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Alcohol and incident atrial fibrillation – A systematic review and meta-analysis☆

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ABSTRACT

Background: Whilst high levels of alcohol consumption are known to be associated with atrial fibrillation (AF), it is unclear if any level of alcohol consumption can be recommended to prevent the onset of the condition. The aim of this review is to characterise the association between chronic alcohol intake and incident AF.

Methods and results: Electronic literature searches were undertaken using PubMed and Embase databases up to 1 February 2016 to identify studies examining the impact of alcohol on the risk of incident AF. Prospective studies reporting on at least three levels of alcohol intake and published in English were eligible for inclusion. Studies of a retrospective or case control design were excluded. The primary study outcome was development of incident AF. Consistent with previous studies, high levels of alcohol intake were associated with an increased incident AF risk (HR 1.34, 95% CI 1.20–1.49, $p < 0.001$). Moderate levels of alcohol intake were associated with a heightened AF risk in males (HR 1.26, 95% CI 1.04–1.54, $p = 0.02$) but not females (HR 1.03, 95% CI 0.86–1.25, $p = 0.74$). Low alcohol intake, of up to 1 standard drink (SD) per day, was not associated with AF development (HR 0.95, 95% CI 0.85–1.06, $p = 0.37$).

Conclusions: Low levels of alcohol intake are not associated with the development of AF. Gender differences exist in the association between moderate alcohol intake and AF with males demonstrating greater increases in risk, whilst high alcohol intake is associated with a heightened AF risk across both genders.

1. Introduction

Atrial fibrillation (AF) poses a significant personal and healthcare burden and is poised to become one of the greatest healthcare challenges of this century. It is associated with significant morbidity and mortality [1], and has demonstrated globally increasing incidence and prevalence rates [2]. Much of the burden related to this condition is due to healthcare resource utilisation with AF related hospitalisations and associated complications demonstrating a rapid global rise [3,4]. New ways of both preventing and treating this condition has become an urgent healthcare need. The association between alcohol and health outcomes is complex with reports of both benefit and harm. Recent data has suggested that whilst alcohol may be associated with some cardiovascular benefits, this may be offset by an increase in mortality, alcohol-related cancers and injury, raising questions about the overall net benefit of alcohol consumption [5].

The association between acute alcohol intake and AF has been extensively described with the term 'holiday heart' first coined nearly 40 years ago, following the observation that atrial arrhythmia-related hospitalisations occurred more frequently in the period after holiday periods and weekends [6]. Since then, numerous studies have described more chronic levels of alcohol intake as a modifiable risk factor for the development of AF, although the strength of this association has varied amongst studies. Furthermore, two recent meta-analyses have described a graded dose response with increasing levels of alcohol consumption demonstrating a greater risk of incident AF [7,8]. However, it is unclear if any level of alcohol intake can be consumed without heightening the risk of AF development. Here, we aim to update the evidence for the strength of the association between various levels of chronic alcohol consumption and incident AF.

2. Methods

2.1. Literature search

This systematic review was performed in accordance with the Meta-Analysis of Observational Studies in Epidemiology guidelines [9]. Electronic literature searches were undertaken using PubMed and Embase databases with no date restriction up to 1 February

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2016 to identify studies examining the impact of chronic alcohol consumption on the risk of incident AF and prognosis in those with established AF. Keywords used include atrial fibrillation, alcohol drinking OR alcohol OR binge drink OR ethanol OR risk OR incidence OR prevalence, dose-response relationship, drug OR dose OR drinking behavior (See eTable 1 in the Supplement for the full search strategy). Reference lists of selected articles were manually searched to ensure all relevant papers had been identified.

2.2. Study selection

2.2.1. Inclusion and exclusion criteria

The primary outcome for this study was the development of incident AF or a combination of AF and atrial flutter. Inclusion criteria for this study were: 1) prospective design; 2) reported at least three categories of alcohol intake; 3) published in English; 4) included only participants who were free of AF of AF/flutter at baseline; 5) reported AF or a combination of AF/atrial flutter as an outcome measure. Exclusion criteria were: 1) retrospective or case control design; 2) described less than three levels of alcohol intake which would not allow ascertainment of a dose response and 3) reported alcohol intake in a dichotomous fashion, i.e. yes or no response or alcohol abusers compared to non-abusers.

2.2.2. Study selection and data extraction

Two investigators (CG and JMLH) independently reviewed all relevant articles to identify studies meeting criteria for inclusion. Any discrepancies were discussed and a consensus decision reached. Data extracted from relevant publications included: first author, years of data collection, year of publication, number of participants, gender balance, mean age, follow up period, reported alcohol categories including reference group used, number and gender in each reported alcohol category, ascertainment of AF diagnosis and covariates adjusted for. Risk of bias in each study was assessed utilising the Quality in Prognosis Studies tool (QUIPS) tool and classified as low, moderate or high [10]. (see eTable 2 in the Supplement).

2.3. Statistical analysis

The hazard ratio (HR) for the development of the outcome was extracted from individual studies according to each category of alcohol intake. The most adjusted model in each study was utilised. Risk estimates reported by sex category were pooled separately. Heterogeneity across studies was assessed using the I^2 statistic. The presence of publication bias was visually assessed using funnel plots of effect size against standard error. A 2-tailed value of $p < 0.05$ was considered statistically significant and all analyses were performed using a random effects model in Review Manager (RevMan) Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

3. Results

1877 articles were identified from the electronic literature search examining the impact of chronic alcohol consumption on incident AF. 1771 were excluded based on title and abstract review leaving 106 articles retrieved for full text review. 97 articles were excluded for reasons outlined in eFigure 1 with a total of 9 studies, incorporating 249,496 participants, meeting criteria for inclusion in the meta-analysis.

Reported mean age was 60.4 ± 10.4 years and 56.6% of the overall study population was female. Seven studies reported incident AF as their primary outcomes measure with two studies including both incident AF and atrial flutter as a primary outcome [8,11]. Most studies were undertaken in either the United States of America or Europe with one study undertaken in Japan [12] and another study incorporating Asian countries in their population [13]. Mean study follow up ranged from 4 to 17.6 years. Eight of the nine included studies had a low risk of bias. One study, published in abstract form only, had a moderate risk of bias [14]. Attempts to contact the authors of this study to obtain further details were unsuccessful. Each analysis was conducted with both the inclusion and exclusion of this study to ensure it did not significantly impact on results obtained. There was no evidence of publication bias.

3.1. Estimation of alcohol consumption

Alcohol intake was assessed by questionnaire in six studies, interview in two studies and was not reported in another study (see eTable 3 in the Supplement for categories of alcohol intake utilised in individual studies). Standard drink definition ranged from 10 to 12 g of ethanol. Confirmation of AF diagnosis was mixed with studies utilising ECG criteria, hospital codes or international classification of disease (ICD) codes. Reference groups varied, with five studies reporting no alcohol intake, and the remaining four using low alcohol intake which was generally classified as less than one standard drink (SD) per week. Remaining categories of alcohol intake varied with two studies reporting gender differences in alcohol classification at the moderate and high levels of intake [15,16]. Three studies reported on a total of 32,684 males separately [11,12,16] and four studies reported on alcohol intake in 73,587 females [11,12,16,17]. Characteristics of the included studies are outlined in Table 1.

3.2. High alcohol intake

The highest alcohol category in each study, compared to the reference group (Table 1), was associated with a significant increase in risk of AF development (HR 1.34, 95% CI 1.20–1.49, $p < 0.001$) without evidence of statistically significant heterogeneity between studies ($I^2 = 22\%$, $p = 0.23$; Fig. 1). Sensitivity analysis excluding studies whose highest alcohol intake was less than three standard drinks (SD) per day did not materially alter this result (HR 1.40, 95% CI 1.19–1.64, $p < 0.001$). Exclusion of one study, which has only been published in abstract form [14], and another study who reported a large variation in their highest alcohol intake group (13–161 g of ethanol per day) [18], also did not significantly alter this result (HR 1.38, 95% CI 1.25–1.55, $p < 0.00001$). High alcohol intake was significantly associated with incident AF in males and females (HR 1.68, 95% CI 1.18–2.41, $p = 0.004$ and HR 1.29, 95% CI 1.01–1.65, $p = 0.04$ respectively). There was no evidence of significant heterogeneity between studies reporting gender differences ($I^2 = 53\%$, $p = 0.12$ and $I^2 = 0\%$, $p = 0.45$ respectively). Utilising crude unadjusted event rates for each of the included studies, the incidence rate per 100 person years for chronic high alcohol consumption is 0.62 (95% CI 0.35–1.08).

3.3. Moderate alcohol intake

Chronic moderate alcohol intake, reported by most studies as 1–2 SD per day, was associated with a small but significantly increased risk of incident AF (HR 1.11, 95% CI 1.05–1.18, $p = 0.0002$) without evidence of statistical heterogeneity between studies ($I^2 = 0\%$, $p = 0.66$; Fig. 2a). Exclusion of one study published in abstract form only [14] did not impact on this result (HR 1.12, 95% CI 1.06–1.18, $p = 0.0001$). Exclusion of two studies, which classified moderate alcohol intake as up to 3 to 4 SD per day for men, did not impact on this result (HR 1.11, 95% CI 1.03–1.19, $p = 0.004$) with no evidence of statistical heterogeneity ($I^2 = 0\%$, $p = 0.77$) [15,18]. Whilst moderate alcohol intake in males was also significantly associated with AF development, this was not the case for females (HR 1.26, 95% CI 1.04–1.54, $p = 0.02$ and HR 1.03, 95% CI 0.86–1.25, $p = 0.74$; respectively) with no evidence of statistical heterogeneity ($I^2 = 0\%$ for both analyses, $p = 0.61$ and $p = 0.86$, respectively; Fig. 2b and c). The incidence per 100 person years utilising crude event rates is 0.48 (95% CI 0.28–0.81) for chronic moderate alcohol intake.

3.4. Low alcohol intake

Consumption of chronic low alcohol compared to the reference group in each study was not associated with risk of AF (HR 1.03, 95% CI 0.98–1.09, $p = 0.22$) with no evidence of significant heterogeneity ($I^2 = 5\%$, $p = 0.4$). There was no evidence of gender variation with non-significant results reported for low alcohol intake in both males and females (HR 1.01, 95% CI 0.82–1.24, $p = 0.93$ and HR 0.93, 95% CI 0.82–1.05, $p = 0.25$; respectively). Four studies reporting on the impact of up to 6–7 SD per week, compared to no alcohol as a reference group, did not demonstrate a significant association with AF (HR 0.95, 95% CI 0.85–1.06, $p = 0.37$; Fig. 3). There was no evidence of statistically significant heterogeneity ($I^2 = 0\%$, $p = 0.83$). The incidence rate per 100 person years utilising crude event rates in the chronic low alcohol intake cohort is 0.45 (95% CI 0.26–0.77).