Alcohol Consumption and Risk of Aging Macula Disorder in a General Population

The Rotterdam Study

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Objective: To investigate the possible relationship between overall or specific alcohol consumption and risk of aging macula disorder (AMD), a synonym for age-related macular degeneration, in a general population.

Methods: Alcohol consumption and risk of early or late incident AMD (iAMD) were examined among all participants in the prospective population-based Rotterdam Study, with complete data on alcohol consumption among 4229 subjects at risk of AMD. Aging macula disorder was graded according to the International Classification and Grading System for AMD by 2 trained professionals who were masked for all other determinants. We used Cox proportional hazards regression models to estimate hazard ratios and corresponding 95% confidence intervals.

Results: During a mean follow-up period of 8.0 years, 600 cases of iAMD were identified, of which 519 were early iAMD and 81 were late iAMD. After correction for age, sex, smoking, complement factor H genotype status, and other potential confounders, we did not find an association between overall or specific alcohol consumption and development of early iAMD or dry or wet late iAMD.

Conclusion: Our findings suggest that overall or specific alcohol consumption is not a risk factor for AMD.

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Because of limited treatment options, aging macula disorder (AMD), a synonym for age-related macular degeneration, imposes a major burden on the quality of life in older Western populations. Of few available treatments, laser photocoagulation, photodynamic therapy, or intraocular injection of vascular endothelial growth factor inhibitors can delay the progression of wet AMD, the neovascular form of late AMD, in a limited number of patients. Therefore, identification of modifiable risk factors is of great importance. Alcohol consumption is a potential modifiable risk factor. Alcohol use is common in the Netherlands; 80% of the Dutch population older than 12 years consume alcohol, and 10% are classified as heavy drinkers, consuming 6 or more glasses of alcohol a day at least once a week. Moderate alcohol consumption is associated with a decreased risk of cardiovascular disease. Increasing evidence that AMD is associated with vascular disease points to an inverse association between moderate alcohol intake and risk of AMD. On the other hand, alcohol is hypothesized to increase oxidative stress or to affect mechanisms that protect against oxidative damage.

Two cross-sectional and 3 incidence studies found an association between alcohol consumption and risk of AMD. However, 4 other cross-sectional and incidence studies could not confirm these results. These inconsistent findings may be attributed to differences in study design, numbers of cases, patient race/ethnicity, or the way in which AMD was diagnosed. Furthermore, the studies citing an association between alcohol intake and risk of AMD could not clarify whether overall or specific alcohol consumption is important. Among prospective studies investigating this association, the Beaver Dam Eye Study is the only one that is comparable to the present study. Both are large population-based studies of primarily northern European–derived individuals that used...
similar grading of AMD and collected data required to perform beverage-specific analyses. Beer consumption is more than 10% higher in the Beaver Dam Eye Study compared with the present study, but wine consumption is approximately 45% higher in the Rotterdam Study. The high prevalence of wine consumption among our population enabled us to investigate the association between wine consumption and incident AMD (iAMD). Therefore, in this population-based cohort we studied the risk of early or late iAMD according to consumption of different levels and types of alcohol.

METHODS

POPULATION

The Rotterdam Study is a prospective population-based cohort study of cardiovascular, locomotor, neurologic, and ophthalmologic diseases in older subjects. In summary, all inhabitants 55 years or older living in Ommoord, a suburb of Rotterdam, the Netherlands, were invited to participate in the study. Of 10,275 eligible individuals, 7,983 (77.7%) participated. The ophthalmologic part of the study started after screening of the participants had begun, leading to 6,780 ophthalmic participants, also with a 78.1% response rate. The Rotterdam Study was approved by the medical ethics committee of Erasmus University, and written informed consent was obtained from all participants. Baseline examinations, including a standard home interview and physical examination at the research center, took place between March 20, 1990, and July 31, 1993, and were followed by 3 examinations from September 1, 1993, to December 31, 1994 (response rate 88.2%), from April 15, 1997, to December 31, 2000 (response rate 80.1%), and from April 23, 2002, to December 31, 2004 (response rate 74.3%).

AMD DEFINITION

To diagnose AMD, 35-mm color photographs were taken of the macular area of each eye using a fundus camera (TRV-30VT; Topcon Corporation, Tokyo, Japan) after dilatation of the pupils with tropicamide, 0.5%, and phenylephrine, 5%. Fundus transparencies and digitized images from the third follow-up examination were graded using ×12.5 magnification according to the International Classification and Grading System for Age-Related Maculopathy and Age-Related Macular Degeneration. Two well-trained graders, each having 11 years of experience and masked for all other participant characteristics, graded the fundus images. The grading procedures and definitions, as well as the graders, were identical at baseline and at follow-up. We modified the nomenclature from age-related maculopathy for AMD, categorizing it as early or late AMD. As referred to herein, late AMD is similar to AMD in that classification system and is classified as dry (geographic atrophy) or wet (neovascular) late AMD.

No (or minimal) AMD was defined as no signs of AMD at all, only small hard drusen (<63 µm), soft distinct drusen (≥63 µm), or pigmented abnormalities. Early AMD included soft indistinct drusen (≥125 µm) or reticular drusen only, soft distinct drusen (≥63 µm) with pigmented abnormalities, or soft indistinct drusen (≥125 µm) or reticular drusen with pigmen-
tary abnormalities. Late AMD was subdivided into dry or wet late AMD. Dry late AMD was defined as any sharply demarcated round or oval area of apparent absence of the retinal pigment epithelium (RPE) larger than 175 µm with visible choroidal vessels and no wet AMD. Wet late iAMD was defined as the presence of a serious or hemorrhagic detachment AMD of the RPE or a sub-

retinal neovascular membrane or subretinal hemorrhage, or periretinal fibrous scar. Disease was classified according to the most advanced stage of AMD in either eye; when dry and wet late AMD were both present in 1 or either eye, patients were classified as having the wet form. Early iAMD was defined as any sign of early iAMD in at least 1 eye during follow-up among participants with no AMD at baseline in either eye. Late iAMD was classified as no or early AMD at baseline and the presence of late iAMD in either eye at follow-up. Lesions that were considered to be the result of generalized disease (such as trauma, high myopia, chorioretinitis, congenital diseases, diabetic retinopathy, or photoagulation for reasons other than for wet late AMD) were excluded from AMD classification.

ALCOHOL CONSUMPTION

Before the baseline examinations at the study center, participants received a checklist on which they indicated all foods and beverages they had consumed at least once during the preceding year. The completed checklist formed the basis of an interview using an extensive semiquantitative food frequency questionnaire at the study center by a trained dietician. The dietary interviews were performed using a computer program that simultaneously checked these data for logical inconsistencies. Participants reported the number of alcoholic beverages they consumed on a weekly basis in each of the following 4 categories: beer, wine, liquor, and moderately strong alcoholic beverages such as port wine or sherry. Nondrinkers were considered abstainers. A drink was defined as 200 mL of beer that contained 8.0 g of alcohol, 100 mL of wine that contained 10.0 g of alcohol, 30 mL of liquor that contained 14.0 g of alcohol, or 75 mL of moderately strong alcohol types that contained 10.5 g of alcohol. By adding the amounts of alcohol in the 4 groups, we calculated the total alcohol consumption per participant in grams per day. Because most of the moderately strong alcoholic drinks were wine types, this category was combined with the wine category in the analyses, leading to 3 nonexclusive groups of persons drinking beer, wine, and liquor. Daily alcohol consump-
tion was categorized as 0, 10 g or less, greater than 10 but no more than 20 g, or greater than 20 g.

ASSESSMENT OF CONFOUNDERS

Information on several potential confounders was collected at baseline. During a home interview, trained research assistants asked participants to detail their smoking habits. Each partici-

pant was categorized as a current, former, or never smoker. Systolic and diastolic blood pressures were measured twice at the right brachial artery while the subject was sitting using a random zero sphygmomanometer. The average of these 2 measurements was used to determine blood pressure levels. Body mass index was calculated as weight in kilograms divided by height in meters squared. Nonfasting blood samples were obtained from all participants. Serum total cholesterol and high-density lipo-

protein cholesterol levels were measured using an automated enzy-
matic procedure. Complement factor H genotypes were de-
termined in genomic DNA (2 ng) extracted according to standard allele discrimination assay procedures from leukocytes (Taq-

man; Applied Biosystems, Foster City, California).

DATA ANALYSIS

We estimated the risk of iAMD associated with alcohol consump-
tion using Cox proportional hazards regression models. Follow-up time in years was used as the time axis of the model. For cases, time to diagnosis was defined as halfway between the last examination without iAMD and the first examination...
The study population consisted of 4229 participants (67.0% of those at risk for late iAMD, 4914 (77.9% of those at risk) participated in at least 1 follow-up examination. Follow-up examinations were missing because of deaths, refusals, or losses to follow-up among some study participants. Our examinations were missed because of deaths, refusals, or losses to follow-up among some study participants. Because the baseline meeting with the dietician was missed, or for various other logistical reasons.

Baseline characteristics of these participants are given in Table 1. The mean time between baseline and the first follow-up examination was 2.0 years, between baseline and the second follow-up was 6.5 years, and between baseline and the third follow-up examination was 11.1 years. During a mean follow-up time of 8.0 years (follow-up range, 0.3-13.9 years), 600 cases of iAMD were identified, of which 519 were early iAMD and 81 were late iAMD. For early iAMD cases, the mean follow-up time from baseline to the development of iAMD was 4.5 years and for late iAMD cases was 6.2 years.

For each risk analysis of a subtype of AMD, the other AMD cases were removed from the study population, as given in the footnotes to Table 2 and Table 3. After correction for age and sex, Table 2 summarizes that total alcohol consumption, analyzed in categories, was not associated with early or late iAMD. We also analyzed alcohol consumption continuously but did not find an association. Because causative mechanisms could differ between dry and wet iAMD, we analyzed these 2 end stages separately. Risk of dry late iAMD increased with higher alcohol intake, whereas risk of wet late iAMD decreased with higher alcohol consumption (Table 3). However, the hazard ratios were not statistically significant (ie, the confidence intervals were large and included 1.0 because of the few incident cases).

In this cohort study, we could not detect an association between overall alcohol consumption and early or late iAMD. In addition, neither beer, wine, nor liquor drinkers were at higher risk for iAMD. With higher alcohol consumption, point estimates increased for dry late iAMD and decreased for wet late iAMD. Although associations were not statistically significant, the trend was statistically significant for dry late iAMD. Whether there exists an association between alcohol consumption and dry late iAMD remains inconclusive.

The Beaver Dam Eye Study found cross-sectionally an association between beer consumption in the past year and late AMD. In the 10-year incidence study, current...
heavy alcohol consumption (defined as the consumption of ≥4 servings of alcoholic beverages daily, corresponding to 46–56 g of alcohol) was associated with wet late AMD (risk ratio, 6.51; 95% confidence interval, 1.41–30.2). However, because only 3 current heavy drinkers developed late AMD and confidence intervals around the risk ratios were large, these results should be interpreted with caution. In the present study, only a single current heavy drinker, classified in the same way as in the Beaver Dam Eye Study, developed wet late iAMD, making comparable end-stage–specific analyses impossible. The Blue Mountains Eye Study, in cross-sectional analyses found no association between AMD and overall alcohol intake and more specifically beer consumption; however, consumption of spirits was associated with the presence of early AMD. The investigators suggested that this is likely to be a chance finding because consumption of spirits was not associated with late AMD or with the presence of any large drusen with a diameter greater than 125 μm. The National Health and Nutrition Examination Survey noted cross-sectionally a protective effect of moderate wine consumption against AMD. The authors did not correct for 2 strong risk factors for AMD (smoking and complement factor H Y402H single-nucleotide polymorphism, a risk factor unknown at that time), and recall bias might have resulted in their finding. A protective effect of wine consumption was also cross-sectionally described by the Los Angeles Latino Eye Study group, who found in addition a stronger association with AMD in heavy drinkers and particularly in beer drinkers. This study comprised a Latino population, and biological mechanisms (eg, the levels of alcohol dehydrogenase) could be different from those in a population of white race/ethnicity. The prospective Copenhagen City Eye Study, in cross-sectional analyses found an increased risk of any AMD with greater daily alcohol intake; however, the test for trend was statistically nonsignificant, and the confidence intervals were large. A puzzling aspect of their results is that they did not find an association between the established risk factor of smoking and AMD. Another prospective study found no overall association between alcohol consumption and iAMD, and only among women was excessive...
alcohol consumption (defined as ≥30 g/d) associated with early and dry late AMD (relative risk, 2.04; 95% confidence interval, 1.22-3.42). In that study, AMD was divided in 2 separate groups, pooled early and dry AMD and wet AMD because of possible different causative mechanisms. Pooling of early and dry AMD is controversial because dry and wet AMD are likely to develop in persons with early AMD.2 The Physicians’ Health Study19 (with a mean follow-up time of 12.5 years) and the population-based Hisayama Study20 (with a mean follow-up time of 5 years) did not detect an association between alcohol intake and iAMD; the authors could not perform beverage-specific analyses.

In contrast to case-control studies, we assessed alcohol consumption before onset of iAMD; therefore, recall bias is not likely to be involved. In our study, self-reported drinking habits may have introduced misclassification in exposure.27 In particular, this might have caused underreporting of alcohol consumption among heavy drinkers and may have diminished our ability to detect an association. However, all other epidemiologic studies investigating the possible association between alcohol consumption and AMD used self-reported data on alcohol intake. In addition, with increasing age, most drinkers reduce their alcohol consumption,28 thereby reducing power. The fact that we did not find an association could partly result from inclusion of former heavy drinkers in the group of alcohol nonconsumers and persons who did not drink because of their poor health status.29 However, additional exclusion of persons who had reduced their alcohol consumption in the past 5 years before baseline did not essentially change our results. The size of the Rotterdam Study, its population-based prospective design, and the fact that we have considered several important confounders strengthen our findings. Fundus images were graded in a standardized way by the same 2 well-trained graders at baseline and at all 3 follow-up visits. In addition, alcohol consumption and type of beverages were classified based on a validated food frequency questionnaire. Therefore, we believe that our findings are an important addition to the existing studies on the subject.

In conclusion, neither overall nor specific alcohol consumption was associated with early or late iAMD in our population-based prospective cohort study. Considering the lack of consistent results among studies, we believe that alcohol consumption is not an important risk factor for AMD.

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