

Mean HDL-C increased in each of the three cohorts with each additional risk allele for *CETP* rs376426 and decreased with each additional risk allele for *CETP* rs1864163 and *ABCA1* rs1883025 (all $P<0.05$, data not shown). There were no consistent statistically significant associations between *LIPC* or *LPL* and HDL-C or between any of the lipid genes and total cholesterol.

### Meta-analysis

In the meta-analysis, using a random effects model, while adjusting for age, sex, and other covariates, higher serum HDL-C was associated with a 10% increase in the risk of incident large drusen area in the macula. Serum total cholesterol, non-HDL-C, total cholesterol/HDL-C ratio, and statin use were not associated with any AMD outcome. *LPL* rs281 was associated with a decreased risk of SI drusen and large drusen area in the macula. Substantial heterogeneity defined as $I^2 > 0.50$ was frequent (67.9% of all meta-analyses in which at least one of the associations for a cohort was statistically significant) when the data from the three studies were combined in meta-analysis (Table 5). After correction for multiple comparisons, we did not find any statistically significant associations between any of the cholesterol measures, statin use, or AMD candidate genes and any of the AMD outcomes in the meta-analysis.

### Serum Lipids and Lipid Pathway Gene Interactions in Relation to Incidence and Progression of AMD

No statistically significant interactions between cholesterol measures and lipid pathway genes or statin use were found for any of the AMD outcomes.

## DISCUSSION

Of a large list of investigated associations between lipids and AMD, we report that only a few were significant in individual studies. In a meta-analysis, after correction for multiple testing, we did not find an association between serum lipids or lipid pathway genes and the incidence or progression of AMD over a 20-year period using data from three population-based cohort studies, the BDES, BMES, and RS. There was substantial heterogeneity among

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the three cohorts. There was no association of the history of use of statins to the incidence and progression of AMD in any of the cohorts.

These findings add to inconsistencies in earlier reports from our studies and others showing weak associations, no associations, or inverse associations of HDL-C and total cholesterol with AMD.[11–22] The heterogeneity among the three cohorts in our study may reflect underlying reasons for the inconsistent associations of these lipids with AMD such as biological differences (e.g., differences in cholesterol levels and rates of smoking, diabetes, etc.) among the populations and studies, residual confounding within one or more of the populations, and/or model misspecification. To minimize heterogeneity, all analyses were performed at a single center using the same modeling process, and the risk factors, covariates and outcome (AMD) were harmonized.[23] Overall hazard ratios from the meta-analysis were calculated using random-effects meta-analysis models to further account for heterogeneity across studies.

There are several possible reasons for the heterogeneity among the studies. First, although data were collected in a similar manner in all three studies, some questions asked and measurements taken were not identical despite the effort to harmonize the differences in definitions of risk factors and covariates among the studies. Therefore, the associations found (HRs presented) may have slightly different interpretations corresponding to the ways the questions were asked in each study. Second, we found statistically significant differences in participant age, sex, and other risk factors for AMD. Third, it is also possible that other lipids such as LDL cholesterol, triglycerides, fatty acids, or oxidized lipids that were not measured in all three studies may have a role in the pathogenesis of drusen and AMD. Finally, other factors (e.g., time of the year each study started, the age criteria for entry into the study, variations in the examination protocols for measurements, use of casual or fasting testing of the serum for lipid levels, and nutritional differences[43] may have led to substantial heterogeneity.

The role of lipids in the pathogenesis of AMD is poorly understood.[47] Lipids have been hypothesized to be involved in the pathogenesis of AMD based on finding lipid deposition in Bruch's membrane and soft drusen.[1–7] Curcio and colleagues[7] have suggested that the deposition of lipids in the Bruch's membrane shares some similarities with the deposition of lipids in the walls of atherosclerotic coronary vessels. Atherosclerotic processes have also been hypothesized to result in capillary closure leading to the incidence and progression of AMD.[44] The BDES previously showed a statistically significant association of carotid intima-media thickness and plaques with incident late AMD.[45] This was also shown cross-sectionally in the RS.[46] However, while an atherosclerotic-like process occurring in eyes at risk for AMD was hypothesized, not finding a significant consistent association between serum HDL-C and SI drusen indicates lack of support for this hypothesis. The reason for this finding is not known. We speculated that serum lipid levels do not reflect locally expressed HDL-C in the RPE and Müller cells that, along with lipid genes *CETP*, *LPL*, *LIPC*, and *APOE* and other molecules, function as a retinal tissue transport system for lipids.[1–7] It is not known whether high levels of serum HDL-C downregulate the expression of HDL-C in the retina, adversely affecting normal lipid transport. This has been

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hypothesized to result in lipid build-up in Bruch's membrane that is ultimately manifest as soft drusen.[7]

A protective effect of statins against AMD was suggested previously.[48,49] The lipid lowering and anti-inflammatory properties of statins were thought to be responsible in part for these findings. Statin use was associated with decreased 10-year incidence of SI drusen in the BMES.[50] However, data from three population-based studies did not show a protective effect of statins with the incidence of early or late AMD.[18,51–53]

The strengths of this study include large population-based samples, repeated measures, and the use of similar standardized protocols over a long period of time and harmonization of AMD level and lesion endpoints. There were also limitations. First was the exclusion of 50% of subjects in the three cohorts due in large part to missing data. Those excluded for reasons other than missing genotype data were more likely to be older and have lower HDL-C and higher total/HDL-C levels than those who were included, which might have resulted in a bias towards the null. Further, individuals included were younger and less likely to have diabetes, be current smokers, have a history of MI, angina, stroke, or cardiovascular disease and were more likely to be physically active than those excluded, which might have resulted in a bias toward the null. When lipid associations were assessed among all participants of the three studies (including those with missing genotype information), the associations between HDL-C and total cholesterol and AMD endpoints were similar (Klein R., unpublished data, August 2013). Second, selective survival and relative lack of power for infrequent outcomes such as GA may also have contributed to not finding associations. Third, multiple analyses have been conducted leading to high chance of having type I errors (i.e., false positive findings). Fourth, differences in ancestry in the three cohorts might also have affected the findings. Principal components analyses using genotyped markers informative for ancestry led us to rule out the possibility that population stratification contributed to our findings.[54] Finally, as the three populations included in this study were composed almost completely of Caucasians, mainly of Northern and Western European descent, the presented results may not necessarily applicable to other races or Caucasian groups not represented in the studies.

In summary, the data from our study did not show a significant association of lipid levels or lipid pathway genes and the incidence or progression of AMD in a meta-analysis of three population-based cohorts over a 20-year follow-up period. There was no evidence of a beneficial effect of statins on the incidence and progression of AMD. The inter-relationships of lipid levels in those genetically at risk of AMD, their effect on choroidal blood vessel anatomy and flow and the development of AMD remains to be elucidated.

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## Biography

**Dr. Ronald Klein** is a Professor of Ophthalmology and Visual Sciences at the University of Wisconsin School of Medicine and Public Health and is interested in ocular epidemiology of age-related eye disease and hypertensive and diabetic retinopathy.

## Appendix

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## Table 1

Timing of the Examination Phases, Number of Persons at Risk for Incident Age-Related Macular Degeneration, and Median Follow-up Time from the Three Continent Age-Related Macular Degeneration Consortium

| | Baseline Examination | | | Second Examination | | | Third Examination | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Years** | **N at risk** | **Median follow-up time (years)** | **Years** | **N at risk** | **Median follow-up time (years)** | **Years** | **N at risk** | **Median follow-up time (years)** |
| BDES | 1988–1990 | 2230 | 4.8 | 1993–1995 | 1644 | 5.3 | 1998–2000 | 1248 | 4.8 |
| BMES | 1992–1994 | 1595 | 4.9 | 1997–1999 | 1115 | 5.2 | 2002–2004 | 613 | 5.2 |
| RS | 1990–1993 | 3128 | 6.4 | 1997–1999 | 2109 | 4.5 | 2000–2004 | 1096 | 6.6 |

BDES, Beaver Dam Eye Study; BMES, Blue Mountains Eye Study; RS, Rotterdam Study.



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**Table 2**

Characteristics at the Baseline Examinations of Participants Included in Analyses from the Three Continent Age-Related Macular Degeneration Consortium.

| | BDES 1988–1990 (N=2227) | | | BMES 1992–1994 (N=1595) | | | RS 1990–1993 (N=3128) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Risk factor** | **% or Mean ± SD** | **Median (IQR)** | **Min–Max** | **% or Mean ± SD** | **Median (IQR)** | **Min–Max** | **% or Mean ± SD** | **Median (IQR)** | **Min–Max** | **P value[a]** |
| Age, years | 59.7 ± 10.1 | 59.0 (16.0) | 43.0–86.0 | 63.8 ± 8.1 | 64.0 (12.0) | 49.0–91.0 | 65.8 ± 6.9 | 65.0 (10.1) | 55.1–95.1 | <0.0001 |
| Sex, male | 43.8 | | | 42.8 | | | 56.3 | | | <0.0001 |
| Hypertension present | 46.7 | | | 69.1 | | | 50.1 | | | <0.0001 |
| Currently smoking | 19.3 | | | 12.1 | | | 21.9 | | | <0.0001 |
| Diabetes present | 8.4 | | | 6.0 | | | 6.8 | | | 0.0001 |
| Pulse pressure, mmHg | 52.2 ± 16.1 | 50.0 (21.0) | 16.0–121.0 | 61.1 ± 16.3 | 60.0 (20.0) | 25.0–152.0 | 65.2 ± 17.7 | 64.0 (24.0) | 20.0–157.0 | <0.0001 |
| Currently physically active | 26.9 | | | 50.7 | | | | | | <0.0001 |
| Body mass index, kg/m$^2$ | 28.6 ± 5.3 | 27.9 (6.3) | 15.0–68.4 | 26.2 ± 4.1 | 25.8 (4.9) | 15.2–49.5 | 26.3 ± 3.5 | 25.9 (4.3) | 16.4–44.2 | <0.0001 |
| Total cholesterol, mg/dL | 232.7 ± 42.8 | 230.0 (54.0) | 102.0–503.0 | 234.2 ± 40.8 | 232.0 (50.3) | 116.0–491.1 | 258.2 ± 45.8 | 255.2 (58.0) | 108.3–696.1 | <0.0001 |
| HDL-C, mg/dL | 53.2 ± 17.9 | 50.0 (23.0) | 8.0–143.0 | 55.8 ± 16.7 | 54.1 (23.2) | 15.5–143.1 | 52.3 ± 14.0 | 50.3 (19.3) | 15.5–243.6 | <0.0001 |
| Non-HDL-C, mg/dL | 179.6 ± 44.7 | 177.0 (56.0) | 56.0–447.0 | 178.4 ± 42.4 | 174.0 (50.3) | 69.6–448.6 | 205.9 ± 46.4 | 201.1 (58.0) | 19.3–653.5 | <0.0001 |
| Total/HDL-C ratio | 4.9 ± 1.9 | 4.6 (2.2) | 1.6–34.4 | 4.5 ± 1.5 | 4.3 (2.0) | 1.6–12.9 | 5.3 ± 1.6 | 5.0 (2.0) | 1.1–22.8 | <0.0001 |
| Using statins | 0.6 | | | 3.3 | | | 2.8 | | | <0.0001 |
| History of MI present | 4.9 | | | 7.4 | | | 8.3 | | | 0.006 |
| History of angina present | 8.6 | | | 10.4 | | | | | | 0.96 |
| History of stroke present | 2.2 | | | 2.8 | | | 2.1 | | | 0.10 |
| History of CVD present | 11.3 | | | 15.1 | | | | | | 0.20 |

| | **%** | **MAF** | **IQS** | **%** | **MAF** | **IQS** | **%** | **MAF** | **IQS** | **P value[a]** |
|---|---|---|---|---|---|---|---|---|---|---|
| *CETP* rs3764261 genotype | | | | | | 1.00 | | | 1.00 | 0.21 |
| A/C | 44.5 | 0.32 | | 45.4 | 0.32 | | 43.2 | 0.33 | | |
| A/A | 11.0 | Typed | | 9.5 | Imputed | | 10.6 | Imputed | | |
| *CETP* rs1864163 genotype | | | | | | 1.00 | | | 1.00 | 0.07 |
| A/G | 36.7 | 0.25 | | 36.6 | 0.25 | | 37.2 | 0.25 | | |

| | % | MAF | IQS | % | MAF | IQS | % | MAF | IQS | P value[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| A/A | 5.6 | Typed | | 6.3 | Imputed | | 6.5 | Imputed | | |
| *ABCA1* rs1883025 genotype | | | 0.98 | | | 0.98 | | | 0.94 | 0.33 |
| C/T | 37.9 | 0.24 | | 37.7 | 0.25 | | 38.8 | 0.25 | | |
| T/T | 5.6 | Imputed | | 5.9 | Imputed | | 6.3 | Imputed | | |
| *LIPC* rs7163555 genotype | | | | | | 0.98 | | | 1.00 | 0.48 |
| G/T | 22.7 | 0.13 | | 22.9 | 0.13 | | 20.9 | 0.12 | | |
| G/G | 1.6 | Typed | | 1.3 | Imputed | | 1.5 | Imputed | | |
| *LPL* rs281 genotype | | | 0.87 | | | 0.92 | | | 0.90 | <0.0001 |
| T/A | 44.2 | 0.31 | | 33.3 | 0.21 | | 42.9 | 0.31 | | |
| T/T | 9.2 | Imputed | | 4.2 | Imputed | | 9.0 | Imputed | | |

*ABCA1*, adenosine triphosphate-binding cassette transporter 1; AMD, age-related macular degeneration; BDES, Beaver Dam Eye Study; BMES, Blue Mountains Eye Study; *CETP,* cholesteryl ester transfer protein; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; IQS, imputation quality score; *LIPC,* lipase C precursor; *LPL*, lipoprotein lipase; MAF, minor allele frequency; MI, myocardial infarction; Min-Max, minimum-maximum; RS, Rotterdam Study.

[a] For any difference among studies; adjusted for age and sex.



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**Table 3**

Differences in Characteristics at Baseline between Individuals Included and Excluded in the Cohorts from the Three Continent Age-Related Macular Degeneration Consortium

| | Included (N=6950) | Excluded for missing genotype (N=2172) | | Excluded for other reasons (N=4690) | | |
|---|---|---|---|---|---|---|
| **Risk factor** | **% or Mean ± SD** | **% or Mean ± SD** | **P value[a]** | **% or Mean ± SD** | **P value[b]** | **P value[c]** |
| Age, years | 63.4 ± 8.7 | 62.5 ± 9.9 | 0.01 | 69.2 ± 10.6 | <.0001 | <.0001 |
| Serum total cholesterol, mg/dL | 244.5 ± 45.5 | 239.6 ± 45.2 | 0.53 | 242.6 ± 47.6 | 0.69 | 0.65 |
| Serum HDL cholesterol, mg/dL | 53.4 ± 16.0 | 52.8 ± 16.5 | 0.01 | 52.3 ± 16.7 | <.0001 | 0.31 |
| Serum non-HDL cholesterol, mg/dL | 191.1 ± 46.9 | 186.8 ± 46.4 | 0.16 | 190.3 ± 48.2 | 0.37 | 0.97 |
| Serum total/HDL cholesterol ratio | 4.96 ± 1.7 | 4.95 ± 1.7 | 0.03 | 5.1 ± 1.8 | <.0001 | 0.10 |
| Hypertension present | 53.4 | 53.7 | 0.47 | 65.6 | <.0001 | 0.06 |
| Pulse pressure, mmHg | 60.0 ± 17.9 | 57.9 ± 18.1 | 0.10 | 64.3 ± 19.0 | 0.29 | 0.65 |
| Body mass index, kg/$m^2$ | 27.0 ± 4.4 | 28.0 ± 5.2 | <.0001 | 26.9 ± 4.8 | 0.03 | 0.11 |
| Sex, male | 43.5 | 41.6 | 0.19 | 39.6 | 0.43 | 0.01 |
| Diabetes present | 7.1 | 8.5 | 0.18 | 13.8 | <.0001 | <.0001 |
| Currently smoking | 18.8 | 18.2 | 0.61 | 21.0 | <.0001 | <.0001 |
| History of myocardial infarction present | 7.0 | 6.7 | 0.57 | 10.6 | 0.00 | 0.01 |
| History of angina present[d] | 9.3 | 9.7 | 0.65 | 15.0 | 0.00 | 0.01 |
| History of stroke present[d] | 2.4 | 3.3 | 0.05 | 5.5 | <.0001 | 0.01 |
| History of cardiovascular disease present[d] | 12.8 | 13.8 | 0.28 | 24.1 | <.0001 | <.0001 |
| Currently physically active[d] | 36.7 | 29.4 | <.0001 | 26.1 | <.0001 | <.0001 |
| Prevalent early AMD | 15.8 | 16.9 | 0.51 | 19.1 | 0.11 | 0.16 |
| Prevalent large drusen area | 5.3 | 4.4 | 0.71 | 7.1 | 0.86 | 0.52 |
| Prevalent large soft indistinct drusen | 8.7 | 9.2 | 0.84 | 10.2 | 0.02 | 0.01 |
| Prevalent pigmentary abnormality | 9.0 | 9.5 | 0.57 | 12.0 | 0.96 | 0.92 |
| *CETP* rs3764261, 1 A risk allele present | 54.6 | | | 54.4 | 0.40 | |
| *CETP* rs1864163, 1 A risk allele present | 43.0 | | | 45.0 | 0.14 | |
| *ABCA1* rs1883025, 1 T risk allele present | 44.2 | | | 46.0 | 0.51 | |
| *LIPC* rs7163555, 1 G risk allele present | 23.4 | | | 23.3 | 0.65 | |
| *LPL* rs281, 1 T risk allele present | 49.8 | | | 51.3 | 0.94 | |

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*ABCA1*, adenosine triphosphate-binding cassette transporter 1; AMD, age-related macular degeneration; *CETP,* cholesteryl ester transfer protein; HDL, high-density lipoprotein; *LIPC,* lipase C precursor; *LPL*, lipoprotein lipase; SD, standard deviation.

[a]For individuals excluded for missing genotype data vs. individuals included, adjusting for age, sex, and study.

[b]For individuals excluded for reasons other than missing genetic data (both eyes ungradable for AMD, cholesterol not measured, statin use not recorded, or died/lost to follow-up) vs. individuals included, adjusting for age, sex, and study.

[c]For individuals excluded for missing genotype data vs. individuals excluded for other reasons adjusting for age, sex, and study.

[d]Only measured in the Beaver Dam Eye Study and Blue Mountains Eye Study; N included = 3797, N excluded = 4688

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## Table 4

Five-year Incidence Averaged over 15 Years of Follow-up for Age-Related Macular Degeneration Endpoints in the Three Continent Age-Related Macular Degeneration Consortium

| Outcome | BDES | BMES | RS | P value[a] |
|---|---|---|---|---|
| Early AMD | 8.1 | 15.1 | 13.0 | <0.0001 |
| Large soft indistinct drusen | 3.3 | 6.3 | 8.6 | <0.0001 |
| Large drusen area | 3.7 | 4.5 | 8.6 | <0.0001 |
| Any pigmentary abnormality | 4.2 | 12.0 | 9.3 | <0.0001 |
| Late AMD | 1.2 | 1.7 | 1.7 | 0.22 |
| Pure geographic atrophy | 0.6 | 0.8 | 0.7 | 0.05 |
| Exudative AMD | 0.7 | 1.2 | 1.1 | 0.24 |

AMD, age-related macular degeneration; BDES, Beaver Dam Eye Study; BMES, Blue Mountains Eye Study; RS, Rotterdam Study.

[a] For any difference among studies; adjusted for age and sex.

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**Table 5**

Associations of Lipid Levels and Lipid Genes to the Incidence of Age-Related Macular Degeneration Outcomes by Cohort and Overall Meta-analysis

| | BDES | | BMES | | RS | | | Overall[a] | |
|---|---|---|---|---|---|---|---|---|---|
| **Outcome and risk factors** | **HR (95% CI)[b]** | **P** | **HR (95% CI)[b]** | **P** | **HR (95% CI)[b]** | **P** | $I^2$ | **HR (95% CI)[b]** | **P** |
| Early AMD | | | | | | | | | |
| Lipid measure[c]/statin use | | | | | | | | | |
| Total cholesterol | 1.01 (0.91, 1.13) | 0.86 | 0.99 (0.89, 1.10) | 0.86 | 0.87 (0.78, 0.97) | 0.01 | 52.9 | 0.96 (0.87, 1.05) | 0.33 |
| HDL-C | 0.98 (0.87, 1.11) | 0.76 | 1.00 (0.89, 1.12) | 0.99 | 1.13 (1.03, 1.25) | 0.01 | 52.8 | 1.04 (0.95, 1.14) | 0.39 |
| Non-HDL-C | 1.02 (0.91, 1.13) | 0.78 | 0.99 (0.90, 1.10) | 0.87 | 0.84 (0.76, 0.94) | 0.002 | 70.7 | 0.95 (0.85, 1.06) | 0.35 |
| Total/HDL-C ratio | 1.00 (0.89, 1.12) | 0.99 | 0.99 (0.89, 1.10) | 0.83 | 0.84 (0.75, 0.94) | 0.002 | 67.1 | 0.94 (0.84, 1.05) | 0.27 |
| Statin use | 0.89 (0.55, 1.42) | 0.61 | 0.93 (0.64, 1.35) | 0.69 | 1.02 (0.69, 1.52) | 0.91 | 0.0 | 0.95 (0.75, 1.20) | 0.66 |
| SNP/risk allele | | | | | | | | | |
| *CETP* rs3764261/A | 1.04 (0.88, 1.23) | 0.62 | 1.09 (0.94, 1.27) | 0.25 | 1.05 (0.90, 1.21) | 0.56 | 0.0 | 1.06 (0.97, 1.16) | 0.19 |
| *CETP* rs1864163/A | 0.95 (0.79, 1.16) | 0.63 | 0.95 (0.81, 1.12) | 0.55 | 0.81 (0.68, 0.97) | 0.02 | 5.0 | 0.90 (0.81, 1.00) | 0.05 |
| *ABCA1* rs1883025/T | 1.03 (0.84, 1.25) | 0.79 | 1.07 (0.91, 1.25) | 0.43 | 0.85 (0.72, 1.00) | 0.06 | 51.4 | 0.98 (0.85, 1.13) | 0.73 |
| *LIPC* rs7163555/G | 1.11 (0.89, 1.40) | 0.36 | 1.03 (0.83, 1.27) | 0.79 | 1.13 (0.92, 1.38) | 0.25 | 0.0 | 1.09 (0.96, 1.23) | 0.17 |
| *LPL* rs281/T | 0.99 (0.83, 1.19) | 0.91 | 0.92 (0.74, 1.14) | 0.43 | 0.95 (0.81, 1.10) | 0.48 | 0.0 | 0.95 (0.86, 1.06) | 0.36 |
| Large soft indistinct drusen | | | | | | | | | |
| Lipid measure[c]/statin use | | | | | | | | | |
| Total cholesterol | 1.01 (0.85, 1.19) | 0.95 | 1.04 (0.89, 1.21) | 0.65 | 1.00 (0.88, 1.13) | 0.97 | 0.0 | 1.01 (0.93, 1.10) | 0.81 |
| HDL-C | 0.99 (0.83, 1.19) | 0.94 | 1.04 (0.90, 1.21) | 0.59 | 1.10 (0.98, 1.24) | 0.10 | 0.0 | 1.06 (0.98, 1.15) | 0.15 |
| Non-HDL-C | 1.01 (0.86, 1.19) | 0.90 | 1.02 (0.88, 1.18) | 0.82 | 0.97 (0.86, 1.10) | 0.61 | 0.0 | 0.99 (0.91, 1.08) | 0.88 |
| Total/HDL-C ratio | 0.97 (0.81, 1.16) | 0.71 | 0.96 (0.81, 1.12) | 0.58 | 0.92 (0.81, 1.05) | 0.23 | 0.0 | 0.94 (0.86, 1.03) | 0.19 |
| Statin use | 1.13 (0.59, 2.18) | 0.71 | 0.82 (0.48, 1.39) | 0.46 | 1.10 (0.70, 1.71) | 0.68 | 0.0 | 1.01 (0.74, 1.36) | 0.97 |
| SNP/risk allele | | | | | | | | | |
| *CETP* rs3764261/A | 1.04 (0.80, 1.35) | 0.78 | 1.14 (0.92, 1.41) | 0.23 | 0.91 (0.76, 1.09) | 0.33 | 18.7 | 1.01 (0.88, 1.17) | 0.84 |
| *CETP* rs1864163/A | 0.80 (0.58, 1.11) | 0.18 | 0.95 (0.74, 1.20) | 0.64 | 0.85 (0.70, 1.04) | 0.10 | 0.0 | 0.87 (0.76, 1.00) | 0.05 |
| *ABCA1* rs1883025/T | 1.09 (0.81, 1.49) | 0.57 | 1.00 (0.79, 1.28) | 0.99 | 0.83 (0.69, 1.00) | 0.05 | 30.7 | 0.94 (0.79, 1.11) | 0.47 |
| *LIPC* rs7163555/G | 1.15 (0.81, 1.63) | 0.44 | 0.97 (0.70, 1.34) | 0.85 | 1.19 (0.94, 1.51) | 0.15 | 0.0 | 1.12 (0.94, 1.32) | 0.20 |
| *LPL* rs281/T | 0.86 (0.65, 1.14) | 0.29 | 0.96 (0.71, 1.31) | 0.80 | 0.83 (0.69, 1.00) | 0.05 | 0.0 | 0.86 (0.75, 0.99) | 0.04 |

| Outcome and risk factors | BDES HR (95% CI)[b] | BDES P | BMES HR (95% CI)[b] | BMES P | RS HR (95% CI)[b] | RS P | $I^2$ | Overall[a] HR (95% CI)[b] | Overall[a] P |
|---|---|---|---|---|---|---|---|---|---|
| Large drusen area | | | | | | | | | |
| Lipid measure[c]/statin use | | | | | | | | | |
| Total cholesterol | 1.14 (1.00, 1.30) | 0.05 | 1.03 (0.85, 1.24) | 0.80 | 0.93 (0.82, 1.06) | 0.26 | 57.6 | 1.03 (0.90, 1.17) | 0.68 |
| HDL-C | 1.05 (0.89, 1.23) | 0.57 | 1.08 (0.91, 1.28) | 0.38 | 1.15 (1.01, 1.30) | 0.03 | 0.0 | 1.10 (1.01, 1.20) | 0.03 |
| Non-HDL-C | 1.12 (0.98, 1.27) | 0.09 | 0.99 (0.83, 1.19) | 0.93 | 0.90 (0.79, 1.02) | 0.09 | 64.8 | 1.00 (0.87, 1.14) | 0.97 |
| Total/HDL-C ratio | 1.01 (0.87, 1.17) | 0.89 | 0.92 (0.76, 1.11) | 0.39 | 0.87 (0.77, 1.00) | 0.05 | 2.9 | 0.93 (0.85, 1.02) | 0.14 |
| Statin use | 0.64 (0.32, 1.30) | 0.22 | 0.75 (0.40, 1.43) | 0.39 | 0.80 (0.47, 1.37) | 0.42 | 0.0 | 0.74 (0.52, 1.06) | 0.10 |
| SNP/risk allele | | | | | | | | | |
| *CETP* rs3764261/A | 1.12 (0.89, 1.41) | 0.33 | 1.12 (0.87, 1.44) | 0.39 | 0.96 (0.80, 1.14) | 0.62 | 0.0 | 1.04 (0.92, 1.17) | 0.55 |
| *CETP* rs1864163/A | 0.70 (0.53, 0.94) | 0.02 | 1.05 (0.80, 1.38) | 0.73 | 0.81 (0.66, 0.99) | 0.03 | 52.1 | 0.84 (0.68, 1.04) | 0.11 |
| *ABCA1* rs1883025/T | 0.88 (0.66, 1.16) | 0.35 | 0.95 (0.70, 1.28) | 0.72 | 0.88 (0.73, 1.06) | 0.17 | 0.0 | 0.89 (0.78, 1.02) | 0.10 |
| *LIPC* rs7163555/G | 1.00 (0.71, 1.39) | 0.99 | 0.91 (0.62, 1.35) | 0.64 | 1.00 (0.77, 1.29) | 0.97 | 0.0 | 0.98 (0.82, 1.17) | 0.81 |
| *LPL* rs281/T | 0.78 (0.62, 0.99) | 0.04 | 0.80 (0.54, 1.18) | 0.26 | 0.83 (0.69, 0.99) | 0.04 | 0.0 | 0.81 (0.71, 0.93) | 0.002 |
| Late AMD | | | | | | | | | |
| Lipid measure[c]/statin use | | | | | | | | | |
| Total cholesterol | 0.98 (0.79, 1.21) | 0.83 | 1.16 (0.84, 1.59) | 0.37 | 1.00 (0.78, 1.30) | 0.98 | 0.0 | 1.02 (0.88, 1.18) | 0.78 |
| HDL-C | 1.25 (1.00, 1.57) | 0.05 | 0.89 (0.65, 1.21) | 0.45 | 1.18 (0.94, 1.49) | 0.16 | 39.0 | 1.13 (0.94, 1.34) | 0.20 |
| Non-HDL-C | 0.90 (0.70, 1.15) | 0.38 | 1.21 (0.89, 1.64) | 0.23 | 0.95 (0.72, 1.26) | 0.73 | 13.2 | 0.99 (0.84, 1.17) | 0.91 |
| Total/HDL-C ratio | 0.76 (0.55, 1.04) | 0.08 | 1.29 (0.96, 1.73) | 0.09 | 0.94 (0.71, 1.24) | 0.65 | 66.5 | 0.97 (0.72, 1.31) | 0.86 |
| Statin use | 1.79 (0.81, 3.91) | 0.15 | 0.76 (0.26, 2.23) | 0.61 | 0.95 (0.29, 3.06) | 0.93 | 0.0 | 1.22 (0.68, 2.18) | 0.51 |
| SNP/risk allele | | | | | | | | | |
| *CETP* rs3764261/A | 0.73 (0.49, 1.09) | 0.12 | 1.15 (0.78, 1.71) | 0.48 | 2.34 (1.66, 3.31) | <.001 | 89.8 | 1.26 (0.64, 2.47) | 0.50 |
| *CETP* rs1864163/A | 0.87 (0.55, 1.36) | 0.53 | 1.22 (0.80, 1.85) | 0.35 | 0.63 (0.39, 1.02) | 0.06 | 52.0 | 0.89 (0.61, 1.29) | 0.52 |
| *ABCA1* rs1883025/T | 0.86 (0.53, 1.40) | 0.55 | 1.12 (0.72, 1.74) | 0.63 | 1.09 (0.71, 1.68) | 0.68 | 0.0 | 1.03 (0.79, 1.33) | 0.83 |
| *LIPC* rs7163555/G | 1.08 (0.65, 1.81) | 0.77 | 1.40 (0.84, 2.31) | 0.19 | 0.61 (0.32, 1.17) | 0.14 | 48.5 | 1.01 (0.65, 1.58) | 0.95 |
| *LPL* rs281/T | 1.02 (0.70, 1.48) | 0.93 | 0.95 (0.56, 1.60) | 0.84 | 0.93 (0.63, 1.37) | 0.71 | 0.0 | 0.97 (0.76, 1.23) | 0.79 |
| Pure GA | | | | | | | | | |
| Lipid measure[c]/statin use | | | | | | | | | |



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| Outcome and risk factors | BDES HR (95% CI)[b] | BDES P | BMES HR (95% CI)[b] | BMES P | RS HR (95% CI)[b] | RS P | $I^2$ | Overall[a] HR (95% CI)[b] | Overall[a] P |
|---|---|---|---|---|---|---|---|---|---|
| Total cholesterol | 0.88 (0.61, 1.26) | 0.47 | 1.03 (0.61, 1.73) | 0.91 | 1.04 (0.78, 1.39) | 0.79 | 0.0 | 1.03 (0.84, 1.25) | 0.80 |
| HDL-C | 1.52 (1.16, 2.00) | 0.002 | 0.83 (0.50, 1.36) | 0.45 | 1.23 (1.03, 1.47) | 0.02 | 60.2 | 1.20 (0.90, 1.61) | 0.22 |
| Non-HDL-C | 0.72 (0.46, 1.14) | 0.16 | 1.12 (0.68, 1.84) | 0.65 | 0.94 (0.68, 1.31) | 0.72 | 0.0 | 0.96 (0.75, 1.23) | 0.75 |
| Total/HDL-C ratio | 0.51 (0.29, 0.90) | 0.02 | 1.44 (0.96, 2.15) | 0.08 | 0.84 (0.57, 1.22) | 0.36 | 78.3 | 0.91 (0.50, 1.64) | 0.75 |
| Statin use | 2.60 (0.91, 7.44) | 0.08 | 0.27 (0.03, 2.43) | 0.25 | 0.64 (0.15, 2.77) | 0.55 | 38.5 | 0.91 (0.50, 1.64) | 0.75 |
| SNP/risk allele | | | | | | | | | |
| *CETP* rs3764261/A | 0.54 (0.29, 1.01) | 0.05 | 1.37 (0.81, 2.32) | 0.25 | 2.33 (1.46, 3.73) | <.001 | 86.0 | 1.20 (0.52, 2.77) | 0.66 |
| *CETP* rs1864163/A | 1.13 (0.61, 2.08) | 0.71 | 1.07 (0.57, 2.04) | 0.83 | 0.50 (0.24, 1.02) | 0.06 | 42.4 | 0.90 (0.60, 1.36) | 0.63 |
| *ABCA1* rs1883025/T | 0.95 (0.49, 1.87) | 0.89 | 1.65 (1.00, 2.71) | 0.05 | 0.88 (0.50, 1.55) | 0.66 | 35.8 | 1.16 (0.76, 1.76) | 0.50 |
| *LIPC* rs7163555/G | 0.99 (0.48, 2.04) | 0.97 | 0.96 (0.44, 2.10) | 0.91 | 0.89 (0.45, 1.79) | 0.75 | 0.0 | 0.91 (0.58, 1.42) | 0.68 |
| *LPL* rs281/T | 0.92 (0.53, 1.59) | 0.75 | 1.16 (0.50, 2.70) | 0.73 | 0.75 (0.46, 1.21) | 0.24 | 0.0 | 0.89 (0.64, 1.25) | 0.51 |
| Exudative AMD | | | | | | | | | |
| Lipid measure[c]/statin use | | | | | | | | | |
| Total cholesterol | 1.10 (0.86, 1.40) | 0.44 | 1.12 (0.77, 1.64) | 0.56 | 0.92 (0.63, 1.34) | 0.66 | 0.0 | 1.06 (0.88, 1.27) | 0.53 |
| HDL-C | 1.05 (0.74, 1.47) | 0.80 | 0.77 (0.53, 1.12) | 0.17 | 1.03 (0.72, 1.49) | 0.86 | 0.0 | 0.95 (0.78, 1.17) | 0.65 |
| Non-HDL-C | 1.08 (0.85, 1.37) | 0.53 | 1.23 (0.87, 1.75) | 0.24 | 0.91 (0.62, 1.35) | 0.65 | 0.0 | 1.08 (0.90, 1.28) | 0.42 |
| Total/HDL-C ratio | 0.98 (0.69, 1.38) | 0.89 | 1.32 (0.98, 1.80) | 0.07 | 0.97 (0.68, 1.40) | 0.88 | 13.9 | 1.09 (0.89, 1.34) | 0.40 |
| Statin use | 1.72 (0.56, 5.26) | 0.34 | 0.98 (0.30, 3.24) | 0.97 | 1.68 (0.51, 5.59) | 0.40 | 0.0 | 1.43 (0.73, 2.80) | 0.30 |
| SNP/risk allele | | | | | | | | | |
| *CETP* rs3764261/A | 0.89 (0.53, 1.51) | 0.67 | 0.88 (0.52, 1.47) | 0.61 | 1.99 (1.34, 2.94) | 0.001 | 77.0 | 1.18 (0.68, 2.05) | 0.55 |
| *CETP* rs1864163/A | 0.61 (0.31, 1.23) | 0.17 | 1.17 (0.75, 1.84) | 0.49 | 0.82 (0.48, 1.41) | 0.48 | 22.6 | 0.90 (0.62, 1.29) | 0.56 |
| *ABCA1* rs1883025/T | 0.76 (0.37, 1.53) | 0.44 | 0.80 (0.45, 1.42) | 0.45 | 1.14 (0.67, 1.94) | 0.64 | 0.0 | 0.91 (0.65, 1.28) | 0.58 |
| *LIPC* rs7163555/G | 1.13 (0.57, 2.23) | 0.73 | 1.68 (0.97, 2.90) | 0.06 | 0.47 (0.18, 1.26) | 0.13 | 59.7 | 1.06 (0.55, 2.07) | 0.86 |
| *LPL* rs281/T | 1.08 (0.66, 1.76) | 0.77 | 0.67 (0.35, 1.29) | 0.23 | 1.02 (0.63, 1.65) | 0.95 | 0.0 | 0.95 (0.70, 1.28) | 0.73 |

*ABCA1*, adenosine triphosphate-binding cassette transporter 1; AMD, age-related macular degeneration; BDES, Beaver Dam Eye Study; BMES, Blue Mountains Eye Study; *CETP,* cholesteryl ester transfer protein; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; GA, geographic atrophy; HR, hazard ratio; *LIPC,* lipase C precursor; *LPL*, lipoprotein lipase; P, P value; RS, Rotterdam Study; SNP, single nucleotide polymorphism.

[a]Overall model and P value are for random-effects meta-analysis model.

[b]Hazard ratios are for each standard deviation above the mean for continuous measures, for using statins compared to not using them, and per additional risk allele (additive model) for each SNP.

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[c]Cholesterol measures were standardized among the studies.

Models adjust for age, sex, body mass index, history of smoking status, diabetes status, and hypertension status. We further adjusted for statin use in the serum lipids and lipid gene models and for HDL-C in the statin use models.