JONNA LEVOLA

Alcohol Problems in Depression

Screening, patterns of drinking and relationship with quality of life

ACADEMIC DISSERTATION
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“Perhaps we'll break through the glass ceilings
Shatter the roof and emerge
From these boxes that they have us in cooped
And grow to smash the mold that they casted of you”

- SHAD -

ABSTRACT

Alcohol problems and depression are central causes of mortality, morbidity and disability as well as impaired quality of life (QoL). Both conditions are common and they often co-occur. Co-morbid alcohol problems and depression can exacerbate one another and screening for one condition in the presence of the other is important. Alcohol use patterns, e.g. binge drinking, are widely known to cause many somatic symptoms and diseases. However, the role of alcohol use patterns in psychiatric disorders such as depression has not been as extensively studied. Alcohol problems as well as alcohol use patterns are known to be associated with QoL in the general population. It is unclear what, if any, the associations between alcohol problems and alcohol use patterns and QoL are among depressed individuals. The aim of this dissertation was to elucidate the relationship between alcohol problems and alcohol use patterns, depression and QoL.

This dissertation is based on four peer-reviewed publications with the following aims. First, a systematic review was carried out in order to summarize the data on health-related quality of life (HRQoL) among alcohol dependent individuals and how depression affects HRQoL in this population. HRQoL is defined as that part of a person's overall QoL that is determined primarily by their health status. Second, the validity of the Alcohol Use Disorders Identification Test (AUDIT) -questionnaire and its abbreviated versions the AUDIT-C and AUDIT-3 in screening for at-risk drinking among depressed individuals was tested. Third, the association between binge drinking and depression was evaluated. Fourth, the associations between alcohol use variables and QoL in depressed and non-depressed individuals were investigated.

The literature review identified 42 studies, which reported on HRQoL or its domains in the context of alcohol dependence. A systematic approach to data collection was applied and the results were reported using the guidelines of narrative synthesis. Alcohol dependence was associated with impaired HRQoL, as well as decrements in domains such as general, mental and physical health, general and social functioning and daily activities. Depression was associated with more severely impaired HRQoL. Treatment improved HRQoL and its domains. Reduction or cessation of alcohol use was a determinant of this improvement in some, but not all, instances.

The other three studies in this dissertation utilized a subsample (n = 4020) of the cross-sectional FINRISK 2007 –study. Data were collected via a mail survey which included e.g. questions regarding socio-demographic information, physical and mental health and health habits. Alcohol use was investigated in more detail during a health check.

The AUDIT and AUDIT-C performed well in screening for at-risk drinking among men and women with self-reported depression. The optimal cut-offs (sensitivity and specificity ≥ 0.75) for men were ≥ 9 for the AUDIT and ≥ 6 for the AUDIT-C. For women, the best cut-offs ≥ 5 for the AUDIT and ≥ 4 for the AUDIT-C, though the specificity of the AUDIT-C among women with more severe depression fell below the defined limit of 0.75. The AUDIT-3 did not perform well in screening for at-risk drinking among women, but among men good levels of sensitivity and specificity were reached with a cut-off of ≥ 2.

The men who had engaged in binge drinking at least four times in the past 28 days had a 2.6-fold risk for depression when compared to men with less frequent binge drinking. This statistically significant association was found after adjusting for total volume of alcohol consumption, severity of alcohol problems measured with AUDIT-score and socio-demographic variables. No such association was found among women.

Depressed men and women reported poorer QoL and higher AUDIT-scores indicating more severe alcohol problems. They drank more and engaged in binge drinking more often than non-depressed respondents did. When analysing all respondents regardless of depression after adjustment for socio-demographic and other variables, both higher AUDIT-score and more frequent binge drinking were statistically significantly associated with impaired QoL; mean weekly alcohol consumption and abstinence were not. Frequency of binge drinking and AUDIT-score were associated with QoL in depressed and AUDIT-score in non-depressed individuals after adjustment for socio-demographic and other variables.

The present results support the importance of screening for and treating alcohol problems among depressed individuals. The results indicate that the AUDIT and AUDIT-C are valid instruments for screening purposes in this population. Attention should also be paid to alcohol consumption patterns, specifically binge drinking. This study found that severity of alcohol problems measured with AUDIT-scores and higher frequency of binge drinking were associated with impaired QoL among depressed individuals, as well as all respondents regardless of depression. Higher frequency of binge drinking was also associated with an increased risk for depression among men. It is an encouraging finding that treatment of alcohol dependence was associated with improvements in QoL.

TIIVISTELMÄ

Alkoholiongelmat ja masennus ovat keskeisiä kansansairauksiamme, kun arvioidaan väestön sairastavuutta, kokonaiskuolleisuutta, menetettyjä työvuosia ja elämänlaatua. Alkoholiongelmat ja masennus ovat yleisiä ja ne esiintyvät huomattavan usein myös samanaikaisesti. Samanaikaisesti esiintyessään ne usein vaikeuttavat toinen toisiaan ja toisen häiriön seulonta onkin tärkeää, jos jompikumpi on todettu. Alkoholin käyttötapojen, esimerkiksi humalajuomisen, tiedetään vaikuttavan monien somaattisten sairauksien ja oireiden syntyyn. Alkoholin käyttötapojen osuutta psyykkisten sairauksien, kuten masennuksen, syntyyn on tutkittu vähemmän. Alkoholiongelmat ja alkoholin käyttötavat ovat yhteydessä elämänlaatuun yleisväestössä. On kuitenkin epäselvää mikä on alkoholiongelmien ja alkoholin käyttötapojen suhde elämänlaatuun masentuneilla henkilöillä. Tämän väitöstutkimuksen tavoitteena oli selvittää alkoholiongelmien, alkoholin käyttötapojen, masennuksen ja elämänlaadun välisiä monimuotoisia yhteyksiä.

Tämä väitöstutkimus perustuu neljään vertaisarvioituun julkaisuun, joiden tavoitteet olivat seuraavat. Ensimmäisessä osatyössä toteutettiin systemaattinen kirjallisuuskatsaus, jonka tarkoituksena oli vetää yhteen tutkimustieto koskien alkoholiriippuvaisten terveyteen liittyvää elämänlaatua ja sitä miten masennus siihen vaikuttaa. Terveyteen liittyvä elämänlaatu on se osa kokonaiselämänlaatua, jonka määrittää pääasiassa henkilön terveydentila. Toisessa osatyössä AUDIT-kyselyn ja sen lyhennelmien AUDIT-C:n ja AUDIT-3:n toimivuutta arvioitiin masentuneiden henkilöiden riskijuomisen seulonnassa. Kolmannessa osatyössä selvitettiin humalajuomisen ja masennuksen välistä yhteyttä. Neljännessä osatyössä tutkittiin alkoholiongelmien ja alkoholin käyttötapojen yhteyttä elämänlaatuun erikseen masentuneilla ja ei-masentuneilla henkilöillä.

Kirjallisuuskatsauksessa tunnistettiin 42 artikkelia, joissa raportoitiin terveyteen liittyvään elämänlaatuun tai elämänlaadun eri osa-alueisiin kuuluvia vaikeuksia alkoholiriippuvaisilla. Tiedonkeruu toteutettiin systemaattisesti ja raportoinnissa noudatettiin narratiivisen synteesin ohjeistoa. Alkoholiriippuvuuden todettiin olevan yhteydessä heikentyneen kokonaiselämänlaadun lisäksi sen osa-alueisiin kuten heikompaan yleiseen, fyysiseen ja psyykkiseen terveyteen, huonompaan yleiseen ja sosiaaliseen toimintakykyyn, sekä päivittäistoimintojen vaikeuksiin. Masennus oli yhteydessä elämänlaadun vakavampaan heikentymiseen. Hoito vaikutti myönteisesti kokonaiselämänlaatuun ja eri osa-alueisiin. Alkoholin käytön lopettaminen tai vähentäminen myötävaikuttivat elämänlaadun kohenemiseen mutta eivät kaikissa tapauksissa olleet sen edellytys.

Kolmessa muussa osatyössä käytettiin FINRISKI 2007 -poikkileikkaustutkimuksen alaotosta (n = 4020). Tutkimukseen valikoituneet saivat postitse kyselyn, joka sisälsi kysymyksiä mm. sosiodemografisista tekijöistä, fyysisestä ja psyykkisestä terveydentilasta ja terveystottumuksista. Lisäksi heidät kutsuttiin terveystarkastukseen, jonka yhteydessä alkoholin käyttöä arvioitiin tarkemmin.

Riskijuomisen seulonta masentuneilla miehillä ja naisilla onnistui AUDIT- ja AUDIT-C -kyselyjä käyttäen hyvin. Miehille sopivimmat (herkkyys ja tarkkuus ≥ 0,75) raja-arvot olivat ≥ 9 AUDIT -kyselylle ja ≥ 6 AUDIT-C -kyselylle. Naisilla vastaavat raja-arvot olivat ≥ 5 AUDIT -kyselylle ja ≥ 4 AUDIT-C -kyselylle, joskin keskivaikeasti masentuneilla naisilla tarkkuus jäi alle 0,75: n. AUDIT-3 ei seulonut riskijuomista naisilla, mutta miehillä hyvä herkkyys ja tarkkuus saavutettiin raja-arvolla ≥ 2.

Miehet, joilla oli esiintynyt humalajuomista ainakin neljä kertaa viimeisten 28 päivän aikana, kärsivät 2,6-kertaa useammin masennuksesta kuin miehet joilla humalajuomista oli harvemmin. Tämä tilastollisesti merkitsevä yhteys säilyi, vaikka alkoholin kokonaiskulutus, alkoholiongelmien vaikeus AUDIT-pisteillä mitattuna ja sosiodemografiset muuttujat vakioitiin. Vastaavaa yhteyttä ei todettu naisilla.

Masentuneilla miehillä ja naisilla oli heikompi elämänlaatu ja korkeammat AUDIT-pisteet viitaten vaikeampiin alkoholiongelmiin. He myös joivat enemmän ja humalajuomista oli tiheämmin kuin miehillä ja naisilla joilla masennusta ei ollut. Kun sosiodemografiset ja muut muuttujat vakioitiin, tiheämpi humalajuominen ja korkeammat AUDIT-pisteet olivat tilastollisesti merkitsevästi yhteydessä heikentyneeseen elämänlaatuun sekä masentuneilla henkilöillä että kokonaisväestössä (joita ei ollut eroteltu masennuksen perusteella). Korkeammat AUDIT-pisteet olivat yhteydessä heikentyneeseen elämänlaatuun henkilöillä, joilla masennusta ei ollut. Alkoholin keskimääräinen kulutus tai raittius eivät olleet yhteydessä elämänlaatuun.

Nämä tulokset tukevat alkoholiongelmien tunnistamisen ja hoitamisen tärkeyttä masentuneilla henkilöillä. Tämän tutkimuksen perusteella AUDIT ja AUDIT-C -kyselyt tarjoavat seulontaan toimivan työkalun. Juomatapoihin, erityisesti humalajuomiseen, on myös syytä kiinnittää huomiota. Alkoholiongelmien vaikeus AUDIT-pisteillä mitattuna ja tiheämpi humalajuominen olivat yhteydessä heikompaan elämänlaatuun niin masentuneilla henkilöillä kuin kokonaisväestössäkin. Tiheämpi humalajuominen lisäsi myös masennuksen riskiä miehillä. Käytännön työn kannalta kannustava löydös oli, että alkoholiriippuvuuden hoito oli yhteydessä elämänlaadun paranemiseen.

CONTENTS

LIST OF PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text by their Roman numerals.

I Levola J, Aalto M, Holopainen A, Cieza A, Pitkänen T (2014). Health-related quality of life in alcohol dependence: a systematic literature review with a specific focus on the role of depression and other psychopathology. Nord J Psychiatry 68:369-384.

II Levola J, Aalto M (2015). Screening for at-risk drinking in a population reporting symptoms of depression: a validation of the AUDIT, AUDIT-C and AUDIT-3. Alcohol Clin Exp Res 39:1186-1192.

III Levola J, Holopainen A, Aalto M (2011). Depression and heavy drinking occasions: a cross-sectional general population study. Addict Behav 36:375-380.

IV Levola J, Pitkänen T, Kampman O, Aalto M (2018). The associations of alcohol use variables and quality of life in depressed and non-depressed individuals: a cross-sectional general population study. Qual Life Res 27:1217-1226.

 In addition, some unpublished data are presented.

ABBREVIATIONS

AUD	Alcohol Use Disorder
AUDIT	Alcohol Use Disorders Identification Test
AUROC	Area Under the Receiver Operating Characteristic
BDI	Beck Depression Inventory
BDI-SF	Beck Depression Inventory – Short Form
CDT	Carbohydrate-Deficient Transferrin
γGT	Gamma-Glutamyltransferase
DALY	Disability Adjusted Life Year
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition - Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition – Text Revision
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
HRQoL	Health-Related Quality of Life
ICD-9	International Statistical Classification of Diseases and Related Health Problems, 9th Revision
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
MDD	Major Depressive Disorder
NIAAA	National Institute on Alcohol Abuse and Alcoholism
OR	Odds Ratio
QALY	Quality Adjusted Life Year
QoL	Quality of Life
QF	Quantity-Frequency
TLFB	Timeline Follow-Back
WHO	World Health Organization

1 INTRODUCTION

Alcohol problems and depression are central causes of mortality, morbidity and disability (Statistics Finland [Tilastokeskus], 2015; Vos et al., 2012; The World Health Organization. Department of Mental Health and Substance Dependence, 2000). Both conditions are attributed with a broad range of psychosocial problems and socio-economic harm, and they widely affect individuals, families and communities (Levola et al., 2014; Cabello et al., 2012; Vos et al., 2012; Papakostas et al., 2004; Angermeyer et al., 2002; Foster et al., 1999).

Alcohol problems and depression are common in the Finnish general population. The prevalence of alcohol problems (including hazardous drinking 5.8%, alcohol abuse 0.5% and alcohol dependence 4.9%) has been reported to be 11.2%. All forms of alcohol problems are more common among men than they are among women; hazardous drinking 8.5 vs. 3.1%, alcohol abuse 0.9 vs. 0.1% and dependence 8.0 vs. 1.8% (Halme et al., 2008). The prevalence of major depression has been reported to be 6.5% (Pirkola et al., 2005). A diagnosis of depression is more common among women (8.3%) than men (4.6%). These prevalence figures indicate that alcohol problems and depression are major health concerns.

In addition to being individually prevalent, alcohol problems and depression also often co-occur (Sullivan et al., 2005). Individuals with alcohol problems have a greater risk of depression compared to those with moderate alcohol use (Hasin and Grant, 2015; Merikangas et al., 1998). Comorbid alcohol problems may in turn exacerbate depression and stand in the way of recovery (Sullivan et al., 2005).

Quality of life (QoL) is an important part of research when studying the individually unique effect of an illness on a person (Laudet, 2011). A large proportion of the population is generally satisfied with their lives (Evans and Huxley, 2002). In the general population, QoL is associated with emotional and physical well-being, marital status, employment and income as well as educational level and social adjustment (Layard et al., 2014). Both alcohol problems and depression are associated with impaired QoL (Angermeyer et al., 2002; Foster et al., 1999), but there may be mediating factors contributing to these associations which are not yet fully recognized. Such mediating factors may include e.g. patterns of alcohol use (Saarni et al., 2008; Foster et al., 1999). There is limited information on the dynamic of the effect of co-occurring alcohol problems and depression on QoL (Danovitch et al., 2016; Saatcioglu et al., 2008; Foster et al., 1999).

It is important in clinical practice to not only recognize those individuals who have alcohol use disorders (AUDs), but also those with at-risk drinking, that is, individuals

who are consuming alcohol in a way that puts them at risk for alcohol-related harm and developing AUDs. An effective method used to screen for at-risk drinking in the general population and among primary care patients is the Alcohol Use Disorders Identification Test (AUDIT) (Aalto et al., 2009; Daeppen et al., 2000; J. B. Saunders et al., 1993).It is necessary to evaluate the validity of the AUDIT in specific populations. Previous research has indicated that cut-offs may require tailoring according to e.g. gender, age and the aim of screening (Aalto et al., 2011; Reinert and Allen, 2007; Reinert and Allen, 2002). Systematic screening among patients presenting with psychiatric symptoms may result in more accurate diagnoses of AUDs (Appleby et al., 1997). The validity of the AUDIT has been tested in e.g. first-episode psychosis (Nesvag et al., 2010). However, despite the common co-occurrence of alcohol problems and depression, there is no previous research on the validity of the AUDIT in screening for at-risk drinking in the context of depression.

In addition to addressing the volume of alcohol use, patterns of alcohol consumption seem to be relevant when assessing alcohol-related harm (The World Health Organization. Department of Mental Health and Substance Dependence, 2000). A pattern of alcohol use, which includes binge drinking i.e. consuming large amounts of alcohol on one drinking occasion, has received attention in alcohol research in recent years. There is some evidence to suggest that, in addition to physical harm, a pattern of binge drinking is associated with psychiatric disorder, e.g. depression (Paljärvi et al., 2009; Manninen et al., 2006). The effect of binge drinking on mental health has not yet been studied as vigorously as that of alcohol dependence and alcohol problems. In addition, previous research has employed inconsistent definitions of binge drinking (Paljärvi et al., 2009; Manninen et al., 2006; Rehm et al., 2006).

The aim of this study was to elucidate the relationship between alcohol problems, depression and QoL. A systematic literature review was performed in order to summarize the data on QoL in alcohol dependent individuals and how diagnosed or self-reported depression affect QoL in this population. The validity of the AUDIT and its abbreviated versions in screening for at-risk drinking was tested in a general population sample with self-reported depression. The association between binge drinking and self-reported depression in the general population were analysed. Finally, the associations between QoL and alcohol use variables, including severity of alcohol problems indicated with AUDIT-scores and binge drinking, were investigated in individuals of the general population with and without self-reported depression.

2 REVIEW OF THE LITERATURE

2.1 Quality of Life

2.1.1 What is Quality of life (QoL) and why is it relevant?

Advances in medicine have led to better public health and longer life expectancy. People today live with chronic diseases more often than die from them, which may account for the increasing research interest in looking at how these extended years are lived (GBD, 2016). The World Health Organization (WHO) has recognized the importance of evaluating and improving people's quality of life (QoL) (The World Health Organization, 1995). It has been stated that in health-related research, emphasis must be put not only on the diagnosis of a disease, but also on health, functioning and well-being (Greenfield and Nelson, 1992).

Despite being recognized as a relevant measure in health-related research, there is no consensus on the definition of QoL (Moons et al., 2006). Different conceptualisations of QoL exist; they range from focusing on functioning in different roles and areas of life to affective states such as happiness, or to quantitative utility scores, which enable cost evaluations in health care (Moons et al., 2006). By measuring QoL it is possible to calculate quality-adjusted life-years (QALYs), a combination of the length and quality of life, which in turn enables direct comparison of the differences between specific health states and the effect of interventions (Dolan, 2000).

Perhaps the most widely accepted conceptualisation of QoL is that it reflects the subjective satisfaction and enjoyment with which an individual views his or her daily life and activities (Veenhoven, 1996; The World Health Organization, 1995). According to this definition, QoL is a broad term encompassing life satisfaction in general, not solely in relation to disease-related limitations on functioning. Quoting Felce (Felce and Perry, 1995): "Quality of life is defined as an overall general well-being that comprises objective descriptors and subjective evaluations of physical, material, social and emotional wellbeing together with the extent of personal development and purposeful activity, all weighted by a personal set of values."

Defining QoL in terms of life satisfaction may be most appropriate, because this definition successfully deals with relevant conceptual problems and it indicates how satisfied one is with life as a whole (Moons et al., 2006). Accordingly, QoL is viewed in

this study as encompassing overall physical, emotional and social well-being and functioning as well as life satisfaction.

2.1.2 Health-related quality of life (HRQoL)

Health-related quality of life (HRQoL) can be considered as that part of an individual's overall QoL that is determined primarily by their health status. HRQoL can be defined in general or with regard to a specific disease and it can be influenced by clinical interventions. HRQoL has been defined as "the functional effects of an illness and its consequent therapy upon a patient, as perceived by the patient" (Schipper et al., 1996).

As is the case with QoL, the conceptualisation of HRQoL is somewhat varied (Fallowfield, 2002; Schipper et al., 1996; Testa and Simonson, 1996; Uutela and Aro, 1993). The primary domains of HRQoL are often reported to be the social, psychological/emotional, physical and occupational areas of an individual's life (Fallowfield, 2002; Testa and Simonson, 1996). In the field of alcohol research, HRQoL has been viewed as not only being connected to the clinical status of an individual's dependence, but comprising domains of general functioning including physical, psychological, social and role-specific functioning, as well as environmental support (Longabaugh et al., 1994).

The term HRQoL has received criticism and its appropriateness has been questioned altogether (Moons, 2004). It has been argued that QoL and health status are distinct concepts (Moons et al., 2006). Despite this criticism, the term HRQoL is widely used in medical research. In this study, the conceptualisation of HRQoL in the context of alcohol dependence encompasses the following primary domains: general health, physical and mental health, as well as general and social functioning and activities of daily life.

2.1.3 Measuring QoL

The spectrum and content of tools used to measure QoL and HRQoL are quite broad (Linton et al., 2016; Moons et al., 2006). Both uni- and multidimensional measurements are commonly used, as are disease-specific and generic measurements. In addition to standardized instruments, other means of evaluation include e.g. qualitative interviewing.

A recent review identified 99 different generic instruments covering 196 different domains of QoL or HRQoL in adults (Linton et al., 2016). The range of disease-

specific instruments appears to be even more diverse. While disease-specific measures may provide more detailed information on the effect of a specific illness on an individual's life, they lack in comparability between disease states.

Single-item measures of global QoL can be used in large population surveys where they have been found to have good validity and reliability (de Boer et al., 2004). Single-item measures can e.g. ask the respondent to rate their perceived overall QoL during a defined time-period on a scale of zero to 10 with zero being the worst possible alternative and 10 the best.

2.2 Alcohol use

2.2.1 Defining alcohol problems

There exists much variation and lack of a universal consensus as to the terminology and definitions of alcohol problems. A common criticism of previous literature has been the difficulty to consistently compare different types of alcohol consumption patterns and their associated health risks due to these inconsistencies (Epstein et al., 2004). Examples of commonly used terms include problem use, misuse, hazardous, heavy and binge drinking, alcohol abuse, alcohol use disorder, harmful use and dependence. In Finland, alcohol problems is often used as an umbrella term to refer to the mutually exclusive groups of hazardous drinkers and those with diagnosable harmful use or alcohol dependence (Seppä et al., 2012).

In addition to inconsistent terminology, alcohol problems can also be defined in many ways. Two common methods are measuring consumed alcohol amounts and categorizing alcohol use in terms of diagnostic categories. When measuring amounts, the longest tradition is with measuring total volume of alcohol consumption, which has been used to link alcohol to certain diseases (Bruun et al., 1975). While total consumption is relevant, increasing attention has been paid to the patterns in which alcohol is consumed (Epstein et al., 2004). Previous studies have been able to establish the role of alcohol consumption patterns in relation to mortality and some diseases (Laramée et al., 2015; Rehm et al., 2006; Kauhanen et al., 1997).

Alcohol consumption can be measured in standard drinks or units or as pure grams (g) of alcohol. It is to be noted, however, that standard drinks or units are hardly standard at all, but vary in different countries. This variation is largely due to market interests and a standard drink is equivalent to the single unit of alcohol typically sold

within a country. In Finland, a standard drink is equivalent to approximately 12 g of absolute alcohol (i.e., 33 cl bottle of beer, 12 cl glass of wine, 4 cl of spirits). In the United States, a standard drink contains 12-14 g of alcohol (i.e., 35 cl bottle of beer, 15 cl glass of wine, 4.4 cl of spirits). In Austria, a standard drink is 6 g of alcohol, in Australia 10 g, whereas in Japan, it contains nearly 20 g (National Institute on Alcohol Abuse and Alcoholism).

At-risk, hazardous and heavy drinking

At-risk, hazardous and heavy drinking are not diagnostic categories but closely inter-related terms, which are used when alcohol consumption is at a level which puts an individual at increased risk for acute or chronic health harm. Their definitions vary in the literature. Hazardous drinking is most often defined as consuming alcohol at a risky level but not meeting the diagnostic criteria for alcohol use disorders (AUDs).

Heavy drinking and at-risk drinking are often used synonymously when alcohol use exceeds set cut-offs. These groups may include individuals with AUDs when their alcohol use exceeds these cut-offs. At-risk drinking in accordance with the Finnish guidelines is ≥ 276-288 g weekly for men and ≥ 144-192 g for women (Current Care guidelines, 2015). In the U.S., the National Institute on Alcohol Abuse and Alcoholism (NIAAA) defines heavy drinking as consuming ≥ 180-210 g weekly for men and ≥ 96-122 g for women (Centers for Disease Control and Prevention, 2016). According to the WHO, risks for chronic harm due to alcohol use are elevated when weekly intake is ≥ 280 g or men and ≥ 140 g for women (The World Health Organization, 2000).

Binge drinking

The definition of binge-drinking - also referred to as heavy episodic drinking or heavy drinking occasions – varies in literature (Manninen et al., 2006; Pitkänen, 2006; Kauhanen et al., 1997; Poikolainen, 1983). The WHO guidelines designate consuming at least 60 g of alcohol for men or 40 g for women on one occasion to constitute a substantial risk for acute harm (The World Health Organization, 2000).

The definition of binge drinking in accordance with the Finnish guidelines is consuming on one drinking occasion ≥ 6-7 standard drinks for men and ≥ 4-5 for women (Current Care guidelines, 2015).

The NIAAA defines binge drinking as a pattern of alcohol consumption that brings the blood alcohol concentration (BAC) level to ≥ 0.08%. This pattern of drinking usually corresponds to ≥ 60-70 g on a single occasion for men and ≥ 48-56 g for

women, generally within about two hours (Centers for Disease Control and Prevention, 2016).

Diagnostic criteria

The International Classification of Diseases, 10th revision (ICD-10) classifies the diagnoses harmful use of alcohol (F10.1) and alcohol dependence (F10.2x) (The World Health Organization, 2016). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) only classifies a diagnosis of AUD the severity of which —mild, moderate, or severe— is based on how many of the 11 criteria are met (American Psychiatric Association, 2013). Prior to the DSM-5, alcohol abuse and dependence were classified separately in the DSM-IV (National Institute on Alcohol Abuse and Alcoholism, 2016). Alcohol dependence was defined quite similarly to that in ICD-10.

Terminology in the present study

In this study, the term "alcohol problems" is used to refer to individuals with hazardous drinking, harmful use or alcohol dependence. The term at-risk drinking is used to refer to individuals – with or without a diagnosable AUD – who consume alcohol in amounts, which exceed the limits for acute or chronic harm set by the WHO (3). Binge drinking is defined according to the Finnish guidelines (51). Alcohol dependence is defined according to either the ICD or DSM and AUDs according to DSM (Table 1). Terminology used in previous literature has been amended in this study to correspond to these definitions when possible.

Table 1. Diagnostic criteria (abridged) of harmful use of alcohol, alcohol abuse, alcohol dependence and alcohol use disorder (The World Health Organization, 2016; American Psychiatric Association, 2013; American Psychiatric Association, 1994).

ICD-10		DSM-IV		DSM-5
Harmful use	Dependence	Abuse	Dependence	Alcohol use disorder (AUD)
A pattern of alcohol use that is causing damage to physical or mental health (no concurrent diagnosis of alcohol dependence).	Three or more of the following have been present together at some time during the previous year.	A maladaptive pattern of alcohol use leading to clinically significant impairment or distress; at least one criterion within a year (never met criteria for dependence).	A maladaptive pattern of alcohol use leading to clinically significant impairment or distress; at least three criteria within 12 months.	The presence of at least two criteria within 12 months. The severity of the AUD is defined as Mild (2-3 symptoms), Moderate (4-5 symptoms) or Severe (≥ 6 symptoms).
Continued drinking despite actual damage to the mental or physical health of the user.	A strong desire or compulsion to drink.	Alcohol use resulting in a failure to fulfil major role obligations.	Tolerance; a need for markedly increased amounts to achieve desired effect or diminished effect of alcohol.	Drinking in larger amounts or over a longer period than intended.
	Difficulties controlling drinking onset, termination, or levels of use.	Recurrent alcohol use in situations in which it is physically hazardous.	Withdrawal; the characteristic withdrawal syndrome or use of alcohol or a closely related substance to relieve withdrawal symptoms.	A persistent desire or unsuccessful efforts to cut down or control alcohol use.
	A physiological withdrawal state; the characteristic withdrawal syndrome or use of the same or a closely related substance to relieve withdrawal symptoms.	Recurrent alcohol–related legal problems.	Drinking in larger amounts or over a longer period than intended.	A great deal of time is spent obtaining, drinking or recovering from alcohol.
	Tolerance; increased doses are required to achieve desired effect.	Continued use despite persisting problems caused or exacerbated by alcohol.	A persistent desire or unsuccessful efforts to cut down or control alcohol use.	Craving or a strong desire to use alcohol.
	Progressive neglect of alternative interests or increased time used to obtain, drink or recover from alcohol.		A great deal of time spent obtaining, drinking or recovering from alcohol.	Alcohol use resulting in a failure to fulfil major role obligations.
	Persistent drinking despite clear evidence of harmful consequences.		Important activities given up or reduced because of drinking.	Continued use despite persisting problems caused or exacerbated by alcohol.
			Continued drinking despite knowledge a health problem that caused by alcohol use.	Important activities given up or reduced because of drinking.
				Recurrent alcohol use in situations in which it is physically hazardous.
				Continued drinking despite knowledge of a health problem caused by alcohol use.
				Tolerance; a need for markedly increased amounts to achieve desired effect or diminished effect of alcohol.
				Withdrawal; the characteristic withdrawal syndrome or use of alcohol or a closely related substance to relieve withdrawal symptoms.

2.2.2 Measuring alcohol use: The Timeline Follow-Back

When measuring alcohol consumption, accuracy and usability are important factors. Self-reports have been the basis upon which estimation of alcohol consumption has been founded (Del Boca and Darkes, 2003; Room, 2000). Self-reports of alcohol consumption have been subject to criticism because of their lack of accuracy; specifically underreporting observed in individuals with alcohol-related problems (Searles et al., 2000).

The Timeline Follow-back (TLFB) is a daily drinking estimation measure, which is based on retrospective self-reports and administered by trained interviewers. The interviewer reviews alcohol consumption with the interviewee day-by-day using key-events of life to help in recalling frequency and amounts of all alcoholic beverages consumed as precisely as possible. The timeframe for the TLFB can vary. In large study samples, the TLFB with a one month window was found to be representative of annual consumption (Vakili et al., 2008). The TLFB is a preferred instrument for measuring alcohol consumption in large study populations (Sobell et al., 1988).

2.2.3 Other methods of measuring alcohol use

Quantity-frequency (QF) methods have been one of the first ways to assess alcohol consumption (Room, 2000). People are asked to report their usual or average consumption: "On how many days of the week have you had a drink?" and "How much alcohol did you drink on a drinking day?"

The major benefit of QF methods is that they are fast to use. QF methods have been widely used to evaluate alcohol consumption in research settings (Room, 2000). However, they have been criticized as underestimating alcohol consumption (Romelsjo et al., 1995; Sobell et al., 1982). When asking about average consumption, days of sporadic heavier drinking – which are associated with alcohol–related problems – tend to go unreported (Rehm et al., 1999).

Concurrent recall methods are based on self-reporting which happens real-time or in a close temporal proximity of the actual drinking occasion. Examples include paper or computerized day-by-day drinking diaries. Concurrent recall methods have been shown to be the most accurate self-reporting method, but they are time-consuming and laborious and have not been used widely in alcohol research (Searles et al., 2000; Carney et al., 1998; Sobell et al., 1988).

2.2.4 Screening for alcohol problems: The Alcohol Use Disorders Identification Test (AUDIT)

Individuals with alcohol problems often seek medical help for reasons other than their drinking, e.g. psychiatric symptoms such as depression (Reid et al., 1986). The AUDIT is a screening tool developed originally for primary care in order to help identify those with at-risk drinking without yet having marked alcohol-related physical or social consequences (Saunders et al., 1993). Today, the AUDIT is widely used in a variety of clinical settings (Aalto et al., 2009; Reinert and Allen, 2007).

The AUDIT consists of 10 questions, which can be divided into two types (Appendix I). The first three questions evaluate drinking quantity and frequency. The remaining questions proceed to evaluate symptoms of harmful use and dependence, which can exist before diagnostic criteria are met. All 10 questions are scored from zero to four thus yielding a maximum score of 40.

In order to improve user-friendliness in clinical settings, several abbreviated versions of the AUDIT have been developed. The most commonly used abbreviations are the AUDIT-C and AUDIT-3. The AUDIT-C consists of the first three questions of the AUDIT which quantify the amount of alcohol consumed (Bush et al., 1998). The AUDIT-3 consists of only the third question from the original AUDIT regarding the frequency of consuming ≥ 6 drinks on a single occasion (Bradley et al., 2003; Bush et al., 1998).

Cut-off points are lower when the purpose of screening is to identify at-risk drinking than AUDs (Reinert and Allen, 2007). When the purpose of screening is to identify at-risk drinkers, the sensitivity and specificity of the AUDIT with cut-offs of ≥ 5 to ≥ 7 have been between 0.73-0.96 and 0.88-0.96, respectively (Reinert and Allen, 2007). When screening for AUDs, the standard cut-off has been ≥ 8 points which has yielded a median sensitivity of 0.86 and a median specificity of 0.89 (Reinert and Allen, 2002). Some evidence indicates that cut-offs should be adjusted by gender (Reinert and Allen, 2007).

For the AUDIT-C, a cut-off of ≥ 4 among men to screen for at-risk drinking has been recommended (sensitivities 0.85-1.00 and specificities 0.53-0.77) (Reinert and Allen, 2007). To screen for AUDs, a recommended cut-off has been ≥ 5 (sensitivities 0.61-0.94, specificities 0.71-0.77). Among females, the recommended cut-offs for at-risk drinking and AUDs have been ≥ 3 (sensitivity 0.91 and specificity 0.52) and ≥ 4 (sensitivities 0.38-0.86, specificities 0.82-0.83), respectively (Reinert and Allen, 2007).

The AUDIT-3 is not consistent in screening for at-risk drinkers: sensitivities have been between 0.51-0.83 and specificities between 0.91-1.00 (Reinert and Allen, 2007) with a cut-off of ≥ 1. The NIAAA has recommended that clinicians use this item as an

initial screening question for at-risk drinking, but the number of drinks should be lowered from six to five drinks per occasion for men and four for women (National Institute on Alcohol Abuse and Alcoholism, 2005).

Some studies have also shown good validity of the AUDIT or its abbreviations in specific sub-populations with psychiatric disorders, e.g. first episode psychosis (Nesvag et al., 2010; Maisto et al., 2000). The validity of the AUDIT-C in screening for alcohol dependence, any AUDs and any AUDs or at-risk drinking among individuals with past year anxiety, mood and personality disorders has previously been studied (Dawson et al., 2005). This study found that the validity of the AUDIT-C was comparable to the validity found in the general population. The validity of the AUDIT-C in screening for at-risk drinking as an independent group was not analysed (Dawson et al., 2005).

2.2.5 Other methods of screening for alcohol problems

The 25-question Michigan Alcoholism Screening Test (MAST) includes questions about drinking behaviour and alcohol-related problems. It is particularly useful in screening for alcohol dependence for which it was originally designed (Selzer, 1971). A review showed sensitivities between 0.36-1.00 and specificities between 0.36-0.96 in screening for AUDs (Storgaard et al., 1994). However, it is not particularly sensitive when screening for less severe problems such as hazardous drinking (Saunders and Kershaw, 1980).

The CAGE questionnaire is short and simple consisting of only four questions (Ewing, 1984). The CAGE has been proven effective in screening for AUDs in primary care with sensitivities between 0.43-0.94 and specificities between 0.70-0.97 (Fiellin et al., 2000). However, the sensitivities of CAGE in screening for at-risk drinking have been between 0.14-0.84 with specificities between 0.79-0.97 (Fiellin et al., 2000).

Even shorter, ultra-brief screening has been tested. These ultra-brief screens use one question to screen for at-risk drinking, e.g. "On any single occasion during the past three months, have you had more than five drinks containing alcohol?" This single question screen had a sensitivity of 0.62 and a specificity of 0.93 (Taj et al., 1998). In a recent meta-analysis of ultra-brief screening of heavy drinking the pooled sensitivity of a single-question approach was 0.55 and a specificity of 0.87 (Mitchell et al., 2014).

Biochemical markers have been advocated as alcohol screening and monitoring tools to substantiate self-reports of alcohol use (Miller and Anton, 2004). The most commonly used biochemical markers have been carbohydrate-deficient transferrin (CDT) and gamma-glutamyltransferase (γGT) (Conigrave et al., 2003). Other

traditional markers have included aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and the red blood cell volume (mean corpuscular volume: MCV) (Conigrave et al., 2003).

A review of the performance of CDT and γGT reported that in primary health care settings and in general population samples they are not usable in screening for at-risk and heavy drinking or AUDs due to very low with sensitivities 0.20 (Salaspuro, 1999). The specificity of CDT has often been found to be over 0.90, as it is not influenced by medications and is elevated in only few instances such as rare genetic variants, very severe liver disease and biliary cirrhosis (81). The specificity of γGT is typically lower due to more confounders such as common medications and hormones (81).

There are many alternative methods with good sensitivity and specificity when screening for AUDs. However, none of these methods perform as well as the AUDIT when the objective of screening is to identify at-risk drinking.

2.2.6 Impact of alcohol problems

Recent statistics indicate that 5.9% of all global deaths, that is 3.3 million deaths annually, are due to alcohol and alcohol has been identified as a component cause for over 200 health conditions (The World Health Organization, 2014). Alcohol related mortality has increased globally (The World Health Organization, 2008). A large proportion of the disease burden attributable to alcohol arises from acute alcohol consumption. Binge drinking puts an individual at risk for acute alcohol-related harm, specifically unintentional and intentional injuries including road traffic crashes, violence, suicides and fatal alcohol-related injuries, as well as sexually transmitted diseases (The World Health Organization, 2014; Baliunas et al., 2010). Among 20-39 year olds, approximately 25% of all deaths are alcohol-attributable (The World Health Organization, 2014). It has also been demonstrated that the pattern of consumption is key in the relationship between alcohol and cardiovascular disease: the potential beneficial cardio-protective effect of relatively low levels of drinking disappears if an individual engages in binge drinking (Goel et al., 2018; Roerecke and Rehm, 2014).

The consequences of long-term alcohol use to an individual's health vary according to e.g. individual risk factors (The World Health Organization, 2014). A few of the most important disease groups for which alcohol is a risk-factor are cardiovascular (Rehm et al., 2016; Roerecke and Rehm, 2014) and gastrointestinal diseases (Rehm et al., 2013; Irving et al., 2009), diabetes mellitus (Baliunas et al., 2009), cancers (Nelson et al., 2013; Rehm and Shield, 2013; Seitz et al., 2012), infectious diseases such as

tuberculosis (Lönnroth et al., 2008) and neurologic and psychiatric disorders such as epilepsy (Samokhvalov et al., 2010) and depression (Fergusson et al., 2009).

Alcohol-related harm does not solely encompass harm to an individual's health, but also socioeconomic harm such as loss of earnings, unemployment or family problems, stigma and barriers to accessing health care (The World Health Organization, 2014). The annual alcohol-related costs to society in Finland are approximately 1.3-1.4 billion Euros of which 300-400 million Euros are attributed to health and welfare services (Official Statistics of Finland, 2015).

Alcohol and alcohol-related conditions contribute substantially to the global burden of disease (The World Health Organization, 2014). According to a recent evaluation, 5.1% of the global burden of disease and injury, as measured in disability adjusted life years (DALYs), was attributable to alcohol (The World Health Organization, 2014). Alcohol-related disability was attributed most prominently to unintentional injuries, neuropsychiatric disorders (e.g. alcohol use disorders) and cardiovascular illness.

AUDs cause even more disability than direct mortality (The World Health Organization, 2014). Alcohol dependence is associated with severe levels of disability and psychosocial impairment (Pitkänen et al., 2016; Levola et al., 2014; Dawson et al., 2009) and disability increases linearly with the severity of alcohol dependence (Dawson et al., 2009).

The repercussions of alcohol with respect to mortality, morbidity and related costs are formidable and efforts should be made to relieve this disease burden.

Health-related Quality of Life and alcohol use

Abstinence or reduction of alcohol consumption have traditionally been the primary treatment goals for alcohol dependence. However, recovery from AUDs has been defined as "a process of change through which an individual achieves abstinence and improved health, wellness, and quality of life" (Center for Substance Abuse Treatment, 2007). Thus, quantification of alcohol consumption is not sufficient to reflect the full range treatment outcomes (Laudet, 2011; McLellan et al., 1996).

Those with alcohol dependence report impaired HRQoL compared to the general population. HRQoL is more severely impaired in alcohol dependence than in many chronic somatic health conditions (Donovan et al., 2005). The relationship between HRQoL and alcohol dependence is moderated by a number of socio-demographic and patient characteristics, including co-occurring psychiatric disorders, age, education and gender (Donovan et al., 2005).

HRQoL is impaired also in at-risk compared to moderate drinkers (Essex et al., 2014; Valencia-Martin et al., 2013; Paul et al., 2011; Volk et al., 1997). At-risk drinkers experience more problems with mental and physical dimensions of HRQoL than do moderate drinkers (Essex et al., 2014). However, some studies have shown no differences or even better scores among moderate and at-risk drinkers when compared to non-drinkers in some domains of HRQoL, e.g. physical activity (Valencia-Martin et al., 2013; Paul et al., 2011).

While the literature showing that HRQoL is impaired among alcohol dependent individuals is quite strong, there is limited information as to the effect of treatment on HRQoL (Daeppen et al., 2014). One prospective observational study reported rapid improvement in the mental dimension of HRQoL following treatment initiation among individuals with alcohol dependence (Daeppen et al., 2014). Improvement of HRQoL was associated to the extent of alcohol use after initiation of treatment; HRQoL measures were close to the general population norm in patients with alcohol dependence with no or nearly no alcohol use.

The effect of alcohol use patterns, specifically binge drinking on HRQoL has been addressed in some studies (Luquiens et al., 2016; Mohamed and Ajmal, 2015; Monahan et al., 2012; Wen et al., 2012; Paul et al., 2011; Okoro et al., 2004; Volk et al., 1997). These studies agree that frequent binge drinking has a negative impact on HRQoL and especially its mental dimensions.

2.3 Depression

2.3.1 Defining depression

Depression is a common mental disorder, which affects an individual's mood and results in a decreased ability to function. Depression is a cause of intense suffering and disability and places the afflicted individual at an increased risk for self-harming behaviour and premature death (Saarni et al., 2007; Osby et al., 2001; Black et al., 1987).

Diagnostic categories

In order to meet the diagnostic criteria for depression, according to the ICD-10, there are 10 depressive symptom criteria, at least four of which must be present most of the

time for a minimum of two weeks (The World Health Organization, 2016). Of the three core symptoms, at least two (depressed mood, loss of interest in everyday activities, reduction in energy) plus at least two of the remaining seven symptoms (disturbed sleep, poor concentration or indecisiveness, low self-confidence, poor or increased appetite, suicidal thoughts or acts, agitation or slowing of movements, guilt or self-blame) are required for diagnosis. Depression is classified into mild, moderate or severe according to the number of depressive symptoms present.

Major depressive disorder (MDD) according to the DSM-5 can be diagnosed when depressed mood or a loss of interest or pleasure in daily activities are present for longer than two weeks (American Psychiatric Association, 2013). Five of the following symptoms must be present: depressed or irritable mood, decreased interest or pleasure in most activities, weight change or change in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, diminished ability to think or concentrate, thoughts of death or suicide. A depressive episode is classified as mild, moderate or severe according to the number of symptoms present.

2.3.2 Screening for depression: the Beck Depression Inventory

Screening of risk-groups is important in order to recognize those individuals who have depressive symptoms even when they are not the primary reason for seeking medical help. Targeted screening is recommended by the Finnish Current Care Guidelines (Isometsä et al., 2009).

There are several possible methods of screening for depression, one of which is the Beck Depression Inventory (BDI). The original 21-question Beck Depression Inventory (BDI) is a screening tool for depression designed for use in the general population (Beck et al., 1988). It has also been found to perform well in screening for depression in primary care (Williams et al., 2002). The BDI was first published in 1961 and then revised in 1971. A modified version, the BDI-II, was published in 1996 (Beck et al., 1996). The BDI is not a diagnostic instrument.

There are four to six alternate responses in the original 21-question BDI. Each question is scored from zero to three points yielding a maximum score of 63 points. While used of screening, the BDI and its version are also used to indicate depression severity with higher total scores indicating more severe depressive symptoms. In the original 21-question BDI, zero to nine points suggests no depression, 10-18 indicates mild to moderate depression, 19-29 indicates moderate to severe depression and 30-63 signifies indicates severe depression (Beck and Beck, 1972).

The BDI has been extensively studied and is widely used in primary care (Beck et al., 1988). The BDI has also been found to be valid in screening for depression in many specific patient populations, e.g. dual diagnosis patients (Lykke et al., 2008).

The Beck Depression Inventory, Short Form (BDI-SF) is a simplified shorter version of the original BDI. It is composed of 13 items (questions 1, 2, 3, 4, 5, 7, 9, 12, 13, 14, 15, 17 and 18 of the original 21-question BDI). In the BDI-SF, the response options for each question have been narrowed down to four for simplification (Beck and Beck, 1972). The BDI-SF has been found to be an adequate alternative to the original BDI (Cathebras et al., 1994; Beck et al., 1974).

In the original study of Beck et al. in 1972, ≥ 4 points on the BDI-SF were defined as indicating mild and ≥ 8 points moderate to severe symptoms of depression in a primary care setting (Beck and Beck, 1972). Other literature supports a score ≥ 8 as indicating depression (Love et al., 2004; Cathebras et al., 1994), while some studies have suggested a higher cut-off of ≥ 10 points (Furlanetto et al., 2005).

2.3.3 Comorbidity with alcohol use

There are four widely accepted classes of explanation models for the common co-occurrence of two disorders: 1) one disorder predisposes to the other, 2) the existence of shared risk factors that predispose persons to both disorders, 3) separate but inter-correlated risk factors that predispose persons to both disorders and 4) the two disorders are reflections or the same condition (Caron and Rutter, 1991). Alcohol use can be the direct cause of psychiatric symptoms or it can exacerbate existing conditions. In some instances, alcohol problems may be the result of an ill-advised attempt to alleviate psychiatric distress.

Alcohol dependent individuals frequently report severe problems with anxiety, distress and depression (Pitkänen et al., 2016) and AUDs commonly co-occur with psychiatric disorders of which affective, anxiety and personality disorders are the most common comorbidites (Hasin et al., 2007; Pirkola et al., 2006).

Depression and alcohol problems

There is a well-documented association between depression and alcohol problems, which cannot be explained solely by the random overlapping of these two conditions (Sullivan et al., 2005; Lynskey, 1998). A systematic review of 35 studies estimated the prevalence of current alcohol problems in depressed patients to be 16%, as compared

to 7% in the general population (Sullivan et al., 2005). This review also demonstrated that alcohol problems complicate treatment of depression and can stand in the way of recovery. In the Finnish general population, major depression was twice as common in individuals with past year alcohol dependence compared to the general population (Pirkola et al., 2006).

Most studies examining the co-occurrence of depression and alcohol problems have focused on the explanation model where causality is presumed (Lynskey, 1998). There is evidence to suggest that alcohol problems may predispose to an increased risk of depression (Fergusson et al., 2009). Furthermore, the risk of depression may increase with alcohol problems in comparison to moderate alcohol use and increase further as alcohol abuse proceeds to alcohol dependence (Merikangas et al., 1998). However, the direction of causality has been proposed both ways i.e. that depression predisposes to alcohol problems via self-medication (Chutuape and de Wit, 1995). A twin-study indicated that amongst males the observed correlations between alcohol problems and depression could be explained by genetic factors but in females, this correlation was explained by individual environmental factors together with either genetic effects or family environment (Tambs et al., 1997).

The explanations for comorbidity are not purely academic, but may have direct implications for treatment (Lynskey, 1998). If depression is secondary i.e. the result of alcohol problems then the appropriate treatment would be reduction or cessation of alcohol use, which would alleviate or eliminate depressive symptoms. On the other hand, if depression is primary and alcohol use is self-medication then treatment of depression should result in reduction of alcohol use. However, if the underlying causes of the two disorders are shared, the treatment of either condition will not necessarily have any effect on the other (Lynskey, 1998). Even if no causality is presumed, it is still possible that one disorder may exacerbate symptoms of the other.

In clinical practice it is often the case that when a patient is presenting with depressive symptoms and alcohol problems, it is difficult to determine what the causality may be. Studies on treatment of comorbid depression and alcohol problems have found that antidepressant medications may improve mood and reduce drinking whether the patients' depression is primary or secondary (Agabio et al., 2018).

2.3.4 Impact of depressive disorders

Depression is associated with excess mortality compared with non-depressed individuals (Cuijpers et al., 2013). The excess mortality associated with depression is mostly due to suicide (Osby et al., 2001; Black et al., 1987).

In the general population, depression is associated with decreased QoL and has been calculated to account for 55% of the loss in QALYs (Saarni et al., 2007; Evans and Huxley, 2002). Globally, depression is the third leading cause of disease burden and the fourth leading cause of disability (The World Health Organization, 2008). Depression has been predicted to rise to the leading non-inflammatory disease cause of disability by the year 2030 (Murray et al., 2012). In the EU-region, the four most disabling single conditions calculated by DALYs are depression, dementias, AUDs and stroke (Wittchen et al., 2011).

Depression results in work disability, which was recently calculated to in Finland to have cost 617 million Euros in disability compensation in a single year (Isometsa et al., 2009). The number of people on disability benefits because of depression has risen dramatically during the past 25 years in Finland, but in the past few years, this trend has broken (Social Insurance Institution of Finland, 2017).

A common feature of depression is recurrence for which the risk is elevated in relation to the number of past episodes and if refractory symptoms persist (Kessing and Andersen, 2005; Kanai et al., 2003). When chronic, depression is a major risk factor for persistence of disability in specifically in the domains of social functioning, emotional and mental health (Cabello et al., 2014).

A systematic review using the International Classification of Functioning (ICF) as a framework identified psychosocial difficulties in the domains of emotional functions, energy and drive, cognitive performance, employment, personal relationships and community life (Cabello et al., 2012). The review found that the presence of comorbidities and more severe depressive symptoms were related to worse psychosocial functioning.

Health-related Quality of Life and depression

Depression has a severe negative impact on HRQoL (IsHak et al., 2011; Papakostas et al., 2004); a finding which has been replicated in the general population (Subramaniam et al., 2013), primary care patients (Riihimäki et al., 2016) and patient cohorts seeking or receiving treatment depression (Trivedi et al., 2006; Rapaport et al., 2005). It has been proposed that treatment studies of MDD should track HRQoL as the ultimate outcome measure of treatment success (IsHak et al., 2011).

Impairment of HRQoL can persist even after symptomatic improvement or recovery of depression and even place patients at risk for relapse (Markkula et al., 2016; Angermeyer et al., 2002). It has been demonstrated that decreased HRQoL predicts depressive symptoms over time (Kuehner and Huffziger, 2009). Therefore,

understanding the factors contributing to impairment of HRQoL in the context of depression can be important in both treatment and relapse prevention.

Symptom severity of depression has been shown to be associated with diminished HRQoL (IsHak et al., 2011). However, the variance in HRQoL in depression cannot be explained by symptom severity alone: socio-demographic variables such as education and income contribute HRQoL as well (Berlim et al., 2008).

Literature on the effect of alcohol problems on HRQoL in the context of depression is limited and somewhat conflicting. A review on HRQoL in the context of alcohol dependence found psychiatric comorbidity to lead to further reduction of HRQoL (Foster et al., 1999). Another study found that symptoms of anxiety and depression accompanying alcohol dependence lead to an increase in severity of the problems associated with the disorder and have a negative effect on HRQoL (Saatcioglu et al., 2008). However, a recent study did not find statistically significant HRQoL differences between individuals with comorbid MDD and AUD than those with MDD without AUD despite the study hypothesis (Danovitch et al., 2016).

It seems that the detrimental effect of depression on HRQoL is widely shown to be true, but it remains somewhat unclear whether alcohol problems contribute to further impairment of HRQoL. More research on factors, which contribute to impaired HRQoL in depression has been called for (IsHak et al., 2013).

2.4 Rationale for the study

Both alcohol problems and depression are associated with impaired QoL (Angermeyer et al., 2002; Foster et al., 1999), however, there is limited information on the dynamic of the effect of co-occurring alcohol problems and depression on QoL (Danovitch et al., 2016; Saatcioglu et al., 2008; Foster et al., 1999).

Despite the common co-occurrence of alcohol problems and depression, there is no previous research on the validity of the AUDIT in screening for at-risk drinking in the context of depression. The AUDIT is an effective method used to screen for at-risk drinking in the general population and among primary care patients (Aalto et al., 2009; Daeppen et al., 2000; Saunders et al., 1993), but it is yet to be evaluated in this specific population.

Even though alcohol use patterns, e.g. binge drinking, are widely known to cause many other diseases, the role of alcohol use patterns in depression has not been as extensively studied. It is also unclear what, if any, the associations between alcohol problems and alcohol use patterns and QoL are among depressed individuals.

3 AIMS OF THE STUDY

I) To systematically review the literature on HRQoL in alcohol dependence with a specific focus on the impact of depression and symptoms thereof, as well as other psychopathology.

II) To validate the AUDIT and its abbreviated versions the AUDIT-C and AUDIT-3 in screening for at-risk drinking in depressed individuals of the general population.

III) To evaluate the association between depression and binge drinking in the general population.

IV) To evaluate the association between alcohol use and problems and quality of life in depressed and non-depressed individuals of the general population.

4 MATERIALS AND METHODS

4.1 Study I

4.1.1 Narrative synthesis: a systematic literature review

A systematic literature review was conducted with the purpose of summarizing existing data on problems with HRQoL in alcohol dependence. The review was carried out as a part of a larger literature review within the scope of a coordination action called PARADISE (Psychosocial fActors Relevant to brAin DISorders in Europe) (Cieza et al., 2015). The aim of the larger PARADISE literature review was to collect information on psychosocial difficulties reported in the context of alcohol dependence.

The systematic literature review used the methodology of narrative synthesis (Popay et al., 2006). Narrative synthesis employs a systematic approach to data search and collection, appraisal of study quality, as well as synthesis of the collected data. Narrative synthesis uses a descriptive approach to data synthesis rather than a numeric one and relies on words to explain the findings and when data are not suitable to be pooled due to differences in study designs (Ryan and Cochrane Work Group., 2013). It can be used e.g. to describe the effects or implications of applied interventions. Narrative synthesis is at best used in systematic reviews or meta-analyses focusing on a wide range of complex questions where the results are difficult to reduce to numbers. It has been utilized in several studies (Coenen et al., 2016; Levola et al., 2014; Cabello et al., 2012). The term narrative synthesis is not to be confused with a narrative review, which does not typically employ a systematic or transparent methodology.

4.1.2 Data collection

MEDLINE and PsychINFO databases were searched for studies published in English between January 2005 and May 2010 (for search terms see Appendix II). The database search was performed by a team at Ludwig-Maximillian University in Munich, which had previous experience on large database searches. The database search identified 1234 references. The references' abstracts were screened to determine whether they met inclusion/exclusion criteria.

The inclusion/exclusion criteria were

1) information on psychosocial difficulties;
2) a diagnosis of alcohol dependence according to the ICD-9, ICD-10 (The World Health Organization, 2016; The World Health Organization, 1975), or the DSM-III-TR, DSM-IV or DSM-IV-TR (American Psychiatric Association, 2000; American Psychiatric Association, 1994; American Psychiatric Association, 1987);
3) included study types: randomized controlled trials, controlled clinical trials, open intervention trials, longitudinal observational studies, cross-sectional studies and qualitative studies;
4) excluded study types: meta-analyses, reviews, editorials, phase I and II studies and studies focusing on persons under the age of 18.

In the case of multiple publications from one dataset, the paper from the journal with the highest impact factor was included. In the case where a decision of inclusion/exclusion could not be made based on the abstract, the reference was classified as ambiguous. In addition to all included papers, full texts of ambiguous references were obtained and thereafter classified as included/excluded. The full texts of 515 papers were obtained, of which 244 were included in the overall analysis of psychosocial difficulties in alcohol dependence.

4.1.3 Data extraction

Data from the 244 included papers were systematically extracted using a predefined protocol (Pitkänen et al., 2016). Extracted data comprised information concerning psychosocial difficulties and their associations and determinants, study characteristics, including the study design and the assessment instruments used. Associations were extracted when they were statistically significant in quantitative studies or identified as such in qualitative studies.

Each paper was ranked according to study quality as poor, acceptable, good or excellent (National Institute for Health and Clinical Excellence, 2014). Poor quality papers were further excluded. Finally, the extracted data was screened to determine whether papers reported on HRQoL or its domains. Because of the existing heterogeneity in the conceptualization of HRQoL in the literature, studies using different definitions of HRQoL and its domains were included.

4.2 Studies II-IV

4.2.1 Data collection

The FINRISK 2007 is a general population study, which was approved by the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa. It comprised a randomly selected total sample of 11 953 persons between the ages 25-74 from six regions in Finland (Peltonen et al., 2008). The sample was randomly selected using the national register (Finnish Population Information System). The sample was stratified according to gender and 10-year age groups. Each age group contained 200 men and 200 women per each area. After sampling, 47 individuals died or moved away from the regions resulting in the total sample size of 11 953.

Several affiliated studies were conducted using smaller subsamples of the FINRISK 2007. The cross-sectional studies II-IV utilized data from a random subsample of FINRISK 2007 (4020 individuals; 67% of the original sample from three regions) for which alcohol use was investigated in detail.

The sample received a questionnaire by mail that included questions regarding socio-demographic information, general health habits, chronic diseases and symptoms, as well as an invitation to a health check. Of the 4020 individuals invited, 2646 (1229 men, 1417 women; 65.8%) attended the health check. During the health check, the participants filled out the AUDIT and the BDI-SF, and were also asked to participate in the TLFB -interview. CDT- and γGT-levels were analysed from venous blood tests for all participants who were between the ages 25-60 (n = 2894).

In study II, all necessary data were available for 1175 respondents (response rate 40.6%) (Figure 1). In study III, 2086 respondents and in study IV, 2215 respondents for whom the necessary data was available were included in the analyses (response rates of 51.9% and 55.1%, respectively). Some previously unpublished analysis in studies III and IV were conducted with all 2646 respondents after imputation of missing data.

Figure 1. Sample selection for study II.

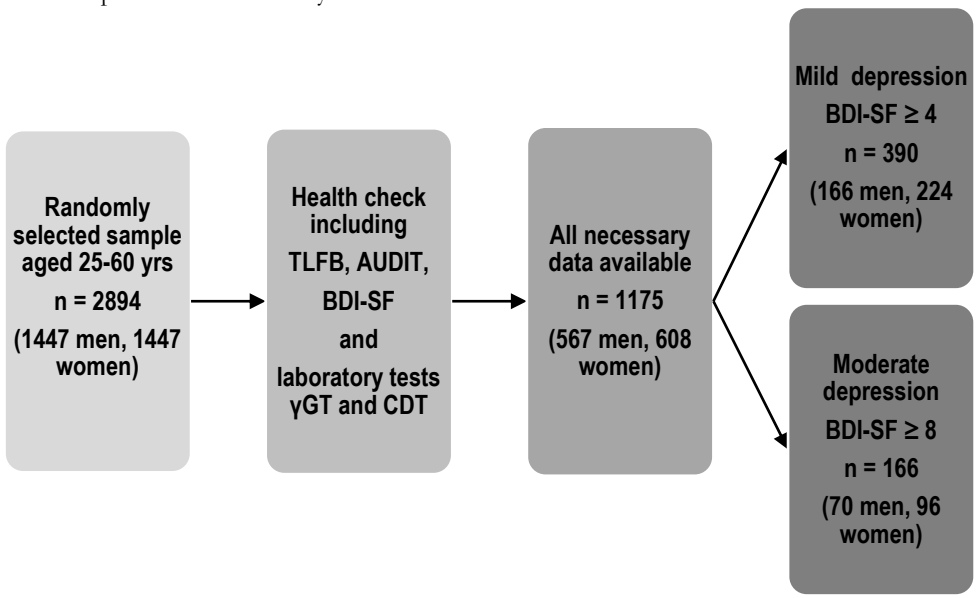
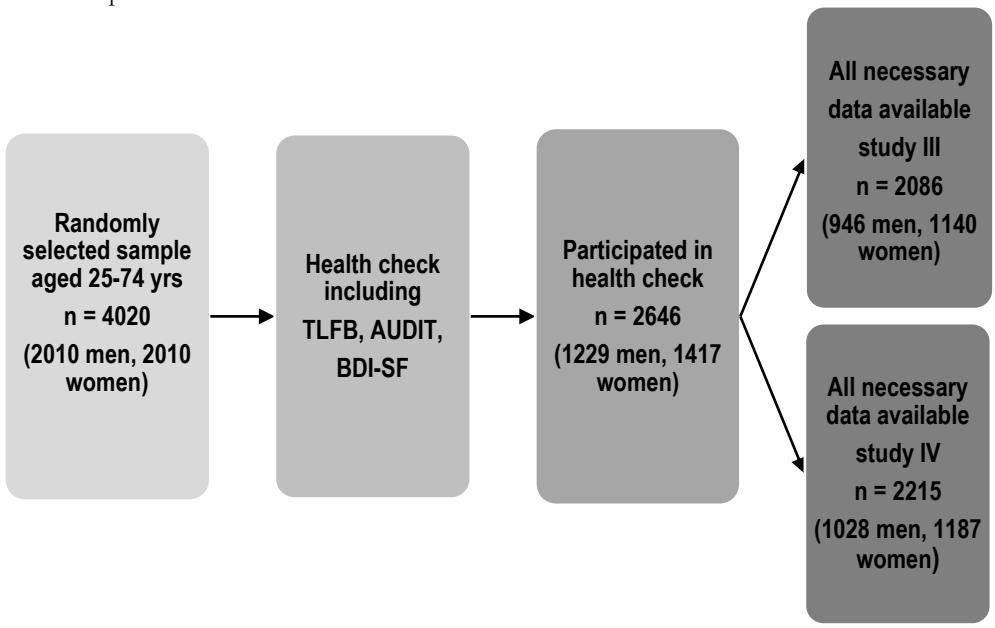


Figure 2. Sample selection for studies III-IV.



4.2.2 Measures

The original full AUDIT in Finnish was used (175). From it, the scores for the abbreviated versions the AUDIT-C and AUDIT-3 were derived for use in study II. In study III, a cut-off of ≥ 8 for the full AUDIT was used to indicate alcohol problems. In study IV, AUDIT-score was used as a continuous variable to indicate severity of alcohol problems.

The TLFB was administered face-to-face by interviewers who had participated in a two-day training session to carry out the interview. The interviewers converted respondents' reports of amounts of alcohol consumed into equivalents of about 12 g of alcohol corresponding to a Finnish standard drink unit (i.e., 33 cl bottle of beer, 12 cl glass of wine or 4 cl drink of spirits). The TLFB covered the previous 28 days. Memory aids (weekends and special occasions) were used to enhance recall of alcohol consumption amounts. The interviewers were blinded to the results of the AUDIT.

At-risk drinking calculated from the TLFB was the gold standard for alcohol use and the reference measure against which the AUDIT, AUDIT-C and AUDIT-3 were validated in study II. At-risk drinking was defined as ≥ 280 g weekly or ≥ 60 g on at least one occasion in the previous 28 days for men, 140 and 40 g, respectively, for women. In studies III and IV, mean weekly alcohol consumption, binge drinking and abstinence were calculated from the TLFB. Binge drinking was defined as consuming ≥ 7 (men) or ≥ 5 (women) drinks on one drinking occasion (II-IV).

Depression was measured by a modified BDI-SF scored on a scale of from zero to 39. There are four to six alternate responses in the original 21-question BDI. In the BDI-SF, the response options for each question have been narrowed down to four for simplification (Beck and Beck, 1972). In the modified BDI-SF used in studies II-IV, four to six response options are given - as in the original BDI - for the 13 questions of the BDI-SF. There is no stabilized cut-off for the screening of depression with the modified BDI-SF. In the original study of Beck et al., a cut-off of ≥ 4 points on the BDI-SF was defined as indicating mild and ≥ 8 points as indicating moderate to severe depression (118).

In study II, a cut-off of ≥ 4 points was used to indicate at least mild and ≥ 8 to indicate at least moderate depression. A cut-off of ≥ 8 points was used in studies III and IV to indicate depression. The groups with mild and moderate depression were not mutually exclusive.

For the purpose of laboratory testing (II), participants had been instructed to fast for four hours prior to laboratory testing. Venous blood samples were collected, handled and analysed using standard methods. The cut-off for elevated γGT-levels was

≥ 80 U/l for men and ≥ 50 U/l for women. The cut-off for elevated CDT-levels was ≥ 1.80% for both men and women. Exceeding the designated cut-off for either γGT or CDT was interpreted as a positive screen for at-risk drinking. A combination of and γGT was also tested, where exceeding the cut-off of either one of the two resulted in a positive screen.

QoL in study IV was a measured with a single-item question of perceived overall QoL on a scale zero to 10 where zero being the worst possible alternative and 10 the best. In studies III and IV, a subject was classified as chronically ill if he/she reported one of the following diseases requiring treatment by a physician in the past 12 months: myocardial infarction, angina pectoris, chronic heart failure, elevated blood-pressure, stroke, cancerous malignancies, chronic asthma, emphysema, chronic bronchitis, rheumatoid arthritis, other articular diseases, chronic back pain, chronic urinary tract infection or nephritis. In study IV, presence of psychiatric comorbidities was categorized dichotomously (yes/no) according to self-reported mental disorders other than depression. Additionally socio-demographic variables such as age (studies II-IV), marital status (studies III-IV) and years of education (III-IV) were included.

4.2.3 Statistical analyses

In study II, the sensitivities and specificities of the AUDIT, AUDIT-C and AUDIT-3 were calculated at different cut-offs in order to determine optimal cut-off points. Sensitivities and specificities were also calculated for CDT and γGT at their designated cut-off levels. An optimal cut-off was designated as having a sensitivity and specificity of over 0.75 with emphasis on specificity. The defined gold standard was at-risk drinking calculated from the TLFB. Area Under the Receiver Operating Characteristic Curves (AUROCs) were calculated.

The association between depression and binge drinking was assessed in study III by creating separate logistic regression models for both genders. Covariates were age group, education years, marital status, chronic illness, AUDIT-score and total weekly alcohol consumption. Logistic regression analyses were used to calculate odds ratios (ORs).

In study IV, the associations between alcohol-related variables and QoL were analysed separately for depressed and non-depressed respondents. Linear regression models were calculated in order to adjust for covariates. Covariates were gender, age, education years, marital status, somatic illness and psychiatric disorders. The main analyses in study IV were also performed using multiple imputation to account for missing data.

Additionally, descriptive statistics (t-test and Fischer's exact test) were used for characterizations of the study population and studying the differences between groups. Inter-correlations were analysed using Pearson's or Spearman's correlation coefficient as appropriate. In all analyses, differences were considered statistically significant at $p < 0.05$.

Data were analysed with SPSS software.

5 RESULTS

5.1 HRQoL in alcohol dependence: the role of depression and other psychiatric comorbidity (I)

A total of 42 articles of at least acceptable quality reported on HRQoL or its domains among alcohol dependent individuals (Table 2). The most common reason for exclusion of the studies, in addition to not reporting on issues relating to HRQoL, was an inconclusive definition of alcohol dependence.

The evidence demonstrating that alcohol dependence was associated with or a primary cause of impairments in overall HRQoL and the domains of general health, mental health, physical health and social functioning was fairly strong. In addition, impairment was reported in the domains of general functioning, activities of daily living, pain and sleep.

Overall HRQoL was impaired in alcohol dependent individuals when compared to the general population (Gunther et al., 2007; Saarni et al., 2007; Malet et al., 2006) or controls (Rosenbloom et al., 2007). All seven longitudinal studies, which applied treatment interventions, reported improvement of HRQoL over time (Florez et al., 2008; Muhonen et al., 2008; Neto et al., 2008; Rus-Makovec and Cebasek-Travnik, 2008; Buu et al., 2007; Dorney-Smith, 2007; Grinshpoon et al., 2007; Martinotti et al., 2007). Four of these studies had a control condition and the improvement could be attributed to the treatment intervention (Florez et al., 2008; Muhonen et al., 2008; Neto et al., 2008; Rus-Makovec and Cebasek-Travnik, 2008; Martinotti et al., 2007).

Problems within the mental health domain were frequently reported (Dawson et al., 2009; Lahmek et al., 2009; LoCastro et al., 2009; Pettinati et al., 2009; Saitz et al., 2009; Udo et al., 2009; Ammon et al., 2008; LoCastro et al., 2008; Rash et al., 2008; Rus-Makovec and Cebasek-Travnik, 2008; Diehl et al., 2007; Easton et al., 2007; Ginieri-Coccossis et al., 2007; Grinshpoon et al., 2007; Hasin et al., 2007; Nordholm and Nielsen, 2007; Panagaria et al., 2007; Saarni et al., 2007). A causal relationship between alcohol dependence and impairment of the mental health domain could be determined in only two studies (Lahmek et al., 2009; Diehl et al., 2007). One of these two studies found that women develop problems related to the mental health domain faster after the onset of alcohol dependence than men (Diehl et al., 2007). Seven additional studies (Pettinati et al., 2009; Saitz et al., 2009; Ammon et al., 2008; Ginieri-Coccossis et al., 2007; Hasin et al., 2007; Panagaria et al., 2007; Saarni et al., 2007) found that problems

in the mental health domain were associated with alcohol dependence. The severity of problems in the mental health domain was associated with the severity of alcohol dependence in one study (Hasin et al., 2007).

Fourteen studies evaluated change in the mental health domain prospectively or retrospectively (Dawson et al., 2009; Lahmek et al., 2009; LoCastro et al., 2009; Pettinati et al., 2009; Saitz et al., 2009; Udo et al., 2009; Ammon et al., 2008; Rash et al., 2008; Rus-Makovec and Cebasek-Travnik, 2008; Diehl et al., 2007; Easton et al., 2007; Ginieri-Coccossis et al., 2007; Grinshpoon et al., 2007; Nordholm and Nielsen, 2007). The vast majority of studies (ten) reported improvements in the mental health domain during follow-up (Lahmek et al., 2009; LoCastro et al., 2009; Pettinati et al., 2009; Saitz et al., 2009; Udo et al., 2009; Ammon et al., 2008; Rus-Makovec and Cebasek-Travnik, 2008; Easton et al., 2007; Ginieri-Coccossis et al., 2007; Grinshpoon et al., 2007). Two additional observational studies reported that positive and negative changes in the mental health domain were determined by the course of alcohol dependence (Dawson et al., 2009; Diehl et al., 2007). Six intervention studies found that improvement in the mental health domain was determined by improvement of alcohol dependence (Lahmek et al., 2009; Pettinati et al., 2009; Rus-Makovec and Cebasek-Travnik, 2008; Easton et al., 2007; Ginieri-Coccossis et al., 2007; Hasin et al., 2007). One study reported no improvement in the mental health domain with treatment among individuals with alcohol dependence and comorbid personality disorder (Nordholm and Nielsen, 2007). Another study reported no improvement of the mental health domain of alcohol dependent individuals with comorbid cocaine dependence despite reduced cocaine and alcohol use, as well as improvement in the domain of psychosocial functioning (Rash et al., 2008).

Impairment in the domain of mental health was associated with psychiatric comorbidities (Lahmek et al., 2009; Ginieri-Coccossis et al., 2007; Nordholm and Nielsen, 2007). Greater improvement of mental health domain scores during an inpatient withdrawal treatment programme was reported among those with the poorest scores upon admission (Lahmek et al., 2009).

A comorbid diagnosis of depression and alcohol dependence was associated with decreased HRQoL in three studies when compared with alcohol dependence without comorbid depression (Gunther et al., 2007; Rosenbloom et al., 2007; Malet et al., 2006). Two additional studies found that symptoms of depression regardless of an official diagnosis were also associated with decreased HRQoL (Ponizovsky, 2008; Rosenbloom et al., 2007). A diagnosis of an anxiety disorder, symptoms of anxiety and psychological distress were associated with poor HRQoL in four studies (Ponizovsky, 2008; Dorney-Smith, 2007; Rosenbloom et al., 2007; Malet et al., 2006).

The domain of general functioning was evaluated in two studies (Duncan et al., 2006; Wilk et al., 2006). One study found poor general functioning to be more common among patients with MDD and comorbid AUD (30.2%) than among patients with MDD only (19.3%) (Wilk et al., 2006). The other study compared patients with alcohol dependence or bulimia nervosa only to patients with comorbid alcohol dependence and bulimia nervosa (Duncan et al., 2006). Both studies suggest that comorbid AUDs contribute to a further reduction in functioning.

The domain of social functioning was evaluated in four studies (Muhonen et al., 2008; Easton et al., 2007; Carpenter et al., 2006; Duncan et al., 2006). Impaired social functioning was reported to be more common among alcohol dependent individuals than those with problem drinking (Carpenter et al., 2006). Social functioning in alcohol dependent individuals with comorbid depression improved with pharmacological interventions (Muhonen et al., 2008).

Table 2. Systematic review of alcohol dependence and HRQoL[1] and its domains. Study designs and major outcomes.

Reference	Study design	Intervention	Control	Follow-up	HRQoL and domains	Main HRQoL-related findings
Dorney-Smith, 2007	Exploratory pilot study	Community matron model incl. case management	--	13 weeks	HRQoL	HRQoL improved in 33% of individuals
Easton et al., 2007	Post-hoc analyses of a RCT[3]	Cognitive-behavioural group or 12 step facilitation group therapy	--	12 weeks	Mental health Physical health Social functioning	All domains improved among those with AD[2] without comorbid drug use.
Florez et al., 2008	Naturalistic, randomized open-label	Naltrexone + psychotherapy	Topiramate + psychotherapy	6 months	HRQoL General health Social functioning	All domains improved in both groups, improvement was larger in topiramate group.
Ginieri-Coccossis et al., 2007	Naturalistic non-controlled	5-week in-patient detoxification	--	5 weeks	Mental health Physical health General functioning Social functioning	All domains improved from intake to discharge.
Grinshpoon et al., 2007	Open-label non-controlled	Sildenafil + AD TAU[4]	--	12 weeks	HRQoL Mental health Physical health Social functioning ADL[5]	All domains improved by 10 to 17%.
Johnson et al., 2008	RCT	Topiramate	Placebo	14 weeks	ADL	Improved in both groups, but larger improvement in topiramate group.
Lahmek et al., 2009	Naturalistic non-controlled	3-week in-patient detoxification programme	--	3 weeks	Mental health Physical health General health Pain Social functioning Vitality	Mental and physical health were impaired vs. the general population. Improvement was possible in all domains with treatment and alleviation of AD. Variables associated to different domains were identified.
LoCastro et al., 2009	RCT	Acamprosate and/or naltrexone + behavioural intervention or medical management	Placebo	1 year	Mental health Physical health Social functioning	All domains improved during the treatment period. Improvement of social functioning was sustained during follow-up. The results for mental and physical health were mixed; some measures showed sustained improvement and others decline during follow-up.
Martinotti et al., 2007	Open-label non-controlled	Aripirazole	--	16 weeks	HRQoL	HRQoL improved during the study period.

Reference	Study design	Intervention	Control	Follow-up	HRQoL and domains	Main HRQoL-related findings
Mueller et al., 2007	Naturalistic	Voluntary participation in self-help groups	Non-participants in self-help groups	1 year	Social functioning	Social functioning improved in both groups. Social functioning was less impaired at baseline in those who chose to attend self-help groups.
Muhonen et al., 2008	RCT	Memantine	Escitalopram	26 weeks +/- 2 weeks	HRQoL Social functioning	Both domains improved statistically significantly during the study period.
Neto et al., 2008	RCT	Sequential combined treatment	TAU	180 days	HRQoL	Improvement in HRQoL was seen in both treatment modalities with no statistically significant difference between the two.
Nordholm and Nielsen, 2007	Naturalistic non-controlled	Cognitive-behavioural therapy or family therapy	Supportive sessions	1 year	Mental health Physical health Social functioning	Social functioning was more impaired in those with cluster B PD[6] vs. without; social functioning improved regardless of comorbid PD. Mental health was more impaired in those with PD and physical health in those with cluster C PD; mental or physical health did not improve.
Pettinati et al., 2009	RCT	Extended-release naltrexone	Placebo	1 year	General health Mental health Physical health Social functioning	Mental health and social functioning were impaired in individuals with AD compared with the general population. All domains improved, improvement was larger on active medication and had more abstinent days during the study period.
Rash et al., 2008	Pooled data from three RCTs	Contingency management	TAU	9 months	Mental health Physical health	Both domains were impaired in AD and comorbid cocaine dependence. Improvement was seen in physical but not mental health.
Rus-Makovec and Cebasek-Travnik, 2008	Prospective controlled observational	In-patient treatment + telephone aftercare	In-patient treatment + no follow-up	2 years	HRQoL Mental health Physical health Social functioning	HRQoL improved in both groups of inpatients. Improvement continued in the intervention group during follow-up vs.controls. Social functioning improved or remained stable in 93%. Mental and physical health improved in both groups, more in the intervention group.
Saitz et al., 2009	Post-hoc analysis	Brief motivational counselling		1 year	Mental health Physical health	AD was associated with impaired mental health but not physical health. Mental health improved during follow-up.
Ammon et al., 2008	Longitudinal observational	--	--	7 years	Mental health Social functioning	Problems in both domains were more common in those with AD vs. problem drinkers Mental health was more impaired among women vs. men. Both domains improved during follow-up.
Buu et al., 2007	Longitudinal observational	--	--	12 years	Residential QoL	Improvement of residential QoL was associated with remission of AD. An unremitted subject tended to stay in or migrate into a more disadvantaged neighbourhood.
Carpenter et al., 2006	Longitudinal observational	--	--	1 year	Social functioning	Impaired social functioning was associated to AD and cluster B PD.
Charney et al., 2010	Longitudinal observational	--	--	12 weeks	Social functioning	Impaired social functioning was associated with worse prognosis of AD.

Reference	Study design	Intervention	Control	Follow-up	HRQoL and domains	Main HRQoL-related findings
Dawson et al., 2009	Longitudinal observational	--	--	3 years	General health Mental health Physical health Pain Social functioning	All domains deteriorated with the onset of or transition into AD. Physical health improved with remission of AD.
Diehl et al., 2007	Longitudinal observational	--	--	1 year	Mental health Physical health General functioning Social functioning	AD caused mental, physical and social problems. Problems developed more quickly after the onset of AD among women than men. General functioning was more impaired among women than men at baseline.
Gual et al., 2009	Longitudinal observational	--	--	20 years	Social functioning	Social functioning is better at 20-year follow-up.
Jorge et al., 2005	Longitudinal observational	--	--	1 year	Social functioning	Those with AD had poorer pre-morbid social support networks and social functioning vs. those without AD.
Udo et al., 2009	Longitudinal observational	--	--	1 year	Mental health General functioning Social functioning	Improvement was reported in all domains.
Duncan et al., 2006	Epidemiological	--	--	--	General functioning	AD exacerbated poor overall functioning in individuals with bulimia.
Gunther et al., 2007	Structure validation of an analytical method	--	--	--	HRQoL Pain Mobility ADL	Problems in all domains, except mobility, were reported more frequently in those with AD vs. the general population.
Hasin and Grant, 2015	Epidemiological	--	--	--	Mental health Social functioning	Impairment in both domains was associated AD. Disability increased with AD severity in both domains.
Jordaan et al., 2009	Cross-sectional	--	--	--	Social functioning	Level of social functioning decreased when AD was very severe.
Kerridge, 2008	Epidemiological	--	--	--	General functioning	Impaired functioning was associated with AD.
Locastro et al., 2008	Cross-sectional	--	--	--	Mental health Physical health Social functioning	All domains were more impaired among those with AD and prior treatments vs. treatment naïve individuals.
Malet et al., 2006	Cross-validation of an analytical method	--	--	--	HRQoL	HRQOL was impaired among those with AD vs. the general population.

Reference	Study design	Intervention	Control	Follow-up	HRQoL and domains	Main HRQoL-related findings
Onen et al., 2005	Cross-sectional	--	--	--	General functioning Sleep	Sleep disturbances were reported by 9%, mean GAF-scores were low (no verified associations with AD).
Panagaria et al., 2007	Cross-sectional	--	--	--	Mental health Physical health Social functioning Pain Vitality	All domains were more severely impaired in individuals with AD with or without liver disease vs. controls.
Ponizovsky, 2008	Cross-sectional	--	--	--	HRQoL	Depressive symptoms were associated with HRQoL in AD men with alcohol-induced erectile dysfunction
Romeis et al., 2005	Twin study	--	--	--	HRQoL	Impaired HRQoL was caused by AD.
Rosenbloom et al., 2007	Cross-sectional	--	--	--	HRQoL General functioning	Both domains were more impaired in AD vs. controls. Poor HRQoL was associated with depressive or anxiety disorders and AD.
Saarni et al., 2007	Epidemiological	--	--	--	HRQoL Mental health Physical health Sleep Mobility Pain ADL	Impairment in all domains was reported among those with AD vs. the general population.
Wilk et al., 2006	Cross-sectional	--	--	--	General functioning	General functioning is more impaired in individuals with depression, bipolar disorder or schizophrenia with vs. without comorbid AD.
Yeh et al., 2008	Qualitative	--	--	--	General health	Almost everyone reported damage to their health due to AD.

[1] Health-Related Quality of Life [2] Alcohol Dependence [3] Randomized Controlled Trial [4] Treatment as Usual [5] Activities of Daily Living [6] Personality Disorder

5.2 Validity of the AUDIT in depression (II)

In this FINRISK general population sample, at least mild depression (BDI-SF score ≥ 4) was reported by 33.2% (29.3% of men; 36.8% of women) and at least moderate depression (BDI-SF score ≥ 8) by 14.0% (12.3% of men; 15.8% of women). At-risk drinking was common according to the given definition. In the total sample, at-risk drinking was reported by 52.2% of the respondents (58.2% of men; 46.5% of women). In the subgroup with mild depression, at-risk drinking was reported by 53.8% (60.2% of men; 49.1% of women) and in the subgroup with moderate depression by 51.8% (60.0% men; 45.8% women).

Based on the AUROCs, the AUDIT performed well among both men with mild (AUROC 0.89) and moderate (0.91) as well as women with mild (0.86) and moderate (0.87) depression. Among men with mild depression, a good level of sensitivity (0.78-0.84) and specificity (0.77-0.87) was reached with the cut-offs of ≥ 8 or ≥ 9 for the AUDIT. Similarly, the optimal cut-off in the subgroup of men with moderate depression was ≥ 9 (sensitivity 0.90, specificity 0.85). Among women with mild depression, both sensitivity (0.79) and specificity (0.76) were acceptable with a cut-off of ≥ 5. Among women with moderate depression, sensitivity was good (0.84), however, specificity fell slightly under the predefined level of 0.75 (0.72). The cut-off of ≥ 5 was nonetheless the most feasible.

Based on the AUROCs, the AUDIT-C also performed well among both men with mild (AUROC 0.89) and moderate (0.90) as well as women with mild (0.84) and moderate (0.85) depression. The optimal cut-off for men with mild and moderate depression was ≥ 6. With this cut-off, sensitivities were 0.83-0.86 and specificities 0.77-0.81. Among women with mild depression, a good level of sensitivity (0.86) and an excellent level of specificity (0.96) were reached with a cut-off of ≥ 4. However, among women with moderate depression, a cut-off ≥ 4 resulted in a high level of sensitivity (0.91), but specificity fell to 0.60. An alternative cut-off of ≥ 5 in this subgroup resulted in a sensitivity of 0.64 and specificity of 0.94.

Based on the AUROCs, the AUDIT-3 performed well among men with mild (AUROC 0.87) and moderate (0.90) depression. The AUDIT-3 did not perform as well as the other questionnaires among women. An optimal cut-off could not be determined and AUROCs demonstrated only moderate accuracy (0.76-0.80). Among men, a good level of sensitivity (from 0.82 to 0.88) and specificity (0.78-0.79) was reached at a cut-off of ≥ 2.

The alcohol-related laboratory markers CDT and γGT did not perform well in screening for at-risk drinking at their designated cut-offs. Sensitivity levels were extremely low (0.10-0.17). When a positive screening result was obtained, their specificity was good or excellent (0.85-0.97). The combination of CDT and γGT performed equally poorly with regards to low sensitivity.

5.3 Binge drinking, depression and QoL (III-IV)

Data regarding alcohol variables and QoL stratified by gender and depression, as well as between-group differences are presented in Table 3. Of all respondents, 20.7% were classified as depressed (18.9% of men, 22.3% of women). In study IV, mean QoL was statistically significantly lower in individuals categorized as depressed vs. non-depressed when both genders were analysed together. Depressed individuals had statistically significantly higher AUDIT-scores and were abstinent more often than non-depressed respondents (IV). Frequency of binge drinking and mean weekly alcohol consumption did not differ statistically significantly between the depressed and non-depressed groups (IV).

Of all respondents regardless of depression classification, 5.3% (7.5% of men, 3.5% of women) reported weekly binge drinking i.e. binge drinking at least four times in the previous 28 days (III). Of the depressed individuals, 7.8% (17.1% of men, 2.0% of women) reported weekly binge drinking (III).

The logistic regression model exploring the association between depression and binge drinking in study III is presented in Table 4. Men with weekly binge drinking during the past 28 days were found to be 2.6 times more likely to be depressed than men who reported binge drinking less often. For women, no such association between depression and binge drinking was found.

In study IV, all socio-demographic variables (age, gender, marital status, years of education), somatic illnesses, psychiatric disorders and alcohol-related variables, except for abstinence, were statistically significantly associated with QoL when analysing all respondents. Being single, divorced or widowed and less educated as well as having a higher AUDIT-score were all associated with impaired QoL regardless of depression classification. Of the alcohol-related variables, among depressed individuals, binge drinking more frequently, higher AUDIT-score and higher mean weekly alcohol consumption were all statistically significantly associated with impaired QoL. In the non-depressed group, having a higher AUDIT-score was associated with impaired QoL. Abstinence was not associated with QoL in either the depressed or the non-depressed groups.

Table 3. Means of alcohol use variables and quality of life among depressed and non-depressed individuals of the general population and differences between genders (independent samples T-test), imputed data. Previously unpublished.

	All (n = 2646)			Non-depressed[1] (n = 2098)			Depressed[1] (n = 548)		
	Women (n = 1417)	Men (n = 1229)		Women (n = 1101)	Men (n = 997)		Women (n = 316)	Men (n = 232)	
	Mean (Std. error mean)	Mean (Std. error mean)	p	Mean (Std. error mean)	Mean (Std. error mean)	p	Mean (Std. error mean)	Mean (Std. error mean)	p
Mean weekly alcohol consumption[2]	2.69	6.04	<0.001	2.70	5.81	<0.001	2.63	7.02	<0.001
	(0.10)	(0.21)		(0.13)	(0.23)		(0.23)	(0.73)	
AUDIT-score	4.05	6.62	<0.001	3.92	6.37	<0.001	4.48	7.70	<0.001
	(0.12)	(0.15)		(0.14)	(0.17)		(0.28)	(0.51)	
Frequency of binge drinking[3]	0.76	2.09	<0.001	0.80	2.02	<0.001	0.60	2.38	<0.001
	(0.05)	(0.11)		(0.06)	(0.12)		(0.10)	(0.35)	
Quality of life	7.55	7.41	0.015	7.83	7.66	0.007	6.58	6.31	0.341
	(0.04)	(0.05)		(0.05)	(0.07)		(0.14)	(0.33)	

[1] Depressed (Beck Depression Inventory, Short Form –score ≥ 8) and non-depressed (< 8) subjects [2] Drinks per week, according to the Timeline Follow-back, mean
[3] Frequency of consuming ≥ 7 Finnish standard drinks for men, ≥ 5 drinks for women on one drinking occasion in past 28 days

When analysing imputed data and after adjusting for covariates, AUDIT-score (Unstandardized coefficient B -0.049, 95% C.I. -0.085 – (-0.012); p = 0.010) and frequency of binge drinking (Unstandardized coefficient B -0.060, 95% C.I. -0.119 – (-0.002); p = 0.043) were statistically significantly associated with QoL in the depressed group. In the non-depressed, AUDIT- score was statistically significantly associated with QoL after adjusting for covariates (Unstandardized coefficient B -0.035, 95% C.I. -0.059 – (-0.011); p = 0.007). When analysing all respondents regardless of depression classification, both AUDIT-score and binge drinking – when analysed independently of each other – were statistically significantly associated with QoL after adjusting for covariates. AUDIT-score (Unstandardized coefficient B -0.048, 95% C.I. -0.062 – (-0.033); p <0.001) had a stronger association with QoL than did binge drinking (Unstandardized coefficient B -0.022, 95% C.I. -0.041 – (-0.003); p = 0.023).

Table 4. Adjusted and unadjusted odds ratios (OR) for depressive symptoms[1] among men and women of the general population.

		MEN n = 946		WOMEN n = 1140	
		OR unadjusted (95% C.I.)	OR adjusted[2] (95% C.I.)	OR unadjusted (95% C.I.)	OR adjusted[2] (95% C.I.)
Age, yrs					
	25-54	1	1	1	1
	55-75	1.57	1.97	1.56	0.67
		(1.07 - 2.30)	(1.27 - 3.07)	(1.15 - 2.13)	(0.46 - 0.96)
Education, yrs					
	> 12	1	1	1	1
	≤ 12	1.30	1.04	1.56	1.56
		(0.89 - 1.91)	(0.69 - 1.57)	(1.15 - 2.13)	(1.10 - 2.20)
Marital status					
	married/cohabited	1	1	1	1
	single/divorced/widowed	2.05	2.11	1.57	1.49
		(1.37 - 3.07)	(1.38 - 3.22)	(1.15 - 2.15)	(1.08 - 2.05)
Chronic illness[3]					
	No	1	1	1	1
	Yes	1.50	1.28	1.69	1.69
		(1.03 - 2.20)	(0.85 - 1.94)	(1.24 - 2.31)	(1.21-2.37)
AUDIT[4] score					
	< 8	1	1	1	1
	≥ 8	2.00	1.89	1.52	1.64
		(1.37 - 2.94)	(1.17 - 3.04)	(0.98 - 2.36)	(0.98-2.74)
Mean weekly alcohol consumption[5] (cont.[6])		1.03	1.00	0.99	0.99
		(1.01 - 1.06)	(0.96 - 1.03)	(0.95 - 1.03)	(0.94-1.05)
Binge drinking[7] per 28 days					
	< 4	1	1	1	1
	≥ 4	3.18	2.57	0.52	0.47
		(1.84 - 5.52)	(1.24 - 5.31)	(0.18 - 1.48)	(0.14-1.58)

[1] Beck Depression Inventory, short form (modified) score of ≥ 8. [2]Adjusted for all other variables. [3]Received treatment by a physician in the past 12 months for at least one of the following: myocardial infarction, angina pectoris, chronic heart failure, elevated blood-pressure, stroke, cancerous malignancies, chronic asthma, emphysema, chronic bronchitis, rheumatoid arthritis, other articular diseases, chronic back pain, chronic urinary tract infection and nephritis. [4]The Alcohol Use Disorders Identification Test. [5] Drinks per week according to the Timeline Follow-back. [6] Continuous variable [7] Frequency of consuming ≥ 7 Finnish standard drinks for men, ≥ 5 drinks for women on one drinking occasion in past 28 days

6 DISCUSSION

6.1 Alcohol problems in depression

6.1.1 Screening

Overall, the AUDIT and AUDIT-C performed well in screening for at-risk drinking among men and women with depression (II). The full AUDIT was slightly superior to the AUDIT-C. The results indicate that cut-offs should be adjusted according to gender, but not according the severity of depression. The AUDIT-3 did not prove to be a valid instrument in screening for at-risk drinking among depressed women, but among men, a good level of sensitivity and specificity was reached. With standard threshold values, the CDT and γGT performed poorly due to low sensitivity.

To the best of knowledge, this is the first study to investigate the validity of the AUDIT and its abbreviations in screening for at-risk drinking among depressed individuals. The AUDIT has previously been evaluated in screening for AUDs in persons with a past-year depressive and/or anxiety disorder (Boschloo et al., 2010). It was found to be accurate in screening for alcohol dependence but not abuse.

Both the AUDIT and AUDIT-C had somewhat lower specificity in the subgroup of women with more severe depression. It could be plausible that more severely depressed women are more susceptible to the adverse effects of alcohol (e.g.Limosin, 2002) and therefore score higher on the AUDIT e.g. on questions regarding guilt of neglecting responsibilities, even if the amounts consumed do not exceed the at-risk limits used in this study. This is supported by the fact that women reporting more severe depression (BDI-SF -score ≥ 8) had higher AUDIT-scores but slightly lower mean weekly alcohol consumption and less frequent binge drinking than non-depressed women (III-IV) or women with less severe depression (II).

When evaluating the validity of screening methods, it is important to consider the target population and the goal of the screening. For example, the cut-off for screening of at-risk drinking among pregnant women could arguably be lower than in the general population because it would be important to identify all individuals with at-risk drinking (true positives) and false positives could be tolerated. Whereas, if the aim were to screen for probable AUDs among young males, the implemented cut-offs could be higher. A higher cut-off will likely result in less false positives, but in return,

some individuals with an AUD may fall below the cut-off (false negatives). Defining optimal cut-offs is a trade-off between sensitivity and specificity.

Optimal cut-offs for the AUDIT, AUDIT-C and AUDIT-3 in the general population have varied in previous studies (e.g.Aalto et al., 2009; Reinert and Allen, 2007; Babor et al., 2001). The cut-offs reported in study II for depressed men (≥ 9 for the AUDIT, ≥ 6 for the AUDIT-C and ≥ 2 for the AUDIT-3) and women (≥ 5 for the AUDIT and ≥ 4 for the AUDIT-C) are the same as those previously reported in the Finnish general population, with the exception of the cut-off for the full AUDIT which was ≥ 8 for men (Aalto et al., 2009). However, other studies have previously recommended lower cut-offs, except for the cut-off of the full AUDIT for women (Reinert and Allen, 2007).

The use of the AUDIT-3 has not been advocated in previous studies due to poor performance (e.g. Aalto et al., 2009) and the fact that the formulation of question 3 (how often do you drink ≥ 6 drinks?) does not allow for adjustment of binge drinking limits according to gender (Reinert and Allen, 2007). The lower validity of the AUDIT-3 among women in this study is possibly due to the definition of at-risk drinking used and its modification (how often do you drink ≥ 4 drinks) might be more valid.

The alcohol-related laboratory markers CDT and γGT did not screen well for at-risk drinking at their designated cut-offs. This could be due to the fact that the designated level of at-risk drinking is lower than the level at which elevation of these markers might be expected to occur (78). The findings of this study are in concordance with previous findings, which do not support the common clinical practice of using laboratory markers as a primary method of screening for at-risk drinking (Conigrave 2003, Fiellin 2000).

6.1.2 Patterns of drinking

A positive association between depression and binge drinking was found among men, but no association depression and binge drinking was found among women (III). The men engaged in binge drinking at least four times during the previous 28 days had a 2.6-fold risk depression. This association was found after adjusting for total alcohol consumption and AUDIT-scores, thus indicating that regular binge drinking is independently relevant with regards to depression among men.

Alcohol problems have previously been reported to be more common in depressed individuals than in the general population (Sullivan et al., 2005; Merikangas et al., 1998). The results of the present study are in concordance with these previous findings. In study IV, depressed individuals had higher AUDIT-scores indicative of

more severe alcohol problems than did non-depressed respondents. However, mean weekly alcohol consumption did not differ statistically significantly between depressed and non-depressed individuals (IV) and was not associated with depression after adjusting for covariates (III). These findings can be understood better when examining the alcohol consumption of the study population. The vast majority of the respondents were moderate drinkers and thus, it is difficult to draw final conclusions on the association between at-risk drinking and depression.

The relationship between drinking patterns and depression has not been studied as thoroughly as that of alcohol problems. Abstinence has been associated with depression in previous studies (e.g. van den Berg et al., 2014); this finding was consistent in the present study as well. Depression was more common among abstinent respondents than among current drinkers and abstaining was more common among depressed than non-depressed individuals. This may indicate that the relationship between alcohol consumption and depression is not linear if abstinent individuals are included in the analyses.

There are some previous findings on the relationship of binge drinking and depression. A positive association has previously been reported between binge drinking and depression irrespective of total alcohol consumption in both genders (Manninen et al., 2006). The results of study III suggest that there may be a difference between men and women. This difference may be due to the fact that the previous study did not include the AUDIT i.e. information on the severity of alcohol problems. Additionally, the reliability of reported alcohol consumption in the present study was of improved quality because of the utilization of the TLFB vs. traditional quantity-frequency methods used in the previous studies (Manninen et al., 2006; Searles et al., 2000; Sobell et al., 1982).

Another study previously reported a positive association between baseline binge drinking and depressive symptoms during a five-year follow-up period, but did not analyse the two genders separately . The definition binge drinking was markedly different and relied on self-reports of inebriation and hangovers to determine the frequency of binge drinking. Self-reported inebriation can be subject to bias due to increased alcohol tolerance and decreased subjective experience of inebriation.

An important question is the difference in the association of depression and alcohol problems between the two genders. With regards to other health issues aside from depression, it is clear that women are not protected from the adverse effects of binge drinking (Rehm et al., 2006; Sullivan et al., 2005; Lynskey, 1998). It has been suggested in previous studies that the causality of alcohol use and psychiatric disorders may be different for women and that depressed women with alcohol problems may suffer

from independent depression (i.e. depression not caused by alcohol use) more often than depressed men with alcohol problems (Wilsnack et al., 2004; Zilberman et al., 2003). It is plausible that depressed women may decrease their total alcohol consumption and/or are less likely to commence with binge drinking with the onset of depression. Recent evidence also suggests that the neurobiology of female and male depression may be different (Labonte et al., 2017)

6.1.3 Relationship with QoL

The literature from 2005 to 2010 addressing problems with HRQoL and its domains in alcohol dependence were summarized with a specific focus on the role of depression and other psychopathology (I). Alcohol dependence was associated with or determined to be a cause of decreases in HRQoL and its domains. Pharmacological and psychosocial treatment interventions for alcohol dependence produced improvements in HRQoL and its domains. Treatment was effective but clear differences between treatment modalities were difficult to determine (LoCastro et al., 2009). In study IV, higher AUDIT-scores and more frequent binge drinking were associated with impaired QoL in the general population after adjusting for covariates. AUDIT-scores reflect severity of alcohol problems and high scores can be indicative of alcohol dependence.

Two previous reviews by Donovan et al. and Foster et al. have addressed the literature on QoL in the context of alcohol dependence in the broader meaning (not restricted to health-related QoL) from 1993 to 2004 (Donovan et al., 2005; Foster et al., 1999). QoL was impaired among those with alcohol dependence when compared with the general population or individuals with other chronic health conditions. However, QoL improved with abstinence or reduced drinking. Despite differences in construct, the results of studies I and IV are in concordance with these findings of the two previous reviews.

In study I, a diagnosis or symptoms of depression were associated with further decreases in HRQoL among those with alcohol dependence. In study IV, higher AUDIT-scores were associated with impaired QoL in individuals with self-reported depression. These findings (I, IV) are suggestive of depression contributing to a further reduction of QoL/HRQoL in alcohol dependent individuals. These present findings are in concordance with the results the review of Foster et al. where psychiatric comorbidities were identified to be relevant in determining QoL in alcohol dependence (Foster et al., 1999).

In study I, changes that resulted from treatment were multidimensional and improvements in other areas of life reflected the overall marked improvement in

drinking. Reduction of alcohol consumption without complete abstinence also resulted in positive changes (LoCastro et al., 2009). In most of the studies reviewed (I), the improvements in different aspects of HRQoL were related to treatment interventions and subsequent reduction or cessation of alcohol use. This finding is in concordance with a previous review where QoL improved with abstinence or greatly reduced drinking (Foster et al., 1999). However, in study I the improvement in HRQoL was not always proportional to the improvement in drinking status (e.g.Neto et al., 2008). This finding strengthens the previous notion that all treatment benefits cannot be captured only by quantification of drinking.

Binge drinking, QoL and depression

Frequency of binge drinking was associated with impaired QoL among individuals with self-reported depression after adjusting for covariates (IV). When analysing the general population irrespective of depression classification, binge drinking was also associated with QoL. To the best of knowledge, previous studies have not examined the effect of binge drinking on QoL in depressed individuals. In the general population, previous studies have shown that frequent binge drinking has a negative impact on QoL (Luquiens et al., 2016; Mohamed and Ajmal, 2015; Monahan et al., 2012; Wen et al., 2012; Paul et al., 2011; Okoro et al., 2004; Volk et al., 1997). The results of study IV are in concordance with these findings in the general population. However, the results of study IV also indicate that the effect of binge drinking on QoL could be different in specific groups e.g. individuals with or without depression. Binge drinking was not associated with impaired QoL in non-depressed individuals. Depression was a more important determinant of impaired QoL than alcohol-related variables. It is plausible that depressed individuals are more vulnerable to the harmful effects of alcohol than non-depressed individuals are.

In a previous study, abstinence was associated with decreased QoL, which according to the authors of that study could be explained, by the large numbers of ex-problem drinkers among abstinent respondents (Saarni et al., 2008). Based on the present results this may not be the case. The present results (IV) suggest that higher prevalence of depressive symptoms rather than previous alcohol problems may explain the impaired QoL among abstinent respondents compared to current drinkers found in the previous study. In the present study, abstinence was not associated with QoL in the general population regardless of depression.

6.2 Strengths and limitations

6.2.1 Study I

In order to eliminate possible biases due to inclusion of studies with selected study populations, data from a wide array of study settings, methodologies, follow-up times, populations and stages of alcohol dependence were included in the present review. Data were extracted from both qualitative studies reporting a subjective, lived experience as well as quantitative results from larger samples. In some cases, HRQoL was not the focus of the study and the data regarding HRQoL and its domains was somewhat sporadic.

The construct of HRQoL is not unambiguous and the definition used in this review may limit direct comparison with previous studies. The review was limited by year (2005-10) and alcohol dependence – not less severe alcohol problems - due to the original strategy of data collection of PARADISE.

6.2.2 Studies II – IV

Epidemiological data were utilized in cross-sectional designs and information on the causality of the present findings cannot be determined. However, these studies have several strengths. First, they utilized a sufficiently large and randomly selected general population sample allowing for better generalizability of the results than would be possible with a selected patient population. However, it is plausible that those individuals with the most severe psychiatric and alcohol-related problems are underrepresented in a general population study such as this one and would be more prevalent among those not attending such a study.

A further strength was the use of the TLFB for evaluation of alcohol consumption. The TLFB with a one-month window is a recommended tool in large epidemiological studies such as this one (Vakili et al., 2008; Sobell et al., 1988; Sobell et al., 1982). Regardless, it is likely that some individuals categorized as abstinent according to the TLFB in Study IV are not long-term abstainers, but are temporarily abstaining. Underreporting may be present in all studies, which rely on self-reported alcohol consumption (e.g.Romelsjo et al., 1995). The effect of this underreporting on the results of this study is probably little but unknown.

The classification into depressed and non-depressed groups was done according to self-reported depressive symptoms using a modified BDI-SF. This slightly modified

version of the BDI-SF is not validated; however, it is unlikely that this would have greatly impacted the major findings of these studies. While the BDI-SF is an instrument created primarily for the screening for depression, it is both widely used in clinical practice and has been extensively studied and found to be valid in detecting depressive symptomatology. In the present studies, it appeared to be effective in screening for depression because with a cut-off of ≥ 8 points, 16% were categorized as depressed compared to the 6.5% prevalence of depressive disorders in the Finnish general population (Pirkola et al., 2005). It was important not only to include patients with diagnosable depression, but also those individuals reporting marked symptoms of depression who are commonly seen in clinical reality.

7 SUMMARY AND CONCLUSIONS

7.1 Summary

The aim of this dissertation was to elucidate the relationships between alcohol problems, depression and QoL. This study utilized epidemiological data from the Finnish general population as well as data from a systematic review of the literature addressing problems with HRQoL in alcohol dependence.

The present results provide new information as to the validity of the AUDIT and its abbreviations for the purpose of screening for at-risk drinking in depressed men and women. The AUDIT and AUDIT-C performed well irrespective of depression and its severity when cut-offs were adjusted by gender. Because this was the first validation study of AUDIT and its abbreviations in screening for at-risk drinking among depressed individuals, comparison of previous results was not possible.

In addition to addressing AUDs and the volume of alcohol use, the present results provide additional evidence for the importance of assessing the patterns in which alcohol is consumed. The fact that binge drinking was associated with depression among men, regardless of total volume of alcohol consumption and AUDIT-scores, together with the finding that binge drinking is associated with impaired QoL in depression, point to the conclusion that assessment of drinking patterns should be considered in this population also in clinical practice and in future studies.

Binge drinking and total alcohol consumption were not associated with depression among women. An important question raised by this finding together with previous research is whether the causality of alcohol problems and psychiatric disorders is different among men and women. The implications of this difference are still somewhat unclear but it seems that gender is a variable that should be taken into account in clinical assessment of comorbid alcohol problems and depression.

The literature reviewed here showed that alcohol dependence was associated with impaired QoL and depression was associated with further decrements in QoL. Despite differences in construct, previous reviews found similar results. An encouraging finding, which was replicated in this study was that treatment had a positive effect on QoL. In the present study, treatment was effective regardless of modality and reduction or cessation of alcohol use was a determinant of the improvement of QoL in some, but not all, instances. The results of the present literature review suggest that the positive effect of treatment may extend beyond what can be measured by alcohol consumption into areas such as interpersonal relationships, general functioning and

occupational issues. A comparison could be offered to harm reduction treatment programs where treatment goals and benefits are not solely measured by reduction of substance use, but more safe ways of using, reduction of health risks and improvement of QoL.

7.2 Implications for clinical practice

The findings reported here are in line with clinical experience where the combination of depression and alcohol problems has been recognized as a common and severe phenomenon, which deserves particular attention. The following recommendations are made based on the present results:

1) At-risk drinking can be reliably identified and should be screened for in depressed individuals with the AUDIT or AUDIT-C using cut-offs adjusted by gender.
2) Addressing binge drinking in the process of evaluation and treatment planning is important as binge drinking is associated with depression among men and appears to be linked to impaired quality of life in both genders.
3) Active treatment of alcohol problems is advised as there is evidence that treatment is effective in improving quality of life, mental health and functioning.

7.3 Future research

This study provided new information on the role of binge drinking as a possible risk factor for depression and impaired QoL in depressed individuals as well as the general population. The role of binge drinking as a possible mediator for alcohol-related harm requires further longitudinal research.

The validity of the AUDIT and its abbreviations for screening of at-risk drinking among depressed individuals was tested for the first time. While the results supported the use of the AUDIT and AUDIT-C as screening instruments in this population, these results need to be replicated in future studies. Clinical studies with real-life patient populations are also warranted.

Previous studies have found at-risk drinking to be associated with impaired QoL. The present results suggest that depression may modify the role of alcohol use on QoL. Previous literature has not taken into account the impact of at-risk drinkers' depression on QoL when investigating the relationship between alcohol use and QoL.

The relationship between depressive symptoms, alcohol consumption and problems and QoL among at-risk drinkers warrants further investigation in future studies.

In alcohol research, traditional drinking measures are still commonly the primary outcomes. The number of and range of studies which address QoL/HRQoL, however, was encouraging, as was the fact that analyses had been conducted in large studies specifically to evaluate the effect of treatment modalities on QoL/HRQoL. This finding may reflect that a more comprehensive view is being adopted when selecting endpoints for intervention studies. An interesting approach to evaluation of treatment efficacy in future research might be to allow the patient to determine what the goals of treatment are. These goals could include e.g. reduction of alcohol use (instead of abstinence), improvement of occupational functioning or alleviation of psychiatric symptoms. The efficacy of treatment interventions would be measured by how well these individual goals are met.

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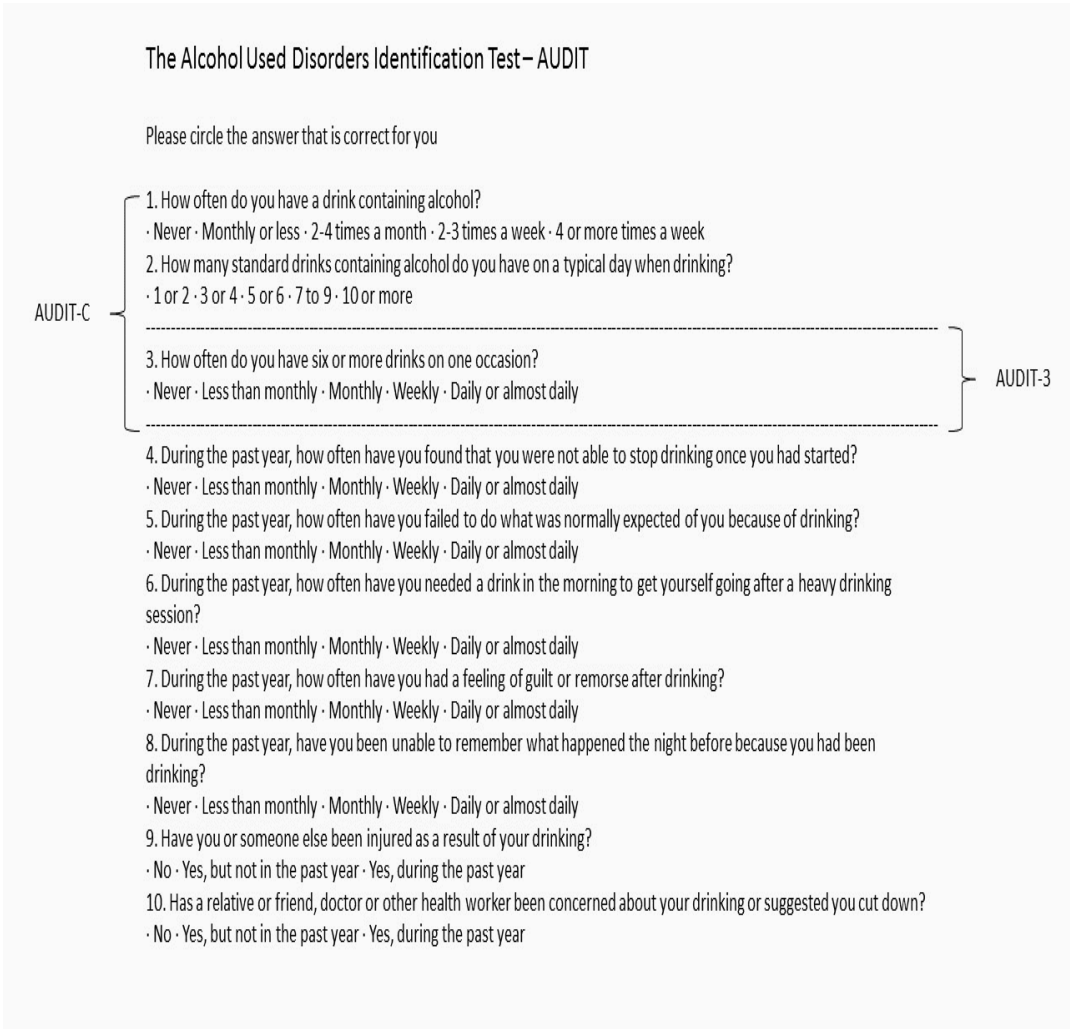
APPENDIX

Appendix I



Appendix II

Original and complete search terms for the literature review on alcohol dependence in the scope of PARADISE.

alcohol-related disorders/alcoholic intoxication/alcoholism in MEDLINE and Alcohol Abuse/Alcoholism/Binge Drinking in PsychINFO. In addition, the following terms in the title or abstract were used: dr?nk * excess * /dr?nk * binge * dr?nk * heavy * /dr?nk * hazard * /dr?nk * problem * /dr?nk * abuse * /dr?nk * influence * /drunk * /alcohol * excess * / alcohol * dependen * /alcohol * use * /alcohol * binge * /alcohol * heavy * /alcohol * hazard * /alcohol * problem * /alcohol * abuse * /alcohol * influence * /alcoholism * /alcoholic * . These diagnosis-related search terms were then combined with the following key words: psychosocial * , Quality of Life/, Personal Satisfaction/, exp Human Activities/and exp Social Support/disabilit * , homelessness, environmental factor * , exp Interpersonal Relations/, paternalism/, prejudice/, psychosocial deprivation/, social values/, exp Social Problems/, Social Adjustment/, social isolation/, stereotyping/, exp Social Environment/, exp emotions/, exp family/, exp socioeconomic factors/, exp life style/, exp Disability evaluation/, Communication Barriers/, Adaptation, Psychological/, Aggression/, Psychological stress/, (community not microbial community), or (sexual * or intimacy).