JAMA Ophthalmology | Original Investigation

Generational Differences in the 5-Year Incidence of Age-Related Macular Degeneration

Karen J. Cruickshanks, PhD; David M. Nondahl, MS; Lauren J. Johnson; Dayna S. Dalton, MS; Mary E. Fisher, PhD; Guan-Hua Huang, PhD; Barbara E. Klein, MD, MPH; Ronald Klein, MD, MPH; Carla R. Schubert, MS

IMPORTANCE Whether a reported decline in the risk of developing age-related macular degeneration (AMD) continued for people born during the Baby Boom years (1946-1964) or later is unknown. These data are important to plan for ocular health care needs in the 21st century.

OBJECTIVES To determine whether the 5-year risk for AMD declined by generation and to identify factors that contributed to improvement in risk.

DESIGN, SETTING, AND PARTICIPANTS Data came from the longitudinal cohort Beaver Dam Eye Study (March 1, 1988, through September 15, 1990, and March 1, 1993, through June 15, 1995) and the Beaver Dam Offspring Study (June 8, 2005, through August 4, 2008, and July 12, 2010, through March 21, 2013). These population-based studies examined residents of Beaver Dam, Wisconsin, aged 43 to 84 years in 1987 through 1988 and their adult offspring aged 21 to 84 years in 2005 through 2008. A total of 4819 participants were at risk for developing AMD based on fundus images obtained at baseline visits. Data were analyzed from February 18, 2016, through June 22, 2017, with additional analyses ending September 22, 2017.

MAIN OUTCOMES AND MEASURES Fundus images were graded for AMD using the Wisconsin Age-related Maculopathy Grading System. The incidence of AMD was defined as the presence at the 5-year follow-up examination of pure geographic atrophy or exudative macular degeneration, any type of drusen with pigmentary abnormalities, or soft indistinct drusen without pigmentary abnormalities.

RESULTS Among the 4819 participants, the mean (SD) baseline age of the cohort was 54 (11) years; 2117 were men (43.9%) and 2702 were women (56.1%). The 5-year age- and sex-adjusted incidence of AMD was 8.8% in the Greatest Generation (born during 1901-1924), 3.0% in the Silent Generation (born during 1925-1945), 1.0% in the Baby Boom Generation (born during 1946-1964), and 0.3% in Generation X (born during 1965-1984). Adjusting for age and sex, each generation was more than 60% less likely to develop AMD than the previous generation (relative risk, 0.34; 95% CI, 0.24-0.46). The generational association (relative risk, 0.40; 95% CI, 0.28 to 0.57) remained significant after adjusting for age, sex, smoking, educational attainment, exercise, levels of non–high-density lipoprotein cholesterol and high-sensitivity C-reactive protein, and use of nonsteroidal anti-inflammatory drugs, statins, and multivitamins.

CONCLUSIONS AND RELEVANCE The 5-year risk for AMD declined by birth cohorts throughout the 20th century. Factors that explain this decline in risk are not known. However, this pattern is consistent with reported declines in risks for cardiovascular disease and dementia, suggesting that aging Baby Boomers may experience better retinal health at older ages than did previous generations.

Invited Commentary page 1424

Journal Club Slides and Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 1464

Author Affiliations: Department of Ophthalmology and Visual Sciences, School of Medicine and Public Health, University of Wisconsin–Madison (Cruickshanks, Nondahl, Dalton, Fisher, B. E. Klein, R. Klein, Schubert); Department of Population Health Sciences, School of Medicine and Public Health, University of Wisconsin–Madison (Cruickshanks, Johnson, Huang); Institute of Statistics, National Chiao Tung University, Hsinchu, Taiwan (Huang).

Corresponding Author: Karen J. Cruickshanks, PhD, Department of Ophthalmology and Visual Sciences, School of Medicine and Public Health, University of Wisconsin–Madison, 610 Walnut St, 1038 WARF, Madison, WI 53726 (kjcruick@wisc.edu).

JAMA Ophthalmol. 2017;135(12):1417-1423. doi:10.1001/jamaophthalmol.2017.5001
Published online November 16, 2017.

The US population experienced increases in longevity during the 20th century. The estimated life expectancy was 59 years for white people born in the United States in 1921, 69 years by midcentury, and 77 years by the end of the century.[1] In the United States, because of this increased life expectancy and the advent of the Baby Boom Generation (1946-1964), estimates suggest that large numbers of adults will experience age-related macular degeneration (AMD), the leading cause of blindness in older adults, increasing the need for vision care for older adults.[2] However, in addition to living longer, older adults appear to have better health than did previous generations. Declines in the risk for cardiovascular disease,[3,4] dementias,[5-7] and other chronic conditions of aging[8,9] have been reported for people born in the first half of the 20th century. The prevalence and 5-year incidence of AMD declined by birth cohort from 1903 to 1942 in the Beaver Dam Eye Study (BDES).[10] However, whether the risk for AMD has declined for the Baby Boom generation, who are now turning 65 years of age at the rate of 10 000 individuals per day, remains unknown.[11]

Rapid declines in the incidence of noncommunicable diseases are considered to be strong evidence that such diseases are partially preventable, because the effect of genetic change is slow and difficult to detect.[8] During the 20th century, tremendous changes occurred in sanitation; housing; occupational safety; air and water quality and other environmental exposures; lifestyle and behavioral factors; availability, quality, and safety of food sources; and socioeconomic conditions; in addition, advances in the treatment and prevention of medical conditions and infectious diseases occurred. Such changes may have contributed to these improvements in risks for noncommunicable diseases across generations.[12,13] However, with increasing obesity and sedentary lifestyles, exposures to new products and medications, and challenging economic conditions that may have unrecognized health risks, the gains made in some health conditions in previous generations may be slowing, flattening, or disappearing, and people born during the Baby Boom years and more recently may not continue to experience healthier aging than their parents.[14-16]

The Beaver Dam Offspring Study (BOSS), which began June 8, 2005, has been following up the adult offspring (born during 1926-1984) of the Epidemiology of Hearing Loss Study, an ancillary study of the BDES cohort (born during 1902-1946).[10,17,18] The purpose of the present study was to analyze the 5-year incidence of AMD by generation to determine whether the risk for AMD continued to decline for people born during the Baby Boom years or later and to identify factors that contributed to improvement in risk.

Key Points

Question Has the risk for age-related macular degeneration declined for people born in the latter half of the 20th century?

Findings In this longitudinal cohort study of the incidence of age-related macular degeneration among 4819 participants, the risk declined by 60% for each successive generation. Members of the Baby Boom Generation was less likely to develop age-related macular degeneration than members of the Silent or the Greatest generations.

Meaning This dramatic decline in the incidence of age-related macular degeneration suggests that aging Baby Boomers may experience better retinal health longer than did previous generations.

Methods

Analyses included data from 2 longitudinal cohort studies that measured the 5-year incidence of AMD: the BDES and the BOSS.[10,17] The BDES is a population-based cohort study of residents of the city and town of Beaver Dam, Wisconsin, aged 43 to 84 years in 1987 to 1988.[10] Participants without AMD at the baseline examinations from March 1, 1988, through September 15, 1990 (at risk of developing AMD), and with 5-year follow-up data from March 1, 1993, through June 15, 1995 (n = 2746), were included in these analyses. The BOSS examined the adult children (21 years or older) of the Epidemiology of Hearing Loss Study cohort from June 8, 2005, through August 4, 2008.[17,18] BOSS participants without AMD at baseline and with 5-year follow-up data from July 12, 2010, through March 21, 2013 (n = 2073), were included in these analyses. Retention of the at-risk group was high; 5274 of 6200 persons (85%) returned for the 5-year follow-up visit, and of those returning, 4819 (91.4%) had gradable images. Approval for this research was obtained from the health sciences institutional review board of the University of Wisconsin–Madison, and informed written consent was obtained from all participants before each examination.

Similar standardized protocols were used in both studies at each examination.[10,17] In the BDES, 30° color fundus photographs centered on the disc (Early Treatment of Diabetic Retinopathy Study [ETDRS] standard field 1) and macula (ETDRS standard field 2) were taken of each eye through pharmacologically dilated pupils. In the BOSS, 45° 8.2-megapixel digital fundus images (ETDRS standard fields 1 and 2) were obtained through pharmacologically dilated pupils (Cgi-45NM fundus camera; Canon Inc). Images were graded by the University of Wisconsin Ocular Epidemiology Reading Center using the Wisconsin Age-Related Maculopathy Grading System.[19] Previous studies have demonstrated that results from the 2 imaging methods are comparable.[20] Among participants without AMD at the baseline visit, incident AMD was defined as the presence of pure geographic atrophy or exudative macular degeneration, any type of drusen with pigmentary abnormalities, or soft indistinct drusen without pigmentary abnormalities.

Measures of retinal vessel caliber were obtained using Ivan software (Fundus Photograph Reading Center, Department of Ophthalmology and Visual Sciences, University of Wisconsin–Madison) from fundus images centered on the optic disc. Individual arterioles and venules were measured from the retinal images according to standardized methods. The mean calibers of retinal arterioles and venules were summarized as the central retinal arteriolar equivalent and the central retinal venular equivalent.[21]

Table 1. 5-Year Incidence of AMD by Age Group

Age Group, y	No. at Risk	No. of Cases	Incidence (95% CI), %
22-39	363	1	0.3 (0.0-1.5)
40-49	1445	15	1.0 (0.6-1.7)
50-59	1596	45	2.8 (2.1-3.8)
60-69	967	72	7.4 (5.9-9.3)
70-79	397	61	15.4 (12.0-19.3)
80-86	51	10	19.6 (9.8-33.1)
All	4819	204	4.2 (3.7-4.8)

Abbreviation: AMD, age-related macular degeneration.

Standardized questionnaires administered as interviews were used to obtain lifestyle, behavioral medical history, and medication data. Age was defined at the baseline examination. Generations were defined by year of birth as the Greatest Generation (857 participants born during 1901-1924), the Silent Generation (2068 participants born during 1925-1945), Baby Boom Generation (1424 participants born during 1946-1964), and Generation X (470 participants born during 1965-1984). Smoking status was based on self-report of past, current, or never smoking. Heavy alcohol consumption was defined as ever consuming 4 or more alcoholic beverages daily. Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or currently taking blood pressure medication. Height and weight were measured at the examination; obesity was defined as a body mass index (calculated as weight in kilograms divided by height in meters squared) of 30 or greater. Diabetes status was defined as a self-report of a physician diagnosis or an elevated hemoglobin A_{1c} level of at least 6.5% (to convert to a proportion of total hemoglobin, multiply by 0.01). Exercise was defined as engaging at least once a week in physical activity long enough to work up a sweat. Participants self-reported use of multivitamins, statins, and nonsteroidal anti-inflammatory drugs (NSAIDs). Time spent outdoors in summer was used as an indicator of baseline sunlight exposure.

Serum total and high-density lipoprotein (HDL) cholesterol levels were measured on nonfasting samples. Non-HDL cholesterol level was calculated. Baseline serum high-sensitivity C-reactive protein (hsCRP) and interleukin 6 (IL-6) assays were performed at the same laboratory at the University of Minnesota.[22] Baseline BDES hsCRP level was measured using a latex particle–enhanced immunoturbidmetric method (Kamiya Biomedical Company) read on a chemistry analyzer (Roche Hitachi 911; Roche Diagnostics). Baseline BOSS hsCRP levels were measured using a latex particle–enhanced immunoturbidimetric assay from Roche Diagnostics read on another chemistry analyzer (Roche Modular P800 Chemistry Analyze; Roche Diagnostics). For both methods, the reference range was 0 to 5 mg/L (to convert to nanomoles per liter, multiply by 9.524); sensitivity, 0.1 mg/L; and interassay coefficient of variation, 4.5%. Baseline hsCRP level was divided into risk groups of less than 1.0, 1.0 to 3.0, and greater than 3.0 mg/L.[22] Baseline serum IL-6 level was measured using the quantitative sandwich enzyme immunoassay technique (high-sensitivity Quantikine kit; R&D Systems). The IL-6 reference range was 0.45 to 9.96 pg/mL, and the laboratory interassay coefficient of variation was 11.7%. The IL-6 levels were analyzed as tertiles.

Analyses were conducted using SAS software (version 9.4; SAS Institute, Inc). Exact binomial CIs were calculated for incidence estimates by age group and overall. Age- and sex-adjusted relative risk (RR) estimates associated with baseline risk factors were calculated using a modified Poisson regression approach with a robust error variance.[23] This approach was used to estimate the RR associated with each successive generation in an age- and sex-adjusted model and a multivariable-adjusted model. In these models, generation was treated as an ordered factor, resulting in estimated RRs associated with one generation compared with the previous generation. Estimated 5-year incidence estimates by generation and by generation and age were plotted from models using the same approach. Similar models were built using indicator variables for generation.

Results

Among the 4819 participants, 2117 were men (43.9%) and 2702 were women (56.1%); the mean (SD) age at baseline was 54 (11) years. The overall 5-year incidence of AMD was 4.2% (204 cases) (**Table 1**) and increased by age group from 1 of 363 participants (0.3%) younger than 40 years to 10 of 51 participants (19.6%) aged 80 to 86 years at baseline. Baseline characteristics of those who developed incident AMD and those who remained free of AMD are shown in **Table 2**. Adjusting for age and sex, there were no associations between smoking, diabetes, hypertension, obesity, exercise, history of heavy alcohol consumption, levels of hsCRP and IL-6, nonsteroidal anti-inflammatory drug use, central retinal arteriolar and venular equivalents, or sunlight exposure and the incidence of AMD. Non-HDL cholesterol level (RR, 1.03; 95% CI, 1.00-1.06), multivitamin use (RR, 0.69; 95% CI, 0.52-0.91), statin use (RR, 0.18; 95% CI, 0.04-0.71), and educational attainment (RR, 0.53; 95% CI, 0.30-0.93) were associated with the age- and sex-adjusted risk for AMD; multivitamin use (RR, 0.74; 95% CI, 0.55-0.98) and educational level (RR, 0.63; 95% CI, 0.46-0.87) remained significant independent predictive factors in a multivariable model.

As shown in **Figure 1**, the age- and sex-adjusted incidence of AMD also varied by generation or birth cohort. The age- and sex-adjusted incidence of AMD was 8.8% among those

Table 2. Baseline Risk Factors by 5-Year Incidence of AMD and Associated Age- and Sex-Adjusted RRs for AMD

Characteristic	Participant Group[a]		
	Incident AMD (n = 204)	No AMD (n = 4615)	Age- and Sex-Adjusted RR (95%CI)
Sex			
Male	94 (46.1)	2023 (43.8)	1.19 (0.92-1.55)
Female	110 (53.9)	2592 (56.2)	1 [Reference]
Smoking			
Never	97 (47.6)	2267 (49.1)	1 [Reference]
Past	79 (38.7)	1481 (32.1)	1.07 (0.79-1.44)
Current	28 (13.7)	866 (18.8)	1.04 (0.69-1.57)
Diabetes	20 (9.8)	270 (5.9)	1.18 (0.75-1.83)
Educational attainment, y			
0-12	154 (75.5)	2329 (50.6)	1.32 (0.91-1.93)
13-15	18 (8.8)	1136 (24.7)	0.53 (0.30-0.93)
≥16	32 (15.7)	1136 (24.7)	1 [Reference]
Hypertension	113 (55.4)	1814 (39.3)	1.08 (0.83-1.43)
Obesity	75 (36.8)	1822 (39.7)	0.95 (0.72-1.24)
Exercise	70 (34.3)	2243 (48.6)	0.80 (0.60-1.07)
History of heavy alcohol consumption[b]	30 (14.7)	757 (16.4)	1.10 (0.75-1.61)
hsCRP level, mg/L			
<1.0	46 (22.8)	1521 (33.7)	1 [Reference]
1.0-3.0	82 (40.6)	1720 (38.1)	1.17 (0.82-1.66)
>3.0	74 (36.6)	1273 (28.2)	1.31 (0.91-1.88)
NSAID use	80 (39.2)	2041 (44.2)	0.85 (0.65-1.12)
Statin use	2 (1.0)	300 (6.5)	0.18 (0.04-0.71)
Multivitamin use	65 (32.0)	1843 (40.1)	0.69 (0.52-0.91)
IL-6 level, mean (SD), pg/mL	3.3 (3.9)	2.7 (5.3)	1.12 (0.88-1.42)[c]
CRVE, mean (SD), μm[d]	228.9 (20.6)	227.5 (21.3)	1.05 (0.99-1.10)[e]
CRAE, mean (SD), μm[f]	149.1 (13.9)	150.3 (14.5)	1.01 (0.92-1.10)[e]
Non-HDL cholesterol level, mean (SD), mg/dL	183 (43)	168 (44)	1.03 (1.00-1.06)[g]
Sunlight exposure			
Low	92 (45.5)	1753 (38.0)	1 [Reference]
Moderate	66 (32.7)	1784 (38.7)	0.90 (0.66-1.23)
High	44 (21.8)	1074 (23.3)	1.00 (0.69-1.46)

Abbreviations: AMD, age-related macular degeneration; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; hsCRP, high-sensitivity C-reactive protein; HDL, high-density lipoprotein; IL-6, interleukin 6; NSAID, nonsteroidal anti-inflammatory drug; RR, relative risk.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; hsCRP to nanomoles per liter, multiply by 9.524.

[a] Unless otherwise indicated, data are expressed as number (percentage) of participants. Percentages have been rounded and may not total 100. Owing to missing data, denominators may not always equal numbers in column heads.

[b] Defined as consumption of 4 or more alcoholic drinks per day at any time.

[c] Calculated for each 1-unit change in natural log pg/mL.

[d] Measured from the retinal images of venules following standardized methods.

[e] Calculated for each 10-μm increase.

[f] Measured from the retinal images of arterioles following standardized methods.

[g] Calculated for each 10-mg/dL increase.

in the Greatest Generation, 3.0% in the Silent Generation, 1.0% in the Baby Boom generation, and 0.3% in Generation X. Adjusting for age and sex, each generation was more than 65% less likely to develop AMD than the previous generation (RR, 0.34; 95% CI, 0.24-0.46) (**Table 3**). Age- and generation-specific 5-year incidences are shown in the eTable in the Supplement.

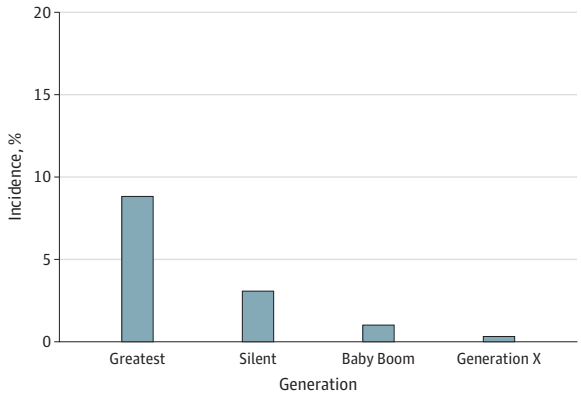
To determine whether potential AMD risk factors mediate this generational trend, we constructed a multivariable model adjusting for age, sex, smoking, educational attainment, exercise, levels of non-HDL cholesterol and hsCRP, and use of nonsteroidal anti-inflammatory drugs, statins, and multivitamins. The generational effect remained statistically significant but was slightly attenuated (RR, 0.40; 95% CI, 0.28-0.58) (Table 3). In addition to generation, only age remained as a significant independent risk factor for AMD. Adjusting for family clusters did not alter these results. A multivariable model using indicator variables for generation showed similar results for each generation. There were no cases of late AMD in the Baby Boom or Generation X cohorts; therefore, analyses of late-stage disease were not possible.

Figure 2 gives the estimated incidence of AMD by generation and age from the multivariable model. When comparing across generations at a specific age, the incidence of AMD was lower among the Baby Boom generation than in the Silent Generation, which had a lower incidence than the Greatest Generation. Generation X is young, but even at this early phase, the estimated incidence appeared to follow this trend, and was lower than the incidence among young Baby Boomers.

Discussion

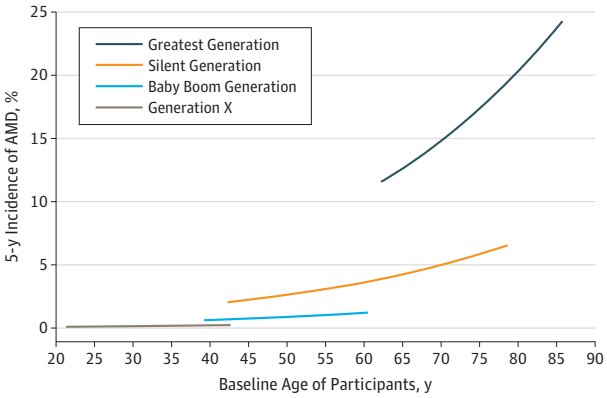
The 5-year incidence of AMD was 60% lower for each successive generation. Therefore, people born during the Baby Boom years were 60% less likely to develop AMD than those from the Silent Generation, who were 60% less likely to develop AMD than those from the Greatest Generation. This dramatic decline in the incidence across 3 generations suggests that environmental and/or behavioral factors are important risk factors in the etiology of AMD, because rapid genetic changes are unlikely.[8] Our results are consistent with

Figure 1. Age- and Sex-Adjusted 5-Year Incidence of Age-Related Macular Degeneration (AMD) by Generation



The Greatest Generation was born from 1901 to 1924; the Silent Generation, from 1925 to 1945; Baby Boom Generation, 1946 to 1964; and Generation X, from 1965 to 1984. The study population included 4819 participants from the Beaver Dam Eye Study and Beaver Dam Offspring Study without AMD at baseline and with 5-year follow-up data.

Figure 2. Estimated 5-Year Incidence of Age-Related Macular Degeneration (AMD) by Generation and Age



The Greatest Generation was born from 1901 to 1924; the Silent Generation, from 1925 to 1945; the Baby Boom Generation, 1946 to 1964; and Generation X, from 1965 to 1984. The study population included 4819 participants from the Beaver Dam Eye Study and Beaver Dam Offspring Study without AMD at baseline and with 5-year follow-up data.

Table 3. Generation Effect on 5-Year Incidence of AMD

Model	No. of Participants	Generation Effect, RR (95% CI)
Adjusted for age and sex		
Full cohort	4819	0.34 (0.24-0.46)
Complete data	4669	0.33 (0.24-0.46)
Multivariable adjusted[a]	4669	0.40 (0.28-0.58)

Abbreviations: AMD, age-related macular degeneration; RR, relative risk.

[a] Includes age, sex, smoking, educational attainment, exercise, high-sensitivity C-reactive protein level, non–high-density lipoprotein cholesterol level, and use of nonsteroidal anti-inflammatory drugs, statins, and multivitamins.

the previously reported decline in risk for participants born before 1943.[10] This study extends the findings to people born during the Baby Boom and represents the largest cohort of aging adults to date. Although adults in Generation X are just beginning to enter the risk years for AMD, they also appear to be experiencing a decline in the risk for AMD, but additional follow-up is needed to determine whether this pattern continues when they become older adults. This pattern is consistent with a recent report of declining prevalence of AMD in European countries.[24]

In this study, smoking, a well-recognized risk factor for AMD,[25] was not associated with the 5-year risk, which is consistent with results from the 5-year follow-up of the BDES[26] and Blue Mountains Eye Study.[27] A decline in smoking exposure in recent decades and the short follow-up may have limited our ability to detect an association. The effect of generation was slightly attenuated but remained statistically significant in the model controlling for potential AMD risk factors, such as smoking, markers of inflammation, non-HDL cholesterol level, educational attainment, medication use, and multivitamin use. These results suggest that other yet-to-be identified modifiable factors may be important contributors to the risk for AMD.

The decline in AMD is consistent with reports of declines in the incidence of cardiovascular disease and dementia observed in the same time period and with improvements in longevity.[1,3-7] These diseases involve vascular and inflammatory pathways, consistent with the pathways hypothesized to be important in the development of AMD. We did not have a baseline measure of atherosclerosis in the BDES cohort; thus, we were unable to directly control for atherosclerosis. Controlling for inflammation did not explain the generation effect, perhaps because short-term exposure to higher levels of inflammation, as captured by the single measure of hsCRP or IL-6 level, may be insufficient to cause damage leading to AMD.

The reasons for the dramatic decline in cardiovascular disease risk, recognized as early as the 1970s, and the more recently recognized decline in dementia risk remain unknown, suggesting that we may never know the reasons for this decline in AMD risk.[28] These generalized improvements in health may be attributed to broad changes in the environment, such as cleaner air and water and improvements in sanitation, which have reduced exposures to neurotoxins, particulates, and infectious agents that may contribute to chronic diseases of aging.[12] Alternatively, with the advent of antibiotics and vaccines, each generation experienced fewer serious infectious diseases of childhood, and the diseases may have been more likely to be milder or of shorter duration.[13] Infectious diseases may have long-term sequelae by increasing the risk for chronic diseases, such as cardiovascular disease, although the exact mechanisms are uncertain.[29] Social stress, another risk factor for chronic diseases of aging,[30] has also differed across generations, because historic events have exposed each generation to dramatically different living conditions, worries, and challenges. The Greatest Generation lived through numerous wars, the Great Depression, and food rationing, which may have had adverse long-term effects on health, including ocular health. Many age-related conditions may have their origins in

childhood or in utero exposures[31]; thus, improvements in maternal health and childhood nutrition and health care may have contributed to the observed decline.

Aging Baby Boomers may be less likely to develop AMD than previous generations if this trend continues as they age into the primary risk years. Thus, projections about future eye health care needs related to AMD may have overestimated the public health burden.[2] The number of older adults in the United States is expected to increase as the Baby Boom cohort ages,[32] but AMD may be associated with increased mortality,[33] and indications suggest that previous gains in life expectancy may not continue,[34] making it difficult to accurately estimate the future number of people who will need medical care for AMD by midcentury. The implications for research include the need for novel hypotheses to identify new ways to reduce the risk for AMD among tomorrow's elders and to determine whether the primary risk factors for AMD vary by generation because of changes in the prevalence of exposures (ie, if the prevalence of a known risk factor declines substantially, another factor may emerge as important). Because the incidence of AMD is low among the Baby Boom generation, large studies will be needed to have adequate power to investigate etiologic risk factors. Combined with improvements in treatments, this rapid and dramatic decline in 5-year incidence suggests that the Baby Boom generation may avoid the loss of vision due to AMD that has been a major source of disability for prior generations.

Strengths and Limitations

The strengths of the study are the population-based design, the high retention rates in both cohorts, the objective assessments of AMD, and measurement of numerous potential confounders. The offspring design of the BOSS reduces the genetic heterogeneity that would be present in unrelated cohorts and increases the probability that any change is attributable to differences in modifiable exposures.

This study is limited by the inability to disentangle birth cohort from period effects. Our approach recognizes this impossibility and assesses the joint effect of risk in people born in different time periods and living through different periods at different ages. When planning for future clinical needs, it is important to know the risk for people entering the major risk period, rather than rely on data generated from the current or past elderly populations.

Although these cohorts predominately consisted of non-Hispanic white individuals, with results that may not be generalizable to other racial/ethnic groups, non-Hispanic white individuals are known to have a higher risk for AMD than African American, Hispanic, and Chinese American individuals.[35] Whether other racial/ethnic groups have experienced the same declining risk across generations or whether the risk has increased needs to be determined. The risk among non-Hispanic white individuals may differ by geographic region[36]; thus, studies of this population living in other regions in the United States are needed (the BDES cohort lived in a single midwestern city during 1987 to 1988). The offspring were not geographically constrained (they could have become adults before their parents moved to Beaver Dam), although most lived in Wisconsin at the time of the baseline examination during 2005 to 2008. Geographic differences also may reflect variation in environmental exposures.

Some of the decline in risk among the BOSS participants may reflect changes in the imaging methods between the 2 studies. The BDES used film-based systems, whereas the BOSS examinations used digital imaging. However, previous work has demonstrated that comparable results are obtained with both systems,[20] the grading for both studies was performed by the same center, and the decline began in the generations included in the BDES, lessening the likelihood that this pattern was caused by measurement differences.

Conclusions

We demonstrated that the 5-year risk of developing AMD was dramatically lower for generations born later in the 20th century than those born earlier. We have extended these findings to the large group of Baby Boomers currently entering the ages at which AMD is detected. Although we were unable to identify the factors that explained the change, this study suggests that modifiable factors contribute to the etiology of AMD. These results suggest that the current epidemic of AMD among the current older population may wane over time and that future research may uncover opportunities for primary prevention of this vision-threatening disorder. Prospective epidemiologic studies are needed to confirm these findings in other populations.

ARTICLE INFORMATION

Accepted for Publication: September 28, 2017.

Published Online: November 16, 2017. doi:10.1001/jamaophthalmol.2017.5001

Author Contributions: Dr Cruickshanks had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Cruickshanks, Johnson, Fisher.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Cruickshanks, Nondahl, Johnson.
Critical revision of the manuscript for important intellectual content: Dalton, Fisher, Huang, B. E. Klein, R. Klein, Schubert.
Statistical analysis: Cruickshanks, Nondahl, Fisher, Huang.
Obtained funding: Cruickshanks.
Administrative, technical, or material support: Cruickshanks, Dalton, B. E. Klein, R. Klein, Schubert.
Study supervision: Cruickshanks.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: This study was supported by grant R01AG021917 from the National Institute on Aging and the National Eye Institute (Dr Cruickshanks), grant U10EY06594 from the National Eye Institute (Drs B. E. Klein and R. Klein), and an unrestricted grant from Research to Prevent Blindness.

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

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent

the official views of the National Institute on Aging, the National Eye Institute, or the National Institutes of Health.

REFERENCES

1. Arias E. United States Life Tables, 2011. *Natl Vital Stat Rep*. 2015;64(11):1-63.

2. Friedman DS, O'Colmain BJ, Muñoz B, et al; Eye Diseases Prevalence Research Group. Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol*. 2004;122(4):564-572.

3. McGovern PG, Pankow JS, Shahar E, et al; The Minnesota Heart Survey Investigators. Recent trends in acute coronary heart disease–mortality, morbidity, medical care, and risk factors. *N Engl J Med*. 1996;334(14):884-890.

4. Ford ES, Roger VL, Dunlay SM, Go AS, Rosamond WD. Challenges of ascertaining national trends in the incidence of coronary heart disease in the United States. *J Am Heart Assoc*. 2014;3(6):e001097. doi:10.1161/JAHA.114.001097

5. Satizabal C, Beiser AS, Seshadri S. Incidence of dementia over three decades in the Framingham Heart Study. *N Engl J Med*. 2016;375(1):93-94.

6. Matthews FE, Stephan BCM, Robinson L, et al; Cognitive Function and Ageing Studies (CFAS) Collaboration. A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II. *Nat Commun*. 2016;7:11398.

7. Gerstorf D, Ram N, Hoppmann C, Willis SL, Schaie KW. Cohort differences in cognitive aging and terminal decline in the Seattle Longitudinal Study. *Dev Psychol*. 2011;47(4):1026-1041.

8. Doll R, Peto R. *The Causes of Cancer*. New York, NY: Oxford University Press; 1981:1197-1312.

9. Doll R. Progress against cancer: an epidemiologic assessment: the 1991 John C. Cassel Memorial Lecture. *Am J Epidemiol*. 1991;134(7):675-688.

10. Klein R, Knudtson MD, Lee KE, Gangnon RE, Klein BE. Age-period-cohort effect on the incidence of age-related macular degeneration: the Beaver Dam Eye Study. *Ophthalmology*. 2008;115(9):1460-1467.

11. Cohn D, Taylor P. Baby Boomers approach 65—glumly. Pew Research Center. December 20, 2010. http://www.pewsocialtrends.org/2010/12/20/baby-boomers-approach-65-glumly/. Accessed June 9, 2017.

12. Garte S. *Where We Stand: A Surprising Look at the Real State of Our Planet*. New York, NY: AMACOM; 2008.

13. Atkinson W, Furphy L, Gantt J, Mayfield M, Rhyne G, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 3rd ed. Atlanta, GA: Centers for Disease Control and Prevention; 1996.

14. Goff DC Jr, Gillespie C, Howard G, Labarthe DR. Is the obesity epidemic reversing favorable trends in blood pressure? evidence from cohorts born between 1890 and 1990 in the United States. *Ann Epidemiol*. 2012;22(8):554-561.

15. Badley EM, Canizares M, Perruccio AV, Hogg-Johnson S, Gignac MA. Benefits gained, benefits lost: comparing Baby Boomers to other generations in a longitudinal cohort study of self-rated health. *Milbank Q*. 2015;93(1):40-72.

16. King DE, Matheson E, Chirina S, Shankar A, Broman-Fulks J. The status of Baby Boomers' health in the United States: the healthiest generation? *JAMA Intern Med*. 2013;173(5):385-386.

17. Klein R, Cruickshanks KJ, Nash SD, et al. The prevalence of age-related macular degeneration and associated risk factors. *Arch Ophthalmol*. 2010;128(6):750-758.

18. Zhan W, Cruickshanks KJ, Klein BE, et al. Generational differences in the prevalence of hearing impairment in older adults. *Am J Epidemiol*. 2010;171(2):260-266.

19. 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.

20. Klein R, Meuer SM, Moss SE, Klein BE, Neider MW, Reinke J. Detection of age-related macular degeneration using a nonmydriatic digital camera and a standard film fundus camera. *Arch Ophthalmol*. 2004;122(11):1642-1646.

21. Knudtson MD, Lee KE, Hubbard LD, Wong TY, Klein R, Klein BE. Revised formulas for summarizing retinal vessel diameters. *Curr Eye Res*. 2003;27(3):143-149.

22. Nash SD, Cruickshanks KJ, Schubert CR, et al. Long-term variability of inflammatory markers in a population-based cohort. *J Am Geriatr Soc*. 2013;61(8):1269-1276.

23. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702-706.

24. Colijn JM, Buitendijk GHS, Prokofyeva E, et al; EYE-RISK consortium; European Eye Epidemiology (E3) consortium. Prevalence of age-related macular degeneration in Europe: the past and the future [published online July 14, 2017]. *Ophthalmology*. 2017;S0161-6420(16)32475-7. doi:10.1016/j.ophtha.2017.05.035

25. Thornton J, Edwards R, Mitchell P, Harrison RA, Buchan I, Kelly SP. Smoking and age-related macular degeneration: a review of association. *Eye (Lond)*. 2005;19(9):935-944.

26. Klein R, Klein BEK, Moss SE. Relation of smoking to the incidence of age-related maculopathy: the Beaver Dam Eye Study. *Am J Epidemiol*. 1998;147(2):103-110.

27. Mitchell P, Wang JJ, Smith W, Leeder SR. Smoking and the 5-year incidence of age-related maculopathy: the Blue Mountains Eye Study. *Arch Ophthalmol*. 2002;120(10):1357-1363.

28. Jones DS, Greene JA. The decline and rise of coronary heart disease: understanding public health catastrophism. *Am J Public Health*. 2013;103(7):1207-1218.

29. Nieto FJ. Infections and atherosclerosis: new clues from an old hypothesis? *Am J Epidemiol*. 1998;148(10):937-948.

30. Cassel J. The contribution of the social environment to host resistance: the Fourth Wade Hampton Frost Lecture. *Am J Epidemiol*. 1976;104(2):107-123.

31. Barker DJ. Childhood causes of adult diseases. *Arch Dis Child*. 1988;63(7):867-869.

32. Vincent GK, Velkoff VA. *The Next Four Decades: The Older Population in the United States: 2010 to 2050*. Washington, DC: US Census Bureau; 2010:25-1138. Current Population Reports.

33. McGuinness MB, Karahalios A, Finger RP, Guymer RH, Simpson JA. Age-related macular degeneration and mortality: a systematic review and meta-analysis. *Ophthalmic Epidemiol*. 2017;24(3):141-152.

34. Xu J, Murphy SL, Kochanek KD, Arias E. *Mortality in the United States, 2015*. Hyattsville, MD: National Center for Health Statistics; 2016. NCHS data brief 267.

35. Fisher DE, Klein BE, Wong TY, et al. Incidence of age-related macular degeneration in a multi-ethnic United States population: the Multi-Ethnic Study of Atherosclerosis. *Ophthalmology*. 2016;123(6):1297-1308.

36. Cruickshanks KJ, Hamman RF, Klein R, Nondahl DM, Shetterly SM; The Colorado-Wisconsin Study of Age-Related Maculopathy. The prevalence of age-related maculopathy by geographic region and ethnicity. *Arch Ophthalmol*. 1997;115(2):242-250.