Birth Cohort Effect on Prevalence of Age-related Maculopathy in the Beaver Dam Eye Study

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The number of people in the United States with age-related maculopathy is increasing in recent years because of increasing longevity. However, it is possible that a birth cohort effect, due to different levels of exposure to risk factors, may explain changes in the prevalence of age-related maculopathy by age. In this report, the authors utilize data from the population-based Beaver Dam Eye Study (1988–2000) to examine this possibility. They propose a strategy to handle issues of longitudinal measurements and risk factor adjustment for analyzing the birth cohort effect. Results from the analysis (after adjusting for known risk factors) showed an apparent independent birth cohort effect on age-related maculopathy. The authors also found a strong positive association between age-related maculopathy and age, when comparing participants from the same birth cohort. The birth cohort effect was the same across different age groups, except for early age-related maculopathy, where older age increased the association. Our findings demonstrate that the birth cohort effect is likely attributable to unmeasured risk factors for age-related maculopathy and limitations of risk factor measurements. Further study of possible unmeasured risk factors that cause the cohort effect may help us understand the etiology of the disease.

cohort effect; cohort studies; generalized estimating equation; macular degeneration; risk adjustment

Abbreviations: CI, confidence interval; OR, odds ratio.

Age-related maculopathy is an important vision-threatening condition in adult Americans. The prevalence of age-related maculopathy is thought to be increasing in the United States and elsewhere in part because of the increasing longevity of the population (1, 2). Independent of age, other factors such as hypertension, multivitamin use, alcohol consumption, and smoking have been shown to be associated with age-related maculopathy in some but not all studies (3). In addition to increasing longevity and the known risk factors for age-related maculopathy, it is possible that a birth cohort effect, due to differences in past exposures to unmeasured risk factors, may explain age differences in the prevalence of age-related macular degeneration. The Beaver Dam Eye Study, a 10-year population-based longitudinal study of age-related ocular disorders, motivates this study and provides us a unique opportunity to examine whether a birth cohort effect is observed for the prevalence of age-related maculopathy.

There are two major challenges in analyzing the birth cohort effect on age-related maculopathy in the Beaver Dam Eye Study. First, in the Beaver Dam Eye Study, each participant was measured at three different time points. The association among measurements needs to be included in the model to yield efficient and correct inferences (4). Second, to better understand the reasons for a birth cohort effect, we want to adjust for known age-related maculopathy risk factors to see whether the birth cohort effect is attributable to them. Statistical methods, developed previously for investigating the birth cohort effect, focus on analyzing registry or survey data that are aggregated into a set of rates and arranged in a two-way table by age group and birth-year period. It is difficult to adjust for individual risk factors in these approaches (5–7).

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TABLE 1. Baseline characteristics of participants at the baseline examination, 5-year follow-up, and 10-year follow-up in the Beaver Dam Eye Study from March 1988 to June 2000

Characteristics at baseline	Baseline examination ($n = 4,926$)	5-year follow-up ($n = 3,722$)	10-year follow-up ($n = 2,962$)
Age (years)	62.04 (11.19)*	60.39 (10.50)	58.85 (9.93)
Gender (%)			
Male	44	43	42
Female	56	57	58
Smoking status (%)			
Never smoker	45	45	47
Past smoker	35	36	35
Current smoker	20	19	18
History of heavy drinking (%)			
Never heavy drinker	83	84	85
Heavy drinker in the past	15	14	13
Current heavy drinker	2	2	2
Multivitamin use (%)			
Never multivitamin user	45	44	42
Multivitamin user in the past	21	22	23
Current multivitamin user	34	34	35
Cholesterol level (mg/dl)	233.60 (44.20)	233.00 (43.55)	232.60 (42.75)
Hypertension (%)			
Normal	63	66	68
Hypertensive	37	34	32

* Numbers in parentheses, standard deviation.

To our knowledge, there have been no population-based studies conducted examining the relation of birth cohort effects with the prevalence of age-related maculopathy. The purpose of our report is to 1) examine this effect in the Beaver Dam Eye Study and 2) propose a strategy for handling the analytic challenges described above.

MATERIALS AND METHODS

The Beaver Dam Eye Study is a longitudinal population-based cohort study that aims at determining the long-term course of common vision-threatening conditions in adult Americans (8, 9). Between September 15, 1987, and May 4, 1988, a private census was performed to identify residents of the city or township of Beaver Dam, Wisconsin, who were 43–84 years of age. A total of 5,924 persons were invited to participate in the study.

Population

Among eligible individuals, 4,926 participated in the baseline examination between March 1, 1988, and September 14, 1990; 3,722 (of whom 38 did not participate in the first examination) participated in the 5-year follow-up examination between March 1, 1993, and June 14, 1995; and 2,962 (of whom 198 did not participate in the first and/or second

examination) participated in the 10-year follow-up examination between March 1, 1998, and June 9, 2000. Table 1 summarizes baseline characteristics of participants at the baseline examination, 5-year follow-up, and 10-year follow-up. There were no substantial differences among the three groups, although the average age was slightly younger and the percentage of hypertension was slightly lower for people that participated in the successive examination phases. The possible reasons for nonparticipation include death, moving out of the area, and refusal (9–11). Comparisons between participants and nonparticipants at all three examinations have been presented elsewhere (9–11).

Procedures and definitions

Similar procedures were used at both the baseline and follow-up examinations and have been described in detail elsewhere (8–15). In brief, 30° color stereoscopic fundus photographs were taken of both eyes of each participant. Preliminary and detailed grading was then carried out on the fundus photographs to determine the presence and severity of specific lesions associated with age-related maculopathy, including largest drusen size, most severe drusen type (in order of increasing severity: hard distinct drusen, soft distinct drusen, soft indistinct drusen, and reticular drusen), increased retinal pigment, retinal pigment epithelial depig-

mentation, exudative macular degeneration (retinal pigment epithelial detachment, subretinal hemorrhage, subretinal fibrosis), and geographic atrophy. A questionnaire was administered for obtaining demographic characteristics and physical conditions.

Detailed definitions for the presence and severity of specific lesions have appeared elsewhere (1, 2, 14, 15). For the purposes of this report, we put our focus to three lesions: soft drusen and early and late age-related maculopathy. Soft drusen was defined by the presence of either soft distinct or indistinct drusen in an eye. Early age-related maculopathy was defined as either the presence of soft indistinct drusen or the presence of any type of drusen with retinal pigment epithelial depigmentation or increased retinal pigment. Late age-related maculopathy was defined as the appearance of either exudative macular degeneration or pure geographic atrophy.

The birth cohort effect is defined as the variation in the prevalence of age-related maculopathy that arises from the different exposures of each birth cohort. Thus, if a birth cohort effect exists, individuals from different birth cohorts would have different chances of developing age-related maculopathy even if the same age. In this report, we are also interested in the "independent" birth cohort effect, adjusting for identified risk factors.

We identified the following as characteristics that could potentially influence the relation among age-related maculopathy, age at the examination, and birth cohort: gender, smoking status, history of heavy drinking, multivitamin use, cholesterol level, and hypertension status. These risk factors were chosen because of a strong relation with age-related maculopathy in previous studies. In the Beaver Dam Eye Study, smoking was related to the prevalence of age-related maculopathy (16), heavy drinking and hypertension were associated with exudative macular degeneration, a lesion that defined late age-related maculopathy (17, 18), and serum cholesterol was inversely associated with age-related maculopathy (19). Vitamin use was found to be associated with the incidence of age-related maculopathy in a clinical trial (20). Definitions of these confounding variables have been described in detail elsewhere (16, 17, 21, 22). In brief, a subject was classified as a current smoker if he/she had smoked more than 100 cigarettes in his/her lifetime and had not stopped smoking; as a former smoker if he/she had smoked more than this number but had not smoked within the last year prior to the examination; and as a nonsmoker if he/she had smoked fewer than 100 cigarettes in his/her lifetime. A current heavy drinker was defined as a person consuming four or more servings of alcoholic beverages daily, a former heavy drinker had consumed four or more servings daily in the past but not within the last year, and a non-heavy drinker had never consumed four or more servings daily on a regular basis. A person was classified as a current vitamin user if he/she had taken at least one vitamin per week in the month prior to the examination; as a past vitamin user if he/she had ever regularly taken vitamins at least once a week but not within the last month; and as never using vitamins if she/he never took vitamins regularly. Serum cholesterol levels were determined by enzymatic procedures (22). Hypertension was defined as a systolic blood pressure of 160 mmHg and/or a diastolic blood pres-

sure of 95 mmHg and/or a history of hypertension using anti-hypertensive medication at the time of the examination.

We adjusted for these potential confounding variables in each model. Measurements of risk factors were taken at each examination; however, multivitamin use and cholesterol level were not available at the 10-year follow-up. In the following analysis, we use the 5-year multivitamin use and cholesterol level as the 10-year measurements.

Conventional approaches for the birth cohort effect: graphical displays and the age-cohort model

Previously developed statistical methods for the birth cohort effect focus on analyzing "rates." For the Beaver Dam Eye Study, we first aggregated data into a two-way table by year of birth and age group in 5-year intervals, and we calculated the prevalence of age-related maculopathy in each cell. Next, to display birth cohort patterns, we plotted the log odds of prevalent age-related maculopathy against age for each birth cohort and used the age-cohort model (5–7) to test the significance of birth cohort and age effects:

$$\log(\lambda_{ca}) = \mu + \alpha_c + \pi_a. \qquad (1)$$

Here, λ_{ca} is the prevalence of age-related maculopathy of the cth birth cohort and ath age group, α_c represents the birth cohort effect of the cth birth cohort, and π_a is the age effect of the ath age group. The statistical significance of each effect is determined by using the likelihood ratio statistic, which follows a chi-square distribution under the null hypothesis.

The age-cohort model is a direct application of Poisson regression (23); therefore, it can be easily implemented by existing statistical software. In addition, graphical presentations of the age-related maculopathy distribution can empirically display birth cohort patterns and provide a comparison with results from the regression approach. However, these methods suffer from significant limitations. First, the Beaver Dam Eye Study is a longitudinal study in which each participant was measured at three different time points (baseline and the 5th year and the 10th year), and thus the age-cohort model, which ignores the association among repeated measurements, would yield inefficient parameter estimates and incorrect inferences (4). Second, these approaches aggregate individual observations into a set of rates for analysis and therefore cannot adjust for individual-level risk factors. As described in the introduction, several risk factors other than age have been identified to be associated with age-related maculopathy. We need to adjust for the known risk factors in order to determine whether there is an independent effect of birth cohort.

A method proposal: Heagerty and Zeger's model

Heagerty and Zeger (24) proposed a statistical model that utilized the generalized estimating equation (25) approach for analyzing repeated measures of categorical data, which is appropriate for this study. In Heagerty and Zeger's model, two regression models are specified: one to describe the marginal means and another to describe the associations among repeated measurements. From the marginal mean model, we
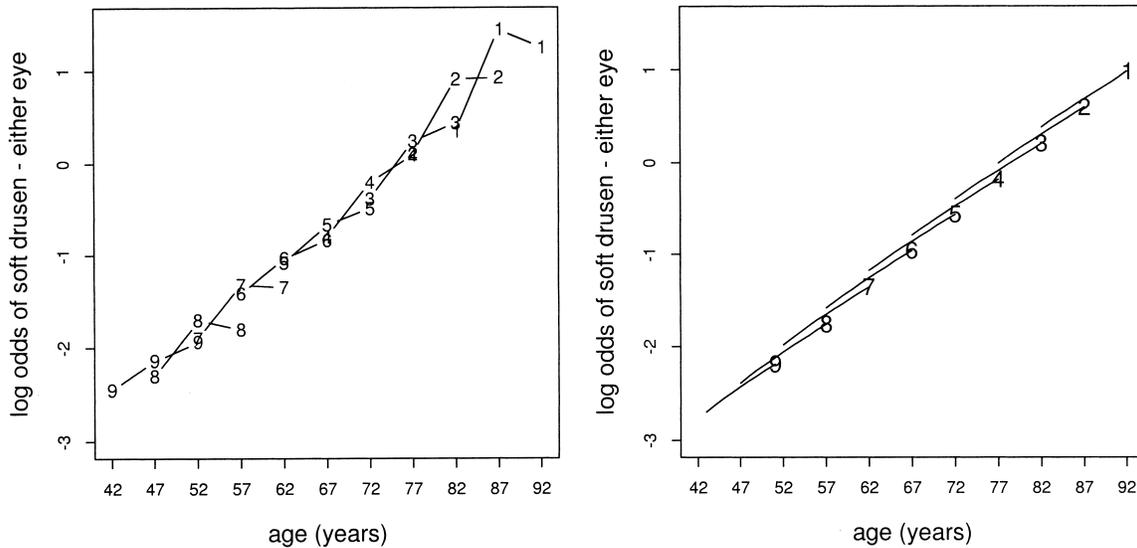
FIGURE 1. Relation of age to log odds of age-related maculopathy for different birth cohorts in the Beaver Dam Eye Study from March 1988 to June 2000. Plots are for soft drusen in either eye; the left panel is the plot based on observed data, and the right panel is the plot based on Heagerty and Zeger's model of equation 2. Birth cohort (birth year): 1, ≤1907; 2, 1908–1912; 3, 1913–1917; 4, 1918–1922; 5, 1923–1927; 6, 1928–1932; 7, 1933–1937; 8, 1938–1942; 9, ≥1943.

can estimate the odds ratio relating the response variable to risk factors. In our study, for example, the odds ratio between age-related maculopathy and birth year (i.e., birth cohort) can be estimated. The association model is used to describe the association among repeated measurements from the same participant. In our study, this model estimates the odds ratio that describes the degree to which developing age-related maculopathy is consistent among repeated measurements within each participant. For more details on Heagerty and Zeger's model, readers can refer to the article by Huang et al. (26).

The endpoints soft drusen and early and late age-related maculopathy in the right, left, and either eye were used as the outcome variables. We fit Heagerty and Zeger's model for each age-related maculopathy endpoint separately adjusting for participant age in 1987, age at the examination, and the risk factors identified in the procedures and definitions section of this report. To be more specific, let Y_{ij} be the indicator of developing age-related maculopathy for the ith participant at the jth examination ($j = 1$ (baseline), 2 (5-year follow-up), and 3 (10-year follow-up)):

$$\log\left[\frac{\Pr(Y_{ij} = 1)}{\Pr(Y_{ij} = 0)}\right] = \beta_0 + \beta_1(\text{risk factors})_{ij} \qquad (2)$$

$$+ \beta_2[(\text{age in 1987})_i - 65] + \beta_3(\text{age}_{ij} - 65),$$

where (risk factors)$_{ij}$ represents all the risk factors identified for the ith participant at the jth examination; (age in 1987)$_i$ is the ith participant's age in year 1987 and is used to represent the birth cohort effect; and age$_{ij}$ is the age of the ith participant at the jth examination.

There are several key features of model 2. A significant positive β_2 means that, at the same age, participants born in the older cohort are $\exp(\beta_2)$ times as likely to develop age-related maculopathy as those from the cohort that is 1 year younger. The age effect $\exp(\beta_3)$ is the odds ratio of developing age-related maculopathy for every 1-year increase in age, comparing people from the same birth cohort. These two effects are adjusted for the identified risk factors. The reason that we centered (age in 1987)$_i$ and age$_{ij}$ at 65 years of age is for ease of interpretation and to avoid collinearity. Based on findings from figures 1 and 2, the decision was made not to put the quadratic term for age$_{ij}$ into the model; the figures showed a linear relation between the log odds of age-related maculopathy and age.

Model 2 gives an overall birth cohort effect and age effect estimations by assuming that there is no interaction between age and birth cohort. In other words, we assume that the lines of log odds age-related maculopathy versus age for different birth cohorts (figure 1) are parallel. To further investigate this parallel assumption, we fit a more complicated Heagerty and Zeger's model with the interaction between birth cohort and age:

$$\log\left[\frac{\Pr(Y_{ij} = 1)}{\Pr(Y_{ij} = 0)}\right] = \beta_0 + \beta_1(\text{risk factors})_{ij} \qquad (3)$$

$$+ \beta_2[(\text{age in 1987})_i - 65] + \beta_3(\text{age}_{ij} - 65)$$

$$+ \beta_4\{[(\text{age in 1987})_i - 65] \times (\text{age}_{ij} - 65)\}$$

A significant positive β_4 means that the odds ratio of developing age-related maculopathy per every 1-year
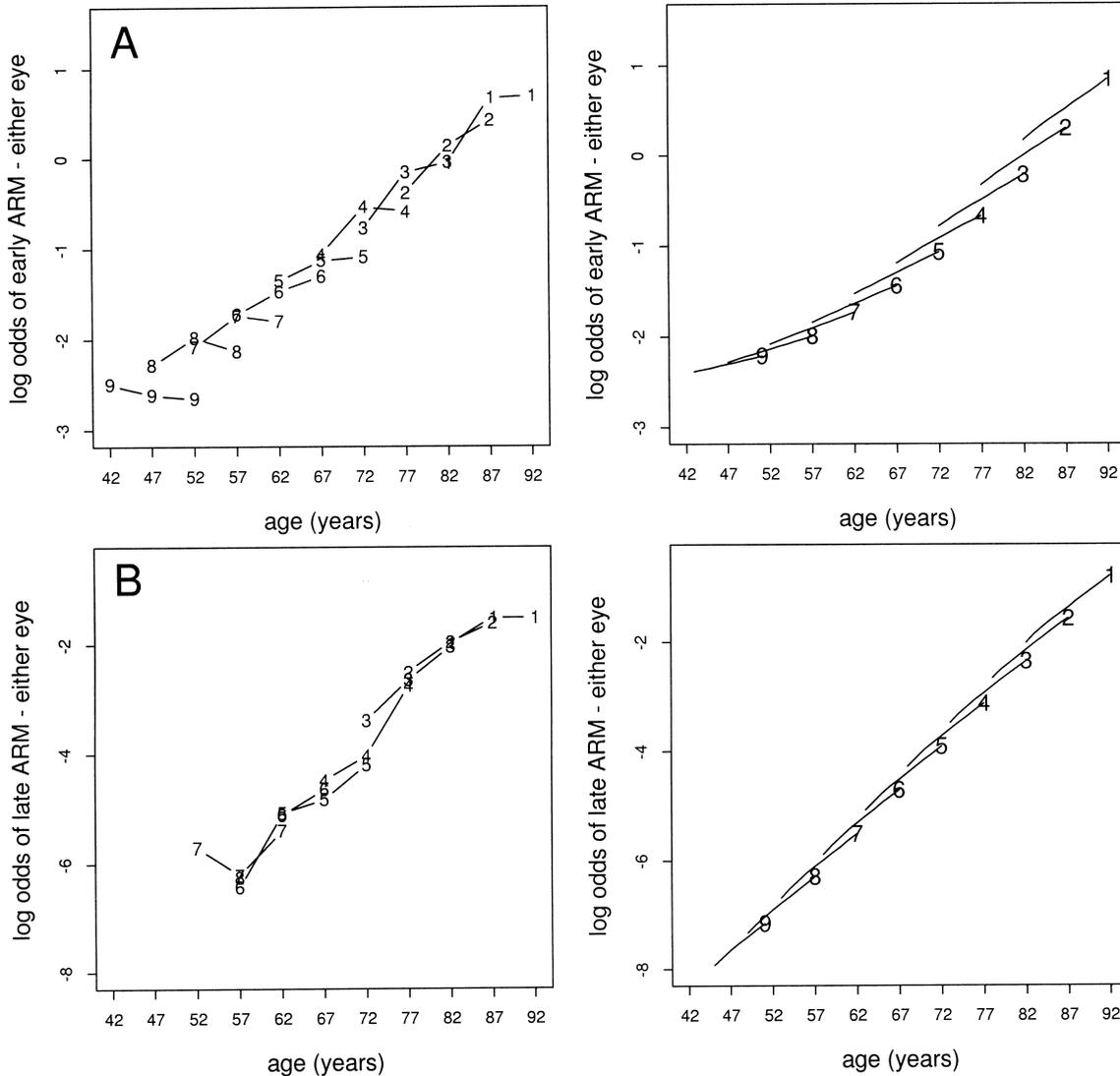
FIGURE 2. Relation of age to log odds of age-related maculopathy (ARM) for different birth cohorts in the Beaver Dam Eye Study from March 1988 to June 2000. A, plots for early ARM in either eye; the left panel is the plot based on observed data, and the right panel is the plot based on Heagerty and Zeger's model of equation 3. B, plots for late ARM in either eye; the left panel is the plot based on observed data, and the right panel is the plot based on Heagerty and Zeger's model of equation 2. Birth cohort (birth year): 1, ≤1907; 2, 1908–1912; 3, 1913–1917; 4, 1918–1922; 5, 1923–1927; 6, 1928–1932; 7, 1933–1937; 8, 1938–1942; 9, ≥1943.

decrease in birth year (the birth cohort effect) is higher for older people than younger people, and the odds ratio of developing age-related maculopathy on age (the age effect) is higher for people from older birth cohorts than for those from younger cohorts.

Implementing Heagerty and Zeger's model for our data, we first fit model 3 to determine whether the parallel assumption described previously was met. For age-related maculopathy endpoints that had significant β_4 values, we calculated the birth cohort effect in each age group and the age effect for each birth cohort. For nonsignificant age-related maculopathy endpoints, we fit model 2 to estimate the overall birth cohort effect and age effect.

The software for fitting Heagerty and Zeger's model can be downloaded from the Internet: http://www.biostat.jhsph.edu/biostat/research/software.shtml under the category "Estimating Equations for Dependent Ordinal Data." Example programs for implementing the software to analyze the birth cohort effect are available from the authors.

RESULTS

Because age-related maculopathy patterns in the right, left, and either eye were similar, results are presented for age-related maculopathy in either eye only. However, when there were significant differences among them, results for individual eyes appear in the text. Odds ratios reported here are

in units: 5 years for birth cohort and age and 50 mg/dl for cholesterol level.

Graphical displays and the age-cohort model

The prevalence of age-related maculopathy in either eye at baseline, 5-year follow-up, and 10-year follow-up was as follows: soft drusen: 25.3 percent, 32.7 percent, and 32.2 percent; early age-related maculopathy: 20.4 percent, 24.7 percent, and 22.8 percent; and late age-related maculopathy: 1.74 percent, 2.11 percent, and 2.78 percent, respectively. For use in graphical displays and the age-cohort model, nine birth cohorts and 11 age groups were constructed (birth cohort: ≤1907, 1908–1912, 1913–1917, 1918–1922, 1923–1927, 1928–1932, 1933–1937, 1938–1942, ≥1943; age groups: ≤44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, ≥90 years). The left panels of figures 1 and 2 show the observed log odds of age-related maculopathy in either eye versus age for different birth cohorts. From the plots, we observed that, as people became older, the chances of developing age-related maculopathy increased. Those in older birth cohorts tended to have higher probabilities of developing early age-related maculopathy than did those from younger cohorts, even with the same age, suggesting a birth cohort effect on early age-related maculopathy. A birth cohort effect was not as apparent for soft drusen as it was for early age-related maculopathy. The prevalence of late age-related maculopathy was equal to zero for people born after 1937, and a less clear birth cohort effect was observed for people born before 1937. A linear relation between the log odds and age was apparent within each birth cohort for all three age-related maculopathy endpoints. This supported the exclusion of the quadratic age term in Heagerty and Zeger's model.

Results from the age-cohort model are shown in table 2. We found that the overall birth cohort effect was significant for early age-related maculopathy but not for soft drusen or late age-related maculopathy. A strong age effect was found for all the endpoints. This was consistent with what we saw in the graphical displays.

Heagerty and Zeger's model

For soft drusen endpoints, the value of β_4 in model 3 was not significant for any of the soft drusen endpoints (p values for soft drusen in the left eye = 0.63, in the right eye = 0.41, and in either eye = 0.08). The odds ratios of developing soft drusen by increasing age were essentially the same across different birth cohorts. We then fit Heagerty and Zeger's model 2 to estimate the overall birth cohort effect and age effect (table 3). The fitted lines of soft drusen over age by birth cohort based on model 2 are shown in the right panel of figure 1. The fitted lines were obtained by, first, smoothing the estimated probability of soft drusen versus age for each birth cohort; second, transforming the resulting probability line to log odds; and finally, plotting the transformed line versus age for each birth cohort. Birth cohort and age effects were observed in both table 3 and the fitted lines. Controlling for age and other risk factor levels, we found that participants from older birth cohorts were 1.11 times as likely to

TABLE 2. Age-cohort model for birth cohort effect on age-related maculopathy in the Beaver Dam Eye Study from March 1988 to June 2000

Lesion variable* and effect	df	LR† (χ^2)	p value
Soft drusen in either eye			
Birth cohort effect	8	6.00	0.65
Age effect	10	98.49	<0.0001
Early age-related maculopathy in either eye			
Birth cohort effect	8	22.25	0.005
Age effect	10	41.85	<0.0001
Late age-related maculopathy in either eye			
Birth cohort effect	7	3.72	0.81
Age effect	8	45.89	<0.0001

  * For soft drusen and early age-related maculopathy, the age-cohort model was fitted with nine birth cohorts and 11 age groups. For the late age-related maculopathy variable, the model was fitted using eight birth cohorts and nine age groups; the following birth cohort-age group pairs were deleted because of the lack of cases in the corresponding cells: 1938–1942, mean age 47 years; 1938–1942, mean age 52 years; ≥1943, mean age 42 years; ≥1943, mean age 47 years; ≥1943, mean age 52 years.

  † LR, likelihood ratio statistic.

develop soft drusen in at least one eye as those in the 5-year-younger cohort. There was an additional independent effect of age (odds ratio (OR) for 5-year increase in age = 1.35). We found some risk factors to be significantly associated with soft drusen after adjusting for birth cohort and age. Past multivitamin users were 0.88 (95 percent confidence interval (CI): 0.79, 0.98) times less likely to develop soft drusen in the left eye than were people who never used multivitamins, and past heavy drinkers were 1.14 (95 percent CI: 1.03, 1.26)

TABLE 3. Heagerty and Zeger's model for birth cohort effect on age-related maculopathy in the Beaver Dam Eye Study from March 1988 to June 2000

Lesion variable* and effect†	OR‡,§	95% CI‡,§
Soft drusen in either eye		
Birth cohort effect	1.11	1.06, 1.15
Age effect	1.35	1.30, 1.40
Late age-related maculopathy in either eye		
Birth cohort effect	1.23	1.06, 1.43
Age effect	1.79	1.58, 2.03

  * For soft drusen, the fitted Heagerty and Zeger's model was adjusted for gender, smoking status, history of heavy drinking, multivitamin use, cholesterol level, and hypertension. For the late age-related maculopathy variable, the fitted model was not adjusted for the identified risk factors, and only participants born before 1937 were included in the analysis.

  † In the model, [(age in 1987)$_i$ − 65] is used for birth cohort effect, and (age$_{ij}$ − 65) is used for age effect.

  ‡ OR, odds ratio; CI, confidence interval.

  § Calculated in the unit of 5-year increase.
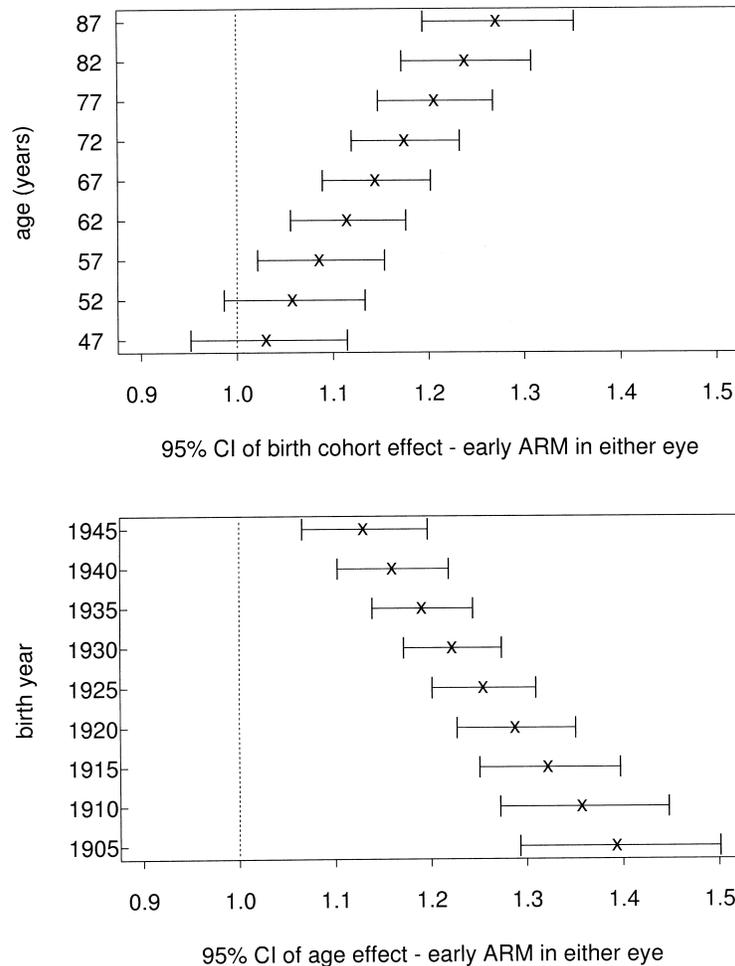
FIGURE 3. Confidence intervals of the birth cohort effect and age effect on early age-related maculopathy (ARM) in the Beaver Dam Eye Study from March 1988 to June 2000. Here, the birth cohort effect is the odds ratio of early ARM for every 5-year decrease in birth year, and the age effect is the odds ratio of early ARM for every 5-year increase in age. Both effects are adjusted for gender, smoking status, history of heavy drinking, multivitamin use, cholesterol level, and hypertension. From left to middle to right, each "line segment" displays the lower 95% confidence limit, estimate, and upper 95% confidence limit. The top panel shows the confidence intervals (CIs) of the birth cohort effects on early ARM in either eye across different ages. The bottom panel shows the confidence intervals of the age effects on early ARM in either eye across different birth cohorts.

times as likely to develop soft drusen in either eye than were those who were never heavy drinkers.

For each early age-related maculopathy endpoint, a significant positive β_4 of model 3 was found (p values for early age-related maculopathy in the left eye = 0.009, right eye = 0.012, and either eye = 0.00006). Figure 3 shows the birth cohort effect on early age-related maculopathy in different ages and its age effect across birth cohorts. There was a significant independent birth cohort effect on early age-related maculopathy in either eye for people aged 55 or more years (figure 3). As age increased, so did the strength of the birth cohort effect. Significant independent age effects were observed across all birth cohorts; the age effect was stronger in older cohorts than in younger cohorts. We found past heavy drinking and lower cholesterol levels to be positively associated with developing early age-related maculopathy in either eye (OR of past heavy drinkers vs. never drinkers =

1.12, 95 percent CI: 1.001, 1.25; OR for every 50-mg/dl decrease in cholesterol level = 1.06, 95 percent CI: 1.001, 1.12).

To examine how the identified risk factors affected the birth cohort effect, we fit Heagerty and Zeger's models without adjusting for risk factors and compared these with the models with risk factor adjustment. The estimated birth cohort effects based on the risk factor-adjusted models were slightly stronger than the estimated effects from the unadjusted models for all soft drusen and early age-related maculopathy endpoints. For example, the estimated odds ratio of developing early age-related maculopathy in either eye for every 5-year decrease in birth year was 1.105 (95 percent CI: 1.058, 1.154) based on the adjusted model and 1.103 (95 percent CI: 1.057, 1.151) based on the unadjusted model. Further analysis, implementing Heagerty and Zeger's model to study the relation between each risk factor and birth cohort

(using the risk factor as the dependent variable and age and birth cohort as independent variables), found that the older the birth cohort, the lower the proportion with the risk factors. As most risk factors were positively associated with the prevalence of age-related maculopathy, the above result might explain the difference between the risk factor-adjusted and the -unadjusted model.

Because the prevalence of late age-related maculopathy was very low (or equal to zero) in younger birth cohorts, Heagerty and Zeger's model did not converge. Therefore, we analyzed only "late age-related maculopathy in either eye" and included only those participants born before year 1937. Because of the results of risk factor adjustment for soft drusen and early age-related maculopathy endpoints, we fit the model without adjusting for the identified risk factors. The β_4 value of model 3 for late age-related maculopathy in either eye was not significant (p value = 0.66). The results of model 2 (table 3) showed that there were both a birth cohort effect and an age effect on late age-related maculopathy in the either eyes for participants born before 1937.

For all age-related maculopathy endpoints, the measurements from the same participant were very highly correlated. For example, measurements of early age-related maculopathy in either eye from the same participant were 109.69 (95 percent CI: 73.45, 163.80) times as likely to be consistent than to be different. Comparing the results between the simple logistic regression without Heagerty and Zeger's longitudinal correction and Heagerty and Zeger's model, we found that both approaches produced similar regression coefficient estimates but that the standard error estimates were different. The two approaches, therefore, provided different conclusions about the birth cohort effect: 1) The birth cohort effect on soft drusen disappeared with logistic regression but was still significant under Heagerty and Zeger's model; and 2) for early age-related maculopathy, the interaction between age and birth cohort was not significant in the logistic regression approach, but Heagerty and Zeger's model gave a significant interaction. These pieces of evidence showed the importance of taking the longitudinal effect into account.

DISCUSSION

In this report, we implemented Heagerty and Zeger's model for analyzing the birth cohort effect. Our results showed that older birth cohorts (earlier year of birth) had a higher age-specific prevalence of age-related maculopathy after adjusting for identified factors, indicating an independent birth cohort effect. We also found that age was positively associated with the prevalence of age-related maculopathy after adjusting for birth cohort. For soft drusen and late age-related maculopathy, the birth cohort effect was the same across different age groups; however, the birth cohort effect on early age-related maculopathy was stronger in older participants.

The birth cohort effect that we observed remained strong after adjusting for known risk factors. This might suggest that earlier "unmeasured" exposures (e.g., diet) may, in part, explain the birth cohort effect. It is also possible that the effect is due to the limitations of the measurement of risk factors. A major concern is underreporting of smoking and drinking history. Underreporting of alcohol consumption or cigarette smoking in people at risk for developing age-related maculopathy would lead to an underestimate of the association between them. If there is differential under-reporting by different age cohorts because of the perceived social acceptability of smoking, for example, this might lead to more residual confounding in some groups compared with others.

In contrast to the age-cohort model, Heagerty and Zeger's approach can take the longitudinal effect into account and adjust for individual-level risk factors. However, all these come at the price of requiring a larger sample size to obtain parameter estimations. Comparing results from both models, we found that the age-cohort model tends to give more conservative estimations than does Heagerty and Zeger's model. Possible interpretations for this difference are the following: first, repeated measurements in the Beaver Dam Eye Study were highly correlated; the age-cohort model ignores this strong correlation and thus results in less efficient parameter estimates (larger variances for estimated parameters). Second, the age-cohort model aggregates individual observations into group data, and therefore this analysis may combine individuals that had different associations with birth cohorts and mask this relation. Our recommendation for using these two models is to use the age-cohort model and graphical displays first for basic findings. Then, Heagerty and Zeger's model can be implemented to ensure that the age-cohort model has not masked the relation between age-related maculopathy and birth cohorts.

In exploring our longitudinal data for the cohort effect, we are concerned with the potential influence of mortality or nonparticipation on our findings. Although age-related maculopathy is not associated with mortality in our population, smoking, age, and birth cohort year are. The weight of these three forces could counter our ability to find evidence of a cohort effect on age-related maculopathy. In addition, we anticipate that the protective effect of higher serum total cholesterol found in our analyses might be obscured because of the relation of that variable to mortality. A protective effect of multivitamin use on either mortality or age-related maculopathy is unlikely to bias our findings of a cohort effect. We cannot infer which specific component(s) of the multivitamin supplement might be protective; it is also possible that vitamin use is simply a marker of a "healthy lifestyle."

In this report, we found a significant difference in the birth cohort effect across age groups only for early age-related maculopathy. It is possible that the presence of soft drusen is genetically or "constitutionally" determined, where more advanced lesions may be more influenced by the effects of environment on an aging or otherwise compromised retina. The lack of a significant difference in late age-related maculopathy may be related to the small number of cases of these lesions.

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