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Interventions for alcohol cessation in people with atrial fibrillation

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of interventions for alcohol cessation compared to usual treatment for people with atrial fibrillation.

BACKGROUND

Description of the condition

Atrial fibrillation (AF) is the most common heart rhythm abnormality globally, with 37 million prevalent cases worldwide, and three million new cases yearly causing 287,000 deaths annually (Dai 2021). There is significant variation in AF rates worldwide, with prevalence highest in North America and Europe. The prevalence is 12 times lower in South Asia, Africa and the Middle East (Joseph 2021). Atrial fibrillation incidence is increasing, and was 31% higher worldwide in 2017 compared to 2007. Projections indicate the prevalence will increase by up to 60% by 2050 (Lippi 2021).

Atrial fibrillation is a chaotic rhythm where a normal atrial contraction is replaced by a disorganised and continuous series of irregular fibrillation waves (350 to 600 per minute), which originate from the area around the pulmonary veins (veins draining the lungs and connecting to the heart). It is caused by multiple and changing re-entry circuits. The atrioventricular node or AV node is responsible for connecting the atria and ventricles electrically (to ensure a coordinated contraction); however in people with AF, only some atrial impulses are filtered through to the ventricles which causes the irregular rhythm of the heart. The rapid atrial rate means that no discernible P waves (electrical waves representing depolarisation/contraction of the atria) may be seen on the electrocardiogram (ECG) (Chen 2018). Atrial fibrillation, which is initially episodic but progresses over time in most patients from paroxysmal AF (episodes of arrhythmia that terminate spontaneously) to persistent AF (episodes that continue for more than seven days and are not self-terminating), and permanent AF (ongoing long-term episodes) (Margulescu 2017).

Myocardial contraction is ineffective in emptying the atria and, subsequently, the ventricles are incompletely filled prior to ventricular contraction. Left ventricular filling and stroke volume can be reduced, causing a drop in cardiac output. Additionally, as the atrial contraction is disorganised, there is a risk of blood stasis in the atria which can increase the person's chance of thromboembolism, particularly stroke (cerebrovascular accident or CVA). There are several independent risk factors for AF, namely, ageing, hypertension, congestive heart failure, coronary artery disease, valvular heart disease and diabetes (Benjamin 1994; Lau 2017; Lilly 2007). Obesity and excessive alcohol use are two lifestyle factors that have been associated with an increased risk of AF and have been a focus of interest for clinicians and researchers within the cardiovascular medicine field (Balbao 2009; Voskoboinik 2016).

Description of the intervention

Abstinence from alcohol (rather than reduced alcohol consumption) is considered to be the appropriate goal in those with dependence, and those with dependence and significant psychiatric physical comorbidity (NICE 2011). In people with AF, there appears to be a dose-dependent relationship between alcohol intake and AF risk. Abstinence from alcohol may prevent the structural, cellular and electrical changes that increase an individual's susceptibility to developing AF, and may reduce AF burden and recurrence in those who have already developed the condition (Roerecke 2021; Voskoboinik 2020). When providing support for abstinence, there should be initial screening and regular assessment and a stepped approach to intervention employed (NICE 2011).

Alcohol brief interventions (ABIs) vary in their exact content and delivery but are broadly described as brief, non-confrontational conversations initiated by healthcare professionals to motivate individuals to alter their drinking behaviour (Scottish Government 2018). However, though they can support abstinence, ABIs typically target those consuming levels of alcohol deemed hazardous or harmful (having negative physical, psychological or social consequences) and their aim is to reduce consumption and alcohol-related harm.

In individuals screened as consuming levels of alcohol deemed harmful or hazardous, and in those with mild alcohol dependence, psychological interventions (e.g. cognitive behavioural therapy, behavioural therapy, couples behavioural therapy, or social network or environment-based therapy) may be an appropriate means of supporting abstinence (NICE 2011). These interventions may be provided in conjunction with pharmacological interventions if the individual specifically requests pharmacological intervention or is not responding to psychological intervention alone (NICE 2011).

In those with mild-moderate, or severe dependence, assisted withdrawal with the aim of abstinence is usually offered via a community-based programme, which should vary in intensity (including whether provided on a residential or outpatient basis) according to the severity of the dependence, available social support and the presence of comorbidities (NICE 2011). Abstinence can easily be tracked with random urine tests for alcohol metabolite ethyl glucuronide to check compliance.

How the intervention might work

In ischaemic cardiovascular disease, a J-shaped dose-response curve has been identified for alcohol consumption – where increased alcohol consumption up to a 'moderate' level (equating to approximately 1 to 2 drinks (standard glass of beer, wine or shot of hard liquor) per day (Qiao 2015)) is associated with better outcomes, but increased alcohol consumption results in worse disease outcomes (Voskoboinik 2016). Alcohol has been reported as being the most common trigger of AF, with consistent, habitual moderate alcohol consumption being associated with an elevated risk due to the destructive effects of alcohol consumption on safeguarding of normal heart rhythm (Voskoboinik 2019). However, it has been suggested that the risk is dose-dependent and begins at a single drink per day (12 g alcohol, hazard ratio 1.16, 95% confidence interval (CI) 1.11 to 1.22, $P < 0.001$) (Csengeri 2021; Groh 2019).

Many mechanisms have been described, but the combination of direct effects of alcohol on cardiac myocytes (fibrosis and injury, leading to oxidative stress and inhibition of calcium release from the sarcoplasmic reticulum), and its influence on the autonomic nervous system (such as vagal inhibition and increased sympathetic activity) result in electrophysiological changes which predispose to AF (Johansson 2020; O'Keefe 2021). Specifically, these are: shorter atrial and pulmonary vein action potentials, a shorter atrial refractory period and slower inter-atrial conduction which potentiates re-entrant AF (Balbao 2009; Voskoboinik 2018). Another potential influence on the development of AF with alcohol consumption is left atrial remodelling as a result of hypertension; alcohol has a well-established link with hypertension, and left atrial dilatation may be accompanied by fibrosis and electrical

remodelling in the atria (Samokhvalov 2010; Schoonderwoerd 2008; Voskoboinik 2018).

Electrolyte disturbances observed in moderate-to-heavy alcohol consumption (> 1 to 2 drinks per day) can be exacerbated with poor food intake, vomiting, malabsorption and diarrhoea (Qiao 2015; Voskoboinik 2019). Furthermore, binge-drinking behaviour, defined by the National Institute on Alcohol Abuse and Alcoholism (NAIAA 2021) as the short-term intake of alcohol (typically five drinks for a male, four drinks for a female) resulting in a blood alcohol level (BAL) > 0.08 g/dL, was also found to be implicated in the activation of stress kinases (c-Jun N-terminal Kinase (JNK2)), which in turn results in the mishandling of calcium (Ca2+) by the sarcoplasmic reticulum and increased atrial arrhythmogenicity (NAIAA 2021). Suppression of JNK2 resulted in suppression of altered calcium pathways, which provides an interesting target for future drug therapy and may also imply a reduction in susceptibility to AF by way of alcohol abstinence (reduced stress-activated kinase activity) (Yan 2018).

Although there are currently limited data available on the direct relationship between abstinence from alcohol and AF, lifestyle modification programmes focused upon weight loss and incorporating a restricted alcohol allowance have shown reduced arrhythmia burden and reverse atrial remodelling (Voskoboinik 2020). Indeed, the mechanisms by which abstinence reduces arrhythmia burden are likely to be multifactorial, and related to how abstinence may impact favourably upon other AF risk factors (such as hypertension and obesity). Regardless, given that Voskoboinik 2020 demonstrated reduced AF burden and recurrence with abstinence, there is potential for the AF population to benefit from alcohol cessation interventions.

Why it is important to do this review

Alcohol cessation as a treatment for AF has become more prominent recently. Atrial fibrillation treatment has previously concentrated on anticoagulation and symptoms control but more recently risk factor control has become more important. For example, recent European Society of Cardiology guidance (the ABC system) has now emphasised the importance of risk factor control with alcohol being emphasised as an important risk factor (Hindricks 2021). However, the AHA guidelines have only mentioned alcohol consumption in passing (AHA 2019).

This is also important as excessive alcohol consumption is a significantly widespread issue, with a significant proportion of adults drinking at higher risk levels in some countries. For example 29.2 million people consume alcohol on a regular basis in the UK (ONS 2018), with males more likely than females to drink over 14 units per week. Almost 360,000 hospital admissions in the UK yearly are a result of alcohol consumption (NHS 2020).

Multiple meta-analyses have linked alcohol and incidence of AF in a dose-dependant manner, but these only analysed observational data (Kodama 2011; Samokhvalov 2010). Not all of these have been clear whether low levels of alcohol intake has a link to AF (Gallagher 2017). However, no meta-analysis has been carried out looking at abstinence as an intervention for reducing AF. There is a need for an up-to-date meta-analysis to look at alcohol abstinence for treatment of AF (Voskoboinik 2020).

OBJECTIVES

To assess the effects of interventions for alcohol cessation compared to usual treatment for people with atrial fibrillation.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), whether randomised at the level of the participant or as a cluster-randomised design. We will include studies reported as full-text, published as abstracts only and unpublished data.

We will exclude crossover trials due to the progression of the disease over time, which makes it difficult to compare arms after crossover, but we will only include data before the crossover.

Types of participants

We will include adults over 18 years of age with a diagnosis of atrial fibrillation (AF) (all types of AF - paroxysmal, persistent, long-term persistent and permanent) of any duration, taking any amount of alcohol.

We will only include trials with participants under 18 years of age if they include a subset of eligible participants, and then only if separate data for the eligible participants is available or if most participants (more than 80%) are eligible.

Types of interventions

We will include trials comparing interventions for alcohol cessation versus usual care.

For alcohol abstinence, we will consider any method, technique or intervention for any period of time. We will compare interventions versus usual treatment (of AF or any usual treatments for alcohol addiction that do not include abstinence). We will exclude trials that involve interventions aiming to reduce alcohol intake rather than abstinence. We will exclude studies comparing different alcohol cessation techniques (head-to-head trials) unless a usual treatment arm is included.

Types of outcome measures

Reporting of one or more of the outcomes listed here in the trial is not an inclusion criterion for the review. Where a published report does not appear to report one of these outcomes, we will access the trial protocol and contact the trial authors to ascertain whether the outcomes were measured but not reported. We will include relevant trials that measured these outcomes but did not report the data at all, or not in a usable format, in the review as part of the narrative.

We are interested in the number of study participants with at least one event, rather than the number of events. We are interested in the longest available follow-up for all outcomes.

Primary outcomes

- Recurrence of AF, defined as any atrial tachyarrhythmia lasting 30 seconds or longer

- Atrial fibrillation burden, defined as the percentage of time the patient was in AF

Secondary outcomes

- All-cause mortality
- Stroke
- Symptoms of AF (assessed with the use of the modified European Heart Rhythm Association symptom classification; range, 1 to 4, with higher scores indicating greater severity of AF symptoms) (Wynn 2014)
- Mood (assessed with the use of the Beck Depression Inventory; range, 0 to 63, with higher scores indicating more severe depression) (Kendall 1987)
- Quality of life (assessed with the use of the Medical Outcomes Study 36-Item Short-Form Health Survey [SF-36]; range, 0 to 100, with higher scores indicating better quality of life) (Stewart 2007)
- Number of patients hospitalised for AF
- Admission for alcohol withdrawal

Search methods for identification of studies

Electronic searches

We will identify trials through systematic searches of the following bibliographic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) on *the Cochrane Library*
- MEDLINE (Ovid)
- EMBASE (Ovid)

The preliminary search strategy for MEDLINE (Ovid) (Appendix 1) will be adapted for use in the other databases. The Cochrane sensitivity-maximising RCT filter (Lefebvre 2011) will be applied to MEDLINE (Ovid) and adaptations of it to the other databases, except CENTRAL.

We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (http://apps.who.int/trialsearch/).

We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

We will not perform a separate search for adverse effects of interventions used for the treatment of the condition.

Searching other resources

We will check reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' websites for trial information.

Data collection and analysis

We will import all the identified abstracts and articles from the databases to Covidence for referencing and screening.

Selection of studies

Two review authors (RJT, TB) will independently screen titles and abstracts of all articles identified by the search, and will code them as either 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there are any disagreements, a third review author (MA) will arbitrate. We will retrieve the full-text study reports/publications and two review authors (RJT, TB) will independently screen the full-text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third review author (AC). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a data collection form for collecting study characteristics and outcome data that has been piloted on at least one study included in the review. One review author (TB) will extract the following study characteristics from included studies.

- Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals and date of study
- Participants: N, mean age, age range, gender, above 75 versus below 75 years of age, binge drinkers (Y/N), length of time in AF, adherence to abstinence (intervention arm only), type of AF (paroxysmal or persistent/permanent), inclusion criteria and exclusion criteria
- Interventions: intervention, comparison, concomitant medications and excluded medications
- Outcomes: primary and secondary outcomes specified and collected, and time points reported
- Notes: funding for trial and notable conflicts of interest of trial authors

Two review authors (SMH, OAM) will independently extract outcome data from included studies. We will resolve disagreements by consensus or by involving a third review author (MA). One review author (TB) will transfer data into the Review Manager 2014 file. We will double-check that data is entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (MA) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (SMH, OAM) will independently assess risk of bias for each study using RoB 2, outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). We will resolve any disagreements by discussion or by involving a third review author (MA). We will assess the risk of bias of a specific result of a trial according to the domains of:

- bias arising from the randomisation process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- bias in selection of the reported result.

We will assess the risk of bias for the outcomes of the included trials that will be included in our summary of findings table.

We will use the signalling questions in the RoB 2 tool and rate each domain as 'low risk of bias', 'some concerns' or 'high risk of bias'. We will summarise the risk of bias judgements across different studies for each of the domains listed for each outcome. The overall risk of bias for the result is the least favourable assessment across the domains of bias.

We will be interested in quantifying the effect of assignment to the interventions at baseline, regardless of whether the interventions are received as intended (the 'intention-to-treat effect'). When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

We will be using the RoB 2 Excel tool to carry out our assessment (https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2). Due to the large amount of data generated by the RoB 2 tool, we will be unable to list all of this in the full review, apart from a RoB 2 table giving overall risk of bias. We will, however, list all the consensus decisions for the signalling questions in a supplemental data file. For cluster-RCTs, we will use the new RoB 2 tool (https://www.riskofbias.info/welcome/rob-2-0-tool/rob-2-for-cluster-randomized-trials) and use the signalling questions from the archived version and the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022).

Measures of treatment effect

We will analyse dichotomous data in terms of risk ratios (RRs) with 95% confidence intervals (CIs). We will analyse continuous data in terms of the mean difference (MD) with 95% CIs, provided the studies have all used the same tool to measure the outcome. If studies have used different tools to measure an outcome (such as quality of life), we will instead use the standardised mean difference (SMD) with 95% CIs. For SMDs, we will use Hedges' (adjusted) 'g' statistic, which uses a pooled standard deviation (SD) in the denominator of its calculation (Higgins 2022). This pooled SD is an estimate of the SD using outcome data from the intervention groups, based on the assumption that the SDs in the two groups are similar. We will interpret an SMD value of less than 0.2 as trivial, between 0.2 and 0.5 as small, between 0.5 and 0.8 as medium, and greater than 0.8 as large (Cohen 1988; Farivar 2004).

In the case of continuous data provided as MD or change from baseline, we will extract data on both change from baseline and post-intervention outcomes if the required means and SDs are available; but MD will be preferred. The advantage of using an MD is that it allows the possibility of combining end of follow-up data with change from baseline data, if reported by different studies. This contrasts with the SMD, where this cannot be done. We will report skewed data narratively as medians and interquartile ranges (Deeks 2021).

Unit of analysis issues

We will be including multi-arm RCTs as well as cluster-RCT trials. We will overcome unit-of-analysis error in a cluster-randomised trial by conducting the analysis at the same level as the allocation. The data will be analysed considering each cluster as a unit of analysis. However, in cluster RCTs in which the unit of analysis is not reported, we will calculate the effective sample size using an intracluster correlation coefficient (ICC) (Higgins 2022).

If we have included trials that could contribute multiple, correlated comparisons with multiple treatment arms we will combine groups to create a single pair-wise comparison for analysis. For continuous outcomes, we will carry out multiple pair-wise comparisons where we split the control group accordingly in order to avoid double-counting.

Regarding multiple observations on patients we will select the longest follow-up from each study.

For crossover trials we will analyse data from the first period only due to issues with carry-over effects.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

If we do not receive a response, we will impute the data missing due to participants' dropout using intention-to-treat analysis (ITT). In the case of missing statistics, and if appropriate, we will use other data analysis and data management software, such as SPSS or Microsoft Excel, to convert reported statistics into the one required for analysis. If important information is missing, such as number of participants, means, or SDs, but standard error, 95% CI or P values are reported, we will calculate an effect estimate, when appropriate, using the generic inverse variance method. We will assume that all missing participants have the same risk as the observed participants in the control group.

Assessment of heterogeneity

We will perform a visual assessment of the forest plots. We will also assess heterogeneity amongst the studies using the Chi^2 test from the forest plot. Heterogeneity may be indicated if there is a statistically significant result ($P < 0.10$). However, if the studies included in the review have small sample sizes, then careful interpretation of the Chi^2 test is needed. In this situation, we will use the I^2 statistic, which measures the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error/chance. The inconsistency amongst the studies will be quantified as follows:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

If we identify substantial or considerable heterogeneity we will report it and explore possible causes by prespecified subgroup analysis. We will look at heterogeneity through both clinical diversity (participants, interventions) within the RCTs) and methodological diversity (study designs and outcome measurement tools used).

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore potential small study biases for the primary outcomes. We will perform a formal statistical test for asymmetry

(Egger 1997). Using Egger's test we will look at the intercept β0. To evaluate the funnel asymmetry, we inspect the size of β0, and if it differs significantly from zero (an effect size is significant; when z ≥ 1.96 or ≤ -1.96). If this is the case, Egger's test will indicates funnel plot asymmetry and thus will be positive, indicating bias.

Data synthesis

We will undertake meta-analyses only where this is meaningful i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

All studies will be included in the primary analysis; to assess the potential effects of studies at high risk and some concerns, we will carry out sensitivity analyses. We will use a random-effects model due to the high probability of heterogeneity in the RCTs that will be included in this review.

If a meta-analysis is not possible, we will present our data narratively using the nine-point checklist in the Synthesis Without Meta-analysis (SWiM) guidance. We will group studies by intervention; we will use vote counting based on the direction of effect; and we will present characteristics, such as study design, sample sizes and risk of bias. We will describe synthesis findings clarifying which studies contribute to each synthesis and also explain the limitations of the synthesis (Campbell 2020).

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses:

- Mean age above 75 years versus mean age below 75 years of age
- Binge drinkers versus non-binge drinkers
- Paroxysmal versus persistent/permanent AF
- Male versus female

We will restrict the subgroup analysis to outcomes with substantial or considerable heterogeneity.

We will use the formal test for subgroup differences in Review Manager 2014 and base our interpretation on this. This procedure consists of undertaking a standard test for heterogeneity across subgroup results rather than across individual study results. An I^2 statistic will also be computed for subgroup differences. We will use a P value of 0.10, rather than the conventional level of 0.05, is sometimes used to determine statistical significance (Deeks 2011).

Sensitivity analysis

We plan to carry out the following sensitivity analyses, to test whether key methodological factors or decisions have affected the main result:

- Exclude randomised studies with high risk of bias and some concerns.
- Repeat the analysis using a fixed-effect model.
- Explore the impact of missing data. If we identify studies where more than 20% of participants have missing data that were unobtainable, we will repeat the analyses, excluding them to determine their impact on the primary analyses.

Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings table using the following outcomes.

- Recurrence of AF, defined as any atrial tachyarrhythmia lasting 30 seconds or longer
- Atrial fibrillation burden, defined as the percentage of time the patient was in AF
- All-cause mortality
- Stroke
- Symptoms of AF (assessed with the use of the modified European Heart Rhythm Association symptom classification; range, 1 to 4, with higher scores indicating greater severity of AF symptoms)
- Mood (assessed with the use of the Beck Depression Inventory; range, 0 to 63, with higher scores indicating more severe depression)
- Quality of life (assessed with the use of the Medical Outcomes Study 36-Item Short-Form Health Survey [SF-36]; range, 0 to 100, with higher scores indicating better quality of life)

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (McKenzie 2021) using GRADEpro GDT. We will justify all decisions to downgrade or upgrade the quality of the evidence using footnotes, and we will make comments to aid reader's understanding of the review where necessary.

Two review authors (AC, RJT) will independently assess the certainty of the evidence, and will resolve any disagreements by discussion or by involving a third review author (MA). Judgements will be justified, documented and incorporated into reporting of results for each outcome.

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The following people conducted the editorial process for this review.

- Co-ordinating Editor/Sign-off Editor (final editorial decision): Professor Rui Providencia, Cochrane Heart, University College London.
- Managing Editors (selected peer reviewers, collated peer reviewer comments, provided editorial guidance to authors, edited the review): Nicole Martin and Ghazaleh Aali, Cochrane Heart, University College London.
- Information Specialist: Farhad Shokraneh, Cochrane Heart, University College London.
- Peer-reviewers (provided comments and recommended editorial decisions): we acknowledge the efforts of the peer and consumer reviewers and editors including Zipporah Iheozor-

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APPENDICES

Appendix 1. Preliminary MEDLINE (Ovid) search strategy

1. Atrial Fibrillation/ or (AF or A-Fib or (Atrial adj3 Fibrillat*) or (Atrium adj3 Fibrillat*) or (Auricular adj3 Fibrilat*) or (Auricular adj3 Fibrillat*)).tw.

2. exp Alcohol Drinking/ or Alcoholism/ or Alcohol-Related Disorders/ or Alcoholics/ or (Alcohol* adj3 (Drink* or Use* or Intake or Intervention* or Education or Program* or Misuse* or Abuse* or Consump*)).tw. or (Drink* adj3 (Behaviour or Hazardous or Harmful* or Dependen*)).tw.

3. ((Randomized Controlled Trial or Controlled Clinical Trial).pt. or Randomi?ed.ab. or Placebo.ab. or Drug Therapy.fs. or Randomly.ab. or Trial.ab. or Groups.ab.) not (exp Animals/ not Humans.sh.)

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CONTRIBUTIONS OF AUTHORS

AC, SMH, SH, MOR and MA wrote the protocol. All other authors edited the protocol. All authors read and approved the final protocol version.

DECLARATIONS OF INTEREST

TB declares no known conflicts of interest.

AC declares no known conflicts of interest.

SMH declares no known conflicts of interest.

SH declares no known conflicts of interest.

MOR declares no known conflicts of interest.

OAM declares no known conflicts of interest.

FA declares no known conflicts of interest.

AK declares no known conflicts of interest.

RJT declares no known conflicts of interest.

JB declares no known conflicts of interest.

MA declares no known conflicts of interest.

PDL declares no known conflicts of interest.

GPRM declares no known conflicts of interest.

FM declares no known conflicts of interest.

SD is past president of the British Association for Cardiovascular Prevention and Rehabilitation.

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