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

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ABSTRACT

Objective: To determine whether a reduction in drinking in individuals with alcohol use disorders resulted in reduced mortality risk.

Data Sources: Electronic searches were performed of MEDLINE, EMBASE, and ISI Web of Science and references of identified articles were searched up to May 2012 using these keywords: (*alcohol dependence* OR *alcohol abuse*) AND (*mortality*) AND (*cohort* OR *follow-up*). Only English-language articles were included.

Study Selection: Sixteen cohort studies were identified that reported all-cause mortality risk by drinking groups measuring change in alcohol intake among people with alcohol use disorders.

Data Extraction: Numbers of participants and deaths in each group; odds ratios (ORs); and demographic, clinical, and methodological variables were extracted.

Results: In comparison to continued heavy drinking, a reduction below heavy levels of alcohol use (including abstention) was associated with a substantially reduced risk of mortality (random-effects pooled OR = 0.41; 95% CI, 0.34–0.50; $P < .001$). The OR was 0.35 (95% CI, 0.20–0.60; $P < .001$) for those who reached abstention and 0.61 (95% CI, 0.39–0.94; $P = .026$) for those who did not reach abstention but substantially reduced their consumption. The pooled OR for abstention compared to reduced consumption was 0.42 (95% CI, 0.19–0.92; $P = .031$). Meta-regression models did not reveal significant influences of study characteristics examined.

Conclusions: Reduction of drinking in alcohol use disorders was associated with a marked reduction in mortality risk for those who reached abstinence or reduced drinking compared to continued heavy drinkers. Those who reached abstention showed the smallest mortality risk, lower than the risk for reduced consumption without abstinence.

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Alcohol use disorders (AUD) can be characterized as a maladaptive pattern of alcohol use leading to clinically significant impairment or distress.[1,2] Since the seminal paper of Edwards and Gross in 1976,[3] AUD have been characterized as a clinical syndrome marked by the concurrence of a number of biological (eg, tolerance, withdrawal), psychological (eg, loss of control), and sociobehavioral (eg, time and efforts spent to maintain habit; social, occupational, and recreational pursuits given up or reduced) phenomena.[4] Not all phenomena must always be present, nor always present with the same intensity. AUD are among the most prevalent mental disorders globally,[5,6] with a yearly prevalence of 3.6% in individuals between 15 and 64 years of age (0.9% in women and 6.3% in men).[7] AUD, especially alcohol dependence, are associated with a high level of disability[6,8] and mortality (last published review: Harris and Barraclough[9]).

Effective treatment is available,[10–12] in the form of psychotherapies,[13,14] pharmacotherapies,[15,16] or a combination of both. The effectiveness of treatment is usually evaluated by measuring whether the patients become abstinent, by more continuous measures such as days of abstinence per time unit, or by measures of reduction of average alcohol consumption or heavy drinking days.[17,18] All of these measures of effectiveness imply that abstinence and reduction of drinking will result in significant improvement of the clinically relevant impairments and distress. However, literature about long-term effects, that is, whether abstinence or reduction in drinking actually produces clinically relevant outcomes in the long run, is scarce. This article tries to fill this gap for mortality, arguably the most important clinical outcome (for an overview on AUD and mortality, see Roerecke and Rehm[19]). More concretely, we tested whether reduction of drinking, including but not limited to abstinence, is actually linked to reductions of mortality. To our knowledge, the association between reduction in alcohol consumption and mortality risk in AUD has never been systematically quantified.

METHOD

Literature Search

This meta-analysis followed the MOOSE guidelines (eAppendix 1).[20] The following electronic databases were searched from their inception to the second week of January 2012 for original articles, excluding letters, editorials, conference abstracts, reviews, and comments: MEDLINE and EMBASE (through Ovid) and Web of Science (Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index). Search terms included the following: (*alcohol dependence* OR *alcohol abuse*) AND (*mortality*) AND (*cohort* OR *follow-up*). The search was updated to the end of May 2012. Additionally, reference lists of identified articles were searched. (See eAppendix 2 for review protocol details.)

Studies were included in the meta-analysis if (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 subjects with 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

Clinical Points

- Mortality risk for alcohol use disorders (AUD) was decreased by more than half in patients who at least reduced their drinking compared to those with continued heavy drinking.
- Decrease in mortality risk was greatest for patients who reached abstinence, but also sizable in those who reduced their alcohol consumption but did not reach abstinence.
- Treatments for AUD with evidence of achieving a reduction in drinking should be supported and clearly preferred to no treatment at all.

data to calculate these for each drinking group; and (6) articles were published in English. Identified references were initially screened for inclusion by title and abstract, followed by full-text review.

Data Extraction

From all relevant articles we extracted authors' names, year of publication, country, year(s) of baseline examination, age, gender, 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. When mortality data on more than 1 follow-up measurement were reported, we chose the mortality assessment closest to 10 years after baseline.[21–24] Authors from primary studies were not contacted in cases of insufficient information in the text.

One author (M.R.) performed the literature search and initial selection of papers to be included into the full-text review. A random selection of 50 abstracts was given to another author (J.R.) to independently conduct the selection, with agreement above 90%. The same 2 authors were also independently responsible for abstracting the data and discussing any difference in abstracted content.

We conducted 4 meta-analyses. First, we abstracted and pooled all studies reporting a comparison of a drinking group with reduced consumption (including abstinence) during follow-up. When more than 2 drinking groups were reported, we used the group with continued high consumption, no improvement, or any alcohol-related problems (hereafter referred to as "continued heavy drinking") as the reference group. We used a conservative approach here because we classified studies reporting a comparison only between abstainers and nonabstainers as a comparison between any reduced drinking and continued heavy drinking. Second, we abstracted and pooled all studies clearly distinguishing abstainers from a continued heavy drinking group. This analysis used only studies clearly separating at least 3 drinking groups, and we excluded drinking groups who showed reduced consumption but were not abstinent. Third, we abstracted and pooled all studies clearly distinguishing reduced consumption from a continued heavy drinking group. Fourth, we conducted a meta-analysis using those who reduced their drinking as the reference group and compared their mortality risk to that of those who reached abstention. This analysis used only studies clearly separating at least 3 drinking groups, and we excluded those with continued heavy drinking. Definitions for each drinking group and their use in the analysis are shown in Supplementary eTable 1.

Quality Assessment

Most quality scores are tailored for meta-analyses of randomized trials of interventions,[25–27] and many criteria do not apply to descriptive longitudinal studies like the ones examined here. Further, the later use of quality scores in meta-analyses remains controversial.[28,29] 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.

Statistical Analysis

Hazard ratios, relative risks, and ORs were treated as equivalent measures of risk. Odds ratios were pooled across studies using inverse-variance weighted DerSimonian-Laird random-effect models to account for between-study heterogeneity.[30] We quantified between-study heterogeneity using Cochran Q[31] and the I^2 statistic.[32] I^2 can be interpreted as the proportion of the total variation in the estimated effects for each study that is due to heterogeneity between studies. Meta-regression was conducted to identify study characteristics possibly influencing the magnitude or direction of an association between drinking groups and mortality. Potential publication bias was examined using the Egger regression-based test.[33] Sensitivity analyses for the influence of single studies on the pooled OR were conducted by omitting studies one by one and re-estimating the pooled OR. All meta-analytic analyses were conducted on the natural log scale in Stata statistical software, version 11.2 (Stata Corp; College Station, Texas).

RESULTS

The literature search identified 1,979 references (Supplementary eFigure 1). After removal of duplicates, 1,730 unique references were screened for inclusion. Of those, after exclusion on the basis of title and abstract, 190 papers were obtained in full text. In total, 16 unique articles[21,23,24,34–46] meeting the inclusion criteria were used in this meta-analysis (Table 1).

Characteristics of Included Studies

Overall, 9 studies were conducted in the United States; 2, in Germany; and 1 each in Sweden, Sri Lanka, Norway, Japan, and Spain (Table 1). The analysis was based on 755 observed deaths, with 4,951 people with AUD in treatment at risk. The time span from baseline to measurement of drinking status at follow-up ranged from 1 to 15 years, with a weighted mean of 3.50 years. Overall follow-up time from baseline to mortality or end of study ranged from 3 to 16 years, with a weighted mean of 8.84 years. Loss to follow-up (including deaths

Table 1. Characteristics of 16 Studies on Reduction in Alcohol Consumption and All-Cause Mortality in Patients With Alcohol Use Disorder, 1981–2012 (chronological order)

Source, Location (period)	Gender	Age at Baseline, y[a]	Participants at Follow-Up (no. of deaths)	Follow-Up Rate (baseline to follow-up for drinking status)	Continued Heavy Drinking During Follow-Up (%)	Death Ascertainment	Adjustment
Polich et al 1981,[34] United States (1976–1980)	Men	45	590 (81)	79% at 18-mo follow-up	38	Official death certificate, confirmation of death by 2 independent sources (treatment staff or relative)	Age-, gender-, and race-standardized
Smith et al 1983,[35] United States (1967–1980)	Women	44	87 (26)	97% at 3-y follow-up	40	Death certificate	Age- and race-standardized
Vaillant et al 1983,[36] United States (1972–1980)	Both	Range, 30–50	100 (29)	94% at study end (8-y follow-up)	47	Death certificate	None
Barr et al 1984,[37] United States (1970–1978)	Both	42	454 (86)	85% at 2-y follow-up	67	Death certificate	Age-, gender-, and race-standardized
Finney and Moos 1991,[38] United States, not reported (8-y follow-up)	Both	49	113 (19)	91% at 2-y follow-up	51	Death certificate	Age- and gender-standardized
Bullock et al 1992,[39] United States (1976–1987)	Men	44	199 (23)	85% at study end (11-y follow-up)	51	Death certificate; California State Department of Health and Vital Statistics; State Department of Motor Vehicles; personal contact with informants, relatives, significant others	Age-standardized
Feuerlein et al 1994,[40] Germany (1981–1985)	Both	Not reported	1018 (83)	90% at 6-mo follow-up	20	Not reported	Age- and gender-standardized; none for a comparison of abstainer or improved vs unimproved[b] (Figures 2–4)
De Silva and Ellawala 1994,[41] Sri Lanka (1986–1991)	Men	39	188 (18)	92% at study end (3-y follow-up)	61	Death certificate, hospital records, records of coroner's inquest	None
Gerdner and Berglund 1997,[42] Sweden (1985–1994)	Both	41	113 (28)	96% at 45-wk follow-up	44	Death certificate	Age- and gender-standardized
Yoshino et al 1997,[43] Japan (1989–1996)	Men	50	172 (31)	66% at 2.7-y follow-up	69	Informant identified from medical records	Age-standardized
Liskow et al 2000,[44] United States (1980–1994)	Men	42	319 (89)	89% at 1-y follow-up	76	Death certificate, Veterans Affairs records, Social Security, nursing home, relatives/friends	None
Vaillant 2003,[23] United States (1976–1980)	Men	47	167 (18)	87% at 47 y of age (10-y follow-up defined as study end for this analysis)	62	National Death Index, credit agencies, motor vehicle department	4-y age range
Bell et al 2004,[45] Norway (1984–2000)	Both	58	82 (70)	100% at study end (15-y follow-up)	70	Postmortem examination (autopsy) in 76% of cases, death certificate	Age, alkaline phosphatase level
Mann et al 2005,[24] Germany (1976–1986)	Both	38	86 (12)	100% at 5-y follow-up (10-y follow-up defined as study end for this analysis)	35	Not reported	None
Timko et al 2006,[46] United States (1985–2004)	Both	35	515 (78[c])	82% at 1-y follow-up	49	National Death Index (death certificate obtained in 88% of dead), contact with relatives, returned mail as "deceased"	Age, gender, marital status, alcohol dependence symptoms at baseline
Gual et al 2009,[21] Spain (1987–1997)	Both	39	748 (64)	89% at 5-y follow-up (10-y follow-up defined as study end for this analysis)	34	Family member, Civil Records Office at the Health Department	None

[a]Mean values unless otherwise noted. [b]Results for this study in Figure 1 are age- and gender-adjusted; results in Figures 2–4 are unadjusted. [c]Estimated.

occurring before follow-up assessment of drinking status) was small in most studies. The mean age for most studies was between 40 and 50 years. Only 1 study[35] reported results separately for women; in studies examining both genders, the majority of subjects were men. Four studies[36,39,41,45] monitored drinking status throughout follow-up to the end of the study, thus giving a more complete history compared to studies assessing drinking status only once during follow-up. For example, Finney and Moos[38] showed that slightly fewer than one-third of patients reporting remission at 2-year follow-up relapsed up to the 10-year end of the study. Several studies made an effort to corroborate patients' information through a proxy informant. We excluded all patients who had been hospitalized from baseline until death within the first 4 weeks in the study among patients with alcoholic liver cirrhosis reported by Bell et al[45] because these patients were forced to be abstinent. However, this exclusion had only a marginal influence on the estimate for this study.

Meta-Analyses

Figures 1–3 show the forest plots for various levels of reduction in drinking compared to continued heavy drinking. The pooled OR for mortality for AUD at baseline in those who had at least reduced their consumption at follow-up (including abstainers and those who improved to social or variable drinking) compared with those who continued heavy drinking (still misusing, experiencing alcohol-related problems, or continuing heavy consumption) was 0.41 (95% confidence interval [CI], 0.34–0.50; $P < .001$, Figure 1). The pooled OR for abstention (excluding reduced drinking without reaching abstention) compared to continued heavy drinking was 0.35 (95% CI, 0.20–0.60; $P < .001$, Figure 2) and for reduced drinking (excluding abstainers) compared to continued heavy drinking was 0.61 (95% CI, 0.39–0.94; $P = .026$, Figure 3). The pooled OR for abstention in comparison to reduced drinking was 0.42 (95% CI, 0.19–0.92; $P = .031$, Figure 4).

Considering the analysis presented in Figure 1, we found no evidence for publication bias (Egger test, $P = .29$). None of the studies had a strong influence on the pooled results. All pooled estimates were well within the pooled confidence intervals when we omitted studies one by one and calculated the pooled OR for the remaining studies. Between-study heterogeneity as indicated by I^2 was very low (8%, $\chi^2_{15} = 16.3$, $P = .36$). Results from separate meta-regression models investigating the influence of study characteristics such as percentage of patients with continued heavy drinking during follow-up ($P = .33$), overall follow-up time to study end ($P = .90$), follow-up time from assessment of drinking status to study end ($P = .39$), time to assessment of drinking status during follow-up ($P = .39$), or a dummy variable depicting no adjustment ($P = .75$) showed no evidence for differential mortality risks by these study characteristics. Only 1 of the studies[46] adjusted for marital status and alcohol dependence symptoms in addition to age and gender. Studies that recorded drinking status throughout the follow-up period until end of study (n = 4)[36,39,41,45] point to a stronger association compared to all studies combined (pooled OR = 0.29; 95% CI, 0.16–0.51). When studies with only men were considered (n = 6),[23,34,39,41,43,44] the pooled OR was 0.46 (95% CI, 0.32–0.65). Such sensitivity analyses were not possible for the analyses presented in Figures 2–4 because of the low number of studies. At least 4 studies in Figures 2–4 adjusted at least for age in their analysis; the pooled odds ratios were almost identical with wider confidence intervals when the respective meta-analyses were restricted to studies with age adjustment.

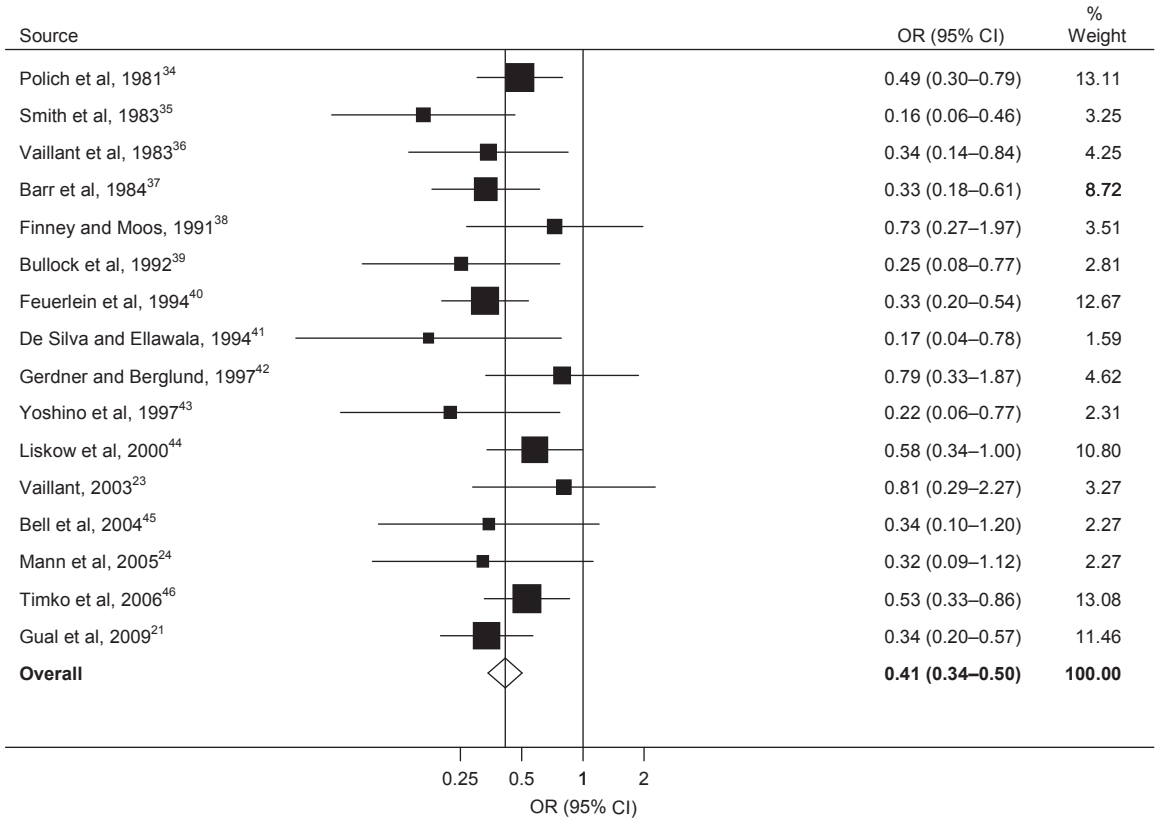
DISCUSSION

The review identified 16 observational cohort studies evaluating mortality risk by drinking status at follow-up in people with AUD in treatment. Pooled results showed that a reduction of drinking was associated with lower mortality more than 8 years after the initiation of treatment. The mortality reduction was marked: people who reduced their drinking had less than half the risk of those who continued their heavy drinking, or, from the other point of reference, people with continued heavy drinking showed a more than 2-fold increased mortality risk compared to people who reduced their drinking. These findings were robust in several sensitivity analyses that excluded studies that did not adjust for age, did not assess drinking status until the end of the study, or reported results for both genders combined. The decrease in mortality risk was largest for AUD patients who reached abstinence but was also sizable for people who continued drinking at a reduced level. In a direct comparison, AUD patients who reached abstention showed half the mortality risk compared with those who reduced their consumption but did not reach abstinence. It should be noted that treatment outcomes are not that stable overall; switches between abstinence and reduced drinking as well as from both states to heavy drinking occur over time.[21,24] Given the high mortality associated with AUD,[9,19,47–49] and the fact that AUD are responsible for the majority of alcohol-attributable deaths,[50] the results are important with respect to public health.

Strengths and Weaknesses of the Study

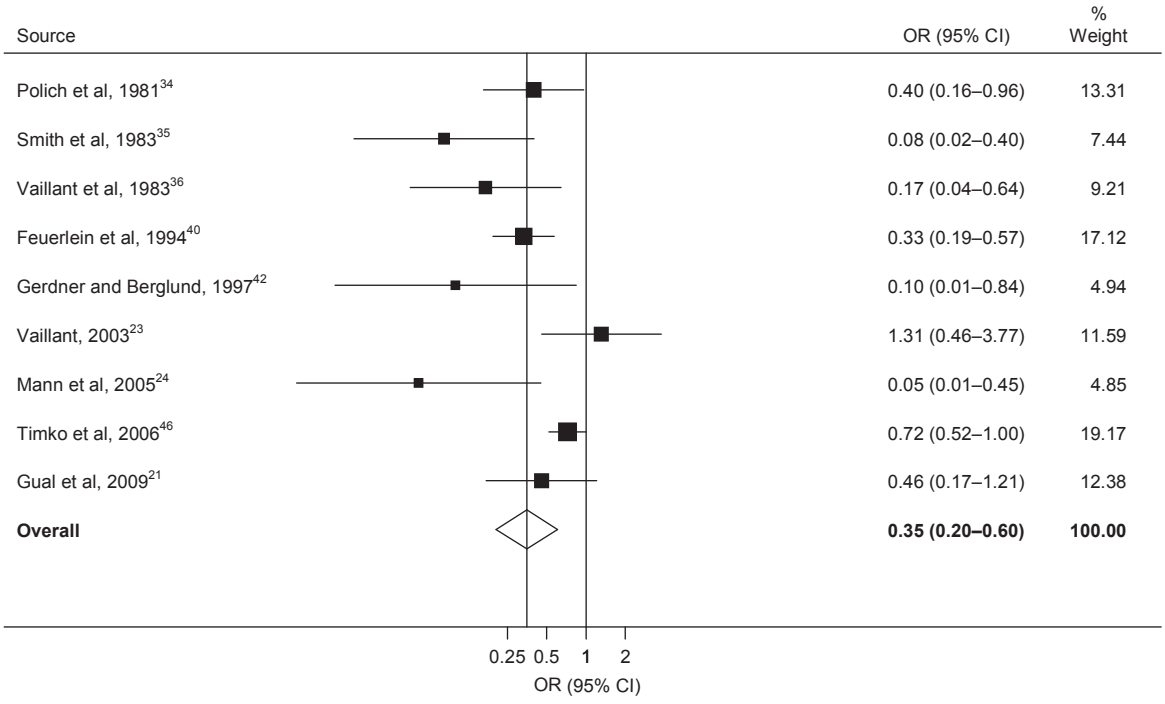
Before we discuss further implications, we need to indicate the limitations of our analyses. First, the analysis was limited to English-language studies, leaving the possibility of unidentified studies. Second, as is the case for all meta-analyses, our analysis was subject to bias and uncontrolled confounding (for example, differences in case severity, comorbidities, or age at onset of AUD) as they were inherent in the primary studies. However, given that most people with AUD die from alcohol-related causes, such as liver cirrhosis, violence, or various cancers,[9] it seems unlikely that factors other than a reduction in drinking would explain our results. One study[46] included in our analysis adjusted for alcohol dependence symptoms at baseline and reported a similar mortality risk compared to our pooled OR. Third, because AUD, as well as other substance use disorders, are often described as chronic relapsing disorders,[51] there may have been considerable misclassification of drinking

Figure 1. Mortality Risk of Reduced Alcohol Consumption (including abstainers) Compared to Continued Heavy Drinking in Alcohol Use Disorders, 1981–2012[a]



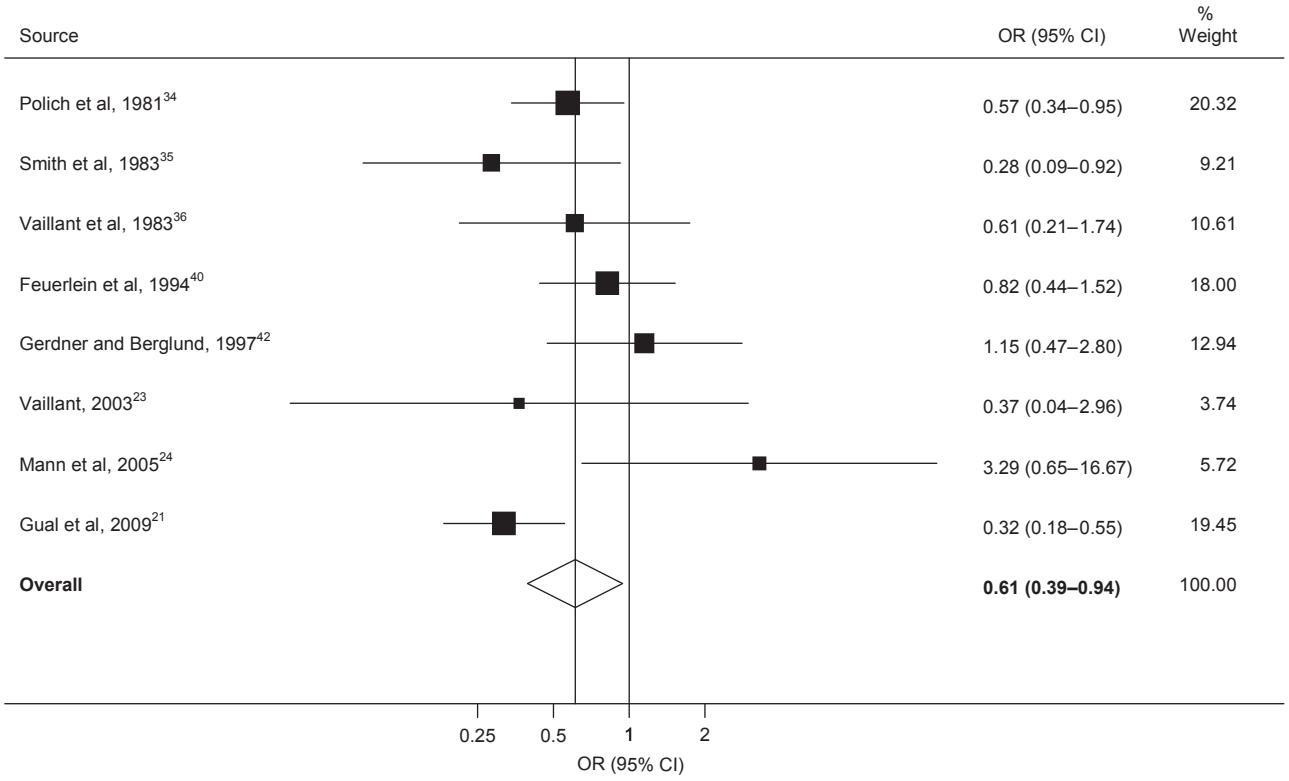
[a]Heterogeneity: $I^2 = 8.0\%$, $\chi^2_{15} = 16.3$, $P = .36$.

Figure 2. Mortality Risk of Abstention Compared to Continued Heavy Drinking[a] in Alcohol Use Disorders, 1981–2012[b]



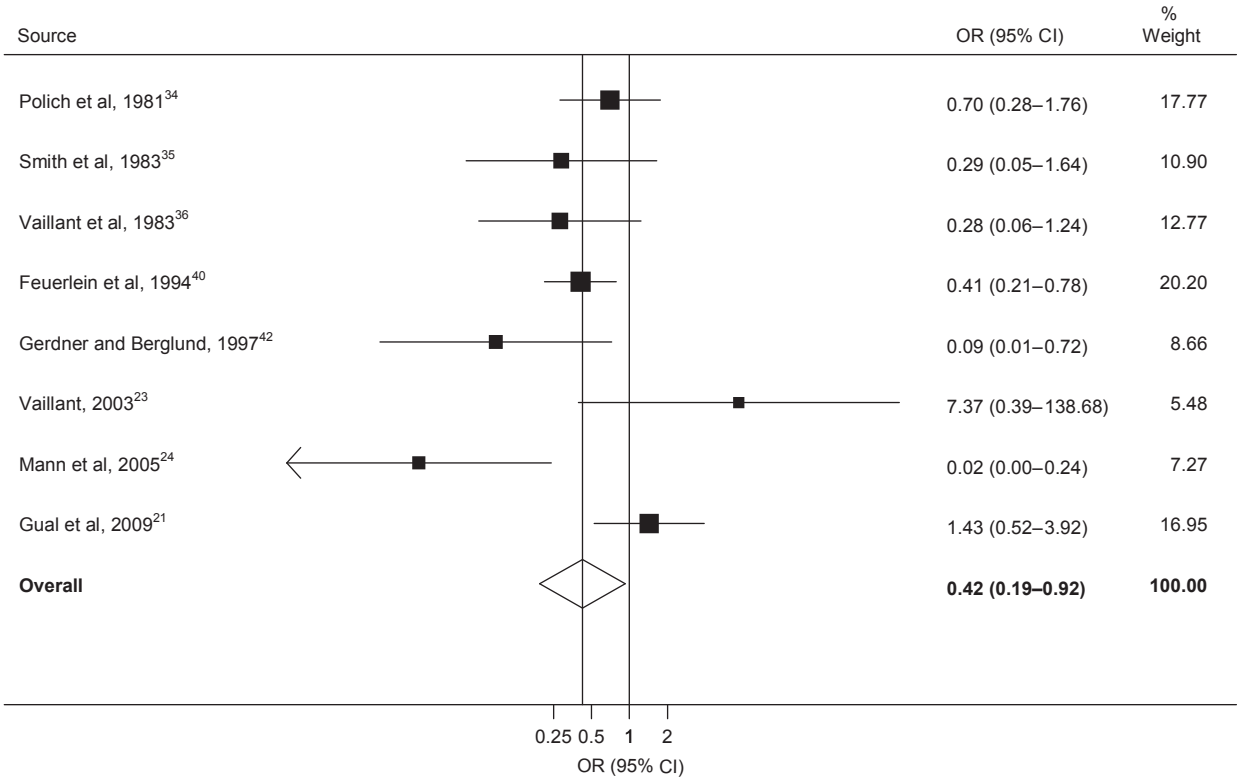
[a]Those who reduced consumption and were not abstinent were excluded.
[b]Heterogeneity: $I^2 = 67.2\%$, $\chi^2_8 = 24.4$, $P = .002$.

Figure 3. Mortality Risk of Reduced Alcohol Consumption (abstainers excluded) Compared to Continued Heavy Drinking in Alcohol Use Disorders, 1981–2012[a]



[a]Heterogeneity: $I^2 = 49.9\%$, $\chi^2_7 = 13.99$, $P = .051$.

Figure 4. Mortality Risk of Abstention Compared to Reduced Alcohol Consumption (continued heavy drinking excluded) in Alcohol Use Disorders, 1981–2012[a]



[a]Heterogeneity: $I^2 = 62.1\%$, $\chi^2_7 = 18.47$, $P = .010$.

status in studies measuring drinking status only once during follow-up. However, a subanalysis using only studies that measured drinking status until the end of the study showed even greater risk reduction than all studies combined. Additionally, although people with AUD were identified by a treatment contact or physician diagnosis, reduction in drinking was mostly self-reported, leaving room for measurement error or social desirability bias.[52,53] However, any misclassification bias of this sort would have resulted in attenuated findings. Thus, our estimates could be considered underestimates. Furthermore, several studies corroborated patient information with proxy information. While the pooled ORs were almost identical when only studies with adjustment at least for age were considered, there were not enough data for further sensitivity or subanalyses. Thus, we cannot exclude the possibility that other, uncontrolled for, factors influenced the association between a reduction in drinking and mortality risk. Given the substantially lower risk found in all analyses, this confounding effect, however, would need to be quite strong in order to explain the presented results.

The substantial and significant effects seen for a change to reduced drinking versus continued heavy drinking and for abstention versus reduced drinking indicated a dose-response relationship. These results further strengthen our finding that it was the reduction in alcohol consumption that was associated with mortality risk rather than another, unmeasured factor. Moderate heterogeneity was found for analyses presented in Figures 2–4, and this may be due to the fact that different studies had different operationalizations of reduction of drinking. However, the overall effect sizes were quite strong despite these differing definitions and operationalizations, thus strengthening the key conclusions of our article.[54]

Comparison With Other Studies

These results in people with AUD corroborate results of drinking reductions in other populations. Overall, reduction of drinking has been shown to result in a reduction of mortality in aggregate-level and individual-level studies.[55] The previous findings may be relevant for the current discussion, as the same biological mechanisms may be at work, only potentiated in people with AUD due to the higher drinking levels.[56] In the general population, a large volume of aggregate-level literature suggests that changes in drinking level are associated with changes in mortality due to alcohol-related diseases, as well as all-cause mortality.[57–59] This literature is based on time-series analyses, and, as is the case with all ecological data, associations can be measured, but causality cannot be established.

However, there are also a number of "natural experiments" that demonstrate how reductions in availability of alcohol can lead to reductions in both drinking and mortality. The most prominent example is the Gorbachev reform of the 1980s, during which legal alcohol production was drastically reduced in the Soviet Union. Even though there was an increase in illegal production, the result was that the overall annual consumption of pure alcohol fell from 14.2 L per capita in 1984 to 10.7 L in 1987—a decrease of some 25%. As a consequence, in that time period, all-cause mortality rates in Russia in the age range of 40–44 years decreased by 39% for men and by 29% for women. But when the alcohol ban was rescinded, annual consumption increased again to slightly more than its former level: 14.5 L per capita. Between 1987 and 1994, when alcohol consumption increased again, all-cause mortality rates more than doubled for men and almost doubled for women in the age range of 40–44 years.[60,61] The mortality caused by diseases most closely linked to AUD such as alcohol poisoning or alcoholic liver cirrhosis decreased even further than all-cause mortality, by over 60% during the ban.[60] (See also Neufeld and Rehm,[62] for similar associations between alcohol consumption, AUD, and mortality in Russia at a different time period.)

In addition, in the population of problem drinkers including but not limited to people with AUD, brief interventions administered to heavy drinkers admitted to general hospitals in a Cochrane analysis resulted not only in a significant reduction of alcohol consumption, but also in a substantial reduction of mortality risk up to a year later (relative risk of dying in the intervention groups = 0.60 [95% CI, 0.40–0.91]; see analysis[63] based on 7 randomized clinical trials[64–70]). This relatively huge effect following brief interventions underlines the fact that relatively modest reductions of average drinking can have marked effects on mortality in heavy drinkers when their overall mortality risk is high, which is the case for people already being hospitalized.

We have listed these studies to illustrate that a reduction of drinking seems to be associated with a reduction of mortality in various populations, not only in people with AUD. While the exact levels of mortality reduction will vary on the basis of the mix of causes of death,[71] the biological pathways are similar, and people with AUD die of causes that are also prevalent in the general population at large, such as injury, cardiovascular disease, liver cirrhosis, and cancer.[9] Thus, while the magnitude of mortality reductions found in our meta-analyses may be specific to people with AUD from inpatient treatment settings, the underlying biological mechanism may apply to other population groups.

Meaning and Implications of the Study Findings

What do these results mean for AUD therapies? Our analysis showed that it is possible to markedly reduce mortality risk for people with AUD, depending on the level of reduction of drinking that can be achieved. Given the sizable mortality risk associated with these disorders, especially alcohol dependence,[19] this is an encouraging result. Both reduced drinking and abstinence produced mortality risks significantly lower than those of continued heavy drinking. Note that our results are not based on abstinence versus reduced drinking as a treatment goal, but are based on the outcome of various therapies irrespective of the original treatment goal. Given that on the one hand individual treatment goals tend to be relatively unstable over

time[21,72] and that there is inconsistent evidence between original treatment goal and longer term outcome[73,74] and on the other hand, as we have shown here, both a reduction in drinking and continued abstinence are associated with reduced mortality risk, it may be best to offer both treatment options to patients.[74] To do so would also be in line with the fact that a considerable portion of patients would prefer reduction as a treatment goal.[72,75] There may be situations in which abstinence is clinically indicated,[76] but even in these situations, from an individual and public health standpoint, it may be better to engage a patient in a treatment with a goal of reduced drinking compared to no treatment at all.

We showed that a reduction of drinking in people with AUD was associated with a marked reduction in mortality risk for those who reached abstinence or reduced drinking compared to people with AUD who continued heavy drinking. Those who reached abstention showed the smallest mortality risk, also compared to people with AUD who reduced their drinking without reaching abstention. Future studies should prospectively follow patients over many years with longitudinal drinking measures and if possible corroborate drinking with collateral reports and alcohol biomarkers (blood and urine tests) to further refine the accuracy of morbidity and mortality prediction. It would also be quite useful if a finer-grained analysis of drinking reduction levels and effects on longer term morbidity and mortality could be provided.

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Author contributions: Dr Roerecke assisted in planning the study, conducted the literature search and systematic review, conducted the analyses, and assisted in the writing of the manuscript. Dr Rehm planned the study, assisted with the analyses, and led the writing of the manuscript. Dr Gual assisted with planning, analysis, and writing of the manuscript. Drs Roerecke and Rehm are guarantors, had full access to all of the data in the study, and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved of the final version of the manuscript.
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Supplementary material follows this article.

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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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List of Supplementary Material for the article

1. **eAppendix 1** MOOSE Checklist
2. **eAppendix 2** Systematic Review Protocol
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4. **eFigure 1** Selection Process

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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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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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2. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7: 177-188.

3. Cochran WG (1954) The combination of estimates from different experiments. Biometrics 10: 101-129.

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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