Supplementary material:

**Opportunities to prevent alcoholic liver cirrhosis in high-risk populations:**

**A systematic review with meta-analysis**

Short title: Alcoholic cirrhosis in high-risk populations

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## **Background**

### **The natural history of alcoholic liver cirrhosis**

The histological observations of alcoholic liver disease can be grouped into three, often overlapping, stages: simple alcoholic steatosis, alcoholic steatohepatitis, and alcoholic liver cirrhosis (1–4).

Simple steatosis is a silent and potentially reversible state of alcoholic liver disease that develops in 80-90% of heavy drinkers (Supplementary figure 2) (3,5–7). Alcoholic steatohepatitis, which also frequently is clinically silent, may develop if heavy drinking continues, and is characterised by various degrees of inflammation and fibrosis (1). In severe instances, it manifests as the less common clinical syndrome of alcoholic hepatitis with a five-year mortality of approximately 50% (8,9).

Yet, the majority of patients present clinically with alcoholic liver cirrhosis (8). Most alcoholic liver cirrhosis patients (76% in Denmark) have developed one or more complications of ascites, variceal bleeding, or hepatic encephalopathy at the time of diagnosis (10). This indicates that liver cirrhosis without complications can be clinically silent as well.

In alcoholic liver cirrhosis, fibrosis is extensive and there are few functioning hepatocytes (1). The five-year mortality is 65% (8). In clinical samples, 20 years of heavy drinking preceded diagnosis in the majority of patients (3,11,12). Cessation of drinking before alcoholic liver cirrhosis is established will prevent disease progression in the majority of patients (13–15). Still, in the case of manifest alcoholic liver cirrhosis, alcohol abstinence is a strong predictor of survival (16), and even regeneration of liver cirrhosis to liver fibrosis has been observed after alcohol abstinence (17).

### **Alcohol amount and drinking pattern as risk factors of alcoholic cirrhosis in the general population**

Alcohol amount is related to risk of alcoholic liver cirrhosis in a dose-dependent manner with an increasing risk observed for increasing alcohol amount (18,19). Alcohol amount as low as 12-24 g per day in men and 12 g per day in women already increases risk for alcoholic liver cirrhosis mortality compared to lifetime abstention (relative risk of 1.6 [95%CI 1.4, 2.0] in men and 1.9 [95%CI 1.1, 3.1] in women) (18). However, alcoholic liver cirrhosis is rare among light and moderate drinkers. The observed prevalence of alcoholic liver cirrhosis morbidity in the Dionysos study was 0.15%, 1%, 2.3%, 4.9%, and 5.7%, in drinkers of <30, 31-60, 61-90, 91-120, and >120 g alcohol per day, respectively (20). And the observed mortality of alcoholic liver cirrhosis is even lower; 0.003-0.16%, 0.05-0.08%, 0.09%, and 0.17% per person-year in drinkers of < 24, 24-48, 48-60, and > 72 g alcohol per day (21,22).

There is some evidence of a threshold-effect at around 80-100 g alcohol per day in men and 50-70 g per day in women, beyond which increasing consumption no longer increases risk further (18,19,23).

Current alcohol amount is more strongly related to risk of alcoholic liver cirrhosis than previous amount (19). Moreover, regarding the pattern of drinking in current drinkers, *daily* drinking in men compared to drinking less frequently, is associated with an increased risk of alcoholic liver cirrhosis even when alcohol amount is taken into account (19,23–25). Drinking outside meal-times, instead of meal-related drinking, was associated with an increased risk in the Dionysos study (26). It is possible that binge drinking (drinking at least four or five units alcohol on one occasion) and the type of alcohol ingested (wine, beer, liquor, homebrewed) are also independent risk factors of alcoholic liver cirrhosis, but this remains unknown (19,27,28).

### **The main preventive interventions for alcohol-related harm in the general and high-risk population**

Interventions targeting individuals of high risk have been assessed in randomized controlled trials (Figure 1). The results indicate that screening and brief/extended interventions can reduce alcohol consumption, alcohol-related disease, and mortality in male heavy drinkers (Supplementary table 4)(29–32). Moreover, cognitive-behavioural therapies, glutamate inhibitors, and opiate antagonists in combination with psychological therapy, have proved to be effective treatments for alcohol dependence (33–36).

The effects of interventions targeting the general population in real-life settings have been assessed in longitudinal observational studies and in modelling studies. Results from such studies indicate that minimum unit pricing for alcohol (37–39), alcohol taxation (40–42), and to a lesser extent limiting alcohol availability (43), have reduced alcohol consumption and alcohol-related harm. Minimum unit pricing on alcohol affects heavy drinkers more than moderate or light drinkers (37). There is limited evidence for the effects of restricting advertising (44–46), health education policies in schools (47), public information campaigns (48), and sensible drinking guidelines (49).

## Supplementary table 1.Bias assessment according to the Newcastle-Ottawa Scale (50) of included observational studies on incidence of alcoholic liver cirrhosis in alcohol-problem cohorts.

|  |  |  |  |
| --- | --- | --- | --- |
|  | *Selection#*  *(A maximum of 4 stars, low risk of bias:* ≥ *3 stars)* | *Comparability#* | *Outcome*  *(A maximum of 3 stars, low risk of bias:* ≥ *2 stars)* |
| *Hospital patients with an alcohol problem diagnosis* | | | |
| Piette  1998  USA | Low risk (\*\*\*\*)  Natiowide sample, diagnostic codes, outcome excluded at study start. | Not relevant | Low risk (\*\*)  Record linkage only, follow-up of 11 years, 95% completeness of follow-up data on cohort |
| Askgaard  2016  Denmark | Low risk (\*\*\*\*)  Nationwide sample, diagnostic codes, outcome excluded at study start. | Not relevant | Low risk (\*\*)  Record linkage only, follow-up of 11 years, 99% completeness of follow-up data on cohort |
| *Heavy drinkers referred to an internal medicine department* | | | |
| Sørensen  1984  Denmark | Low risk (\*\*\*)  Somewhat representative - one hospital, structured interview, outcome excluded at study start. | Not relevant | Low risk (\*\*)  Record linkage on those who were dead, blinding of outcome of earlier liver biopsi, follow-up 12 years, 78% were followed up |
| Marbet  1987  Switzerland | Low risk (\*\*\*)  Somewhat representative - one hospital, structured interview or history by family, outcome excluded at study start. | Not relevant | Low risk (\*\*)  Blind assessment of outcome, follow-up 8 years, 61% were followed up |
| Motoo  1992  Japan | High risk (\*\*)  Selected group, medical chart review for alcohol history, outcome excluded at study start | Not relevant | Unclear/high risk (\*)  Assessment of outcome not described, follow-up 8 years, cohort members defined according to follow-up biopsy availability |
| Teli  1995  UK | High risk (\*\*)  Somewhat representative - one hospital, medical chart review and interview for alcohol history, outcome excluded at study start. | Not relevant | Low risk (\*\*)  Biopsy, medical chart review, and causes of death register. Follow-up 11 years. Follow-up on 44% patients – however, these were handlet as outcome negative, which could underestimate the cirrhosis incidence. |
| *Patients seeking treatment for alcohol problems (specialized treatment center or psychiatric department)* | | | |
| Polich  1981  USA | Low/unclear risk (\*\*)  Somewhat representative – a big sample who was admitted from alcoholism treatment. Unclear if outcome was excluded at study start. | Not relevant | High risk (\*)  Underlying course of death from register, validating not obvious alcohol-related deaths by information with local informants |
| Lambie  1983  New Zealand | Low/unclear risk (\*\*\*)  Somewhat representative – large sample from one alcohol clinic, unclear if outcome was excluded at study start. | Not relevant | High risk (\*)  Record linkage, only underlying cause of death. Follow-up 2 years – too low. Complete follow-up – but cases may be missed. |
| Berglund  1984  Sweden | Low/unclear risk (\*\*\*)  Somewhat representative – large sample from one psychiatric department by diagnostic codes, unclear if outcome was excluded at study start. | Not relevant | High risk (\*)  Underlying cause in cause of death register. Follow-up 18 years. Nearly complete follow-up – but cases may be missed. |
| Higuchi  1987  Japan | Low risk (\*\*\*)  Somewhat representative – large sample from one alcohol clinic, outcome was not an exclusion criterion at study start. | Not relevant | High risk (\*)  Underlying cause in cause of death register and hospital records. Follow-up 7 years. |
| Ågren  Sweden  1987 | Low/unclear risk (\*\*\*)  Somewhat representative – large sample from one alcohol centre by diagnostic codes, unclear if outcome was excluded at study start. | Not relevant | Low risk (\*\*\*)  All causes of death considered on death certificate and 75% validated with necropsy report and medical chart review. Nearly complete follow-up. Follow-up 6 years. |
| Lindberg  Sweden  1988 | Low risk (\*\*\*)  Somewhat representative – large sample from one alcohol centre/hospital by diagnostic codes,  outcome was not an exclusion cruterion at study start. | Not relevant | High risk (\*)  Record linkage, only underlying cause of death. Follow-up 7 years. Complete follow-up is expected. |
| Ohara  1989  Japan | High risk (\*)  Not representative – only including those 25% with known causes of death, outcome was not an exclusion cruterion at study start. | Not relevant | High/unclear risk (\*)  Death certificates. Unclear if all causes of death were considered. Follow-up 6 years. |
| Lewis  1995  USA | High risk (\*)  Not representative – small sample from two hospitals. outcome was not an exclusion cruterion at study start, but was measured so possible to distingush new cases. | Not relevant | Low/unclear risk (\*\*\*)  Interview with relatives and death certificates were retrived. Unclear if all causes of death were considered. Follow-up 20 years. |
| Denison  1997  Sweden | Low risk (\*\*\*)  Somewhat representative – large sample from one detoxification ward by diagnostic codes,  outcome was not an exclusion cruterion at study start. | Not relevant | High/unclear risk (\*)  Death certificates. Unclear if all causes of death were considered.  Follow-up 4 years – too low. |
| Noda  2001  Japan | Low risk (\*\*\*)  Somewhat representative – sample of alcohol dependent treated as inpatients or outpatients in one city by use of medical records.  Outcome was not an exclusion cruterion at study start. | Not relevant | High risk (\*)  Death certificates using the underlying cause of death. Follow-up 8 years. |
| Kamper-Jørgensen  2004  Denmark | Low risk (\*\*\*\*)  Somewhat representative – very large cohort from one alcohol treatment center. Outcome was an exclusion cruterion at study start | Not relevant | High/unclear risk (\*)  Death certificates with nearly complete data. Unclear if all causes of death were considered. Follow-up 14 years. |
| Costello  2006  USA | Low risk (\*\*\*)  Representative – large cohort from one alcohol treatment center. Outcome was not an exclusion criterion at study start. | Not relevant | High/unclear risk (\*)  Death certificates using the underlying cause. In case of missing – using hospital records and autopsy reports. Follow-up 33 years. |
| Haver  2009  Sweden | High risk (\*\*)  Selected group of high functioning women receiving first treatment for alcohol problems at one center.  Outcome was not an exclusion criterion at study start | Not relevant | High/unclear risk (\*\*)  Death certificates with complete follow-up. Unclear if all causes of death were considered. Follow-up 20 years. |
| Saieva  2012  Italy | Low risk (\*\*\*)  Somewhat representative – large cohort from one alcohol treatment center by medical records. Outcome was not an exclusion cruterion at study start. | Not relevant | High/unclear risk (\*)  Death certificates with nearly complete follow-up. Unclear if all causes of death were considered.  Follow-up 10 years. |
| Park  2013  Korea | Low risk (\*\*\*)  Somewhat representative – large cohort from one psychiatric hospital department by medical records with mainly alcohol problems. Outcome was not an exclusion cruterion at study start | Not relevant | High/unclear risk (\*)  Cause of death register with nearly complete follow-up. Unclear if all causes of death were considered.  Follow-up 6 years. |
| Rivas  2013  Spain | Low risk (\*\*\*)  Somewhat representative – large cohort from two hospitals by diagnostic codes. Outcome was not an exclusion cruterion at study start | Not relevant | High/unclear risk (\*)  Death certificates. Unclear if all causes of death were considered. Follow-up 3 years – too low. |
| Morandi  2015  Italy | Low risk (\*\*\*)  Somewhat representative – large cohort from one alcohol treatment center by diagnostic codes. Outcome was not an exclusion cruterion at study start | Not relevant | High/unclear risk (\*\*)  Cause of death register with nearly complete follow-up. Unclear if all causes of death were considered. Follow-up 7 years. |

#The selection of non-exposed as well as comparability of study controls in the studies was not relevant to consider as bias in this systematic review because only incidence in the whole cohort was measured.

## Supplementary table 2. Bias assessment according to Hoy et al. 2012, Journal of Clinical Epidemiology (51), of included observational studies on the alcohol amount consumed by alcoholic liver cirrhosis patients.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| First author  Year  Country | External validity | | | | Internal validity | | | | | | |
| Represen-tativeness of national population? | Represen-tativeness of target population? | Sample selection? | Non-response bias? | Direct data collection from subjects? | Acceptable case definition? | Validity and reliability of parameter instrument? | Same mode of data collection for all subjects? | Length of shortest prevalence period appropriate? | Numerator and denominator appropriate? | Summary |
| Norton  1987  Australia | High risk  (only 26 women from 8 hospitals in Sydney) | Low risk  (all who were first-time admitted) | Low risk  (included 91% of all who were first-time admitted) | Low risk  (79% participation rate) | Low risk (yes by interview and medical chart) | Low risk  (histology, clinical, scan and viral hepatitis excluded) | Unclear risk  (not validated questionnaire) | Low risk  (yes) | Low risk (yes – alcohol prior to admission) | Low risk  (yes) | Low risk |
| Sarin  1988  India | High risk  (attending one department) | Low risk  (all who attended the department and had been drinking 5 years or more) | Low risk (included all who attended the department) | Low risk (100% participation rate) | Low risk (yes interview with the patient and a relative in 86% of cases) | Low risk (based on histology and using the International Liver Group Criteria) | Unclear  (not validated questionnaire, but presence of a relative) | Low risk  (yes) | Low risk (lifetime alcohol consumption) | Low risk  (yes) | Low risk |
| Parrish  1991  USA | Low risk  (random sampling of all dead) | Unclear risk  (not stated) | Low risk (random using all causes of death on the certificate) | Low risk (response rate from next of kin 89%) | High risk (interview of relatives only) | Unclear risk (not described) | Unclear  (not described validation of interview) | Low risk  (yes) | Low risk (lifetime alcohol consumption) | High risk  (inappropriate categories of alc consumption) | High/unclear risk |
| Batey  1992  Australia | High risk  (sample of men from two hospitals) | Low risk  (all who were first-time admitted were approached) | Low risk  (all who were first-time admitted were approached) | Unclear/high risk  (only including those capable of interview) | Low risk  (yes by interview) | Low risk  (histology, clinical, scan and viral hepatitis excluded) | Low/unclear risk  (not described validation of interview, however the same research assistant undertook all interviews) | Low risk  (yes) | Low risk (lifetime alcohol consumption) | Low risk  (yes) | Low risk |
| Bellentani  1997  Italy | Low risk  (participants in a population-based study of liver disease prevalence) | Low risk  (all invited) | Low risk  (all in the community were invited) | High risk (participation rate overall was 69%, however, ill cirrhosis patients are expected to be underrepresented) | Low risk  (yes, by questionnaire) | Low risk (histology and viral hepatitis excluded) | Low risk (validated frequency questionnaire) | Low risk  (yes) | Low risk (current consumption) | Low risk  (yes) | Low risk |
| Nakamura  2004  Japan | High risk  (those attending one Alcohol treatment center) | Low risk  (all who were admitted were approached) | Low risk (included all who attended the department) | High risk (participation rate 16%) | Low risk  (yes by interview) | Low risk (Child Pugh scala and viral hepatitis excluded) | Unclear risk  (not described validation of interview) | Low risk  (yes) | Low risk (lifetime alcohol consumption) | Low risk  (yes) | Low risk |
| Aparisi  2008  Spain | High risk  (attending one department) | Low risk  (all first-time referred were approached) | Low risk (included nearly all who attended the department) | Unclear risk (not described) | Unclear risk (not described) | Low risk (histology and viral hepatitis excluded) | Unclear risk  (not described) | Low risk  (yes) | Low risk (yes – alcohol prior to admission) | Low risk  (yes) | Low/unclear risk |
| Stroffolini  2010  Italy | Low risk (referred to 9 units across Italy) | Low risk  (all first-time referred were approached) | Low risk (included all who attended the departments) | Low/unclear risk  (not described) | Low risk  (yes, by questionnaire) | Low risk (liver biopsy or in the presence of  clinical, biochemical and ultrasound signs) | Unclear risk  (not described validation of questionnaire) | Low risk  (yes) | Low risk (yes – alcohol prior to admission) | Low risk  (yes) | Low risk |
| Alvarez  2011  Spain | High risk  (attending one department) | Low risk  (all first-time referred were approached) | Low risk (included nearky all who attended the department) | Low risk  (83% were included) | Unclear risk  (not described) | Low risk (histology and viral hepatitis excluded) | Unclear risk  (not described) | Low risk  (yes) | Low risk (yes – alcohol prior to admission) | Low risk  (yes) | Low risk |
| Horie  2012  Japan | Low risk  (nationwide survey) | Low risk  (all major hospital institutions were asked for participants) | Unclear risk (not described) | Low/unclear risk  (not described) | Unclear risk  (not described) | Low risk  (according to the Japan Etiology of Liver Cirrhosis Study Group) | Unclear risk  (not described validation) | Low risk  (yes) | Low risk (yes – alcohol prior to admission) | Low risk  (yes) | Low/unclear risk |
| Xie  2013  China | High risk  (one hospital) | Low risk  (all attendees identified by medical records) | Low risk  (all included) | Low risk  (all included) | Low risk  (discharge records) | Low risk (exclusion of vital and other causes of liver disease) | Unclear risk  (not described validation) | Low risk  (yes) | Low risk (current alcohol consumption) | Low risk  (yes) | Low risk |
| Ray  2014  India | High risk (attending one department) | Unclear risk  (not described) | Unclear risk  (not described) | Unclear risk  (not described) | Unclear risk  (not described) | Low risk (histology and exclusion of non-alcohol related causes) | Unclear risk  (not described) | Unclear risk  (not described) | Low risk (lifetime alcohol consumption) | Low risk  (yes) | Low/Unclear risk |

## Supplementary table 3. Bias assessment according to Hoy et al. 2012, Journal of Clinical Epidemiology (51), of included observational studies on alcohol-related healthcare contacts prior to alcoholic liver cirrhosis diagnosis.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| First author  Year  Country | External validity | | | | Internal validity | | | | | | |
| Represen-tativeness of national population? | Representativeness of target population? | Sample selection? | Non-response bias? | Direct data collection from subjects? | Acceptable case definition? | Validity and reliability of parameter instrument? | Same mode of data collection for all subjects? | Length of shortest prevalence period appropriate? | Numerator and denominator appropriate? | Summary |
| *Previous healthcare contacts with obvious alcohol problems* | | | | | | | | | | | |
| Otete  2015a\*  UK | Low risk  (Nationwide primary care and hospital register) | Low risk  (yes, all who had a first diagnosis of cirrhosis) | Low risk (all included) | Low risk  (register-based) | Low risk (data obtained from register) | Low risk (yes read codes for harmful drinking in general practice) | Unclear  (not validated – likely underestimation) | Low risk (yes) | Low risk  (6 years) | Low risk (yes) | Low risk |
| Askgaard  2017  Denmark | Low risk  (Nationwide cohort) | Low risk  (all seen at the hospital in Denmark) | Low risk (all included) | Low risk  (register-based) | Low risk (data obtained from register) | Low risk (diagnostic codes for alcohol problems) | Low risk (although some underestimation is likely) | Low risk (yes) | Low risk (10 years) | Low risk (yes) | Low risk |
| *Previous healthcare contacts with conditions that may be alcohol-related* | | | | | | | | | | | |
| Verril  2006  UK | High risk  (One hospital) | Low risk  (all patients with histology and medical history of alcoholic liver disease) | High risk (not including those without liver biopsy) | Low risk  (medical chart review) | Low risk (medical chart) | Low risk (chart notes indicating alcohol-related disease) | High risk (underestimation likely since not information from other hospitals) | Low risk (yes) | Low risk  (7-10 years) | Low risk  (yes) | Low risk |
| Otete  2015b\*  UK | Low risk  (Nationwide primary care and hospital register) | Low risk  (yes, all who had a first diagnosis of cirrhosis) | Low risk (all included) | Low risk  (register-based) | Low risk (data obtained from register) | Low risk (diagnoses indicating alcohol-related disease) | Unclear risk  (not validated diagnoses of injuries, cancer, heart disease etc.) | Low risk (yes) | Low risk  (6 years) | Low risk  (yes) | Low risk |
| *Previous healthcare contacts with any unspecified health problem* | | | | | | | | | | | |
| Verril  2006  UK | High risk  (One hospital) | High risk  (only patients capable of interview) | Unclear risk  (not described) | High risk  (only patients capable of interview) | Low risk (interview) | Low risk | Unclear risk (recall bias) | Low risk (yes) | Low risk  (5 years) | Low risk  (yes) | Low risk |
| Otete  2015a\*  UK | Low risk  (Nationwide primary care and hospital register) | Low risk  (all who had a first diagnosis of cirrhosis) | Low risk (all included) | Low risk  (register-based) | Low risk (data obtained from register) | Low risk (all contacts assessed) | Low risk  (health contacts in primary care) | Low risk (yes) | Low risk  (6 years) | Low risk  (yes) | Low risk |

\*Otete 2015a and 2015b are two studies describing the same study population. For references see Table 3 in the original paper.

## Supplementary table 4. The main preventive interventions for alcohol-related harm in the general and high-risk population. Adapted from Anderson et al., Lancet 2009 (52).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Intervention | Target population | Evidence | Effect | Recommended by authorities |
| *Preventive interventions targeting high-risk populations* | | | | |
| Screening and brief/extended intervention | Hazardous or harmful drinkers | Primary care(29)  Hospital wards(30,31)  Emergency setting(32) | Reduced consumed alcohol amount (NNT = 9), mortality, and alcohol-related harm. No clear evidence for women. | NICE(53)  OECD(54)  WHO(55) |
| Cognitive-behavioural therapies | Alcohol dependent | (56) | Increased abstinence at 1 year | NICE(33)  OECD(54) |
| Glutamate inhibitor in combination with psychological therapies | Alcohol dependent | (34,35) | Increased abstinence at 1 year (NNT = 9) | NICE(33)  OECD(54) |
| Opiate antagonists in combination with psychological therapies | Alcohol dependent | (36) | Reduced drinking at 3 months (NNT = 9) | NICE(33)  OECD(54) |
| *Preventive interventions targeting the general population* | | | | |
| Minimum unit price for alcohol | All | (37,38) | Reduced alcohol amount; harmful drinkers most affected. | NICE(53)  OECD(54)  WHO(55) |
| Alcohol taxation | All | (40,41) | Reduced alcohol amount. Reduced acute and chronic alcohol-related harm | OECD(54)  WHO(55) |
| Limiting alcohol availability - reducing outlet density and days and hours of sale | All | (43) | Reduced binge-drinking and mean alcohol amount. Reduced alcohol-related harm. | NICE(53)  OECD(54)  WHO(55) |
| Alcohol advertising restrictions | All | (44–46) | Indirect evidence: Advertising increase consumed alcohol amount, in all drinkers and heavy drinkers.Young people and children most affected. | NICE(53)  OECD(54)  WHO(55) |
| Health education policies in schools | Youngsters | (47) | No prolonged effect on consumed alcohol amount, some increased knowledge. | OECD(54)  WHO(55) |
| Public information campaigns | All | (48) | Sparsely studied. No recognised effect. | OECD(54)  WHO(55) |
| Sensible drinking guidelines | All | (49) | No scientifically-published assessment | WHO(55) |

Abbrevations: NNT: Number needed to treat; NICE: The National Institute of Care and Excellence**;** OECD: The Organisation for Economic Co-operation and Development; WHO: World Health Organization

Supplementary figure 1. Forest plots of the proportion of alcoholic liver cirrhosis patients drinking a) <80 g alcohol per day, b) 80-200 g alcohol per day, and c) >110 g alcohol per day. The size of squares for each study represents the weight used in the random-effects model.

a)

b)

c)

Supplementary figure 2. The natural history of alcoholic liver cirrhosis. Prevalence of histological stages in relation to years of continuous heavy drinking. Abstinence increase the likelihood of liver regeneration (3,5,15)

## References

1. Lefkowitch JH. Morphology of alcoholic liver disease. Clin. Liver Dis. 2005;9:37–53.

2. O’Shea RS, Dasarathy S, McCullough AJ. Alcoholic liver disease. Am. J. Gastroenterol. 2010;105:14–32; quiz 33.

3. Naveau S, Giraud V, Borotto E, *et al.* Excess weight risk factor for alcoholic liver disease. Hepatology 1997;25:108–11.

4. Masarone M, Rosato V, Dallio M, *et al.* Epidemiology and Natural History of Alcoholic Liver Disease [Internet]. Rev. Recent Clin. Trials 2016;44:167–174.Available from: isi:000082782800002

5. Lieber CS, Jones DP, Decarli LM. Effects of Prolonged Ethanol Intake: Production of Fatty Liver Despite Adequate Diets. J. Clin. Invest. 1965;44:1009–1021.

6. Mathurin P, Beuzin F, Louvet A, *et al.* Fibrosis progression occurs in a subgroup of heavy drinkers with typical histological features. Aliment. Pharmacol. Ther. 2007;25:1047–1054.

7. Adachi M, Brenner DA. Clinical syndromes of alcoholic liver disease [Internet]. Dig. Dis. 2006;23:255–263.Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-33644652173&partnerID=40&md5=ce055c152c42c9e2a62af5f47ed920b9

8. Deleuran T, Vilstrup H, Becker U, *et al.* Epidemiology of Alcoholic Liver Disease in Denmark 2006-2011: A Population-Based Study [Internet]. Alcohol Alcohol. 2015;50:352–357.Available from: http://www.alcalc.oxfordjournals.org/cgi/doi/10.1093/alcalc/agv003

9. Lucey MR, Mathurin P. Alcoholic Hepatitis. NEJM 2009;56:2758–69.

10. Jepsen P, Ott P, Andersen PK, *et al.* Clinical course of alcoholic liver cirrhosis: A Danish population-based cohort study. Hepatology 2010;51:1675–1682.

11. Nakamura Y, Kobayashi Y, Ishikawa A, *et al.* Severe chronic pancreatitis and severe liver cirrhosis have different frequencies and are independent risk factors in male Japanese alcoholics. J. Gastroenterol. 2004;39:879–887.

12. Barrio E, Tomé S, Rodríguez I, *et al.* Liver disease in heavy drinkers with and without alcohol withdrawal syndrome. [Internet]. Alcohol. Clin. Exp. Res. 2004;28:131–6.[cited 2013 Dec 13] Available from: http://www.ncbi.nlm.nih.gov/pubmed/14745311

13. Marbet UA, Bianchi L, Meury U, *et al.* Long-term histological evaluation of the natural history and prognostic factors of alcoholic liver disease. J. Hepatol. 1987;4:364–372.

14. Colman JC, Morgan MY, Scheuer PJ, *et al.* Treatment of alcohol-related liver disease with (+)-cyanidanol-3: a randomised double-blind trial. [Internet]. Gut 1980;21:965–969.Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1419277&tool=pmcentrez&rendertype=abstract

15. Teli MR, Day CP, James OFW, *et al.* Determinants of progression to cirrhosis or fibrosis in pure alcoholic fatty liver. Lancet 1995;346:987–990.

16. Verrill C, Markham H, Templeton A, *et al.* Alcohol-related cirrhosis--early abstinence is a key factor in prognosis, even in the most severe cases. [Internet]. Addiction 2009;104:768–74.[cited 2014 Dec 1] Available from: http://www.ncbi.nlm.nih.gov/pubmed/19344445

17. Takahashi H, Shigefuku R, Maeyama S, *et al.* Cirrhosis improvement to alcoholic liver fibrosis after passive abstinence [Internet]. Case Reports 2014;2014:bcr2013201618-bcr2013201618.Available from: http://casereports.bmj.com/cgi/doi/10.1136/bcr-2013-201618

18. 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;29:437–445.

19. Askgaard G, Grønbæk M, Kjær MS, *et al.* Alcohol drinking pattern and risk of alcoholic liver cirrhosis: A prospective cohort study. [Internet]. J. Hepatol. 2015;62:1061–7.Available from: http://www.sciencedirect.com/science/article/pii/S0168827814009234

20. Bellentani S, Tiribelli C. The spectrum of liver disease in the general population: Lesson from the dionysos study. J. Hepatol. 2001;35:531–537.

21. Boffetta P, Garfinkel L. Alcohol drinking and mortality among men enrolled in an American Cancer Society prospective study. Epidemiology 1990;1:342–348.

22. Eliasen M, Becker U, Grønbæk M, *et al.* Alcohol-attributable and alcohol-preventable mortality in Denmark: an analysis of which intake levels contribute most to alcohol’s harmful and beneficial effects. [Internet]. Eur. J. Epidemiol. 2014;29:15–26.[cited 2014 Aug 5] Available from: http://www.ncbi.nlm.nih.gov/pubmed/24129661

23. Kamper-Jørgensen M, Grønbaek M, Tolstrup J, *et al.* Alcohol and cirrhosis: dose--response or threshold effect? J. Hepatol. 2004;41:25–30.

24. Zakhari S, Li TK. Determinants of alcohol use and abuse: impact of quantity and frequency patterns on liver disease. Hepatology 2007;46:2032–2039.

25. Hatton J, Burton A, Nash H, *et al.* Drinking patterns, dependency and life-time drinking history in alcohol-related liver disease. Addiction 2009;104:587–92.

26. Bellentani S, Saccoccio G, Costa G, *et al.* Drinking habits as cofactors of risk for alcohol induced liver damage. Gut 1997;41:845–850.

27. Mathurin P, Bataller R. Trends in the management and burden of alcoholic liver disease [Internet]. J. Hepatol. 2015;62:S38–S46.Available from: http://linkinghub.elsevier.com/retrieve/pii/S016882781500166X

28. European Association for the Study of Alcoholic Liver Disease. EASL Clinical Practical Guidelines: Management of Alcoholic Liver Disease. J. Hepatol. 2012;57:399–420.

29. O’Donnell A, Anderson P, Newbury-Birch D, *et al.* The impact of brief alcohol interventions in primary healthcare: A systematic review of reviews. Alcohol Alcohol. 2014;49:66–78.

30. Mdege ND, Fayter D, Watson JM, *et al.* Interventions for reducing alcohol consumption among general hospital inpatient heavy alcohol users: A systematic review [Internet]. Drug Alcohol Depend. 2013;131:1–22.Available from: http://dx.doi.org/10.1016/j.drugalcdep.2013.01.023

31. Mcqueen J, Te H, Allan L, *et al.* Brief interventions for heavy alcohol users admitted to general hospital wards ( Review ). Cochrane Database Syst Rev. 2011;Aug 10

32. Nilsen P, Baird J, Mello MJ, *et al.* A systematic review of emergency care brief alcohol interventions for injury patients. J. Subst. Abuse Treat. 2008;35:184–201.

33. National Institute for Health and Care Excellence. Alcohol dependence and harmful alcohol use: full guideline. 2011.

34. Rösner S, Leucht S, Lehert P, *et al.* Acamprosate for alcohol dependence (Review). Cochrane Libr. 2011;

35. Mann K, Lehert P, Morgan MY. The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis. Alcohol. Clin. Exp. Res. 2004;28:51–63.

36. Rösner S, Leucht S, Vecchi S, *et al.* Opioid antagonists for alcohol dependence (Review). Cochrane Libr. 2010;

37. Holmes J, Meng Y, Meier PS, *et al.* Effects of minimum unit pricing for alcohol on different income and socioeconomic groups: A modelling study [Internet]. Lancet 2014;383:1655–1664.Available from: http://dx.doi.org/10.1016/S0140-6736(13)62417-4

38. Purshouse RC, Meier PS, Brennan A, *et al.* Estimated effect of alcohol pricing policies on health and health economic outcomes in England: an epidemiological model. Lancet 2010;375:1355–1364.

39. Zhao J, Stockwell T, Martin G, *et al.* The relationship between minimum alcohol prices, outlet densities and alcohol-attributable deaths in British Columbia, 2002-09. Addiction 2013;108:1059–1069.

40. Wagenaar AC, Tobler AL, Komro KA. Effects of alcohol tax and price policies on morbidity and mortality: A systematic review. Am. J. Public Health 2010;100:2270–2278.

41. Wagenaar AC, Salois MJ, Komro KA. Effects of beverage alcohol price and tax levels on drinking: A meta-analysis of 1003 estimates from 112 studies. Addiction 2009;104:179–190.

42. Wagenaar AC, Maldonado-Molina MM, Wagenaar BH. Effects of alcohol tax increases on alcohol-related disease mortality in Alaska: Time-series analyses from 1976 to 2004. Am. J. Public Health 2009;99:1464–1470.

43. Campbell CA, Hahn RA, Elder R, *et al.* The Effectiveness of Limiting Alcohol Outlet Density As a Means of Reducing Excessive Alcohol Consumption and Alcohol-Related Harms [Internet]. Am. J. Prev. Med. 2009;37:556–569.Available from: http://dx.doi.org/10.1016/j.amepre.2009.09.028

44. Anderson P, Bruijn A De, Angus K, *et al.* Special issue: The message and the media: Impact of alcohol advertising and media exposure on adolescent alcohol use: A systematic review of longitudinal studies. Alcohol Alcohol. 2009;44:229–243.

45. Gallet CA. The demand for alcohol: A meta-analysis of elasticities. Aust. J. Agric. Resour. Econ. 2007;51:121–135.

46. Saffer H, Dave D, Grossman M. A Behavioral Economic Model of Alcohol Advertising and Price [Internet]. Health Econ. 2016;25:816–828.Available from: http://www.ncbi.nlm.nih.gov/pubmed/25919364%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4889554%5Cnhttp://doi.wiley.com/10.1002/hec.3186

47. Jones L, James M, Jefferson T, *et al.* A review of the effectiveness and cost-effectiveness of interventions delivered in primary and secondary schools to prevent and / or reduce alcohol use by young people under 18 years old EXECUTIVE SUMMARY. 2007;1–21.

48. Giesbrecht N. Reducing alcohol-related damage in populations: Rethinking the roles of education and persuasion interventions. Addiction 2007;102:1345–1349.

49. Anderson P, Chisholm D, Fuhr DC. Effectiveness and cost-effectiveness of policies and programmes to reduce the harm caused by alcohol. Lancet 2009;373:2234–2246.

50. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. :http://www.ohri.ca/programs/clinical\_epidemiology/.

51. Hoy D, Brooks P, Woolf A, *et al.* Assessing risk of bias in prevalence studies: Modification of an existing tool and evidence of interrater agreement [Internet]. J. Clin. Epidemiol. 2012;65:934–939.Available from: http://dx.doi.org/10.1016/j.jclinepi.2011.11.014

52. Anderson P, Chisholm D, Fuhr DC. Effectiveness and cost-effectiveness of policies and programmes to reduce the harm caused by alcohol. Lancet 2009;373:2234–2246.

53. National Institute for Health and Care Excellence. Alcohol-use disorders: prevention. NICE Clin. Guidel. 2010;

54. OECD. Tackling Harmful Alcohol Use: Economic and Public Health Policy [Internet]. OECD Publishing; 2015. Available from: http://www.oecd-ilibrary.org/social-issues-migration-health/tackling-harmful-alcohol-use\_9789264181069-en

55. World Health Organization. Globbal strategy to reduce the harmful use of alcohol [Internet]. World Heal. Organ. 2010;44.Available from: www.who.int/substance\_abuse

56. National Institute for Health and Care Excellence. Alcohol-use disorders: diagnosis and clinical management of alcohol-related physical complications. 2010.