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Published in:
Drug and Alcohol Dependence

DOI:
10.1016/j.drugalcdep.2021.108806

Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

Drug and Alcohol Dependence 225 (2021) 108806

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

"Take Care of You" – Efficacy of integrated, minimal-guidance, internet-based self-help for reducing co-occurring alcohol misuse and depression symptoms in adults: Results of a three-arm randomized controlled trial

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ARTICLE INFO

Keywords:
Alcohol
Depression
Co-occurring disorders
Internet
Cognitive Behavioral Therapy
Motivational interviewing

ABSTRACT

Background: Depression and harmful alcohol use are two of the top five leading causes of years of life lost to disability in high-income countries. Integrated treatment targeting both at the same time is often considered more complicated and difficult and, therefore, more expensive. Consequently, integrated internet-based interventions could be a valuable addition to traditional care.

Methods: A three-arm randomized controlled trial was conducted comparing the effectiveness of (1) an integrated, minimal-guidance, adherence-focused self-help intervention designed to reduce both alcohol use and depression symptoms (AFGE-AD); (2) a similar intervention designed to reduce alcohol use only (AFGE-AO), and (3) internet access as usual (IAU) as a control condition, in at least moderately depressed alcohol misusers from February 2016—March 2020. We recruited 689 alcohol misusers (51.6 % males, mean age = 42.8 years) with at least moderate depression symptoms not otherwise in treatment from the general population. Six months after baseline, 288 subjects (41.8 %) were reachable for the final assessment.

Results: All interventions yielded reduced alcohol-use after six months (AFGE-AD: -16.6; AFGE-AO: -19.8; IAU: -13.2). Those who undertook active-interventions reported significantly fewer standard drinks than controls (AFGE-AD: $p = .048$, d=0.10; AFGE-AO: $p = .004$, d=0.20). The two active-intervention groups also reported significantly less severe depression symptoms than controls (AFGE-AD: $p = .006$, d=0.41; AFGE-AO: $p = .008$, d=0.43). Testing revealed noninferiority between the two interventions.

Conclusions: This study documented sustained effectiveness of the first integrated, fully internet-based self-help intervention developed for the reduction of both alcohol use and depression symptoms in at least moderately depressed adult alcohol misusers recruited from the general population.

1. Introduction

Depression and harmful alcohol use are two of the top five leading causes of years of life lost to disability (DALYs) in high-income countries (WHO, 2008). In 2016, harmful alcohol use alone accounted for an estimated 3.0 million deaths and 131.4 million DALYs, representing 5.3 % of all deaths and 5.0 % of all DALYs (Shield et al., 2020). Taken together, substance use (including alcohol), depression, and other mental disorders account for 7.4 % of the total global burden of disease (Whiteford et al., 2013). There is also substantial co-occurrence of substance use and other mental disorders; these dual-diagnosis disorders, also called co-occurring disorders (COD), are not the exception,

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https://doi.org/10.1016/j.drugalcdep.2021.108806
Received 28 January 2021; Received in revised form 14 April 2021; Accepted 15 April 2021
Available online 18 June 2021

with concomitant alcohol use disorders and depression especially common (Kessler et al., 2003; Schuckit, 2006). CODs are associated with considerable adverse outcomes (Sullivan et al., 2005). Alcohol misuse or abuse is two to three times higher among those who suffer from depression than in the general population (Swendsen et al., 1998). Moreover, risky alcohol use is associated with a higher probability of developing affective disorders (Bott et al., 2005). Treating COD is often considered more complicated and difficult (Roeloffs et al., 2001) and, therefore, more expensive than treating either of these two disorders separately. Since internet-based interventions can be administered with minimal to no cost, they could be an invaluable addition to traditional care.

In recent years, increasing numbers of internet-based interventions have been developed and evaluated. These interventions target various groups with problematic substance use (Amann et al., 2018; Frohlich et al., 2018; Schaub et al., 2012, 2019) and addictive behaviors (Baumgartner et al., 2019; Bothe et al., 2020). These internet-based interventions have the capacity to reach at-risk individuals in the early stages of potentially more severe mental health disorders, which might, in turn, reduce some of the burden placed upon public health services (Smit et al., 2011).

There have been several successful implementations of internet-based interventions for adult problem drinkers. A review of nine studies in 2011 (Riper et al., 2011) found a medium effect size on alcohol consumption (g = 0.44), with greater effects observed with longer treatments (g = 0.61) than with single-session, personalized normative feedback interventions (g = 0.27). Another review of 16 studies in 2014 (Riper et al., 2014b) revealed a small, but significant effect size (g = 0.20). In a more recent individual-patient data meta-analysis (Riper et al., 2018) of 19 randomized controlled trials of internet interventions targeting problem drinking, a significant decrease of 5.02 standard drinks ($g = 0.26$) over the preceding seven days was identified, relative to controls.

Similarly, there has been an increase in the number of internet-based treatments for depression, which have proven effective in controlled trials both for adults (Hedman et al., 2012) and adolescents (Ebert et al., 2015). Wright et al. (2019) report a pooled effect size of g = 0.502 post-treatment in their meta-analysis of 40 randomized controlled trials comparing internet-based and other computerized psychological treatments against control conditions (e.g., waiting list, treatment as usual, different treatment).

There is growing evidence that combined treatment of both alcohol misuse and depression may be effective. In a meta-analysis conducted by Riper and colleagues (Riper et al., 2014a), the combination of Cognitive Behavioral Therapy (CBT) and Motivational Interviewing (MI), predominantly delivered via face-to-face therapy, proved effective at treating subclinical and clinical alcohol use disorders and major depressive disorders (combined treatment) relative to control conditions, with small overall effect sizes post treatment (g = 0.17 for decreased alcohol consumption and g = 0.27 for decreased depression symptoms, respectively). Interestingly, digital interventions (after a brief session with a therapist) performed better than face-to-face treatment, with respect to reducing depression symptoms (g = 0.73 versus g = 0.23, respectively, $p = .030$). Additionally, relative to non-integrated treatment, integrated treatment in patients with dual-diagnosis disorders can reduce treatment duration, increase satisfaction with treatment (Schulte et al., 2011), and decrease costs. Motivational interviewing is designed to increase patients' motivation for change. Lack of motivation is very common in patients with either alcohol misuse or a depressive disorder, and low motivation is associated with poor treatment engagement and poor outcomes (Miller and Rollnick, 2012).

There have been some trials involving computer-based (offline) treatment for integrated treatment for alcohol and depression, most notably the work from Kay-Lambkin and colleagues (Kay-Lambkin et al., 2017, 2009). The aforementioned trial compared therapist-delivered treatment plus computer-based treatment (combined treatment) and therapist-delivered treatment alone with a control condition. The combined treatment had the largest effects. Furthermore, a recent meta-analysis (Schouten et al., 2021) found significant effects of digital interventions (including computer-based, internet-based and text-message based interventions) on depressive symptoms at 3 months (g = 0.34, p = .030) and non-significant effects at 6-months (g = 0.29, p = .15). The results for alcohol use were non-significant at 3-months (g = 0.14, p = .07) and significant at 6-months (g = 0.14, p = .005). Even though these effects were small, they are promising.

Two integrated, fully internet-based self-help intervention have been developed for co-occurring depression and problematic alcohol use. One in youth (Deady et al., 2016) that was shown to be effective for both outcomes in the short term (post-treatment), when compared against an attention–control condition' albeit, not long term (6 months). The other for students (Wiens, 2002) showed no significant main results post-treatment (1 month). However, to our knowledge, no such intervention studies have yet been published that have examined the effects of combined treatment for the general adult population.

This paper reports the efficacy of a minimal-guidance internet-based self-help intervention called *Take Care of You*. The program was developed in 2016, with multiple RCTs involving variants of the program currently underway (Frohlich et al., 2018; Kaal et al., 2020; Schaub et al., 2018). More specifically, the current three arm randomized controlled trial compared the efficacy of 1) a combined internet-based self-help intervention with adherence-focused guidance enhancement (AFGE) designed to reduce both alcohol consumption and depression symptoms (AFGE-AD); 2) an internet-based self-help intervention with adherence-focused guidance that targets problematic alcohol use only (AFGE-AO); and 3) an internet as usual (IAU) control condition, all among adult problem drinkers with co-occurring depression symptoms. *A priori*, we expected that the combined intervention (AFGE-AD) would generate greater improvements in depression symptoms and intervention satisfaction than the alcohol-only intervention (AFGE-AO), but similar reductions in alcohol-related outcomes (Schaub et al., 2016).

It is essential to note that this study had to be completed during the COVID-19 pandemic that started December 2019 in the city of Wuhan in Central China. By 11 March 2020, the World Health Organization (WHO) had declared COVID-19 a pandemic (WHO, 2020). To deal with this global pandemic, most countries enacted various lockdown measures to circumvent the spread of this infectious disease. A review investigating the psychological burden caused by quarantine highlights the psychological strain on those who are not allowed to participate in social life (Brooks et al., 2020). Besides these lockdown measures, the pandemic created various states of uncertainty, which were felt by a tremendous number of people, leading to difficult psychological consequences. In one study, the prevalence of depressive symptoms in the US increased by more than 200 % during the COVID-19 pandemic, from 8.5 % of the population before the pandemic to 27.8 % during it (Ettman et al., 2020). Similarly, a study in Germany revealed increased symptoms related to generalized anxiety (44.9 %), depression (14.3 %), psychological distress (65.2 %) and COVID-19-related fear (59 %) (Bäuerle et al., 2020). It is reasonable to speculate that some people may drink more alcohol to deal with these negative consequences as a coping mechanism. These effects may be reflected in the heighted online sales of alcohol by US consumers in March 2020; this included an 240 % increase in internet alcohol sales, including strong liquors (spirits) increased by 75 %, wines by 66 %, and beers by 42 % (Micallef, 2020). In their study, Chodkiewicz et al. (2020) found that participants currently drinking more than before the pandemic started reported worse mental health than other groups; coped less well with everyday functioning; and suffered more from depression, low self-esteem, and suicidal thoughts. Providing widespread help that can even be used even while those seeking help stay at home could be crucial during such difficult times.

2. Methods

2.1. Study design

The currently-reported study was a three-arm, randomized controlled trial that compared two web-based self-help interventions (AFGE-AD, AFGE-AO) in their ability to reduce problematic alcohol use and depression symptoms, against each other and against a waiting list control group in which participants received a baseline assessment, psycho-educative information, and access to the internet as usual (IAU). Each intervention lasted for six weeks, followed by an immediate short assessment of satisfaction (t_1) for the active interventions, followed by further follow-up three months after the baseline assessment (t_2) and a final survey six months post baseline (18 weeks post treatment, t_3). All participants received email reminders for follow-ups and subsequent telephone calls if they did not complete the survey. Controls using IAU were provided access to the intervention provided in study arm 1 after their 6-month follow-up assessment.

Participants were randomized, by computer, to one of the three conditions, in a 1:1:1 ratio. Participants in the active interventions did not know to which active intervention they had been assigned; however, subjects in the IAU group knew they had been placed on a waiting list. The study was conducted in accordance with the 2013 Declaration of Helsinki. The study was approved by the Ethics Committee of the Canton of Zurich on April 7th, 2015 (KEK-ZH-Nr: 2015-0082) and registered at Current Controlled Trials, traceable as ISRCTN10323951. A detailed study protocol was published on May 25th, 2016 (Schaub et al., 2016).

2.2. Recruitment, inclusion, and exclusion criteria

We primarily recruited participants in Switzerland, Germany, and Austria from February 2016 through March 2020 through two websites (www.takecareofyou.ch, www.alkcoach.at), advertisements in relevant internet forums and newspapers (or online versions thereof), and search engine website advertisements. Inclusion criteria were (1) age $\geq$18 years; (2) a score $\geq$8 on the Alcohol Use Disorder Identification Test [AUDIT (Saunders et al., 1993)], indicating no less than at-risk alcohol use at the present time; (3) a score $\geq$ 10 on the Center for Epidemiologic Studies Depression Scale [CES-D (Cole et al., 2004)], indicating at least moderate symptoms of depression, (4) regular access to the internet, and (5) good command of the German language. Exclusion criteria were (1) participation in any other psycho-social or pharmacological treatment for the reduction/cessation of alcohol use or the reduction of depression symptoms; (2) the use of opioids, cocaine or amphetamine type stimulants over the preceding 30 days and/or cannabis use more than three times weekly over the preceding 30 days; (3) prior treatment for cardiovascular problems; (4) past suicidal ideations or plans; and (5) for female participants: pregnancy or breastfeeding. We had two major deviations from the study protocol (Schaub et al., 2016). First, due to regulatory issues, which would have required users to send in hand-signed informed consent forms which defeats the purpose of having an anonymous program in the first place, the Netherlands dropped out of the study. Second, a mitigation strategy was utilized, lowering the CES-D cut-off from 16 upwards to 10 upwards, as very few interested users were eligible to participate in the program with the higher threshold.

2.3. Sample size calculation

On the basis of expert opinions, we estimated a small effect size of Cohen's d = 0.25 for the reduction in the weekly number of standard drinks between study arms 1 and 3 at six months post randomization. This resulted in a sample size of n = 199 for each study arm (597 in total) to detect a small effect size with 80 % power and an alpha error of 5 % (two-tailed testing).

2.4. Treatment arms

Both active interventions consisted of a dashboard and eight psycho-educative modules — based on CBT (Marlatt and Donovan, 2005) and MI (Miller and Rollnick, 2012)— that were designed to reduce problematic alcohol use. Motivational Interviewing mainly consisted of a balance of pros and cons exercise for alcohol use reduction and continuous motivational e-mail messages. Adherence-focused guidance enhancement in the active interventions was based on the supportive-accountability model of Mohr et al. for providing guidance for internet interventions (Mohr et al., 2011). The guidance consisted of two elements: adherence monitoring and feedback. Adherence monitoring included regularly checking whether participants have completed modules or filled out their consumption diary and then sending them reminders if they have not. The reminders were formulated in an encouraging and motivational style.

These elements were incorporated fully automatically through the program. Feedback was automatically generated based on participants' success or failure of decreasing their consumption according to their entries in the consumption diary. Participants also had the opportunity to contact their eCoach for further feedback. The integrated intervention (AFGE-AD) contained behavioral self-help exercises targeting symptoms of depression (Hides et al., 2010) and social problem solving (D'Zurilla and Nezu, 1982), while AFGE-AO consisted of self-help exercises targeting alcohol misuse only. To minimize additional content as a possible confounding factor, the corresponding modules in the AFGE-AD intervention were designed to have approximately the same quantity of material. The modules included stories of six fictional companions who appeared within the modules at key points, with the goal of encouraging reflection on potential questions raised by the modules. All eight modules were freely accessible from the start, though it was recommended that users progress through the modules in the order in which they were presented and complete 1–2 modules per week. Table 1 summarizes the content and structure of the eight psycho-educative modules.

Both active interventions also incorporated a consumption and activity diary, weekly (semi-)automated motivational and AFG-based email feedback, and reminders for users to fill out the dairy and continue the program. The semi-automated motivational emails were sent out by an eCoach, depending on certain answers of the participants in particular modules. These feedback emails included suggestions for working on a particular module.

Those in the control group were granted access to the internet as usual (IAU), since it was deemed impossible and unethical to prevent participants in this group from seeking out other internet support or face-to-face treatment options during the waiting period. A detailed description of the interventions and their technical specifications is provided in the study protocol paper (Schaub et al., 2016).

At all times, an "instant help"- webpage was available to all participants, with instructions on what subjects could do if their situation became unbearable or they felt themselves in an emergency situation. These instructions contained psycho-educational self-help instructions, as well as phone numbers for professional healthcare providers and emergency helplines.

2.5. Measurements

The primary outcome measure of interest was the quantity of alcohol used over the previous seven days, estimated as the number of standard drinks and assessed by timeline follow-back, in accordance with the Timeline Follow-Back (TLFB) method (Sobell and Sobell, 1996). The measure used in the current study referred to a time frame of 7 rather than 30 days as the original. The shorter time frame was chosen as it may be more accurate (Hoeppner et al., 2010). Furthermore, the here-used measure was presented online rather than in-person. This mode of presentation does not seem to impact the accuracy of participants' answers and may even make them more comfortable reporting their use

Table 1
Module contents and comparisons between study arm 1 (AFGE-AD) and study arm 2 (AFGE-AO).

No	AFGE-AD: Alcohol and depression self-help	AFGE-AO: Alcohol self-help only
M1	**Introduction** • Introductory words (tailored to arm 1) • Pro and Contra of drinking • Core motive for change • Confidence of change • Introduction to consumption diary, mood barometer and planning of positive activities	**Introduction** • Introductory words (tailored to arm 2) • Pro and Contra of drinking (same as arm 1) • Core motive for change (same as arm 1) • Confidence of change (same as arm 1) • Introduction to consumption diary
M2	**Strategies for goal achievement** • Introduction • Changing habits • Alcohol at home • Alcohol for relaxation • My personal strategies (tailored to arm 1)	**Strategies for goal achievement** • Introduction (same as arm 1) • Changing habits (same as arm 1) • Alcohol for relaxation • My personal strategies (tailored to arm 2)
M3	**Say Yes** • Positive activities • Common problems	**Say No** • Thanks, I don't drink • Common problems
M4	**Worries and Problems** • Relation of depression and problems • 6-step plan	**Identify risk situations** • Identify risk situations • Seemingly unimportant decisions
M5	**Craving** (same in both arms) • Forms of craving (physical & mental) • Craving and conditioned triggers • How to handle craving	
M6	**Dealing with slips** (same in both arms) • Define what you consider a slip • How to deal with it • Plan your reaction for future slips	
M7	**Meeting your Needs** • Sleep: tips for better sleep hygiene • Rumination: 6 ways to deal with it • Social contacts: importance of and how to (re)enforce them	**Progressive Muscle Relaxation** • Basic overview • FAQ • Exercise in written words • Guided instructions via audio file
M8	**Preserve success** (same in both arms) • Your toughest moments? • Most helpful modules? • Your top 5 strategies?	

(Pedersen et al., 2012).

Secondary outcomes included the number of drinking days per week assessed by the TLFB; the severity of alcohol use disorder, assessed using the *Alcohol Use Disorders Identification Test* (AUDIT (Saunders et al., 1993)); change in depression severity (*Centre of Epidemiologic Studies of Depression Scale* [CES-D (Cole et al., 2004)]); a combined alcohol and depression measure, defined as simultaneously falling below the AUDIT cut-off of 8 and the CES-D cut-off of 10; years of lifetime consumption of substances of abuse using the FDA (*Fragebogen Substanzanamnese*) derived from the EuropASI (Kokkevi and Hartgers, 1995); mental distress, rated using the short version of the Mental Health Inventory (MHI-5 (Rumpf et al., 2001)); quality of life, measured using the five-level variant of the five-dimensional EuroQol instrument (EQ-5D-5 L (Group, 1990)); work ability, measured employing the single-item Work Ability Index (WAI (Ahlstrom et al., 2010)); client satisfaction with the treatment program (ZUF-8 (Schmidt and Wittmann, 2002)); and treatment adherence (number of finished modules). Lastly, we asked all participants if they had used any treatment or help other than *Take Care of You* during their six months in the study and, if so, to identify it from a predefined list of services. Table 2 overviews the measurement items used and times measured. More details regarding study measures are provided in the study protocol (Schaub et al., 2016).

2.6. Statistical analysis

Data were analyzed according to the intention-to-treat principle (ITT). To address missing data for the ITT analyses, we applied multiple imputation procedures using the software package "MICE" (van Buuren and Groothuis-Oudshoorn, 2011) in R (version 3.6.1) (R Core Team, 2019), which is a minor deviation from the study protocol, wherein we suggested using the package "Amelia". MICE involves specifying a multivariate distribution for the missing data and drawing imputations from their conditional distributions using Markov chain Monte Carlo techniques. Imputations were performed separately for the three conditions, but using the same set of variables. This has been shown to result in correct treatment effect estimates in RCTs (Sullivan et al., 2018). All socio-demographic, as well as primary and secondary outcome variables that had been assessed in all three intervention groups were included in the imputation. As recommended, 20 imputation sets were employed (van Buuren and Groothuis-Oudshoorn, 2011). Reported outcomes used the ITT results from the imputed datasets, but complete case analysis (CCA) results also are reported in the attached detailed tables and supplementary table.

For investigating treatment effects, multivariable linear regression models were generated and tested. Change scores between baseline and follow-up served as dependent variables for the primary and all secondary outcomes, with study condition set as the independent variable; each outcome was adjusted for its baseline value and using external help. For binary outcomes, logistic regression models were generated and tested. Individuals lost to follow-up were compared against those who completed the 6-month assessment (completers) in baseline characteristics across study conditions. The use of linear mixed models (LMMs), including a time-study arm interaction term (as described in the protocol paper (Schaub et al., 2016)) was impossible, as the models did not converge. To investigate whether combined treatment for depression and alcohol resulted in a similar reduction in alcohol

Table 2
Assessment instruments.

Assessments / instruments	Baseline (t_0)	6 weeks (t_1)	3-month follow-up (t_2)	6-month follow-up (t_3)
Socio-demographics	X			
FDA	X			
AUDIT	X		X	X
CES-D	X		X	X
Number of weekly standard drinks[a]	X		X	X
Number of weekly consumption days[a]	X		X	X
MHI-5	X		X	X
Suicidal ideations or plans	X		X	X
EQ-5D-5L	X		X	X
TiC-P	X		X	X
WAI presenteeism	X		X	X
ZUF-8[b]		X		
Intervention adherence[c]				

[a] TLFB = Timeline Follow-Back.
[b] This instrument will only be applied to intervention arms 1 and 2.
[c] Continuous assessment over 6 weeks.

consumption as with alcohol treatment alone, a CI approach was used to estimate the effect size, reflecting the difference between the two study arms, with a two-sided 0.05 level of significance (Piaggio et al., 2012). The equivalence margin was set, *a priori*, at d = 0.20, corresponding to the smallest value indicating a relevant effect (Wiens, 2002).

Several participants were directly or indirectly impacted by the government-ordered lockdown measures employed mid-March 2020 in Switzerland, Austria, and Germany. For analytical purposes, we categorized three groups of participants, in terms of the lockdown's effect on their time in the study: unaffected: those who finished their program and follow-up assessments before mid-March (12.3); indirectly affected: those who finished their program before the lockdown, but had their final survey during the lockdown; and directly affected: those who worked through the program during the lockdown. Subgroup analysis using complete case data was performed to explore possible effects.

Reported effect sizes were calculated for changes from baseline to follow-up (d_w) and between the two intervention groups and controls (d). As suggested elsewhere, d = 0.20 was adopted to indicate a small, d = 0.50 a medium, and d = 0.80 a large effect (Cohen, 1988).

3. Results

3.1. Participation flow

Fig. 1 overviews the trial flow. Between February 2016 and August 2020, a total of 1388 people registered online for the program, among whom 689 were considered eligible and randomized to the three study arms. Three months after baseline, we were able to reach 327 subjects (47.5 % of the initial 689); this number dropped to 288 (41.8 %) for the final 6-month assessment.

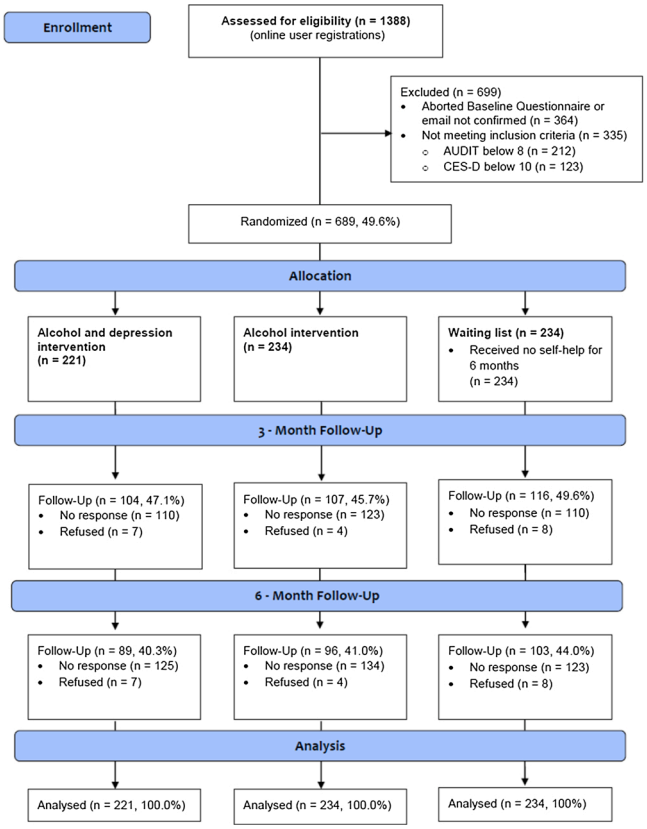

Fig. 1. CONSORT-EHEALTH trial flowchart: overview of participant flow.

3.2. Baseline characteristics

Of the 689 participants, 356 (51.7 %) were male, and the average age was 42.8 (SD = 11.7). The biggest share (n = 271, 39.3 %) were from Austria, followed closely by 232 (33.7 %) from Switzerland and 178 (25.8 %) from Germany. The average participant had used alcohol almost daily (5.4 days, SD = 1.8) over the preceding seven days. Participants in the three different intervention arms differed significantly in gender distribution ($p = .049$) and number of alcohol-consumption years ($p = .017$).

Complete case analysis of baseline data and study group comparisons are summarized in Table 3.

3.3. Primary outcome

Fig. 2 depicts the subjects' decrease in standard drink consumption throughout study participation. Three months after baseline, users in both active interventions reported significantly greater reductions in alcohol consumption than IAU controls, by averages of 17.4 ($d_w = 0.82$, SD = 23.96) and 20.9 standard drinks ($d_w = 1.12$, SD = 23.38), respectively, compared to 14.2 standard drinks ($d_w = 0.42$, SD = 32.8) in controls (AFGE-AD: B=−5.82, P = .013, d = 0.11; AFGE-AO: B=−8.79, $p < .001$, d=0.24). These effects persisted six months after baseline, with participants in both active interventions still experiencing significantly greater reductions in their alcohol use than controls: mean reductions of 16.56 ($d_w = 0.72$, SD = 26.2) and 19.8 ($d_w = 0.99$, SD = 24.2) versus 13.2 standard drinks ($d_w = 0.39$, SD = 39.8; AFGE-AD: B=−6.51, $p = .048$, d=0.10; AFGE-AO: B=−9.17, $p = .004$, d=0.20)

There was no significant difference between the two active interventions at either the 3-month ($p = .206$) or 6-month follow-up assessment ($p = .366$). Equivalence testing between the two active interventions was not significant, demonstrating an observed effect size in excess of the upper bound equivalence margin of d=0.20 ($p = .211$) but not the lower bound of the predefined margin ($p < .001$), indicating noninferiority between the integrated and alcohol-only interventions.

Detailed results for primary outcomes are summarized in Table 4.

3.4. Secondary outcomes

At 6-month follow-up, participants in the AFGE-AO group reported significantly fewer consumption days over the previous seven days, including an average decrease of 1.9 days ($d_w = 0.93$, SD = 2.4) relative to baseline versus a decrease of 0.9 days ($d_w = 0.39$, SD = 2.3) in controls (B=−1.01, $p = .005$, d=0.42). No significant difference was detected between the decrease of 1.4 ($d_w = 0.66$, SD = 2.2) in the AFGE-AD and IAU ($p = .120$) group subjects. See also Table 5.

A significant difference was noted in the decrease in alcohol use disorder severity (AUDIT) between both active interventions and the control condition (AFGE-AD: M = 5.0, SD = 6.7, $d_w = 0.77$, B=−3.36, $p = .003$, d=0.54; AFGE-AO: M=6.2, SD=5.7, $d_w = 1.04$, B=−4.48, $p < .001$, d=0.80; IAU: M=1.7, SD=5.4 $d_w = 0.26$); but, again, no significant difference was noted between the two active interventions ($p = .313$).

Similarly, subjects in both active intervention groups had greater CES-D score reductions —averaging 6.6 ($d_w = 0.79$, SD = 9.3) and 7.3 ($d_w = 0.84$, SD = 11.6) — than controls, averaging 2.6 ($d_w = 0.30$, SD = 10.0; AFGE-AD: B=−3.95, $p = .006$, d=0.41; AFGE-AO: B=−4.15, $p = .008$, d=0.43); but there again was no significant difference between the active interventions ($p = .890$).

Combining the CES-D and AUDIT measures to see which subjects fell below threshold levels in both measures, significantly more participants in the AFGE-AO group (10.7 %) fell below these two cut-offs than controls (1.1 %, $p = .031$); however, the 5.9 % rate observed in AFGE-AD subjects ($p = .093$) was not statistically greater than the control rate. A greater decrease in the CES-D score was significantly associated with a larger decrease in the AUDIT score ($p < .001$), and vice versa ($p < .001$).

All three treatment groups decreased their mean MHI-5 score, with

Table 3
Baseline-Data of participants.

	AFGE-AD n = 221	AFGE-AO n = 234	IAU n = 234	Total n = 689	Statistical Analysis *(Chi-Square, ANOVA or Kruskal-Wallis-Test)*
Gender, n (%)					$X^2(2, N = 689) = 6.03, p = .049$*
Female	105 (47.5)	136 (58.1)	115 (49.1)	333 (48.3)	
Male	116 (52.5)	98 (41.9)	119 (50.9)	356 (51.7)	
Age, *M (SD)*	43.6 (11.8)	41.7 (11.4)	43.1 (11.8)	42.8 (11.7)	$F(2,686) = 1.59, p = .204$
Highest education, n (%)					$X^2(10, N = 689) = 5.46, p = .855$
Primary school	6 (2.7)	3 (1.3)	4 (1.7)	13 (1.9)	
Apprenticeship	47 (21.3)	40 (17.1)	42 (17.9)	129 (18.7)	
Secondary school	44 (19.9)	62 (26.5)	53 (22.6)	159 (23.1)	
Technical college	40 (18.1)	42 (17.9)	45 (19.2)	127 (18.4)	
University	79 (35.7)	84 (35.9)	85 (36.3)	248 (36.0)	
Not specified	5 (2.2)	3 (1.3)	5 (2.1)	13 (1.9)	
Country of origin, n (%)					$X^2(6, N = 689) = 8.47, p = .206$
Switzerland	63 (28.5)	87 (37.2)	82 (35.0)	232 (33.7)	
Austria	95 (43.0)	91 (38.9)	85 (36.3)	271 (39.3)	
Germany	58 (26.2)	55 (26.2)	65 (27.8)	178 (25.8)	
Other	5 (2.2)	1 (0.4)	2 (0.9)	8 (1.2)	
Alcohol Use Disorder (AUDIT, Range 0–40), *M (SD)*	19.7 (6.0)	19.9 (5.5)	19.9 (5.6)	19.8 (5.7)	$F(2,686) = 0.10, p = .908$
Centre for Epidemiological Studies Depression Scale (CES-D, Range 0–60), *M (SD)*	22.2 (7.8)	22.9 (7.6)	22.0 (6.9)	22.4 (7.4)	$F(2,686) = 0.77, p = .462$
Mental Health Inventory (MHI-5, Range 5–25), M(SD)	14.8 (3.6)	15.1 (3.3)	14.7 (3.1)	14.9 (3.3)	$F(2,686) = 0.91, p = .402$
EuroQol Health Score (EQ-5D-5 L Range 0–100), M(SD)	68.8 (16.6)	69.4 (14.7)	68.5 (17.5)	69.0 (16.3)	$F(2,684) = 0.33, p = .722$
Number of Standard Drinks[1], M(SD)	34.8 (23.5)	36.0 (23.0)	39.0 (43.4)	36.6 (31.7)	$F(2,672) = 1.08, p = .339$
Number of Consumption Days[a], M(SD)	5.2 (1.9)	5.4 (1.7)	5.4 (1.8)	5.4 (1.8)	$F(2,682) = 0.80, p = .451$
Number of Consumption Years, M(SD)					
Alcohol	15.3 (10.4)	13.0 (9.3)	15.6 (11.3)	14.6 (10.4)	$F(2,666) = 4.07, p = .017$*
Alcohol risky use[b]	10.2 (9.6)	8.9 (8.2)	10.7 (10.5)	9.9 (9.5)	$F(2,639) = 1.98, p = .139$
Cannabis	2.1 (4.9)	1.9 (3.8)	2.0 (5.6)	2.0 (4.8)	$F(2,520) = 0.08, p = .922$

[a] Last 7 days.
[b] Risky Use is defined as 5 or more standard drinks per day at least 3 days per week. A standard drink is defined as 5 cl spirits, 15–20 cl wine or 33–45 cl beer, CES-D cut-off: 10, AUDIT cut-off: 8.

no significant inter-intervention differences detected. The mean WAI score increased significantly in the AFGE-AD group (M=−1.1, SD = 3.0, $p < .001$, d=−0.50) relative to the small increase observed in controls (M = 0.3, SD = 2.6). The WAI score also increased in AFGE-AO group subjects, but this increase was not statistically greater than the increase in controls (p=.209).

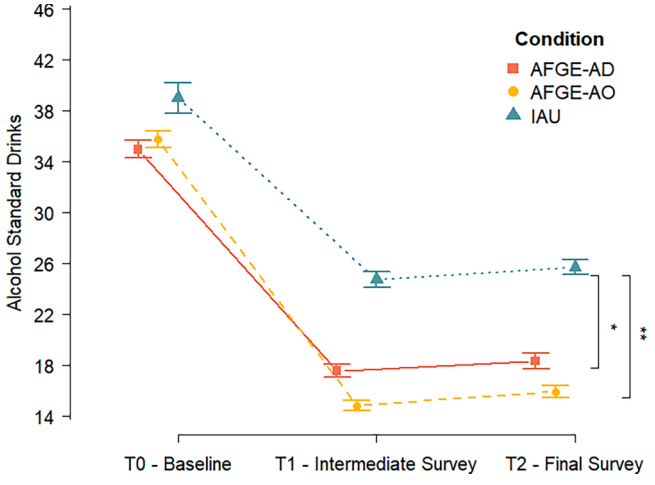

Fig. 2. Decreases in Standard Drink consumption over the preceding 7 days, according to TLFB (Timeline Follow-Back). At the final survey (6-months) both intervention groups (AFGE-AD, AFGE-AO) showed significant higher decrease in alcohol standard drinks than controls (*, d = .10, p < .05; **, d = .20, p < .01).

With regards to self-reported TLFB abstinence, 11.8 % and 13.8 % of AFGE-AD and AFGE-AO participants reported abstinence over the last seven days, neither of which was significantly higher than the 8.2 % abstinence rate observed in controls (AFGE-AD: $p = .693$; AFGE-AO, $p = .193$).

3.5. Adherence & user satisfaction

Participants in the AFGE-AD group completed an average of 3.7 (SD = 2.8) modules versus 3.9 modules (SD = 2.9) among AFGE-AO subjects (t_{451}=−0.91, $p = .362$). Participants in the IAU group were most likely to remain in the study (44.0 %), but there was no significant difference between the groups ($\chi^2 = 0.74$, $p = .690$).

There was no significant difference between the two active interventions in level of user satisfaction (AFGE-AD: M = 24.6, SD = 3.6, AFGE-AO: M = 22.6, SD = 5.1, $t_{48} = 1.62$, $p = .056$).

3.6. Using external services

Forty-six participants (16.5 %) reported using external services for their alcohol problem over the course of their study participation. The external service most frequently used was a psychologist, with 19 instances of contact (41.3 % of all external service use), followed by other unspecified services with 16 (34.8 %). Nine reported seeking other internet counselling (19.6 %), eight sought the services of local drug counsellors (17.4 %), six sought care from a psychiatrist (13.0 %), and five a general practitioner (10.9 %). There was no significant difference between the three intervention arms in the rate of external service use ($\chi^2 = 0.92$, $p = .632$).

Table 4
Regression analysis results.

Outcome	*AFGE-AD versus control after 6 months (ITT analysis)*				*AFGE-AO versus control after 6 months (ITT analysis)*			
	B[a]	95 % CI		*p*	B[a]	95 % CI		*p*
	Imputed Data (n = 689)				Imputed Data (n = 689)			
Standard Drinks[b]	−6.52	−12.97	−0.07	.048*	−9.13	−15.17	−3.09	.004**
Consumption Days[b]	−0.58	−1.32	0.17	.125	−0.99	−1.69	−0.30	.006**
AUDIT	−3.39	−5.47	−1.30	.002**	−4.51	−5.98	−3.04	<.001***
CES-D	−3.95	−6.72	−1.18	.006**	−4.15	−7.18	−1.12	.008**
MHI-5	−4.78	−11.49	1.93	.156	−4.72	−11.84	2.39	.184
WAI	1.21	0.53	1.88	<.001***	0.71	−0.43	1.84	.209
Abstinence[b]	−0.20	−1.19	0.79	.693	−0.59	−1.48	0.30	.139
CES-D & AUDIT[c]	−1.83	−3.97	0.31	.093	−2.63	−4.69	−0.56	.031*

ITT = Intention to Treat; AUDIT = Alcohol Use Disorders Identification Test; CES-D = Centre of Epidemiologic Studies of Depression Scale; MHI-5 = Mental Health Inventory; WAI = Working Ability Index.
[a] Condition as predictors for group effect.
[b] Last 7 days according to TLFB.
[c] Falling below CES-D cut-off 10 and AUDIT cut-off 8.

3.7. Dropout analysis

Participants who dropped out were significantly more likely to be male ($\chi^2 = 0.74$, $p = .023$), younger ($t_{581} = 2.19$, $p = .029$), and have a lower educational level ($\chi^2 = 14.58$, $p = .012$). They also reported at baseline more standard drinks ($t_{641}=-2.54$, $p = .011$) and fewer alcohol use years ($t_{571} = 2.11$, $p = .036$); scored higher on the AUDIT ($t_{649}=-2.14$, $p = .032$) and CES-D ($t_{630}=-2.46$, $p = .014$); reported less working ability ($t_{490} = 2.09$, $p = .037$) and finished fewer modules ($t_{483} = 10.15$, $p < .001$) than those who completed follow up. Full dropout analysis is summarized in Table S2.

3.8. Exploratory data analysis: COVID-19

In total, 134 (19.4 %) participants were affected by lockdown measures. Of these, 71 were affected indirectly (10.3 %) and 63 directly (9.1 %). On average, participants who were not affected by lockdowns decreased their alcohol use significantly more than those who were directly affected by them, decreasing by an average of 14.9 (SD = 23.4) standard drinks versus just 5.4 (SD = 17.0) standard drinks ($t_{38} = 2.57$, $p = .014$) in controls. This reduction in alcohol use in lockdown-unaffected subjects was not greater, however, than the decrease observed in those indirectly affected, who reduced their alcohol consumption by an average of 9.3 (SD=19.0) standard drinks ($t_{65} = 1.66$, $p = .101$).

Unaffected subjects also decreased their AUDIT score by 4.4 (SD = 6.1), which was a significantly greater reduction than the 1.6 (SD = 5.2) observed by directly affected subjects ($t_{37} = 2.62$, $p = .012$), but not relative to the 3.5 (SD=4.3) decrease observed in those only indirectly affected by lockdowns ($t_{74} = 1.16$, $p = .249$). Participants not affected by the lockdown decreased their CES-D score by 5.4 (SD=9.1), versus those indirectly affected by 7.6 (SD=7.9) and those directly affected by 2.7 (SD=8.9). The reduction in CES-D score was significantly greater between those indirectly and directly affected by lockdowns ($t_{49} = 2.33$, $p = .024$), but no significant difference was observed between those who were unaffected and directly affected ($t_{32} = 1.49$, $p = .147$).

4. Discussion

In this study, we compared two active online interventions — one which offered users treatment of both their depression and their alcohol misuse (AFGE-AD), and a second which only addressed alcohol issues (AFGE-AO) — against a waiting list control group of subjects who were allowed internet as usual (IAU) use only. Participants in both of these active intervention groups reported significantly fewer standard drinks than controls, both three and six months after initiation of the six-week program. These main effects were small at three months (AFGE-AD: d = .11, AFGE-AO: d = .24), but they were significant, and this significant small effect was maintained through the six-month follow-up survey (AFGE-AD: d = .10, AFGE-AO: d = .20). Equivalence testing showed noninferiority between the combined/integrated and the alcohol-only treatment arms, suggesting that this combined intervention was no worse than the intervention targeting alcohol use alone, in terms of reducing the number of standard drinks that individuals consumed.

The effect sizes for alcohol-consumption reduction were smaller than we expected, but consistent with the effect sizes reported for previous research examining face-to-face treatment (g = 0.19 (Riper et al., 2014a)), and greater than what was reported for another, previously-studied integrated internet program (DEAL, d=−0.09), which targeted co-occurring depression symptoms and problematic alcohol use in young adults (Deady et al., 2016). The DEAL project achieved a large post-treatment effect (d = 0.99) that vanished by three months, whereas our program appeared to maintain its beneficial effects for up to six months. More dramatic results, indicating a medium to large effect size, were observed in terms of reducing the AUDIT score in both active intervention groups, relative to controls (AFGE-AD: d = .56, AFGE-AO: d = .80), which adds further credence to the effectiveness of these programs, since the AUDIT measures symptoms of both alcohol dependence and risky use.

Regarding depression symptoms, both active interventions reduced CES-D scores significantly more than internet as usual (IAU) (AFGE-AD: d = .41, AFGE-AO: d = .43). These effects are similar to the one observed for the DEAL project (d = 0.39 (Deady et al., 2016)) and slightly higher than those reported in the meta-analysis on integrated face-to-face therapy published by Riper and colleagues (g = 0.27 (Riper et al., 2014a)). The effects achieved in the AFGE-AO group were surprising, as no content in that intervention was specifically tailored to target depression symptoms. It seems that the reduction in alcohol use alone might have alleviated moderate depression symptoms, as well. This may stem from our choice of a non-clinical sample that averaged less severe depressive disorders than the patient populations evaluated in the face-to-face intervention studies analysed by Riper et al. (2014a). We also observed a significant positive and bidirectional relationship between reduced depression outcomes and alcohol use, consistent with the meta-analysis performed by Nunes and Levin (2004). The relationship between alcohol use and depression symptoms seems to be reciprocal, whereby increased alcohol use leads to worse negative emotions and vice versa (Witkiewitz and Villarroel, 2009).

A priori, we hypothesised that the integrated intervention (AFGE-AD) would reduce depression symptoms more than the alcohol-only intervention (AFGE-AO), which we failed to demonstrate, despite showing the overall effectiveness of both interventions compared to controls. Several circumstances could have impacted the integrated program's success. To begin with, during recruitment we did not specify that we

Table 5
Means, standard deviations and achieved effect sizes.

Outcome	Baseline		3 months after baseline (complete cases)			95 % CL		3 months after baseline (ITT analysis)			95 % CL		6 months after baseline (complete cases)			95 % CL		6 months after baseline (ITT analysis)			95 % CL	
	Mean	SD	Mean	SD	d[a]			Mean	SD	d[a]			Mean	SD	d[a]			Mean	SD	d[a]		
IAU (n = 234)			Followed Up (n = 119)					Imputed Data (n = 234)					Followed Up (n = 103)					Imputed Data (n = 234)				
Standard Drinks[b]	39.02	43.36	25.25	23.04				24.74	21.68				24.92	19.89				25.70	21.06			
Consumption Days[b]	5.35	1.79	4.64	2.25				4.51	2.28				4.50	2.27				4.54	2.30			
AUDIT	19.91	5.57	18.65	6.37				18.79	6.68				18.36	6.73				18.25	7.09			
CES-D	22.03	6.86	18.37	10.09				18.88	10.41				17.24	9.49				19.37	10.52			
MHI-5	48.31	15.43	40.48	18.39				41.54	18.78				37.70	19.34				40.99	20.63			
WAI	6.92	2.63	7.28	2.15				6.92	2.40				7.51	2.61				6.80	3.09			
AFGE-AD (n = 221)			Followed Up (n = 105)					Imputed Data (n = 221)					Followed Up (n = 90)					Imputed Data (n = 221)				
Standard Drinks[b]	34.76	23.50	17.85	21.72	.24	−.03	.50	17.56	17.94	.11	−.07	.29	19.36	27.12	.18	−.11	.46	18.34	21.94	.10	−.09	.28
Consumption Days[b]	5.23	1.87	3.86	2.24	.30	.03	.56	4.08	2.24	.11	−.08	−.29	3.80	2.26	.25	−.04	.53	3.86	2.29	.21	.03	.39
AUDIT	19.69	6.04	15.02	6.24	.47	.20	.73	15.45	6.18	.51	.31	.68	14.02	6.80	.44	.15	.72	14.69	6.94	.54	.35	.72
CES-D	22.23	7.73	14.77	7.75	.25	−.02	.51	15.90	8.12	.35	.16	.53	15.38	8.70	.09	−.17	.35	15.56	9.17	.41	.22	.59
MHI-5	49.14	17.95	36.60	18.06	.11	−.15	.37	36.91	18.64	.28	.09	.46	36.42	18.57	.00	−.28	28	36.67	19.46	.25	.06	.43
WAI	6.81	2.52	7.55	2.21	−.17	−.43	.10	7.02	2.73	−.15	−.33	.04	7.99	1.92	−.31	−.59	−.02	7.85	2.06	−.50	−.68	−.30
AFGE-AO (n = 234)			Followed Up (n = 108)					Imputed Data (n = 234)					Followed Up (n = 96)					Imputed Data (n = 234)				
Standard Drinks[b]	36.01	23.03	13.38	13.92	.52	.25	.78	14.83	13.62	.24	.05	.41	15.01	17.68	.46	.17	.73	15.93	17.30	.20	.02	.38
Consumption Days[b]	5.40	1.71	3.47	2.33	.62	.34	.88	3.65	2.35	.36	.17	.53	3.51	2.30	.47	.18	.75	3.52	2.31	.42	.23	.59
AUDIT	19.87	5.51	14.35	6.10	.80	.51	1.05	14.55	6.31	.71	.51	.89	12.96	6.01	1.36	1.03	1.65	13.69	6.39	.81	.61	.99
CES-D	22.85	7.59	15.36	9.35	.36	.10	.62	16.12	9.22	.36	.17	.53	15.06	9.17	.34	.07	.59	15.55	9.68	.43	.24	.61
MHI-5	50.38	16.69	35.76	18.84	.36	.09	.62	37.54	19.26	.30	.11	.48	34.25	18.43	.29	.01	.57	36.97	18.84	.28	.09	.46
WAI	7.11	2.41	7.76	2.45	−.19	−.45	.07	7.60	2.71	−.15	−.33	.03	7.83	2.36	−.21	−.48	.07	7.63	2.64	−.21	−.39	−.03

ITT = Intention to Treat; AUDIT = Alcohol Use Disorders Identification Test; CES-D = Centre of Epidemiologic Studies of Depression Scale; MHI-5 = Mental Health Inventory; WAI = Working Ability Index.

[a] Condition as predictors for group effect.

[b] Last 7 days according to TLFB.

were offering an intervention that targets both alcohol use and depression. Combined with reducing the CES-D inclusion threshold from a minimum score of 16 to 10 may have resulted in us recruiting individuals who not only were not expecting an intervention targeting depressive symptoms, but also might not actually have been suffering appreciably from them. Our recruitment might, therefore, have benefited from clearer communication. Secondly, part of our study was conducted during the COVID-19 pandemic, which may have had unforeseen effects on the results of our program. Little is known about the effects that such a global crisis can have on a participant's response to such programs, which could differ greatly from normal circumstances. The participants' mobility may have been limited by either lockdown measures or fear of infection. This may have reduce social gatherings with or without alcohol. Over time, we should learn more about such unprecedented times and its consequences on programs like ours.

Lastly, but maybe most obviously, is that the content tailored towards depression in our integrated program was neither specific nor effective enough. The content we used was based on face-to-face therapy, adapted, and then integrated into our internet intervention. Using more established material from previously-successful online interventions might be more effective in future iterations of the program. Another idea would be to restructure and reorder our program to offer content for depression earlier on in the program.

Regardless of all these explanations, the combined intervention was as successful at reducing depression symptoms as the alcohol-only intervention. Future research should consider offering different options depending on the severity of depression at baseline. Furthermore, sub-group analyses could possibly be helpful to identify groups of participants for which an integrated program is more effective than an alcohol only program.

We expected users' level of satisfaction would be greater with the integrated than alcohol only intervention, but whatever increased satisfaction we observed with the former ultimately failed to achieve statistical significance, albeit only barely ($p = .056$). Both interventions were fairly well received by participants, which also is apparent by the number of completed modules, with users of the active integrated and alcohol-only interventions averaging 3.7 and 3.9 modules respectively, out of a possible eight modules. Relative to other programs, these numbers are high, as internet interventions often suffer greatly from low adherence and user retention (Eysenbach, 2005).

5. Limitations

This study had three major limitations. First, we had to readjust the inclusion criteria to achieve our target sample size and, as such, included people with less severe depressive symptoms. This means that it is not clear whether some of the people we included in our analysis even needed treatment for depression, which in turn may limit both the overall effectiveness and generalizability of our combined treatment. Secondly, the study had a high overall attrition rate (58.8 %), which is common with these kinds of intervention, but introduces more uncertainty. We used multiple imputations in an attempt to deal with any bias that might have resulted from this. Lastly, all measures were self-reported, and it is possible that many of our subjects portrayed themselves in a better light or answered queries more favorably than they actually felt, merely to please the study team (Davis et al., 2010). This said, evidence has been published suggesting that the anonymous nature of the internet may help people to be more open and honest and, thereby, provide more accurate self-evaluations (Fullwood et al., 2009).

6. Conclusions

In the context of a three-arm randomized controlled trial, the first fully-integrated internet intervention targeting both alcohol misuse and depression was found to be effective at alleviating both among at least moderately-depressed, adult alcohol misusers in the general public.

Even though the main effects were small, they could be maintained for six months, which is promising. Future research can use and build upon our results to gain additional understanding and subsequently develop even more effective interventions. Online interventions, like *Take Care of You*, can be a valuable addition to the general healthcare system, given that they generally are very cost-effective and can run automatically with minimal human support. Additionally, the remote nature of online interventions means that they have the capacity to provide support to people anywhere, including the comfort of their own homes.

Role of funding source

Funding for this trial was received from the Swiss Foundation for Alcohol Research (grant No SSA #247) and through internal funds from the Swiss Research Institute for Public Health and Addiction (ISGF). The funding sources had no role in the writing of the manuscript or the decision to submit for publication. Content is solely the responsibility of the authors and does not necessarily represent the official views of the Swiss Foundation for Alcohol Research or the Swiss Research Institute for Public Health and Addiction.

Authors' contributions

MPS had the initial idea for this study. CB prepared the first draft of the paper and final manuscript. AW, CB, DDE, DL, MB and MPS developed the interventions for study arms 1 and 2. AW and CB programmed and implemented the *Take Care of You* study websites. DM helped to develop and adapt the Austrian version of the website. DDE, DM, LS, MA, MB, and SH provided continuous feedback on the development of the interventions and the present study paper. CB performed statistical analysis. CB, MA, MPS, and SH thoroughly revised the first versions of the study paper. All authors approved the final version of the manuscript submitted for publication. CB is the guarantor.

Declaration of Competing Interest

DE has served as a consultant to/on the scientific advisory boards of Sanofi, Novartis, Minddistrict, Lantern, Schoen Kliniken, Ideamed and German health insurance companies (BARMER, Techniker Krankenkasse) and a number of federal chambers for psychotherapy. He is also stakeholder of the Institute for health training online (formerly GET.ON/nowHelloBetter), which aims to implement scientific findings related to digital health interventions into routine care.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2021.108806.

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