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Research Article

Risk of All-Cause Mortality in Alcohol-Dependent Individuals: A Systematic Literature Review and Meta-Analysis☆

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ABSTRACT

Background: Alcohol dependence (AD) carries a high mortality burden, which may be mitigated by reduced alcohol consumption. We conducted a systematic literature review and meta-analysis investigating the risk of all-cause mortality in alcohol-dependent subjects.
Methods: MEDLINE, MEDLINE In-Process, Embase and PsycINFO were searched from database conception through 26th June 2014. Eligible studies reported all-cause mortality in both alcohol-dependent subjects and a comparator population of interest. Two individuals independently reviewed studies. Of 4540 records identified, 39 observational studies were included in meta-analyses.
Findings: We identified a significant increase in mortality for alcohol-dependent subjects compared with the general population (27 studies; relative risk [RR] = 3.45; 95% CI [2.96, 4.02]; $p < 0.0001$). The mortality increase was also significant compared to subjects qualifying for a diagnosis of alcohol abuse or subjects without alcohol use disorders (AUDs). Alcohol-dependent subjects continuing to drink heavily had significantly greater mortality than alcohol-dependent subjects who reduced alcohol intake, even if abstainers were excluded ($p < 0.05$).
Interpretation: AD was found to significantly increase an individual's risk of all-cause mortality. While abstinence in alcohol-dependent subjects led to greater mortality reduction than non-abstinence, this study suggests that alcohol-dependent subjects can significantly reduce their mortality risk by reducing alcohol consumption.

1. Introduction

Alcohol use is one of the greatest risk factors for disease and disability (Rehm, 2011; Nutt et al., 2010; Rehm et al., 2009), and alcohol dependence (AD) seems to account for the majority of this burden (Rehm et al., 2012; Rehm et al., 2013). The risk of mortality has been shown to increase as alcohol consumption increases, both for lifetime risk and absolute annual risk, with absolute annual risk almost doubling as alcohol consumption increases from 10 g/day to 100 g/day (Rehm et al., 2011). In addition to the clinical burden of AD experienced by individuals (François et al., 2014), AD has wider societal consequences, including substantial direct and indirect economic costs (Rehm et al., 2012; Laramée et al., 2013).

Until the 1970s, alcohol use disorders (AUDs) were widely called 'alcoholism'; by this time, however, it was apparent that AD could be considered as a separate diagnosis (Edwards and Gross, 1976). The current version of the *International Classification of Diseases* (ICD-10) continues to categorise harmful use and AD as separate diagnoses (World Health Organization, 1992), while the latest edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) has integrated alcohol abuse and AD into a single AUD diagnosis (American Psychiatric Association, 2013). In clinical practice, there is often no formal assessment of diagnoses (ie. alcohol abuse vs AD), but for treatment in specialised healthcare services it is safe to assume

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that most of the cases would qualify as the more severe form of AUD, corresponding to AD (Rehm et al., 2015a).

Previous systematic literature reviews (SLRs) and meta-analyses have examined the relative risk (RR) of all-cause or cause-specific mortality in people with AUDs compared with the general population or with controlled drinkers (Roerecke et al., 2013; Roerecke and Rehm, 2014; Roerecke and Rehm, 2013). One meta-analysis found an RR of 3.38 (95% CI [2.98, 3.84]) for men and 4.57 (95% CI [3.86, 5.42]) for women in clinical settings compared to the general population (Roerecke and Rehm, 2013); another found that individuals treated for AUDs reduced their mortality risk by more than half if they were able to reduce their alcohol consumption, compared to those individuals who continued to drink heavily (Roerecke et al., 2013). However, to our knowledge there are currently no systematic reviews focusing on the risk of all-cause mortality in alcohol-dependent individuals only.

Treatment for AD, and AUDs more widely, has traditionally focused on promoting abstinence as the only acceptable treatment goal. However, some patients may prefer a goal of non-problem drinking (Wallhed Finn et al., 2014). In recent years, there has been an increased emphasis on an alternative harm-reduction approach that attempts to help alcohol-dependent patients achieve a reduction in alcohol consumption without the need to completely abstain, consequently reducing the risk of harmful consequences associated with alcohol use (European Medicines Agency (EMA), 2010; National Institute for Health and Care Excellence (NICE), 2011). Reduced consumption of alcohol in individuals with AUDs has been shown to be beneficial, resulting in a significant reduction in mortality compared to continued heavy drinking (Roerecke et al., 2013), and is also predicted to improve the associated economic and societal burdens (Laramée et al., 2014).

In this study, we aimed to conduct an SLR and meta-analysis on the increased risk of all-cause mortality among individuals with AD compared to the general population, individuals without AUDs, and individuals qualifying for a diagnosis of alcohol abuse; and to examine the key factors affecting this risk. We also aimed to review the effect of reduced alcohol consumption among alcohol-dependent individuals.

2. Methods

2.1. Systematic Literature Review

An SLR was conducted in accordance with PRISMA guidelines (Moher et al., 2015) to identify studies reporting on mortality in alcohol-dependent subjects. MEDLINE, MEDLINE In-Process, Embase and PsycINFO were searched using the Ovid SP platform, and the Cochrane Library was searched using the Wiley Online platform. Search strings included terms relating to AD and mortality (Supplementary Tables 1 and 2). All searches were conducted on 26th June 2014; databases were searched for studies published from database conception up to that date.

Titles and abstracts of all studies identified in the database searches were screened using pre-defined eligibility criteria. Full texts for all potentially eligible studies were acquired and screened again. Screening at both stages was performed independently by two reviewers, with disagreements resolved by consensus or third-reviewer arbitration.

Studies were included if they were published in English and met the following criteria: they reported on subjects with AD; the study design was a randomised controlled trial (RCT), non-RCT, prospective observational study, retrospective cohort study, nested case–control study, systematic review or meta-analysis; mortality outcomes were reported for alcohol-dependent subjects; mortality in alcohol-dependent subjects was compared to mortality in an appropriate comparator population (including the general population, subjects without AUDs, subjects qualifying for a diagnosis of alcohol abuse, or alcohol-dependent subjects with differing levels of alcohol consumption); and a measure of association (hazard ratio [HR], odds ratio [OR], RR, standardised mortality ratio [SMR]) with 95% confidence intervals (CIs), or sufficient data to calculate these, was reported.

The "general population" comparator subgroup represented an unselected population of individuals in terms of drinking behaviour. This control group could therefore include a mixture of alcohol-dependent subjects, subjects qualifying for a diagnosis of alcohol abuse, abstinent subjects or individuals with any other level of pathological or non-pathological drinking. On the other hand, "subjects without AUDs" could be defined in a study as "non-alcoholics", "subjects without AD or alcohol abuse diagnosis" or any similar definition.

Studies involving alcohol-dependent subjects were included irrespective of whether a formal definition of AD (e.g. ICD or DSM) had been used to identify them. For studies involving "alcoholics", the definition of alcoholism was reviewed to determine whether it was operationally similar to a diagnosis of AD (included) or alcohol abuse (excluded).

The reference lists of all included full texts were scanned for further potentially relevant studies. These studies then underwent full text review using the same criteria as studies identified in the database searches.

The study design, methodology, patient population parameters and outcomes for all studies included in the SLR were extracted into a pre-specified grid. Data extraction was performed by a single individual with independent verification by a second reviewer, with disagreements resolved by consensus or third-reviewer arbitration. It was planned that the quality and potential for bias of included RCTs would be assessed using the criteria provided by the York Centre for Reviews and Dissemination (Centre for Reviews and Dissemination, 2009) and the quality of non-RCTs would be assessed using the TREND checklist (Des Jarlais et al., 2004). The quality of observational studies was assessed using a checklist designed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Research Practices Taskforce, which includes domains for relevance and credibility. Credibility questions related to study design and data analysis, among others (Berger et al., 2014). Quality assessments were conducted from the perspective of the populations and outcomes of interest to this review. All studies found to be relevant and credible were eligible for meta-analysis.

2.2. Meta-Analyses

Meta-analyses were conducted in accordance with MOOSE guidelines (Stroup et al., 2000). Results from the included studies were pooled for meta-analysis by comparator population. Given the methodological heterogeneity of studies identified in this SLR (e.g. differences between studies in mean age, source of the alcohol-dependent population, and reference groups) a random-effects model was judged to be appropriate for this meta-analysis (parallel analyses used fixed-effect models). HRs, ORs, RRs and SMRs were assumed to approximate the same measure of risk (Rothman and Greenland, 1998).

Included studies were pooled for meta-analyses based on measures of association being available for the following comparisons: alcohol-dependent subjects vs the general population, subjects without AUDs, or alcohol abusing subjects; or alcohol-dependent subjects who continued to drink heavily vs alcohol-dependent subjects who reduced their alcohol intake (abstainers excluded), alcohol-dependent subjects who reduced their alcohol intake (abstainers included), or abstinent alcohol-dependent subjects.

Where the same patients were included in two or more studies, the study involving the greatest number of alcohol-dependent subjects was included in the meta-analysis.

To test the robustness of the findings, subgroup meta-analyses were performed within studies that compared alcohol-dependent subjects vs the general population, by a number of pre-specified study- and patient-level characteristics. This included a subgroup analysis by the definition of AD used within the study (strictly defined AD, such as