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# Alcohol Consumption and Age-related Macular Degeneration: A Systematic Review and Dose–response Meta-analysis

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## ABSTRACT

**Purpose:** To perform a systematic review on the association between alcohol consumption and risk of age-related macular degeneration (AMD) using a meta-analytical approach.

**Method:** Systematic literature research was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines. Both categorical and dose–response meta-analysis was performed separately for early and late AMD. A fixed-effect model was used to calculate pooled effect estimates with 95% confidence interval (CI).

**Result:** Seven studies were included in the analysis with 4,566 and 440 cases of early and late AMD, respectively. Compared to the nondrinkers or occasional drinkers, the pooled effect estimates for early AMD with moderate (1.19, 95% CI [1.03–1.37]) and heavy (1.24, [1.10–1.39]) alcohol consumption, but not light (0.95, [0.90–1.06]) alcohol consumption, were statistically significant. However, the pooled effect estimates for late AMD with light (1.03, [0.79–1.33]), moderate (1.13, [0.83–1.55]), and heavy (0.98, [0.63–1.53]) alcohol consumption were found to be insignificant. A linear dose–response relationship was established ( $P < .05$ ) between alcohol consumption and risk of early AMD, and the pooled effect estimate for an increase in alcohol consumption of 10 g/day was 1.14 (1.08–1.21).

**Conclusion:** Moderate and heavy alcohol consumption could increase the risk of early AMD, but not late AMD, with a linear dose–response relationship.

## ARTICLE HISTORY

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## KEYWORDS

Alcohol consumption; age-related macular degeneration; dose–response; meta-analysis; observational study

## Introduction

Age-related macular degeneration (AMD) is a chronic and degenerative disease of the retina. It contributed to 4.4% of vision impairment and 5.9% of blindness in people older than 50 years worldwide in 2015,<sup>1</sup> and is projected to affect 288 million people in 2040.<sup>2</sup> The health burden of AMD increased radically<sup>3</sup>; however, currently available treatments are ineffective in most patients.<sup>4</sup> Therefore, identification of modifiable risk factors related to AMD has become a major concern in public health.

The retina is found to be susceptible to oxidative damage,<sup>5</sup> suggesting that considering alcohol as a modifiable risk factor is biologically plausible. Many observational epidemiology studies have investigated the relationship between alcohol consumption and AMD. Results were inconsistent for both early and late AMD, with a few findings suggesting an increased,<sup>6–10</sup> or decreased risk,<sup>11,12</sup> and others suggesting no relationship.<sup>13–15</sup> Two meta-analyses<sup>16,17</sup> were conducted to address this uncertainty, and both of which have reported that alcohol consumption increased the risk of early AMD but not late AMD. However, they did not consider the association

of different alcohol consumption levels with early and late AMD, and the exact nature of the dose–response relationship remains unclear.

Therefore, the current meta-analysis was performed separately for early and late AMD based on previous observational studies with the following objectives: primarily, to quantify the risk of AMD associated with light, moderate, and heavy alcohol consumption; subsequently, to quantify the dose–response relationship between alcohol consumption and the risk of AMD.

## Materials and methods

This study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>18</sup> Ethical approval and informed consent were not required, as aggregate data were extracted from published studies. The literature search, study selection, data extraction, and quality assessment were reviewed by two authors (Jingjing Zhang and Yangyang Liu). Any inconsistencies or disagreements were resolved by the third author (Toshiharu Mitsuhashi)

### Literature search

The systematic literature search was conducted in PubMed, Embase, Web of Science, Cochrane Library, and two gray literature databases (The gray literature Report and the OpenGrey) from their inception to September 10, 2020, and no language restriction was set. The following MeSH terms and text words were used: “Alcohol Drinking” OR “Alcohol consumption” OR “Alcohol intake” AND (“Macular Degeneration” OR “Age-Related Maculopathy” OR “Age-Related Degeneration” OR “Macular Dystrophy”) (detailed search strategies are available in the Text S1). Further, the reference lists from the retrieved articles were also reviewed to identify additional studies by manual searches, and relevant articles were tracked through automatic email alerts from the databases during the preparation of our manuscript.

### Study selection

Studies were included if the following inclusion criteria were satisfied: 1) human observational epidemiology studies designed as an original cross-sectional, a case-control, or a cohort study; 2) exposure variable was alcohol consumption and it was quantified; 3) outcome was the risk of AMD; 4) multivariate-adjusted effect estimates [relative risk (RR), hazard ratio (HR), odds ratio (OR)] and 95% confidence intervals (CIs) are reported, or data are adequate to be calculated, and nondrinkers and/or occasional drinkers are considered the reference category; 5) if more than one study included the same study population, the most recent or most informative study was included.

In addition, any study that met the above criteria, but reported only specific alcohol beverages, was excluded as non drinkers of a specific beverage could consume other types of alcohol.

### Data extraction

The following information was extracted from each study: the first author’s name, the year of publication, the country where the study was conducted, study design, sex, age at baseline, the total number of cases and participants, the definition of AMD, categories of alcohol consumption, and effect estimates with their 95% CIs in each alcohol consumption category. If a study provided separate estimates for men and women, data were extracted separately. In addition, for studies reporting results for various covariate analyses, the effect estimate adjusted for the most potential confounders was selected.

### Quality assessment

In previous studies,<sup>19,20</sup> the Newcastle–Ottawa Scale (NOS) and the criteria recommended by the Agency for Healthcare Research and Quality were selected to evaluate the quality of the cohort or case-control studies and cross-sectional studies, respectively. A full list of their items and each included study awarded points are provided in Table S1 and S2.

### Statistical analysis

The measurements of alcohol consumption were converted into a standard unit (g/day). If alcohol consumption was quantified as drink per week and unspecified in the original study, as in previous studies,<sup>21,22</sup> it would be converted according to the assumption that one drink corresponded to 12 g.

Meta-analysis was performed separately for early AMD and late AMD using two steps in the current study. A fixed-effect model was used to pool the effect estimates with their 95% CIs when heterogeneity was not significant; otherwise, a random-effect model was used. Foremost, the categorical analysis with non/occasional drinkers as the reference was used to evaluate the association between light (0–12 g/day), moderate ( $\geq 12$ –24 g/day), and heavy ( $\geq 24$  g/day) alcohol consumption and the risk of AMD using a semi-parametric method. Based on the midpoints of the upper and lower boundaries of original reported categories, the quantity of alcohol consumption was assigned to the above three levels. If the highest category was open-ended, the midpoint was set at 1.2-fold the lower boundary<sup>23</sup>; whereas, the lower boundary was defined as zero when the lowest category was open-ended. In addition, if more than one midpoint of alcohol consumption categories in the same study was assigned to the same level, the corresponding effect estimates were combined by the method proposed by Hamling et al.<sup>24</sup> Next, dose–response analysis was performed by the method described by Orsini et al.,<sup>25,26</sup> according to the features of exposure and outcome, assumption about their relationship, and the advantage of splines model. Restricted cubic splines with three knots at percentiles 10%, 50%, and 90% of distribution were first created. Then, the *P* value for non-linearity was calculated by testing the null hypothesis that the coefficient of the second spline was equal to 0. If its value was not  $< 0.05$ , other regression models, such as linear regression, piecewise regression, natural polynomial regression, and fractional polynomial regression, would be fitted. If the original studies could provide enough information, priority was given to non-linear and then linear models. In this step, the studies that both considered at least three quantitative exposure categories and provided the number of participants and cases in each category were included. The midpoints described above were also used as a dose for analysis.

Statistical heterogeneity across studies was evaluated using the *Q*-statistical and  $I^2$  percentages.<sup>27</sup> If the *P* value was  $< 0.10$  and  $I^2$  value was  $> 50\%$ , heterogeneity was identified as statistically significant, and subgroup analysis was used to explore the sources of heterogeneity. To test the robustness of our results, sensitivity analysis was performed by excluding one study each time from the categorical and dose–response analysis. If more than 10 original studies were included in the meta-analysis, a publication bias should be examined by funnel plots with a statistical test. All statistical analyses were conducted using STATA, version 15.1 (STATA, College Station Texas, USA). A two-tailed *P* value  $< .05$  was considered to be significant, except where otherwise specified.

## Results

### Search results and study characteristics

The results of the study selection process are shown in Figure 1. From 290 articles identified during the initial literature search, according to the inclusion and exclusion criteria, seven articles were included in the meta-analysis.<sup>6–8,13,14,28,29</sup> The manual search of the reference lists from relevant reviews and retrieved articles did not yield any additional eligible studies for the final analysis. The characteristics of the included studies are summarized in Table S3. There were six cohort studies,<sup>6,13,28</sup> and one cross-sectional study,<sup>8</sup> published between 1999 and 2016. Three studies were conducted in the United States,<sup>13</sup> two in Europe,<sup>7</sup> and one each in Australia,<sup>6</sup> and South Korea. Five studies presented results for both early and late AMD,<sup>7,13,28</sup> one study for early only, and one for late only.<sup>6</sup> Among 114,550 participants, 4,566 had early AMD, and among 93,351 participants, 440 had late AMD. Five studies did not distinguish between sex,<sup>7,8,14,29</sup> one study performed stratified analyses by sex corresponding to two cohorts,<sup>28</sup> and one study reported the results for men only.<sup>13</sup> Age was adjusted for all included studies, and smoking status was also adjusted for most studies.<sup>6,13,14,28,29</sup> The overall quality of the

included studies was high, and only two studies<sup>7,29</sup> were assigned a score equal to six using NOS.

### Categorical analysis

The pooled effect estimates for early and late AMD with different alcohol consumption levels compared with nondrinkers or occasional drinkers are shown in Figures 2 and 3, respectively. A fixed-effect model was used for all analyses in this step. For early AMD, the pooled effect estimates were 0.98 (95% CI 0.90–1.06) for light, 1.19 (1.03–1.37) for moderate, 1.24 (1.10–1.39) for heavy alcohol consumption, with acceptable heterogeneity across studies (light:  $I^2 = 0.0\%$ ,  $P$  value for heterogeneity = 0.667; moderate:  $I^2 = 0.0\%$ ,  $P = .487$ ; heavy:  $I^2 = 38.8\%$ ,  $P = .162$ ). This indicated that moderate and heavy alcohol consumption were associated with an increased risk of early AMD. For late AMD, the pooled effect estimates for light (1.03, 95% CI 0.79–1.33), moderate (1.13, 0.83–1.55), and heavy (0.98, 0.63–1.53) alcohol consumption were found to be statistically insignificant, with acceptable heterogeneity across studies (light:  $I^2 = 35.1\%$ ,  $P$  value for heterogeneity = 0.173; moderate:  $I^2 = 0.0\%$ ,  $P = .656$ ; heavy:  $I^2 = 0.0\%$ ,  $P = .471$ ).

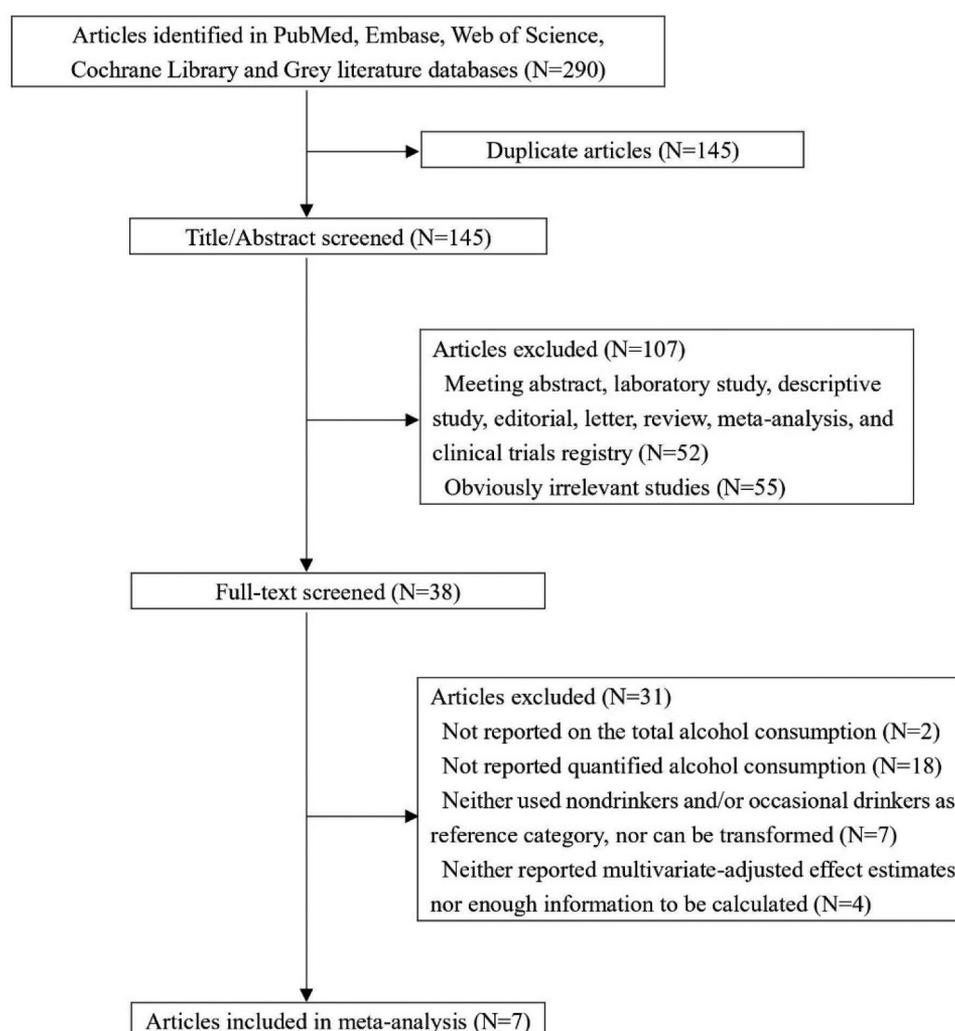
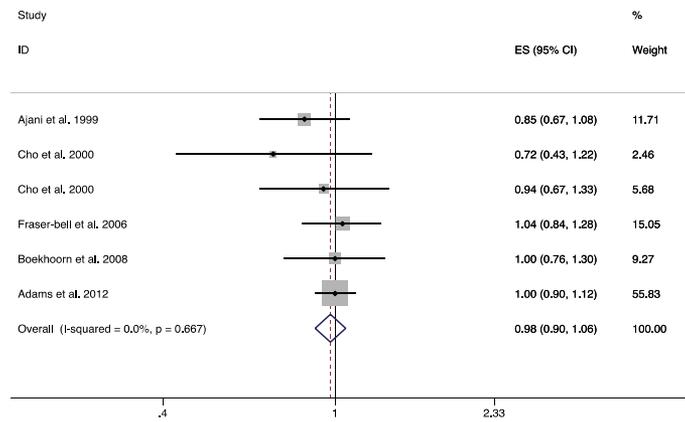
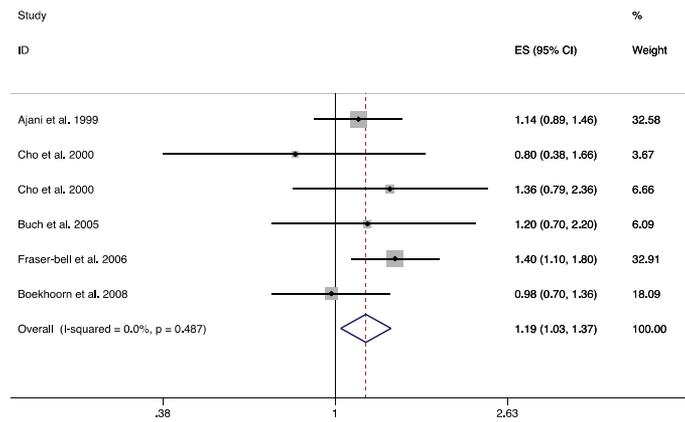


Figure 1. Flow chart of the literature search and study selection process.

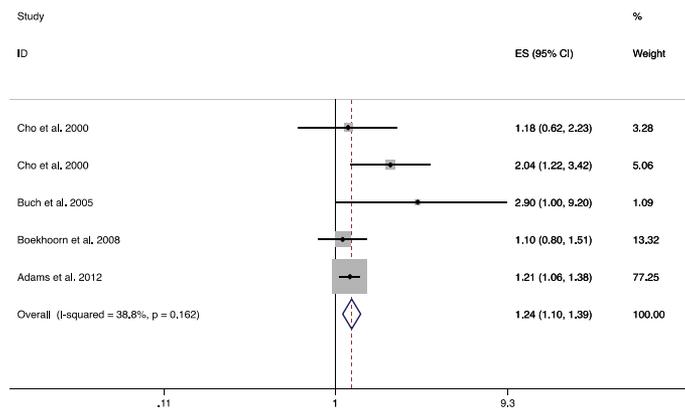
**a. Light alcohol consumption**



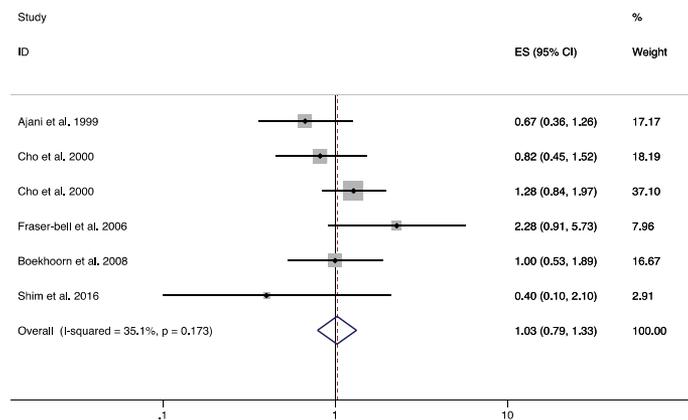
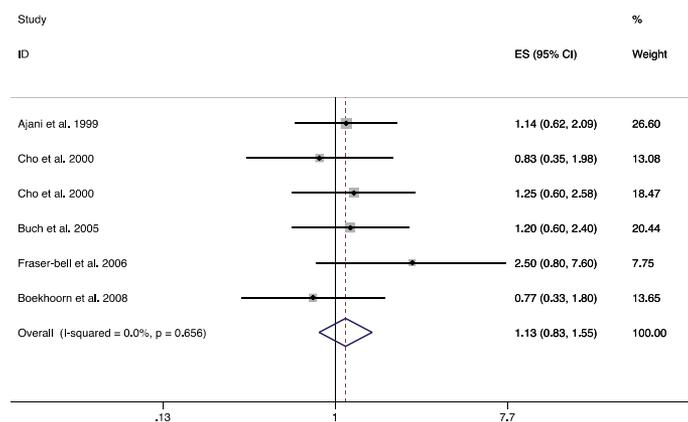
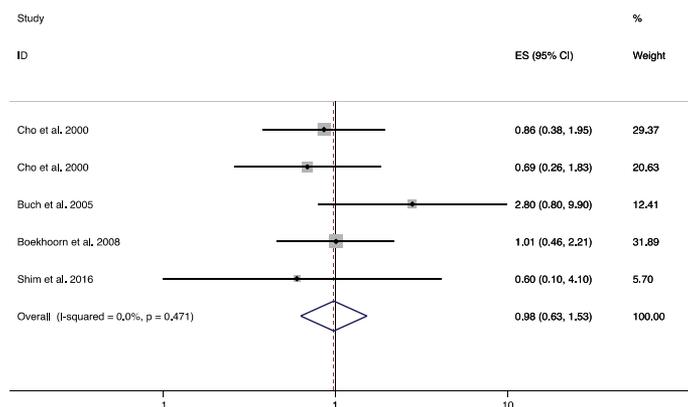
**b. Moderate alcohol consumption**



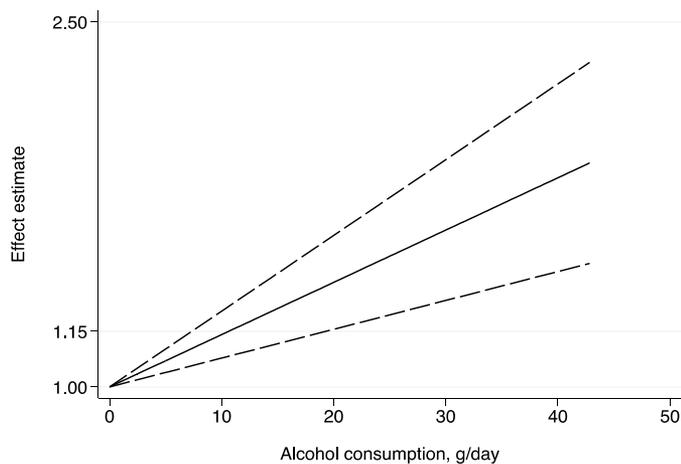
**c. Heavy alcohol consumption**



**Figure 2.** Pooled effect estimates for early AMD with light (a), moderate (b), and heavy (c) alcohol consumption compared with non-drinkers or occasional drinkers. Squares represent study-specific effect estimates and the size of the square reflects the study-specific statistical weight; horizontal lines represent 95% confidence intervals; the diamond and the dash line represent the pooled effect estimates and its 95% confidence interval. ES, effect estimate, including relative risk, hazard ratio and odds ratio. CI, confidence interval.

**a. Light alcohol consumption****b. Moderate alcohol consumption****c. Heavy alcohol consumption**

**Figure 3.** Pooled effect estimates for late AMD with light (a), moderate (b), and heavy (c) alcohol consumption levels compared with non-drinkers or occasional drinkers. Squares represent study-specific effect estimates and the size of the square reflects the study-specific statistical weight; horizontal lines represent 95% confidence intervals; the diamond and the dash line represent the pooled effect estimates and its 95% confidence interval. ES, effect estimate, including relative risk, hazard ratio and odds ratio. CI, confidence interval.



**Figure 4.** Dose-response relationship between alcohol consumption and risk of early AMD. The solid line represents effect estimates and the dash lines represent the 95% confidence interval.

This showed that there was no association between alcohol consumption and risk of late AMD.

### Dose-response analysis

One study<sup>6</sup> that did not provide the number of cases for each category was excluded. The fixed-effect model was used in the dose-response analysis. For early AMD, the evidence of relationship fitting restricted cubic splines regression ( $P = .13$ ) could not be found as there was insufficient information for testing piecewise regression, natural polynomial regression, and fractional polynomial regression model; and the linear relationship ( $P < .05$ ) was observed as shown in Figure 4, with no statistically significant heterogeneity ( $P$  value in non-linearity test = 0.58 and  $P$  value in the linearity test = 0.35). Furthermore, the pooled effect estimate for an increase in alcohol consumption of 10 g/day was 1.14 (95%, 1.08–1.21). For late AMD, neither non-linear ( $P = .97$ ) nor linear ( $P = .63$ ) relationship with alcohol consumption was found in the analysis, with no statistically significant heterogeneity ( $P$  value in non-linearity test = 0.68 and  $P$  value in the linearity test = 0.64).

### Sensitivity analysis

Despite excluding one study each time, we found no changes in the direction of pooled effect estimates of early AMD for both moderate and heavy alcohol consumption in the categorical analysis; when the study by Fraser-Bell et al. was excluded, the pooled effect estimate for moderate alcohol consumption was not found statistically significant due to a wide CI (see Table S4). Further, even in the linear relationship between alcohol consumption and risk of early AMD in the dose-response analysis, the direction of pooled effect estimates did not change (see Table S5).

### Discussion

Based on the seven observational studies involving 114,550 participants for early AMD and 93,351 participants for late AMD, the results of the current meta-analysis suggested that

moderate and heavy alcohol consumption, and not light alcohol consumption, could increase the risk of early AMD. Moreover, there was a linear relationship between the risk of early AMD and alcohol consumption; the risk increased by 14% for each 10 g/day increment in alcohol consumption. However, all investigated relationships between alcohol consumption and the risk of late AMD were not significant.

In two previous meta-analyses related to the same topic, Chong et al.<sup>16</sup> found that heavy alcohol consumption (more than three drinks per day) was associated with an increased risk of early AMD, whereas the relationship with late AMD was inconclusive; Dinu et al.<sup>17</sup> reported that the highest alcohol consumption was associated with a significantly increased risk of early AMD but not late AMD. However, they both conducted the meta-analysis only based on the comparison of the lowest and highest level of alcohol consumption, the results could be too rough. Besides, alcohol consumption was measured in different methods among the included studies; some measured frequency, whereas others measured quantity, which might be the reason for the significant heterogeneity. In the current study, through standardization with three levels of alcohol consumption, more comprehensive analyses were performed, and more accurate results were obtained in the categorical and dose-response analysis, compared to the results of the previous studies.

Our results suggested that moderate and heavy alcohol consumption could increase the risk of early AMD; however, the association was not found on light alcohol consumption. This might be because former drinkers were regarded as the nondrinkers and misclassified into the reference category, leading to an underestimation of the risks on all levels and narrowing the gap between light and reference. Contrary to these findings, the results of the excluded two studies<sup>11,12</sup> indicated that alcohol consumption reduced the risk of early AMD. However, in the cross-sectional studies, reverse causation cannot be completely ruled out from their results.

Compared with early AMD, no different mechanisms were provided for late AMD in previous studies; therefore, alcohol consumption could increase the risk of late AMD similarly.<sup>4</sup> However, all explored relationships between alcohol consumption and the risk of late AMD were not significant in the current study, which is consistent with most previous studies. These results might be because of the following reasons. Primarily, the small numbers of cases for late AMD affected the statistical accuracy of analyses. According to the results of the previous study, the prevalence of early and late AMD was 8.01% and 0.37%, respectively.<sup>2</sup> Subsequently, during the progression from early to late AMD, because of the sick-effect, patients of early AMD would quit drinking considering the high risk of late AMD, which dilutes the proportion of late AMD among drinkers. In addition, especially older adults have been diagnosed as diabetic retinopathy or were deceased before the ascertainment of late AMD. Hence, as a competing event, it led to the distortion of the results. Finally, the survivor effect, those who consumed alcohol till the presentation of late AMD, could be more resilient to the adverse effects of alcohol,<sup>30</sup> attenuating the estimates of late AMD.

Few studies have investigated the dose-response associations between alcohol consumption and the risk of AMD.

Smith et al.<sup>15</sup> and Knudtson et al.<sup>31</sup> reported that there were no dose–response relationships of alcohol consumption with AMD. The inconsistency of their results with ours might be because separate cases were not considered for early and late AMD along with the small number. Although other studies<sup>8,14,28</sup> found that the trend was statistically significant for early or late AMD, the exact nature of the dose–response relationships, whether linear or non-linear, was not evaluated and clarified. In the current study, the results showed a significant linear relationship with alcohol consumption for early AMD, and the risk increased by 14% for each 10 g/day increment. A previous study<sup>32</sup> suggested that alcohol consumption was linearly associated with a higher risk of cardiovascular diseases that might support the findings because of the similar mechanisms. Furthermore, the inconsistent results of categorical and dose–response analysis on the association between light alcohol consumption and risk of early AMD could imply that when compared with point estimates, the trend estimate was less influenced by the misclassification of former drinkers.

The strength of the current study included a large sample size, high quality of included studies, acceptable heterogeneity across studies, and comprehensive assessment of the association between alcohol consumption and AMD risk by categorical and dose–response analysis.

Nevertheless, several potential limitations should also be considered. First, alcohol consumption was assessed by self-report and only once at baseline in the included studies, which could lead to an underestimation of the association with the risk of AMD. However, the reproducibility and validity of self-reported alcohol consumption in various populations had been reported reasonably,<sup>33</sup> and behaviors were relatively stable over time in older individuals, except in those with a serious illness or close to death.<sup>34</sup> Second, former drinkers were regarded as the nondrinkers and misclassified into the reference category. Unfortunately, this issue cannot be addressed because most of the included studies did not report the effect estimates between the former drinker and lifetime abstainers separately. In addition, occasional drinkers were defined as the reference category in one of the included studies, not the same as others, which could have biased the results. However, a previous study<sup>34</sup> indicated that classifying occasional drinkers as nondrinkers cannot lead the significant downward bias in effect estimates of alcohol consumption. Besides, after excluding this study in the sensitivity analysis, the main results were unchanged in the current study. Third, not only the quantity but also consumption patterns could play an important role in the effect of alcohol consumption, such as binge drinking or with meals. Unfortunately, they were not performed in the current study because none of the included studies provided this information, and should be considered in future studies. Fourth, the associations of very high alcohol consumption with the risk of AMD were not confirmed in the current study because the heavy level was open-ended, which influenced the linear association of the dose–response. However, among the general population, only few older adults would consume very high levels of alcohol.<sup>35</sup> Fifth, different methods were used to

assess AMD among the included studies, including different diagnostic criteria with or without photographic documentation of AMD signs with visual acuity criteria, and different data collection methods that blind assessment or linkage with the medical record. However, heterogeneity was always acceptable in the current study, and it would be the non-differential misclassification. Sixth, it is well-known that bias due to confounders do exist in observational studies, although some can be adjusted as covariates. The adjustment strategies varied among the included studies, which introduced uncertain bias in the pooling analysis. However, there is limited ability to control the bias using statistical adjustment, and how the different adjustment strategies influence the pooled effect estimates is still unclear. Even so, certain effective covariates, including age and smoking status, had been adjusted in most studies. Further methodological studies are needed to assess confounder adjustment strategies and clarify the effect of adjusted estimates from original study on pooled effect estimates. Seventh, some factors can interact with alcohol consumption by influencing alcohol dehydrogenase activities or variants, such as sex and ethnicity.<sup>36,37</sup> Unfortunately, as only one included study<sup>28</sup> performed separate analyses for men and women, and the studies on the risk of AMD in Africa and Asia were scarce,<sup>38</sup> stratified analyses was not conducted in the current study. Future studies on the interaction of alcohol consumption and other factors are necessary. Eighth, we could not confirm whether the single cross-sectional study included<sup>8</sup> could introduce a bias in the meta-analysis. However, this study had a high-quality score by standard assessment criteria with acceptable heterogeneity across studies. Therefore, it could not be excluded from analysis. The bias of including cross-sectional studies in meta-analysis should be confirmed in future studies. Finally, as an inevitable problem, publication bias could exist in the current study, and the statistical test for funnel plots was not performed because there were fewer than 10 included studies. In future updates, it would be further investigated.

In conclusion, this meta-analysis indicated moderate and heavy alcohol consumption could increase the risk of early AMD, but not late AMD, with a linear dose–response relationship. Nevertheless, attentiveness is required on public health recommendation of alcohol consumption for AMD protection, which should also consider the balance of risk on other diseases.

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## Declaration of interest statement

The authors report on conflicts of interest.

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