



Review

What is the cause of death, when alcohol dependent persons die prematurely?

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ABSTRACT

Background: Although individuals with alcohol use disorder (AUD) have a significantly shorter lifespan than the general population, there is sparse evidence on cause of death when alcohol dependent people die prematurely. Especially the somatic causes of death are shed less light on.

Aim: To determine the cause of premature death in individuals with AUD based on recent studies.

Methods: This systematic review summarizes evidence from the last 10 years with cohort studies consisting of AUD patients with the subsequent outcome of cause of death and with at least two years of follow-up.

Results: Nine studies were included of which only two were assessed to be of good quality. Furthermore, two studies were of moderately good and acceptable quality, respectively. This review found increased mortality in AUD individuals with the main causes of death being malignancy, and problems of the cardiovascular- and the digestive system.

Conclusion: Malignancy was the most common cause of death in the included AUD cohorts, but the overall quality of the included studies in this review is low. There is a need for high-quality studies to better understand cause-specific mortality among AUD individuals.

1. Introduction

Harmful use of alcohol¹ accounts for about 3.3 million deaths globally every year, representing 5.9% of all deaths (WHO, 2018). Alcohol use disorders (AUDs) have previously been estimated to be the largest disease category contributing to the alcohol-attributable global burden of disease. AUDs include alcohol dependence, alcohol abuse and, in the International Classification of Diseases (ICD), the harmful use of alcohol (Rehm et al., 2009). In the most recent Global Burden of Disease study, AUDs were found to be the most prevalent of all substance disorders (Deegenhardt et al., 2018).

In Denmark, alcohol-related death accounts for approximately 5.5% of all deaths and is, therefore, an important cause of mortality and morbidity (The Danish Health Authority and Statens Serum Institut, 2015). Even though the average lifespan in Denmark is 82,9 and 79,0 years for women and men, respectively, it is essential to point out the significantly shorter average life expectancy of people with AUDs (National Danish Statistics, 2018; Westman et al., 2015). In a Scandinavian study, Westman et al. (2015) concluded that people hospitalized with AUDs die 24–28 years earlier than people in the general

population (Westman et al., 2015).

The reliable Danish health care register provides a unique opportunity to study cause of mortality. Based on recent statistics from the Danish National Health Register from 2016, we know that the five most common causes of death in Denmark are ischemic heart diseases, lung cancer, chronic obstructive pulmonary disease (COPD), other heart diseases and cerebral vascular diseases (National Health Authority, 2018). However, studying cause of death related to people with AUDs has shown to be more complex. While a significant proportion of the disease burden attributed to alcohol consumption is caused by unintentional and intentional injuries, including violence, suicides and road traffic crashes, more research about the most common somatic causes of early mortality for alcohol dependent people is needed (WHO, 2018).

In a systematic review and meta-analysis regarding cause-specific mortality risk among patients treated for AUD, Roerecke and Rehm (2014) found a significantly higher mortality risk compared to the general population. The most common cause of death in men was cardiovascular disease (CVD), followed by trauma, cancer and digestive diseases. Meanwhile, in women, the most common cause was trauma, followed by CVD, digestive diseases and cancer. Based on their findings

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¹ The concept of “harmful use of alcohol” in this context is different from “harmful use of alcohol” as a diagnostic category in the ICD-10 Classification of Mental and Behavioural Disorders (WHO, 1992).

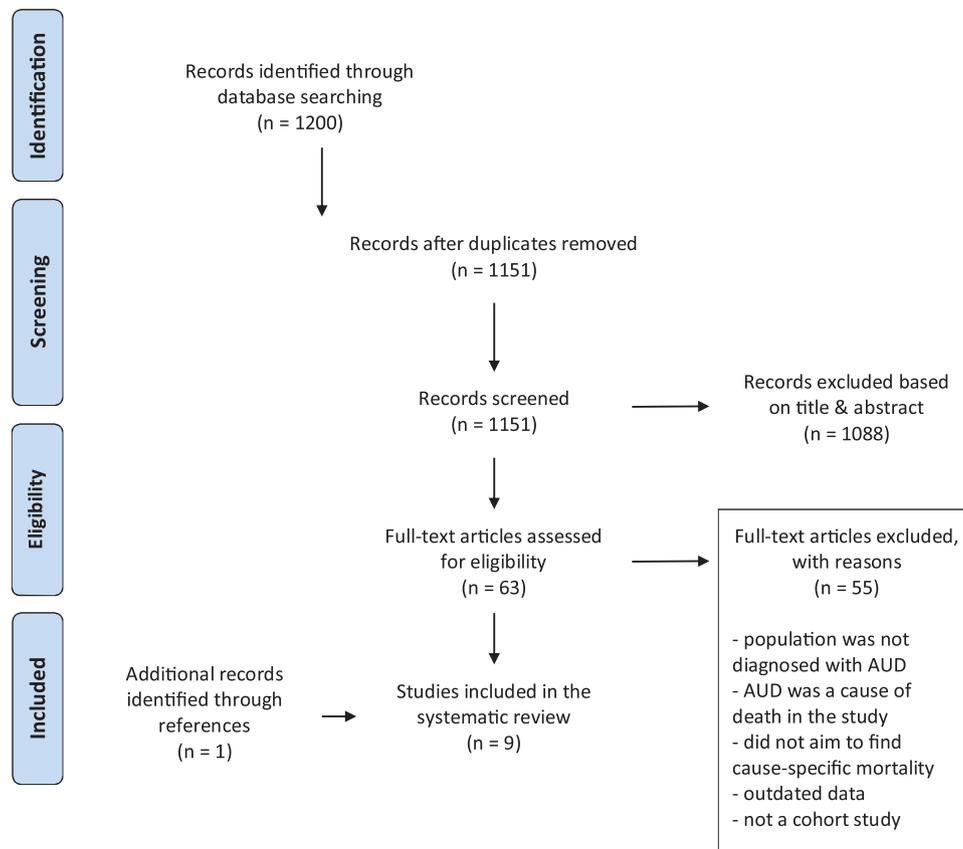


Fig. 1. PRISMA Flowchart.

of the specific somatic causes of death, the review underlines the importance of screening for somatic disease and the initiation of interventions to reduce the stated risks. While we agree in the implication of finding these specific somatic causes of death in AUD patients, their review includes rather outdated studies (Roerecke and Rehm, 2014).

In the present systematic review, drawing on recent cohort studies, we aim to determine the cause of death when alcohol dependent persons die prematurely.

2. Methods

We used the guidelines described by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) in order to conduct this review (PRISMA Checklist, 2009).

2.1. Criteria for considering studies for this review

2.1.1. Types of Studies

We considered only cohort studies eligible for inclusion as the design is optimal for studying several causes of death overtime in the same cohort of AUD patients (Juil, 2012). Due to its ranking in the evidence hierarchy compared to other designs, a systematic review of cohort studies would increase the level of evidence (Maibach and Gorouhi, 2012). The cohort studies were included if they had a minimum follow-up of two years, were written in English, and published within the last 10 years.

2.1.2. Types of Participants

Studies with patients above 18 years of age and diagnosed with an AUD by a physician according to a valid classification system; International Classification of Disease or Diagnostic and Statistical Manual of Mental Disorders (DSM) were included. In- and out-patients, regardless of their gender and treatment-status, were eligible for

inclusion. Studies reporting AUD as the cause of death in the population were excluded since the aim was to find the specific causes of death within the AUD population. Therefore, reporting AUD as the sole cause of death was not specific enough. Studies enrolling patients without an AUD as their primary diagnosis were excluded.

2.1.3. Outcome Measures

Primary outcome was cause-specific mortality in AUD patients. Studies were included if they reported the somatic causes of death and the proportion of participants that died in every disease category.

2.2. Information sources and search terms

The literature was reviewed through PubMed and Scopus between March and April 2018. The following search terms were used in both databases to identify relevant articles:

((Alcohol pendent OR Alcoholic OR Alcohol abuse OR Alcohol disorder OR alcoholism OR binge drinking OR Alcohol Dependence OR Alcohol Addiction OR Alcohol Use Disorder OR Alcohol Use Disorders) AND (cause OR causes OR reasons OR reason OR "causative factor" OR "causal agent" OR killer) AND (Premature death OR Premature mortality OR Premature Mortalities OR Premature Death OR Premature Deaths OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Mortality Determinants" OR "Mortality Determinant" OR "Differential Mortalities" OR "Differential Mortality" OR "Age-Specific Death Rate" OR "Age-Specific Death Rates" OR "Death Rate" OR "Death Rates" OR "Mortality Rate" OR "Mortality Rates"))

In PubMed, the filters "publication dates" and "languages" were used to limit potential articles to the last 10 years of publication and English, respectively. In Scopus, the advanced search function was used and the search was limited to "title-abstract-keywords". Furthermore, the publication dates were selected manually dating back to and including 2008.

2.3. Selection of studies

The data collection process is illustrated in Fig. 1. Two review authors (A.M.A.G and E.F) independently assessed all titles and abstracts in the above-mentioned databases to determine whether the articles met the inclusion criteria. In case of disagreement between the reviewing authors or lack of information in the title/abstract to ascertain potential for inclusion, full articles were assessed and discussed to obtain consensus.

Throughout the screening process, reference lists of potential and included articles were searched and the articles were enrolled if they met the inclusion criteria.

In case of missing outcome data, study authors were contacted and asked for additional data. Otherwise, they were excluded from this review.

2.4. Assessment of quality

Information about causes of death in each study was extracted by the two review authors independently and the quality of the included studies was independently assessed, using a valid and acknowledged checklist made specifically for cohort studies (Center for Clinical Guidelines Checklists, 2004). In case of disagreement, a consensus between the authors was obtained through careful discussion. Questions in the checklist not relevant for this review were noted as “Not relevant”. That includes item 1.4 “Is the possibility that some participants had the disease (outcome) at baseline, discussed?”. Based on the completed checklists, an overall assessment in correlation with the aim of the review was made. Thus, when evaluating the study quality, the emphasis was on how well each study provided answers regarding cause of death in alcohol dependent patients. In addition to the checklist, each study was assessed according to the following characteristics: (1) sample size of 1000 patients or more, to counter the bias of small studies having disproportionate influence in reviews; (2) follow-up rates of 90% or greater, to counter attrition bias. Thus, both aforementioned characteristics and the checklist were used in evaluating each study’s capacity to answer the aim of this review.

3. Results

The search identified 1200 potential articles, where 49 duplicates were identified and removed. Articles were then screened by title and abstract, yielding 63 articles that were assessed in more detail. Of the 63, only eight articles met our inclusion criteria. An additional article, found through reference lists during the title and abstract screening, was added. Handsearching the reference lists of the articles that met the inclusion criteria identified no additional studies eligible for inclusion (see Fig. 1).

The majority of the included studies ($n = 5$) were from Spain with two hospital units providing cohorts for four separate reports (Fuster et al., 2015; Fuster et al., 2014; Sanvisens et al., 2014; Rivas et al., 2013; Campos et al., 2011). Three studies were from Italy and one from Finland (Pavarin et al., 2017; Morandi et al., 2015; Saieva et al., 2012; Markkula et al., 2012). Table 1 presents an overview of each included study, summarizing the population, results and relevant conclusion and assessment of quality for this review.

The included studies were all without intervention. They were also all of cohort design, two of which were retrospective. Seven articles reported a median follow-up time ranging from 2.8 to 9.6 years (Fuster et al., 2015; Fuster et al., 2014; Sanvisens et al., 2014; Rivas et al., 2013; Campos et al., 2011; Pavarin et al., 2017; Saieva et al., 2012). The remaining articles had a follow-up time of 17 and eight years, respectively (Morandi et al., 2015; Markkula et al., 2012).

Most of the studies ($n = 6$) enrolled patients admitted to either a hospital or an alcohol center. Of these, four studies included patients admitted for detoxification at the same health care units during a

different span of time (Fuster et al., 2015; Fuster et al., 2014; Sanvisens et al., 2014; Rivas et al., 2013). Of the remaining three studies, Pavarin et al. (2017) included outpatients in their study population, whereas Morandi et al. (2015) included AUD patients, who received at least one treatment at the Alcohol Center of the Modena Local Health Unit. Lastly, Markkula et al. (2012) employed a dataset from a nationally representative sample of the Finnish population aged above 30 years.

Of the included studies, two were deemed as being of good quality (Pavarin et al., 2017; Saieva et al., 2012), one being of moderately good quality (Morandi et al., 2015) and one study with acceptable quality (Campos et al., 2011). The remaining studies were assessed to be of low quality (Fuster et al., 2015; Fuster et al., 2014; Sanvisens et al., 2014; Rivas et al., 2013; Markkula et al., 2012). None of the four separate reports, comprising patients admitted at the same two hospitals, were considered to be of acceptable quality.

3.1. Mortality

Measured mortality rate (MR), standardized mortality rate (SMR) or ratio, depending on what measure was reported in each article, was extracted. Where it was possible, the number of patients who passed away, as well as the age at death, was noted to help quantify the term “premature” death.

Saieva et al. (2012) included the biggest cohort, consisting of 2652 alcohol dependent patients. At the end of the study, 636 (28.9%) patients died, resulting in an SMR of 5.0 (95% CI: 4.6–5.4). The study found a mean age at death of 58.1 years \pm 13.0 with no difference between genders. Pavarin et al. (2017) counted 346 (14.7%) patients, who died at a mean age of 55.3 and 54.6 years for men and women, respectively. They calculated a SMR of 4.88 (95% CI: 4.39–5.42). Approximately the same age at death was found in Morandi et al. (2015), giving an age at death of 58.97 \pm 12.23 years. In this cohort of 2499 AUD patients, 435 (17.4%) deaths occurred, concluding an overall standardized mortality ratio of 5.53 (95% CI: 5.03–6.07). A higher standardized mortality ratio was found by Campos et al. (2011); 8.6 (95% CI: 7.7–9.7), focusing mainly on Alcohol Withdrawal Syndrome in 1265 patients, of which 289 (22.85%) died during follow up. Increased mortality was also found in Markkula et al. (2012), which reported a Hazard Ratio of 1.77 (95% CI: 1.12–2.80).

The separate reports, comprising patients from the same two hospitals, found increased mortality rates. While three of them reported MRs of approximately 3×100 p-y, Fuster et al. (2015) reported a crude mortality rate for AUD patients with no viral infection of 2.7×100 p-y (95% CI: 2.0–3.6).

Accordingly, all of the included studies showed increased mortality, thereby underlining the higher risk of premature deaths in AUD patients.

3.2. Cause of death

All included studies provided data about the causes of death according to the International Classification of Diseases. Studies of good, moderate and acceptable quality were chosen as a starting point to assess the common causes of death. Malignancy was reported as the primary cause of death in these studies (Campos et al., 2011; Pavarin et al., 2017; Morandi et al., 2015; Saieva et al., 2012). Saieva et al. (2012) and Morandi et al. (2015) reported 31.4% and 32.18% of deaths caused by malignant tumors, respectively. Pavarin et al. (2017) reported the primary cause of death as “neoplasm” (29.19%) in 101 AUD patients, of which at least 89 were reported as malignant. Campos et al. (2011), whose study was deemed as acceptable quality, reported 25% of the total deaths to be caused by malignancy, making it a leading cause of death in the study as well.

Despite the common primary cause of death in the aforementioned four articles, the second- and third most common cause of death differed in these studies. Saieva et al. (2012) and Campos et al. (2011)

Table 1
Characteristics of Individual Cohort Studies.

Author	Study design (done)	Population	Results	Conclusion	Quality of the study
Pavarini et al. (2017)	Cohort study with 17 years of follow-up after baseline. The average follow-up period was 6.5 years.	n = 2,363 All subjects diagnosed as alcoholics according to the DSM-III and DSM-IV. Mortality archives at the local health authority of residence were used to verify the cause of death using the ICD-10 codes.	346 patients (14.7% of the entire cohort) died during the follow-up period. Elevated and statistically significant SMRs were found in both genders.	Most common cause of death: neoplasm (29.19%) circulatory system (17.34%) digestive system (17.34%) traumatic episodes (9.54%) respiratory system (5.78%) Most common cause of death: malignant neoplasms (32.18%) cardiovascular diseases (21.15%) digestive system (16.78%) accidents and violence (12.18%) mental disorders (4.37%) Most common cause of death: liver-related (37.4 %) cancer-related (21.2%) cardiovascular (13.3%)	Good quality. The study is of good quality because of the high follow-up rate (97.8 %) and the study population (n = 2,363)
Morandi et al. (2015)	Retrospective cohort study with 30 years of follow-up after baseline. The median observation period was 7.04 years (4.11–10.34).	n = 2,499 All subjects had received at least one treatment for AUD at the Alcohol Centers of the Modena Local Health Unit. During the follow-up, diagnoses were recorded using the 9th and 10th revision of the International Classification of Diseases and Causes of Death.	435 deaths occurred during the 30-year follow-up period. A statistically significant excess of risk of mortality for all causes among the alcoholics was found, compared with the general population.		Moderately good quality. The study is by its nature, being a retrospective study, of low quality but the high follow-up rate (97.7 %) and the large study population elevate the study to be of moderately good quality.
Fuster et al. (2015)	Longitudinal cohort study. The median follow-up was 3.8 years (IQR: 1.8–6.5).	n = 909 The study included alcohol dependent patients admitted for detoxification at two hospital units. Causes of death were recoded according to the ICD-10 codes. At admission, laboratory parameters including systemic inflammation markers were recorded.	118 patients (12.9 % of the cohort) had died at the end of the study. The mortality rate was found to be 3.06×100 p-y (95% CI: 2.54–3.65). The presence of anemia in patients with alcohol dependence admitted for detoxification was associated with an elevated risk of mortality.		Low quality. Despite the wide range of patient-level data, the study has sparse focus on the cause of death in the study population which makes it of low quality.
Fuster et al. (2015)	Longitudinal cohort study with a median follow-up of 3.1 years (1.5–5.1).	n = 675 Patients admitted for treatment of AUD between 1999 and 2008 in two hospital detoxification units located in metropolitan Barcelona, Spain. Patients received a diagnosis of alcohol dependence according to DSM-IV. Causes of death were established with the ICD-10. Three categories of patients were established: (1) participants without viral infections (75.7%), (2) participants with HCV infection alone (14.7%), and (3) participants with HCV and HIV infection (8.1%). n = 5,023 Patients admitted for hospital detoxification at three tertiary care facilities located in Barcelona, Spain and its metropolitan area. Patients were classified into three categories: (1) heroin-, (2) cocaine- or (3) alcohol-dependent. 690 patients were categorized as alcohol dependent. DSM-III-R, DSM-VI and DSM-VI-TR were used as the main criteria for the referrals to drug treatment facilities.	78 patients (11.4%) had died at the end of the study. Crude mortality rate of patients without viral infections was 2.7×100 p-y (95% CI: 2.0–3.6). HCV infection increased the estimate of the HR for all-cause mortality according to viral infections: 1.32 among those with HCV infection and 3.86 for those with HCV/HIV coinfection. Younger patients ($= < 43$ years) with HCV infection were more likely to die than those without viral infections (HR: 3.1). HCV infection confers a worse prognosis of disease even in patients with shorter duration of alcohol exposure. 145 (21.0%) died in the alcohol-dependent group Alcohol-dependent patients had the highest mortality rate in the present study (3.3) followed by heroin (3.1) and cocaine (2.8).	Most common causes of death: Liver-related (32.4%) Cancer (18.7%) Cardiovascular (13.5%) Non-natural (12.2%) HIV/AIDS (8.1%)	Low quality. The study is of low quality due to its lack of external validity.
Sanvisens et al. (2014)	Longitudinal cohort study. The alcohol-dependent patients had a median follow-up of 4.8 (IQR: 3.1–7.8) years after admission for treatment.	n = 5,023 Patients admitted for hospital detoxification at three tertiary care facilities located in Barcelona, Spain and its metropolitan area. Patients were classified into three categories: (1) heroin-, (2) cocaine- or (3) alcohol-dependent. 690 patients were categorized as alcohol dependent. DSM-III-R, DSM-VI and DSM-VI-TR were used as the main criteria for the referrals to drug treatment facilities.		Most common causes of death in alcohol dependent patients: Liver (21.4%) Neoplasm (19.3%) Non-natural (15.9%) Cardiovascular (15.2%) HIV/AIDS (11.7%)	Low quality. Despite the long follow-up and an acceptable population size, the quality of the study is reduced to low quality due to no inclusion of secondary substance of abuse or systematic assessment of psychiatric comorbidity.

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Table 1 (continued)

Author	Study design (done)	Population	Results	Conclusion	Quality of the study
Rivas et al. (2013)	Cohort study. Median follow-up after discharge 3.1 (IQR: 1.5-5.1) years.	Causes of death was established in accordance with ICD-9 and ICD-10. n = 686 Patients with severe alcohol use disorder admitted for detoxification. Criteria for inclusion was a diagnosis of a substance-use disorder according to DSM -IV. Causes of death were established in accordance with the ICD-10 criteria.	78 patients had died by the end of the study. Overall mortality rate: 3.28×100 p-y, almost 20 times higher than the age-adjusted mortality of the general population.	Most common causes of death: Liver related (29.3%) Neoplasia (18.7%) Cardiovascular (16.0%) Non-natural (12.0%) Infectious (10.7%) Other (13.3%)	Low quality. Not having looked into psychiatric comorbidities increases risk of confounding and therefore reduces the quality of the study to low.
Saieva et al. (2012)	Cohort study. Median follow-up period was 9.6 years (IQR: 5.3-21.9).	n = 2,652 All patients reported a high CAGE test and have been diagnosed as alcoholics according to their status of alcohol dependence (ICD-9). Patients residing outside Tuscany (n = 149) and patients with incomplete or inaccurate demographic data (n = 225) were excluded Cause of death certificates were coded according to ICD-9.	636 patients (28.0%) died. Study showed a 5-fold increase in total mortality in comparison with the general population of the area.	Most common causes of death: Malignant tumors (31.4%) Digestive system (25.3%) Circulatory system (15.1%)	Good quality. Due to the large cohort size, the long term follow-up and the completeness of the retrieval of individual causes of death (follow-up was not available for only 6 patients), this study is of good quality.
Markkula et al. (2012)	Cohort study design with a follow-up period of eight years.	n = 6,372 Patients were from the 15 largest towns and 65 health care districts in Finland. 238 were diagnosed with alcohol use disorder. CIDI was used to diagnose psychiatric disorders using DSM-IV criteria. Causes of death were coded according to ICD-10.	21 (8.8%) of the AUD patients died during the follow-up period. Individuals in all three groups on mental disorders had a statistically significant risk of increased mortality (HR: 2.32-2.55). In AUD patients a HR of 1.77 (95% CI: 1.12-2.80) was reported. Only depressive and alcohol use disorders remained significant when controlling for psychiatric comorbidity and sociodemographic factors, health status and smoking. 289 (22.8%) patients died during the study period. Mortality in the patient cohort was higher than in the reference cohort. AWS was associated with an increased risk of mortality after adjusting for age, sex and smoking (adjusted HR: 12.7%). The age- and sex-standardized mortality ratio in patients with AWS was 8.6.	Most common causes of death in the alcohol use disorder patients: Other unnatural death (28.6%) Cardiovascular (28.1%) Tumour (18.6%) Suicide (14.0%) Other natural deaths (10.0%)	Low quality. This study is of low quality because of its small sample size and the unknown follow-up rate.
Campos et al. (2011)	Retrospective cohort design. Median follow-up period was 2.8 years (IQR: 0-10.08).	n = 1,265 Patients admitted to a single university hospital in the northwest of Spain with a final diagnosis of AWS. Study population included both patients who were admitted for AWS and patients who developed AWS during hospital admission. Causes of death were obtained according to ICD-9-CM. Reference cohort included 1,362 individuals from the general population in the same area.	Most common causes of death: Malignancy (25%) Liver disease (24%) Cardiovascular disease (21%) Respiratory disease (9%) Infection (5%) Neurological disease (3%)	Acceptable quality. Having a retrospective study design, different baseline characteristics in the two cohorts and lack of follow-up in the reference group (45.3%) reduces the quality of the study. However, the study did adjust for several confounders and limited the study to a specific population, which makes it of an acceptable quality.	

SMR: Standardized Mortality Rates.

HR: Hazard Ratio.

p-y: person-years.

IQR: Interquartile Range.

CAGE: test focusing on Cutting down, Annoyance by criticism, Guilty feeling, and Eye-openers.

CIDI: Composite International Diagnostic Interview.

AWS: Alcohol Withdrawal Syndrome.

found problems with the digestive system to be the second leading cause with 25.3% and 24% of the deaths, respectively. Liver disease was the main contribution to the ranking of the digestive system. This composition of liver disease being the main contributor to the “digestive system”-category applies to all the included studies reporting “digestive system” as a cause of death. Both Saieva et al. (2012) and Campos et al. (2011) found the circulatory system to account for third most common deaths in their cohorts with 15.1% and 21%, respectively.

In contrast, Morandi et al. (2015) noted circulatory system as the second leading cause of death, causing 21.15% of all deaths and the digestive system as the third most typical cause of death with 16.78% of all deaths. Pavarin et al. (2017) found the same number of deaths (17.34%) for both the circulatory and digestive system.

Markkula et al. (2012) reported “other unnatural death” as their leading cause of death, followed by problems with the cardiovascular system and neoplasia.

The four separate reports, comprising of patients admitted at the same two hospitals, found the primary cause of death to be liver-related.

4. Discussion

This review found increased mortality in AUD patients with the main causes of death being malignancy and problems related to the cardiovascular- and digestive system. We searched for causes of death in alcohol dependent persons when they die prematurely. In conducting this paper, it became clear that the evidence regarding our aim is not extensive, as we ended up with only nine studies after going through approximately 1200 studies. Furthermore, only four studies were of sufficient quality to strengthen the foundation of our conclusion; two “good quality”, one “moderately good quality” and one “acceptable quality”.

Since our aim was to find the cause of premature death in alcohol dependent people, we found it convenient to consider the mortality in the included cohorts. Increased mortality in AUD patients was found in all studies, though most of the studies cannot underline this sufficiently because of their low quality (Fuster et al., 2015; Fuster et al., 2014; Sanvisens et al., 2014; Rivas et al., 2013; Markkula et al., 2012). Five studies were deemed as low quality, four of which were studies enrolling patients at the same hospitals. Despite the patients being enrolled over a different course of time, we could not eliminate the possibility that the same patients could be included in several of these studies. Considering the possible overlap across the study cohorts, each study is at high risk of reporting the exact same mortality. Despite the potential bias, these four studies were assessed throughout the review process and contributed to the review conclusion. The low-quality studies reported on small sample sizes as evident in Markkula et al. (2012), which enrolled only 238 AUD patients with 21 deaths occurring during follow-up. Considering the small sample size, it is not sufficient to conclude on the increased mortality.

Nonetheless, the overall evidence showcasing increased mortality and thereby premature death in alcohol dependent patients has grown over time. The remaining studies were comprised of much larger cohorts and concluded significantly increased mortality as well. This is in line with what has previously been reported. Schwarzinger et al. (2017) reported in a large cohort study a threefold higher risk of death in AUD patients (Schwarzinger et al., 2017).

Saieva et al. (2012) was the only study to include a significant number of female patients (35.4%), showing higher SMR for women in comparison with the female general population than gender-specific SMRs for men. Nonetheless, women showed a significantly better survival rate in comparison with men several years after enrollment. The study does, however, point out that despite women being more vulnerable to the effects of alcohol and the differences in alcohol metabolism based on previous research, women are quicker to seek

treatment and are often referred to specific alcohol centers at first light symptoms. Morandi et al. (2015) concluded in his study that the hazard of dying was lower for the female gender, pointing out a gender difference as well. While addressing AUD as a general issue is important, it is even more relevant to dedicate more research on gender differences with regards to AUD.

The above-mentioned low-quality studies were also less valuable in regard to finding cause of death in AUD patients. The studies’ shortcomings, as explained above, were the primary reason for this. However, Saieva et al. (2012), which was the largest cohort study consisting of 2652 alcoholics with a median follow-up period of 9.6 years (IQR: 5.3–21.9), reported malignant tumors as the most common cause of death. Several large-sized population-based studies were consistent with this finding (Campos et al., 2011; Pavarin et al., 2017; Morandi et al., 2015). Furthermore, all the studies with sufficient quality reported cardiovascular- and digestive system as the other two most common causes of death. In a systematic review and meta-analysis, Roerecke and Rehm (2014) found the most common causes of death to be CVD, trauma, digestive diseases and cancer (Roerecke and Rehm, 2014). The order of these causes differed with regard to gender, CVD being the primary cause of death in men and trauma in women. Our review reported similar common causes of death, the main difference being the leading cause of death, which in our review was malignancy. This finding was unexpected as we, in relation to conventional knowledge of alcohol’s attribution to liver diseases, were expecting problems of the digestive system to be the main cause of death (WHO, 2015). A reason for the unexpected result could be the inclusion of recent studies. This calls for a shift in how to approach AUD patients in regard to both research and clinical practice. For future research in AUD patients, more attention should be shed on malignancy as a cause of death. This could be done through longer follow-up periods in cohort studies to detect different cases of malignancy. Furthermore, it encourages thorough research on the specific types of malignancy caused by AUD. As it pertains to clinical practice, our findings underline the importance of early screening of AUD patients, since detecting malignancy in early stages could be crucial to prolonging the life expectancy (WHO, 2016). To achieve these goals in the future, a more cohesive approach, with better coordination between psychiatric and somatic specialties, is needed in the treatment of these patients.

Several limitations were present in our review. First, the included studies were entirely restricted to the European countries, making our conclusion less globally representable. Moreover, with only one study from northern Europe and the rest of the studies from the Mediterranean, more caution is required with the generalizability of the results due to the different drinking-cultures within Europe. While Mediterranean drinking habits are characterized by large prevalence of daily drinkers consuming alcohol with meals, in the Nordic countries binge-drinking is more common (Shield et al., 2013). Second, only articles written in English were considered for inclusion, leaving out studies written in other languages. Third, most of the studies did not take aspects of the alcohol consumption into account. The ones that did, did not report the changes in patterns of alcohol consumption during follow-up, leaving out the possibility of detecting remissions, repeated alcohol treatment and inter-individual differences. This leads to the issue of how the majority of the included studies consisted of patients who had already sought help at an alcohol center or been admitted to a hospital at the time of inclusion. With these cohorts, our review is mostly describing severe cases of AUD, leading to an overestimation of the outcomes both in the included studies- and our review level. Fourth, the majority of each cohort in every study consisted predominantly of the male gender, with one study including 64% males while the rest enrolled approximately 80% men in their reports. While it is unsure what implication the gender difference might have on the conclusion, it is important to take this into consideration.

One of the inclusion criteria stated that patients enrolled in the included studies should be minimum 18 years of age. Two studies did,

however, report IQR ranging under 18 years with no further specification of the number of patients under that age-limit (Morandi et al., 2015; Saieva et al., 2012). After discussing the possible number of patients under 18 years in each study, and the impact it would have on our final outcomes, we decided to keep the articles as part of the review. While some patients might be younger than planned, our main focus was to find patients diagnosed with an AUD rather than a specific age-group. Dealing with sparse research on the AUD population, we found that this rather insufficient aspect of the articles did not validate exclusion. Fuster et al. (2015), whose aim was to analyze the impact of HCV infection on patients with AUD to better understand their synergistic effect on mortality, was also included. The reason for not excluding the study was primarily that the majority (75.7%) of the enrolled patients with AUD in this study were HCV-negative. Thus, the study met all the criteria in our review despite having a slightly different aim. Lastly, this review only included studies published within the last 10 years. It is possible that being this restrictive could have limited our ability to include more studies. However, in a recent retrospective cohort study, Schwarzingler et al. (2017) point out that evidence on cause-specific mortality was rather old. Therefore, the rationale of this systematic review was to corroborate previous findings in this research field based on most recent studies.

However, this review had important strengths. At the outset, we chose to narrow the inclusion criteria in an effort to minimize the grey areas of this literature field, thereby enhancing the accuracy of the included studies for our aim. For example, by having the criteria of being diagnosed according to a valid classification system, people with high alcohol intake, without being diagnosed as alcohol dependent, were excluded. In addition, the focus was on recent research published within the last 10 years, thereby excluding outdated studies. Furthermore, the majority of the included studies consisted of large cohorts. Using this approach, there was a reduction in the possibility of small studies having disproportionate influence in our review.

The findings of this systematic review indicate that the most common causes of death in AUD patients are malignancy, CVD and digestive system. Malignancy was reported as the most common cause of death across the studies. Similar causes of death were reported in a previous meta-analysis. Despite having included several large cohort studies, the overall quality was low. The lack of evidence with regard to our aim requires more convincing research in this field. If our review outcomes can be confirmed in future research, more focus on preventing the reported causes of death is needed for AUD patients.

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Contributors

All authors contributed to the design of this study. Ali M. Abdul Ghani and Edris Faiz were involved in data collection. All authors participated in manuscript preparation and have approved the final version of the manuscript.

Conflict of interest

No conflict declared.

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