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# Supplementary Material

**Article Title:** Reduction of Alcohol Consumption and Subsequent Mortality in Alcohol Use Disorders: Systematic Review and Meta-Analyses

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## Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Reduction of alcohol consumption and subsequent mortality in alcohol use disorders: systematic review and meta-analysis. Compliance with MOOSE guidelines

| **Reporting background should include** | **Included** | **Page** |
|---|---|---|
| Problem definition | Yes | 5 |
| Hypothesis statement | Yes | 5 |
| Description | Yes | 5 |
| Type of exposure or intervention used | Yes | 6 |
| Type of study designs used | Yes | 6 |
| Study population | Yes | 6 |
| **Reporting of search strategy should include** | | |
| Qualifications of searches (e.g. librarians and investigators) | Yes | 6 |
| Search strategy, including time period included in the synthesis and keywords | Yes | 5,6 |
| Effort to include all available studies, including contact with authors | Yes | 6 |
| Databases and registries searched | Yes | 5,6 |
| Search software used, name and version, including special features | Yes | 5 |
| Use of hand searching (e.g. reference lists of obtained articles) | Yes | 6 |
| List of citations located and those excluded including justification | No | |
| Method of addressing articles published in languages other than English | Yes | 6 |
| Method of handling abstracts and unpublished studies | Yes | 6 |
| Description of any contact with authors | Yes | 6 |
| **Reporting methods should include** | | |
| Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | Yes | 6,7 |
| Rationale for the selection and coding of data (eg, sound clinical principles or convenience) | Yes | 6,7 |
| Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability) | Yes | 6 |
| Assessment of confounding (eg, comparability of cases and controls in studies where appropriate) | Yes | 7,8 |
| Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results | Yes | 6,7 |
| Assessment of heterogeneity | Yes | 7,8 |
| Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | Yes | 7,8 |
| Provision of appropriate tables and graphics | Yes | 27-33 |
| **Reporting of results should include** | | |
| Graphic summarizing individual study estimates and overall estimate | Yes | 31-33 |
| Table giving descriptive information for each study included | Yes | 28,29, online supplement |
| Results of sensitivity testing (eg, subgroup analysis) | Yes | 10 |
| Indication of statistical uncertainty of findings | Yes | 9,10 |
| **Reporting of discussion should include** | | |
| Quantitative assessment of bias (eg, publication bias) | Yes | 10 |
| Justification for exclusion (eg, exclusion of non–English-language citations) | No | |
| Assessment of quality of included studies | Yes | 7 |
| **Reporting of conclusions should include** | | |
| Consideration of alternative explanations for observed results | Yes | 11-12 |
| Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review) | Yes | 14 |
| Guidelines for future research | Yes | 14 |
| Disclosure of funding source | Yes | 2 |

# Systematic Review Protocol

**Title:** Reduction of alcohol consumption and subsequent mortality in alcohol use disorders: systematic review and meta-analysis

## Protocol Information

**Dates**
Systematic review conducted from November 2011-January 2012.
Searches were updated in May 2012.

**Stage**
Review completed in May 2012.
Current stage: Meta-analysis completed.

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**Funding sources**
Support to the Centre for Addiction and Mental Health (CAMH) for salaries of scientists and infrastructure has been provided by the Ontario Ministry of Health and Long Term Care.

**Conflicts of interests**
JR may have a potential conflict of interest as he is part of the Scientific Board of Nalmefene, which is a chemical compound currently being submitted by Lundbeck (a pharmaceutical company) to the European Medicines Agency for the treatment of alcohol dependence.
MR declares no known conflicts of interest.

**Collaborators**

None.

## Review Methods

**Review questions**
What is the relative risk for mortality among people with alcohol use disorders stratified by drinking level?

**Searches**
The following electronic databases were searched from their inception to second week of January (updated to fourth week of May 2012) for original articles, excluding letters, editorials, conference abstracts, reviews, and comments: MEDLINE and EMBASE (through OVID), Web of Science (Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index). Search terms included: (alcohol dependence OR alcohol abuse) AND (mortality) AND (cohort OR follow-up). Additionally, reference lists of identified articles were searched.

**URL to search strategy**
None.

**Condition or domain studies**
Alcohol use disorders and mortality.

**Participants/population**
Inclusion: (1) a prospective or historical cohort study design was used; (2) participants had an AUD diagnosis at baseline; (3) all-cause mortality was the outcome; 4) studies reported findings for a comparison of AUD who had reduced or improved their drinking within a given follow-up period, and those who continued to drink alcohol at the same or higher levels, had alcohol-related problems or did not improve; 5) studies reported a measure of risk and its variance, or enough data to calculate these; (5) articles were published in English.
Exclusion: Adolescents (<18 years).

**Intervention/exposure**
Reduction in drinking levels in alcohol use disorder is the exposure of interest.

**Comparators/controls**
Mortality rates for alcohol use disorders that continue heavy drinking or experience problems from alcohol consumption from the same setting as the exposure group.

**Types of studies to be included initially**
Observational studies (historical or prospective cohort studies).

**Context**
Mortality rates for alcohol use disorders stratified by reduction of drinking from the same study setting.

**Primary outcomes**
All-cause mortality.

**Secondary outcomes**
None.

**Data extraction**
MR did the initial selection of papers to be included into the full text review. A random selection of 50 abstracts was evaluated for inclusion by JR. Full-text articles with uncertain eligibility were discussed by MR and JR until consensus was reached. From all relevant articles MR and JR abstracted authors' names, year of publication, country, year(s) of baseline examination, age, sex, setting, assessment of AUD diagnosis at baseline, number of participants at follow-up, drinking status at follow-up, follow-up time, number of observed deaths among participants after follow-up, adjustment for potential confounders, and odds ratio (OR) and its standard error for each reported drinking group. Primary authors were not contacted by the authors in case insufficient information was provided in the article.

**Risk of bias**
Considering our inclusion and exclusion criteria, we specifically decided against the use of the Newcastle-Ottawa-Scale (NOS), or any other quality scale. Many of the characteristics included in the NOS were part of our inclusion/exclusion criteria or subgroup analyses. The NOS thus would not have been able to distinguish the quality of selected studies in our analysis. This would be similar for other scales we are aware of. Thus, we decided to incorporate quality assessment differently by including quality components such as study design into the inclusion and exclusion criteria. In addition, we used potential quality criteria as independent variables in meta-regressions.

**Strategy for data synthesis**
Studies using the same exposure measurement and an appropriate comparator reporting all-cause mortality per exposure group as the outcome will be pooled using random-effect estimates because of differences in epidemiological setting. Raw number of deaths, standardized mortality ratios, relative risks, or odds ratios in each drinking level group at follow-up will be considered as measures of risk of death.

Odds ratios will be pooled across studies using inverse-variance weighted DerSimonian-Laird random-effect models to account for between-study heterogeneity [2]. We will quantify between-study heterogeneity using Cochran's Q [3] and the $I^2$ statistic [4]. $I^2$ can be interpreted as the proportion of the total variation in the estimated slopes for each study that is due to heterogeneity between studies. $I^2$ values above 50% were considered substantial. Potential publication bias will be examined using Egger's regression-based test [5]. When publication bias was to be detected, we will use the non-parametric trim-and-fill method proposed by Duval and Tweedie to evaluate the effect of such publication bias [6]. Sensitivity analyses for the influence of single studies on the pooled risk will be conducted omitting studies one by one and re-estimating the pooled OR. All meta-analytical analyses will be conducted on the natural log scale in Stata statistical software, version 11.2 (Stata Corp, College Station, Texas), and $p<.05$ (two-sided) will be considered statistically significant.

**Analysis of subgroups or subsets**
Meta-regression (when the number of studies included allows such analysis) will be used to identify study characteristics, such as follow-up time, time to assessment of drinking status at follow-up, follow-up rate, percentage of patients with continued heavy drinking during follow-up, and adjustment for potential confounders. Subgroup analyses will be completed in case significant effects were detected. Additional sub-group analyses were conducted based on follow-up time assessment and for men only.

**Type of review**
Prognostic.

**Language**
English.

**Country**
Canada.

**Dissemination plans**
Publication in peer-review journal.

**Keywords**
Alcohol use disorder, Reduction in drinking, Mortality, Systematic review, Meta-analysis

**Details of any existing review of the same topic by the same authors**
None.

**Review status**
Completed, but not published.

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**Supplementary eTable 1. Sample origin and definition of drinking status at follow-up in 16 studies on reduction in alcohol consumption and all-cause mortality in patients with alcohol use disorder, 1981-2012 (chronological order)**

| | | | Drinking groups at follow-up | | | |
|---|---|---|---|---|---|---|
| Source | Baseline sample | Assessment of drinking status during follow-up | Abstention | Reduced drinking | Any reduced drinking | Continued heavy drinking |
| Polich et al. 1981 [34], USA, 1976-1980 | Consecutive admissions to randomly selected treatment centers nationwide (stratified by region and setting) in 1976 | Interview | Abstainer (≥1 years) | Partial abstention (1-11 months) or no dependence symptoms (last 30 days) | Abstention or reduced drinking | Any dependence symptoms (last 30 days) |
| Smith et al. 1983 [35], USA, 1967-1980 | Consecutive admissions for alcoholism to two psychiatric hospitals in St. Louis area, 1967 to 1968 | Interview and confirmation by proxy | Abstainers (based on predominant drinking pattern during 3-year follow-up) | Social or variable drinker (based on predominant drinking pattern during 3-year FU) | Abstention or reduced drinking | Problem drinker (based on predominant drinking pattern during 3-year FU) |
| Vaillant et al. 1983 [36], USA, 1972-1980 | First 110 patients admitted for alcohol withdrawal to inpatient ward at the Cambridge and Somerville Program for Alcohol Rehabilitation at the Cambridge Hospital | Contact every 18 months during 8-year follow-up. Interviewed by at least 3 different clinicians. Corroboratory evidence obtained from treatment staff, AA meetings. Information from 10 to 20 sources. | Stable remission defined as community residence and no known alcohol-related problems last 3 years (at end of follow-up in 1980 or before death). Most were abstinent (less than 1 drink a month and not more than 1 episode of intoxication last 24 months). | Not in stable remission, but not chronic alcoholism (could be institutionalized, or abstinent for months, or improved but not asymptomatic) | Abstention or reduced drinking | Chronic alcoholism defined as symptomatic heavy drinking (damage to health, occupation, or relationships)) for at least six months of each of the last three years and one or more hospitalizations for detoxification (at end of follow-up or before death). |
| Barr et al. 1984 [37], USA, | First inpatient admission for | Not reported | Not reported | Not reported | Not misusing (self- | Misusing |

| | | | | | | |
|---|---|---|---|---|---|---|
| 1970-1978 | alcoholism to abstinence-oriented program (Eagleville Hospital, Pennsylvania, 92% men). For those who were institutionalized during the follow-up period, the drinking status before institutionalization was used. | | | | reported abstinence in 134 and self-reported controlled drinking in 14 out of 148 AUD at 2-year follow-up) | |
| Finney & Moos 1991 [38], USA, not reported (8 years follow-up) | Alcoholic patients from 5 residential facilities, who participated in follow-up at 6 to 8 months after treatment and had returned to a family setting. | Mailed questionnaire. | Not reported | Not reported | Not readmitted, not missed work, less than 5 oz ethanol per drinking day in last month, less than 3 oz ethanol per day on average in last month, no drinking problems in last year | All others |
| Bullock et al. 1992 [39], USA, 1976-87 | DSM-III alcohol dependence recruited from Alcoholism Treatment Program of the San Diego Veteran Affairs Medical Center and local chapters of AA, 1976 to 1987. Other neuropsychiatric history was excluded. 61% abstinent for at least 1 month prior to enrolment. 39% abstinent for at least 18 months at baseline. | Not reported | N/A | Not reported | Continuously sober throughout follow-up period | All others |
| Feuerlein et al. 1994 [40], Germany, 1981-1985 | Alcoholics (73% men) treated at 21 inpatient treatment centres | Interview | Abstinence | Improved (not defined) | Abstention or reduced drinking | Unimproved (not defined) |
| De Silva & Ellawala 1994 [41], Sri Lanka, 1986-91 | All patients admitted to Sumithrayo Rehabilitation Unit for alcohol dependence (defined as being alcoholic, and referred by a consultant psychiatrist and who have failed interventions in the past). Definition of alcoholic based on WHO standards (1951). | Formal interview every 3 months, corroborated by family member | Not reported | Not reported | Abstinent, infrequent. or controlled drinking (twice a week or less (between 8g and 40g pure alcohol per occasion) | All others |

| | | | | | | |
|---|---|---|---|---|---|---|
| Gerdner & Berglund 1997 [42], Sweden, 1985-94 | Consecutive patients who completed 5-week AA programme (72% men). 74% classified as late-stage chronic alcoholics. Most were severely alcohol-dependent and socially unstable. | Mailed questionnaire to patient and social worker. | Total abstinence (no drinking episode last 12 months or since discharge) | Less than 3 relapses and/or further inpatient treatment last 12 months or since discharge | Abstention or reduced drinking | 3+ relapses and/or further inpatient treatment last 12 months or since discharge |
| Yoshino et al. 1997 [43], Japan, 1989-96 | Alcoholics consecutively hospitalized at the Komagino Hospital Alcoholism Unit, 1989 to 1990. DSM-III criteria for alcohol abuse/dependence. | Mailed questionnaire to patient and informant identified from medical records independently. | N/A | Not reported | Abstinence | All others |
| Liskow et al. 2000 [44] USA, 1980-94 | Consecutive inpatients with treatment for alcoholism at the Kansas City VA Medical Center between 1980 to 1984, all fulfilled DSM-IV criteria for alcohol dependence/abuse. Those too medically or cognitively impaired to complete interview or living too far from medical center to complete follow-up procedure were excluded. | Interview | Not reported | Not reported | Abstinence | All others |
| Vaillant 2003 [23], USA, 1976-1980 | Past or present DSM-III diagnosis of alcohol abuse/dependence at age 47 for 1929 birth cohort | 2-hour semi-structured interview at age 47 (among those with past or current AUD identified from 1929 birth cohort | Abstinence (less than 1 drink/month); | Reduced drinking (former alcohol abuser consuming more than 1 drink/month but no problems); | Abstention or reduced drinking | Clear past history of alcohol abuse or one or more problems |
| Bell et al. 2004 [45], Norway, 1984-2000 | Consecutively admitted with alcoholic liver cirrhosis to one medical department from 1984 to 1988. IV drug users were excluded.65% men | Interview | Not reported | Not reported | Abstinent or less than 10 g per day over follow-up period | All others |

| | | | | | | |
|---|---|---|---|---|---|---|
| Mann et al. 2005 [24], Germany, 1976-86 | Consecutively admitted for alcohol dependence in 1976. Patients with drug dependence, dependence on anxiolytics, polydrug users, schizophrenic psychosis, or severe somatic disease requiring in-patient treatment were excluded. | Psychiatrist interview, time table to recall drinking periods | Abstinence (no alcohol at all last 12 months) | Improved defined as never more than 60g pure ethanol (men) and 30g (women) per drinking day, no signs of severe alcohol-related diseases present | Abstention or reduced drinking | Unimproved defined as all others or development of other drug dependence/abuse |
| Timko et al. 2006 [46], USA, 1985-2004 | First contact with alcoholism treatment program (regardless of subsequent treatment). 53% men. | Not reported | Abstinence (last 6 months) | Not reported | Abstinent last 6 months or in remission (no, light, or moderate drinking last 6 months; 3 or less oz ethanol/drinking day in last month; never intoxicated last month, no drinking-related problems last 6 months) | All others |
| Gual et al. 2009 [21], Spain, 1987-97 | First admission with DSM-III criteria for alcohol dependence in eight Addiction Treatment Centers (81% men) | Interview by psychiatrist or clinical psychologist | None or <5 drinks/occasion and never or <1 occasion/month (last 12 months) | <5 drinks/occasion and ≥1 occasion/month, but <7 days/week (last 12 months) | Abstention or reduced drinking | ≥5 drinks/occasion or daily drinking (last 12 months) |

AA, Alcoholics Anonymous; AUD, alcohol use disorders; DSM, Diagnostic and Statistical Manual of Mental Disorders; N/A, Not applicable; WHO, World Health Organization

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**Supplementary eFigure 1. Selection process**