Summary of changes made: The changes made have been highlighted in yellow. These include clarifications regarding efficacious findings reported in the text, avoiding pejorative terminology, as well as clearer sentences and explanations.

Predicting and Preventing Alcohol Relapse in Liver Transplant Patients for Alcohol-Related Liver Disease: A Systematic Review

ABSTRACT

Background: Despite a 450% increase in UK alcohol-related liver disease mortality over the last 30 years, little evidence-based guidelines exist regarding recidivism prevention post-liver transplant for alcohol-related liver disease.

Methods: A systematic review was conducted to identify demographic variables predictive of alcohol relapse and effective psychosocial interventions for alcohol-related liver disease patients post-liver transplant. Medline; CINAHL; EMBASE; PsychInfo; Web of Science; Clinical Trials Register; Electronic Theses Online Service (ETHOS) were searched from inception to 2017.

Results: Variables most significantly predictive of alcohol relapse post-transplant were: less than twelve (<12) months pre-liver transplant abstinence; presence of children; poor pre-liver transplant psychosomatic evaluation; non-compliance with post-liver transplant treatment plan; and active insurance policies. Structured management was the most effective psychosocial intervention in preventing alcohol relapse.

Conclusion: Findings should be interpreted cautiously due to limited and poor quality evidence. Rigorously designed further research of the psychosocial interventions targeting predictive demographic variables is recommended.

Keywords: transplantation; systematic review; substance abuse; alcohol liver disease; post-liver transplantation.

Summary box:

'What does this paper contribute to the wider global clinical community?'

- This paper provides an analysis of current research on psychosocial interventions for alcohol relapse in alcohol-related liver disease patients post-transplant;
- Increases awareness to the wider global clinical community of the most predictive demographic variables for alcohol relapse in this patient group;
- Details the most predictive alcohol usage demographic variables that effective psychosocial interventions could target when preventing alcohol relapse in alcohol-related liver disease patients post-transplant.

INTRODUCTION

Alcohol dependence treatment has been widely researched, ranging from brief interventions to pharmacotherapies accompanying withdrawal management e.g. acamprosate, naltrexone. A diverse array of psychosocial interventions are used in alcohol misuse treatment, with the most common being motivational interviewing and; cognitive behavioural therapy, including coping skills training, behavioural couple's therapy and relapse prevention (Raistrick and Tober 2004). There has been significant progress in the development of these evidence-based psychosocial interventions, with the treatments considered essential to an alcohol misuse treatment programme and research supporting positive behavioural change (Jhanjee 2014). Furthermore, a number of self-help approaches are also available for alcohol dependence. For example, Alcoholics Anonymous (AA) focuses on shared experience and mutual support to recover from addiction, with an approximate membership of two million (Alcoholics Anonymous 2001). Whilst there is an evidence-base for alcohol dependence treatment as detailed above, minimal research has been conducted into alcohol-related liver disease post-transplant.

The 2011 National Institute for Health and Clinical Excellence (NICE) guidelines make recommendations for alcohol dependence, yet there are no specific guidelines in the treatment of alcohol-related liver disease (NICE 2011) This is concerning considering there has been a 450% increase in alcohol-related liver disease mortality in the United Kingdom (UK) over the last 30 years (British Liver Trust 2009). Furthermore, increased importance on tackling alcohol dependence is currently at the forefront of NHS England's 2015 Mental Health Taskforce (NHS England 2015). Whilst systematic reviews have focused on alcohol dependence treatment (Pittler 2005; Miller 2011; Klimas et al. 2013), no systematic review was found on preventing alcohol relapse in alcohol-related liver disease patients post-transplant to date.

It remains uncertain whether the psychosocial interventions used for alcohol misuse will be as efficacious for liver transplant patients for alcohol-related liver disease (Kaner et al. 2009; Addolorato et al. 2013; Khan 2016). Although an argument could be that both populations have similar alcohol problems, the requirements for liver transplantation are stringent. The expectation for liver transplantation for alcohol-related liver disease is a documented alcohol abstinence of at least 6-months pre-transplant to predict long-term sobriety and ensure liver function recovery (Bird et al. 1990). However, this rule does not necessarily predict recidivism, with alcohol use post-transplant approaching 50% during the initial 5 years (Fairbanks 2012).

The overarching aim of this systematic review is to not only ascertain effective psychosocial interventions to prevent alcohol relapse in this population, but also identify specific demographic variables that such psychosocial interventions could target to ensure effective treatment. Both aspects of this review may assist nurses in developing an evidence-based post-liver transplant patient risk profile, as well as

contribute to the specific post-liver transplant psychosocial interventions delivered by liver transplant nurses.

METHOD

Data sources, search strategy, and study selection

Searches were conducted in January 2017 for published literature across four databases as well as searches for unpublished studies on three websites: Medline (1946-December 2017); CINAHL (1937-2017); EMBASE (1980-2017); PsychInfo (1806-2017); Web of Science; Clinical Trials Register; Electronic Theses Online Service (ETHOS). The key search terms were: liver transplant (MeSH), alcohol (MeSH), liver transplantation (free-text), alcohol$ (free-text). Free-text was used to maximise search sensitivity. Search thoroughness was increased with a reference list search of the included studies.

The primary author (IR) inspected all search citations, followed by relevant abstracts being identified independently and in parallel by the authors IR, IN, and MLW. IR undertook data extraction from included papers. At each stage, the entire review team reviewed the searches, screening of abstracts and full-texts, and results from data extraction. Review team discussion allowed for the resolving of any uncertainties. Author JS conducted an independent re-inspection of a random 20% sample for reliability.

Data extraction, study quality assessment, and analysis strategy

This review adopted a narrative systematic analysis approach (Sin and Norman, 2013). In accordance with the NICE Guidelines Manual (NICE 2012), data was extracted from all included studies for: **1)** demographic variables predicting alcohol relapse; **2)** psychosocial interventions. Data obtained included information about the sample, method, outcome and outcome measures. The included studies were critically appraised against the 'Critical Appraisal Skills Programme (CASP)' tool (Public Health Resource Unit 2012) and the relevant study reporting guidelines to determine risk of bias.

RESULTS

Overview of literature

Figure 1 illustrates the search process and total number of included and excluded studies in this review. A total of 8564 studies were retrieved following the search, with 23 studies finally included in the review. Three authors were contacted (with one response) to retrieve unreported or unclear study information. Seven studies were excluded due to alcohol relapse not assessed as the study outcome (Abosh et al. 2000, Harper et al. 2010; Stilley et al. 2010; Telles-Correia 2011); study not completed (Weinrieb et al. 2001); and, intervention effectiveness not being investigated (Zibari et al. 1996; Georgiou et al. 2003).

Overview of included studies

Included study designs were case-control (n=11); cohort (n=10); qualitative (n=1); and randomised controlled trials (n=1). The primary outcome was alcohol use post-liver transplant. Data collection methods included questionnaires (n=7); record review (n=7); clinical interview (n=4); self-reports (n=2); objectives scales (n=2); psychosomatic evaluation (n=1). Included studies were from the USA (n=10), Europe (n=9), Canada (n=1), UK (n=1), Australia (n=1), and East Asia (n=1). Table 1 summarises the characteristics of the included studies.

Quality of included studies

Using the CASP quality assessment criteria, three studies were judged to be low risk of bias, 12 studies medium risk of bias, and 8 high risk of bias (see Table 1 for a quality rating for each included study).

Overall, reporting of the included case-control and cohort studies conformed largely to the STROBE checklist (von Elm et al. 2008). However factors contributing to potential risks of bias include unjustified sample size, lack of validated outcome measures, and study withdrawals. The qualitative study by Newton (2006) met the majority of the COREQ criteria (Tong et al. 2007). However, the study failed to discuss reflexivity and data saturation. Furthermore, the randomised controlled trial conducted by Weinrieb et al (2011) did not fully meet CONSORT criteria (Schulz et al. 2010) nor fulfil checklist items such as appropriately describing the trial design, the method used to generate the random allocation sequence, or the type of randomisation.

Demographic variables predicting alcohol relapse

A total of 19 studies reported on demographic variables predicting alcohol relapse post-liver transplant. Two analyses were performed to ascertain these variables:

1) Calculating the number of studies identifying a particular demographic variable as significantly predictive -

Proportion of studies finding a statistically significant result with the demographic variable (%)
=
(Number of studies with significant results for the demographic variable/Total number of studies analysing the particular demographic variable) x100;

2) Ranking the variables –

Table 2 presents the most predictive demographic variable to least predictive of alcohol relapse post-transplant following the above calculation.

The variables most significantly predictive of alcohol relapse post-transplant are: <12 months pre-liver transplant abstinence; presence of children; poor pre-liver transplant psychosomatic evaluation; non-compliance with post-liver transplant

treatment plan; and, active insurance policies. However, the findings should be interpreted cautiously due to poor quality study designs.

Psychosocial interventions to prevent alcohol relapse

A total of four psychosocial intervention studies were included in this review (see Table 1): structured management (Bjornsson et al. 2005), clinical/medical management (Addolorato et al. 2013), substance abuse treatment using the 12-step programme (Rodrigue et al. 2013), and motivational enhancement (Weinrieb et al. 2011). Alcohol use post-transplant is the primary dichotomous outcome in these studies. However no usable data is provided by Weinrieb et al (2011).

All four interventions used an individual format. The motivational enhancement intervention had contact time between 4-7 sessions over 3-6 months (Weinrieb et al. 2011). The contact time is unclear in the remaining interventions (Bjornsson et al. 2005; Addolorato et al. 2013; Rodrigue et al. 2013). Overall, follow-up ranged from 3-55 months in the interventions structured management (Bjornsson et al. 2005), substance abuse treatment (Rodrigue et al. 2013), and motivational enhancement (Weinrieb et al. 2011). The clinical/medical management intervention (Addolorato et al. 2013) was unclear regarding follow-up. Both the Addolorato et al (2013) and Bjornsson et al (2005) studies were found to have medium risk of bias, with a low risk of bias in Rodrigue et al (2013). Weinrieb et al (2011) had a high risk of bias due to a lack of detail regarding the randomisation process, unclear use of the intention-to-treat approach, and not using conventional alpha levels to predict sample size due to no similar previous papers having been conducted. As a result, the risk of committing a Type I error is increased.

A suitable alpha level (i.e. significance level) at 5% was adopted by the three studies (Bjornsson et al. 2005; Addolorato et al. 2013; Rodrigue et al. 2013) to define the risk of a Type I error. The studies each have significant *p*-values – thus, the null hypothesis that the interventions have no effect on alcohol use post-transplant can be rejected. Although positive odds ratios are found for alcohol use in these studies, statistical significance is not necessarily indicated. None of the three studies report confidence intervals, and the *p*-value does not indicate the actual size of the difference between the two groups i.e. 'intervention' and 'no intervention' group. Due to the missing confidence intervals, the uncertainty level around the odds ratio is unclear. Additionally, the controlling of all confounding factors cannot be ensured retrospectively. Thus, these three studies may have overestimated or underestimated the odds ratio. The three studies each appropriately use the independent t-test to compare two unrelated group means on the same continuous variable. However the three studies do not discuss the dependent variable's approximate normal distribution for the independent variable groups, which would have aided assessment of study validity. Lastly, none of the four studies report a theoretical basis or the evidence-based origins of intervention development.

DISCUSSION

A wide-range of demographic variables were found to predict alcohol relapse in alcohol-related liver disease patients post-transplant. Presence of children, poor pre-liver transplant psychosomatic evaluation, non-compliance with post-liver transplant treatment plan, active insurance policies, and <12 months pre-liver transplant abstinence were found to be more predictive of alcohol use post-transplant than social circumstances, networks and personal relationships.

Lower post-transplant alcohol use was found using three interventions: structured management (Bjornsson et al. 2005), clinical/medical management (Addolorato et al. 2013), substance abuse treatment using the 12-step programme (Rodrigue et al. 2013). The structured management psychosocial intervention was found to be marginally more effective than the other interventions for alcohol-related liver disease patients (Bjornsson et al. 2005).

Strengths and weaknesses of the study

A lack of studies on demographic variables predictive of alcohol relapse has emerged from this review. Consequently, the ranking of these variables was tentative due to poor quality study designs. Thus, the wide range of variables were identified across studies but collectively no clearly significant variables were supports by the overall data.

Overall, the intervention studies are largely incomparable due to poor descriptions and minimal information, suggesting insufficient evidence to report firm conclusions. Nevertheless, as this review reflects the best available evidence, and with no other accessible study matching the review criteria, it can be assumed these findings provide a foundation for future research. A limitation of this review is the substantial statistical and methodological heterogeneity between an already small number of intervention studies preventing a meta-analysis.

CONCLUSION

Alcohol-related liver disease appears to be a poorly understood illness, with wider literature predominantly focusing on other areas of alcohol misuse. Considering the seriousness of alcohol-related liver disease, the focus should be on the emotional, physical and financial impact the illness has on the patient and caregiver, as well as the increasing NHS costs to treat these patients.

RELEVANCE TO CLINICAL PRACTICE

The findings suggest that future research investigates further the predictive validity of the demographic variables most predictive of alcohol relapse. A point of consideration could be using the list of alcohol usage predictive demographic variables to inform the selection of transplant candidates in the future. This is due to the rising NHS costs to treat alcohol liver disease patients (British Liver Trust

2009); however, moral and ethical questions may be raised about treatment availability that are beyond the scope of this review.

Three psychosocial intervention studies report desirable results in preventing alcohol relapse post-transplant: structured management (Bjornsson et al. 2005), clinical/medical management (Addolorato et al. 2013), substance abuse treatment (Rodrigue et al. 2013). It may be beneficial for such psychosocial interventions to focus on the demographic variables most predictive of alcohol relapse during intervention implementation to ensure effective treatment. Further research (particularly randomised controlled trials) is required to ascertain clinical effectiveness of such interventions.

From this review, it is possible for nurses to explore and to develop an evidence-based patient risk profile to inform the assessment and care management of post-liver transplant patients. Furthermore, the risk variables identified in the review could contribute to the specific post-liver transplant psychosocial interventions delivered routinely by liver transplant nurses.

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TABLES AND FIGURES

Study	Sample Size	Method -Format - Intervention contact time (if applicable)	Control Group	Follow Up	Risk of Bias
1. Addolorato *et al* (2013) Italy	92	-Clinical and medical management, involving counselling and pharmacological treatment. -Unclear contact time	Seen by consultant psychiatrists addiction experts	Unclear	Medium
2. Pfitzmann *et al* (2007) Germany	290	-Patient and family statements	None	2-15 years	Medium
3. Weinrieb *et al* (2011) USA	91	-Randomised Controlled Trial - MET: feedback and counselling style to motivate change. -4 to 7 sessions over 3 to 6 months	TAU	3-12 months	High
4. DiMartini *et al* (2010) USA	208	-ATLFB, caregiver questionnaire, clinic appointments and interviews by transplant psychiatrist	None	3-6 months for 10 years	Medium
5. De Gottardi *et al* (2007) Switzerland and France	387	-HRAR, alcohol use post-LT.	None	61.2±47.5 months	Medium
6. DiMartini *et al* (2006) USA	167	-Alcohol use post-LT, carer questionnaire, psychiatrist interviews.	None	5 years	Low
7. Kelly *et al* (2006) Australia	100	-Alcohol use post-LT.	None	5.6 years	Low

8. Perney *et al* (2005) France	61	-Alcohol use post-LT, pre and post-LT alcohol consumption questionnaire.	None	6–126 months	Medium
9. Osorio *et al* (1994) USA	86	-Alcohol use post-LT, pre and post-LT alcohol consumption questionnaire, interviews	NALD	7-21 months	Medium
10. Bjornsson *et al* (2005) Sweden	197	-*S*tructured management: evaluated by specialised consultant. Alcohol dependence treatment i.e. 12-step method. Post-LT: team social worker and LT coordinator appointments. -Unclear contact time.	NALD	31 months	Medium
11. Miguet *et al* (2004) France	51	-Alcohol use post-LT, alcohol behaviour questionnaires.	TAU	35.7 months	High
12. Jauhar *et al* (2004) USA	111	-Alcohol use post-LT, laboratory tests, interviews	None	44.1 ± 3.7 months	Medium
13. Gish *et al* (2001) USA	61	-Alcohol use post-LT, pre and post-LT psychiatric assessment.	None	6.9 years	High
14. Mackie *et al* (2001) UK	133	-Alcohol use post-LT, post-LT alcohol use questionnaire.	NALD	25 months	High
15. Burra *et al* (2000) Italy	51	-Alcohol use post-LT, pre-LT alcohol use questionnaire, psychosocial interviews (pre and post-LT)	None	3-12 months	High

16. Foster *et al* (1997) USA	63	-Alcohol use post-LT, pre-LT psychosocial interviews	None	49.3±21 months	High
17. Gedaly *et al* (2008) USA	147	-Alcohol use post-LT, liver function tests	None	41.2 months	Medium
18. Newton (2006) USA	76	-Alcohol use post-LT	None	None	Medium
19. Karim *et al* (2010) Canada	80	-Alcohol use post-LT, laboratory tests	None	Unclear	Medium
20. Egawa *et al* (2010) Japan	195	-Alcohol use post-LT, patient and family interviews with psychiatrist	None	3-4962 days	High
21. Rodrigue *et al* (2013) USA	138	-SA treatment: 12-step program, attending weekly individual and group sessions -Unclear duration of treatment.	No SA treatment	55 months	Low
22. Deruytter (2013) Belgium	108	-Alcohol use post-LT, pre and post-LT alcohol use questionnaire.	None	Mean 55 months.	High
23. Hartl *et al* (2011) Germany	226	-Alcohol use post-LT; post-LT psychiatric screening.	LT for diagnoses other than ALC	31±23 months	Medium

Table 1 Characteristics of included studies[a]

[a] LT: liver transplant; ALD: alcohol-related liver disease; ALC: alcohol liver cirrhosis; NALD: non-alcohol-related liver disease; TAU: treatment as usual; MET: Motivational Enhancement Therapy; SA: Substance Abuse; HRAR: High-Risk Alcohol dependence Relapse scale.

Table 2 Demographic variable ranking

Demographic Variable (ranked from most-to-least predictive of alcohol relapse post-transplant)	Proportion of included studies identifying the demographic variable as significantly predictive of alcohol relapse post-transplant (%)
<12 months pre-liver transplant abstinence	100
Presence of children	100
Poor pre-liver transplant psychosomatic evaluation	100
Non-compliant with post-liver transplant treatment plan	100
Active life insurance policy or other insurance policies at liver transplant	100
Mental illness	80
Patient or family lacks insight into alcohol problem	75
≤6 months pre-liver transplant abstinence	73
Other substance use e.g. tobacco, illegal drugs	70
Pre-liver transplant alcohol rehabilitation (protective variable)	67
Divorced/separated/alone	62.5
Family alcohol dependence history	57
Positive support network (protective variable)	50
Pre-liver transplant alcohol misuse or dependence diagnosis	50
High HRAR score (≥3)	50
Social issues e.g. unemployed, unstable housing	43
Age <40 years at liver transplant	40
Age >50 years at liver transplant	40
Married/significant other (protective variable)	40
Female gender	20

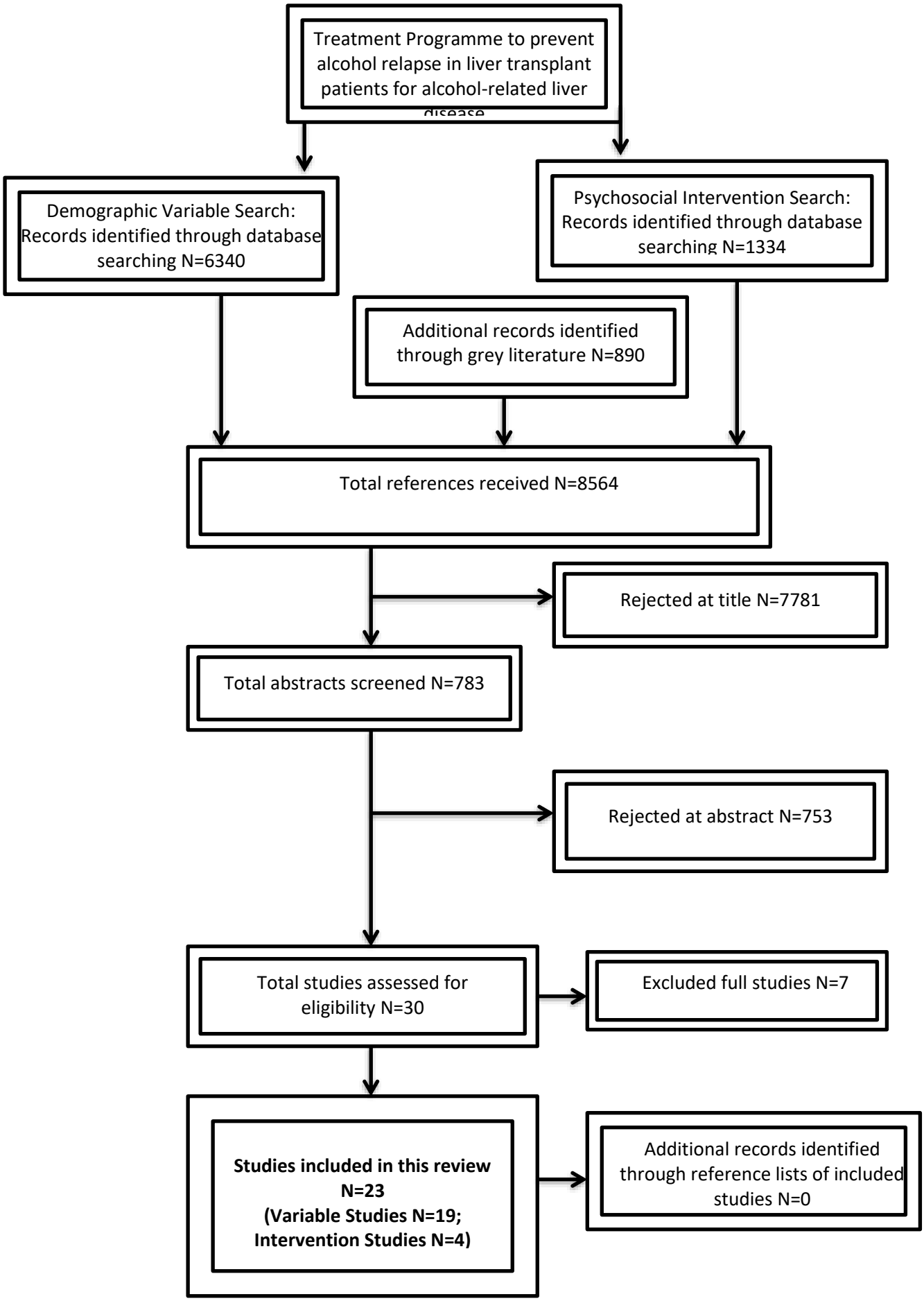

Figure 1 PRISMA flow diagram of the study selection process