Alcohol intake and the risk of glioma: A systematic review and updated meta-analysis of observational study

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Abstract
The association between alcohol intake and the risk of glioma has been widely studied, but these results have yielded conflicting findings. Therefore, we conducted this systematic review and updated meta-analysis to systematically evaluate the association between alcohol intake and the risk of glioma. A systematic literature search of relevant articles published in PubMed, Web of Science, CNKI and Wan fang databases up to December 2021 was conducted. Pooled estimated of relative risk(RR) and 95% confidence interval(CI) were calculated using fixed-effects models. A total of eight articles with three case-control studies involving 2706 glioma cases and 2189927 participants were included in this meta-analysis. A reduced risk of glioma was shown for the low-moderate alcohol drinking versus non-drinking (RR=0.87; 95%CI: 0.78, 0.97; P=0.014). In addition, there was no evidence of an increased risk of glioma in the heavy alcohol drinking compared with non-drinking (RR=0.89; 95%CI: 0.67, 1.18; P=0.404). The findings suggest an inverse association between low-moderate alcohol drinking and the risk of glioma, in the absence, however, of a dose-response relationship. More prospective studies are needed to provide further insight into the association between alcohol drinking and glioma risk.

Keywords: Alcohol intake; Glioma; Meta-analysis; Systematic review; Epidemiology

Abbreviations
CNS: Central nervous system, RR: Relative risk, HR:Hazard ratio, OR:Odds ratio, CI:Confidence interval, NOS:Newcastle-Ottawa Quality Scale.
Introduction
Glioma is a devastating tumour of the central nervous system (CNS), accounting for approximately 80% of adult malignant brain tumours\(^1\). It is reported that the global incidence rate of glioma is 3.7 per 100000 for males and 2.6 per 100000 for females\(^2\). Despite the low incidence rate, glioma is associated with high mortality and poor prognosis\(^3\). Indeed, apart from few established risk factors, such as exposure to ionizing radiation, white race/ethnicity, little is known regarding the effect of modifiable risk factors (e.g. diet and alcohol intake) on glioma\(^4\). Therefore, identifying the relationship of alcohol intake with glioma is valuable.

Over the past decades, alcohol intake has been recognized as an important risk factor for several types of cancer, including breast cancer\(^5\), colorectal cancer\(^6\) and liver cancer\(^7\). Alcohol is neurotoxic and can traverse the blood-brain barrier. A previous study has described the short and long-term effects of excessive alcohol consumption on brain function and pathology\(^8\). To date, substantial epidemiological studies have explored the relationship between alcohol consumption and the risk of glioma\(^9\)\(^\)\(^\)\(^-\)\(^13\). But, results from these studies have been inconsistent. In the NIH-AARP diet and Health Study, Braganza et al., found the significant inverse associations between alcohol and beer intake and glioma risk\(^9\). In addition, a recent report from three prospective cohort studies, also found a significant inverse association between alcohol intake and glioma risk in both men and women\(^11\). However, in a hospital-based case-control study, Burch and his colleagues found that wine consumption was associated with an elevated risk of glioma\(^13\). Furthermore, a previous meta-analysis from 19 observational studies has shown no material association between alcohol consumption and risk of glioma\(^14\). Therefore, to clarify the exact association between alcohol intake and glioma risk, we conducted this systematic review and updated meta-analysis to summarize the evidence from observational studies published up to December 2021.

Material and Methods
This systematic review and meta-analysis has adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines\(^15\), and was written according to the Meta-analysis of Observational Studies in Epidemiology proposal\(^16\).
Literature search strategy
A comprehensive literature search was performed using the PubMed, Web of Science, CNKI and Wan Fang databases to identify relevant articles written in the English and Chinese languages published through December, 2021, with the following search terms: (“alcohol” OR “ethanol” OR “alcohol drinking” OR “alcohol intake”) AND (“glioma” OR “gliblastoma” OR “brain cancer” OR “brain tumour”). The search was restricted to human studies. Moreover, we also reviewed the computer retrieved studies for reference lists by hand-searching.

Studies included criteria
Two independent reviewers (Shu L and Jin FB) read the abstracts of articles retrieved in the initial search to identify human studies that examined the relationship between alcohol intake and the risk of glioma. Differences between the two independent reviewers were resolved by consensus and referred to the third reviewer if necessary. When all agreed, the full-text versions of articles were reviewed against inclusion and exclusion criteria for this meta-analysis. Studies were included if they met the follow criteria: (1) an original study reporting the association between alcohol intake and glioma risk; (2) used a case-control, nested case-control or cohort design; (3) estimates of relative risk(RR)(OR, hazard ratio, rate ratio) with corresponding 95% confidence intervals(CI) were provided (or sufficient data to calculate them);(4) If the data in original publication lacked sufficient detail, the corresponding author of the study was contacted for additional information by email. Studies were excluded if they met one of based on the follow criteria: written in a language other than English or Chinese; not performed on humans; reviews and letters; studies with insufficient data. Finally, eight studies reported the association between alcohol intake and the risk of glioma.

Data extraction
Two reviewers(Shu L and Jin FB) independently extracted the following data from included studies: the first author’s last name, publication year, geographic, study design, age for cases and participants, number of cases and controls or participants, type of controls, methods used for collection of data on exposure, exposure classification, confounders adjusted for, and the OR, RR or HR estimates with corresponding 95% CI for the heavy drinking, low-moderate drinking versus non-drinking. Any discrepancies were resolved with a group discussion with a third investigator(Yu D).
Definition of “high intake” and “moderate intake”

The different forms of alcohol intake were converted into grams of ethanol per day (e.g. 1 drink = 12.5 g, 1 mL = 0.8 g, 1 U = 8 g, 1 oz = 28.35 g of ethanol) (17). Alcohol intake > 25 g/d (or 2 drinks/d) for men or > 12.5 g/d (or 1 drink/d) for women was defined as high intake of alcohol or heavy alcohol drinking; alcohol intake < 12.5 g/d for men and < 7.5 g/d for women was defined as low intake of alcohol or low alcohol drinking, and alcohol intake of > 12.5 g/d and < 25 g/d for men or > 7.5 g/d and < 12.5 g/d for women was defined as moderate alcohol drinking (18).

Assessment of heterogeneity

We performed the Cochran’s Q test and I² statistic to test and quantify the heterogeneity among the included studies. A P value of Q-test > 0.10 indicated an absence of heterogeneity between included studies, and the fixed-effects model was used to calculated the pooled RRs. If a P value of Q-test ≤ 0.10 indicated a high degree of heterogeneity among studies, then the random-effects model (DerSimonian and Laird method) was used (19).

Quality assessment

The Newcastle-Ottawa Quality Scale (NOS) was applied to assess the quality of the included studies in this meta-analysis (20). This scale includes 4 points for selection, 2 points for comparability, and 3 points for the assessment of outcomes. Finally, studies with a score of greater or equal to 7, were identified as high-quality studies (21). Disagreements were resolved by discussion to reach a consensus.

Data synthesis and statistical analysis

To identify the relationship between alcohol intake and glioma risk, we used meta-analysis to summarize the risk estimate for the heavy drinking, low-moderate drinking versus non-drinking using OR, RR, and HR and corresponding 95% CI for the included studies. Given the prevalence of glioma was relatively low, OR and HR were directly considered as RR (22). Multivariable adjusted ORs, HRs and RRs with corresponding 95% CIs from individual studies were combined to produce an overall RR. Publication bias was assessed by inspection of the funnel plot and by formal testing for “funnel plot” asymmetry using Begg’s test and Egger’s test (23). Moreover, sensitivity analysis was carried out to determine whether sex, study design, geographic area, and study quality affected study conclusions. All statistical analyses were carried out using the STATA software, version 12 (Stata Corp, College Station, TX, USA). Statistical tests were two-sided with P-value < 0.05 accepted as statistically significant.
Results

Overview of included studies for the systematic review
An electronic literature search in PubMed, Web of Science, CKNI, and Wan fang database identified 401 studies, 393 of which were excluded based on the reasons listed in Figure 1. Eight articles met the inclusion criteria and were included in this meta-analysis, including 5 cohort studies and 3 case-control studies. The characteristics of the included studies were summarized in Table 1.

Alcohol-drinking
The heavy alcohol drinking was characterized by high intakes of alcohol-containing beers, wines, and spirits. Pooled results from six articles (including eight original studies) identified a heavy alcohol drinking (Figure 2). Figure 2 showed no evidence of an increased risk of glioma in the heavy alcohol drinking versus non-drinking (RR=0.89; 95% CI: 0.67, 1.18; P=0.404). Data from these studies were assessed using random-effects model, and there was significant heterogeneity (I²=43.7%, P=0.087). Eight articles reporting eleven original studies identified a low-moderate alcohol drinking in this meta-analysis (Figure 3). There was evidence of a reduced risk of glioma in the low-moderate alcohol drinking compared with non-drinking (RR=0.87; 95% CI: 0.78, 0.97; P=0.014). A fixed-effects model was used to assess the data, and there was no evidence of heterogeneity (I²=0.0%, P=0.656).

Publication bias
Inspection of funnel plots did not reveal evidence of asymmetry (Figure 4, Figure 5). Egger’s test for publication bias was not statistically significant (heavy alcohol drinking versus non-drinking: P=0.536; low-moderate alcohol drinking versus non-drinking: P=0.458).

Quality assessment
The quality of included studies using Newcastle-Ottawa criteria is detailed in Appendix 1. When included studies received a score of six or higher, they would be deemed to be of relatively higher quality [9-12,23-26].

Sensitivity analysis
The sensitivity analysis revealed that differences in age, sex, ethnicity and study design had an effect on the relationship between alcohol intake and glioma risk. When moderate alcohol drinking was compared with non-drinking, the alcohol intake/glioma association was stronger when subjects were women, white and more than 50 years old, and study design was cohort.
these variables have a strong effect on relationship between alcohol intake and glioma risk, their differences may partially explain the heterogeneity between studies (Table 2).

**Discussion**

Existing evidence on the role of alcohol intake and the incidence of glioma is limited and inconsistent. To the best of our knowledge, this is the latest systematic review and meta-analysis on the effect of alcohol intake on glioma. In this study, we found a significant inverse association between low-moderate alcohol drinking and the risk of glioma. Meanwhile, no significant association between heavy alcohol drinking and the risk of glioma was observed. Data from eight articles involving 2706 glioma cases and 2189927 participants were included in this meta-analysis. Our findings provide further evidence on the role of alcohol intake and the risk of glioma, though the lack of a dose-response relationship suggests caution in the interpretation of results.

In our analyses, the significant inverse association was identified between low-moderate alcohol drinking and the risk of glioma. Our findings are inconsistent with a previous meta-analysis of alcohol consumption and the risk of glioma\(^{(14)}\). Qi et al. reported no material association between alcohol consumption and risk of glioma (total alcohol drinks vs non-drinks: RR=0.96, 95%CI:0.89-1.04)\(^{(14)}\). In their meta-analysis, the main analysis is “ever and alcohol drinkers versus nondrinkers”. Qi and colleagues didn’t analyze the relationship between different levels of alcohol consumption and the risk of glioma. Thus, a lack of consideration for the association between different drinking group and glioma could contribute somewhat the variance in results. In a comprehensive meta-analysis of alcohol consumption and risk of brain tumors, Galeone and colleagues also found that alcohol drinking did not appear to be associated with adult brain cancer\(^{(17)}\). The difference to our study is that Galeone et al. did not analyze glioma or glioblastom separately from other brain tumors. This analysis of combination of glioma and other brain tumors could make these findings more confounding. Also, inclusion of eight articles reporting eleven original studies with a larger sample size might explain the modest stronger association observed in our meta-analysis. In contrast, a more recent report from three prospective cohort studies found a significant inverse association between alcohol intake and glioma risk in both men and women\(^{(11)}\). Cote et al. estimated HRs of glioma and 95% CIs by category of alcohol intake and adjusted the covariates including BMI, smoking status, and total caloric intake. In the NIH-AARP Diet and Health Study, an analysis including 704 glioma cases
also identified significant inverse, dose-dependent associations between alcohol and beer intake and risk of glioma, but no associations for wine or liquor. In short, the evidence linking alcohol consumption with glioma is inconsistent. Although ethanol has been classified as carcinogenic to humans by the International Agency for Research on Cancer (IARC), there are several plausible explanations for this favorable effect of low-moderate alcohol drinking on glioma. First, xanthohumol, a flavonoid present in beer, has exhibited its anticancer properties via inhibition of various signaling pathways, e.g., disruption of the activation of transcription factors, suppression of multiple protein kinases, and regulation of the expression of genes which related to cell proliferation, angiogenesis, and apoptosis. Second, laboratory evidence has also shown that certain components of red wine, such as phenols, may play an important role in reducing the growth and development of glioma. These mechanisms mentioned above could explain the observed association between low-moderate alcohol drinking and risk of glioma. Meanwhile, in this study, we observed no significant association between heavy alcohol drinking and glioma risk. Our results are inconcordant with a previous study, which suggests that alcohol consumption increases the risk of glioblastoma consistent with a dose-response relationship. Alcohol drinking has been consistently considered as an important risk factor for cancers. Data from the Melbourne Collaborative Cohort study including 67 glioblastoma cases showed no significant differences for those drinking <20 g/d of alcohol, but a higher risk for those drinking 40-59 g/d (HR=3.07, 95%CI: 1.26-7.47) and ≥60 g/d (HR=2.54, 95%CI: 0.92-7.00), compared to lifetime abstainers. Although we observed no significant association between heavy alcohol drinking and glioma risk in this study, several plausible mechanisms have also been proposed. First, alcohol is an identified human carcinogen that penetrates the blood-brain barrier and thus may play an important role in the development of glioma. Second, acetaldehyde is an intermediate product of alcohol metabolism, which have been shown to induce DNA lesions, generate free radicals, and damage enzymes involved in DNA repair and antioxidant protection. Third, animal studies have also shown that N-nitroso compounds contained in alcohol can result in brain tumors. In a hospital-based case-control, Hurley et al., found no significant association between heavy alcohol consumption and risk of glioma in both men and women, however, the risk estimate was only adjusted for age and reference rate and residual confounding was possible. In case-control studies of alcohol consumption in particular, the risk of recall bias may be substantial, and this bias may affect the relationship between
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alcohol intake and glioma risk\(^{(34)}\). There are several possible explanations for the null association. First, alcohol intake might have changed during the follow-up, such as after a diagnosis of glioma. This change in alcohol intake could attenuate the association between heavy alcohol drinking and the risk of glioma. Second, we were unable to analyze the effect of specific alcohol types on glioma, because limited data were available. Finally, to the above mentioned, some constituents in alcoholic beverages, e.g. beer, red wine have been reported to have anticancer properties\(^{(30-31)}\).

**Strengths and limitations**

This systematic review and meta-analysis had its own strengths and limitations. First, this is the latest systematic review and meta-analysis on alcohol intake in relation to the risk of glioma. We not only have an update on the earlier meta-analysis (Qi et al. in 2014)\(^{(14)}\), but also further clarify the relationship between heavy alcohol drinking and low-moderate alcohol drinking and glioma risk. Second, the cases of glioma have been diagnosed through clinical manifestations, pathological section or endoscopic ultrasonography, avoiding misdiagnosis. Third, no signs of publication bias were evident in the funnel plot, and the statistical test for publication bias was non-significant. However, several limitations should be noted in this study. First, due to this meta-analysis was based on observational studies(i.e. case-control or cohort design), confounding factors are often of concern. Thus, we cannot rule out the probability that these findings were susceptible to recall and selection bias. Second, there was an inconsistent adjustment for potential confounders in the included studies. As a result, the data included in our analysis might suffer from differing degrees of completeness and accuracy. Third, because of scanty data be available in included studies, we were unable to assess separately various types of glioma, e.g glioblastoma, oligodendro-glioma. Finally, the potential publication bias may distort the relationship between alcohol intake and glioma risk.

**Conclusion**

In conclusion, this systematic review and updated meta-analysis suggests an inverse association between low-moderate alcohol drinking and the risk of glioma. However, the lack of a dose-risk relationship for these findings indicates caution in their interpretation. Our findings need to be affirmed in further randomized controlled trials or large prospective studies.
Ref Acknowledgements
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Conflicts of interest
The authors declare no conflict of interest associated with this paper.

Authorship
The authors’ responsibilities were as follows: L. S. and F.-B.J. took responsibility for data integrity and the accuracy of data analysis. L.S. was responsible for study concept and design. F.-B.J. and D.Y. acquired the data. L.S. and D.Y. were responsible for analysis and interpretation of the data. L.S. performed the statistical analysis. F.-B. J. and L. S. drafted the manuscript. All authors critically revised the manuscript for important intellectual content

Ethical Standards Disclosure
Ethics approval and consent to participate is not required for this study.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
References
Table 1 Characteristics of studies on alcohol intake and risk of glioma (–2021)

<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Country</th>
<th>Study design</th>
<th>No. of cases and controls/cohort</th>
<th>Age</th>
<th>Duration of follow-up</th>
<th>Information on alcohol drinking</th>
<th>RR/HR/OR (95% CI)</th>
<th>Adjustment or matched for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branga nza et al. 2014[9]</td>
<td>United States</td>
<td>Cohort</td>
<td>477095</td>
<td>50-71y</td>
<td>10.5y</td>
<td>Alcohol</td>
<td>0.65(0.47-0.90), 0.96 (0.63-1.48) for heavy drinking in men and women, 0.92 (0.69-1.24),0.79(0.54-1.16) for low- moderate drinking in men and women</td>
<td>Education, marital status, and race/ethnicity.</td>
</tr>
<tr>
<td>Hurley et al. 1996[10]</td>
<td>Australia</td>
<td>Case-control</td>
<td>416 cases, 422 controls</td>
<td>20-70y</td>
<td>-</td>
<td>Alcohol consumption</td>
<td>1.36(0.73-2.51), 0.93(0.38-2.25) for heavy drinking in men and women, 1.30(0.66-2.54), 0.55(0.30-0.99) for low- moderate drinking in men and women</td>
<td>Age and reference rate</td>
</tr>
<tr>
<td>Cote et al. 2021[11]</td>
<td>United States</td>
<td>Cohort</td>
<td>237505</td>
<td>25-75y</td>
<td>26.2y</td>
<td>Total alcohol</td>
<td>0.62(0.39-0.97) for heavy drinking, 0.9</td>
<td>Age(months), smoking status (never vs. past vs. current),</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Type</td>
<td>Number</td>
<td>Age Range</td>
<td>Alcohol Intake</td>
<td>Calculation</td>
<td>Additional Factors</td>
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<tr>
<td>Baglietto et al. 2011[12]</td>
<td>Australia</td>
<td>Cohort</td>
<td>39766</td>
<td>27-81y</td>
<td>0.62(0.6-1.30) for low-moderate drinking in women; 0.57(0.36-0.89) for low-moderate drinking in men</td>
<td>calendar year, BMI(&lt; 25 kg/m² vs. ≥ 25-&lt; 30 kg/m² vs. ≥ 30 kg/m²), and total caloric intake (quintiles)</td>
<td>Sex, country of birth, total energy intake from diet, level of education and coffee consumption</td>
<td></td>
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<tr>
<td>Hu et al. 1999[24]</td>
<td>China</td>
<td>Case-control</td>
<td>129 cases (73 gliomas, 56 meningiomas) 256 controls</td>
<td>20-74y</td>
<td>-</td>
<td>3.22(1.5-1.7) for heavy drinking; 0.80(0.3-2.2) for low-moderate drinking</td>
<td>Income, education, cigarette smoking, selected occupational exposures and total energy intake</td>
<td></td>
</tr>
<tr>
<td>Efird et al. 2004[25]</td>
<td>United States</td>
<td>Cohort</td>
<td>133811</td>
<td>≥25y</td>
<td>0.4(0.1-2.8) for heavy drinking; 0.90(0.6-1.4) for low-moderate drinking</td>
<td>Cigarettes, cigars, pipes, sex, race, education and coffee.</td>
<td></td>
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</tbody>
</table>
| Benson et al. 2008[26] | UK | Cohort | 1.3 million | Middle-aged | 1.11(0.92-1.35) for low-moderate drinking | Height, BMI, smoking status, socioeconomic status, age at first birth, strenuous.
| Ryan et al. 1992[27] | Australia | Case-control | 110 cases and 417 controls | 25-74y | Alcohol | 1.0(0.53-1.91) for heavy drinking; 0.86(0.47-1.60) for low-moderate drinking | Age, sex and subject’s own smoking history |

UK: United kingdom; BMI: Body mass index; Y: Years; Branganza 1, Hurley 1, cote 1, et al. represent the data for men. Branganza 2, Hurley 2, cote 2, et al. represent the data for women.
Table 2 Alcohol intake and glioma: sensitivity analysis

<table>
<thead>
<tr>
<th>Study characteristic</th>
<th>Category</th>
<th>Number</th>
<th>Heavy alcohol drinking (95% CI)</th>
<th>Low-moderate alcohol drinking (95% CI)</th>
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</thead>
<tbody>
<tr>
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<tr>
<td>Age</td>
<td>&gt;50</td>
<td>5</td>
<td>0.80 (0.55, 1.17)</td>
<td>0.88 (0.78, 0.99)</td>
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<tr>
<td></td>
<td>&lt;50</td>
<td>3</td>
<td>1.12 (0.75, 1.67)</td>
<td>0.78 (0.56, 1.11)</td>
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<tr>
<td>Sex</td>
<td>Men</td>
<td>3</td>
<td>0.90 (0.44, 1.83)</td>
<td>0.91 (0.74, 1.12)</td>
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<tr>
<td></td>
<td>Women</td>
<td>3</td>
<td>0.80 (0.59, 1.07)</td>
<td>0.85 (0.73, 0.98)</td>
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<tr>
<td></td>
<td>Men and</td>
<td>5</td>
<td>1.16 (0.50, 2.69)</td>
<td>0.88 (0.66, 1.19)</td>
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<tr>
<td></td>
<td>women</td>
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<tr>
<td>Ethnicity</td>
<td>White</td>
<td>7</td>
<td>0.89 (0.67, 1.18)</td>
<td>0.87 (0.78, 0.97)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>1</td>
<td>-</td>
<td>0.80 (0.30, 2.17)</td>
</tr>
<tr>
<td>Study design</td>
<td>Case-</td>
<td>3</td>
<td>1.12 (0.75, 1.67)</td>
<td>0.78 (0.56, 1.11)</td>
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<td></td>
<td>control</td>
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<tr>
<td></td>
<td>Cohort</td>
<td>5</td>
<td>0.80 (0.55, 1.17)</td>
<td>0.88 (0.78, 0.99)</td>
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</table>
## Appendix 1 Alcohol intake and glioma: Assessment of Study Quality

<table>
<thead>
<tr>
<th>Studies</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
<th>Score</th>
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<tbody>
<tr>
<td>Hu et al 1999</td>
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<tr>
<td>Benson et al 2008</td>
<td>* *</td>
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<td>8</td>
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<tr>
<td>Baglitto et al 2011</td>
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<td>9</td>
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<tr>
<td>Cote et al 2021</td>
<td>* * *</td>
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<td>9</td>
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<tr>
<td>Braganza et al 2014</td>
<td>* *</td>
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<tr>
<td>Ryan et al 1992</td>
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<td>9</td>
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<tr>
<td>Efird et al 2004</td>
<td>* * *</td>
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<td>7</td>
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<tr>
<td>Hurley et al 1996</td>
<td>* *</td>
<td>* *</td>
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<td>7</td>
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</table>

*For case-control studies, 1 indicates cases independently validated; 2, cases are representative of population; 3, community controls; 4, controls have no history of blood pressure disease; 5A, study controls for age; 5B, study controls for additional factor(s); 6, ascertainment of exposure by blinded interview or record; 7, same method of ascertainment used for cases and controls; and 8, non response rate the same for cases and controls. For cohort studies, 1 indicates exposed cohort truly representative; 2, non exposed cohort drawn from the same community; 3, ascertainment of exposure; 4, outcome of interest not present at start; 5A, cohorts comparable on basis of age; 5B, cohorts comparable on other factor(s); 6, quality of outcome assessment; 7, follow-up long enough for outcomes to occur; and 8, complete accounting for cohorts.*