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TREATMENT OF ALCOHOL DEPENDENCE IN PRIMARY CARE

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Treatment of Alcohol Dependence in Primary Care

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By

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To Elsa, Hedda and Olof

Popular science summary of the thesis

Alcohol dependence is a common disorder that causes or contributes to over 200 health conditions and premature death. Many of the diseases that high alcohol consumption contributes to are common health problems in primary care e.g., hypertension, sleeping disturbances, and gastro-intestinal problems. A small percentage of alcohol dependent individuals are reached with treatment. One reason for this is the stigma attached to alcohol problems.

The majority of alcohol dependent individuals have a dependence with low to moderate severity. These individuals are often well-functioning and socially stable, however concerned about their drinking but do not feel they belong in specialized addiction clinics. Primary care is viewed as an appealing treatment option for these individuals. However, few routines are in place for the treatment of alcohol dependence and hazardous use of alcohol in Swedish primary care. General practitioners (GP) in primary care feel they have insufficient time and limited competence in the field of alcohol. Therefore, it is important to provide GPs with treatments that are time-efficient and feasible to use.

The overall aim with this thesis was to investigate new approaches aimed at enhancing professionals to identify and to treat alcohol dependence in primary care. This was investigated in the following four studies.

Study I investigated an internet-delivered cognitive behavioral (iCBT) program for alcohol dependent patients in primary care. 264 patients from primary care centers in Stockholm Region were randomized to either iCBT plus usual treatment in primary care (TAU) or to TAU only. The hypothesis in this randomized controlled study was that iCBT+TAU was more effective than TAU only. The iCBT program was a self-help program including five parts with different themes. As clear routines for treating alcohol dependence are rare, TAU will vary. Therefore, the involved GPs were offered a short training on giving feedback on assessment questionnaires and results from blood tests and on how to use medications for alcohol dependence before the study was initiated.

The result showed that there was no difference in mean weekly alcohol consumption between the groups after 12 months. Not all patients in the iCBT+TAU group initiated the iCBT program. When analyzing only those who actually initiated the iCBT program, the combination of iCBT and TAU resulted in lower mean weekly alcohol consumption compared to TAU at 12 months.

In **Study II** the aim was to investigate how socio-demographic (e.g., age, gender, employment status) and clinical (e.g., dependence severity, psychological health) factors influenced the outcome in Study I. The only factor that was found to influence the outcome was severity of dependence. Patients with severe dependence reduced their alcohol consumption more between baseline and 3 months compared to moderately dependent patients in TAU. The moderately dependent patients continued to reduce their consumption between month 3 and 12, while severely dependent patients increased their consumption during this period. To conclude, reduced alcohol consumption over time was found for moderately dependent patients treated in primary care with both treatment options. The severely dependent patients had a more limited effect, suggesting a possible need for more care within a specialized addiction clinic.

Study III was a qualitative study where 10 GPs with prior experience as care providers in Study I were interviewed. The aim was to study how GPs experience the management of patients with alcohol dependence in primary care, current treatment routines and their view on iCBT. The study showed that the GPs found it important to discuss alcohol with patients due to its impact on patients' health and they found most patients open to discuss their alcohol consumption. Routines for treating alcohol dependence were rare according to the GPs. Few available treatment options and perceived limited competence in the field of alcohol were expressed as hindering factors when working with alcohol dependence. The GPs believed that if iCBT was a treatment to offer patients it might facilitate discussions about alcohol. The iCBT program was viewed as an attractive treatment option for some patients and to have the potential to reduce stigma. iCBT does not require GPs themselves to learn a new treatment

method which may reduce the workload and enable the use of iCBT in primary care.

In **Study IV** the aim was to investigate how the combination of two implementation strategies impacted on clinical activity related to alcohol problems in primary care. 128 of all 223 publicly funded primary care centers in Region Stockholm participated in the study and provided data from relevant registers. The two strategies were a) a new policy, making prevention and treatment of alcohol dependence mandatory in primary care, and b) a digital training for all professions in how to identify and treat alcohol dependence in primary care. The new policy was introduced in February 2021 and the training was launched ten months after implementation of the new policy. Data was collected from registers for six different time periods 1) before the new policy was introduced, 2) after the new policy was introduced but before the training was made available, and 3) after the training was made available. A modest increase was found in some of the clinical activities that were related to working with alcohol problems in primary care after the new policy was introduced, but the digital training did not add any further increases. One explanation to this finding might be that few professionals appear to have participated in the training.

In summary, treatment of alcohol dependence in primary care is effective both for patients receiving TAU and for patients treated with iCBT plus TAU. Not all patients initiated iCBT, but those who utilized the iCBT program in combination with TAU reduced their weekly alcohol consumption more than the TAU group. Severity of dependence influenced the outcome in Study I. Moderately dependent patients reduced their weekly alcohol consumption during treatment and continued to reduce their consumption at 12 months follow-up. Severely dependent patients reduced their weekly alcohol consumption during treatment, but increased their consumption after end of treatment, suggesting a need for more care. The GPs involved in the studies viewed iCBT as a convenient

treatment option for some patients and having access to iCBT might facilitate discussions about alcohol. Regarding implementation strategies, the new policy, making alcohol interventions mandatory in primary care was associated with a modest increase in some alcohol-related activities, whereas no additional benefit was found for a brief digital training course in prevention and treatment of alcohol dependence.

Abstract

Alcohol dependence is a common disorder and contributes to substantial morbidity and mortality globally. Only 10–20 percent engage in treatment, which makes alcohol dependence the mental disorder with the largest treatment gap. Most individuals with alcohol dependence have a dependence of low to moderate severity. These individuals are concerned about their drinking but are not interested in seeking treatment in specialized care. Primary care, however, is viewed as an appealing treatment option for these individuals. In Swedish primary care few routines are in place for the treatment of alcohol use disorders (AUD). General practitioners (GP) are hesitant to engage in this field. Time concerns and perceived limited competence constitutes barriers for the identification and treatment of alcohol dependence in primary care.

The overall aim with this thesis was to study new approaches aimed at enhancing the identification and treatment of alcohol dependence in primary care.

Study I was a randomized controlled superiority trial including 264 participants with alcohol dependence in primary care in Stockholm. The objective was to test the efficacy of an internet-delivered cognitive behavioral therapy (iCBT) program for alcohol dependent patients in primary care. Our hypothesis was that iCBT, a five-module self-help program, when added to treatment as usual (TAU) was more efficacious than TAU only. As clear routines for treating alcohol dependence are lacking, TAU will vary. Therefore, the involved GPs were offered a one-hour training in giving feedback on assessments and biomarkers and providing pharmacotherapy for AUD. Linear mixed effects models were used to analyze primary and secondary outcomes. No significant differences between the groups were seen for the primary outcome of mean weekly alcohol consumption at 12 months in the intention-to-treat analysis. The per-protocol analysis showed that when including only patients who actually initiated the iCBT program, the combination of iCBT and TAU resulted in lower mean weekly alcohol consumption compared to TAU at 12-months.

Study II was a secondary analysis based on data from Study I with the aim to investigate the role of socio-demographic and clinical predictors for outcome in Study I, using linear mixed effects models. Primary outcome was mean number of standard drinks the last 30 days. Severity of dependence was the only variable that was found to moderate treatment outcome. Patients with severe dependence showed a significantly larger reduction in alcohol consumption between baseline and 3 months compared to moderately dependent patients in TAU. The moderately dependent patients continued to reduce their consumption between 3- and 12 months, while the severely dependent patients increased their consumption during this period. To conclude, reduced alcohol consumption over time was found for moderately dependent patients treated in primary care with both iCBT+TAU and TAU, while the effect for severely dependent patients was more limited, suggesting a possible need for more care.

Study III was a qualitative interview study with the aim to investigate how GPs experience the management of patients with alcohol dependence in primary care, current treatment routines and their view on iCBT. Ten GPs from primary care clinics in Stockholm (5/5 women/male) with prior experience as care providers in Study I were recruited via purposeful sampling and interviewed. Interview data was analyzed using qualitative content analysis. The GPs found alcohol important to discuss due to its impact on patients' health. They found most patients open to discuss their alcohol consumption. Routines for treating alcohol dependence were rare. Limited time, treatment options and perceived limited expertise were expressed as hampering factors when working with alcohol dependence. GPs believed that iCBT as a treatment option might facilitate discussions about alcohol with patients. The iCBT program was viewed as an attractive treatment option to some patients and did not require GPs to acquire behavioral treatment skills, potentially enhancing its implementation.

Study IV was a prospective longitudinal register-based study including 128 of all 223 publicly funded primary care clinics in Region Stockholm. The aim was to investigate the extent to which the combination of two implementation

strategies impacted on alcohol-related clinical activity in primary care in Region Stockholm. The two strategies were a) a new policy making prevention and interventions of AUD mandatory in primary care and b) training in the 15-Method. The new policy was introduced on February 2021 and training in targeted screening and treatment of AUD for primary care professions was launched ten months after implementation of the new policy. Data from registers were collected at six time periods; at three months before the new policy was launched; at three and nine months after the new policy was launched, but before training was available; at six, 12 and 18 months after training was available. Seven measures that reflect alcohol-related clinical activities were obtained from the primary care electronic case files and were analyzed with Generalized Estimating Equations. From low levels of alcohol-related clinical activities at baseline, a modest increase in some of the alcohol-related clinical activities was found 9 months after the new policy. The training in the 15-Method was not associated with further increases. Few professionals appear to have participated in the training. While a policy making alcohol interventions mandatory, combined with a training program, has strong support from implementation science, more implementation strategies seem necessary to impact on how clinicians in primary care can handle AUD.

The main conclusions of the thesis were that treatment of alcohol dependence in primary care is efficacious both for patients receiving TAU and for patients treated with iCBT plus TAU. For patients that utilized the iCBT program in combination with TAU, additive efficacy was found on mean weekly alcohol consumption. Severity of dependence predicted treatment outcome for alcohol dependent patients in primary care. Moderately dependent patients reduced their weekly alcohol consumption during treatment and continued to reduce their consumption at 12 months follow-up. Severely dependent patients reduced their weekly alcohol consumption during treatment, but increased their consumption after end of treatment, suggesting a need for more care. The GPs involved in the studies viewed iCBT as a convenient treatment option for some

patients and having access to iCBT might facilitate discussions about alcohol. Regarding implementation strategies, the new policy making alcohol interventions mandatory in primary care was associated with a modest increase in some alcohol-related activities, whereas no additional benefit was found for a brief digital training course in prevention and treatment of alcohol dependence.

List of scientific papers

- I. **Hyland, K.**, Hammarberg, A., Hedman-Lagerlöf, E., Johansson, M., Lindner, P., & Andreasson, S. (2023). The efficacy of an internet-based cognitive behavioral program added to treatment-as-usual for alcohol-dependent patients in primary care: a randomized controlled trial. *Addiction* (Abingdon, England), 118(7), 1232–1243. <https://doi.org/10.1111/add.16157>
- II. **Hyland, K.**, Romero D., Andreasson S., Hammarberg A., Hedman-Lagerlöf E., Johansson M. Outcome predictors of treatment via the internet for alcohol dependence in primary care: results from a randomized controlled trial (manuscript).
- III. **Hyland, K.**, Hammarberg, A., Andreasson, S., & Jirwe, M. (2021). Treatment of alcohol dependence in Swedish primary care: perceptions among general practitioners. *Scandinavian Journal of Primary Health Care*, 39(2), 247–256. <https://doi.org/10.1080/O2813432.2021.1922834>
- IV. **Hyland K.**, Hammarberg A., Hedman-Lagerlöf E., Wiklund O., Rosendahl I., Andreasson S. & Nilsen P. Addressing alcohol problems in primary care: combining new policy and training involving targeted screening (manuscript).

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List of abbreviations

AA	Alcoholics Anonymous
AUD	Alcohol Use Disorder
AUDIT	Alcohol Use Disorders Identification Test
CBT	Cognitive Behavioral Therapy
CDT	Carbohydrate Deficient Transferrin
CSQ	Client Satisfaction Questionnaire
DALYs	Disability-Adjusted Life Years
DSM	Diagnostic Statistical Manual of Mental Disorders
EQ-5D	EuroQol-5 Dimension
GP	General Practitioner
HADS	Hamilton Anxiety and Depression Scale
iCBT	Internet Cognitive Behavioral Therapy
ICD	International Classification of Diseases
ITT	Intention to Treat
MET	Motivational Enhancement Therapy
MI	Motivational Interviewing
PP	Per Protocol
RCT	Randomized Controlled Trial
SBI	Screening and Brief Interventions
TAU	Treatment as Usual
TLFB	Timeline Follow Back

TSF Twelve Step Facilitation

VAS Visual Analogue Scale

WHO World Health Organization

Introduction

Alcohol dependence is widespread globally and causes or contributes to substantial physical, psychological, and social harm (WHO, 2018). Only a minority of individuals with alcohol dependence are reached with treatment (Rehm et al., 2015a). Alcohol dependence stands out among mental disorders regarding the substantial treatment gap with only 10–20 percent of affected individuals entering treatment (Kohn et al., 2004; Rehm et al., 2015; Carvalho et al., 2019; SAHMSA, 2020). At the same time, alcohol use disorders (AUD) are among the most prevalent mental disorders with a point estimate of 1.4 percent (Rehm et al., 2019). Most individuals with alcohol dependence, around 75 percent, have a low to moderate level of dependence and are socially well-functioning (Andreasson et al., 2013). Mainly due to the stigma associated to alcohol problems, affected individuals prefer to seek treatment in primary care settings, rather than in specialized care (Wallhed-Finn et al., 2014; Field et al., 2013). Hence, primary care emerges as a promising arena for the treatment of alcohol dependence. Two key factors play a pivotal role in the successful identification and treatment of alcohol dependence within primary care. First, it is essential to motivate general practitioners (GPs) to initiate conversations about alcohol, given its significant contribution as a primary risk factor for a range of health-related issues commonly encountered in primary care (Griswold et al., 2018). Second, healthcare providers in primary care must have access to treatment options that are not only suitable but also practical and feasible to use in their clinical work.

Given this context, the overarching aim of my doctoral studies is to study novel approaches aimed at enhancing the identification and treatment of alcohol dependence in primary care.

Part 1 covers a background and review of previous research literature, including epidemiology, alcohol related harm, treatment in specialized care and in primary care and treatment via the internet. In part 2, the overall and specific aims of the thesis are outlined. In part 3, the methods used in the studies are presented, and followed by the main results in part 4. Part 5 encompasses a discussion and interpretation of the results followed by conclusions, in the context of the

research questions. In addition, this part addresses the limitations of the studies and reflections regarding future perspectives for further research. Lastly, acknowledgments and references are provided, followed by the four scientific papers.

1 Literature review

1.1 Alcohol use

1.1.1 Hazardous use, harmful use, AUD, alcohol dependence

Hazardous drinking is defined as a quantity or pattern of drinking that places the individual at risk for adverse health events (WHO, 2022). According to Swedish guidelines, that were recently updated, low risk consumption is up to nine drinks per week or three drinks on a single occasion for women and men, where one standard drink contains 12 g of pure alcohol (National Board of Health and Welfare, 2023). The diagnosis harmful use of alcohol implies an alcohol consumption that results in physical or psychological harm e.g., injuries, cardiovascular diseases, or depressive symptoms.

The diagnosis of alcohol dependence has long been used in the literature and is found both in the Diagnostic Statistical Manual (DSM) and in the International Classification of Diseases (ICD). The latest version of the DSM was introduced in 2013 in which the diagnosis is entitled alcohol use disorder (AUD) (DSM-5, 2013). AUD includes 11 diagnostic criteria and intends to capture the dimensional aspects of problematic alcohol use, with the level of severity being evaluated based on the number of criteria met. 2–3 criteria correspond to mild AUD, 4–5 criteria to moderate AUD and 6–11 criteria to severe AUD (Box 1).

The tenth edition of the International Classification of Diseases (ICD-10) (WHO, 1992) is widely employed and used within the Swedish healthcare system. For the diagnosis alcohol dependence, full-filling three or more of the six specified diagnostic criteria during the last 12 months is required (Box 1). Furthermore, ICD-10 makes a distinction between harmful use and dependence.

Box 1

Diagnostic criteria for alcohol use disorder (DSM-5)

1. Alcohol is often taken in larger amounts or over a longer period than was intended.
2. Persistent desire or unsuccessful efforts to cut down or control alcohol use.
3. A great deal of time is spent in activities necessary to obtain, use, or recover from effects of alcohol use.
4. Craving, or a strong desire or urge to use alcohol.
5. Recurrent alcohol use resulting in a failure to fulfill role obligations at work, school, or home.
6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by alcohol use.
7. Important social, occupational or recreational activities are given up or reduced because of alcohol use.
8. Recurrent alcohol use in situations in which it is physically hazardous.
9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
10. Tolerance
11. Withdrawal

Diagnostic criteria for alcohol dependence (ICD-10)

1. A strong desire or sense of compulsion to drink alcohol
2. Difficulties in controlling drinking behavior in terms of its onset, termination, or levels of use
3. Withdrawal
4. Tolerance
5. Neglect of alternative activities because of drinking, increased amount of time necessary to obtain or drink or to recover from the effects of alcohol
6. Persisting with drinking despite clear evidence of overtly harmful consequences

1.1.2 The two worlds of alcohol problems

Researchers within the field of alcohol adopt different viewpoints, depending on whether they are considering a clinical or a population health perspective. In neurobiological research, alcohol dependence is usually described as a chronic relapsing brain disease, involving complex interactions between recurrent drug

exposure, biological, and environmental factors (Leshner, 1997; Volkov et al., 2007). This perspective is based on the clinical population, but to a lesser degree non-treatment seeking individuals in the population meeting the criteria for alcohol dependence (Cunningham et al., 2012). This distinction between the clinical population, which typically comprises middle-aged men with a more intense recurring chronic condition, and the general population where alcohol dependence is prevalent in younger and socially stable individuals, is termed “the two worlds of alcohol dependence”. This concept was initially introduced in a publication by the World Health Organization (WHO) in 1977 (Room, 1977; Storbjörk et al., 2008). Furthermore, this distinction is also reflected in the literature as most addiction research is limited to the clinical population, with the consequence that we know less about the individuals with moderate dependence who reflect the majority of alcohol dependent individuals (Andreasson et al., 2013; Cunningham et al., 2012). The large group with mild and moderate alcohol dependence might go unnoticed within health care if professionals adapt to the perspective of alcohol dependence being a chronic relapsing brain disease. This might result in that patients are not asked about their alcohol consumption nor get necessary treatment when needed.

1.1.3 Epidemiology

The proportion of the Swedish population that met the criteria for alcohol dependence according to DSM-IV was approximately four percent in the years 2013–2021 (CAN, 2022). The proportions that had at least mild AUD according to DSM-5, was around 11 percent in 2017–2021 (CAN, 2022). In the large epidemiologic survey NESARC-III (N = 36,309) non-institutional adults in the US were interviewed face-to-face and the current prevalence of AUD was 14 percent, and the lifetime prevalence was 29 percent (Grant, et al., 2015). The National Survey on Drug Use and Health (NSDUH) is based on web-based or in person interviews (N = 31,730 and 38,120) with non-institutionalized individuals aged 12 or older in the US (SAMHSA, 2021). The 12-months prevalence of AUD was found to be 11.3 percent. In general population studies in the European Union, the 12-months prevalence of alcohol dependence was 3.4 percent and in European primary health care settings 8.7 percent (Rehm et al., 2015a; Rehm et al., 2015b). 76.7 percent of individuals with harmful use were male globally (Bryazka et al., 2022). In Stockholm County, 18 percent of men and 15 percent of women have a hazardous use according to the Alcohol Use Disorders

Identification Test–Consumption (AUDIT–C) including only the three questions on consumption in the full 10–item AUDIT (Bartelink et al., 2023).

1.1.4 Alcohol related harm

In the latest Global Burden of Disease study in 2016, it was concluded that harmful use of alcohol is linked to more than 200 diseases, injuries, and other health conditions, e.g., liver diseases, cardiovascular diseases, depression, suicides, cancers, road injuries, alcohol poisoning (WHO, 2018a). Alcohol contributes to 5.1 percent of the global burden of disease and injury (WHO, 2018a). Globally, alcohol was accountable for 7.2 percent of all premature mortality among adults in 2016. Among individuals aged 15–19 years in Sweden, alcohol consumption stands as the primary risk factor for disability–adjusted life years (DALYs) (WHO, 2018a). Harmful use of alcohol does not only affect the individual, but also leads to harm to others and significant social and economic losses at the societal level (WHO, 2018a). Numerous studies exploring the potential health protective benefits of alcohol have been released over the years. However, the systematic analysis for the Global Burden of Disease Study established that the risk of all–cause mortality escalates as alcohol consumption increases, and the best possible level of consumption that minimizes health loss is zero (Griswold et al., 2018). The latest systematic analysis for the Global Burden of Disease Study 2020 reported protective effects by low alcohol consumption for individuals aged > 40 years (Bryazka et al., 2022). This result has led to extensive debate and has been questioned due to the methodology used and the interpretations of the findings (Manthey et al., 2022). Nevertheless, WHO, adhere to their previous statement that no level of consumption is safe, and this is since 2022 also the recommendation in the World Heart Federation policy brief (WHO, 2023; WHF, 2022).

1.2 Treatment gap

A substantial number of individuals with alcohol dependence do not seek treatment. Many individuals recover without treatment, but treatment can reduce the duration of the problem period and prevent the harm caused by alcohol (Dawson et al., 2005; Tuithof et al., 2013; Tucker et al., 2020). With a treatment gap at around 80 percent, alcohol dependence has the largest treatment gap among mental disorders (Kohn et al., 2004; Rehm et.al, 2015; Carvalho et al., 2019). In a European study, only 30.3 percent of patients with AUD were identified and among these only 22.3 percent received treatment

(Rehm et al. 2015). In the US, the proportion of individuals with alcohol dependence who entered treatment was even lower (Kranzler et al., 2018). A systematic review and meta-analysis found that globally around one in six individuals in the general population with AUD were offered treatment (Mekonen et al., 2021). Repeated surveys since 2013 by the National Board of Health and Welfare in Sweden, reveals that less than one percent of all patients in primary care are provided with interventions for unhealthy drinking habits, and there have been no improvements during the period 2013–2021 (National Board of Health and Welfare, 2021). Given that alcohol dependence is almost as prevalent as diabetes mellitus type 2, one of the major common health conditions in the general population in Sweden (Nationella Diabetesregistret, 2023), it is notable that only a small fraction of patients with alcohol dependence are reached with treatment.

1.3 Barriers to seeking treatment

Several reasons have been proposed for the low proportion of individuals with alcohol dependence who receive treatment. One reason is related to the stigma associated with alcohol dependence. AUD is more stigmatized than other health related disorders and stigma constitutes one barrier to not seeking treatment (Kilian et al., 2021; Wallhed-Finn et al., 2023). An expectation that treatment would result in being labeled as an “alcoholic” and suggested an abstinence-based treatment approach using disulfiram or residential care might constitute a barrier to seeking treatment (Wallhed Finn et al., 2014). Other reasons for not seeking treatment are lack of awareness of the risks related to alcohol consumption or a wish to handle the problem oneself (May et al., 2019; Venegas et al., 2021). Fear of consequences like losing one’s job or being unable to spend time with children is another reason for not seeking treatment (Wallhed Finn et al., 2023). A preference for non-abstinence treatment goals and an expectation that treatment implies abstinence is a commonly expressed barrier (Wallhed Finn et al., 2023; Mann et al., 2017; Probst et al., 2015; Venegas et al., 2021). Primary care has the potential to lower the barriers for seeking treatment and will be discussed more in the “Barriers and facilitators” section.

1.4 The role of the environment and alcohol policy to reduce alcohol consumption

The transition of alcohol consumption to AUD or alcohol dependence may be prevented by several factors. Parenting factors like parental monitoring, parental

involvement and support and parent-child relationship quality is negatively associated with risk of adolescent alcohol consumption (Yap et al., 2017). More restrictive parental attitudes towards adolescents' alcohol consumption may have contributed to the decline in drinking among 15-16 years old adolescents in Sweden and Denmark in recent years (Ramstedt et al., 2022).

There is strong evidence that strategies like making alcohol less available and taxes making alcohol more expensive are highly cost-effective to reduce consumption and alcohol related harm (Andersson et al., 2009; Chrisholm et al., 2018). In cooperation with international collaborators, WHO launched the SAFER initiative in 2018 (WHO, 2018b). "SAFER" represents an acronym for the five most cost-effective interventions at reducing harm associated with alcohol: "**S**trengthen restrictions on alcohol availability, **A**dvance and enforce drink driving countermeasures, **F**acilitate access to screening, brief interventions, and treatment, **E**nforce bans or comprehensive restrictions on alcohol advertising, sponsorship, and promotion, **R**aise prices on alcohol through excise taxes and pricing policies". The Swedish government has implemented a comprehensive alcohol policy with the objective of minimizing the medical and social harms associated with alcohol by reducing overall consumption (Regeringen, 2021).

1.5 Pharmacological treatment of harmful use and dependence

Three pharmacotherapies are approved by the US Food and Drug Administration (FDA) for use in AUD treatment; acamprosate, disulfiram and naltrexone. The European Medicines Agency (EMA) have in addition also approved nalmefene for use in AUD treatment. In Sweden acamprosate, disulfiram and naltrexone are given the highest recommendation by the Swedish National Board of Health and Welfare (National Board of Health and Welfare, 2015).

Disulfiram is only recommended when abstinence is the goal, as adverse reactions due to accumulation of acetaldehyde occur in the presence of alcohol (Kranzler et al., 2018). Disulfiram intake under supervision has better outcomes than un-supervised intake but may be helpful also for patients motivated for sobriety (Skinner et al., 2014). Further, the awareness of a potential adverse reaction from disulfiram seems to impact an individual's drinking behavior (Mutschler et al., 2016).

Both naltrexone and acamprosate has been in use since the 1990s and are found to mitigate the reinforcing effects of alcohol consumption and reduce craving

(Franck et al., 2013). In a meta-analysis of 27 randomized controlled trials (N = 7519) it was found that naltrexone reduced the risk to relapse to both any drinking and heavy drinking while acamprosate reduced the risk to relapse to any consumption, but not to heavy drinking (Jonas et al., 2014). Although studies of naltrexone and acamprosate show moderate, but significant, effects on the reduction of alcohol consumption they are underutilized in treatment with between 3–8 percent of patients with AUD receiving pharmacotherapy (Ray et al., 2019; Rittenberg et al., 2020; Wallhed Finn et al., 2021a). In a Swedish cohort study (N = 132,733) including adults with AUD, the odds for prescriptions were lower for patients with lower income or education, higher age, and co-morbid somatic disorders (Wallhed Finn et al., 2021a). Moreover, repurposed pharmacotherapies e.g., baclofen, topiramate and gabapentin, are suggested for the treatment of AUD (Burnette et al., 2022). Novel pharmacotherapies, not yet approved by FDA and EMA, have the potential to achieve advancements in precision medicine, or personalized medicine, and tailored treatments for the AUD population (Burnette et al., 2022).

1.6 Psychosocial interventions

Psychosocial interventions found to be effective in treating alcohol dependence and AUD include i.e., motivational enhancement therapy (MET), cognitive behavioral therapy (CBT), the community reinforcement approach (CRA), and 12-step facilitation (TSF). These treatments seem to be similarly efficacious based on published systematic reviews the last 20 years (Miller et al., 2002; Martin et al., 2012; Kelly et al., 2020). Project MATCH, one of the largest treatment trials conducted, found all three treatment options (CBT, MET and TSF) equally efficacious in reducing alcohol consumption (Project MATCH, 1997). Project MATCH also aimed to investigate if patient characteristics predicted different outcomes in the three treatment modalities. The results showed that all treatments offered in this study resulted in little difference in outcomes despite clinical- and sociodemographic attributes among participants (Project MATCH, 1997). This result indicates that that it is not necessary to match patients to a specific type of treatment, a result which has been subsequently replicated in several well-designed clinical trials, e.g., COMBINE and UKATT, hence they all work if affected individuals are reached with treatment (Anton et al., 2006; UKATT, 2005). Since MET and CBT is included as the treatments in this thesis, these treatments will be discussed in more detail below.

1.6.1 Motivational Enhancement Therapy (MET)

MET is based on the principles of Motivational Interviewing (MI) and aims at strengthening the individual's motivation to alter behaviors (Project MATCH, 1997; Miller et al., 2012). MET includes assessments of the patient's alcohol problems and related consequences, giving feedback on the assessments, creating a written change plan and strengthening the patient's motivation for change.

1.6.2 Cognitive Behavioral Therapy (CBT)

CBT models for AUD operate under the assumption that behaviors related to alcohol use and the negative consequences associated with the use can be altered by strengthening alternative behaviors that replace alcohol consumption (Marlatt et al., 1985). CBT models also highlight the importance of acquiring specific coping strategies related to alcohol use such as seeking social support or declining offers to drink (McCrary et al., 2009). CBT programs include distinct components such as goal setting, self-monitoring alcohol consumption, and a functional analysis. The functional analysis is a structured method for identifying triggers, and short- and long-term factors that reinforce the problematic behavior. A CBT treatment supports the patient with training to cope with craving and handle risk-situations.

1.6.3 The 15-Method

The 15-Method was developed to be delivered by primary care practitioners considering the time constraints and the context of this setting (The 15-Method, 2021). The 15-Method is a stepped care model for the treatment of hazardous use and alcohol dependence in primary care and is based on MET and CBT. The model comprises three steps. The first step includes the identification of problem drinking and a brief advice. The second step includes assessment and giving personalized feedback on assessments and biomarkers. In the third step pharmacotherapy and/or four sessions of MET/CBT are provided. The MET/CBT sessions include motivation to change, goal setting and self-monitoring alcohol consumption, identifying risk-situations, and problem solving. The 15-method has demonstrated its potential as a promising approach for the treatment of alcohol dependence in primary care (Wallhed Finn et al., 2018; Wallhed Finn et al., 2020).

1.6.4 Efficacy of psychosocial interventions

Typical effect-sizes for psychosocial interventions are in the low to moderate level and well-defined psychosocial therapies are more effective than unstructured therapies (Martin et al., 2012; Carvalho et al., 2019). Key effective elements in successful therapies have not been clearly identified (Magill et al., 2015; Miller et al., 2015). Yet, various general mechanisms of behavior change have been proposed. These include goal setting, enhancing self-efficacy, structured approaches of working with problem behaviors, self-monitoring of alcohol consumption, and non-specific factors like therapeutic alliance and the technical skills of therapists (Hallgren et al., 2019; Holzhauer et al., 2020; Morgenstern et al., 2000).

1.6.5 Controlled drinking

The literature does not support abstinence as the only goal for treatment of AUD. A recent review replicated earlier reviews and presented evidence that controlled drinking is a viable treatment goal, even for some individuals with more severe AUD (Henssler et al., 2021; Sobell et al., 1987). Further, treatments with abstinence as a goal did not differ from those with controlled drinking goals concerning the maintenance of drinking reductions or patient psychosocial functioning (Henssler et al., 2021). However, another trial found that individuals with a milder dependence severity, lower baseline consumption, a low level of negative mood-symptoms and who do not frequently engage in heavy drinking in their social circles are more likely to achieve controlled drinking during treatment (Witkiewitz et al., 2017). Given an evidence base for controlled drinking, treatments with non-abstinence goals can be more frequently offered patients and might contribute to lower the threshold for treatment seeking.

1.7 Treatment of AUD in primary care

1.7.1 Screening and brief intervention

Screening and brief intervention (SBI) was introduced by WHO in the 1970s and was intended to manage hazardous and harmful alcohol consumption in primary care. SBI have been evaluated in numerous studies but have not been successfully implemented in clinical practice (Segura et al., 2018; van Beurden et al., 2012; Nielsen et al., 2023). A review on systematic reviews found knowledge gaps regarding the effectiveness for SBI across different population groups and settings, regarding which are the most effective intervention components and

the duration of intervention effects (O'Donnell et al., 2014). Based on the current knowledge, it appears that clinicians who have limited time should prioritize short and simple interventions with focus on prompting individuals to document their alcohol consumption (O'Donnell et al., 2014). Knowledge was established already in the 1970s that short, structured treatments are as effective as longer treatments (Edwards et al., 1977). The median duration of brief intervention given was 25 minutes in a frequently cited review (Kaner et al., 2007). The fact that more extended interventions add no significant additional effect over shorter brief interventions in alcohol consumption for hazardous and harmful drinkers in primary care was later concluded in another Cochrane review by the same author (Kaner et al., 2018). In this review an extended intervention was defined as comprising more than five sessions or having a total combined session duration exceeding 60 minutes. Another limitation discussed regarding SBI studies is the modest reduction in alcohol consumption in combination with the lack of effect on biological markers (Saitz, 2014). This might indicate that SBI efficacy in fact is unknown, and the modest effects of alcohol consumption from SBI might be due to social desirability bias i.e., patients underreport their alcohol consumption due to social desirability (Saitz, 2014).

1.7.2 Screening in primary care

An additional challenge is that GPs are reluctant to do general screening for alcohol problems and consequently screening is rarely used (Brown et al., 2016). An evaluation of general screening compared to targeted screening i.e., screening of patients presenting conditions associated with high alcohol consumption (i.e., mental health problems, hypertension, gastrointestinal problems, minor injuries, liver diseases) found that the odds of being screened positive for hazardous drinking were higher in the group receiving targeted screening (Coulton et al., 2017). However, most of those screening positive with general screening would have been missed by targeted screening (Coulton et al., 2017). Given that general screening is not applied in primary care, targeted screening could be considered as an alternative approach.

1.7.3 Screening, Brief Intervention and Referral to Treatment

Until recently, no RCT-studies have evaluated the efficacy of SBI for alcohol dependent patients (Saitz, 2010). To reach those with more severe alcohol problems, Screening, Brief Intervention and Referral to Treatment (SBIRT) programs were developed (Babor et al., 2007; Babor et al., 2017). These programs

include efforts to refer individuals to treatment in specialized care when needed (Babor et al., 2007; Babor et al., 2017). A thematic meeting of the International Network on Brief Interventions for Alcohol & Other Drugs (INEBRIA) with the objective to synthesize recent evidence about SBI was held in Stockholm in 2017 (Glass et al., 2017). The meeting concluded, not only that implementation of SBI remained a challenge, but also that there was insufficient evidence for the referral to specialized treatment—part in SBIRT (Glass et al., 2017). Future directions from the meeting included the need for developing new models to address, identify and treat alcohol dependence in primary care.

1.7.4 Treatment of alcohol dependence in primary care

Already in 1990, a study published in *The Lancet* found treatment for problem drinkers as effective in primary care as treatment in specialized care also of more severely dependent drinkers (Drummond et al., 1990). This finding was recently replicated when a stepped care program including brief interventions and pharmacotherapy for alcohol dependence in primary care (The 15-Method, 2021) was compared to specialized care and found no differences between the sites (Wallhed Finn et al., 2020).

1.7.5 Pharmacotherapy as treatment in primary care

A systematic literature review including studies from primary care settings in Europe, North America, Australia, and South Africa concluded that knowledge and prescription of pharmacotherapy for AUD is insufficient (Morgane, 2021). Moreover, this review revealed that there are a limited number of studies evaluating the efficacy of pharmacotherapy for AUD, and despite the existence of guidelines for psychological and medical management, they have not been customized to primary care practice. In a scoping review from the US including 47 intervention studies from primary care settings utilizing FDA-approved pharmacotherapy for AUD (disulfiram, naltrexone and acamprosate), it was concluded that the integration of AUD pharmacotherapy into primary care settings may be followed by enhanced process measures and outcome measures of care (Hyland C.J. et al., 2023). A systematic review of studies published worldwide from 1998–2020 examined the effectiveness of models of care with varying intensity for AUD in primary care (Rombouts et al., 2020). The review concluded that psychosocial and/or pharmacotherapy models of care have the potential to increase treatment uptake. Moreover, to make clear which patients are most appropriate for AUD treatment in primary care, more studies

are required (Rombouts et al., 2020). The prescription rate of pharmacotherapy was investigated in a regional primary care practice-based research network in the US including 47,502 patients with at least one documented primary care visit (Hallgren et al., 2020). The prescription rate was found to be 7.8% for patients with a documented AUD diagnosis (Hallgren et al., 2020).

1.8 Digital interventions

The term digital intervention refers to an intervention that directly targets individual users for prevention or treatment. These interventions are delivered through dedicated programs, web-browsers or applications to a computer, a tablet, or a phone. An internet intervention goes beyond an informational website and includes interactive elements such as exercises, assessments, self-monitoring tools and sometimes therapist-support (Ritterband et al., 2006). For this thesis, I will mainly focus on internet interventions with the aim on supporting an individual in changing drinking of alcohol. These interventions include brief advice or more extended programs used in psychological face-to-face treatment (Cunningham et al., 2011).

1.8.1 Internet-based Cognitive Behavioral Therapy (iCBT)

Internet-based Cognitive Behavioral Therapy (iCBT) is grounded in the principles of CBT and typically include several sessions or modules with different themes delivered via the internet. Research for more than 20 years has shown that iCBT is as efficacious as face-to-face CBT for several problems and disorders including AUD (Andersson et al., 2019; Riper, et al., 2018). An updated systematic review and meta-analysis of the clinical effects for psychiatric and somatic disorders, found face-to-face CBT equally effective as guided iCBT (Hedman-Lagerlöf et al., 2023). In a five-country trial iCBT for anxiety and depression was successfully implemented and viewed as a valuable part of mental health care (Titov et al., 2018). Critical elements of successful iCBT included for example their establishment as specialized iCBT clinics integrated with mental health services, their utilization of evidence-based and well-developed iCBT programs and the assessment and reporting on outcomes (Titov et al., 2018). Internet interventions for mental disorders and AUD have the capacity to enhance access to treatment that are evidence-based, to mitigate stigma and to be cost-effective (Cunningham et al., 2011; Titov et al., 2020; Rohrbach et al., 2023). A meta-analysis of 19 randomized controlled trials among individuals with hazardous drinking found internet-interventions efficacious in reducing alcohol consumption (Riper

et al., 2018). A study comparing face-to-face treatment vs. iCBT for AUD in specialized care found iCBT non-inferior to face-to-face treatment to reduce alcohol consumption (Johansson et al., 2020).

1.8.2 Therapist guided versus self-guided interventions

Internet alcohol interventions can be pure self-help/self-guided interventions, with no personal contact during the intervention. In assisted self-guided interventions, a person provides guidance on how to use the self-help intervention or reminds the user to engage with it. In guided interventions, the user has contact with a therapist via electronic communication throughout the intervention period. Most studies show that therapist guided interventions are more effective than self-guided interventions in reducing alcohol consumption (Karyotaki et al., 2021; Riper et al., 2018). However, for some patients self-guided interventions are equally effective when delivered within a structured care process (Titov et al., 2015; Wallace et al., 2017). In a small Swedish trial, an internet intervention with eight modules based on MI and CBT, was investigated for individuals with hazardous drinking (Sundström et al., 2016). Participants who received the self-help program and an added therapist guidance reported lower alcohol consumption than the unguided group at ten-weeks follow up (Sundström et al., 2016). When the same intervention was used in another trial for AUD, participants had a telephone assessment prior to start and filled-out weekly measures. This structured care process resulted in similar adherence and reduction of alcohol consumption six- and 24-months post treatment in the therapist-guided and the self-guided group (Sundström et al., 2020; Eék et al., 2023). Clinician time spent was one hour per participant in the self-guided group, compared to approximately three hours for therapist-guided group (Sundström et al., 2020).

1.8.3 Implementation of digital interventions in health care

A systematic review had as part of its aim to study the feasibility of different types of digital interventions for substance use disorders (Nesvåg et al., 2018). Single interventions, such as one-way or interactive text messaging, or text-messaging combined with a simple monitoring module, appeared easy to implement. However, more complex interventions including for example systems for monitoring or check-ups, required more technological and organizational support to implement (Nesvåg et al., 2018). Another study aimed to investigate primary care professionals' perceptions regarding a digital intervention for

harmful drinkers (Lopez-Pelayo et al., 2019). It was the digital intervention used in the EFAR-Spain study, an RCT where facilitated access to a website for reducing alcohol consumption in primary care was used, that was aimed to be evaluated (Caballeria et al., 2021). The professionals found the website useful when discussing alcohol with patients and traditional barriers to SBIRT were overcome by the digital intervention (Lopez-Pelayo et al., 2019). Further, the professionals reported that the low feedback rate from patients and difficulties among elderly and low-socioeconomic populations in using the digital intervention was hampering factors for the intervention. In a qualitative study, primary care professionals were interviewed regarding implementing a digital application for AUD (Mogk, et al., 2023). They perceived training, electronic health record tools, and having dedicated clinicians to provide the apps as effective implementation strategies (Mogk, et al., 2023).

1.8.4 Patients' perspective on digital interventions

Digital interventions have been found to be attractive to and reach people with AUD that do not attend specialized care (Khadjeseri et al., 2015; Sinadinovic et al., 2010). The possibility to access digital interventions anonymously, has been found to reduce the barrier to seeking treatment for a highly stigmatized health condition as AUD (Khadjeseri et al., 2015; Ekström et al., 2020). Taking patients' preferences for development of clinical interventions into account have become increasingly emphasized and have the potential to play a crucial role for improving retention and outcomes for patients (Swift et al. 2021). In a qualitative study, participants with hazardous and harmful consumption treated with therapist-guided iCBT were interviewed after end of treatment about their views on iCBT (Lunde et al., 2022). Patients perceived iCBT making them more aware of their consumption and its drawbacks and provided them with tools to change their alcohol consumption. Further, participants expressed that they appreciated the anonymity and flexibility with iCBT but expressed a wish for more individualization of the program (Lunde et al., 2022).

To summarize, iCBT has proven to be efficacious in treating AUD as well as hazardous use, but to our knowledge there are yet no studies on iCBT for alcohol dependence in primary care.

1.9 Barriers and facilitators for implementing treatment for AUD in primary care

As mentioned above, AUD are among the disorders with the lowest treatment prevalence and the situation is likewise worldwide. This is the case even though there are effective and cost-effective treatments available which have demonstrated similar effectiveness as treatments for other health conditions (Rehm, et al., 2018; Rehm et al., 2015a; Leucht et al., 2015).

1.9.1 Patients' perspective

On the patient level, lack of awareness regarding the problem, and stigma or shame constitute obstacles to seeking treatment (Schomerus et al., 2010; Probst et al., 2015; Kilian, et al., 2021; Wallhed Finn et al., 2023). However, a recent study found patient preferences for consulting a GP in primary care regardless of the level of perceived stigma (Wallhed Finn et al., 2023). This suggests a high level of trust in GPs and their important role in addressing and treating AUD (Coste et al. 2016; Wallhed Finn et al., 2020). In qualitative interview studies with patients, they seem to prefer treatment in primary care compared to specialized care and they find alcohol acceptable to discuss in primary care, especially if they have co-occurrent health conditions (Barry et al., 2016; O'Donnell et al., 2020). Patients who were interviewed found it important to be provided with necessary information about how alcohol affects their health (O'Donnell et al., 2020). This knowledge enables them to do healthy lifestyle choices which eventually can be the trigger to a positive change (O'Donnell et al., 2020).

1.9.2 Professionals' perspective

To address alcohol by raising patients' curiosity about how alcohol impact their present clinical condition, referred to as pragmatic case-finding or targeted screening, was found to be a promising approach among Norwegian GPs interviewed (Lid et al., 2012; Lid et al., 2015). Stigmatization towards patients with AUD have been reported among health care professionals, in addition to the self-stigma patients experience (van Boekel et al., 2013). Other obstacles that prevent GPs to engage in treating AUD are time constraints and perceived lack of training in handling alcohol problems, that are viewed as more complicated and time-consuming than other health related conditions (Nygard et al. 2011; Anderson et al., 2014; Keuhorst et al., 2014; Geirsson et al., 2006). GPs accept the task of treating alcohol-related health problems (Rehm et al., 2015c; Nygaard et al., 2010; Holmqvist et al., 2008). However, they tend to perceive their role more

as treating health problems which may be alcohol related (Nygaard et al., 2011; Lid et al., 2012; Lid et al., 2015). Encouragingly, a population-based cross-sectional survey conducted in routine healthcare in Sweden 2010 and 2017 found that it was more likely to have conversations about alcohol in 2017 compared to 2010, a development that had occurred since the National Guidelines for Disease Prevention Methods (National Board of Health and Welfare, 2011) was published in 2011 (Karlsson et al., 2019). In a cluster-randomized controlled trial primary care clinics were randomized to a training program for the implementation of SBI or to waitlist (Rosario et al., 2021). The training was based on the Behavior Change Wheel/Theoretical Domains Framework approach tailored to the barriers and facilitators for implementing SBI (Michie et al., 2011; Cane et al., 2012). The intervention clinics increased alcohol screening, but not the brief intervention activity per screen-positive (Rosario et al., 2021).

1.10 Implementation of alcohol interventions

Implementation research reveals that alcohol interventions cannot be implemented without stakeholder and management support or without appropriate training and resources (Kaner 2010a; Kaner 2010b; Nilsen et al., 2011; Fitzgerald, 2017). It should be ensured that the professionals have enough time, and resources to implement alcohol interventions using validated screening tools. In a systematic review, including both qualitative and quantitative studies on implementation of SBI, 35 of the 47 included studies were carried out in primary care (Johnson et al., 2010). Implementation was limited by lack of training, resources, workload, and support from management. The SHAMSA project in the US identified essential contextual factors that affected the implementation and delivery of alcohol interventions, e.g., simultaneous technological innovation, accessibility to treatment, physical environment, patient characteristics, and geographical location (Babor et al., 2017). In summary, most implementation projects of alcohol interventions have evaluated the implementation effect from a combination of training and management support, or one strategy at a time. We have not found any previous studies which have evaluated the effect of regulations or policies to implement alcohol interventions in primary care.

1.11 Predictors of outcome in treatment of AUD

A systematic review of predictors of outcome for AUD from studies between 1977–2005 indicated that minimal psychiatric comorbidity, low severity of dependence, high alcohol-related self-efficacy, strong motivation for change, and a treatment goal of achieving abstinence as consistent predictors of successful treatment outcome over various studies (Adamson et al., 2009). A meta-analysis of moderators of internet interventions revealed that age above 55, male gender and lower education were associated with better treatment outcomes for problem drinkers (Riper et al., 2018). This result contrasted with an earlier study by the same author, that found improved outcomes for more educated participants (Riper et al., 2008). Often predictors that demonstrate significance in one study may not maintain their significance in another, and occasionally the predictive relationship can even be reversed in direction (Dale et al., 2017). Hence, the review by Henssler et al. found no statistical differences on low-risk drinking outcome between abstinence- or controlled drinking as goal for individuals with AUD (Henssler et al., 2021). An analysis of data from three large alcohol trials (COMBINE, MATCH and UKATT) found low dependence severity, lower baseline consumption, few negative mood symptoms, and low social support for drinking were more likely to achieve low-risk drinking (Witkiewitz et al., 2017). There are, to our knowledge, no studies on predictors of treatment outcome for iCBT in primary care.

2 Research aims

2.1 Overall aim

The overall aim of this thesis was to study new approaches for the identification and treatment of alcohol dependence in primary care.

2.2 Specific aims of the studies

Study I: To investigate if an iCBT program added to treatment as usual (TAU) is more efficacious in reducing alcohol consumption than TAU for alcohol dependent patients in primary care.

Study II: To investigate the role of socio-demographic and clinical characteristics as predictors of outcome of iCBT added to TAU vs. TAU for alcohol dependent patients in primary care.

Study III: To examine general practitioners' attitudes to the management of patients with alcohol dependence in primary care, current treatment routines and their view on iCBT as a new treatment approach in primary care.

Study IV: To investigate the extent to which the combination of two implementation strategies, a) a new policy which makes alcohol interventions mandatory in primary care and b) training in the 15-method, affects alcohol-related clinical activities among professionals in primary care.

3 Materials and methods

3.1 Study I: The efficacy of an internet-based cognitive behavioral program added to treatment as usual for alcohol dependent patients in primary care: a randomized controlled trial

3.1.1 Aim

To investigate if an open-ended iCBT program added to TAU is more effective than TAU for alcohol dependent patients in primary care.

3.1.2 Design

A two-group, parallel, randomized controlled superiority trial. Alcohol dependent participants from 14 primary care centers in Stockholm, Sweden, were randomly assigned to iCBT+TAU or to TAU with a 1:1 allocation and were followed-up at 3 and 12 months.

3.1.3 Participants

Potential participants were informed about the study via leaflets at the primary care study sites or at a primary care consultation, advertisements in local newspapers and on websites (see Figure 1).



Figure 1. Example of the advertisement in a local newspaper used for recruitment to the clinical trial. "Would you like to feel better with less alcohol? Could you consider seeking treatment at your primary care center? Then perhaps this is the study for you! Visit www.alkoholohalsa.se to read more and register. Your participation is voluntary and protected by healthcare confidentiality". Research principle is Stockholm Region and Karolinska Institutet.

Using the study website, interested individuals accessed more information regarding the study, provided their informed consent and completed screening assessment in the on-line platform. If inclusion criteria were fulfilled (> 18 years of age, three or more criteria for alcohol dependence according to the ICD-10 (WHO, 1992) and > 6 points for women/> 8 points for men for hazardous consumption according to the AUDIT (Babor et al., 2001), eligible individuals were automatically invited to create a personal account and complete baseline assessment. The assessment was kept brief to minimize the risks of assessment reactivity (McCambridge et al., 2011). Hereafter, eligible individuals were contacted via telephone by the study coordinator, who was a nurse clinically trained in the field of addiction and psychiatry, to ensure data quality and completeness and to advise individuals who met exclusion criteria to seek appropriate care. The exclusion criteria were serious mental illness, substance-use disorder other than alcohol and nicotine, need of specialized treatment in psychiatry or addiction care, cognitive impairment, and lack of Swedish language skills.

3.1.4 Randomization

Participants who gave informed consent and completed assessments in the on-line platform were randomized to treatment with either iCBT+TAU or TAU only. The randomization was conducted in blocks of 20, according to a fully automated procedure in the on-line platform. The study coordinator randomized the participants by activating a link only she had access to. Participants were informed by the study coordinator about their group allocation and were asked to provide a blood test for biomarkers and were scheduled for an appointment with their GP at their primary care center.

3.1.5 Interventions

TAU: TAU was delivered at the primary care center. In both treatment arms, the GPs gave participants feedback on the assessments and biomarkers and designed a treatment plan based on current routines on treating alcohol

problems at the primary care center. All GPs were offered a short training session in providing feedback on assessments and biomarkers and pharmacotherapy (acamprosate, disulfiram, naltrexone, nalmefene) prior to the study. Written instructions, including contact details, were provided to the primary care centers to inform colleagues who could not take part in the training. The GPs were instructed to refer patients they usually refer, e.g., when addiction was assessed as too severe to treat in primary care, when liver enzymes were heavily raised or other somatic or psychiatric conditions requiring specialized care.

iCBT: The iCBT+TAU group was offered iCBT in addition to TAU. The iCBT was delivered on-line at the same platform that was used for assessments in the study. iCBT was an extended self-help intervention with automated e-mails, with feedback and reminders to start and complete the assignments that were given to the participants. The iCBT program was based on self-help material used in previous trials of iCBT in specialized care (Johansson et al., 2020; Johansson et al., 2017; Sundström et al., 2016). The content and exercises in the program were based on motivational interviewing, relapse prevention and behavioral self-control training. The program was divided into five main modules: (1) motivation to change, (2) drinking-goal and self-control strategies, (3) behavioral analysis of drinking and risk-situations, (4) general problem-solving and (5) preventing relapse. There were also three optional problem-solving modules (handling feelings, drink-refusal skills, and handling cravings). iCBT was an open-ended intervention, meaning that participants could log on to the treatment platform as often and for as long as they wanted. For each assignment, an informational text was provided, and a home assignment was included, but all assignments were possible to use in the order preferred by the participants. The treatment was fully automated, and no therapist contact was provided.

3.1.6 Data collection

All data was extracted from the assessments that the patients provided on the on-line platform used in the study. The biological markers were collected from the patient files at the primary care center after the participants had provided their blood-tests.

3.1.7 Outcome measures

The primary outcome measure was alcohol consumption defined as mean grams per week at 12-month follow-up. Consumption was self-reported using the

timeline follow-back (TLFB) during the last 30 days (Sobell et al., 1996). The primary comparison statistic was the difference in mean weekly consumption between study groups.

Secondary outcomes were: Alcohol consumption in mean grams per week at 3-month follow-up and mean number of days with heavy drinking ($\geq 4/5$ drinks for women and men) per month measured with TLFB (Sobell et al., 1996). Hazardous use was assessed with the AUDIT total score (Babor et al., 2001). Severity of dependence was assessed by the self-reported number of ICD-10 criteria for alcohol dependence (WHO, 1992). Symptoms of anxiety and depression were assessed with the Hospital Anxiety and Depression Scale (HADS) (Zigmond et al., 1983). Health-related quality of life was assessed with the Equation 5D-5L questionnaire (Herdman et al., 2011). Based on TLFB, the number of alcohol-free days during the last 30 days was explored. Client satisfaction questionnaire, CSQ, was used to assess satisfaction with treatment at 3 months follow-up (Larsen et al., 1979). Levels of phosphatidylethanol (PEth), gamma-glutamyl transferase (GGT), aspartate amino transferase (AST) and alanine amino transferase (ALT).

The primary and secondary outcomes were assessed on-line at baseline and at 3- and 12-months post-randomization.

3.1.8 Sample size

The study was designed to detect a minimum between-group effect size of $d = 0.4$, which required a sample size of 100 participants in each arm to achieve a power of 80% with an alpha of 0.05 and using an independent-samples t-test for weekly alcohol consumption at 12-month follow-up. Given an estimated dropout in iCBT of 30%, 264 participants were included in the study (Melville et al., 2010).

3.1.9 Data analysis

As per the trial protocol, the change in the primary outcome (weekly alcohol consumption at 12-month follow-up) was modeled using linear mixed effects models, according to the intention-to-treat (ITT) principle and with missing data estimated (per model, with no additional predictors) using restricted maximum likelihood estimation, under the missing at random (MAR) assumption. This missing mechanism was deemed clinically plausible and reasonable (Jakobsen, et al., 2017): measures were collected independent of treatment adherence (i.e.,

not only those who remained in treatment continued to contribute data), on-line administration of measures made it convenient to contribute data and provided data had no impact on continued treatment. Multiple imputations were not run prior to mixed effects modeling, as simulations and empirical findings suggest no additional benefits of this approach. Sensitivity analyses, with a missing not at random (MNAR) assumption and first observation carried forward (FOCF) imputation, was run on significant mixed models.

Due to difficulties in modeling a trajectory with so few data points and no obvious grounds for equidistance (Hesser, 2015), we opted to include only random intercepts and to treat time as a factor (rather than numeric), with the 3-month follow-up (mid-study measurement) as reference, in interaction with group. This mid-study reference was chosen to reflect observed (and assumed) trajectories, with marked differences between slopes on either side of the reference. Factorial time made time-coding intervals for blood test outcomes necessary (as blood tests could not be administered with the same precision as on-line self-ratings), requiring balancing maximization of sample size with avoiding misclassification bias. Analysis of secondary variables followed the same strategy as described above for the primary outcome.

From these mixed models, estimated marginal means (with confidence intervals) were calculated for each arm and time-point (with degrees of freedom using the Satterthwaite method), with pairwise contrasts at each time-point. ITT analyses was complemented with per-protocol (PP) analyses. PP analyses included all participants in the iCBT+TAU arm that completed at least one module of iCBT. PP analyses included all participants in the TAU arm, as all participants were scheduled for an appointment with their GP per study arm. Cohen's effect sizes were calculated using estimated marginal means and observed standard deviations. Analyses were conducted in the R version 3.6.3 statistical environment using the lme4 (Bates et al., 2015), lmerTest (Kuznetsova et al., 2017), and emmeans packages (R-package emmeans, 2022).

3.2 Study II: Outcome predictors of treatment via the internet for alcohol dependence in primary care: results from a randomized controlled trial

3.2.1 Aim

To investigate predictors of outcome of treatment with iCBT+TAU vs. TAU for primary care patients with alcohol dependence. Patients' baseline characteristics, including socio-demographic and clinical factors were analyzed as potential predictors.

3.2.2 Design

A secondary analysis based on data from an RCT in which participants were randomized to an internet-based cognitive behavioral program (iCBT) as an add-on to treatment as usual (TAU) or to TAU only (i.e., Study I).

3.2.3 Participants

The sample included in this study was the same as in Study I.

3.2.4 Procedure

Study procedures were the same as in Study I. For a full account of the original trial's design, procedures, and outcomes, see Study I (Hyland, K et al., 2019; Hyland, K et al., 2023).

3.2.5 Outcomes

Primary outcome measure was mean number of standard drinks the last 30 days using the Timeline Follow-Back method (Sobell et al., 1996), adhering to the outcome definition in the parent trial. A standard drink contains of 12 grams of alcohol. Other outcome measures used in the parent study included mean weekly drinking, number of days with heavy drinking ($\geq 4/5$ drinks for women and men) and alcohol free days during the last 30 days using the TLFB, problematic alcohol use assessed with the AUDIT total score (Babor et al., 2001), self-reported number of ICD-10 criteria for alcohol dependence (WHO, 1992), symptoms of anxiety and depression assessed with Hospital Anxiety and Depression Scale (HADS) (Zigmond, et al. 1993), and health related quality of life assessed with EQ 5D-5L (Herdman et al., 2011).

3.2.6 Predictors

The potential predictors included were decided by the research team prior to analyses and based on available evidence in the literature. A correlation matrix was calculated and measures with a correlation magnitude that exceeded R 0.5 considered for exclusion. To avoid overlaps or multi-collinearity, several potential clinical predictors were excluded from analyses and sociodemographic predictors dichotomized. AUDIT, which combines consumption and dependence criteria, was excluded due to overlap with alcohol dependence. Weekly consumption, binge drinking and days with no alcohol consumption were excluded due to overlap with number of drinks the last 30 days. EQ 5D-5L, HADS depression and HADS anxiety were excluded due to overlap with HADS total score. The final sociodemographic predictors used were age (centered), gender (female/male), relationship status (married/cohabiting versus living alone/widowed), education level (higher education or not), and employment status (employed or not). The final clinical measures used were severity of alcohol dependence assessed by number of ICD-10 criteria at baseline (moderate: 3-4, severe: 5-6 criteria), and symptoms of anxiety and depression assessed with HADS total score at baseline.

3.2.7 Data analysis

These secondary analyses extend the analytical approach of the parent study (i.e., Study I) which modelled the change in outcome using linear mixed effects models. The analyses were conducted in accordance with the intention-to-treat principle, with missing data accounted for by restricted maximum likelihood estimations. Consistent with the original study, time was treated as a categorical variable due to non-uniformly spaced intervals and limited data points, with the 3-month follow up serving as the reference. Only random intercepts were included. Beyond the scope of the original trial evaluation, which considered the effect of time and treatment and their interaction on the outcome, we further included seven candidate predictors, each in separate models, resulting in seven different models. The five socio-demographic and two clinical factors presented above were included as fixed effects, and each separate model additionally included two- and three-way interaction terms for each combination of treatment, time, and the individual predictor. The three-way interaction thus tested if there was a difference in effect over time between treatment groups as a function of the predictor. Such an effect is sometimes referred to as a moderator. An alpha level of 0.05 was used to determine statistical significance.

As this was an exploratory study aiming to identify potential treatment effect moderators rather than confirming their existence, no adjustments for multiple comparisons were conducted. To compare the performance of the candidate predictor models with a reference model (which only included treatment, time, and their interaction as fixed effects), we used the likelihood ratio test based on the maximum likelihood estimator. For absolute measures of goodness-of-fit, we calculated both marginal and conditional R², representing the variance explained by fixed effects alone and the variance explained by both fixed and random effects, respectively. Initially, our plan was to include all significant candidate predictors in a single model, to investigate the effect of each significant predictor above and beyond the influence of other covariates. For this purpose, we computed a correlation matrix including all candidate predictors to identify pairs of moderators that could potentially induce multicollinearity. However, it turned out to be unnecessary to include multiple moderators in the same model due to mainly non-significant results, see results below. All analyses were conducted within the R (v. 4.2.3) statistical software environment (R Core Team, 2023), using the lme4 (Bates et al., 2015) and lmerTest (Kuznetsova et al., 2017) and performance (Lüdtke et al., 2021) packages.

3.3 Study III: Treatment of alcohol dependence in Swedish primary care: perceptions among general practitioners

3.3.1 Aim

To describe general practitioners' (GPs) attitudes to the management of patients with alcohol dependence in primary care and current treatment routines and their view on a new treatment approach; iCBT.

3.3.2 Design

A qualitative interview study with ten GPs employed at the participating primary care clinics in Study I. The interviews were analyzed using qualitative content analysis.

3.3.3 Participants

GPs were recruited via purposeful sampling (Patton 2014; Malterud et al., 2016) from the primary care clinics that participated in Study I with experience in the follow-up of patients taking part in the study.

3.3.4 Data collection

An open-ended, semi-structured interview guide was used covering current treatment routines and GPs' attitudes and views on the iCBT for alcohol dependence. The interview guide was developed by the first and third author and it was piloted with three participants. The first author conducted the pilot interviews and a qualitative researcher outside the project gave feedback on the interview guide. The pilot interviews were not included in the study. The first author conducted all ten interviews that lasted for 30–40 min. After the first two interviews the last author read, and approved the way interviews were performed. Examples of questions asked were: 'What is your experience in working with alcohol dependence?'; 'How do you find that patients react when they are asked questions about their alcohol habits?'; 'What, if anything would make it easier to discuss patients' alcohol habits?'; 'Elaborate on your view towards iCBT.' For a full description, see (Hyland K, et al., 2021).

3.3.5 Data analysis

The interviews were digitally recorded, transcribed verbatim and analyzed with inductive content analysis focusing on the manifest content as described by Graneheim and Lundman (Graneheim et al., 2004). An inductive content analysis was applied where categories are derived from data, that is, the categories are not pre-determined. The interviews were read several times by the first and last authors as a first step of the analysis. Guided by the aim of the study the first author identified meaning units that were condensed and labelled with codes which were then discussed with the last author and altered until agreement was reached. To increase the credibility of the analysis, regular meetings between the first and last authors were held throughout the different stages of the process. Through continuous comparisons of similarities and differences, the codes were abstracted to preliminary sub-categories and categories. The next step was to initiate a reflective interpretative process which involved working back and forth between meaning units, codes, and preliminary sub-categories and categories. In the final step and to further strengthen the credibility of the analysis the sub-categories and categories were reviewed and confirmed by the second and third author.

3.4 Study IV: Addressing alcohol problems in primary care: Combining new policy and training including targeted screening

3.4.1 Aim

To investigate the extent to which the combination of two implementation strategies, a) a new policy making alcohol interventions mandatory in primary care and b) training in the 15-Method, impacted on alcohol-related clinical activities in primary care in Region Stockholm.

3.4.2 Design

A prospective longitudinal register-based study.

3.4.3 Participants

128 primary care clinics, or 57 per cent of all 223 publicly funded primary care clinics in Region Stockholm, were approached and agreed to provide data and were active for the whole study period.

3.4.4 Interventions

The Region Stockholm is responsible for providing publicly funded healthcare services to approximately 2.4 million residents of Stockholm. A new healthcare policy was introduced in the Region Stockholm in February 2021 which clarifies that primary care now is the front line for psychiatric care, including the management of harmful use and dependence of alcohol. New agreements have been established with the 223 primary care clinics within Region Stockholm, explicitly stating that the management of AUD is now an integrated part of these agreements. In the past, the management of alcohol problems largely depended on individual practitioner discretion, and most patients with drinking problems were referred to specialized care.

Ten months later, the Region Stockholm launched a brief digital training for primary care professions on how to identify and treat harmful use and moderate alcohol dependence according to the 15-Method manual based on targeted screening, Motivational Enhancement Therapy (MET) and Cognitive Behavioral Therapy (CBT) (The 15-Method, 2021). In recent years the 15-Method has proved to be a promising approach in treating alcohol dependence in primary care (Wallhed Finn et al., 2020). Training consisted of a digital course in a short version (1 hour) or a longer version (2.5 hours), which all professions in all 223 primary care clinics in Region Stockholm were offered. The digital course

included information, questions, exercises, case examples, reflections, films, and self-help material to patients. The intention with the training in the 15-Method is to learn how to raise the topic about alcohol, assess the severity of alcohol disorder, how to give advice about hazardous and harmful use of alcohol and how to treat alcohol dependence with psychological and pharmacological treatment (The 15-Method, 2021).

3.4.5 Data collection

The main level of analysis was the primary care clinic and applies to all alcohol-related clinical activities by all professions, please see the seven indicators below. Data from registers were collected at six time periods i.e., during 30 days at six timepoints. The first data collection started three months before the new policy was launched (baseline). The second and third data collections started three and nine months after the new policy was launched, but before training was available, and measured the impact of the new policy. The last three data collections started six, 12 and 18 months after training was made available, and measured the impact of the training in the 15-Method, as a growing number of professionals had taken part in the training. In this way, each primary care clinic constituted its own control.

Data were obtained from the primary care electronic case files that indicate change in clinical activities targeted at each of the three steps in the 15-method: raising the topic of alcohol, assessing the severity of alcohol disorder and treatment of alcohol dependence. The choice of seven indicators was dictated by the information available in the electronic case files. The specific indicators for the three steps of the 15-Method were:

- *Raising the topic about alcohol consumption:* This was measured by the frequency of

- (1) Structured documentation on alcohol habits: weekly alcohol consumption and heavy drinking occasions.

- *Assessing the severity of alcohol disorder:*

- (2) Use of the AUDIT (Alcohol Use Disorders Identification Test) instrument (Babor et al., 2001)

- (3) Ordering of blood tests for biomarkers of heavy drinking (CDT or PEth).

- *Treatment of alcohol dependence:*

(4) Prescription of pharmacotherapy for harmful use and dependence (naltrexone, nalmefene, acamprosate, disulfiram)

(5) Registered alcohol related diagnoses: harmful use of alcohol and alcohol dependence

(6) Completed brief advice and extended advice regarding hazardous use, harmful use, and dependence of alcohol, registered using KVÅ-codes, Klassifikation av Vårdåtgärder (Classification of care measures)

(7) Referrals to specialized addiction care

3.4.6 Data analysis

GEE (Generalized Estimating Equations) was used for the analyses of the two events (new healthcare policy and web-based training in the 15-Method) during follow-up that was expected to have an impact on each of the components for the seven indicators analyzed in the study. GEE model is a population-averaged (i.e., marginal) model highly suitable for the purpose of the study, based on register data with no missing values. Three working correlation structures was tested for each indicator (independent, exchangeable, and AR1). Since GEE models are not fit via maximum likelihood, they are not comparable in terms of AIC or likelihood tests. Instead, a Quasi-likelihood method was used to compare models with different correlation structures (Pan, 2001) with the lowest QIC value representing the best fitting model. To handle that the standard errors may be wrong if a mis specified working covariance structure is used, the Huber-White "sandwich estimator" for robustness was used.

To analyze the impact of the first event during follow-up (i.e., new healthcare policy) only the three first time periods of follow-up was used in the analysis where the time periods were handled as a categorical variable, which give a separate estimate for each time period instead of a linear average value. For the analyses of the second event during follow-up (i.e., web-based training in the 15-Method), all six time periods of follow-up were used in a RD (Regression Discontinuity) model for each of the seven indicators. This technique is useful to study "jumps" in the data and basically involves adding a dummy variable to the model with a value of 1 for the time periods after the event of interest and a value of zero for the time periods before the event of interest.

The frequency of all seven indicators was divided by the number of patients who were listed at each primary care center at each study period. The quota was

then multiplied by 10,000 so the result then becomes the incidence per 10,000 patient-months.

A Care Need Index (CNI) was included in all the models to the seven indicators. This index is provided by Statistics Sweden and uses socioeconomic conditions in to identify risk for illness in the area where the primary care center is located (Care Need Index, CNI). An index value higher than one indicates higher need of care than the average in the Region and an index value lower than one indicates a lower need of care than the average. In the analysis the index was centered around one.

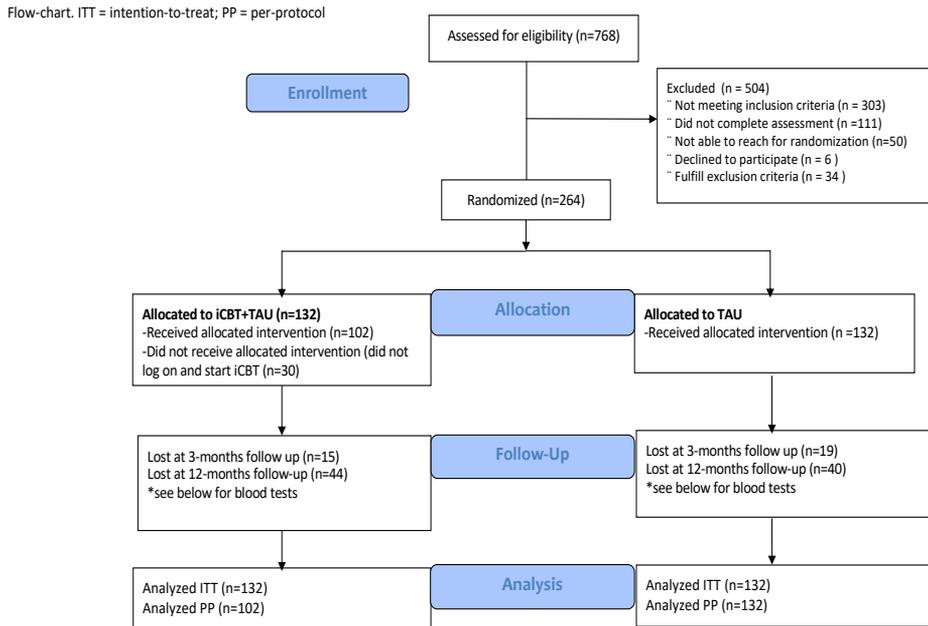
The study investigates behavior change among all primary care professions at participating primary care clinics in the Region Stockholm. Power calculation was not needed since the study concerned an entire population. All analyses were performed using R Statistical Software (R Core Team, 2023) and the R Package geepack for Generalized Estimating Equations (Halekoh et al., 2006).

4 Results

4.1 Study I

264 participants were randomly allocated to the two study arms (see flow-chart in Figure 2).

Figure 2. Flowchart Study I



*Number of individuals providing blood tests at follow-up (%), see table:

Analysis	iCBT+TAU, 3-months	iCBT+TAU, 12-months	TAU, 3-months	TAU, 12-months
PEth	56 (42.4)	20 (15.5)	59 (44.7)	23 (17.4)
GGT	55 (41.7)	22 (16.7)	59 (44.7)	24 (18.2)
AST	55 (41.7)	23 (17.4)	60 (45.5)	24 (18.2)
ALT	55 (41.7)	22 (16.7)	60 (45.5)	24 (18.2)

The participants, with a mean age of 51 years, comprised 148 female and 116 male participants, who were moderately dependent, highly educated and mostly employed and cohabiting. There were no significant differences between treatment groups in any of the variables at baseline (Table 1).

Table 1. Demographic data and baseline values

	TAU (n = 132)	iCBT+TAU (n = 132)
Gender (n, %)		
Male	54 (40.9)	62 (47.0)
Female	78 (59.1)	70 (53.0)
Age [mean (range)]	52 (28–80)	50 (23–77)
Education (n, %)		
Not completed compulsory education	0 (0.0)	1 (0.8)
9 years of education	6 (4.5)	6 (4.5)
12 years of education	35 (26.5)	41 (31.1)
Higher education	88 (66.7)	82 (62.1)
Other	3 (2.3)	2 (1.5)
Source of income (n, %)		
Employment	106 (80.3)	97 (73.5)
Pension	24 (18.2)	23 (17.4)
Other	2 (1.5)	12 (9.1)
Marital status (n, %)		
Married/cohabiting	80 (60.6)	84 (63.6)
Live alone	49 (37.1)	45 (34.1)
Widowed	3 (2.3)	3 (2.3)
AUDIT risk-level (n, %)		
≤ 15	19 (14.4)	26 (19.7)
16–19	22 (16.7)	31 (23.5)
20–40	91 (68.9)	75 (56.8)
Weekly alcohol consumption (g) [mean (SD)]	263.77 (137.09)	284.45 (184.89)
Heavy drinking days per month [mean (SD)]	10.96 (7.45)	10.89 (8.38)
Alcohol-free days per month [mean (SD)]	9.86 (7.51)	9.41 (7.25)
ICD-10 criteria dependence [mean (SD)]	4.03 (0.99)	4.32 (1.07)
AUDIT total score [mean (SD)]	21.17 (5.07)	21.00 (5.64)
HADS scale anxiety [mean (SD)]	10.40 (3.37)	9.79 (3.20)
HADS scale depression [mean(SD)]	6.12 (3.68)	5.57 (3.65)

Equation 5D 5 L VAS [mean (SD)]	62.89 (20.18)	65.43 (20.68)
PEth [mean (SD)]	0.65 (1.03) <i>n</i> = 93	0.58 (0.68) <i>n</i> = 100
GGT [mean (SD)]	0.68 (0.75) <i>n</i> = 95	0.62 (0.93) <i>n</i> = 100
AST [mean (SD)]	0.49 (0.25) <i>n</i> = 95	0.49 (0.28) <i>n</i> = 102
ALT [mean (SD)]	0.50 (0.30) <i>n</i> = 95	0.46 (0.28) <i>n</i> = 101

Abbreviations: ALT = alanine amino transferase; AST = aspartate amino transferase; AUDIT = Alcohol Use Disorders Identification Test; EQ-5D-5L = EuroQoL-5 dimension; GGT = gamma-glutamyl transferase; HADS = Hospital Anxiety and Depression Scale; iCBT = internet-based cognitive behavioral therapy; ICD = International Classification of Disease; Peth = phosphatidylethanol; TAU = treatment-as-usual.

4.1.1 Treatment utilization

There was no difference in attention to the first appointment to the GP or in the number of visits at the primary care center between the groups. 30 out of 132 participants (23%) randomized to iCBT+TAU never logged on and initiated iCBT. 69 participants (52%) in iCBT+TAU and 92 participants (70%) in TAU were prescribed pharmacotherapy ($\chi^2 = 8.42, P = 0.004$). The follow-up rate at 3-months was 87% (230/264) and at 12-months 68% (180/264), with no difference in attrition rate between treatment groups.

4.1.2 Primary outcome analysis

The ITT analysis revealed no significant difference in the reduction of mean weekly alcohol consumption between the groups at the 12-month follow-up. The PP analysis included only those who completed at least one module of iCBT in the allocated treatment (*n* = 102) and resulted in significantly reduced alcohol consumption in the iCBT+TAU group compared with TAU (*n* = 132) (Table 2).

Table 2. Primary outcome; estimated means and pointwise between-group differences with 95% CI for primary outcome at 12-month follow-up (ITT and PP analysis data set).

	iCBT+TAU	TAU	Difference in drinking quantities	<i>P</i> -value	Cohen's <i>d</i>
ITT (MAR)	133.56 (100.94–166.19)	176.20 (144.04–208.35)	42.64	0.068	0.23
ITT (MNAR)	172.80 (150.00–196.80)	195.60 (171.60–219.60)	22.80	0.205	0.16
PP (MAR)	107.46 (71.17–143.74)	176.00 (144.21–207.80)	68.54	0.010	0.42
PP (MNAR)	153.60 (128.40–178.80)	194.40 (171.60–216.00)	40.80	0.019	0.31

Note: In missing at random (MAR) analyses, the minor difference in estimated (MAR) values of the TAU arm between ITT and PP analyses reflects that missing data were estimated per model, not per model and arm. Estimated means for the TAU arm from last observation carried forward (LOCF) [missing not at random (MNAR)] models also differ between ITT and PP, due to covariate adjustment being based on whole sample mean.

Abbreviations: iCBT = internet-based cognitive behavioral therapy; ITT = intention-to-treat; PP = per-protocol;

TAU = treatment-as-usual; CI = confidence interval.

4.1.3 Secondary outcome analysis

All symptom scores in both groups at the 3- and 12-month follow-ups were reduced compared with baseline in the secondary outcomes. No significant differences between the groups in any of the secondary outcomes at the 3- and 12-month follow-ups were found in the ITT analysis (Table 3). The PP analysis on the secondary outcomes included those who completed at least one module of iCBT in the allocated treatment (n = 102). The results showed more alcohol-free days and a reduction in symptoms of depression for the iCBT+TAU group compared to TAU at the 12-month follow-up.

Table 3. Secondary outcomes; estimated means and pointwise between-group differences with 95% CI for secondary outcomes at 3-month follow-up (3MFU) and 12-month follow-up (12MFU) (ITT analysis data set).

Variable (mean)	iCBT+TAU 3MFU (95% CI)	iCBT+TAU 12MFU (95% CI)	TAU 3MFU (95% CI)	TAU 12MFU (95% CI)	Difference 3MFU	P-value 3MFU	Cohen's <i>d</i>	Difference 12MFU	P-value 12MFU	Cohen's <i>d</i>
Weekly alcohol consumption (g)	157.79 (128.13–187.45)	See Table 2	181.58 (151.56–211.61)	See Table 2	23.794	0.269	0.15	See Table 2	See Table 2	See Table 2
Heavy drinking days per month	5.63 (4.30–6.97)	4.79 (3.32–6.26)	5.93 (4.58–7.28)	5.93 (4.48–7.38)	0.298	0.758	0.045	1.141	0.279	0.15
Alcohol-free days	14.93 (13.51–16.35)	17.17 (15.61–18.73)	15.08 (13.65–16.52)	15.24 (13.71–16.78)	0.155	0.880	0.018	-1.925	0.084	0.23
ICD-10 criteria dependence	2.70 (2.44–2.96)	2.16 (1.86–2.45)	2.86 (2.60–3.13)	2.31 (2.02–2.60)	0.163	0.389	0.11	0.150	0.474	0.079
AUDIT total score	15.15 (14.08–16.23)	12.98 (11.80–14.16)	15.28 (14.19–16.36)	13.75 (12.59–14.92)	0.122	0.875	0.023	0.774	0.360	0.11
HADS scale anxiety	8.05 (7.48–8.63)	7.42 (6.80–8.05)	8.18 (7.60–8.76)	7.64 (7.02–8.26)	0.130	0.754	0.040	0.222	0.621	0.068
HADS scale depression	4.01 (3.38–4.64)	3.29 (2.60–3.98)	3.87 (3.24–4.50)	4.14 (3.47–4.82)	-0.139	0.759	0.041	0.858	0.082	0.25
Equation 5D 5 L VAS	71.85 (68.33–75.37)	71.71 (67.76–75.66)	71.95 (68.38–75.53)	73.03 (69.15–76.91)	0.103	0.968	0.0054	1.321	0.639	0.068

Variable (mean)	iCBT+TAU 3MFU (95% CI)	iCBT+TAU 12MFU (95% CI)	TAU 3MFU (95% CI)	TAU 12MFU (95% CI)	Difference 3MFU	P-value 3MFU	Cohen's <i>d</i>	Difference 12MFU	P-value 12MFU	Cohen's <i>d</i>
PEth	0.52 (0.35–0.70)	0.59 (0.35–0.82)	0.51 (0.34–0.68)	0.46 (0.23–0.68)	-0.008	0.948		-0.129	0.436	
GGT	0.75 (0.53–0.97)	0.72 (0.40–1.04)	0.67 (0.46–0.89)	0.73 (0.43–1.03)	-0.081	0.605		0.007	0.976	
AST	0.48 (0.39–0.58)	0.48 (0.33–0.63)	0.58 (0.48–0.67)	0.44 (0.29–0.58)	0.093	0.173		-0.043	0.684	
ALT	0.47 (0.40–0.55)	0.49 (0.37–0.60)	0.54 (0.47–0.62)	0.50 (0.40–0.61)	0.07	0.193		0.016	0.842	

Note: Effect sizes for biomarkers are not shown due to few blood samples provided at follow-ups.

Abbreviations: ALT = alanine amino transferase; AST = aspartate amino transferase; AUDIT = Alcohol Use Disorders Identification Test; EQ-5D-5L = EuroQol-5 dimension; HADS = Hospital Anxiety and Depression Scale; iCBT = internet-based cognitive behavioral therapy; ICD = International Classification of Diseases; Peth = phosphatidylethanol; TAU = treatment-as-usual; CI = confidence interval; VAS = visual analog scale; ITT = intention-to-treat.

4.2 Study II

There were no significant differences in any measures between the two treatment groups at baseline. Trial participants had a mean age of 51 years, 56 percent were females and 44 percent were males. Participants were overall highly educated, employed, co-habiting, and had a moderate severity of dependence. The follow-up rate at 3-months was 87% (230/264) and at 12-months 68% (180/264), with no difference in attrition rate between treatment groups.

4.2.1 3-months follow-up

Only one predictor, severity of dependence, had a significant effect on change in alcohol consumption over time and moderated outcome of treatment. In these

linear effects model presented in Table 4, participants with moderate dependence in TAU was used as a reference and the intercept (64.478, SE = 6.586, $p < .001$) represent the number of drinks the last 30 days for these participants at 3 months follow-up which was used as the reference time-point. Participants in both iCBT+TAU and TAU with moderate dependence reduced their drinking between baseline and 3 months follow-up, with no significant difference between the groups (time_0-3 m*ICBT: 13.473, SE = 8.45, $p = 0.112$). Participants with severe dependence showed a larger reduction in alcohol consumption between baseline and 3 months compared to moderate dependent drinkers in TAU (time_0-3m*ICD: 28.905, SE = 9.893, $p = 0.004$). The model also revealed a significant three-way interaction of dependence and group allocation on the change in alcohol consumption between baseline and 3 months (time_0-3m*ICBT*ICD: -31.93, SE = 14.557, $p = 0.029$). This result implicates that the interaction effect of dependence severity on change in alcohol consumption between baseline and 3 months was different depending on group allocation or that the effect of treatment group on change in alcohol consumption between baseline and 3 months is different depending on severity of dependence. For detailed information on this three-way interaction, please see subgroup analysis below.

4.2.2 12-months follow-up

Between 3- and 12-months moderate dependent drinkers reduced their drinking significantly in both TAU (time_3-12m: -14.401, SE = 6.954, $p = 0.039$) and iCBT+TAU, but with no significant difference between treatment groups (time_3-12m*ICBT: 0.812, SE = 9.369, $p = 0.931$). In contrast, the severe dependent drinkers in both TAU and iCBT+TAU increased their drinking significantly between 3 and 12 months compared to those with moderate dependence (time_3-12*ICD: 27.447, SE = 10.922, $p = 0.012$). There was no significant three-way interaction of dependence and group allocation on the change in alcohol consumption (time_3-12m*ICBT*ICD: -7.893, SE = 16.53, $p = 0.633$) (Table 4).

Table 4. Linear mixed effects model with severity of dependence, treatment, and time, as predictors of mean number of standard drinks during the last 30 days.

(Intercept)	64.478 (SE = 6.586, p < .001)
time_0-3m	22.561 (SE = 6.289, p < .001)
time_3-12m	-14.401 (SE = 6.954, p = 0.039)
ICBT	-15.012 (SE = 8.853, p = 0.091)
ICD	-10.569 (SE = 10.338, p = 0.307)
time_0-3m*ICBT	13.473 (SE = 8.45, p = 0.112)
time_3-12m*ICBT	0.812 (SE = 9.369, p = 0.931)
time_0-3m*ICD	28.905 (SE = 9.893, p = 0.004)
time_3-12m*ICD	27.447 (SE = 10.922, p = 0.012)
ICBT*ICD	21.595 (SE = 15.21, p = 0.156)
time_0-3m*ICBT*ICD	-31.93 (SE = 14.557, p = 0.029)
time_3-12m*ICBT*ICD	-7.893 (SE = 16.53, p = 0.633)

Estimated unstandardized regression coefficients from the linear mixed effects model, Standard Errors (SE) within parentheses. ICD was coded as 0=moderate dependence (3-4 ICD-10 criteria), 1= severe dependence (5-6 ICD-10 criteria). ICBT was coded as 0=TAU, 1=ICBT+TAU.

To further understand the three-way interaction described above and the development in alcohol consumption over different time points, estimated means in different subgroups as defined as group allocation and dependence severity were calculated and plotted in Figure 3.

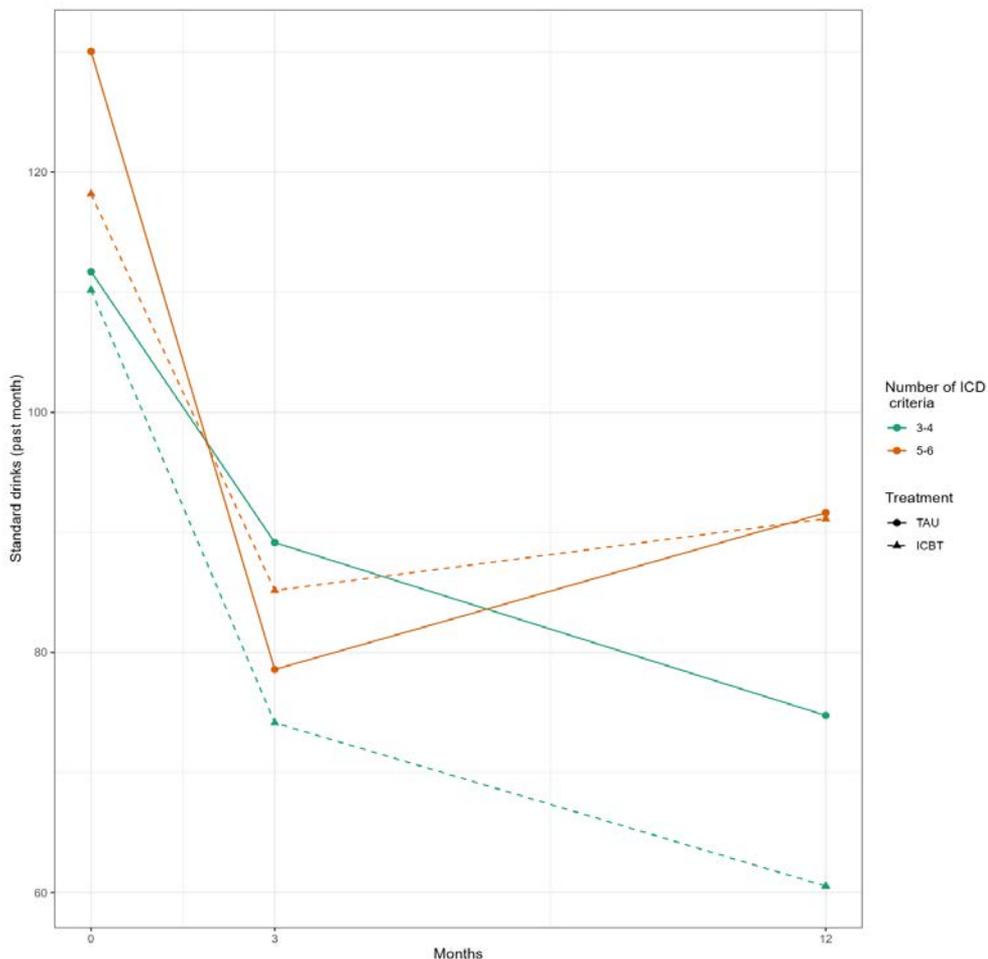


Figure 3. Estimated mean number of standard drinks last 30 days at different time points for moderate (N= 168) and severe (N=96) alcohol dependent participants per treatment group.

The only significant difference found in the subgroup analysis was that participants in TAU with severe dependence reduced their drinking to a higher degree between baseline and 3 months than participants in TAU with moderate dependence at baseline (Table 5).

Table 5. Subgroup analysis of estimated differences in changes in standard drinks last 30 days between baseline and 3 months.

Subgroup contrast	
TAU moderate vs. severe dependence	28.9 (SE = 9.89, p = .003)
TAU+ICBT moderate vs. severe dependence	-3.03 (SE = 10.7, p = .777)
Moderate dependence TAU vs ICBT+TAU	-18.5 (SE = 11.9, p = .119)
Severe dependence TAU vs ICBT+TAU	13.5 (SE = 8.45, p = .111)

Post-hoc analysis of three-way interaction based on linear mixed effects model with severity of dependence as predictor.

In the remaining prediction models, no significant interaction effects were found.

4.3 Study III

Three main categories with different sub-categories emerged from the data and are presented in Table 6.

Table 6. Categories and sub-categories

Categories		
Current Routines for Alcohol Treatment in Primary Care	Experiences working with Alcohol Dependence	Experiences working with Internet Treatment
Sub-categories		
Asking Questions about Alcohol	Challenges talking about Alcohol	Factors enabling the use of Internet Treatment
Patients' Motivation to change their Drinking Habits	Challenges working with Alcohol Patients	Factors hampering the use of Internet Treatment
	Factors affecting Patients' Alcohol Consumption	

4.3.1 Current routines for alcohol treatment in primary care

The GPs considered addressing alcohol is important as alcohol can affect patients' health. General screening was not used, and they sometimes forgot, did not have time to or thought that they did not have reason to ask about alcohol e.g., if there were no visible signs of high alcohol consumption. Raising patients' interest in how alcohol affects patients' clinical condition was viewed as a technique to motivate patients to change their consumption, as previously described (Lid et al., 2012; Lid et al., 2015). Some GPs took a more informative approach and advised patients to cut down due to their current health problems. Follow-ups on biomarkers of heavy drinking could be a way to motivate patients to change.

4.3.2 Experiences working with alcohol dependence

Alcohol was sometimes challenging to discuss, and the GPs viewed alcohol as a sensitive subject to talk about both for patients and occasionally for GPs themselves, which has been found in previous studies (Wallhed Finn et al., 2014; Wallhed Finn et al., 2023). Hence, GPs thought that patients sometimes denied their drinking due to shame, especially women, and they were cautious not to increase those feelings. Nevertheless, the GPs found most patients being open and positive when asked about their drinking, which has been previously described in a qualitative study on patients' experiences (O'Donnell et al., 2020). If alcohol was the main reason for a visit in primary care, which seldom occurred, it was easier to talk about alcohol. Other challenges in their work with alcohol patients mentioned by the GPs were the lack of routines for working with alcohol problems, insufficient training in how to initiate conversations about alcohol, how to use pharmacotherapy, and to use alcohol diagnoses in the patient files. Another challenge was time-constraints, and difficulties associated with finding time for follow-up visits. Further, the GPs considered it important to have effective treatment options to offer patients.

4.3.3 Experiences working with internet treatment

If iCBT was a treatment option, the likelihood to ask questions about alcohol could potentially increase according to the GPs. The GPs thought iCBT could reduce stigma for patients, they found iCBT practical and convenient for active people who would otherwise not have the time to visit the GP, and a way to strengthen patients' self-efficacy. The provision of resources, i.e., time and enough

employees, would be needed to make iCBT useful as a routine. The possibility to initiate iCBT from the patient file system and to be provided with automated feedback could be a way to increase the feasibility of iCBT. GPs believed that iCBT would be less useful for elderly or individuals with limited computer experience and for those who would prefer personal contact prior to iCBT. They found iCBT having a potential to be timesaving as the GPs do not have to learn a new treatment method.

4.4 Study IV

At baseline, during one month with start at the timepoint three months prior to the new policy which stipulates that alcohol interventions are mandatory was launched, there were low levels of alcohol related clinical activity at the primary care clinics included in the study (Table 7). Table 7 presents the raw data on which the analyses are based on, and actual frequency at each time period of each reported indicator. For example, at baseline there were in total 117 prescriptions of drugs for harmful use and dependence during a month in the participating primary care clinics, which represents 57 percent of all primary care clinics in Region Stockholm.

Table 7. Total frequency of the seven indicators for 128 participating PC-clinics over the six time periods of measurement.

Time period	Frequency of structured documentation	Use of the AUDIT instrument	Ordering of blood tests for biomarkers of heavy drinking	Prescription of drugs for harmful use and dependence	Registered alcohol related diagnoses	Completed brief and extended advice	Referrals to specialized addition care
Baseline	9350	538	508	117	526	647	100
3 months post policy	8599	523	525	107	604	562	92
9 months post policy	10285	654	781	147	674	622	111
6 months post training	11376	611	785	112	710	571	96
12 months post training	11897	904	959	116	840	722	146
18 months post training	12265	693	984	144	780	567	137

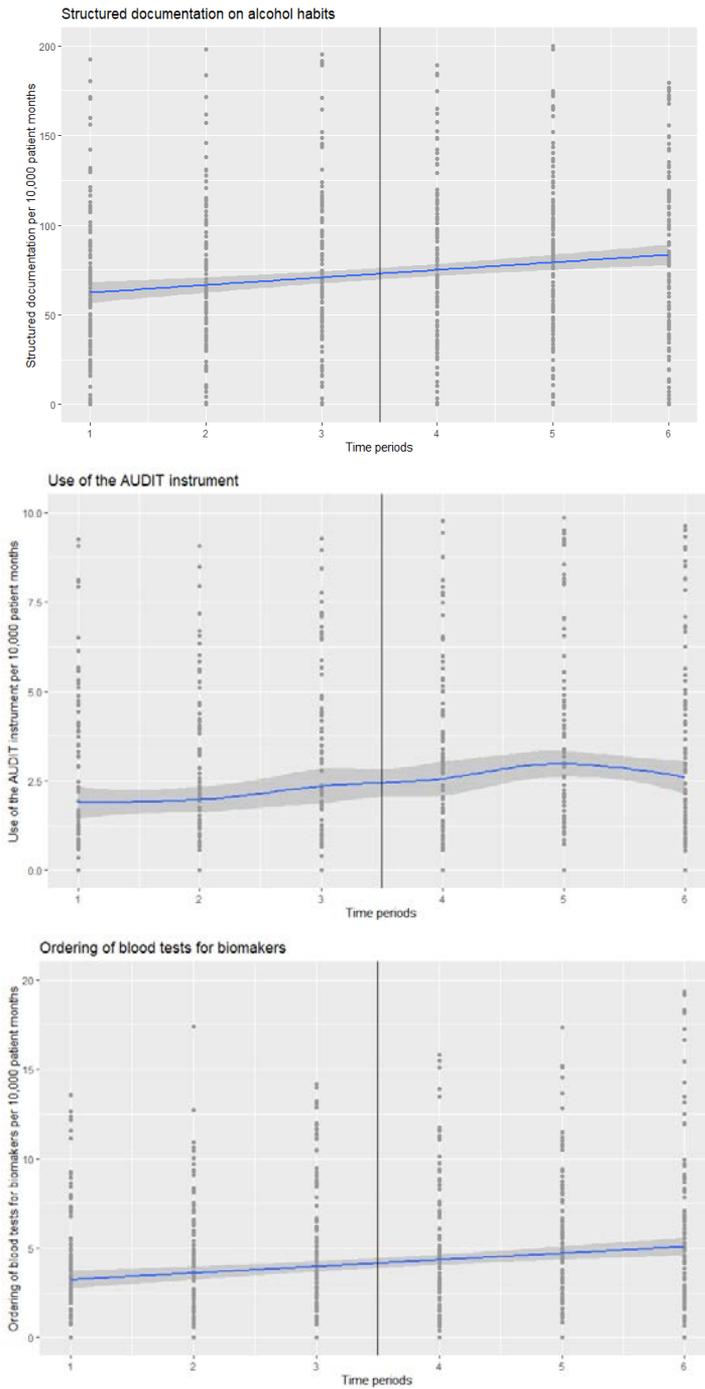
There was a modest, but statistically significant increase from baseline for the following three indicators 9 months after the initiation of the new policy: frequency of structured documentation on alcohol habits, ordering of blood tests, and registered alcohol related diagnoses (Table 8).

Table 8. Results for the analyses of changes at second (3 months after the launch of the policy) and third time periods (9 months after the launch of the policy) of follow-up compared to time period one (baseline).

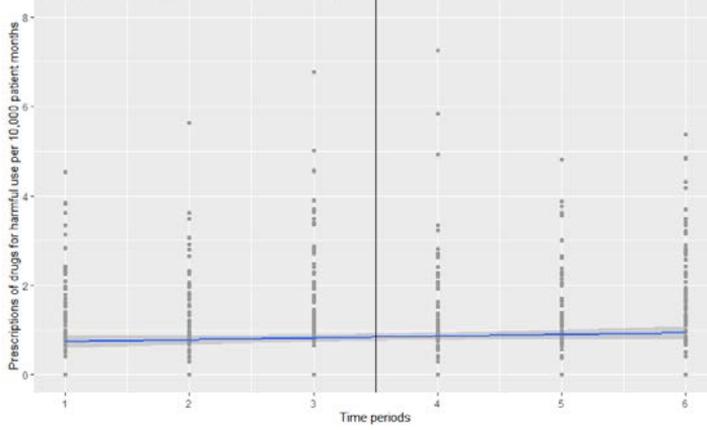
Indicators	Intercept	Second time period				Third time period			
	Estimate	Estimate	Std. error	Wald	P-value	Estimate	Std. error	Wald	P-value
Frequency of structured documentations	64.21	-3.60	3.48	1.07	0.300	9.43	4.03	5.47	0.019
Use of AUDIT	3.94	0.05	0.40	0.02	0.895	0.84	0.47	3.234	0.072
Ordering of blood tests	3.51	0.11	0.28	0.15	0.694	1.37	0.41	10.95	0.001
Prescription of drugs for harmful use and dependence	0.85	-0.01	0.16	0.01	0.937	0.25	0.13	3.79	0.052
Registered alcohol related diagnoses	3.64	0.45	0.28	2.55	0.110	1.03	0.29	12.50	< .001
Completed brief and extended advice	4.97	-0.81	1.00	0.66	0.420	-0.26	0.91	0.08	0.780
Referrals to specialized addiction care	0.60	0.12	0.13	0.89	0.350	0.29	0.15	3.85	0.050

No additional improvement was observed at 6, 12 and 18 months after the training in the 15-method was made available, but the increase that occurred before the training was made available was maintained during the follow-up (Figure 4). There was no significant increase over the two-year follow-up period at any measurement point for four indicators: use of AUDIT, prescription of drugs for harmful use and dependence, completed brief and extended advice and referrals to specialized addiction care.

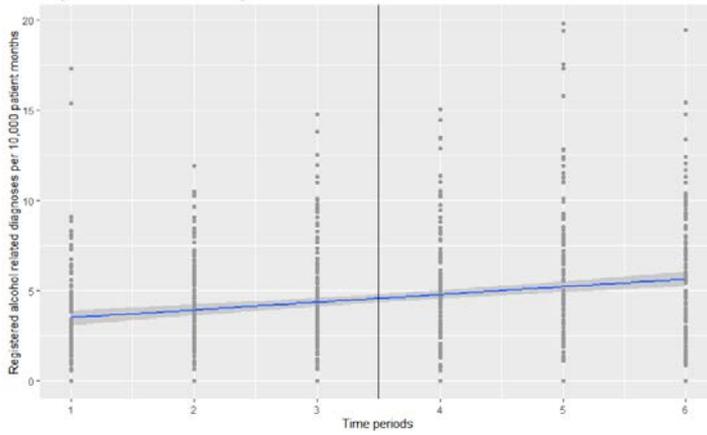
Figure 4. Regression Discontinuity models for all seven indicators from baseline and the five follow-up periods.



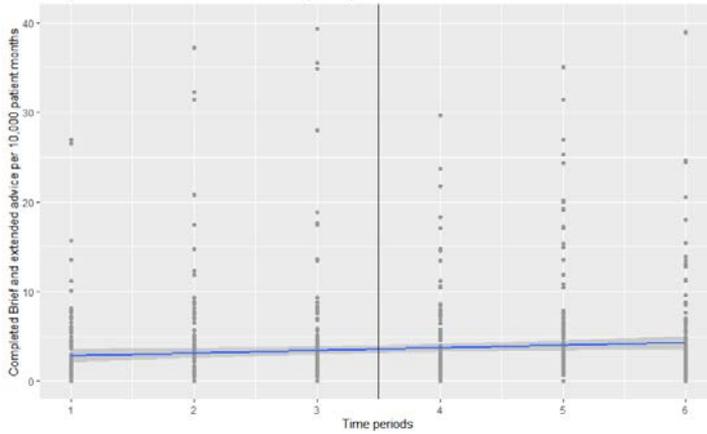
Prescriptions of drugs for harmful use and dependence



Registered alcohol related diagnoses



Completed brief and extended advice regarding hazardous use of alcohol



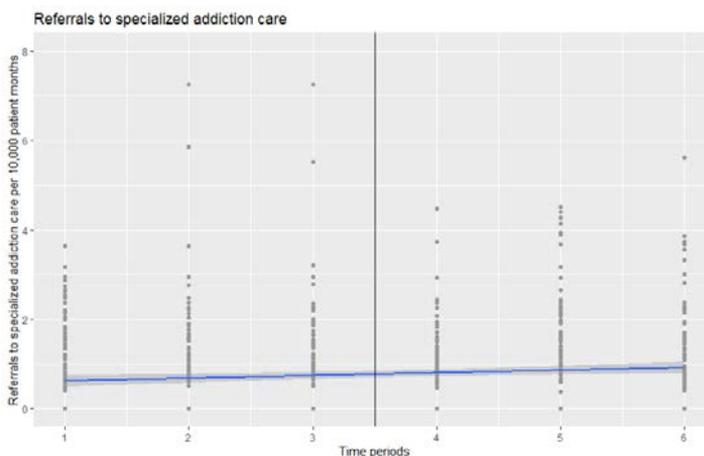


Figure 4. Regression Discontinuity models for all indicators during the follow-up periods

No precise figures on attendance to the training in the 15-Method were available, as the training program was freely available on the internet. Voluntary course evaluations were filled out by 177 professionals from primary care in Region Stockholm during the time-period since the training was made available, out of which 21 were GPs. The attendance to the training is likely to be low given this information.

4.5 Ethical considerations

All research is subject for ethical considerations based on different ethical principles. First there is an ethical dilemma involving the potential risks and the rights of the participants, and on the other hand the hypothetical knowledge that might be acquired from the research study findings. A second consideration is about violation of personal integrity for the involved participants. This implies that information about participants is protected by confidentiality, justice, potential conflicts of interests i.e., if the funder who finances the research has its own interest in the result. Thirdly, it is important that the research maintains scientific quality. Scientific quality implies competent researchers, to be well versed in the current state of knowledge, the feasibility of the research, and having an intention to publish the research in a non-judgmental manner in scientific journals. Compliance with good clinical practice (GCP) and the principles outlined in the Declaration of Helsinki is the best way to minimize discomfort for the participants involved in research (World Medical Association Declaration of Helsinki, 2013). Out of respect for individual autonomy and integrity, eligible participants in research are asked to provide informed consent

before participation. The consent is voluntary and preceded by comprehensive information about the study and their right to withdraw at any point and contact information to the principal investigator. This contributes to voluntariness and transparency. Research on people, human tissue or sensitive personal data undergo ethical review by the Swedish Ethical Review Authority to protect participants involved in research.

All studies in this thesis have undergone ethical review and received approval. In Study IV we got an advisory opinion from the Ethical Review Authority, who had no objections to the research project as no procedures or any other form of intervention will be performed on a research subject, and no processing of personal data will take place. In all studies (except Study IV) informed consent according to the principles mentioned above, has been used. In Study I, II and IV, only aggregated data has been published which cannot be linked to any individual. All data were stored according to guidelines to ensure the confidentiality of the participants. In Study III, participants details were modified, to prevent any reader from identifying specific individuals.

In studies involving sensitive and potentially stigmatizing subjects like alcohol problems, participants might find parts of a study uncomfortable or violating. The research team was well established in both clinical practice and research within the relevant field. Study I (and II) entailed offering treatment for alcohol dependence at primary care centers in Stockholm. General practitioners and other professions at the participating primary care centers were informed about the study's approach, but not as familiar with the study population as the research team. To reduce the risk for individuals of feeling singled out, all visitors to the primary care clinic during a specific time frame were provided with a flyer informing them about the study. All participants in the study were offered treatment as usual and were not withheld of treatment. However, the participants in the intervention group got an add on treatment, iCBT, in addition to treatment as usual. For those who did not get randomized to iCBT, this might have been a disappointment. Patients with severe mental illness, a need for specialized care within addiction or psychiatry or with cognitive impairment were excluded from participation because an informed decision to participate had to be possible. Previous research in the field suggests minimal risk of harm in the study, and guidelines are in place for when participants should be referred to specialized care.

In conclusion, possible risks with participation in the studies in this thesis were reduced by adhering to GCP and the Declaration of Helsinki, using the informed consent procedure, and prioritizing the welfare of the participants. Furthermore, it is probable that the advantages of study participation, such as decreased alcohol consumption or referral for additional treatment, outweighed the associated risks for the individuals involved in the studies.

5 Discussion

The overall aim with this thesis was to study new approaches for identification and treatment of alcohol dependence in primary care.

5.1 Internet-based treatment of alcohol dependence in primary care (Study I)

Study I in the thesis was, to our knowledge, the first study up to this point on internet-based treatment for alcohol dependence in primary care. Our hypothesis was that iCBT+TAU would reduce weekly alcohol consumption at 12-months follow-up more than TAU only, but no significant advantage was found in favor of iCBT+TAU when compared to TAU in the ITT-analysis. One possible explanation for this negative finding could be that TAU provided in the study probably was more extensive than usually provided in primary care. For instance, pharmacotherapy was prescribed to 70 percent of participants in the TAU-group and 52 percent of iCBT+TAU participants, which is significantly higher compared to prescription rates in previous studies conducted in primary care (Wallhed Finn et al., 2020; Hallgren et al., 2020). The short training in giving feedback on biomarkers and assessments and pharmacotherapy the participating GPs were offered before study recruitment in combination with the fact that GPs were aware they participated in a study might have contributed to the high prescription rate. When analyzing only participants who started iCBT and completed at least one module in the iCBT program (the per protocol study), they continued to reduce their alcohol consumption significantly more than the TAU group. As 30 of the 132 participants (23%) in the iCBT+TAU group never initiated iCBT, drawing conclusions about the completers become challenging. All participants had reduced their weekly consumption and their heavy drinking days at 3-months, and the reduction persisted at the 12-months follow-up. The effect sizes are consistent with previous internet-studies involving individuals with high alcohol consumption in primary care and communities, and they are also consistent with findings from other studies on psychosocial interventions (Riper et al., 2018; O'Donnell et al., 2014; Martin et al., 2012).

Limited time and perceived limited competence in handling patients with alcohol dependence in primary care (Nygard et al. 2011; Anderson et al., 2014;

Keuhorst et al., 2014) contributes to the large treatment gap for alcohol dependence (Kohn et al., 2004; Rehm et.al, 2015; Carvalho et al., 2019). An advantage of providing iCBT is the ease of administration and the potential not to add too much to the workload for the GPs, making iCBT a potentially valuable complement to usual care. iCBT might have a dual effect as the availability of a treatment to offer patients makes it more likely to raise discussions about alcohol. This can broaden the accessibility of evidence-based treatment for alcohol dependent patients in primary care.

5.2 Predictors of outcome in treatment via the internet for alcohol dependence in primary care (Study II)

In study II we explored socio-economic- and clinical potential predictors of outcome in iCBT as an add-on-treatment to TAU compared to TAU only for alcohol dependence in primary care. Hence, this is a secondary analysis of data collected from the 264 participants in a randomized controlled trial described in Study I.

The only predictor that moderated change in weekly alcohol consumption over time was severity of dependence at baseline. The severely dependent patients in both groups had a higher baseline alcohol consumption than the moderate dependent patients and reduced their alcohol consumption significantly more at the 3-month follow-up compared to the moderately severe dependent drinkers in TAU. There are several hypothetical explanations for this finding. As consumption was higher at baseline among more severely dependent patients, a greater reduction may be explained by regression to the mean, as previously discussed in the field of alcohol research (McCambridge et al., 2014). Another possible explanation is that severely dependent patients suffer more from their drinking and are more motivated to reduce their drinking.

The moderately severe dependent patients from both groups also reduced their drinking significantly from baseline to 3 months. The iCBT+TAU group had a slightly larger reduction than the TAU group, but the difference was not significant. This implies that, once identified, primary care is a possible option for the treatment of moderate alcohol dependent patients.

A significant three-way-interaction of dependence severity and iCBT+TAU on the change in alcohol consumption between baseline and 3 months was found.

This result implicates that the interaction effect of dependence severity on change in alcohol consumption between baseline and 3 months was different depending on group allocation or that the effect of treatment group on change in alcohol consumption between baseline and 3 months is different depending severity of dependence.

Between 3- and 12 months the patients with moderate dependence in both groups reduced their drinking significantly. The severely dependent patients in TAU increased their alcohol consumption compared to those with moderate dependence. Nevertheless, weekly alcohol consumption was still lower at 12 months than at baseline for the severely dependent patients.

This was an exploratory analysis but adds information to previous internet studies (Riper et al., 2018). A conclusion to draw is that regardless of dependence severity, a reduction of consumption that lasted for 12 months is achievable which, to our knowledge, has not been evaluated before for alcohol dependent patients treated with iCBT in primary care. Nevertheless, severely dependent patients from the TAU group consumed approximately 30 more standard units (=12 g of alcohol) per month compared to the moderately dependent patients in the iCBT+TAU group at 12 months. This implies that treatment for alcohol dependence can be initiated in primary care, but that the more severely dependent patients should be provided with more treatment. Therefore, assessing dependence severity can guide the GPs when they do their treatment plans for alcohol dependent patients. This finding is consistent with findings in a previous study in primary care where patients with severe alcohol dependence had better treatment outcomes in specialist care than in primary care (Wallhed Finn, et al., 2018). Considering that most individuals with alcohol dependence have a moderately dependent (Andreasson et al., 2013) and expresses preferences for treatment in primary care (Probst, 2015; Wallhed-Finn, 2014; Barry, 2016) the findings from this exploratory study contribute to the body of evidence supporting treatment of alcohol dependence in primary care. The results from this study imply that once identified, most individuals with alcohol dependence can effectively reduce their drinking through a brief treatment in primary care. Furthermore, adding iCBT may enhance outcomes for moderate dependent patients.

5.3 Treatment of alcohol dependence in primary care; perceptions among general practitioners (Study III)

In Study III, ten general practitioners from the primary care centers involved in Study I were interviewed with the objective of capturing their perspectives on iCBT, a novel treatment for alcohol dependence in primary care. The interviews were also conducted to elicit their views on working with alcohol dependent patients and current treatment routines from this perspective.

The GPs viewed alcohol important to discuss due to its health effects and negative influence on different health conditions common in primary care. Nevertheless, it depends on the GPs own literacy of how alcohol can affect health whether questions are asked or not. Questions aimed at quantifying the consumption was common. To motivate patients to change their consumption the GPs tried to raise the patients' interest on how alcohol can affect their own health conditions (Lid et al., 2012; Lid et al., 2015). General screening was not applied, and the GPs estimated the frequency of visits where questions about alcohol were discussed to 5–50 percent. The GPs were aware that alcohol can be a stigmatizing subject to discuss, especially for women, but perceived some patients expecting the GP to discuss alcohol. Identifying alcohol problems in patients with higher socio-economic background was challenging, in part because there were no external signs of high consumption and therefore questions were not asked. The GPs perceived they lacked routines for treating alcohol dependence, were unaware how their colleagues work with alcohol problems and lacked training in how to raise questions about alcohol in a constructive way, how to use alcohol-diagnoses and how to prescribe alcohol medications. They also mentioned limited time as challenging.

Positive features with iCBT as an available treatment to offer mentioned were its potential to reduce stigma and its potential to start more discussions about alcohol. Furthermore, iCBT did not necessitate GPs to learn a new treatment method themselves. iCBT is a practical and timesaving treatment option for patients who might otherwise abstain from treatment due to practical constraints or limited time. To make iCBT work as routine, professions who are provided with time to engage in this as well as the possibility to link iCBT to the datafile system was required according to the GPs. For patients that prefer personal contact, with cognitive impairment and without computer experience iCBT was not an option according to the GPs.

Considering that patients, particularly those with co-occurring health conditions, tend to favor treatment of alcohol problems in primary care over specialized care (O'Donnell et al., 2020) and given that referral to specialized care often do not achieve its intended goal (Glass et al., 2017) it becomes crucial for GPs to have access to treatments they deem suitable and practical to use. The presence of iCBT has the potential to make it easier to engage in discussions about alcohol according to the GPs in this study. Additionally, another qualitative study discovered that GPs regarded a stepped care program for alcohol dependence in primary care (Wallhed Finn et al., 2018) as a promising and user-friendly approach (Wallhed Finn et al., 2021b).

5.4 Addressing alcohol problems in primary care (Study IV)

Study IV investigated the impact of a new policy in Region Stockholm for treating alcohol problems in primary care on alcohol related activities carried out by healthcare professionals. The new policy now mandated the provision of prevention and treatment of alcohol-related problems in primary care. Ten months after the new policy a digital training in targeted screening and treatment of harmful consumption and dependence of alcohol was made available (The 15-Method, 2021).

Starting from low levels of alcohol related activities the new policy resulted in small but statistically significant increases in three out of seven alcohol related clinical activities. This increase remained during the 2.5 years follow-up.

There was no add-on effect after the digital training in the 15-Method was made available to all professions in primary care in Region Stockholm. One obvious reason that can be suggested for the lack of an additive effect of the training, was that, most certainly, only a fraction of clinicians had taken part in the offered training. A hypothetical explanation for not taking part in the training might have been a lack of incentives from management to participate.

Research in the field of implementation science indicates that achieving successful implementation often necessitates the utilization of multiple strategies, primarily due to the need to overcome multiple barriers (Oxman et al., 1995; Powell et al., 2019; Gustavsson et al., 2023). Effective implementation is facilitated by strong professional support for a clinical method, robust infrastructural support, evidence-based interventions, and screening tools that

are not too time-consuming (Kaner et al., 2010b). Requirements from the management have not been evaluated in previous alcohol implementation projects, however senior management support and training have been assessed as indispensable (Kaner et al., 2010a; Wolf, 2008). To our knowledge, there has not been any systematic follow-up conducted by the stakeholder Region Stockholm on whether alcohol related clinical activities were carried out. Further, the extent to which local management support or reinforce new methods is also unknown. The same applies to whether clinicians had the possibility to or were encouraged to set aside time to take part in the digital training.

Implementation of effective interventions within the field of preventing and treating alcohol-related problems is a major challenge, and there are, to our knowledge, no previous studies that have investigated the effects of policies intended to increase alcohol related clinical activities in primary care. The same applies for evaluating the potential change in practice following a new policy in combination with the availability of a digital training for professionals in primary care. A strength in this study is the utilization of registry data. Registry data allows an investigation into what healthcare professionals do rather than relying on self-reported data, providing a more objective perspective (Nilsen et al., 2022).

5.5 Limitations

The studies presented in this thesis have some important general and specific limitations. A general limitation that applies to the issue of external validity is that clinical studies often necessitate homogenous study populations. Consequently, the inclusion criteria for participants in Study I and II were stringent. The participants in Study I and II had an overall moderate dependence severity, were highly educated, co-living, and employed. Hence, a significant limitation is that the findings observed may not necessarily be applicable to more severely dependent patients. Furthermore, if the participants are self-selected, as was the case in Study I and II, the findings cannot be generalized to the entire untreated population of individuals with alcohol dependence. Another general limitation in alcohol research is that a considerable part of data is self-reported which also is the case in study I and II. A systematic review indicates that discrepancies between self-reported data and biomarkers exist, but the degree of these disparities varied extensively (Grüner Nielsen et al., 2021). Yet another

general limitation in alcohol research is that assessment reactivity can impact outcomes, that is assessments of alcohol use inherently incorporate a therapeutic component (Bertholet et al., 2005; Jonas et al., 2012).

Our intention in Study I and II was to gain data from biomarkers, but motivating participants to provide blood tests at follow-ups was challenging. One possible explanation for the few blood tests provided was that the Covid-19 pandemic made patients less willing to visit a laboratory for providing a blood test. Pharmacotherapy was more frequently prescribed in the TAU group. Another limitation regarding Study I and II is that the availability to iCBT may have had a negative impact on the readiness for GPs to prescribe, or for patients to accept, pharmacotherapy in the iCBT+TAU group. Patients in Study I and II may have perceived iCBT+TAU as a more appealing treatment option than TAU only, which might have introduced a bias. A possible important limitation for Study I and II is the limited sample size. As no previous studies on internet-based treatment for alcohol dependent patients in primary care did exist when planning the study, it was difficult to establish an adequate power calculation. Hence, the lack of statistically significant differences between the treatment groups could be a type II error.

In Study III the small number of GPs was a limitation. Also, the risk for participant bias due to the involved GPs might have had a more optimistic attitude to iCBT than GPs in general, since they were engaged as care givers in Study I. However, the GPs' experiences about iCBT are essential to get a general understanding using a qualitative study design. To overcome bias, we used equal gender distribution, we used quotations in the result section for the readers to gain a judgement of the credibility and authenticity of the findings. The credibility and thrust wordiness of the study was reinforced by having the first author collect the data and the last author collaborating closely with the first author to analyze data.

Regarding study IV, the training was available 24/7 via the internet without requirements to log on. The lack of reliable information on how many of the professionals completed the training offered is a limitation. Additionally, considering the correlational nature of this study we cannot draw any conclusions on causality, i.e., determine whether the observed changes in the indicators were a result from policy change, the digital training, or some other factors.

6 Conclusions

6.1 Study I

We found no significant between-groups changes favoring iCBT added to TAU versus TAU only for alcohol dependent patients in primary care in the ITT-analysis. The high utilization of pharmacotherapy within the TAU group might have confounded the results as well as insufficient statistical power. In the PP-analysis, which only included participants that initiated the iCBT program, the iCBT+TAU group showed significantly lower mean weekly alcohol consumption compared to the TAU group at 12 months follow-up. Weekly alcohol consumption and heavy drinking days were reduced for all participants during follow-ups compared to baseline with effect sizes align with previous internet-based and psychosocial treatment studies. The result from this study is promising, as many individuals with alcohol dependence are open to the idea of seeking treatment in primary care.

6.2 Study II

Severity of dependence was the only variable that moderated treatment outcome. The severely dependent patients reduced their alcohol consumption significantly more than the moderately dependent patients in TAU between baseline and 3 months. The moderately dependent patients from both groups continued to reduce their alcohol consumption between 3 and 12 months, while the severely dependent patients increased their consumption from 3 to 12 months. This implies a need for extended monitoring post-treatment to identify and prevent potential relapses and determine possible needs for more or specialized care. The number of fulfilled ICD-10 criteria for alcohol dependence can be a useful tool for primary care practitioners when planning treatment for alcohol dependent patients.

6.3 Study III

Integration of alcohol treatment into routine practices is not established in primary care. Alcohol was viewed as having a substantial impact on patients' health and was found important to discuss with patients. Limited treatment options and a perceived limited expertise in treating alcohol dependence among GPs were expressed as hampering factors in their work with alcohol patients. GPs considered iCBT as an appealing treatment option for certain patients. The implementation of the iCBT program did not require GPs to acquire behavioral

treatment skills, potentially enhancing its implementation. Having access to iCBT as a treatment option for alcohol dependent patients might facilitate discussions about patients' alcohol habits.

6.4 Study IV

Starting from initially low levels of activity a modest increase in alcohol-related clinical activities was found in Region Stockholm following the implementation of a new healthcare policy. The new policy clarified the inclusion of prevention and treatment of alcohol problems in the agreements with primary care. A digital training in targeted screening and treatment of AUD was made available approximately ten months after the new policy had been implemented but did not result in a significant increase in alcohol-related activity. While implementing a policy that mandates alcohol interventions, combined with a training program, is well-supported by implementation science, additional implementation strategies may be required to influence how clinicians in primary care can handle AUD. There is a strong indication that very few professionals participated in the training. The low participation rates might be indicative of the substantial workload that defines primary care.

7 Points of perspective

7.1 SBI, SBIRT and targeted screening

Primary care has long been regarded as the ideal setting for treating alcohol problems due to its extensive reach across the entire population. The World Health Organization (WHO) has strived for this approach since the late 1970s which resulted in the development of the widely used screening tool AUDIT and the development of Screening and Brief Intervention (SBI) as a primary care intervention for hazardous and harmful drinkers (Babor et al., 2001). A significant amount of research has demonstrated the effectiveness of SBI in reducing alcohol consumption among individuals with hazardous and harmful use, but the implementation in primary care has not been successful (Segura et al., 2018; van Beuden et al., 2012). This is partly because SBI implies general screening which general practitioners do not carry out. Another complicating factor is that SBI was not developed for alcohol dependent patients and as a result, its effectiveness for treating alcohol dependence has not been studied. This is the reason why SBIRT was developed for referral to specialized care (Babor et al., 2007; Saitz, 2010; Babor et al., 2017). However, there is no evidence that SBIRT increases treatment seeking in specialist care (Glass et al., 2015; Glass et al., 2017). Treating alcohol dependence is viewed as complicated and time-consuming by GPs and they perceive they lack sufficient training in treating alcohol dependence (Nygard et al. 2011; Anderson et al., 2014; Keuhorst et al., 2014; Geirsson et al., 2006). New approaches that are effective, feasible, and time effective for treating alcohol dependence in primary care are needed.

Alcohol causes and contributes to many disorders and health problems commonly seen in primary care e.g., hypertension, atrial fibrillation, depression, skin diseases, gastrointestinal disorders (WHO 2018). Targeted screening or pragmatic screening can serve as an alternative to general screening even if is not as sensitive as general screening (Reinholdz et al., 2011; Lid et al., 2012; Lid et al., 2015). Targeted screening may fail to identify excessive drinkers compared to general screening, but as general screening is hardly carried out, targeted screening can still offer significant advantages for public health (Nilsen et al., 2023). Targeted screening can be effective by raising patients' curiosity about how alcohol can impact their present clinical condition and warrants further research.

7.2 Possibilities for treatment seeking in primary care

Most patients have a moderate severity of dependence and express a preference for treatment in primary care compared to specialized care, particularly patients with somatic comorbidities (Andreasson et al., 2013; O'Donnell et al., 2020; Wallhed Finn et al., 2023). In Project MATCH, described above, both CBT, MET and TSF, were equally effective (Project MATCH, 1997) and since 1990, studies have found treatment of alcohol dependence equally effective in primary care as in specialized care (Drummond et al., 1990; Wallhed Finn et al., 2020). Even though effective treatments are offered, treatment seeking remains rare (Rehm et al., 2015a). A known barrier for treatment seeking is the stigma attached to alcohol problems (Schomerus et al., 2010; Wallhed Finn et al., 2023). So, the question is how the stigma associated to alcohol can be reduced and how the barriers for seeking treatment can be lowered.

We know that internet-based treatments can reduce stigma (Cunningham et al., 2011). To stop using stigmatizing language is another way to potentially reduce stigma. Presenting AUD as a continuum rather than a binary disorder may be relevant for future research. Studies have found a continuum perspective to be a promising approach to reduce stigma associated with psychiatric disorders and increased problem recognition among harmful drinkers (Peter et al., 2021; Morris et al., 2020). By normalizing and de-dramatizing the issue of alcohol and adopting a patient centered approach where the patient's goal for a consumption reduction becomes indicative might be a promising approach. This approach might be achievable within primary care if practitioners raise questions about alcohol. Providing professionals with allocated time and support for training and practical tools for managing alcohol dependence might be the next step. However, implementation research shows that requiring new routines in health care demands, in addition to providing training, support from stakeholders and local management to become clinical reality (Kaner 2010a; Kaner 2010b; Nilsen et al., 2011; Fitzgerald, 2017). Future studies to consider could involve obtaining more support from management to ensure that professionals can participate in the offered training programs.

7.3 Internet-based treatment in primary care

Additional clinical trials with larger sample sizes would be a valuable step toward increasing the evidence base for iCBT. Considering the relatively limited resources needed for the iCBT intervention evaluated in Study I, iCBT might be a

practical and cost-effective treatment option. The ambition of comparing iCBT versus TAU was relevant, but this was a challenging study as no routines for treating AUD in primary care are in place. Hence, the content of TAU differs between GPs and between primary care centers. Another approach could be to manualize TAU and compare with iCBT. In planning Study I, we hypothesized that TAU would have been less effective than it turned out to be. However, it is encouraging that GPs participating in a study, in combination with a brief training, treated alcohol dependence with effect sizes comparable to other established methods (Riper et al., 2018; O'Donnell et al., 2014; Martin et al., 2012). Severity of dependence was found to moderate treatment outcome in Study II, a finding that needs to be studied further. Also, further studies are needed to acquire more knowledge on which alcohol dependent patients are appropriate to treat with iCBT in primary care.

In a qualitative study based on interviews with GPs (Study III) the GPs suggested that patients' motivation to involve in iCBT could potentially be enhanced if incorporating a chat forum to the iCBT program. Here patients can provide mutual support and interact with one another. The GPs in Study III also found it essential to have access to start iCBT via the patients' electronic case files and to get messages from the patient files when a patient proceeded in the treatment. This is also something worth investigating further. Another approach could involve examining possible enhanced effects of therapist guided iCBT for alcohol dependence in primary care, as some previous studies have found positive results for depression and problem drinkers (Karyotaki et al., 2021; Riper et al., 2018). Yet another approach could be to interview patients about their view on iCBT.

7.4 Training and policy

Patients believe that GPs and nurses possess necessary skills and expertise to ask about patients' drinking from a health promotion perspective, and patients' see it as their responsibility to provide enough information to support that role (O'Donnell et al., 2020). Further, patients interviewed in this study (O'Donnell et al., 2020) found advice and information about alcohol and healthier lifestyle choices as a standard primary care component regardless of whether the advice is followed now or plant a seed for future positive changes. The prerequisite for being able to offer treatment is to ask about patients' alcohol habits in a way that makes them want to tell how they drink. In Study IV training in the 15-method was offered all professions in primary care (The 15-Method, 2021). The

15-method includes targeted screening and has a stepped-care approach, including brief intervention, assessment, and psychological and pharmacological treatment. It has a scientific foundation in MET and CBT. Targeted screening is based on addressing alcohol when it is clinically relevant rather than conducting general screening which is a premise for SBI (Reinholdz et al., 2011; Lid et al., 2012; Lid et al., 2015). In Study IV we found no additional effect from training after initial small increases in alcohol related clinical activities from the new policy making it mandatory to treat alcohol dependence in primary care. Given that only a limited number of clinicians participated in the training, the next step in investigating its effects could involve conducting a study where training in the 15-method is actively promoted, made time for, and made mandatory by local management. Another approach is to conduct further follow-ups as in Study IV over longer periods of time. Tailored implementation of iCBT for common mental health disorders was evaluated in a multicenter study where a theory-based framework, ItFits-toolkit, was used (Vis et al., 2023). There was a small positive effect that the self-guided toolkit supported local implementers in developing tailored implementation strategies and identifying local barriers to enhance implementation. This is an approach that can be further investigated within primary care.

Giving professionals in primary care adequate time and resources to fulfill their comprehensive mission is a prerequisite for reducing the treatment gap for AUD and the development of primary care as the base of treatment for AUD.

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