Does advice based on biomarkers of liver injury or non-invasive tests of liver fibrosis impact high-risk drinking behaviour: A systematic review with meta-analysis

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Abbreviations:

RCT	Randomised control trial
GGT	Gamma-Glutamyltransferase
IU/L	International Units/Litre
CI	Confidence Interval
ArLD	Alcohol-Related Liver Disease
UK	United Kingdom
ELF	Enhanced Liver fibrosis
ICD	International Classification of Diseases
DSM	Diagnostic and Statistical Manual of Mental Disorders
SD	Standard deviation
MCV	Mean Corpuscular Volume
FIB-4	Fibrosis-4
STL	Southampton traffic light
NICE	The National Institute for Health and Care Excellence
ROB	Risk of Bias

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Abstract

Background

Alcohol dependence affects over 240 million people worldwide and attributed to 3 million deaths annually. Early identification and intervention are key to prevent harm. We aim to systematically review literature on the effectiveness of adding advice based on biomarkers of liver injury or non-invasive tests of liver fibrosis (intervention-based advice) to prevent alcohol misuse.

Methods

Electronic search was conducted on Ovid Medline, PubMed, EMBASE, Psychinfo and CINAHL for articles published up to end of February 2020. Additionally, we searched study citations, Scopus, Ethos and Clinical trials. The primary outcome measure was changed in self-reported alcohol consumption analysed by random-effects meta-analysis. Secondary outcomes included change to liver blood markers and alcohol-related health outcomes.

Results

14 RCT and 2 observational studies comprising n=3763 participants were included. Meta-analyses showed a greater reduction in alcohol consumption and liver biomarkers for the intervention compared to control group: mean difference for weekly alcohol intake was -74.4 gram/week (95%CI -126.1, -22.6, p=0.005); and mean difference for GGT -19.7 IU/L (95% CI -33.1, -6.4, p=0.004). There was a higher incidence of alcohol attributed mortality, number of days spent in the hospital, physician visits and sickness absence in the non-intervention group. The quality of the included studies was moderate for RCT's and high for observational studies.

Conclusions

The review confirmed a significant association between the addition of intervention-based advice in routine care to the reduction of harmful alcohol consumption, GGT and alcohol-related mortality. The findings support the inclusion of this type of advice in routine alcohol care.

Keyword: Alcoholism, biomarkers, gamma-Glutamyltransferase, Drinking Behaviour Systematic Reviews, Liver fibrosis

Short summary

Mortality due to alcohol-related liver disease is rising. Early identification and intervention are key to prevent future harm. More reliable non-invasive markers of liver fibrosis are available, but they are not integrated into alcohol services. Adding intervention-based advice into routine alcohol care is effective in reducing harmful alcohol intake.

Introduction

Alcohol is a leading, but preventable cause of liver disease. A quarter of the population in the United Kingdom (UK) drink above recommended levels and 10% are harmful drinkers(Williams et al., 2014). Worldwide nearly 240 million people are alcohol dependent, with alcohol use attributed to 3 million deaths annually and over 200 medical conditions. The use of alcohol screening and brief intervention has been advocated for by the World Health Organisation (WHO) over the last 20 years and by the National Institute for Health and Care Excellence (NICE) for a decade(NICE, 2010; World Health, 2001). Despite the existence of multiple alcohol behaviour change interventions, their use does not appear to have been optimised in the UK. This is illustrated by the 400% rise in liver disease mortality in the UK over the last three decades(Williams et al., 2014)and a predicted 75% increase in age-standardised annual mortality due to alcohol-related liver disease (ArLD) by 2040(Julien et al., 2020).

ArLD progresses silently from a simple fatty liver to cirrhosis leading to liver failure and eventually, death. Early identification of high-risk drinking behaviour followed by intervention to support behaviour change is pivotal to prevent ongoing and future harm(Verrill et al., 2009). The cessation of alcohol misuse is the single most important factor in defining long term prognosis(Verrill et al., 2009). Once in contact with specialist liver centres and with knowledge of their liver disease, half of all patients stop drinking, but unfortunately, more than 50% of them die before their liver function has time to improve(Sheron et al., 2013). The advice based on biological markers, such as diagnostic tests, indicating exposure to a harmful substance, increased susceptibility or the presence of a disease is more likely to promote behaviour change(Bovet et al., 2002; Buffels et al., 2006). There is emerging evidence that the addition of biomarker-based advice to personalised health care communications enhances motivation to overcome addictive behaviour(DiClemente et al., 2001; Kreuter and Wray, 2003). For hazardous and harmful alcohol users, a simple liver fibrosis test and personalised feedback prompted reductions in alcohol use in those with and without evidence of liver damage(Sheron et al., 2013).

Most heavy drinkers at risk of liver disease and in contact with alcohol services do not have access to testing for the assessment of liver disease severity(BritishLiverTrust, 2019; Williams et al., 2020). Historically, liver biopsy is the gold standard to assess the cause and severity of liver disease(Berger et al., 2019), but recently reliable non-invasive markers of liver fibrosis, such as blood tests and portable imaging, have become available(Loomba and Adams, 2020). Providing tailored advice based on biomarker feedback in people at risk of liver disease may affect their drinking behaviour(Noar et al., 2007). However, at present these markers are not widely incorporated into alcohol treatment settings(Williams et al., 2020). The potential of combining early diagnostic interventions and advice has not been extensively explored in alcohol services. We aimed to establish the impact of adding advice based on diagnostic tests for ArLD (intervention-based advice) to routine care and to compare the usefulness of intervention-based advice to non-intervention-based advice on reducing alcohol consumption amongst people with high-risk drinking behaviour.

Methods

Search strategy

This systematic review was conducted following PRISMA process. Electronic search was conducted on 25th-February-2020 using Ovid Medline, PubMed, EMBASE,

Psychinfo and CINAHL to identify articles published from inception to date of search. References of retrieved articles were hand-searched. Search for grey literature was conducted using Scopus, Ethos, and Clinical trials. Search strategy was based on a population, intervention, comparator and outcome (PICO) model and a local expert librarian were consulted to support search strategy development. A protocol is available on Prospero (CRD42020164185).

Selection criteria

Included study designs were randomised controlled trials (RCTs), mixed-method trials, retrospective studies, cohort studies, and controlled or uncontrolled prospective studies. Studies with follow up of less than three months were excluded.

Following PICO based eligibility criteria was applied.

Population: Inclusion: Adult participants of any gender with a history of alcohol misuse, defined as: consumption >14 units/week, a physician diagnosis of alcohol misuse, or a diagnosis defined by Alcohol Use Disorders Identification Test (AUDIT) score, ICD 10 or DSM 5 Criteria.
Exclusion: Participants with known ArLD or who had previous treatment for ArLD.

Intervention: Intervention based advice (advice based on any measure of liver blood tests or fibrosis including (but not limited to): imaging (e.g. Fibroscan(Echosens, 2020)/transient elastography), liver biopsy, simple blood markers (e.g. liver enzymes), or blood markers of fibrosis (e.g. the Enhanced Liver Fibrosis test (ELF), FIB-4 score, APRI score).

Comparator: Non-intervention based advice (advice does not include feedback on liver disease diagnostic tests) including but not limited to; brief advice (BI), simple advice (SA), alcohol identification and brief advice (AIBA), identification and brief advice (IBA) and Standard Care

Primary study Outcome: Change in self-reported alcohol intake or alcohol score (AUDIT).

Secondary study outcomes: Change in liver blood markers, mortality, sickness days and any other outcomes.

Rayyan-QRCI systematic review software, Endnote (version-X9) and Microsoft Excel were used to screen, remove duplicate entries, and record reviewers' decisions.

Data extraction

Data were extracted on an adapted Cochrane data extraction form. Data on alcohol use was converted to gram/week of pure alcohol and for gamma-glutamyl transferase (GGT) to IU/Litre. Further details on the search strategy and data extraction can be found in the supplementary appendix (info S1 and info S2).

Assessment of risk of bias (ROB) and Quality assessment

Cochrane Risk of Bias tool "Rob 2" was used to assess the quality of included randomised control trials, whilst the "Robin 1" tool was used to assess observational cohort studies (Cochrane).

Data synthesis and statistical analysis
Cochrane Review Manager (RevMan version-5.3) was used to complete the statistical analyses.

Analysis was undertaken on all studies for the intended primary outcome of change in self-reported alcohol consumption and repeated for the following subgroups: i) sex (male vs female); ii) baseline alcohol intake (>250 g/week vs <250g/week); iii)) study type (RCT vs observational); and iv) diagnostic method (liver blood test vs fibrosis marker)

Where available, main data were analysed per protocol for secondary outcomes of change in GGT, MCV, non-invasive liver fibrosis score, impact on alcohol-related significant episodes i.e. hospital or emergency admission per year, mortality, and sickness.

There was insufficient data to undertake subgroup analyses by study type, diagnostic method, and change in non-invasive liver fibrosis score.

To calculate effectiveness where available pre, post and mean difference data on weekly self-reported alcohol intake and liver blood markers were extracted. A p-value of <0.05 was considered significant. Due to expected heterogeneity of studies, a random-effects meta-analysis with weighted average differences, standard deviation (SD) and a 95% confidence interval was performed. For studies without evidence of heterogeneity, fixed-effects models were used. Forest plots were used for graphical display of estimated study results and funnel plots for publication bias. Where the data were not suitable for meta-analysis, a narrative description was performed.

Sensitivity analysis
Given the variability of control conditions between studies, a sensitivity analysis was undertaken by restricting the meta-analysis to compare different forms of control conditions (i.e. no advice, brief advice (BI) and brief advice at request) to the intervention group.

Two reviewers (MS and HK) independently completed article screening, data extraction and ROB assessment. Any conflicts were resolved by two other authors (JM and SR).

Results
Total of 35 articles were identified. After full-text reading, 15 articles were excluded as the content did not meet the inclusion criteria (figure1). Of the 20 included articles 16 were different studies, 14 RCTs and two observational. Kristenson et al.(2002; 1985; 1983; 1981) published four studies using the same cohort but different intervals of follow-up and Nilssen et al.(1991; 2004) published one year and nine years follow-up on the same cohort. The repeated publications of the same cohort were managed by taking data on the primary outcomes of interest up to three years of follow-up and taking mortality and morbidity data from later publications. The characteristics of included studies are summarised in table1.

Participants
A total of n=3763 participants were recruited (RCT n=3291). Pooled dropout was 33% in the intervention group and 34% in the control group; study recruitment and dropout rates are provided in table 1. The mean age of participants was 43.2years (SD+/- 4.4). 80% of participants in the RCT's were male, seven studies (table1) included only a

single-sex. The studies were performed in predominantly Caucasian populations, although detail on ethnic distribution was missing.

Interventions

In intervention group, the advice was given based on blood tests or markers of liver injury concerning alcohol intake. The studies used the following biomarkers feedback: GGT and MCV(Aalto et al., 2000; Aalto et al., 2001; Anderson and Scott, 1992; Antti-Poika et al., 1988; Gentilello et al., 1999; Israel et al., 1996; Kristenson et al., 1981; Nilssen, 1991; Persson and Magnusson, 1989; Romelsjo et al., 1989; Scott and Anderson, 1991; Seppä, 1992; Tomson et al., 1998), FIB-4 score(Kahler et al., 2018), Southampton traffic light (STL) scores(Sheron et al., 2013) and Fibroscan readings(Matthews et al., 2019). The advice was tailored using these markers in relation to alcohol intake. Across control groups, participants either received no advice, advice which did not include biomarker feedback (brief advice) or BI only at the participant's request (table 1).

Outcomes

Self-reported alcohol consumption

Pooled mean alcohol intake for the intervention group at baseline (pre-intervention) was 307 g/week (SD+/-155.7) and post-intervention was 198.2 g/week (SD+/- 76.7), the post-intervention reduction was 108 g/week (36%). Pooled means for the control group were 316.1 g/week (SD+/-166.6 range) and 294 g/week (SD+/- 174), respectively the reduction in alcohol intake was 22g/week (7%).

Pre and post-intervention data on alcohol intake for follow-up at three years in both groups were available in nine studies(figure2a). A meta-analysis revealed the weighted mean average difference of weekly alcohol intake between the intervention and control (Brief and/or no advice) groups was -74.4 g/week (95%CI -126.1 to -22.6). The results favoured the positive effect of intervention-based advice including feedback on laboratory tests or markers of fibrosis to reduce alcohol intake (p=0.005). There was statistically significant heterogeneity between studies (I^2=98%) and there was no evidence of publication bias (figure3a).

The following RCT's (Kristenson et al., 1983; 1981; Nilssen, 1991; Persson and Magnusson, 1989; Seppä, 1992; Tomson et al., 1998) were not included in the meta-analysis as pre and post-intervention data on self-reported alcohol intake was not collected in both groups. Kristenson et al.(1983; 1981) did not collect follow up data on alcohol intake post-intervention. In the Persson and Magnusson(1989) study post-intervention data was only reported in the intervention group (n=36), of whom 21 reduced their alcohol intake. The studies by Nilssen et al.(1991) and Tomson et al.(1998) showed significant reductions in alcohol use in the intervention group, but pre-intervention data in controls was not collected. In the Seppä (1992) trial, quantitative data on alcohol consumption was not collected but 7% of men and 11% of women from the study cohort reported a general reduction in alcohol intake.

In the Sheron et al.(2013) study, liver fibrosis was calculated using the STL score. The advice was based on patients' STL fibrosis and AUDIT score. At 12 month follow up, 42% had reduced their drinking by one AUDIT grade; participants receiving amber/red results (possible or probable liver fibrosis) were significantly more likely to reduce by one AUDIT grade or more than those with a green result (liver fibrosis unlikely) (p =.011).

On restricting the analysis to gender: The male-only participant studies (figure 2b) analysis demonstrated a weighted mean average difference in weekly alcohol intake between the intervention and control groups of -86.8 gram/week (95% CI -182.7 to 9.1), but was not statistically significant (p=0.08). The I^2 was 71% (p = 0.02) indicating statistically significant heterogeneity between studies. Analysis of the female-only studies(figure 2c) showed a significant (p<0.01) reduction in alcohol intake across the whole study group but no significant difference between groups with a weighted mean average difference of weekly alcohol intake between the groups was -11.1g/week (95% CI -36.9 to 14.6), (p=0.4).

On stratifying studies using baseline alcohol intake above or below 250g/week, the effect of the intervention remained significant irrespective of participant baseline alcohol intake (>250g/week, weighted mean average difference -98.32 g/week 95% CI -179.07 to -17.58, p=0.02); (<250g/week, weighted mean average difference -46.40, 95% CI -60.11 to -32.67, p=<0.0001)(figure 2d,e)

Liver blood markers

The GGT and MCV were used as a marker of excess alcohol intake and a decline in their results were taken as an indication of a reduction in alcohol intake. Data concerning pre and post-changes in GGT for both groups were available in 10 studies (SF1a) and for MCV in 5 (SF2a) studies respectively.

Gamma-glutamyltransferase (GGT)

The pooled mean pre and post-intervention GGT levels for the intervention group were 86.2 IU/L (SD+/- 39.5) and 76.2 IU/L (SD+/-44.7), reduction 24%; for the control group, these were 65.4 IU/L (SD+/-24.1) and 71 IU/L (SD+/-39.7), reduction 7% respectively.

Meta-analysis on the studies providing pre-and post-data on change in GGT between the intervention and control groups (SF1a), showed a weighted mean average difference of -19.7 IU/L (95% CI -33.0, -6.4). The change was statistically significant (p=0.004) and favoured the intervention over the control group. The I^2 was 93% indicating statistically significant heterogeneity between studies. There was no significant publication bias (figure3b).

On subgroup analysis (SF1d) the change was only significant if baseline alcohol intake was >250 gram/week, weighted mean average difference -23.04 (95% CI -44.78, -1.31), p=0.04. The change became non-significant (p >0.05) on restricting the analysis to male and female subgroups.

Mean corpuscular volume (MCV)

The pooled mean pre and post MCV values for the intervention group were 95.6 femtoliter/cell (SD+/-2.4) and 94.8 femtoliter/cell (SD+/-2.8). For the control group, these values were 95.4 femtoliter/cell (SD+/-3.3) and 94.9 femtoliter/cell (SD+/-3.5) respectively. Given that heterogeneity was not evidenced (I^2 = 0%; p = 0.94) a fixed-effect meta-analysis was conducted on the studies (n=5) using MCV values as an outcome measure, showing a weighted mean difference of 0.36 femtoliter/cell (95% CI -0.3, 1.0, p=0.26) (SF2a).

The change remained non-significant (p>0.5) on restricting the analysis to baseline alcohol intake >250 gram/week, male and female subgroups (SF2d).

Mortality
Kristenson et al.(2002) conducted follow up at 13 years (median) and reported 37% of deaths in the intervention group and 48% deaths in the control group were alcohol-related. The authors reported a statistically significant difference in alcohol-related death survival curves (risk ratio 1.9, 95% CI 1.0 – 3.8). Tomson et al.(1998) reported two deaths in the control group Over two years but none in the intervention group, the cause of death was not specified. Whereas Gentilello et al.(1999) reported no significant difference in death rates (Intervention group 2.7%, Control group 2.3%) at 12 months.

Sickness absence
At four year follow up, Kristenson et al.(1985; 1983) reported the number of sickness days in the control group rose from a mean 24.7 days/year to 51.9 days/year ($p < 0.05$) with minimal change in the intervention group. In Persson and Magnusson(1989), the intervention group demonstrated significantly ($p<0.05$) reduced total sickness absence, change was more marked in female participants. Tomson et al.(1998) reported no significant change to sickness absence in the whole study cohort. In both studies, the control group received no advice.

Engagement with secondary care liver services
Matthews et al.(2019) conducted a prospective community observational study over six months on self-reporting as harmful drinkers. Participants underwent a Fibroscan, those with readings >7.1Kpa were referred to a nurse lead clinic for further investigation based on which a secondary care referral was made. The authors showed high patient engagement with secondary care liver services in those going through the pathway, however, this study lacked a control condition or comparison group.

Other outcomes
On average, control group participants spent more days in the hospital (ratio 2.2) and had more physician visits. In contrast, overall the intervention group reduced the total number of physician visits, had a 47% reduction in new injuries, and less traffic violation and police arrests(Gentilello et al., 1999; Israel et al., 1996; Kristenson et al., 1983; Persson and Magnusson, 1989) (Table 1).

Sensitivity analysis
On separating the analyses by control group type (intervention versus no advice; intervention versus brief advice; intervention vs brief advice at request (table2).

The weighted mean average difference in weekly alcohol intake was -254.4 g/week; -54.2 g/week and -77.7 g/week respectively, the change was non-significant ($p=0.27$, $p=0.11$, $p=0.16$). However, the difference was statistically significant when comparing intervention to combined groupings of no advice and BI at request ($p=0.03$).

In the case of GGT, the change was significant both for comparing intervention to no-advice, weighted mean average difference -37.41 IU/Litre (95% CI -71.2, -3.7, $p=0.03$) and intervention versus BI, the weighted mean average difference -36.54 IU/Litre (95%CI -36.6, -7.9, $p=0.002$).

For MCV data was insufficient to compare the intervention to no-advice and change was non-significant on comparing intervention to BI or BI at request ($p=02.8$, $p=0.53$)

Risk of Bias Assessment(ROB)
ROB for the RCTs is given in (SF3) Most authors described the method used for randomisation, apart from (Nilssen, 1991). Due to the nature of the studies, blinding was not possible. Main area for high concern was missing outcome data; few studies reported high rates of missing data but failed to satisfactorily describe how the missing data was handled.

Sheron et al.(2013) had a moderate risk of bias as GPs were advised to refer patients with moderate to high-risk drinking behaviour which might have confounded AUDIT score outcomes. Matthews et al.(2019) study had a low risk of bias.

Discussion
This is the first systematic review to evaluate the effectiveness of advice based on liver disease diagnostic tests or markers of liver injury (intervention-based advice) on alcohol intake in high-risk drinkers. We demonstrated a significant beneficial effect on self-reported alcohol consumption with a 36% decrease in alcohol consumption in the intervention-based advice group as compared to 7% with standard care (control). This substantial effect was mirrored by a similar fall in GGT; 24% in the intervention group and 7% in standard care. Although the number of studies reporting these outcomes was smaller, intervention-based advice was more effective in reducing alcohol attributed sickness absence, the number of days spent in the hospital, the number of physicians visits and long term mortality, compared to routine care or non-intervention-based advice. Reducing alcohol consumption reduces liver injury and is well known to improve the outcome of physical health problems such as liver disease which result from it. There is also the potential that earlier engagement of individuals with significant liver disease in secondary care services, which was demonstrated here, allows the implementation of NICE approved interventions, such as endoscopy for varices, potentially improving outcomes.

Our findings are consistent with those in respiratory medicine, showing the addition of intervention based advice to standard care can increase the chances of change in addictive behaviour(Bovet et al., 2002; Buffels et al., 2006; McClure, 2004). The reviews by Bryant et al.(2013) and Miller et al.(2013) have demonstrated strong support for use of personalised feedback to prompt reductions in alcohol use and alcohol-related problems. Personalised feedback involves the provision of objective data regarding alcohol misuse, risk of alcohol-related problems, and comparisons to normative drinking patterns. Motivation to change behaviour may depend on the perceived likelihood of a negative health outcome occurring and a belief that behaviour change can reduce their risk of harm(Weinstein and Nicolich, 1993). Providing personalised biomarker feedback could increase risk awareness and therefore the likeliness that an individual will change their behaviour.

The results are relevant and applicable to the high-risk drinking population of the UK and Europe, with well-matched age range and ethnicity distribution(Digital, 2020; WHO, 2018). The studies were undertaken in routine community clinical settings which makes its application suitable in day to day primary medical practice, although there is minimal data on the use of such advice in inpatient or emergency care settings. Overall 80% of participants in RCTs were male. A gender-based analysis for self-reported alcohol intake did reveal a reduction in alcohol for the intervention group in both genders as compared to controls, but the difference did not reach statistical significance. This might be because of a lack of statistical power due to the limited

number of studies including women. The gender and ethnic distribution, however, reflect the population trends observed across Europe and high-income countries(Kaner, 2010; WHO, 2018).

The sensitivity analysis for intervention based advice against no advice and brief advice showed a non-significant change in self-reported alcohol but a significant change in GGT. However, when control conditions were pooled a significant interaction effect was observed. This is likely due to small sample sizes for each type of control condition and methodological nuances such as cross-contamination. The interaction effect remained significant irrespective of baseline alcohol intake.

The included RCT's had some methodological uncertainties. InIsrael et al.(1996) and Tomson et al.(1998), participants in the control group received brief initial feedback on GGT levels which might have caused cross-contamination among groups. This should, however, be a bias away from intervention-based advice being beneficial. The studies used varying behaviour interventions like motivational interventions and counselling sessions. Most trials in this review used GGT and MCV values as a marker of alcohol misuse and to assess the effectiveness of the intervention. However, both of these markers have very low sensitivity and specificity as a diagnostic tool for alcohol abuse(Jastrzębska et al., 2016), perhaps explaining the small changes. Their utility is hampered by the variability of results among different age groups, gender and ethnicity, and by the potential of false-positive results due to other conditions like diabetes, smoking, obesity, vitamin B12 or folate deficiency and haematological diseases(Allen, 2003; Jastrzębska et al., 2016). In this context, the potential impact of such biomarkers in the diagnosis of liver injury due to alcohol is limited, although the size of the impact seen on markers and alcohol intake in this review is impressive. Most studies in this review only reported short term outcomes and therefore there is uncertainty over the validity of the longer-term change. Only two studies reported outcomes beyond five years(Kristenson et al., 2002; NILSSEN, 2004). This lack of long term outcomes is not however limited to the impact of intervention based advice; previous systematic reviews on alcohol brief advice faced similar deficiencies related to the long term effect of alcohol interventions(Kaner et al., 2009).

Limitations to the review are noted. First, there was significant heterogeneity between the trials in self-reported alcohol intake and laboratory tests (GGT) which has been reflected in our meta-analysis. A random effect analysis was used assuming the estimated reduction in alcohol consumption of 74.4g/week is averaged across populations and settings, providing support for the observed reduction. The lack of adequate concealment might have caused an overestimation of the treatment effect(Kypri et al., 2007), though it would not always have been possible to blind participants or the person providing advice due to the nature of interventions. Another potential source of bias was a loss to follow up or dropout. However, most trials (table 1) adopted an intention to treat analysis which likely overcomes this bias. The studies which lacked this method might have introduced reporting bias but the overall estimated reduction in alcohol consumption is substantial. Further, the accuracy of self-reported alcohol intake might be questionable; it decreases as consumption of alcohol increases, which might have caused self-report biases in the outcomes(Evans et al., 1984; Northcote and Livingston, 2011). The review may not generalise to non-Caucasian populations as all the studies were done in white predominant countries with minimal information on ethnic distribution and the search strategy was restricted to the English language. Finally, despite the inclusion of gender-specific analyses,

female patients were underrepresented in the data. Future research should focus on greater inclusivity of diverse populations.

Conclusion

This systematic review strongly suggests that intervention based advice is effective in reducing harmful alcohol intake. However, future work should explore the relative effect of different components of an intervention and types of brief advice, which patient or delivery related factors are needed to successfully implement the interventions, and finally to develop interventions which are appropriate across diverse ethnic populations, genders, and clinical settings.

Tables and figures

Author (year)	**Sample**††† Age (years) Size (n*) Gender Dropout ITT	**Design** (Setting/Country Starting Year Follow up Duration)	**Interventions** (IG= Intervention group/s CG= Control group)	**Results/Findings**†† (As per study measures of outcome) GGT=IU/Litre Alcohol intake=g/week
Kristenson et al 1981-85, 2002	46 n=585 M=585 F=0 n=177 Yes	RCT Community Malmo Sweden Screening from 1975-1981 2, 3, 5,13 years	**Intervention Group:** Tapered counselling and biofeedback based on GGT. **Control Group**: An invitation letter was sent for a repeat blood test in 2 years	**Change in Gamma GT:** A significant reduction within but not between groups **Sickness Days** Significant increase in CG **Hospital days** CG spent more days **Mortality at 13 years** Twice as high alcohol-related deaths in the control group
Poika et al 1988	39 n=120 M=120 F=0 n=31 No	RCT Inpatient Helsinki Finland Started 1985 6 Months	**Intervention Group:** Brief counselling, biofeedback on blood test concerning alcohol **Control Group**: No advice was given, a follow-up was offered at 6 months	**Alcohol Use** IG- significantly reduced CG- Significantly worsen Improved- IG 50%, CG 20% **Change in Gamma GT:** No statistically significant difference noted both between and within groups
Persson et al 1989	44 n=78 M=61 F=17 n=23 No	RCT Somatic Outpatient Karlstad Sweden Started 1982 1- 2 year	**Intervention Group:** Brief counselling, and biofeedback based on labs concerning alcohol. **Control Group:** No contact or discussion about alcohol. All participants were invited at 1 year for a repeat blood sample	**Alcohol Use:** IG- 21 out of 36 reduced CG- No follow-up data **Change in gamma GT:** A non-significant reduction in both groups **Sickness days:** Significant reduction in IG **Physician Consultations:** Non-significant decrease of in IG and increase in CG
Romelsjo et al	46 n=83 M=70 F=13 n=21 No	RCT Community Stockholm Sweden 1984 1 year	**Intervention Group:** GP provided biofeedback on GGT concerning alcohol. **Control Group:** GP advised to cut down on alcohol intake	**Alcohol Use:** No significant change between or within groups **Change in gamma GT:** No significant ($p > 0.05$) change between or within groups.
Scott et al 1990	45 n=72 M=0 F=72 n=22 Yes	RCT Community Oxford UK 1989 1 year	**Intervention Group:** GP delivered Brief (10 minutes) advice plus biofeedback on blood test concerning alcohol intake **Control Group:** No advice from GP except at their request.	**Alcohol use:** There was a significant reduction in the whole study group **Change in gamma GT:** No significant change within or between groups **Dependence score:** Significant improvement in both groups.
Nilssen et al 1992,2004	41 n=338 M=290 F=48	RCT Community Tromso Norway -	**Intervention Group:** **Major Intervention Group:** 15 minutes intervention,	**Alcohol use:** IG- significant improvement in CG- increase **Change in gamma GT:**

	n=18 Yes	1 & 9 year	biofeedback on GGT concerning alcohol intake **Minor Intervention Group**: 10 minutes intervention, possible reasons for elevated GGT discussed, a booklet containing information on GGT and alcohol. **Control Group:** No Intervention	IG- a significant reduction CG- increase **Change in gamma GT at 9 years:** All three groups receiving treatment (control, minor and major) displayed significant GGT reduction. No significant difference between groups
Anderson et al 1992	44 n=154 M=154 F=0 n=54 Yes	RCT Community Oxford UK - 1 year	**Intervention Group:** GP delivered Brief (10 minutes) advice plus biofeedback on blood test concerning alcohol intake. **Control Group:** No advice from GP except at their request.	**Alcohol Use:** At 1 year Follow up 18% of men in IG reduced their alcohol intake compared with 5% in CG **Change in gamma GT/MCV** No significant change within or between groups
Seppa et al 1992	54 n=178 M=140 F=38 n=83 No	RCT Community Tampere Finland - 1 year	**Intervention Group:** Brief advice and biofeedback on MCV concerning alcohol. Follow up every 3 months with repeat brief session and biofeedback **Control Group:** Counselling but no biofeedback	**Alcohol use:** Men- 7% stated a reduction in the whole cohort Women- 11% stated a reduction in the whole cohort. **Change in MCV:** No significant reduction both within and between groups
Israel et al 1996	30-60** n=105 M=46 F=59 n=32 No	RCT Community Cambridge Ontario Canada - 1 year	**Intervention Group:** Received 30-minute cognitive behaviour treatment biofeedback on GGT concerning alcohol. **Control Group:** Received brief advice on reducing alcohol intake and Pamphlet.	**Alcohol Use:** IG group had a 70% reduction in mean alcohol intake per four weeks and CG had 46% reduction **Change in gamma GT:** IG showed 32% mean reduction from baseline. No significant reduction in CG **Physician Visits:** IG mean reduction of 34% CG no significant change
Tomson et al 1998***	45 n=222 M=(61)† F=(14)† n=147 Yes	RCT Community Stockholm Sweden - 2 years	**Intervention Group:** A nurse-delivered Intervention focussed on factors that facilitated controlled drinking. GGT was used as biomarker feedback. **Control Group:** GP discussed possible causes of elevated GGT. No alcohol-specific advice given.	**Alcohol Use:** IG- Significant reduction CG- no data at baseline **Change in gamma GT:** IG-Significant reduction CG- Non-significant increase **Sickness days** No significant reduction in the whole cohort **Mortality** IG- No death CG- 3 deaths
Gentilello et al 1999	36 n=762 M=625 F=137 n=353 Yes	RCT Inpatient Washington USA October 1994 1 year	**Intervention Group:** A 30-minute motivational interview with psychologist comprises of personalised feedback and biofeedback	**Alcohol use:** Significant reduction of weekly alcohol intake in IG as compared to CG (p=0.03) **Trauma Recurrence:**

			on abnormal laboratory values. **Control Group:** Control patients requesting help for a drinking problem were assisted in obtaining it.	The intervention group had a 47% reduction in new injuries **Mortality:** No difference in death rate between 2 groups (2.7% in intervention, 2.3% in controls) **Traffic Violation:** Fewer in IG
Aalto et al 2000	41 n=118 M=0 F=118 n=40 Yes	RCT Community Tampere Finland 1994 3 year	**Intervention Group:** Group A: received sessions at baseline, 2, 6, 12, 18, 24, and 30 months. Group B: received brief intervention at baseline, 12, and 24 months. Both groups received Biofeedback **Control Group:** GP provided general advice	**Alcohol Use:** The change was not statistically significant in all groups **Change in gamma GT:** GGT decreased in IG A and B but increased CG, the difference was not significant **Change in MCV:** Significant reduction in MCV in the whole study group. **Self-estimation of Mental health:** Poorer in intervention group A and B
Aalto et al 2001	42 n=296 M=296 F=0 n=94 Yes	RCT Community Tampere Finland 1994 3 year	**Intervention Group:** Group A: received sessions at baseline, 2, 6, 12, 18, 24, and 30 months. Group B: received brief intervention at baseline, 12, and 24 months. Both groups received Biofeedback **Control Group:** GP provided general advice	**Alcohol Use:** 25-53% reduce alcohol intake in the whole cohort. **Change in gamma GT:** No significant change within or between groups **Change in MCV:** A significant change in MCV between baseline and 3 years follow up in each group (all significant at (p <.01)
Sheron et al 2013	34 n=393 M=229 F=164 n=90 Yes	Prospective observational Community Southampton UK - 1 year	Liver fibrosis was checked by using Southampton Traffic light (STL) test††††, results were sent to GP who provided biofeedback.	**Alcohol use (AUDIT score):** 42% had reduced their drinking, participants receiving amber/red grades were significantly more likely to reduce than green group
Kahler et al 2018	42 n=180 M=180 F=0 n=19 No	RCT Outpatient Boston USA 2011 1 year	**Intervention Group:** Motivational intervention and biofeedback on Fib-4 score†††††. **Control Group:** Assessment only	**Alcohol use:** Significant reduction of alcohol intake in the intervention group (p<0.04) **FIB-4 score*:** No Significant change
Mathews et al 2018***	79 - - - - Yes	Prospective observational study Edinburgh UK 2014 1 year	Individuals who self-identified as harmful drinkers attended for a Fibroscan.	**Compliance with further assessment:** 100% engaged in further assessment **Attendance at specialist services:** 92 % attended the first medical appointment **Attendance at 6 months:** 90% attended 6 months follow up

Table 1: The characteristics of the included studies (ITT-intention to treat)

*Number recruited

**Age range

***Tomson et al and Mathews et al, no information on gender distribution at recruitment

†Number of the participant at follow-up, no information on distribution at recruitment

††Not all findings are included

†††Age -mean, Gender- F=Female, M=Male distribution of total recruited

††††Southampton Traffic light (STL) test:

Combines several different tests and clinical markers, which are given a score that indicates the patient's likelihood of developing liver fibrosis and cirrhosis Green – No evidence of severe fibrosis but early damage cannot be excluded Amber – Liver fibrosis likely but not certain Red – Fibrosis almost certain, possible severe fibrosis or cirrhosis.

†††††FIB-4 Score: The score combines patient age, platelet count, AST and ALT to give a fibrosis score.

Sensitivity analysis	Mean Difference	95% CI	I^2	P-Value
Change in self-reported alcohol intake (gram/week) †				
IBA vs No advice	-254.37	-705.49, 196.74	89%	0.27
IBA vs BI	-54.18	-120.21, 11.85	89%	0.11
IBA vs BI at request	-77.71	-185.41, 29.98	99%	0.16
IBA vs No advice or BI at request	-103.02	-195.04, -11.0	99%	0.03*
Change in gamma-glutamyl transferase (GGT) (IU/Litre †				
IBA vs No advice	-37.41	-71.16,-3.67	95%	0.03*
IBA vs BI	-22.21	-36.54, -7.89	58	0.002*
IBA vs BI at request	5.35	-2.87, 61.0	0%	0.20
IBA vs No advice or BI at request	-19.92	-43.89, 4.04	95%	0.10
Change in Mean Corpuscular Volume MCV (femtoliters/cell) ††				
IBA BI at request	0.59	-0.49, 1.68	0%	0.28
IBA vs BI	0.24	-0.52, 1.01	0%	0.53

Table 2: Sensitvity analysis (IBA-intervention based advice, BI-Brief advice)

†Random effect Meta-analysis

††Fixed effect Meta-analysis, data was insufficient to compare IBA to no advice

*Statistically significant (<0.05)

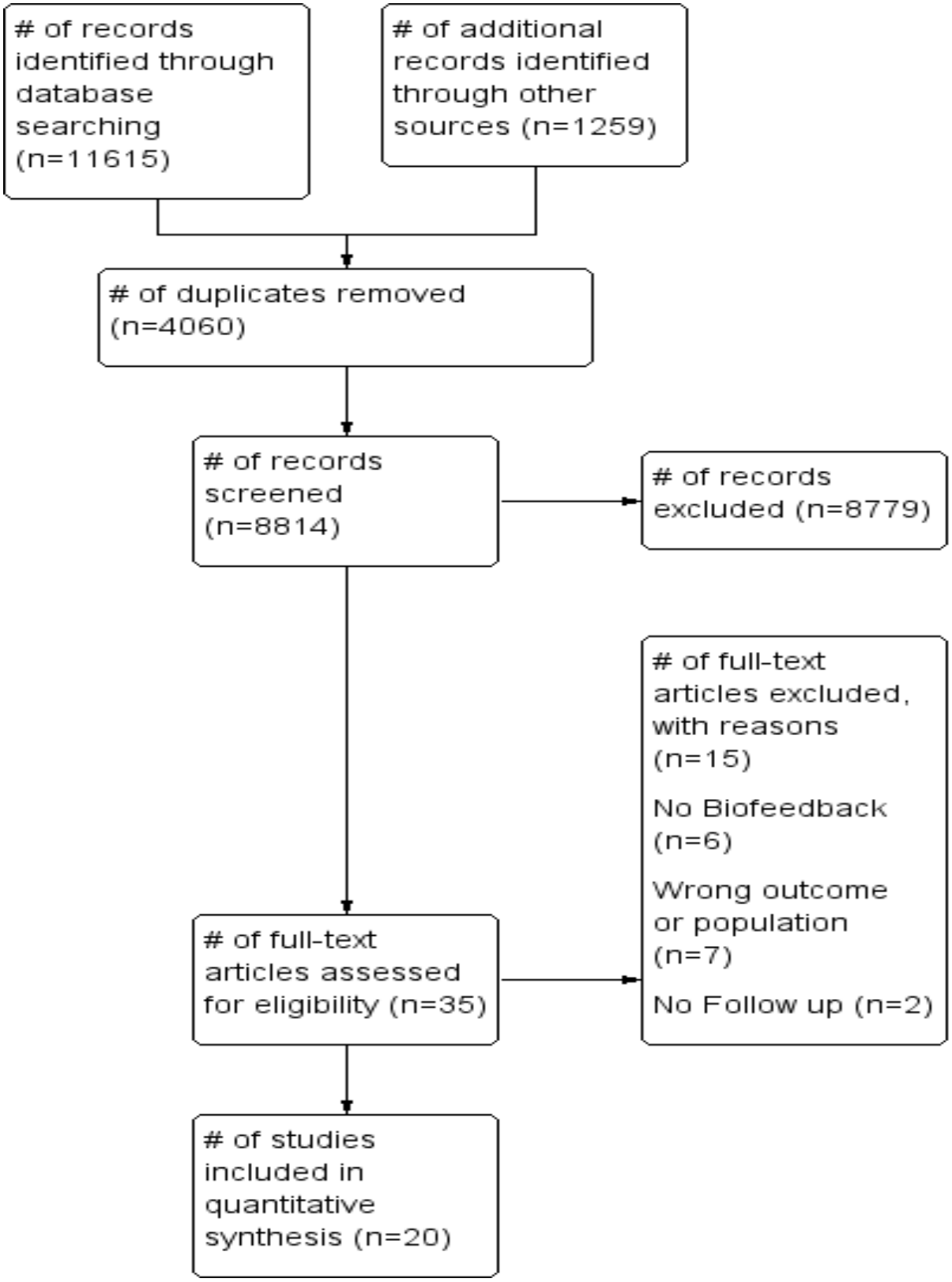
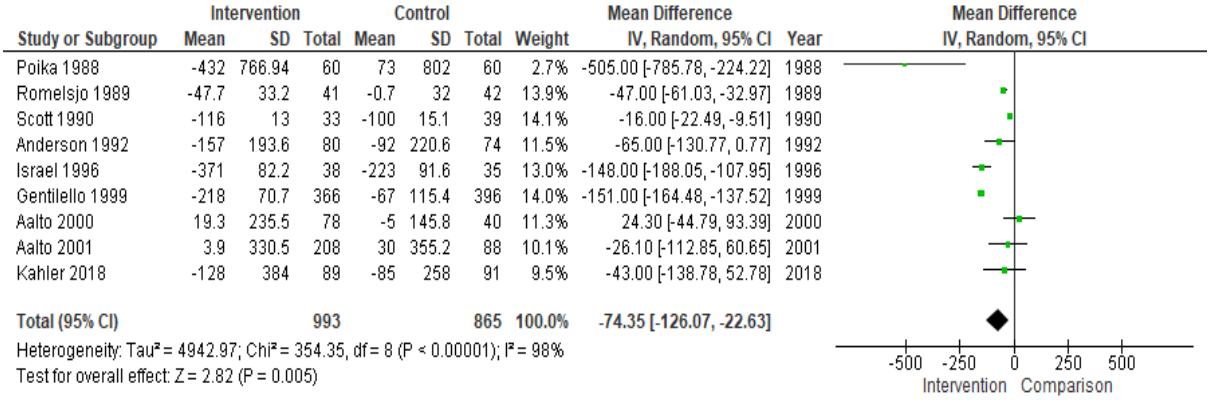


Figure 1: Prisma study flow diagram

a)



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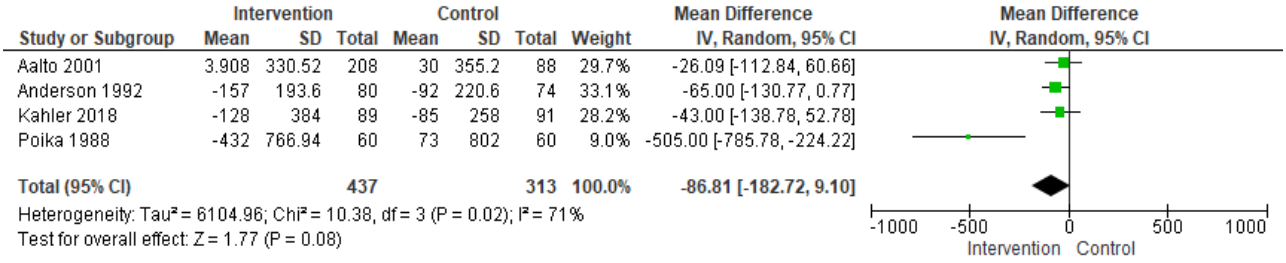
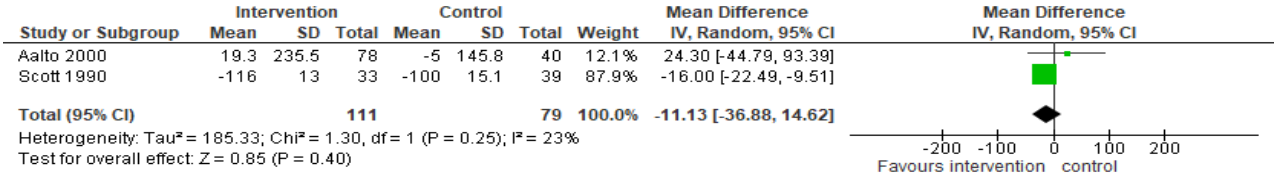
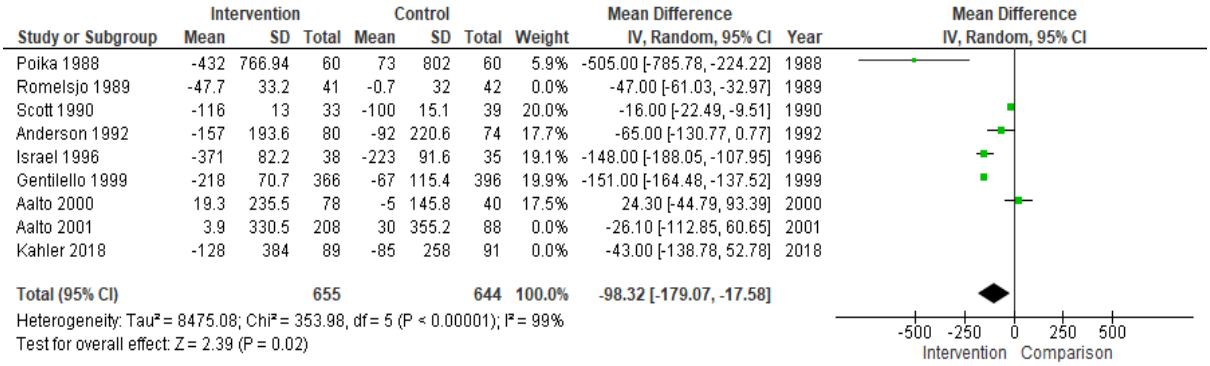


c)



d)



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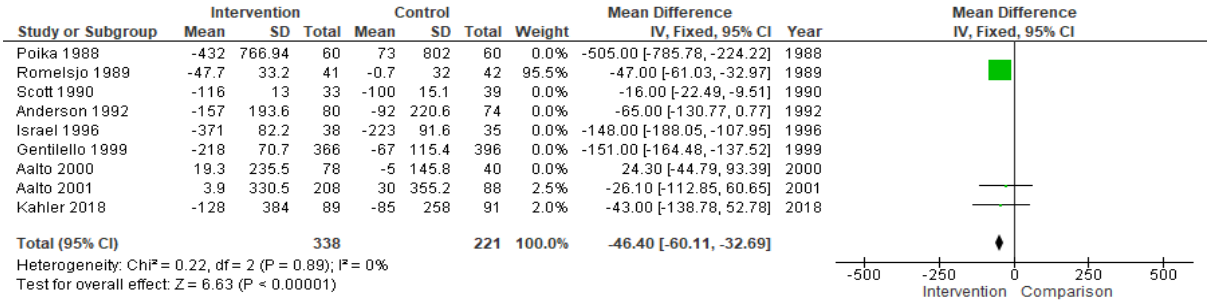
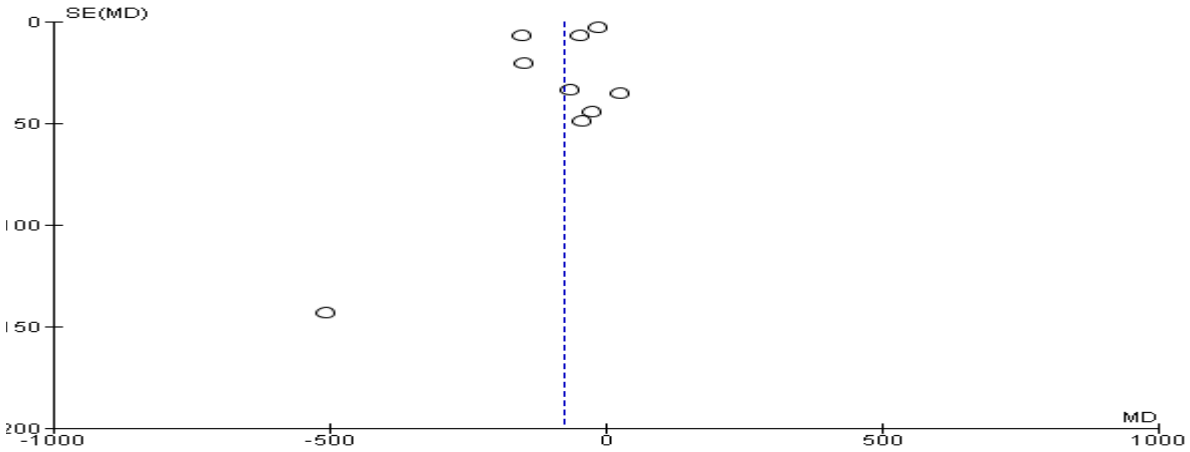
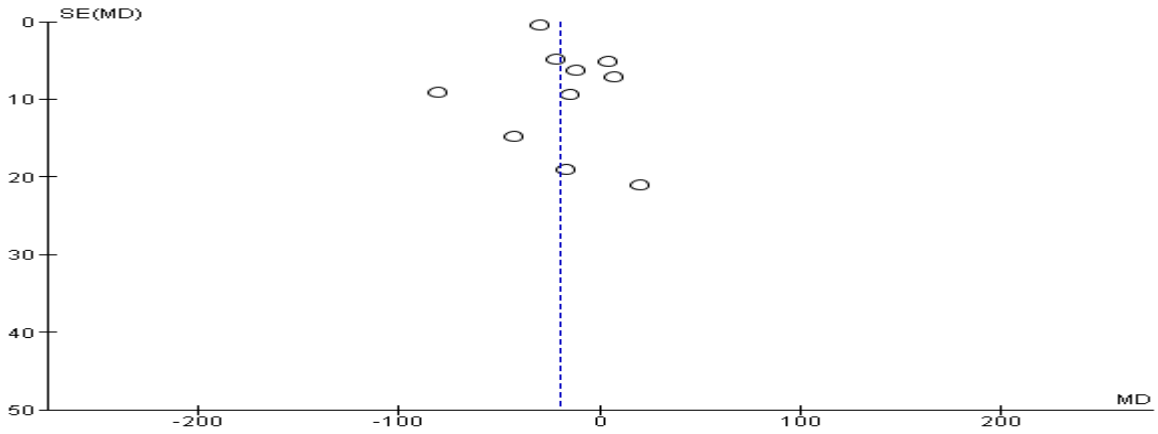


Figure2: Change in self-reported alcohol intake (gram/week) **a)** Intervention based advice versus Brief and Brief advice at request and no Advice **b)** Male only **c)** Female only **d)** alcohol intake >250 gram/week **e)** alcohol intake <250 gram/week

a)



b)



c)

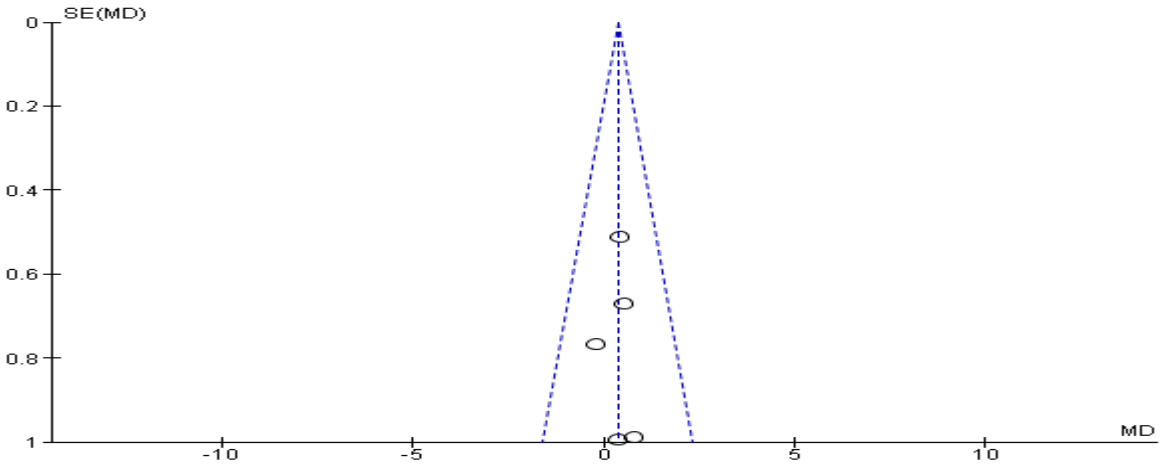


Figure 3: Funnel plots for publication bias **a)** Change in self-reported alcohol intake (gram/week) **b)** Change in GGT (IU/Litre **c)** Change in MCV

References:

Aalto, M, Saksanen, R, Laine, P *et al.* (2000) Brief intervention for female heavy drinkers in routine general practice: a 3-year randomized, controlled study. *Alcoholism, clinical and experimental research* **24**: 1680-6.

Aalto, M, Seppa, K, Mattila, P *et al.* (2001) Brief intervention for male heavy drinkers in routine general practice: a three-year randomized controlled study. *Alcohol and alcoholism (Oxford, Oxfordshire)* **36**: 224-30.

Allen, JP (2003) Use of Biomarkers of Heavy Drinking in Health Care Practice. *Military medicine* **168**: 364-67.

Anderson, P and Scott, E (1992) The effect of general practitioners' advice to heavy drinking men. *British journal of addiction* **87**: 891-900.

Antti-Poika, I, Karaharju, E, Roine, R, Salaspuro, M (1988) Intervention of heavy drinking--a prospective and controlled study of 438 consecutive injured male patients. *Alcohol and alcoholism (Oxford, Oxfordshire)* **23**: 115-21.

Berger, D, Desai, V, Janardhan, S (2019) Con: Liver Biopsy Remains the Gold Standard to Evaluate Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. *Clinical Liver Disease* **13**: 114-16.

Bovet, P, Perret, F, Cornuz, J, Quilindo, J, Paccaud, F (2002) Improved smoking cessation in smokers given ultrasound photographs of their own atherosclerotic plaques. *Preventive medicine* **34**: 215-20.

BritishLiverTrust (2019) <2019 British liver trust The-alarming-impact-of-liver-disease-FINAL-June-.pdf>.

Bryant, ZE, Henslee, AM, Correia, CJ (2013) Testing the effects of e-mailed personalized feedback on risky alcohol use among college students. *Addictive behaviors* **38**: 2563-67.

Buffels, J, Degryse, J, Decramer, M, Heyrman, J (2006) Spirometry and smoking cessation advice in general practice: a randomised clinical trial. *Respiratory medicine* **100**: 2012-7.

Cochrane Cochrane risk-of-bias tool.

DiClemente, CC, Marinilli, AS, Singh, M, Bellino, LE (2001) The role of feedback in the process of health behavior change. *Am J Health Behav* **25**: 217-27.

Digital, N (2020) Statistics on Alcohol, England 2020.

Echosens, PF (2020) Fibroscan.

Evans, JR, Ogston, S, Guthrie, A, Johnston, B, McKechnie, L (1984) The relationship between liver function tests and alcohol intake in patients admitted to an alcoholism unit. *Ann Clin Biochem* **21 (Pt 4)**: 261-7.

Gentilello, LM, Rivara, FP, Donovan, DM *et al.* (1999) Alcohol interventions in a trauma center as a means of reducing the risk of injury recurrence. *Ann Surg* **230**: 473-83.

Israel, Y, Hollander, O, Sanchez-Craig, M *et al.* (1996) Screening for problem drinking and counseling by the primary care physician-nurse team. *Alcoholism, clinical and experimental research* **20**: 1443-50.

Jastrzębska, I, Zwolak, A, Szczyrek, M, Wawryniuk, A, Skrzydło-Radomańska, B, Daniluk, J (2016) Biomarkers of alcohol misuse: recent advances and future prospects. *Przeglad gastroenterologiczny* **11**: 78-89.

Julien, J, Ayer, T, Bethea, ED, Tapper, EB, Chhatwal, J (2020) Projected prevalence and mortality associated with alcohol-related liver disease in the USA, 2019–40: a modelling study. *The Lancet Public Health* **5**: e316-e23.

Kahler, CW, Pantalone, DW, Mastroleo, NR *et al.* (2018) Motivational interviewing with personalized feedback to reduce alcohol use in HIV-infected men who have sex with men: A randomized controlled trial. *Journal of consulting and clinical psychology* **86**: 645-56.
Kaner, E (2010) Brief alcohol intervention: time for translational research. *Addiction (Abingdon, England)* **105**: 960-5.
Kaner, EF, Dickinson, HO, Beyer, F *et al.* (2009) The effectiveness of brief alcohol interventions in primary care settings: a systematic review. *Drug and alcohol review* **28**: 301-23.
Kreuter, MW and Wray, RJ (2003) Tailored and targeted health communication: strategies for enhancing information relevance. *Am J Health Behav* **27 Suppl 3**: S227-32.
Kristenson, H, Hood, B, Peterson, B, Trell, E (1985) Prevention of alcohol-related problems in urban middle-aged males. *Alcohol (Fayetteville, NY)* **2**: 545-9.
Kristenson, H, Ohlin, H, Hulten-Nosslin, MB, Trell, E, Hood, B (1983) Identification and intervention of heavy drinking in middle-aged men: results and follow-up of 24-60 months of long-term study with randomized controls. *Alcoholism, clinical and experimental research* **7**: 203-9.
Kristenson, H, Osterling, A, Nilsson, JA, Lindgarde, F (2002) Prevention of alcohol-related deaths in middle-aged heavy drinkers. *Alcoholism, clinical and experimental research* **26**: 478-84.
Kristenson, H, Trell, E, Hood, B (1981) Serum-gamma-glutamyltransferase in screening and continuous control of heavy drinking in middle-aged men. *Am J Epidemiol* **114**: 862-72.
Kypri, K, Langley, JD, Saunders, JB, Cashell-Smith, ML (2007) Assessment may conceal therapeutic benefit: findings from a randomized controlled trial for hazardous drinking. *Addiction (Abingdon, England)* **102**: 62-70.
Loomba, R and Adams, LA (2020) Advances in non-invasive assessment of hepatic fibrosis. *Gut* **69**: 1343-52.
Matthews, K, MacGilchrist, A, Coulter-Smith, M, Jones, J, Cetnarskyj, R (2019) A nurse-led FibroScan((R)) outreach clinic encourages socially deprived heavy drinkers to engage with liver services. *Journal of clinical nursing* **28**: 650-62.
McClure, J (2004) Motivating prepartum smoking cessation: a consideration of biomarker feedback. *Nicotine Tob Res* **6 Suppl 2**: S153-61.
Miller, MB, Leffingwell, T, Claborn, K, Meier, E, Walters, S, Neighbors, C (2013) Personalized feedback interventions for college alcohol misuse: an update of Walters & Neighbors (2005). *Psychol Addict Behav* **27**: 909-20.
NICE (2010) Alcohol-use disorders: prevention.
Nilssen, O (1991) The Tromso Study: identification of and a controlled intervention on a population of early-stage risk drinkers. *Preventive medicine* **20**: 518-28.
NILSSEN, O (2004) LONG-TERM EFFECT OF BRIEF INTERVENTION IN AT-RISK ALCOHOL DRINKERS: A 9-YEAR FOLLOW-UP STUDY. *Alcohol and Alcoholism* **39**: 548-51.
Noar, SM, Benac, CN, Harris, MS (2007) Does tailoring matter? Meta-analytic review of tailored print health behavior change interventions. *Psychological bulletin* **133**: 673-93.
Northcote, J and Livingston, M (2011) Accuracy of self-reported drinking: observational verification of 'last occasion' drink estimates of young adults. *Alcohol and alcoholism (Oxford, Oxfordshire)* **46**: 709-13.

Persson, J and Magnusson, PH (1989) Early intervention in patients with excessive consumption of alcohol: a controlled study. *Alcohol (Fayetteville, NY)* **6**: 403-8.
Romelsjo, A, Andersson, L, Barrner, H *et al.* (1989) A randomized study of secondary prevention of early stage problem drinkers in primary health care. *British journal of addiction* **84**: 1319-27.
Scott, E and Anderson, P (1991) Randomized controlled trial of general practitioner intervention in women with excessive alcohol consumption. *Drug and alcohol review* **10**: 313-21.
Seppä, K (1992) Intervention in alcohol abuse among macrocytic patients in general practice. *Scandinavian journal of primary health care* **10**: 217-22.
Sheron, N, Moore, M, O'Brien, W, Harris, S, Roderick, P (2013) Feasibility of detection and intervention for alcohol-related liver disease in the community: the Alcohol and Liver Disease Detection study (ALDDeS). *Br J Gen Pract* **63**: e698-e705.
Tomson, Y, Romelsjo, A, Aberg, H (1998) Excessive drinking--brief intervention by a primary health care nurse. A randomized controlled trial. *Scandinavian journal of primary health care* **16**: 188-92.
Verrill, C, Markham, H, Templeton, A, Carr, NJ, Sheron, N (2009) Alcohol-related cirrhosis--early abstinence is a key factor in prognosis, even in the most severe cases. *Addiction (Abingdon, England)* **104**: 768-74.
Weinstein, ND and Nicolich, M (1993) Correct and incorrect interpretations of correlations between risk perceptions and risk behaviors. *Health Psychol* **12**: 235-45.
WHO (2018) <2018 WHO global stats report on alcohol and health.pdf>.
Williams, R, Aithal, G, Alexander, GJ *et al.* (2020) Unacceptable failures: the final report of the Lancet Commission into liver disease in the UK. *Lancet* **395**: 226-39.
Williams, R, Aspinall, R, Bellis, M *et al.* (2014) Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. *Lancet* **384**: 1953-97.
World Health, O (2001) Brief intervention for hazardous and harmful drinking : a manual for use in primary care / Thomas F. Babor, John C. Higgins-Biddle. Geneva: World Health Organization.