Title

All-cause and cause-specific mortality rates of patients treated for alcohol use disorders: a meta-analysis

Abstract

Background

Although alcohol use disorders (AUD) are known to increase the relative risk of all-cause and some cause-specific mortalities, the absolute mortality rates of the AUD population are unknown. Such knowledge would benefit planners of the provision of services for this population, including in prioritising the identification and/or treatment of diseases likely to cause their death.

Methods

We conducted a systematic review of studies in English, reporting the cause-specific mortality rates among people treated for AUD. Number of deaths by cause, and total person-years of follow-up were extracted. All-cause and cause-specific mortality rates per 1000 person-years were meta-analysed assuming random effects.

Results

31 studies were included. Participants were mainly middle-aged males. The quality of studies was generally good. 6,768 all-cause deaths in 276,990.7 person-years of follow-up (36,375 patients) were recorded and the pooled all-cause mortality rate was 27.67/1000 person years (py) (95% confidence interval (CI) 23.9, 32.04). The commonest cause of death in the AUD population was cardiovascular disease (CVD) (6.9/1000py (95%CI 5.61, 8.49)), followed by gastrointestinal deaths (5.63/1000py (95%CI 4.1, 7.74)), unnatural deaths (4.95/1000py (95%CI 4.01, 6.09)), neoplasms, respiratory diseases and substance use disorders.

Conclusions

Patients with AUD have increased rates of all-cause and cause-specific mortality compared to the general population. Like the general population, they are most likely to die of CVD. In contrast to the general population, gastrointestinal and unnatural deaths are the next most common causes of death. We believe these facts should be considered when planning healthcare services for patients with AUD.

Introduction

Alcohol use disorders (AUD), a clinical term describing alcohol dependence and alcohol abuse [1], are one of the most prevalent mental disorders worldwide, affecting an estimated 4.1% of the global population aged 15 to 64 years [2].

AUDs are recognised to increase the risk of all-cause mortality and a number of specific causes of death [3–5]. Roerecke has conducted two meta-analyses of the relative risk of all-cause or cause-specific mortality in this population. The first estimated that the risk of all-cause mortality in male patients with AUD in treatment settings is 3.38 times that of the general population, whereas in women it is 2.57 [6].

In the second, Roerecke assessed the cause-specific standardized mortality ratios (SMR) of the same population. They found that the conditions that have the greatest relative risk of mortality in men with AUD are mental health disorders, digestive diseases and injuries (19.8, 10.74, and 6.64 times the risk within the standard population respectively) [7].

Although relative mortality measures (such as the SMR, or relative mortality risk), being measures of effect, are useful in demonstrating an association between AUD and deaths from specific causes, the 'absolute' mortality rate, being a measure of disease frequency, would be of benefit to public health practitioners in planning or prioritising the allocation of resources to provide suitable health interventions to prevent deaths from

these causes in the AUD population. This is because this measure provides a more accurate estimate of disease burden within populations [8,9], and is used and often required in population health needs/status assessments [10,11]. As yet, no systematic review of the absolute mortality rates of the AUD population is available.

We therefore aimed to address this knowledge gap by systematically reviewing the cause-specific mortality rates in the AUD population.

Methods

Search strategy

We conducted a systematic literature search in the Medline (via OVID), EMBASE (via OVID), CINAHL and PsycINFO databases from inception to March 2015. We used broad terms related to the concepts of 'alcohol' AND 'misuse' AND 'death', both through use of free text and indexed search terms. The full search strategy is available as Supplemental Information, Table S1.

We included papers which fulfilled all the following criteria: 1) reported results from cohort studies, or intervention trials with a non-intervention arm; 2) contained patients treated for AUD; 3) included study endpoints of cause-specific mortality and presented rates on the basis of person-time, or other information that allowed transformations to this measure and 4) were published in English.

We also searched for additional articles to include by checking the reference lists of included studies, and the titles or abstracts of conference or symposia for the last five years of Alcohol Research UK; the American Society of Addiction Medicine; the Association for Medical Education and Research in Substance Abuse; the Medical Council on Alcohol; the National Institute on Drug Abuse (NIDA) International Forum; and the Society for the Study of Alcohol.

We largely followed published guidelines on the conduct and reporting of systematic reviews: one in general [12], and another of observational studies in particular [13].

Screening

Title, abstract and full text screening were performed independently by two reviewers (AA and KF for titles, and AA and TC for the other stages). Disagreements were resolved through consensus. Any remaining discrepancies were discussed with a 3rd reviewer (TC for titles, and KF for the other stages).

Where multiple articles reported the same study, we included the one reporting the highest number of person-years.

Data Extraction

Data from all included studies were extracted by AA using a standardised extraction tool containing the following items:

Study report characteristics: Author; year of the study; title of the article; location of study.

Quality appraisal: Quality appraisal was conducted using an adaptation of the Newcastle Ottawa Scale (NOS) [14] (available in Supplemental Information, Table S2). This adaptation omitted questions relating to the non-exposed cohort as they were inapplicable in our review. Adequacy of

length of follow up was set as being six months: the definition of chronicity or long-term as used by the World Organization of Family Doctors [15].

Mortality data: we extracted (for combined-genders) number of patients with AUD at risk, number of deaths in total and by cause, and person-years of follow up.

We categorised the reported causes of deaths firstly into eleven broad groups. These are: neoplasms; cardiovascular; neurological; respiratory; gastrointestinal; genitourinary; endocrinological and metabolic; immunological diseases; unnatural or violent deaths; substance use disorders; and infectious diseases. We also grouped the causes of deaths into nine narrow groupings. These were: cancers; coronary heart disease; stroke; hypertension; cirrhosis; diabetes mellitus; suicide; alcohol-use disorder; and Human Immunodeficiency Virus infection or Acquired Immune Deficiency Syndrome (HIV/AIDS). These disease groupings were not predetermined, but instead formed pragmatically, using the disease terminologies or the diagnostic codings reported in the included studies.

Analysis

Mortality rates were obtained by dividing the number of deaths by the reported total person-years at risk, and were reported in 1000 person-year (py) units (with 95% confidence intervals (CI)). All analyses are presented for all ages and both sexes combined, as separate results could not be extracted from the majority of the original study reports. Information

provided in other ways was, where possible, transformed to enable us to calculate mortality rates and 95%CIs. These transformations are adapted from those used by Degenhardt et al [16]. The full list of transformations is described in Supplemental Information S3.

The extracted information on cause-specific number of deaths and person-years for each cause of death was used to generate standard errors of cause-specific mortality. Mortality rates and their respective standard errors were pooled across studies for each cause of death category in turn. For each study and each cause of death, the natural logarithm of the mortality rate (number of deaths/1000 person-years) was estimated, with standard errors computed assuming a Poisson distribution for the number of deaths. These were then pooled assuming random effects using a DerSimonian-Laird random-effect model to allow for between-study heterogeneity, which was estimated by the I^2 statistic [17,18]. We present the meta-analysed combined-gender crude cause-specific mortality rates by broad and narrow cause of death groups for each study.

We also present the specific causes of death as proportions of all-cause death (referred to here as proportional mortality (PM)). This measure may be useful for public health practitioners who might not have access to sufficient information to form the denominators of risk or rate measures [19,20].

Cause-specific mortality proportions for a given study were calculated by dividing the number of deaths due to specific cause of death by the number

of all-cause deaths in the study (and presented as percentages). The proportional mortalities and their respective standard errors were pooled across studies in a similar process to the one described above.

Finally we present a comparison of the age-standardised mortality rate per 1000 population between the current study and the 2013 WHO Global Burden of Disease (GBD) Study which reports the 1-year mortality rates for the 2010 global general population[21] for the top five causes of death in this review.

All analyses were conducted using Stata 14 [22].

Results

Flow of included papers

The initial search identified 11644 unique citations. Title and abstract screening excluded 10446 of these. Inter-rater agreement for the title screen was moderate (κ=0.49) and for the abstract screen substantial (κ=0.74)[23]. All disagreements were resolved by consensus with no referrals needed for decision by a third reviewer.

The screening of the full text of the remaining 386 papers resulted in 355 study reports being rejected for the following reasons: were not cohort studies or trials with non-intervened arms (n=42); were not studies of patients who received treatment for AUD (n=135); did not report cause-specific mortality (n=137); data were presented in a form which could not allow calculation of mortality rates in person years (n=27); or contained data from a study included previously in this review (n=14).

No additional relevant published studies were identified from the references of included papers or the searches of conference titles or abstracts.

31 studies were thus identified for inclusion in this review.

A flow diagram for the selection of studies, and the bibliography of studies excluded after full text evaluation, are presented in Supplemental Information Figure S4 and Bibliography S5 respectively.

Characteristics of included studies

The 31 cohort studies included in this review reported 36,375 patients treated for AUD (combined-genders), followed up for a total of 276,990.7 person-years. 6768 all-cause deaths were recorded [24–54].

Fourteen studies were from Europe (eight from western or northern Europe and six from southern Europe), nine from North America, five from Asia (four from the advanced economies of Japan and Taiwan, and one from Sri Lanka), two from New Zealand and one from South Africa. The maximum follow-up time of the studies ranged from three to 42 years (mean=14.06 years). The average follow-up observed per participant ranged from 1.5 to 18 years (mean=7.48 years).

All 28 studies that reported gender breakdown had at least 50% male participants (range: 50-100%; median=79.98%). Six studies had only male participants. All 28 studies reporting age at baseline had an average age of study participants of at least 30 (range: 34.7-59; median: 44).

Table 1 summarises the characteristics of included studies.

Table 1: Characteristics of individual studies

[TABLE 1 HERE]

Key
[1]: mean
[2]: median
[3]: mode
[4]: actual loss to follow-up not reported or could not be estimated. This figure represents the maximum possible loss to follow up assuming that all those who did not die were lost to follow up.
[a:] Fuster, D. et al. "Impact of Hepatitis C Virus Infection on the Risk of Death of Alcohol-Dependent Patients." Journal of Viral Hepatitis 22.1 (2014): 18–24. Journal of Viral Hepatitis.
na: not reported or available

Risk of bias assessment

Overall, the quality of included studies was good, with all included papers scoring 4 or more from a total of 6. All 31 studies scored fully for questions related to ascertainment of AUD status and death, and adequacy of length of follow up. Twelve papers did not report whether the sampled cohort was representative of all the patients receiving therapy for AUD, and 16 papers did not report the proportion of the cohort that was lost to follow up. The quality assessment of the included studies is presented in Supplemental Information Table S6.

Meta-analysis of all-cause mortality rates

All-cause mortality among these predominantly middle-aged adults was 27.67/1000py (95%CI 23.9, 32.04) (Figure 1). The heterogeneity was high at I^2=96.9%. This estimate remained high when subgroup analyses were conducted using the following variables: demographic (average age; percent of males; country income level), clinical (the AUD subtype (AUD in general vs alcohol dependence only); mortality rate size), and methodological (study quality; whether there was a reported diagnostic system used to categorise causes of deaths).

[FIGURE 1 HERE]

Figure 1: Forest plot of pooled crude mortality rates: All-Cause Mortality

Meta-analysis of cause-specific mortality rates

The diagnostic coding or terminology used to define the broad and narrow cause of death groups are presented in Supplemental Information: Tables S7.1 and S7.2.

The forest plots of pooled crude mortality rates for the five most common cause of death are presented in Supplemental Information Tables and Figures S8.1 to S8.5. Details of all-cause and cause-specific mortality rates for each study are presented in Supplemental Information Tables S9.1 and S9.2. We did not present the pooled rates for two specific causes of deaths (hypertension and HIV) as only two studies contributed data.

The highest cause-specific pooled mortality rate was that for cardiovascular diseases (6.9/1000py (95%CI 5.61, 8.49)), followed by gastrointestinal diseases (5.63/1000py (95%CI 4.1, 7.74), unnatural deaths (4.95/1000py (95%CI 4.01, 6.09)), neoplasms (4.47/1000py (95%CI 3.34, 6.00)), and respiratory diseases (1.42/1000py (95%CI 0.96, 2.10)).

This is summarized in table 2.

Table 2: All-cause and cause-specific mortality rates

[TABLE 2 HERE]

Note: the table reports pooled crude rates, for combined-genders

Meta-analysis of the proportional mortality of specific causes of death

Presenting this as cause-specific proportional mortality, the largest proportional mortality was recorded by cardiovascular diseases, making up 24.55% of deaths (95%CI 20.14, 28.96). This was followed by gastrointestinal diseases (20.35% (95%CI 16.39, 24.31)), unnatural deaths (18.2% (59%CI 15.07, 21.34)), neoplasms (14.93% (95%CI 11.35, 18.51)), and substance use disorders (5.24% (95%CI 3.76, 6.71)). This is summarized in Table 3.

Table 3: Proportional mortality of specific causes of death

[TABLE 3 HERE]

Note: the table reports pooled proportions, for combined-genders

Comparison of rates and proportional mortality to those of the global population

Lastly, table 4 compares the differences in the pattern of specific causes of death in the alcohol treatment population as distinct from the 2010 global general population [21]. The all-cause mortality in the alcohol treatment population is more than three times that of the general population (27.67/1000py vs. 8.8/1000). The population of patients with AUD share cardiovascular diseases as the most common cause of death (mortality rate (MR): 6.9 vs 2.93/1000py; proportional mortality (PM): 24.55 vs 31.53%). However, gastrointestinal deaths, consisting mostly of cirrhosis (MR: 5.63 vs 0.38/1000py; PM: 20.35 vs 6.5%), and unnatural deaths (MR: 4.95 vs 0.7/1000py; PM: 18.2 vs 8.7%) rank higher in terms of mortality rates as

well as proportional mortality in patients with AUD than they do in the general population, supplanting the rank of neoplasms and infectious diseases.

Table 4: Comparisons of meta-analysed mortality rates and proportional mortality versus those reported in the WHO GBD 2013 study for all-cause deaths and the top five most common causes of deaths.

[TABLE 4 HERE]

Note: this table reports crude combined-gender rates and proportions

Discussion

We have presented pooled estimates from the published health literature of the all-cause and cause-specific mortality rates of AUD treatment patients, and established the most common causes of deaths for this population.

Evidence from 36,375 patients, followed up for a total of 276,990.7 person-years, across 31 studies reveal that the crude all-cause mortality rates in this population, formed largely of middle-aged adults, is 27.67/1000py. The specific causes of death with the highest mortality rates are cardiovascular diseases (6.9/1000py), followed by gastrointestinal diseases (5.63/1000py), unnatural deaths (4.95/1000py), neoplasms (4.47/1000py), and respiratory diseases (1.42/1000py).

Strengths and limitations

The presentation of absolute mortality rates may render our results more useful in the prioritization and planning of health services for specific populations (such as patients with AUD in this case) than would the relative risk measures [8,9], reported by previous reviews of this subject [6,7].

We found that the quality of the studies included in this review was generally good. All the studies include good ascertainment of alcohol use disorders, linkage to national registers for deaths, and loss to

follow up (where reported) was low (i.e. <20% [55]). Where loss to follow up was not explicitly reported [31,41], we believe that the loss to follow up was unlikely to differ greatly to the other studies, as these studies also recorded outcomes via linkage to national registration systems where mortality ascertainment is largely complete [56,57].

There are nevertheless some biases that we should consider when interpreting our study.

Firstly, there is the matter of the generalisability of the participants of the included studies. We have concentrated on populations receiving treatment for AUD as this is a fairly accessible AUD population, and one likely to have had AUD carefully assessed. Given that the included studies were predominantly conducted in advanced economies, recruited mostly middle-aged males, and that we reported rates for combined genders, the findings of this review are likely to be generalisable to similar AUD populations and not to other AUD populations with different demographic, clinical, socioeconomic or other characteristics. An example of such a population might be that described by Gunnarsdottir et al. [58], where the AUD population was sampled in the emergency care setting, and consisted of a lesser proportion of males (63.7%) than ours, and had mortality rates less than those found in this review (e.g. all-cause mortality 12.62 vs 28.08/1000py).

Secondly, we found significant heterogeneity in the meta-analysed estimates of pooled crude mortality rates. Sources of this heterogeneity may include differences in the demographic or clinical characteristics of participants [59]. Certainly, there was variation in age ranges of participants, ethnic make-up of the range of countries, and the income classification of countries (and these, across different time periods) in the included studies.

Variation in the AUD treatment regimens themselves might contribute to variation in outcome. Methodological diversity is also possible since there could be variation in the coding of causes of deaths: whether as 'mode of death' (e.g. cardiac arrest) or as 'the underlying cause of death' (e.g. chronic kidney disease) [60]. The included studies do not specify which of these two approaches was used.

Being a diagnosis made up of either of two elements (alcohol harmful use/abuse, or dependence) under DSM IV [1], it is probable that the effect of these two subsets of AUD on mortality is not homogenous. Under DSM V, the distinction between these two subgroups within AUD are removed. The change in diagnostic coding may therefore hide a potentially important difference in the mortality rate between these two AUD subgroups, and it is important therefore to recognize the need for similarly robust estimates of the mortality experience of

both subgroups. Unfortunately, currently available data does not permit this.

Nevertheless, it has been shown that those with alcohol dependence are more likely to be categorized as AUD under DSM IV, and those with alcohol abuse less so. This results in AUD treatment populations under DSM V having similar prelavences to those of the AUD population under DSM IV [61]. Patients treated for AUD under DSM V are therefore likely to be similar to patients being treated for AUD under DSM IV, and one could reasonably predict that the mortality rates would be similar.

Considering the likelihood of alcohol dependence being classified as AUD, as noted above, and that those with alcohol dependence are more likely to be treated compared to those with alcohol abuse, it follows that our AUD treatment population are those likely to have alcohol dependence. Our results therefore are more likely to reflect mortality in alcohol dependence rather than alcohol abuse.

Comparison to previous literature

There have not been previous systematic reviews of mortality rates of alcohol misusers with which to compare our findings. This is perhaps unsurprising as Dickersin has previously highlighted that systematic reviews of "descriptive information" (e.g. disease

mechanisms, incidence and prevalence of a condition) are fewer than those of analytical research (i.e. of interventions) [62].

We have demonstrated that the all-cause mortality rates were more than three times (3.14) that of the general population figures quoted in the 2013 WHO Global Burden of Disease Study [21]. Comparing this to Roerecke's 2013 study, they observed a not too dissimilar risk estimate in his study (3.38) [6], lending support to the validity of our results.

Additionally, we found that although both the AUD and general populations share CVDs as the most common cause of death, gastrointestinal and unnatural deaths are much more common in the AUD population than they are in the general population.

When compared to the ranks of conditions with the highest standardized mortality ratios (SMR), Roerecke found that these were firstly mental health diseases, followed by digestive diseases, injuries, endocrine diseases, and respiratory diseases. Cardiovascular diseases and cancers were causes of death with the 6th and 7th highest SMR [7]. Clearly, this demonstrates that the ranks of the SMRs or other relative risks or rates of specific causes of death do not necessarily correspond to those of absolute risks or rates.

Policy implications

The potential importance of this work is as much in informing what patients with AUD do not die of as in what they do. We have shown that CVD remains the commonest cause of death in this group, and so those planning or delivering health care to these patients, should not neglect to assess markers of cardiovascular risk, nor opportunities to reduce that risk. However, the reduced rates of malignant deaths relative to gastrointestinal or unnatural ones, suggest that in this group it may be sensible to devote more resources to liver disease, for example, than to cancer screening. As non-invasive methodologies to screen for advancing liver disease have now been developed, attention to the earlier detection of this may provide opportunities to benefit these patients, for instance, via prophylaxis against variceal bleeding. Such action has clear potential for benefit when one considers that the currently available evidence suggests nearly half of liver disease in England presents with decompensation (such as variceal bleeding or ascites) [63]. Such screening for specific causes of deaths is currently in place for populations suffering from certain other conditions at increased risk of mortality (e.g. chronic kidney disease in those with type 2 diabetes) [64,65].

Other than informing the prioritisation of finite resources, and its resulting influence on clinical practice, this work could also help public

health professionals. Those involved in health planning can use the pooled mortality rate information provided here, for instance in health needs assessments [66], to compare against those observed in their jurisdictions, or to estimate the amount of resources they might need to allocate to patients with AUD in their own locations in a year.

Finally, based on the demonstration that those conditions with high relative rates of mortality do not necessarily also have high absolute mortality rates, it is pertinent that health researchers respond to the need for public health relevance by increasing the reporting of measures of frequency or occurrence, and not only relative measures of association.

Conclusions

Our systematic review presents pooled crude absolute all-cause and cause-specific mortality rates. Like the general population, patients under treatment for AUD are most likely to die of CVDs. However, in contrast to the general population, the ranks of the other common causes of deaths differ, with gastrointestinal and unnatural deaths being the next most common causes of deaths. We believe that these facts should be borne in mind when planning healthcare services for those with AUDs.

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