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Cause-specific mortality risk in alcohol use disorder treatment patients: a systematic review and meta-analysis

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Abstract

Background: Alcohol use disorders (AUD) are highly disabling. Recent studies reported much higher relative risks for all-cause mortality in AUD patients compared with earlier studies. Systematic evidence regarding cause-specific mortality among AUD patients has been unavailable to date.

Methods: Studies were identified through MEDLINE, EMBASE and Web of Science up to August 2012. Following MOOSE guidelines, prospective and historical cohort studies assessing cause-specific mortality risk from AUD patients at baseline compared with the general population were selected. Data on several study characteristics, including AUD assessment, follow-up period, setting, location and cause-specific mortality risk compared with the general population were abstracted. Random-effect meta-analyses were conducted.

Results: Overall, 17 observational studies with 6420 observed deaths among 28 087 AUD patients were included. Pooled standardized mortality ratios (SMRs) after 10 years of follow-up among men were 14.8 (95% confidence interval: 8.7–24.9) for liver cirrhosis, 18.0 (11.2–30.3) for mental disorders, 6.6 (5.0–8.8) for death by injury and around 2 for cancer and cardiovascular diseases. SMRs were substantially higher in women, with fewer studies available. For many outcomes the risk has been increasing substantially over time.

Conclusions: Cause-specific mortality among AUD patients was high in all major categories compared with the general population. There has been a lack of recent research, and future studies should focus on the influence of comorbidities on excess mortality risk among AUD patients. Efforts to reduce these risks should be a priority, given that successful treatment reduces mortality risk substantially for a relatively common psychiatric disease.

Key words: Alcohol use disorder, cause of death, liver cirrhosis, cardiovascular disease, injuries, cohort studies, systematic review, meta-analysis

Key Messages

- Compared with the general population, people with alcohol use disorders in treatment had a more than10-fold risk for mortality from liver cirrhosis and mental disorders, a 7-fold risk for injury fatalities and a 2-fold risk for cardiovascular and cancer deaths.
- The mortality risks associated with major causes of death for men were markedly higher than previously described in the literature.
- The mortality risks for many causes of death have been increasing over time; case severity might play a role in this increase.
- Given the high mortality risks for people with alcohol use disorders, screening for somatic disease and interventions to reduce risks should be initiated.

Introduction

Alcohol use disorders (AUD), comprising alcohol dependence and alcohol abuse, are one of the most prevalent mental disorders, affecting an estimated 3.6% of the population between 15 and 64 years of age worldwide (men = 6.3%; women = 0.9%).[1] The overwhelming majority of people with AUD, whether identified by Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria, do not receive treatment, with less than 10% treated in Europe or the USA (for the US: Hasin *et al.*[2] (DSM-IV); for Europe: Rehm *et al.*[3] (DSM or ICD) and Alonso *et al.*[4] (DSM-IV); for an overview:[5]; in fact the treatment gap for AUD is larger than for any other mental disorder.[5]

Like most other mental disorders, AUD have been considered to be more disabling than fatal,[6–8] and a meta-analysis from 1998 in part supported this view,[9] with relatively low estimated all-cause standardized mortality ratios (SMRs) for AUD of 1.80 [95% confidence interval (CI): 1.76–1.84] for men and 3.84 (95% CI: 3.54–4.15) for women. However, the underlying analyses included several definitions of heavy alcohol use and the samples were taken from various clinical and non-clinical contexts, including from drunk driver databases, Veteran Affairs databases and general population surveys. There is evidence that different sampling is associated with differing mortality risks, with clinical samples of AUD showing higher levels of mortality compared with general population surveys.[10,11] Moreover, more recent publications indicated a higher level of AUD-related mortality risks for clinical populations compared with earlier publications.[12–15]

This led to a reexamination of mortality associated with AUD via systematic review and meta-analyses, which indeed found a higher relative risk than previously assumed, specifically for AUD patients.[16] This article tries to go one step further and examines the underlying causes of death in AUD treatment patients. The cause-specific mortality risk among participants in treatment for AUD, i.e. for the most severe cases of AUD,[17] has not been systematically examined to our knowledge. However, cause-specific mortality is important, as it has clinical implications for treatment of AUD such as the decision to include systematic screening for other diseases.

Materials and Methods

Search strategy

This meta-analysis followed the MOOSE guidelines.[18] The following electronic databases were searched from their inception to the first week of August 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: (alcohol dependence OR alcohol abuse) AND (mortality) AND (cohort OR follow-up). Additionally, reference lists of identified articles were searched.

Eligibility criteria

Studies were included in the meta-analysis if they: (i) used a prospective or historical cohort study design; (ii) reported mortality risk for diagnosed participants currently in AUD treatment (in- or outpatient, this includes DSM-III and IV 'alcohol abuse and dependence' and International Classification of Diseases [ICD-9 and 10] 'harmful use' or 'non-dependent alcohol abuse' and 'alcohol dependence') compared with the general population; (iii) reported cause-specific mortality as the outcome; (iv) reported a measure

of relative risk (SMR, hazard ratio, relative risk, odds ratio) compared with the general population, and its variance or enough data to calculate these; (v) were at least age-standardized or -adjusted and sex-stratified; (vi) were of English-, German- or Spanish-language. Articles 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, follow-up duration (years), setting, assessment of AUD diagnosis, mean age at baseline, sex, number of observed deaths among AUD patients, number of total patients with AUD included, adjustment for potential confounders, and relative risk (RR) and its standard error. Causes of death abstracted were: cardiovascular diseases (CVD, sub-categories were heart diseases and cerebrovascular diseases), cancers, injuries (sub-categories were unintentional injuries and suicide), digestive diseases (sub-category was liver cirrhosis), mental diseases, respiratory diseases (sub-category was pneumonia) and endocrine diseases (sub-category was diabetes). In case only liver cirrhosis, heart disease, pneumonia or diabetes were reported in primary studies, we also used these estimates in overall categories such as digestive disease, CVD, respiratory diseases or endocrine diseases. This decision was made because the vast majority of deaths were observed in those sub-categories.

The above described categorization was derived from death categories known to be associated with heavy drinking or AUD.[9,19,20] Several versions of the International Classification of Diseases (ICD) were used in primary studies, but all studies were based on death certificates, oftentimes using additional sources of information about the cause of death.

Quality assessment

Most quality scores are tailored for meta-analyses of randomized trials of interventions (e.g. see Moher *et al.*[21]) and many criteria do not apply to descriptive longitudinal studies like the ones examined here. Also, the use of quality scores in meta-analyses remains controversial.[22,23] 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. One author performed the literature search and abstracted the data. To control for subjectivity, 10 papers were randomly selected and extracted by the second author. No changes in abstraction were recorded. Authors from primary studies were not contacted in case insufficient information was provided.

Statistical analysis

SMRs (i.e. comparisons of mortality risks of people with AUD with the age- and sex-specific general population; see[24]), hazard ratios, odds ratios and relative risks were treated as equivalent measures of risk. All analyses were stratified by sex. We excluded estimates when both exposure and control group reported one or less deaths in both groups. When sub-categories within our classification of cause of death categories were the only ones reported, we combined those by summing up observed and expected death from each sub-category, or by combining the reported RRs using fixed-effect modelling to derive one effect estimate per category per study for each analysis. SMRs were pooled across studies using inverse-variance weighted DerSimonian-Laird random-effect models to allow for between-study heterogeneity.[25] We quantified between-study heterogeneity using Cochran's Q[26] and the I^2 statistic.[27] 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 that influenced the association between AUD in treatment and cause-specific mortality. Potential publication bias was examined using Egger's regression-based test.[28] These tests were only conducted when there were 10 or more studies available.[29] Sensitivity analyses for the influence of single studies on the pooled SMRs were conducted omitting studies one by one and re-estimating the pooled SMRs. All meta-analytical analyses were conducted on the natural log scale in Stata statistical software, version 11.1 (Stata Corp, College Station, TX).

Results

Literature search

The literature search identified 2063 references (Figure 1, available as Supplementary data at *IJE* online). After removal of duplicates, 1805 unique references were screened for inclusion. Of those, after exclusion based on title and abstract, 193 papers were obtained in full text. In total, 17 unique articles meeting the inclusion criteria were used in this meta-analysis (Table 1). Overall, six studies were conducted in Sweden, three each in the USA and Japan and one each in Norway, Canada, the UK, Italy and Iceland. In total, 6420 deaths were observed among the AUD patient group, with 28 087 people with AUD at risk. Follow-up

Table 1. Characteristics of 17 studies on alcohol use disorder (AUD) in treatment and cause-specific mortality, 1967–2012

Source	Sex	Location, period	Mean follow-up time, years	No. of deaths / sample size (AUD patients)	Treatment setting	AUD identification	Assessment of causes of deaths	Control group	Adjustment
Brenner 1967[69]	W, M	USA, 1954–61	6	217/1343	4 alcoholism treatment facilities in California	Treatment in specialized clinic	Death certificates, ICD 6th and 7th Revision, accidents (E800-962)	General population	Age- and sex-standardized
Sundby 1967[70]	M	Norway, 1925–62	30	433/1716	Ulleval Hospital, Psychiatric Department, Olso	Diagnosis of alcoholism	National Central Bureau of Statistics comparison wiyh Oslo mortality statistics, ICD 7th revision CVD, heart disease, cerebrovascular diseases, cancer, mental disorders, unintentional injuries, suicide, endocrine diseases	General population	Age- and sex-standardized
Schmidt & de Lint 1972[71]	W, M	Canada, 1951–64	8	738/6478	Toronto Clinic of the Addiction Research Foundation	All patients with physical examination at entry for alcoholism treatment at specialized clinic	Death records in Ontario, other provinces, and some foreign countries, CVD, heart disease, cancer, mental disorders, digestive diseases, liver cirrhosis, unintentional injuries, suicide	Ontario general population	Age- and sex-standardized
Salum 1972[72]	M	Sweden, 1956–66	7.5	275/1026	Beckomberga Hospital	Diagnosed acute, mental and physical disturbance in association with drinking periods and delirium tremens in the acute stage	National Central Bureau of Statistics, ICD 7th revision, underlying cause (CVD 400-468), unintentional injuries (E 800-962, E 964-999), suicide (E 963, E 970-979), CVD (400-468), cancer (140-239), liver cirrhosis (581), digestive system (530-587 except 581), respiratory diseases (470-527 not tuberculosis), mental disorders (300-326)	General population	Age-standardized
Lindelius *et al.*, 1974[73]	W, M	Sweden, 1962–71	7.5	44/257	St Goeren's Hospital	Self-admittance to psychiatric unit with diagnosis alcoholism or alcohol abuse	Central Bureau of Statistics, underlying cause, CVD, unintentional injuries, suicide, digestive diseases, liver cirrhosis, respiratory diseases, cancer, mental disorders	General population	Age-, sex- and time period-standardization
Adelstein & White 1976[74]	W, M	UK, 1953–74	14	794/2070	4 London mental hospitals, mental health enquiry	Inpatient treatment for alcoholism	Death certificate, underlying cause, ICD 8th Revision, cancer (140-239), mental disorders (290-315), CVD (390-458), respiratory diseases (460-519), digestive diseases (520-577), accidents (E800-999)	General population	Age- and sex-standardization

(Continued)

Table 1. Continued

Source	Sex	Location, period	Mean follow-up time, years	No. of deaths / sample size (AUD patients)	Treatment setting	AUD identification	Assessment of causes of deaths	Control group	Adjustment
Thorarinsson 1979[75]	M	Iceland, 1951–74	13	573/2863	National Psychiatric Register	First admission to in- or outpatient institution	Death certificate, underlying cause, ICD 7th Revision, CVD, heart disease, cancer, liver cirrhosis, unintentional injuries, suicide, mental disorders	General population	Age-standardized
Polich *et al.*, 1981[76]	M	USA, 1973–77	4	95/755	8 of 44 NIAAA Alcoholism Treatment Centers	Admission to specialized programme for alcoholism	ICDA-8 underlying cause, CVD, heart disease (410-429, 440), cerebrovascular disease (430-458), respiratory diseases (460-519), liver cirrhosis (571), unintentional injuries (800-807, 810-823, 825-949), suicide (950-959), cancer (140-209), mental disorders (303)	General population	Age-, sex-, and race-standardized
Smith *et al.*, 1983[77]	W	USA, 1967–80	11	31/103	2 hospitals	Admission for alcoholism to psychiatric hospital	Death certificates, autopsy reports, CVD, digestive diseases, unintentional injuries, cancer, respiratory diseases	General population	Age-standardized
Berglund 1984[78]	W, M	Sweden, 1949–80	18	537/1312	Department of psychiatry	First inpatient admission for chronic alcohol intoxication according to multidimensional diagnostic rating schedule	National Central Bureau of Statistics, underlying cause, ICD 8th Revision, CVD, cancer, digestive diseases, mental disorders, respiratory diseases, trauma	General population	Age-, sex-, and time period-standardization
Higuchi 1987[79]	W, M	Japan, 1973–84	6.5	110/553	National Institute on Alcoholism, Kurihama National Hospital	First admission for DSM-III criteria for alcohol abuse/dependence	Death certificate and hospital records, ICD 9th Revision, CVD, heart disease (393-398, 402, 404, 410-429), cerebrovascular disease (430-438), cancer (140-208), digestive diseases, liver cirrhosis (571), unintentional injuries (E800-949), suicide (E950-959)	General population	Age- and sex-standardized
Lindberg & Agren 1988[80]	W, M	Sweden, 1969–83	6.5	1332/4543	Magnus Huss Clinic, Karolinska Hospital	First admission for alcoholism to specialized clinic	National Central Bureau of Statistics, underlying cause, ICD 8th Revision, CVD, heart disease, liver cirrhosis, mental disorders, cancer, respiratory diseases, digestive diseases, trauma, suicide, endocrine diseases	General population	Age- and sex-standardized
Ohara *et al.*, 1989[81]	M	Japan, 1972–84	6	238/1021	Hattori hospital	Discharged with diagnosis of alcohol dependence	ICD 9th Revision heart disease, cancer, liver cirrhosis, unintentional injuries, suicide, endocrine diseases	General population	Age- and sex-standardized

(Continued)

Table 1. Continued

Source	Sex	Location, period	Mean follow-up time, years	No. of deaths / sample size (AUD patients)	Treatment setting	AUD identification	Assessment of causes of deaths	Control group	Adjustment
Denison *et al.*, 1997[82]	M	Sweden, 1986–91	3.5	140/1049	University Psychiatric Clinic, Lilhagen Hospital	Inpatients for detoxification, DSM-III-R criteria for alcohol dependence	Death certificate, underlying cause, ICD 9th Revision, CVD, heart disease (410-414), cerebrovascular disease (430-436), cancer (104-208), mental disorders (303), liver cirrhosis (571), injuries (800-995), endocrine diseases	General population	Age, calendar year, and length of follow-up adjustment
Noda *et al.*, 2001[12]	M	Japan, 1972–92	7.8	110/306	Takatsuki City, all in- or outpatient treatment facilities	Diagnosis of alcohol dependence/psychosis	Death certificate, underlying cause, ICD 9th Revision, CVD, heart disease, cerebrovascular disease, digestive diseases, liver cirrhosis, cancer, respiratory diseases, unintentional injuries, suicide, endocrine diseases	General population	Age- and time period-standardization
Haver *et al.*, 2009[33]	W	Sweden, 1981–2007	20	117/420	Early Treatment for Women with Alcohol Addiction (EWA) Unit, Karolinska Hospital	First admission for alcohol treatment (second sample 96% met DSM-III-R criteria for alcohol dependence)	Swedish Causes of Death Register, ICD 8th, 9th, and 10th Revision, CVD, heart disease, digestive diseases, liver cirrhosis, respiratory diseases, cancer, mental disorders, unintentional injuries, suicide	General population	Matched on year of birth, marital status, SES, education
Saieva *et al.*, 2012[13]	W, M	Italy, 1985–2006	10.7	636/2272	Alcohol Centre treatment	Physician diagnosis alcohol dependence (ICD-9)	Regional Mortality Register, ICD 9th Revision, CVD, heart disease, cerebrovascular disease, cancer, digestive diseases, liver cirrhosis, respiratory diseases, mental disorders, unintentional injuries, endocrine diseases	General population	Age- and sex-standardized

W, M, results stratified by sex for women and men, respectively; W, women only; M, men only; AUD, alcohol use disorder; CVD, cardiovascular disease; ICD, International Classification of Diseases; ICDA, International Classification of Diseases, Adapted for Use in the United States; DSM, Diagnostic and Statistical Manual of Mental Disorders; NIAAA, National Institute on Alcohol Abuse and Alcoholism; SES, socio-economic status. ICD codes were included where reported.

[a]Estimated.

time ranged from 2.8 to 30 years with a weighted average of 11.5 and 10.5 years among men and women, respectively. All but one study reported SMRs.

Alcohol use disorder in treatment and cause-specific mortality

Pooled SMRs for cause-specific mortality are displayed in Table 2 for men and Table 3 for women (for forest plots of major causes of death please see eFigures 2–15, available as Supplementary data at *IJE* online). All pooled SMRs were substantial, with narrow confidence intervals. In men, mental disorders showed the highest SMR (19.80; 95% CI: 12.20–32.14), but with the least actual deaths reported across categories of death. Risk for digestive diseases was in the double digits as well. CVD and cancer mortality risks were about 2-fold compared with the general population. The most prevalent cause of death in men was CVD (weighted mean 27%, range 15–43), followed by trauma (26%, range 7–73), cancer (16%, range 6–33) and digestive diseases (12%, range 2–29). In women, trauma was most prevalent (29%, range 11–71), followed by CVD (21%, range 16–29), digestive diseases (19%, range 8–33) and cancer (18%, range 6–26). Subcategories of CVD, such as heart disease and cerebrovascular diseases as well as diabetes showed similarly elevated mortality risks compared with more general categories. Similar results were seen in women; however, injuries, liver cirrhosis and mental disorders showed 20- to 30-fold mortality risks compared with the general population. The number of women in primary studies was generally lower than the number of men, reflecting gender difference in prevalence of AUD (see above).

Meta-regression and sensitivity analyses

None of the studies in the analyses had a strong influence on the pooled results. All pooled estimates were well within the confidence intervals when omitting studies one by one and calculating the pooled SMR for the remaining studies. Between-study heterogeneity was generally high in all analyses as indicated by I^2 (see Tables 2 and 3). Because of the low number of studies available for women, regression-based tests were only conducted among men. Only one of nine disease outcomes showed some evidence for publication bias (Table 2). The trim-and-fill adjustment yielded a lower estimate for CVD in men (SMR = 1.59; 95% CI: 1.27–1.99) with four additional studies imputed. Meta-regression models showed that death from suicide was positively associated with increasing mean age at baseline (SMR = 1.06; 95% CI: 1.00–1.12 for a 1-year step); digestive diseases and liver cirrhosis were negatively associated with increasing mean duration of follow-up (SMR = 0.91; 95% CI: 0.85–0.97 per 1-year increase in follow-up); and digestive disease positively with increasing mean (calendar) year of baseline (SMR = 1.05; 95% CI: 1.02–1.08 for a 1-year step) and respiratory diseases (SMR = 1.02; 95% CI: 1.01–1.07). Regarding the distribution of causes of death among all deaths, the percentage of CVD deaths among all deaths in AUD patients decreased with increasing mean year of baseline (−0.37; 95% CI: −0.61 to −0.12 per 1-year increase), and digestive diseases increased (0.36; 95% CI: 0.082–0.65).

Cumulative meta-analyses based on mean (calendar) year of baseline assessment showed that CVD (Figure 1), digestive disease (Figure 2) and endocrine disease (Figure 3) mortality risk increased about 2- to 3-fold over time in men. These changes were quite similar for sub-categories of CVD

Table 2. Alcohol use disorder (AUD) in treatment and cause-specific mortality in men, 1967–2012

Cause of death	No. of studies	No. of AUD deaths	SMR	(95% CI)	*P*-value for heterogeneity	I^2 (%)	*P*-value for publication bias
Injuries	13	1205	6.64	(5.03–8.76)	<0.001	95	0.90
Unintentional injuries	12	510	4.67	(3.40–6.41)	<0.001	88	0.95
Suicide	12	428	8.75	(6.35–12.06)	<0.001	88	0.67
Cardiovascular diseases	14	1442	2.11	(1.73–2.57)	<0.001	92	0.014
Heart diseases	10	875	1.84	(1.48–2.28)	<0.001	87	0.13
Cerebrovascular diseases	9	186	1.76	(1.27–2.43)	<0.001	73	N/A
Cancer	13	796	1.73	(1.35–2.20)	<0.001	89	0.44
Digestive diseases	13	558	10.74	(6.24–18.47)	<0.001	97	0.77
Liver cirrhosis	12	470	14.75	(8.74–24.88)	<0.001	96	0.68
Respiratory diseases	13	287	3.50	(2.64–4.63)	<0.001	79	0.68
Pneumonia	5	126	3.43	(2.53–4.65)	0.058	56	N/A
Mental disorders	9	203	19.80	(12.20–32.14)	<0.001	90	N/A
Endocrine diseases	6	47	5.11	(1.87–13.94)	<0.001	89	N/A
Diabetes	4	42	5.17	(1.48–18.03)	<0.001	93	N/A

CI, confidence interval; N/A, not applicable.

Table 3. Alcohol use disorder (AUD) in treatment and cause-specific mortality in women, 1967–2012

Cause of death	No. of studies	No. of AUD deaths	SMR	(95% CI)	*P*-value for heterogeneity	I^2 (%)	*P*-value for publication bias
Injuries	9	243	19.83	(14.55–27.04)	<0.001	73	N/A
Unintentional injuries	6	96	21.85	(10.01–47.70)	<0.001	81	N/A
Suicide	6	60	16.39	(10.66–25.19)	0.099	46	N/A
Cardiovascular diseases	9	197	2.94	(2.01–4.430	<0.001	82	N/A
Heart diseases	6	100	2.82	(1.44–5.52)	<0.001	87	N/A
Cerebrovascular diseases	4	34	2.57	(1.31–5.04)	0.016	71	N/A
Cancer	8	150	1.99	(1.41–2.79)	0.006	65	N/A
Digestive diseases	9	158	18.14	(11.56–28.47)	<0.001	82	N/A
Liver cirrhosis	6	110	27.60	(16.73–45.56)	<0.001	78	N/A
Respiratory diseases	7	57	4.97	(3.72–6.64)	0.53	0	N/A
Pneumonia	4	24	4.90	(3.18–7.57)	0.70	0	N/A
Mental disorders	6	45	29.73	(15.66–56.43)	0.045	56	N/A
Endocrine diseases	2	5	3.52	(0.72–17.14)	0.25	24	N/A
Diabetes	2	5	4.52	(1.74–11.74)	0.35	0	N/A

CI, confidence interval; N/A, not applicable.

and digestive diseases. Fewer studies were available in women, and such changes were generally not evident, except for a slight increase in cancer mortality (Figure 4).

Discussion

Our meta-analysis of relative mortality risk in people with AUD in treatment showed high cause-specific pooled SMRs across the board, in line with a recent meta-analysis on all-cause mortality.[16] The mortality risk for many causes of death categories was increasing over time. However, there was a striking lack of recent evidence as only two studies with a baseline assessment after 1990 were identified. Clearly, given the effect sizes found, there is a dire need for more detailed studies on cause-specific mortality in AUD patients, in particular given the increase in mortality risk over time seen for CVD, digestive and endocrine diseases in men, and cancer mortality in women in the cumulative meta-analyses.

Limitations

Some limitations (both general and specific) apply to our meta-analysis. First, the analysis was limited to English-, German- and Spanish-language studies, leaving the possibility of unidentified studies. Second, there was large between-study heterogeneity detected in all analyses. This heterogeneity would be more important if the effects were small; however, all pooled SMRs were large. Nevertheless, we expect that there was at least some clinically important heterogeneity within our sample of studies, and later studies focused on alcohol dependence or detoxification indicating increased case severity. Differences in case severity (including comorbidities), results or type of treatment received, or uncontrolled confounding all may have contributed to any observed between-study heterogeneity. Whereas our study did not differentiate between AUD treatment outcomes, it seems likely that the SMRs for mortality in people with AUD who relapse or continue to drink heavily are even higher than we report in this meta-analysis, given the reduced mortality risk for people with AUD who reduce their consumption or become abstinent (see below and Hasin *et al.*,[2] Rehm *et al.*,[30] and Roerecke *et al.*[31]).

Which causes of deaths are avoided by successful AUD treatment and by which degree might be differential by category of cause of death, as different causes have differential pathways. Again, exploring the pathways from AUD to death should be a priority for future research, as our knowledge in this area seems only rudimentary. In addition, since average drinking at baseline in alcohol treatment varies considerably between studies and countries, the same formal inclusion criterion of AUD in treatment can be linked to a variety of different underlying exposures in terms of level and patterns of drinking as well as severity of AUD.[32] Only one study[33] reported risk estimates adjusted for more than just age; one other study also adjusted for length of follow-up. Thus, confounding from factors other than age and sex could not be examined in our study. Furthermore, the lack of recent studies is problematic because characteristics of AUD may have changed over time with regard to treatment availability or uptake, comorbidities or age distribution. Because our meta-analysis included a comparison of AUD patients in treatment with the general population, we cannot comment on the cause-specific mortality risks of AUD identified in

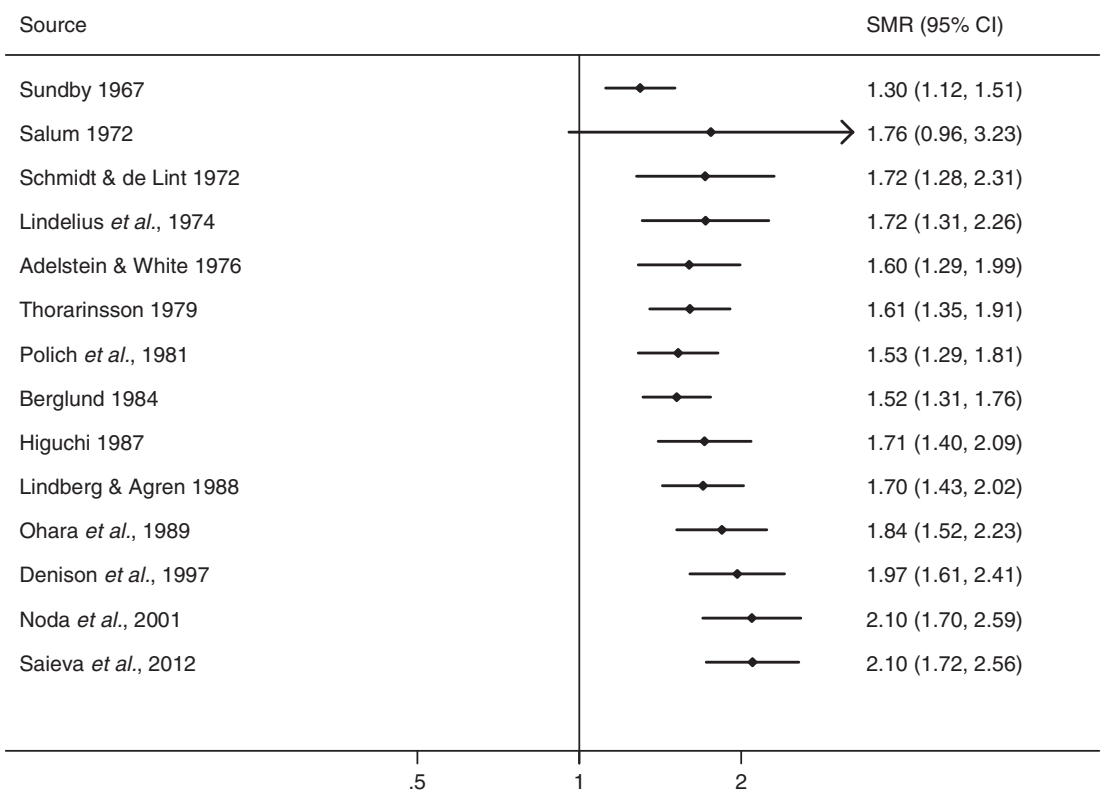

Figure 1. Cumulative meta-analysis for alcohol use disorder in treatment and cardiovascular mortality in men, 1967–2012.

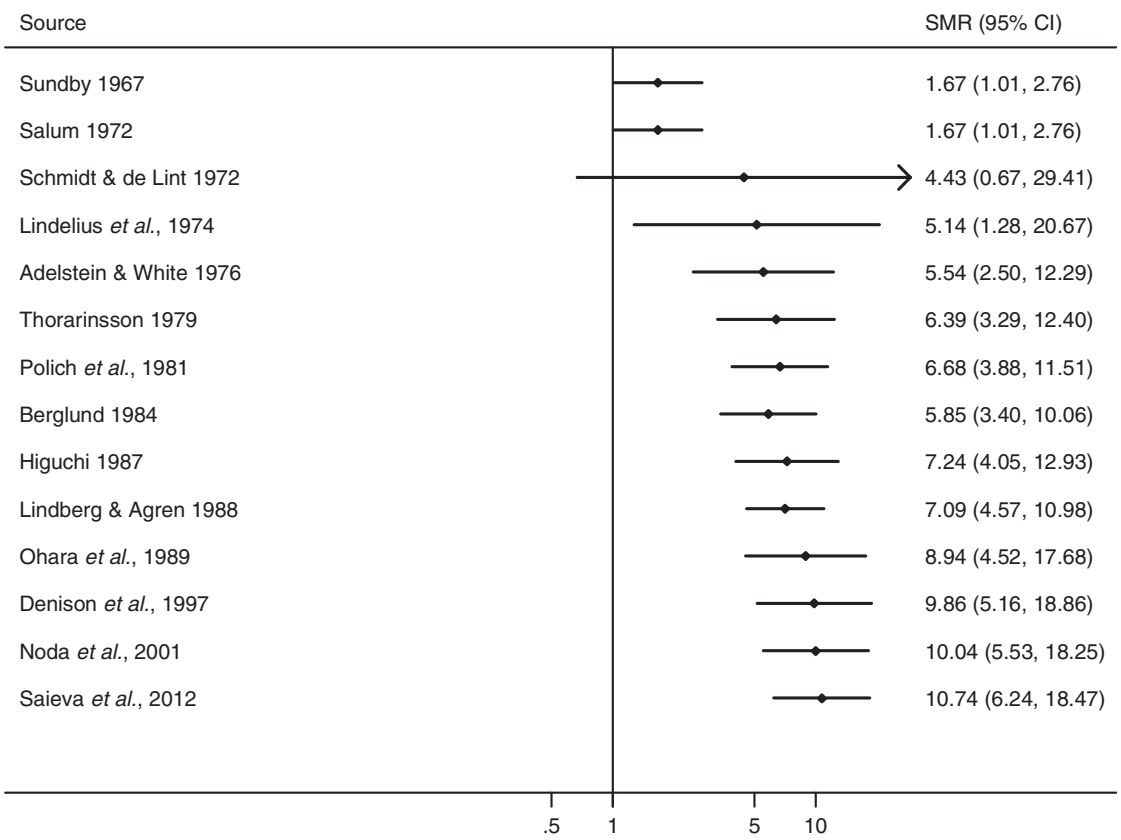

Figure 2. Cumulative meta-analysis for alcohol use disorder in treatment and digestive mortality in men, 1967–2012.

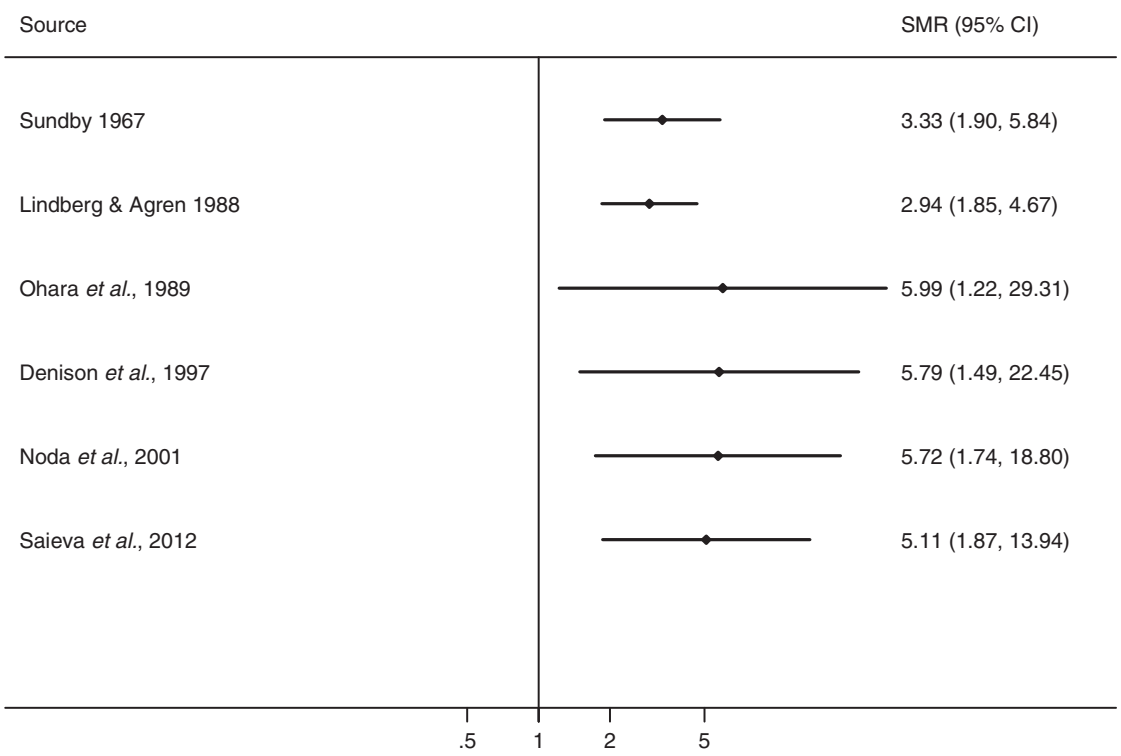

Figure 3. Cumulative meta-analysis for alcohol use disorder in treatment and endocrine mortality in men, 1967–2012.

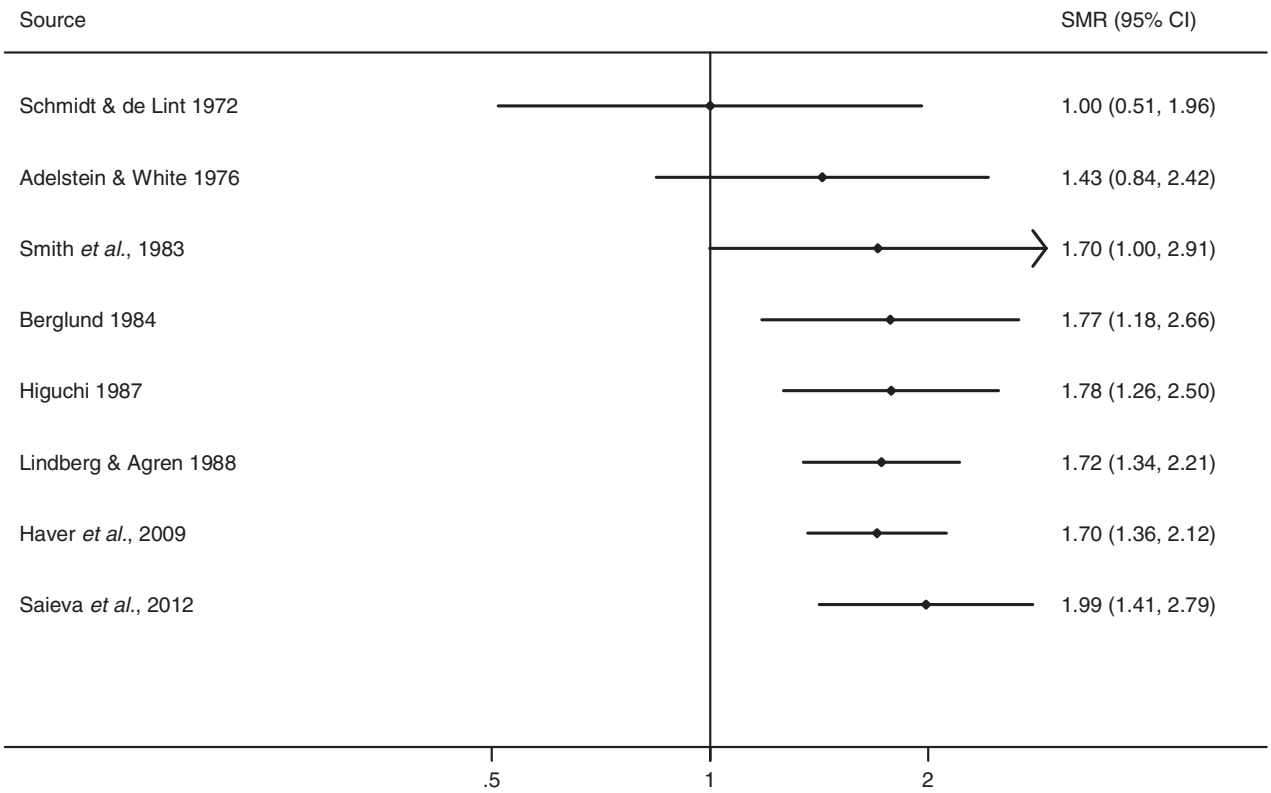

Figure 4. Cumulative meta-analysis for alcohol use disorder in treatment and cancer mortality in women, 1967–2012.

population surveys. Although the risks are expected to be slightly lower when based on lower all-cause mortality risk,[16] the most severe cases of AUD are typically missed in population surveys[34] such as people in treatment,[35,36] and in marginalized populations, i.e. the homeless[37] and prisoners.[38]

Causes of death

In the following, we will discuss cause-specific outcomes. Given the often emphasised beneficial effect of alcohol consumption on CVD, in particular heart disease outcomes and possibly diabetes, it has to be noted that none of the causes of death in people with AUD in treatment examined here showed any beneficial association. Although there is good epidemiological and short-term experimental evidence for a beneficial effect on ischaemic disease and possibly diabetes from regular low-level alcohol consumption,[20,39–42] based on our meta-analysis there is a substantially elevated risk for diabetes, all CVD in general and heart disease in particular in the highest alcohol consumption group as measured by current AUD treatment at baseline. This corroborates the findings of Russian studies, where high SMRs had been found for CVD including heart disease linked to very heavy drinking (e.g. Zaridze *et al.*[19]). One open question is whether prolonged binges pose additional problems compared with chronic heavy drinking, if the overall exposure is the same.[43]

The risk for several cancers is positively correlated with level of alcohol consumption. Recently, the list of cancers causally affected by alcohol consumption was expanded to now include oral cavity, pharynx, larynx, oesophagus, liver, colorectal and female breast cancer.[44,45] There is a clear dose-response relationship for all cancers described, and a relatively long latency.[44]

The effects of alcohol on several gastrointestinal disease categories are evident by several ICD categories having 'alcohol' or 'alcoholic' in their name, such as alcoholic gastritis, alcoholic liver disease or alcohol-induced pancreatitis.[46] The negative effects of alcohol consumption on these diseases grow exponentially with higher alcohol consumption.[47,48] This would explain the relatively high SMRs for gastrointestinal diseases compared with cancer. Another category for cause of death with high risk for people with AUD was mental disorders. In earlier studies, this category included mostly 'alcoholism'. Although the absolute number of deaths in this category was relatively small, the SMRs were substantial. The comorbidity between AUD and other mental disorders is quite high,[49,50] but causality is not clear, as AUD could be caused by mental disorders, mental disorders could be caused by AUD, or a third factor such as genetic vulnerability could cause both.

Our estimates for suicide were twice as high among men, and similar among women compared with the last review.[51] One reason might be that Wilcox *et al.* included not only treatment samples but also population samples. Comorbidity among AUD patients who commit suicide seems to be high, in particular depression[52] (see also above). A recent cohort study showed that among AUD patients without other psychiatric disorders the risk was similar to our findings; however, when other psychiatric disorders were present, adjusted risk estimates associated with AUD were much lower, about half the suicide risk compared with unadjusted estimates.[53]

A causal effect from alcohol on injuries has long been established, with a causal mechanism being mainly heavy drinking episodes and the resulting high blood alcohol level[54] which is very characteristic of people with AUD.[49,55]

Heavy drinking has been identified as a major cause for respiratory disease,[56] explaining the higher risk of these causes of death for people with AUD. The causal pathway is mainly via a compromised immune system,[57] and the risks for pneumonia have been mainly established for heavy drinking above a certain threshold.[58]

Implications

People with AUD who seek treatment were associated with high mortality risk in all major causes of death categories. A lack of systematic investigations on why some mortality risks were increasing over time among AUD patients warrants further research. The high mortality risks shown in this analysis should not be interpreted that treatment for AUD does not work. On the contrary, several studies (e.g.[59–62]) showed that a reduction of drinking substantially reduced total mortality risk (see also Rehm *et al.*[30]). The risk of injury death is extremely high, in particular in women, and targeted prevention should be considered for those seeking treatment. Health-care contacts, such as AUD treatment, open a window of opportunity for intervention, trying to reduce this high mortality from disease and injury. Treatment for AUD should include screening for these common diseases among people with AUD (such as liver cirrhosis or common CVD—see European Association for the Study of the Liver[63] for liver cirrhosis, or http://guideline.gov/content.aspx?id=34783 for CVD).

Given the high mortality risk for all major disease categories, screening for AUD should be more routinely incorporated into medical practice for somatic diseases in primary and secondary healthcare settings. This may help to identify people with alcohol problems and AUD earlier and reduce the development of more severe forms of addiction, while simultaneously reducing detrimental effects of alcohol consumption on the underlying conditions.

This could be done via the General Practice system with proven effective screening and brief interventions.[64] This setting also seems to be important because many people with AUD have general practitioner contact.[65] However, it will be necessary to implement an incentive system to guarantee uptake of such techniques in daily practice.[66]

The potential impact of brief interventions on mortality can also be seen in hospital settings. The last Cochrane review found a reduction of 40% of mortality within 1 year after brief interventions in such settings in randomized controlled trials, mainly conducted in internal and injury wards.[67] This shows the potential of even minimal interventions in settings with high risk, where reduction of drinking level is crucial for survival.[30] However, brief interventions may need to include not only one but several sessions to be most effective.[68]

Of course, reduction of mortality risk is not restricted to brief interventions, but is associated with all interventions which successfully reduce volume of drinking including, but not limited to, formal treatment. Based on effectiveness of current interventions for AUD, it was estimated that almost 12 000 alcohol-attributable deaths in the EU could be saved within 1 year if treatment rates were to be increased to 40%.[3] The high rates of mortality shown here thus could markedly be reduced if more interventions for problem drinking and AUD were implemented.

Conclusion

Cause-specific mortality among people with AUD in treatment showed markedly higher and increasing mortality risks compared with the general population than previously thought in most major categories, including CVD. Efforts to reduce these risks should be a priority, given that successful treatment reduces mortality risk substantially for a relatively common disease. There is a lack of recent research and future studies should focus on potential influence of age differences and comorbidities on excess mortality risk in people with AUD.

Supplementary Data

Supplementary data are available at *IJE* online.

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References

1. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol use disorders. *Lancet* 2009;**373**:2223–33.
2. Hasin DS, Stinson FS, Grant BF. Prevalence, correlates, disability and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry* 2007;**64**:830–42.
3. Rehm J, Shield KD, Rehm MX, Gmel G, Frick U. Modelling the impact of alcohol dependence on mortality burden and the effect of available treatment interventions in the European Union. *Eur Neuropsychopharmacol* 2013;**23**:89–97.
4. Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, ESEMeD/MHEDEA Investigators. Use of mental health services in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand* 2004;**109**:47–54.
5. Kohn R, Saxena S, Levav I, Saraceno B. The treatment gap in mental health care. *Bull World Health Organ* 2004;**82**:858–66.
6. Samokhvalov AV, Popova S, Room R, Ramonas M, Rehm J. Disability associated with alcohol abuse and dependence. *Alcohol Clin Exp Res* 2010;**34**:1871–78.
7. World Health Organization. *World Health Report 2001: Mental Health: New Understanding, New Hope*. Geneva: World Health Organization, 2001.
8. Vos T, Flaxman AD, Naghavi M *et al*. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**:2163–96.
9. Harris EC, Barraclough B. Excess mortality of mental disorder. *Br J Psychiatry* 1998;**173**:11–53.
10. Storbjörk J, Room R. The two worlds of alcohol problems: who is in treatment and who is not? *Addict Res Theory* 2008;**16**:67–84.
11. Zaridze D. Impact of extreme drinking on mortality. In: Boyle P, Boffetta P, Lowenfels AB *et al*. (eds). *Alcohol: Science, Policy, and Public Health*. Oxford, UK: Oxford University Press, 2013.
12. Noda T, Imamichi H, Tanaka H. Cause-specific mortality risk among male alcoholics residing in the Osaka metropolitan area. *Psychiatry Clin Neurosci* 2001;**55**:465–72.
13. Saieva C, Bardazzi G, Masala G *et al*. General and cancer mortality in a large cohort of Italian alcoholics. *Alcohol Clin Exp Res* 2012;**36**:342–50.
14. Campos J, Roca L, Gude F, Gonzalez-Quintela A. Long-term mortality of patients admitted to the hospital with alcohol withdrawal syndrome. *Alcohol Clin Exp Res* 2011;**35**:1180–86.
15. Rivas I, Sanvisens A, Bolao F *et al*. Impact of medical comorbidity and risk of death in 680 patients with alcohol use disorders. *Alcohol Clin Exp Res* 2012;**37**(Suppl 1):E221–27.

16. Roerecke M, Rehm J. Alcohol use disorders and mortality – A systematic review and meta-analysis. *Addiction* 2013;**108**: 1562–78.
17. Rehm J, Anderson P, Gual A *et al*. The tangible common denominator of substance use disorders: a reply to commentaries to Rehm *et al*. (2013). *Alcohol Alcohol* 2013;**49**:118–22.
18. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA* 2000;**283**:2008–12.
19. Zaridze D, Brennan P, Boreham J *et al*. Alcohol and cause-specific mortality in Russia: a retrospective case-control study of 48,557 adult deaths. *Lancet* 2009;**373**:2201–14.
20. Rehm J, Baliunas D, Borges GLG *et al*. The relation between different dimensions of alcohol consumption and burden of disease – An overview. *Addiction* 2010;**105**: 817–43.
21. Moher D, Pham B, Jones A *et al*. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;**352**:609–13.
22. Greenland S, O'Rourke K. On the bias produced by quality scores in meta-analysis, and a hierarchical view of proposed solutions. *Biostatistics* 2001;**2**:463–71.
23. Herbison P, Hay-Smith J, Gillespie WJ. Adjustment of meta-analyses on the basis of quality scores should be abandoned. *J Clin Epidemiol* 2006;**59**:1249–56.
24. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology.* 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2008.
25. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–88.
26. Cochran WG. The combination of estimates from different experiments. *Biometrics* 1954; **0**:101–29.
27. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21**:1539–58.
28. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**: 629–34.
29. Sterne JA, Sutton AJ, Ioannidis JP *et al*. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;**343**:d4002.
30. Rehm J, Roerecke M. Reduction of drinking in problem drinkers and all-cause mortality. *Alcohol Alcohol* 2013;**48**:509–13.
31. Roerecke M, Gual A, Rehm J. Reduction of alcohol consumption and subsequent mortality in alcohol use disorders: systematic review and meta-analysis. *J Clin Psychiatry* 2013;**74**:e1181–89.
32. Mann K, Lemenager T, Hoffmann S *et al*. Results of a double-blind, placebo-controlled pharmacotherapy trial in alcoholism conducted in Germany and comparison with the US COMBINE study. *Addict Biol* 2013;**18**:937–46.
33. Haver B, Gjestad R, Lindberg S. Mortality risk up to 25 years after initiation of treatment among 420 Swedish women with alcohol addiction. *Addiction* 2009;**104**:413–19.
34. Shield K, Rehm J. Difficulties with telephone-based surveys on alcohol in high-income countries: the Canadian example. *Int J Method Psych* 2012;**21**:17–28.
35. Roche AM, Freeman T, Skinner N. From data to evidence, to action: findings from a systematic review of hospital screening studies for high risk alcohol consumption. *Drug Alcohol Depend* 2006;**83**:1–14.
36. De Wit M, Jones DG, Sessler CN, Zilberberg MD, Weaver MF. Alcohol-use disorders in the critically ill patient. *Chest* 2010;**138**:994–1003.
37. Fazel S, Bains P, Doll H. Substance abuse and dependence in prisoners: a systematic review. *Addiction* 2006;**101**:181–91.
38. Fazel S, Khosla V, Doll H, Geddes J. The prevalence of mental disorders among the homeless in Western countries: systematic review and meta-regression analysis. *PLoS Med* 2008;**5**:e225.
39. Roerecke M, Rehm J. The cardioprotective association of average alcohol consumption and ischaemic heart disease: a systematic review and meta-analysis? *Addiction* 2012;**107**:1246–60.
40. Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. *BMJ* 2011;**342**:d671.
41. Patra J, Taylor B, Irving H *et al*. Alcohol consumption and the risk of morbidity and mortality from different stroke types – a systematic review and meta-analysis. *BMC Public Health* 2010;**10**:258.
42. Baliunas D, Taylor B, Irving H *et al*. Alcohol as a risk factor for type 2 diabetes – A systematic review and meta-analysis. *Diabetes Care* 2009;**32**:2123–32.
43. Gmel G, Kuntsche E, Rehm J. Risky single occasion drinking: bingeing is not bingeing. *Addiction* 2011;**106**:1037–45.
44. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Alcohol Consumption and Ethyl Carbamate*. Lyon, France: International Agency for Research on Cancer, 2010.
45. Boyle P. Alcohol consumption and breast cancer risk. In: Boyle P, Bofetta P, Lowenfels AB *et al*. (eds). *Alcohol: Science, Policy, and Public Health*. Oxford, UK: Oxford University Press, 2013.
46. World Health Organization. *International Classification of Diseases and Related Health Problems, 10th Revision*. Geneva: World Health Organization, 2007.
47. Irving HM, Samokhvalov A, Rehm J. Alcohol as a risk factor for pancreatitis. A systematic review and meta-analysis. *JOP* 2009;**10**:387–92.
48. Rehm J, Taylor B, Mohapatra S *et al*. Alcohol as a risk factor for liver cirrhosis – a systematic review and meta-analysis. *Drug Alcohol Rev* 2010;**29**:437–45.
49. Schuckit MA. Alcohol-use disorders. *Lancet* 2009;**373**:492–501.
50. Kessler RC. The epidemiology of dual diagnosis. *Biol Psychiatry* 2004;**56**:730–37.
51. Wilcox HC, Conner KR, Caine ED. Association of alcohol and drug use disorders and completed suicide: an empirical review of cohort studies. *Drug Alcohol Depend* 2004;**7**(Suppl 76):S11–19.
52. Berglund M, Ojehagen A. The influence of alcohol drinking and alcohol use disorders on psychiatric disorders and suicidal behavior. *Alcohol Clin Exp Res* 1998;**22**(Suppl 7)**:**3335–455.
53. Flensborg-Madsen T, Knop J, Mortensen EL, Becker U, Grønbaek M. Alcohol use disorders increase the risk of completed suicide – irrespective of other psychiatric disorders. A longitudinal cohort study. *Psychiat Res* 2009;**167**:123–30.

54. Taylor B, Irving HM, Kanteres F *et al*. The more you drink, the harder you fall: a systematic review and meta-analysis of how acute alcohol consumption and injury or collision risk increase together. *Drug Alcohol Depend* 2010;**110**:108–16.
55. Dawson DA, Li TK, Grant BF. A prospective study of risk drinking: At risk for what? *Drug Alcohol Depend* 2008;**95**:62–72
56. Samokhvalov A, Shuper PA, Rehm J. Infectious disease. In: Boyle P, Boffetta P, Lowenfels AB *et al*. (eds). *Alcohol: Science, Policy, and Public Health*. Oxford, UK: Oxford University Press, 2013.
57. Szabo G. Alcohol's contribution to compromised immunity. *Alcohol Res Health* 1997;**21**:30–41.
58. Samokhvalov AV, Irving HM, Rehm J. Alcohol consumption as a risk factor for pneumonia: systematic review and meta-analysis. *Epidemiol Infect* 2010;**138**:1789–95.
59. Vaillant GE, Clark W, Cyrus C *et al*. Prospective study of alcoholism treatment. Eight-year follow-up. *Am J Med* 1983;**75**: 455–63.
60. Bullock KD, Reed RJ, Grant I. Reduced mortality risk in alcoholics who achieve long-term abstinence. *JAMA* 1992;**267**: 668–72.
61. De Silva HJ, Ellawala NS. Influence of temperance on short-term mortality among alcohol-dependent men in Sri Lanka. *Alcohol Alcohol* 1994;**29**:199–201.
62. Bell H, Jahnsen J, Kittang E, Raknerud N, Sandvik L. Long-term prognosis of patients with alcoholic liver cirrhosis: a 15-year follow-up study of 100 Norwegian patients admitted to one unit. *Scand J Gastroenterol* 2004;**39**:858–63.
63. European Association for the Study of the Liver. EASL clinical practical guidelines: management of alcoholic liver disease. *J Hepatol* 2012;**57**:399–420.
64. Kaner EF, Beyer F, Dickinson HO *et al*. Effectiveness of brief alcohol interventions in primary care populations. *Cochrane Database Syst Rev* 2007;**18**:CD004148.
65. Mertens J, Weisner C, Ray G, Fireman B, Walsh K. Hazardous drinkers and drug users in HMO primary care: Prevalence, medical conditions, and costs. *Alcohol Clin Exp Res* 2005;**29**: 989–98.
66. Nilsen P. Brief alcohol intervention – where to from here? Challenges remain for research and practice. *Addiction* 2010; **105**:954–59.
67. McQueen J, Howe TE, Allan L, Mains D, Hardy V. Brief interventions for heavy alcohol users admitted to general hospital wards. *Cochrane Database Syst Rev* 2011;**8**:CD005191.
68. Mdege ND, Fayter D, Watson JM, Stirk L, Sowden A, Godfrey C. Interventions for reducing alcohol consumption among general hospital inpatient heavy alcohol users: A systematic review. *Drug Alcohol Depend* 2013;**131**:1–22.
69. Brenner B. Alcoholism and fatal accidents. *Q J Stud Alcohol* 1967;**28**:517–28.
70. Sundby P. *Alcoholism and Mortality*. Oslo: Universitetsforlaget, 1967.
71. Schmidt W, de Lint J. Causes of death of alcoholics. *Q J Stud Alcohol* 1972;**33**:171–85.
72. Salum I. Delirium tremens and certain other acute sequels of alcohol abuse. A comparative clinical, social and prognostic study. *Acta Psychiatr Scand* 1972;**48**(Suppl 235):13–45.
73. Lindelius R, Salum I, Agren G. Mortality among male and female alcoholic patients treated in a psychiatric unit. *Acta Psychiatr Scand* 1974;**50**:612–18.
74. Adelstein A, White G. Alcoholism and mortality. *Popul Trends* 1976;**6**:7–13.
75. Thorarinsson AA. Mortality among men alcoholics in Iceland, 1951-74. *J Stud Alcohol* 1979;**40**:704–18.
76. Polich JM, Armor DJ, Braiker HB. *The Course of Alcoholism: Four Years After Treatment*. New York: John Wiley & Sons, 1981.
77. Smith EM, Cloninger CR, Bradford S. Predictors of mortality in alcoholic women: a prospective follow-up study. *Alcohol Clin Exp Res* 1983;**7**:237–43.
78. Berglund M. Mortality in alcoholics related to clinical state at first admission. A study of 537 deaths. *Acta Psychiatr Scand* 1984;**70**:407–16.
79. Higuchi S. Mortality of Japanese female alcoholics: a comparative study with male cases. *Jpn J Alcohol Drug Depend* 1987;**22**:211–23.
80. Lindberg S, Agren G. Mortality among male and female hospitalized alcoholics in Stockholm 1962-1983. *Br J Addict* 1988;**83**:1193–200.
81. Ohara K, Suzuki Y, Sugita T. Mortality among alcoholics discharged from a Japanese hospital. *Br J Addict* 1989;**84**:287–91.
82. Denison H, Berkowicz A, Oden A, Wendestam C. The significance of coronary death for the excess mortality in alcohol-dependent men. *Alcohol Alcohol* 1997;**32**:517–26.