Evaluation of adding the community reinforcement approach to motivational enhancement therapy for adults aged 60 years and older with DSM-5 alcohol use disorder

a randomized controlled trial

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Brief alcohol treatment for 60+ years

Title:

Evaluation of adding the Community Reinforcement Approach to Motivational Enhancement Therapy for Adults Aged 60 Years and Older with DSM-5 Alcohol Use Disorder: A Randomised Controlled Trial

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**Abstract:**

**Aim:** To examine whether adding the Community Reinforcement Approach for Seniors (CRA-S) to Motivational Enhancement Therapy (MET) increases the probability of treatment success in people ≥ 60 years old with alcohol use disorder (AUD).

**Design:** A single blind multi-centre multinational randomized (1:1) controlled trial.

**Setting:** Outpatient settings (municipal alcohol treatment clinics in Denmark, specialized addiction care facilities in Germany, and a primary care clinic in the USA).

**Participants:** Between January 2014 and May 2016, 693 patients aged 60+ years and fulfilling DSM-5 criteria for AUD participated in comparing MET (n=351) and MET + CRA-S (n=342).

**Intervention and comparator:** MET (comparator) included four manualized sessions aimed at increasing motivation to change and establishing a change plan. CRA-S (intervention) consisted of up to eight further optional, manualized sessions aimed at helping patients to implement their change plan. CRA-S included a specially designed module on coping with age and age-related problems.

**Measurements:** The primary outcome was either total alcohol abstinence or an expected blood alcohol concentration of ≤ 0.05% during the 30 days preceding the 26 weeks follow-up (defined as success) or blood alcohol concentration of >0.05% during the follow-up period (defined as failure). This was assessed by self-report using the Form 90 instrument. The main analysis involved complete cases.

**Findings:** The follow-up rate at 26 weeks was 76.2% (76.9% in the MET group and 76.0% in the MET+CRA-S group). The success rate in the MET group was 48.9% (95% CI=42.9%–54.9%) vs. 52.3% (95% CI=46.2%–58.3%) in the MET+CRA-S group. The odds of success in the two conditions did not differ (odds ratio 1.22, 95% CI=0.86–1.75, p = 0.26, Bayes
factor=0.10). Sensitivity analyses involving alternative approaches to missing values did not change the results.

**Conclusions:** In older adults with an alcohol use disorder diagnosis, adding the ‘Community Reinforcement Approach for Seniors’ intervention to brief outpatient Motivational Enhancement Therapy treatment did not improve drinking outcome.

**Key words:**
Alcohol use disorder, older adults, brief treatment, Motivational Enhancement Therapy, Community Reinforcement Approach, randomized trial
Introduction:

Although the rates of alcohol use disorder (AUD) and unhealthy drinking are lower among older adults compared to younger adults (1-3), they are still considerable. In the USA, 6.7% of older adults have reported alcohol abuse, dependence, or dependence symptoms (4), and 14.5% have a harmful consumption, e.g. above the NIAAA-recommended limits (5). Recent large-scale studies, the National Survey on Drug Use and Health (NSDUH) (6) and the National Epidemiological Survey on Alcohol and Related Conditions III (1), have reported similar one-year prevalence estimates of AUD for those aged 65 years or older, namely 2.1% and 2.3%, respectively. In Germany, 25.2% exceed the maximum daily intake (12 and 24 grams of ethanol for women and men, respectively) (7), and in Denmark 20.9% exceed the low risk weekly consumption guidelines (7 standard drinks (1 standard drink = 12 grams of ethanol) for women and 14 for men) (3). In Europe, the 12-month prevalence of AUD in older adults has been reported to be 5.2% (8) and 10.2% heavy drinkers, e.g. 15 or more standard drinks in the last week (9). This, together with the expected increase in the number of older adults across the rest of the century (10), presents a growing healthcare challenge.

Studies on treatment of older adults with AUD are relatively sparse. Two reviews, one published in 2013 by A. Kuerbis and P. Sacco and the other in 2015 by U. Bhatia and colleagues, spanning 32 years of research on treatments for substance abuse among older adults found a total of 28 studies (11, 12). Studies included in the reviews have mostly been mixed-aged studies that report age-specific results. Both inpatient and outpatient settings have been studied, encompassing pharmacological and psychosocial interventions, e.g. naltrexone, cognitive behavioral therapy, motivational enhancement, brief advice, education, case management services, and length of treatment. In the mixed-age studies, overall, the group of older adults generally had lower AUD severity. Despite differences in designs, settings, and interventions, studies have consistently shown that older adults respond to
treatment as well as or better than younger adults. Some studies indicate that greater treatment adherence among older adults contributes to better outcomes compared to younger adults (13-16). Kuerbis and Sacco emphasize that age-specific treatment addressing life stage concerns, such as loneliness, grief, and loss could enhance successful treatment of older adults (17-20). Such age-adapted treatments could also address risk factors such as social networks that encourage social alcohol use (17, 21, 22). Both reviews conclude that there is a need for further research focused on evidence-based treatments, such as treatments based on motivational interviewing or CBT since only a few such studies have been conducted so far by, for example, Schonfeld, Dupree, and co-workers (19, 20).

We therefore investigated whether a manualized, brief, outpatient treatment based on motivational interviewing/Motivational Enhancement Therapy (MET) (23) could be improved by adding sessions with age-adapted, CBT-oriented content based on the Community Reinforcement Approach (CRA) (24) in a sample of older adults with DSM-5 AUD. The CRA utilizes familial, social, recreational, and occupational reinforcers to aid patients in the recovery process. The goal of CRA is to rearrange multiple aspects of the patient’s "community" so that a sober lifestyle becomes more rewarding than one dominated by alcohol. Since loneliness, as well as a social network involving alcohol, is hypothesized to influence the drinking of seniors, we considered CRA adjusted for seniors to be a meaningful treatment approach.

Methods:

Study Design and Settings

The study design has been described in detail elsewhere (25, 26). The study was conducted from January 2014 to May 2016 as a single-blind randomized (1:1) controlled trial comparing MET to MET followed by CRA adapted for seniors, in the following abbreviated as CRA-S.
Three countries (six sites) participated: Denmark (Copenhagen, Aarhus, and Odense), Germany (Munich and Dresden), and the USA (Albuquerque, New Mexico). In Denmark, treatment was provided in municipal outpatient alcohol treatment facilities. These clinics provide free treatment to all persons seeking care, with or without referral. In Germany, free treatment is offered by a specialized outpatient addiction care system. For this study, free treatment was provided at outpatient treatment centers at the research institutions. In the USA, the trial was implemented in a primary care clinic. Alcohol treatment was provided free of charge through the study and was not otherwise available at the clinic. In all three countries, detoxification, if necessary, was completed before beginning participation in the study.

**ETHICS**

The protocol as well as patient information about the study was approved by the local ethics committee structures at each site/country.

**Participants**

All patients who sought treatment on a self-referral basis, by referral from general practice or hospital, as in Denmark and Germany, or screened positive for alcohol problems during clinical evaluation at the primary care site in the USA, and fulfilled the inclusion criteria, were invited to participate in the trial. **Inclusion criteria:** Aged 60 or over and fulfilling the DSM-5 criteria for AUD (27). Because of an implementation error, DSM-IV criteria for dependence or abuse (28) was used at the site in the USA. However, all patients at the American site had at least two DSM-5 criteria for AUD and therefore met diagnostic criteria for DSM-5 AUD. **Exclusion criteria were:** (1) Seven or less correct answers (out of ten questions) in the informed consent comprehension quiz, indicating probable cognitive
impairment or failure to fully understand the implications of participating in the study. (2) Current psychotic symptoms. (3) Severe depression. (4) Manic episode in the three months prior to screening or a lifetime diagnosis of bipolar disorder. (5) Current suicidal thoughts/behaviour. (6) Use of illicit opioids and/or illicit stimulants (*all other forms of medication were allowed, including opioids if used as medically prescribed*). (7) Participation in other alcohol treatment programs in the 30 days prior to screening, except for treatment solely for detoxification. (8) Patients without decision-making capacity, e.g. with legally authorized representatives. Randomization was conducted centrally using an urn randomization procedure (also called an adaptive biased-coin randomization) stratified by site to ensure that treatments were distributed evenly across sites while still being random (29).

**Interventions**

**MET Treatment:** MET consisted of four manualized sessions (the first session could last up to 90 minutes, otherwise the sessions lasted approximately 60 minutes each), one per week, similar to the initial two phases of the Combined Behavioral Intervention (CBI) from Project COMBINE (30, 31). Treatment content consisted of motivational interviewing, functional analysis, involvement of a significant other in the last session, if possible, and the development of a personal change plan. The functional analysis was considered important since not only motivation but also the ability to recognize situations of risk was deemed essential to brief treatment for a clinical population. In this condition, the personal change plan focused exclusively on self-directed activities after the four sessions were completed.

**MET+CRA-S Treatment:** Following the first four sessions described above, up to eight additional one-hour weekly manualized sessions were selected by therapist and patient to implement the change plan. This was accomplished through a menu of five optional modules
addressing specific areas pertaining to AUD. Four of the CRA-S modules were based on the manual and procedures for CBI: 1) Coping with Craving; 2) Mood Management Training; 3) Building a Sober Network; and 4) Social and Recreational Counselling; but focus in the sessions, handouts, examples, etc. was geared to the senior population. Furthermore, and unique to CRA-S, a module focusing on coping with aging was developed. While some of the original modules already addressed ways to secure sober alternatives to drinking, this module, Coping with Aging, addressed older adults’ needs, challenges and attendant losses. The manuals for this study are available for download at webcitation.org: MET alone (32) and MET+CRA-S (33). Based on the first four sessions and the change plan, the additional number and type of modules in the extended treatment were chosen by the patient within the bounds of eight additional sessions. In summary, the interventions consisted of standardized modules with detailed descriptions of content and procedures, with the flexibility to allow the patient to choose the modules relevant to their problem profile.

*Therapist training and supervision*

The therapists delivered both the MET and the CRA-S sessions. The training program had two steps: First, a minimum of two therapists from each site participated in a “train the trainers” conference in Denmark before study start. At this 5-day conference, the therapists were introduced to the therapies and trained extensively. These trained therapists subsequently trained all other participating therapists locally at each site. Therapy sessions were audio-recorded. Local supervisors at each site, experienced in the treatment and in supervision, continuously reviewed sessions from each therapist and delivered feedback to ensure compliance with the treatment manuals. Ongoing supervision included biweekly Skype meetings between all local supervisors and the overarching supervisors on treatment
delivery in order to discuss delivery across sites and ensure adherence to the treatment manual.

Therapist adherence: A random sample of sessions (10%) was scored by independent coders using the methodology of MITI 4 (Motivational Interviewing Treatment Integrity), assessing both relational and technical aspects of Motivational Interviewing. 86% of the randomly drawn sessions met the threshold values for good or fair quality on all four benchmarks, as described in the MITI 4 manual (34). The inter-coder reliability on all measures in the MITI 4 was calculated by the Intra Class Correlation (ICC) using a two-way model, consistency of agreement, average-measure, and mixed effects (35). The average ICC was 0.78, which was deemed good (36).

Measures

Patients were assessed at screening, baseline, at the end of MET treatment (4 weeks after baseline), at the end of MET+CRA-S treatment (12 weeks after baseline), at 26 weeks after baseline (the time of primary outcome), and at 48 weeks after baseline. Screening included the Mini-International Neuropsychiatric Interview (M.I.N.I.) (version 5.0.0) (37) to assess inclusionary and exclusionary diagnoses of mental disorders. Two additional questions were added to module J (substance use disorders) to address craving as defined in the DSM-5 criteria for AUD (38). The American site ascertained DSM-IV abuse and dependence criteria, so craving was not assessed and abuse criteria were not recorded for individuals who met criteria for dependence, leading to a smaller range of the symptom count for the American site.

Baseline and follow-up assessments included alcohol consumption daily in the 90 days leading up to baseline and each follow-up point (Form 90) (39). Form 90 includes body weight. Blood Alcohol Content (BAC) was based on the self-reported consumption derived
from the Form 90 using the Widmark formula (40), which includes the weight of the patient, the amount alcohol consumed, and the amount of time during which alcohol was consumed. Further, severity of dependence (Alcohol Dependency Scale, ADS) (41) and quality of life (WHOQOL-BREF) (42) were collected, as well as, at baseline, information on sociodemographic characteristics.

**Outcomes of treatment**

*Primary outcome* was “treatment success”, defined as a Blood Alcohol Content (BAC) ≤ 0.05% at all times in the past 30 days, including total abstinence. Our a priori hypothesis was that at least 50% in the MET group would reach the success criterion and that at least 10% more would meet the success criterion in the MET+CRA-S group at 26 weeks after baseline.

*Secondary outcomes* included measurements of change in drinks per week, change in number of binge drinking days, and quality of life.

**Statistical Analysis**

The initial sample size was based on a one-sided comparison of two proportions with probabilities of success of 50% (MET) and 60% (MET+CRA-S), a significance level of 5% and a power of 90%. This resulted in a required sample size of 846. As we expected a 15% loss to follow-up, we originally planned to include 1,000 patients.

For descriptive statistics, we used one-way analysis of variance to compare quantitative variables at baseline across countries, and chi-square statistics to compare categorical variables. The primary analysis used a complete-case multiple logistic regression model to investigate the effect of treatment success. Adjustments for country, gender, age, education, marital status, ADS, and previous treatment history were made by including these as additional predictors in the model, in order to reduce residual variation and increase precision.
of the estimates (43). For the secondary outcomes, we used the multiple regression models with the same set of predictors, except that for each outcome, we included the corresponding baseline value. Visual inspection of the residual from each model was used to verify the normality assumption of the multiple linear regression models.

We investigated the potential impact of missing observations through three different approaches: First, we examined if any of the baseline predictors were associated with missingness at follow-up, and found no significant associations. Second, we imputed outcomes for the multiple logistic regression model that maximally favored either MET treatment or the MET+CRA-S treatment to consider two extreme missing data mechanisms. Third, we used multiple imputations based on controlled consumptions in the period before 26 weeks to impute the controlled consumption status at 26 weeks. Details of the multiple imputation procedure are presented in the supplementary material. The multiple imputation approach gave the same conclusion, and estimates that were not statistically different from the complete cases analysis results. Consequently, we based the multivariable analyses on completers and report the complete case results. Only for the two extreme imputation situations did we obtain different results, but we decided conservatively not to consider these extreme situations. Lastly, we present treatment success for completers in the two groups as well as the treatments’ success rates in the two groups, assuming all missing are treatment failures. Results are presented at country level, but as randomization was performed at site level, results at site level can be seen in the supplementary material.

Results:

Enrollment and Follow-up

Figure 1 summarizes the patient flow through the study. A total of n=899 were approached for participation and n=693 were included in the study, equivalent to 88%. Enrollment proved
to be much more difficult than anticipated. Due to time and financial constraints, enrollment for this project was stopped at n=693. This number still enabled the study to obtain a power of 84%, based on the described input parameters. The main reasons for exclusion of screened potential participants were failure to meet the inclusion criteria or unwillingness to participate. The distribution of patients was 341 (49.2%) from Denmark, 203 (29.3%) from Germany, and 149 (21.5%) from the USA. Of the 693 patients, 351 (50.6%) were randomized to MET treatment and 342 (49.4%) to MET+CRA-S treatment. At 26 weeks follow-up (the defined primary outcome point) data were available for 76.2% (ranging from 72.4% and 74.2% in Germany and Denmark, respectively, to 87.2% in USA). Overall, 81 (23.1%) in the MET group and 82 (24.0%) in the MET+CRA-S group were lost to follow-up or had incomplete follow-up data (Figure 1).

Sample Characteristics
The patients’ median age was 64.0 years (first and third quartile (Q1, Q3) 62.0, 68.0)), most patients were men (59.7%), had an education level equivalent to undergraduate (53.1%), and were retired (62.6%) (Table 1 and Table S1 in Supplement). Approximately half were living with a partner (46.9%). Across countries, some significant differences were found: German patients were in general older, more often female, had a higher level of education, and were more likely to be retired and living with a partner compared to Danish and American patients (Table 1).

Alcohol use disorder characteristics
The median age (Q1, Q3) at onset of AUD was 49.0 years (30.0, 59.0) (Table 1). The majority of patients had never received treatment for AUD before (56.1%). About half of the patients had severe AUD according to the DSM 5 criteria (54.9%), including the US subjects.
Nevertheless, most patients (72.0%) rated themselves as mildly alcohol dependent, equivalent to a score in the first quartile of the Alcohol Dependence Scale. In the 30 days prior to baseline, the median number (IQR) of drinking days was 21.0 (21.0), of which 12.0 (23.0) were binge-drinking days, and median of the average consumption was 52.0 (67.9) grams of pure alcohol per day, with 90.0 (79.4) grams per drinking day (Table 1). Danish patients had more severe AUD compared to the German patients. Danish patients also had more previous treatments for AUD than both American and especially German patients and consumed more alcohol per drinking day. A decline in alcohol consumption was detected during the 30 days immediately before baseline compared to the previous 30 days, e.g. day 60-31 before baseline (pre-baseline). This was primarily due to a decline in consumption among the Danish patients, in terms of amount consumed, number of drinking days, and number of binge drinking days.

_Treatment exposure_

Table 2 presents treatment exposure in the two groups, by country and site. Some differences in exposure were found. Across sites, treatment exposure in the MET alone group ranged from 68% to 95% participating in all four sessions, while exposure to all MET sessions in the MET+CRA-S group ranged from 79% to 96%. Overall, 83% of the MET group received all four sessions compared to 88% in the MET+CRA-S group. At all sites, some patients randomized to the additional CRA-S decided not to participate in any CRA-S sessions, ranging from 6% to 24%, overall 16%. 37% received all eight CRA-S sessions.
Definition of Treatment Outcome: MET Compared to MET + CRA-S

**Primary Outcome**

Among the 530 patients completing the 26-week interview, 132 (48.9%) in the MET group and 136 (52.5%) in the MET+CRA-S group had treatment success (BAC ≤ 0.05% including abstinence at all times in the 30 days prior to the interview (Table 3)). Assuming patients lost to follow-up or with incomplete follow-up were all treatment failures, 37.6% (MET, 132/351) and 39.8% (MET+CRA-S, 136/342) could be considered treatment successes. Whether treatment success meant controlled drinking or total abstinence varied between countries. Overall, 27.4% (74/270) reported total abstinence at week 26 in the MET group compared to 31.2% (81/260) in the MET+CRA-S group (Table 3).

Applying a multiple logistic regression model controlling for country, gender, age, cohabitant status, education, severity of AUD and number of previous treatments, did not show a significant difference in treatment success between MET and MET+CRA-S (odds ratio 1.22, 95% CI, 0.86 to 1.75, p = 0.26, Bayes factor=0.10 supporting the hypothesis of no effect) (Table 4). Increasing age was associated with increased probability of treatment success, and female gender was associated with lower probability compared to male gender (Table 4). All other variables in the model, including country, were not significantly associated with probability of treatment success. Since differences in treatment exposure were found across the sites in the different countries, site was added to the regression model, but this did not change the difference in outcome between MET and MET+CRA-S significantly, and no statistically significant differences were found between the sites (see Table S4 in Supplement). By fitting an additive binomial regression model, the adjusted difference in treatment effect was 0.06 (6 percentage points 95% CI -3.8 to 16.0) (data not shown).
Secondary Outcomes

Both MET and MET+CRA-S led to reductions in alcohol intake in terms of number of drinking days, number of binge drinking days, and amount of alcohol consumed per week when comparing pre-baseline (day 60 to 31 before baseline) to 26 weeks follow-up (Table 5). Patients in both treatment groups also increased their quality of life as measured by WHOQoL-Brief version. An increase was found in all four domains (physical, psychological, social, and environmental), although increases were small. No statistical differences in the level of change were found between the MET and MET+CRA-S groups, neither in alcohol consumption nor quality of life (Table 5).

Discussion:

Adding CRA-S to MET did not increase the probability of treatment success. 48.9% in the MET group and 52.5% in the CRA-S group met the success criterion of abstinence or controlled drinking at follow-up. The difference was not statistically significant in a multivariable model; the odds of treatment success increased 22% for MET+CRA-S compared to MET (odds ratio 1.22 95% CI, 0.86 to 1.75, p = 0.26). Our finding is consistent with a recent meta-analysis showing that more treatment does not necessarily lead to better outcomes (44). Similarly, a recent study on alcohol treatment in primary care did not find that more treatment improved outcome in a stepped-care design (45). Further, it has been reported that, despite longer treatment adherence among older adults, the 30 day abstinence rate was not significantly different from that of younger adults (16).

In the present study of older adults, the only predictors of treatment success were age and gender, with greater age and male gender associated with improved outcome. A systematic review from 2009 of predictors of treatment outcome for AUD in all age groups found five studies reporting better outcomes in older patients, and two studies that found better
outcomes in younger patients (46). Eight studies reported better outcomes in women, and only one study better outcomes in men. Given that our sample is limited to patients age 60 and older, it is possible that the moderating effects of age and gender are not the same as in the rest of the patient population.

Drinking days and binge drinking days decreased in both treatment groups, approximately 7 and 8 days, respectively, in the MET group and 9 and 10 days in the MET-CRA-S group. Quality of life improved slightly in both groups. Although these findings are encouraging, the study design does not allow us to determine how much of this improvement is related to the specific treatments delivered in the study vs. the non-specific effects of deciding to participate in a study and receiving attention and assessment in the course of it.

A difference in follow-up rates between countries was found. This is to be expected in a multi-site study but may have impacted the findings. However, no changes in main results were found in the multivariable analysis when imputing missing data. The treatment exposure was fairly high for MET treatment in both groups, but the exposure to CRA-S was lower, as 16% did not receive any CRA-S sessions, and only 37% received all 8 CRA-S sessions. This diminishes the contrast between the groups and may at least partly explain why we found no difference in treatment success between the groups. The relative lower exposure to MET+CRA-S could indicate less acceptance of longer treatment. On the other hand, termination of CRA-S treatment could in some cases also be because the patient felt that he or she had achieved the goal set at start of treatment, or an example of the good-enough level model, e.g. individual treatment response, including individual outcome trajectory (47). It should be noted that the cited study on individual trajectories was based on a broad segment of participants, with ages ranging from 12 to 86 years and so not specifically on older adults (47).
Limitations

A main limitation of this study is the lack of a control group. Traditionally, a clinical trial would include a “treatment as usual (TAU)” or a “placebo” group. However, the present study was conducted simultaneously in three countries with different treatment cultures and traditions; therefore, a general or common ecologically valid TAU could not be constructed. Thus, because of the study design, our findings do not provide a measure of the effect of either intervention vs. no treatment or TAU. Further, the study was not powered to examine differences between participating countries; all main analyses were only adjusted for country and site.

We had to terminate enrollment before reaching the a priori target of 846 evaluable patients, thus not achieving the power calculated above. However, the difference found between MET and MET+CRA-S of 3.4% (52.3% vs 48.9%) is far from the 10% point we deemed clinically relevant. Thus, the main finding would likely not have changed substantially had the study reached the recruitment target.

Conclusions:

To summarize, we found no evidence that the 12-week MET+CRA-S treatment was associated with greater improvement in terms of drinking behavior than a 4-week MET treatment alone in seniors with DSM-5 AUD, and the two treatments showed comparable small improvements in quality of life.
References


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Table 1. Characteristics of patients: Sociodemographics, severity of Alcohol Use Disorder, age of onset, previous treatments, and actual consumption before baseline

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<td>42 (28.2)</td>
<td>48 (23.6)</td>
<td>142 (20.5)</td>
<td></td>
</tr>
<tr>
<td>Unemployed, n (%)</td>
<td>37 (10.9)</td>
<td>18 (12.1)</td>
<td>5 (2.5)</td>
<td>60 (8.7)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Retired, n (%)</td>
<td>214 (62.8)</td>
<td>75 (50.3)</td>
<td>145 (71.4)</td>
<td>434 (62.6)</td>
<td></td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>38 (11.1)</td>
<td>14 (9.4)</td>
<td>5 (2.5)</td>
<td>57 (8.2)</td>
<td></td>
</tr>
<tr>
<td>Living with partner</td>
<td></td>
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</tr>
<tr>
<td>Yes, n (%)</td>
<td>152 (44.6)</td>
<td>58 (38.9)</td>
<td>115 (56.7)</td>
<td>325 (46.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>AUD, DSM 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild, n (%)</td>
<td>22 (7.0)</td>
<td>2 (1.3)</td>
<td>59 (29.2)</td>
<td>81 (15.7)**</td>
<td></td>
</tr>
<tr>
<td>Moderate, n (%)</td>
<td>60 (19.2)</td>
<td>147 (98.7)*</td>
<td>77 (38.1)</td>
<td>1377 (26.6)**</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Severe, n (%)</td>
<td>231 (73.8)</td>
<td></td>
<td>66 (32.7)</td>
<td>297 (57.7)**</td>
<td></td>
</tr>
<tr>
<td>Missing, n</td>
<td>28</td>
<td>0</td>
<td>1</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Alcohol dependence***</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or mild, n (%)</td>
<td>216 (63.9)</td>
<td>89 (59.7)</td>
<td>192 (94.6)</td>
<td>497 (72.0)</td>
<td></td>
</tr>
<tr>
<td>Moderate, n (%)</td>
<td>97 (28.7)</td>
<td>47 (31.5)</td>
<td>11 (5.4)</td>
<td>155 (22.5)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Severe, n (%)</td>
<td>25 (7.4)</td>
<td>13 (8.7)</td>
<td>0 (0.0)</td>
<td>38 (5.5)</td>
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</tr>
<tr>
<td>Missing, n</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
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<tr>
<td>Age at onset of AUD</td>
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<tr>
<td>Median (Q1, Q3)</td>
<td>47.0 (35.0, 58.0)</td>
<td>42.0 (20.0, 58.0)</td>
<td>50.0 (30.0, 60.0)</td>
<td>49.0 (30.0, 59.0)</td>
<td>0.08</td>
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<tr>
<td>Missing, n</td>
<td>80</td>
<td>72</td>
<td>28</td>
<td>180</td>
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<td>Previous treatment episodes for AUD</td>
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<td></td>
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<tr>
<td>0, n (%)</td>
<td>130 (38.1)</td>
<td>94 (63.1)</td>
<td>165 (81.3)</td>
<td>389 (56.1)</td>
<td></td>
</tr>
<tr>
<td>1-2, n (%)</td>
<td>129 (37.8)</td>
<td>40 (26.8)</td>
<td>28 (13.8)</td>
<td>197 (28.4)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>3+, n (%)</td>
<td>82 (24.0)</td>
<td>15 (10.1)</td>
<td>10 (4.9)</td>
<td>107 (15.4)</td>
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<tr>
<td>Alcohol consumption day 30 to 1 before baseline</td>
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</tr>
<tr>
<td>Average consumption (grams/day)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>47.0 (16.1, 89.8)</td>
<td>59.5 (31.6, 87.3)</td>
<td>54.4 (30.9, 96.0)</td>
<td>52.0 (22.6, 90.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>Average consumption (grams/drinking day)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>108.8 (71.5, 166.9)</td>
<td>77.6 (59.4, 138.4)</td>
<td>73.3 (53.5, 105.3)</td>
<td>90.0 (60.6, 140.0)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Drinking days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>15.0 (5.0, 24.0)</td>
<td>26.0 (16.0, 30.0)</td>
<td>27.0 (17.0, 30.0)</td>
<td>21.0 (9.0, 30.0)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Average consumption (grams/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>75.2 (29.0, 132.0)</td>
<td>60.7 (34.6, 89.6)</td>
<td>58.3 (35.0, 98.2)</td>
<td>65.8 (33.5, 113.6)</td>
<td>0.02</td>
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<tr>
<td>Alcohol consumption day 60 to 31 before baseline</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average consumption (grams/ day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Average consumption (grams/drinking day)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

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<table>
<thead>
<tr>
<th></th>
<th>Median (Q1, Q3)</th>
<th>Missing, n</th>
<th>Median (Q1, Q3)</th>
<th>Missing, n</th>
<th>Median (Q1, Q3)</th>
<th>Missing, n</th>
<th>Median (Q1, Q3)</th>
<th>Missing, n</th>
<th>Median (Q1, Q3)</th>
<th>Missing, n</th>
<th>Median (Q1, Q3)</th>
<th>Missing, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drinking days</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>109.8 (72.0, 168.0)</td>
<td>43</td>
<td>78.1 (60.9, 140.0)</td>
<td>4</td>
<td>75.0 (54.0, 113.8)</td>
<td>6</td>
<td>93.9 (62.9, 144.0)</td>
<td>53</td>
<td>&lt; 0.0001</td>
<td></td>
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<tr>
<td>Missing, n</td>
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<tr>
<td>Binge drinking days</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>26.0 (12.2, 30.0)</td>
<td>7</td>
<td>27.0 (16.0, 30.0)</td>
<td>0</td>
<td>28.0 (16.0, 30.0)</td>
<td>2</td>
<td>27.0 (15.0, 30.0)</td>
<td>9</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing, n</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>19.0 (4.0, 30.0)</td>
<td>7</td>
<td>16.0 (4.0, 16.0)</td>
<td>0</td>
<td>18.0 (3.0, 30.0)</td>
<td>2</td>
<td>18.0 (4.0, 30.0)</td>
<td>9</td>
<td>0.40</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*The USA site diagnosed according to DSM IV, therefore the American patients could not be assessed in more detail than of having at least moderate severity according to DSM-5.

**Based on Danish and German data as the American data were excluded from this analysis.

***Based on the four quartiles in ADS(41), None/mild (1. Quartile), Moderate (2. Quartile), severe (3. and 4. Quartile)
Table 2. Treatment exposure at the different sites in the study

<table>
<thead>
<tr>
<th></th>
<th>Denmark</th>
<th>Germany</th>
<th>USA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Copenhagen</td>
<td>Odense</td>
<td>Aarhus</td>
<td>Munich</td>
</tr>
<tr>
<td>N</td>
<td>136</td>
<td>107</td>
<td>98</td>
<td>121</td>
</tr>
<tr>
<td>MET, n</td>
<td>66</td>
<td>53</td>
<td>49</td>
<td>63</td>
</tr>
<tr>
<td>MET+CRA-S, n</td>
<td>70</td>
<td>54</td>
<td>49</td>
<td>58</td>
</tr>
</tbody>
</table>

| MET sessions in MET  |                      |         |        |        |         |             |
| 0 MET session, n (%) | 1 (2)               | 2 (4)   | 0 (0)  | 1 (2)  | 2 (5)   | 2 (3)       | 8 (2)  |
| 1-3 MET session, n (%) | 2 (3)  | 15 (28) | 3 (6)  | 9 (14) | 1 (2)   | 21 (27)     | 51 (15) |
| 4 MET session, n (%) | 63 (95) | 36 (68) | 46 (94) | 53 (84) | 38 (93) | 56 (71)     | 292 (83) |

| MET sessions in MET+CRA-S |                      |         |        |        |         |             |
| 0 MET session, n (%) | 4 (6)               | 3 (6)   | 0 (0)  | 2 (3)  | 1 (2)   | 4 (6)       | 14 (4)  |
| 1-3 MET session, n (%) | 1 (1)               | 7 (13)  | 2 (4)  | 3 (5)  | 3 (7)   | 11 (16)     | 27 (8)  |
| 4 MET session, n (%) | 65 (93) | 44 (81) | 47 (96) | 53 (91) | 37 (90) | 55 (79)     | 301 (88) |

| CRA sessions in MET+CRA-S |                      |         |        |        |         |             |
| 0 CRA-S sessions, n (%) | 8 (11)              | 12 (22) | 3 (6)  | 8 (14) | 5 (12)  | 17 (24)     | 53 (15) |
| 1-2 CRA-S sessions, n (%) | 8 (11)  | 3 (6)   | 10 (20) | 4 (7)  | 2 (5)   | 7 (10)      | 34 (10) |
| 3-7 CRA-S sessions, n (%) | 24 (34) | 18 (33) | 36 (73) | 16 (28) | 20 (49) | 16 (23)     | 130 (38) |
| 8 CRA-S sessions, n (%) | 30 (43)  | 21 (39) | 0 (0)  | 30 (52) | 14 (34) | 30 (43)     | 125 (37) |

MET: Motivational Enhancement Therapy
CRA-S: Community Reinforcement Approach for Seniors
Table 3. Treatment success at different points in time after baseline. Treatment success defined as a Blood Alcohol Content (BAC) of ≤ 0.05% at all times in the past 30 days at each assessment. Total abstinence is also presented at each follow-up. Data from completers are presented. In bold: primary outcome.

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>MET</th>
<th>MET+CRA-S</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Denmark</td>
<td>USA</td>
</tr>
<tr>
<td>4 weeks, End of MET treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment success, n (%)</td>
<td>93 (61.2%)</td>
<td>24 (33.3%)</td>
</tr>
<tr>
<td>Abstinent, n (% of treatment success)</td>
<td>68 (73.1%)</td>
<td>7 (29.2%)</td>
</tr>
<tr>
<td>12 weeks, End of MET+CRA treatment</td>
<td>n = 140</td>
<td>n = 72</td>
</tr>
<tr>
<td>Treatment success, n (%)</td>
<td>77 (55.0%)</td>
<td>26 (36.1%)</td>
</tr>
<tr>
<td>Abstinent, n (% of treatment success)</td>
<td>53 (68.8%)</td>
<td>11 (42.3%)</td>
</tr>
<tr>
<td>26 weeks, primary outcome</td>
<td>n = 125</td>
<td>n = 69</td>
</tr>
<tr>
<td>Treatment success, n (%)</td>
<td>67 (53.6%)</td>
<td>31 (44.9%)</td>
</tr>
<tr>
<td>Abstinent, n (% of treatment success)</td>
<td>45 (67.2%)</td>
<td>12 (38.7%)</td>
</tr>
<tr>
<td>48 weeks</td>
<td>n = 110</td>
<td>n = 25</td>
</tr>
<tr>
<td>Treatment success, n (%)</td>
<td>59 (53.6%)</td>
<td>5 (31.2%)</td>
</tr>
<tr>
<td>Abstinent, n (% of treatment success)</td>
<td>40 (67.8%)</td>
<td>3 (60.0%)</td>
</tr>
</tbody>
</table>

MET: Motivational Enhancement Therapy, CRA-S: Community Reinforcement Approach for Seniors. n represents the maximum number of individuals available at a given time.
Table 4. Treatment success of MET+CRA-S compared to MET at 26 weeks. Treatment success defined as at least controlled intake (a Blood Alcohol Content (BAC) ≤ 0.05% at all times in the 30 days before assessment) or total abstinence.

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MET+CRA-S</td>
<td>1.22</td>
<td>0.86-1.75</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Variables included in the model:
- Country, Denmark = ref
  - Germany: 0.97, 0.59-1.58, 0.89
  - USA: 1.08, 0.68-1.70, 0.75
- Gender, male = ref
  - Female: 0.57, 0.39-0.83, 0.004
- Age, 60 years = ref
  - Age*: 1.07, 1.03-1.12, 0.001
- Living with partner, no = ref
  - Yes: 1.25, 0.87-1.81, 0.23
- Education, no degree = ref
  - Undergraduate: 1.05, 0.67-1.65, 0.82
  - Graduate/post graduate: 0.64, 0.36-1.12, 0.12
- Alcohol dependence**, none/mild = ref
  - Moderate: 0.93, 0.59-1.45, 0.74
  - Severe: 0.76, 0.34-1.69, 0.50
- Previous treatments for AUD, 0 = ref
  - 1-2: 1.30, 0.85-2.01, 0.22
  - 3+: 1.34, 0.73-2.46, 0.34

MET: Motivational Enhancement Therapy, CRA-S: Community Reinforcement Approach for Seniors, AUD: Alcohol Use Disorder
*OR refers to the risk per year after the age of 60
**Based on the four quartiles in ADS(41), None/mild (1. Quartile), Moderate (2. Quartile), severe (3. and 4. Quartiles)
Table 5. Change in secondary outcome between baseline and time of primary outcome (26 weeks follow-up).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MET Baseline</th>
<th>MET 26 weeks</th>
<th>Change</th>
<th>MET+CRA-S Baseline</th>
<th>MET+CRA-S 26 weeks</th>
<th>Change</th>
<th>Adjusted effect</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of drinking days, mean</td>
<td>20.9</td>
<td>13.7</td>
<td>-7.2</td>
<td>22.3</td>
<td>13.3</td>
<td>-9.0</td>
<td>-0.6</td>
<td>-2.5 – 1.3</td>
</tr>
<tr>
<td>Number of binge drinking days, mean</td>
<td>16.1</td>
<td>7.7</td>
<td>-8.4</td>
<td>18.1</td>
<td>7.6</td>
<td>-10.5</td>
<td>-0.7</td>
<td>-2.5 – 1.0</td>
</tr>
<tr>
<td>Average drinks per week</td>
<td>44.3</td>
<td>19.7</td>
<td>24.6</td>
<td>47.4</td>
<td>19.1</td>
<td>-28.3</td>
<td>-0.9</td>
<td>-4.7 – 2.8</td>
</tr>
<tr>
<td>WHOQOL</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical domain</td>
<td>12.9</td>
<td>13.3</td>
<td>0.4</td>
<td>12.7</td>
<td>13.2</td>
<td>0.4</td>
<td>-0.09</td>
<td>-0.3 – 0.2</td>
</tr>
<tr>
<td>Psychosocial domain</td>
<td>13.3</td>
<td>13.8</td>
<td>0.4</td>
<td>13.0</td>
<td>13.6</td>
<td>0.6</td>
<td>0.07</td>
<td>-0.2 – 0.3</td>
</tr>
<tr>
<td>Social domain</td>
<td>14.1</td>
<td>14.8</td>
<td>0.7</td>
<td>13.8</td>
<td>14.6</td>
<td>0.8</td>
<td>-0.01</td>
<td>-0.4 – 0.4</td>
</tr>
<tr>
<td>Environment domain</td>
<td>16.7</td>
<td>17.0</td>
<td>0.3</td>
<td>16.5</td>
<td>16.8</td>
<td>0.3</td>
<td>-0.07</td>
<td>-0.3 – 0.2</td>
</tr>
</tbody>
</table>

MET: Motivational Enhancement Therapy
CRA-S: Community Reinforcement Approach for Seniors
WHOQOL: The World Health Organization’s WHOQOL-BREF (42). Each domain consists of a series of questions that are rated on a Likert interval scale from 1 (very poor) to 5 (very good). The sum in each domain is calculated for each participant and the mean is presented in the table.

*Adjusted effect shows the adjusted change of each outcome when comparing MET+CRA-S to MET (reference); for example, the number of drinking days was reduced by 0.6 days for MET+CRA-S compared to MET only, and not statistically significant (95% CI -2.5 – 1.3).

All confidence intervals show that the differences found between the two treatments were not statistically significant.
Figure 1. Participant Flow for patients randomized to Motivational Enhancement Therapy (MET) and MET followed by Community Reinforcement Approach for Seniors (CRA-S)

899 Assessed for eligibility
- 194 Excluded
  - 115 Not meeting inclusion criteria
  - 75 Declined to participate
  - 4 Other reasons

705 Enrolled
- 12 Excluded by data cleaning as they failed to meet inclusion criteria

693 Randomized

351 Allocated to MET
- 310 Complete follow-ups at 4 weeks
  - 10 Incomplete follow-ups
  - 31 Lost to follow-up
- 291 Complete follow-ups at 12 weeks
  - 13 Incomplete follow-ups
  - 47 Lost to follow-up
- 270 Complete follow-ups at 26 weeks
  - 11 Incomplete follow-ups
  - 70 Lost to follow-up
- 258 Complete follow-ups at 48 weeks
  - 70 Incomplete follow-ups
  - 23 Lost to follow-up

342 Allocated to MET+CRA-S
- 305 Complete follow-ups at 4 weeks
  - 13 Incomplete follow-ups
  - 24 Lost to follow-up
- 275 Complete follow-ups at 12 weeks
  - 23 Incomplete follow-ups
  - 44 Lost to follow-up
- 260 Complete follow-ups at 26 weeks
  - 3 Incomplete follow-ups
  - 79 Lost to follow-up
- 250 Complete follow-ups at 48 weeks
  - 79 Incomplete follow-ups
  - 13 Lost to follow-up