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Running Head: TWO YEAR FOLLOW-UP OF THE MOSAIC TRIAL

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Abstract:

Objective: This study reports follow-up data from a multi-centre randomized controlled trial (n=142) comparing the Maudsley Model of Anorexia Nervosa Treatment for Adults (MANTRA) with Specialist Supportive Clinical Management (SSCM) in outpatients with broadly defined anorexia nervosa (AN). At 12 months post-randomization, all patients had statistically significant improvements in body mass index (BMI), eating disorder (ED) symptomatology and other outcomes with no differences between groups. MANTRA was more acceptable to patients. The present study assessed whether gains were maintained at 24 months post-randomization.

Methods: Follow-up data at 24 months were obtained from 73.2% of participants. Outcome measures included BMI, ED symptomatology, distress, impairment, and additional service utilization during the study period. Outcomes were analyzed using linear mixed models.

Results: There were few differences between groups. In both treatment groups, improvements in BMI, ED symptomatology, distress levels and clinical impairment were maintained or increased further. Estimated mean BMI change from baseline to 24 months was 2.16kg/m^2 for SSCM and 2.25kg/m^2 for MANTRA (effect sizes of 1.75 and 1.83 respectively). Most participants (83%) did not require any additional intensive treatments (e.g. hospitalization). Two SSCM patients became overweight through binge-eating.

Discussion: Both treatments have value as outpatient interventions for patients with AN.

Two Year Follow-Up of the MOSAIC Trial: a Multi-Centre Randomised Controlled Trial Comparing Two Psychological Treatments in Adult Outpatients with Broadly Defined Anorexia Nervosa

Until recently, only a handful of small-scale underpowered randomized controlled trials (RCTs) had been conducted in adults with AN[1]. Latterly, high quality studies[2] and large-scale trials[3] testing different outpatient treatments have emerged. Nonetheless, a recent systematic review on outpatient treatments for adults and older adolescents with AN concluded that so far, when comparing individual psychological therapies with each other, no specific treatment was consistently superior to any other specific approach[4]. The review recommended that larger RCTs of longer treatment duration and follow-up are needed.

We recently published a large multi-centre trial[5,6] (Maudsley Outpatient Study of Treatments for Anorexia Nervosa and Related Conditions; MOSAIC) comparing two outpatient treatments for adults with AN: one was the Maudsley Model of AN Treatment for Adults (MANTRA)[7-11], the other Specialist Supportive Clinical Management (SSCM)[12,13]. Both treatments resulted in statistically significant improvements in body mass index (BMI) (with large within-group effect sizes at 12 months) and reductions in ED symptomatology, other psychopathology and clinical impairment over time, but with no statistically significant difference between groups at either 6 months or 12 months post-randomization. Improvements in neuro- and social-cognitive measures were less consistent. One SSCM patient died during treatment. Compared to SSCM, MANTRA patients rated their treatment as statistically significantly more acceptable and credible at 12 months. There was no difference between groups in additional service consumption. In the subgroup of participants who were more severely ill at baseline (i.e. had a BMI of below 17.5 kg/m^2) MANTRA appeared to have a non-significant advantage both at 6 and 12 months in terms of greater increases in BMI.

However, evidence from the first trial that used SSCM[14] suggests that the effects of SSCM, i.e. the comparison treatment used here, may diminish over time, making the need for longer-term follow-up particularly pressing. In addition, MANTRA is a new treatment where longer-term outcomes are not

known. The aim of the present study therefore was to assess the longer-term outcomes (24 months post-randomization) of both treatments.

METHODS:

This is a 24-month follow-up study of a multi-centre two-arm superiority trial (the MOSAIC trial), which evaluates the efficacy, cost and cost-effectiveness of MANTRA versus SSCM in adult outpatients with AN. Full details of the trial protocol can be found elsewhere[5]. The main hypothesis of the follow-up study was in line with that of the main study, i.e. MANTRA will be superior to SSCM in producing greater weight gain and greater improvement in eating-disorder related and other psychopathology in adults with broadly defined AN at 24-month follow-up.

Details on participants, study procedures, assessments, sample size calculations, trial interventions and statistical analyses can be found in the online appendix.

RESULTS

The following measures were prioritised for follow-up analysis at 24 months: BMI, weight, Eating Disorders Examination[18,19] (EDE; Global and Restraint, Eating concern, Shape Concern, and Weight Concern subscales), Depression Anxiety and Distress Scale-21[20] (DASS), Obsessive Compulsive Inventory-Revised[21] (OCI-R), and Clinical Impairment Assessment[22] (CIA).

Participant Flow and Baseline Characteristics:

The baseline data can be found in our main paper[6]. The CONSORT diagram of the study is presented here (Figure 1). A total of 104/142 participants (73.2%) provided primary outcome data at 24 months, 79.2% (57/72) in the MANTRA group and 67.1% (47/70) in the SSCM group. This difference was not statistically significant (p=0.105). Of the 38 patients with missing data, 11 had actively withdrawn from participation, one patient had died, and the remainder were lost to follow-up. All 142 initially randomized participants were included in the ITT analysis.

<u>Treatment Outcomes:</u>

No baseline variables were found to be predictive of later missingness. As in our main paper[6], only non-completion of treatment was predictive of loss to follow-up at 24 months: 54.75% of non-completing participants compared to 13.68% of completers had missing primary outcome data at 24-month follow-up (p<0.001).

Table 1 shows estimated group differences at 24 months and the corresponding estimated means, standard errors and effect sizes, accounting for the fact that treatment adherence predicts missingness (using multiple imputation) and allowing for therapist effects.

Mean BMI (primary outcome) did not differ significantly between groups at 24 months (p=0.85) and the between group effect size was small (standardized coefficient 0.08). Figure 2 shows predicted mean BMI at all three post-randomization time points (originating from the observed mean at baseline). On inspection of the data it became clear that the SSCM mean had been driven up by two patients with BMIs of 25 and 29 kg/m^2, in both cases through binge eating. We re-ran the BMI analysis removing the two outliers. The predicted mean outcome for MANTRA was 18.73 (SE 0.39) and for SSCM was 18.33 (SE 0.39) kg/m^2 (p=0.38). (Note: Outcomes in both groups are slightly different from before as the multiple imputation data sets were different, as the observations from the outliers couldn't be used to help impute missing data.) The estimated mean outcome change from baseline to 24 months was 2.11 kg/m^2 for MANTRA (p<0.001) and for SSCM was 1.73 kg/m^2 (p<0.001).

Mean EDE Global score also did not differ significantly between groups at 24 months (p=0.97). Nor did most of the other secondary outcomes with the exception of the OCI-R where there was a statistically significant difference between groups, favoring SSCM. Associated standardized between group effect sizes were small to moderate (Cohen's d≤0.36).

Table 2 shows estimated mean outcome change and associated within-group effect sizes from baseline to 24 months by group. There was a statistically significant improvement in BMI in both groups after commencing treatment, with mean BMI in the MANTRA group estimated to increase from baseline to month 24 by 2.25 (95% CI 1.42 to 3.09). Respective figures in SSCM were 2.16 (95% CI 1.34 to 2.98). In both groups, there was also statistically significant change between baseline and 24 months for EDE Global and most EDE subscale scores (with the exception of Eating Concern), DASS, OCI-R and CIA scores. Associated effect sizes were either very large to large (BMI, EDE global score, DASS and CIA) or medium (EDE: weight, shape and restraint scores, OCI-R).

Recovery Rates

Our definitions of recovery and partial recovery were based on those previously used in other studies[2] and were as follows: recovered: BMI>18.5 kg/m^2 and EDE Global Score <2.77; partially recovered: BMI$\leq$17.5 kg/m^2 and EDE$\leq$2.77 or BMI between >17.5 kg/m^2 and $\leq$18.5 kg/m^2 or BMI>18.5 kg/m^2 and EDE>2.77; not recovered: BMI$\leq$17.5 kg/m^2 and EDE>2.77. Recovery rates by group at 24 months were calculated in two ways. Firstly, as proportions of actually available data (n=102 participants; MANTRA, n=56; SSCM, n=46) and secondly with the full baseline number (n=142) of participants as the denominator (ITT sample).

Proportions calculated based on available data were as follows: In MANTRA 18/56 (32.15%) were fully recovered, 32/56 (57.15%) partially recovered and 6/56 (10.7%) not recovered. In SSCM 13/46 (28.3 %) were fully recovered, 26/46 (56.5%) were partially recovered and 7/46 (15.2%) not recovered.

When proportions were calculated based on ITT data they were as follows: In MANTRA 18/72 (25%) were fully recovered, 32/72 (44.4%) were partially recovered, 6/72 (8.3%) were not recovered and 16/72 (19.4%) were missing. In SSCM 13/70 (18.6 %) were fully recovered, 26/70 (37.1%) were partially recovered, 7/70 (10%) not recovered and 24/70 (34.3%) were missing.

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Subgroup analyses

Two subgroup analyses were conducted. Firstly, the sample was restricted to those with baseline BMI below 17.5 kg/m^2 (MANTRA: n=56; SSCM: n=49) because our two previous studies[6,11] suggested that MANTRA may be advantageous in more underweight patients. The cut-off of a BMI below 17.5 was chosen as it is part of the ICD-10 criteria[33] for AN and also for comparability with other studies[2]. At 24 months, in this more severe group, the BMI difference was 0.45 kg/m^2 (p=0.43, 95% CI -0.154 to 0.65) in favor of MANTRA. The predicted BMI changes were 2.48 kg/m^2 and 2.04 kg/m^2 for those in the MANTRA and SSCM groups respectively.

Secondly, to evaluate the effect of treatment receipt, another subgroup analysis included only treatment completers (MANTRA: n=54, SSCM: n=41). In the completers the BMI difference at 24 months was 0.38 kg/m^2 (p=0.42, 95% CI -1.3 to 0.54) in favor of MANTRA.

Additional Service Utilization

A full cost-effectiveness analysis will be presented elsewhere. We consider here only intensive (i.e. hospital-based) treatments, such as in-patient admissions for the ED or for psychiatric comorbidities or day-care/home treatments, as these are the biggest cost drivers. During the whole 24 month period, 24 patients (16.9%; 12 in each treatment group) had additional intensive treatment. Of these, 17 patients had ED treatment (8 MANTRA, 9 SSCM) and 7 others only received psychiatric treatment (4 MANTRA, 3 SSCM). Days of treatment ranged from 3 to 366. In the MANTRA treatment group, between baseline and 12 months, eight patients had additional psychiatric treatment; three of these also had additional treatment during months 13 to 24. Four additional MANTRA patients had intensive treatment during year 2 (month 13 to 24) only. In SSCM, between baseline and 12 months ten patients had additional psychiatric treatment, five of these also needed additional treatment between 13 and 24 months. Two additional patients needed intensive treatment during year two (13 to 24 months). There were no statistically significant differences between treatment groups in numbers of people receiving intensive treatment or in mean number of additional treatment days.

DISCUSSION

Our hypothesis that MANTRA would be superior to SSCM at 24 months in terms of clinical outcomes was not confirmed. In both groups, however, improvements made at 12 months in terms of BMI, ED symptoms and secondary outcomes were either maintained or increased further by 24 months. Estimated mean BMI change from baseline to 24 months was 2.16 kg/m^2 for SSCM and 2.25 kg/m^2 for MANTRA patients, with associated effect sizes of 1.75 and 1.83 respectively. There were no overall group differences in outcomes, except on the OCI-R where there were greater improvements in the SSCM group.

Importantly, in SSCM there was no suggestion that improvements diminish over time. The previous study in which SSCM's effects seemed to diminish over time was much smaller, but the follow-up period was longer, with only 12 patients assessed at the 5-year follow-up[14].

Full recovery rates in both treatments were modest, at 25% to 32.2% for MANTRA and 18.6% to 28.3% for SSCM, depending on which denominator was used. Perhaps these modest recovery rates are not surprising given that our study included patients with very low baseline BMIs, provided they were medically stable. The lowest BMI at baseline was 13.4 kg/m^2. Our definition of recovery is potentially limited by the fact that people up to BMI 18.5 kg/m^{2}were included in the trial and that having a BMI above 18.5 kg/m^2 together with a normal EDE global score was counted as fully recovered. Theoretically, this leaves open the possibility that people could be counted as being recovered despite having minimal weight gain only. However, this was not the case: We checked the 13 patients who had a BMI between 18.5 and 19.0 kg/m^2 at two-year follow-up, i.e. those who were candidates for having recovered with minimal weight gain. They had a mean BMI increase of 2.14 ($\pm$ 0.76) kg/m^2. The BMI increase in this group from baseline to 24 months ranged from 1.07 to 3.65 kg/m^2.

Across both groups, most participants (83%) did not need any additional intensive treatment, such as in-patient or day-care treatment for their eating disorder or other psychiatric in-patient care. This is an important finding, as in-patient and day-care treatments are the main cost-drivers in the treatment of AN.

Subgroup analyses of more severely ill patients and of treatment completers continued to show a non-significant trend favoring MANTRA.

Whilst for most patients outpatient treatment was a safe and beneficial treatment option, there were also some harms noted. As previously reported, there was one death in the SSCM group and, also in SSCM, two patients became overweight through binge eating. The latter deserves comment, as uncontrollable weight gain is what AN patients themselves fear most. It is possible that SSCM patients may not have been as well equipped as MANTRA patients in dealing with urges to binge, due to this treatment's lack of emphasis on teaching skills beyond regular eating. However, the numbers are too small to reach any firm conclusions here.

Our findings can most readily be compared against those from two other recent studies - one is the Oxford case series of enhanced CBT (CBT-E; n=50) by Fairburn et al.[2], the other the ANTOP study (n=242)[3] from Germany, where patients received either focal psychodynamic therapy, CBT-E or optimized treatment as usual. In both studies, patients had a broadly similar average illness severity to ours at baseline, in terms of their BMI (Fairburn et al.[2]: 16.5 kg/m^2; ANTOP study[3]: 16.7 kg/m^2. Having said that there were important differences between these studies in terms of illness duration, with the Fairburn study[2] having a much shorter illness duration (mean 3 years) compared to the ANTOP study[3] and the MOSAIC trial[6] where the illness duration was around 7 years. Moreover, the inclusion criteria of these studies were quite different, with the Fairburn study[2] including patients with a BMI between 15 and 17.5 kg/m^2 and the ANTOP study[3] including patients with a BMI between 15 and 18.5 kg/m^2, whereas in the MOSAIC trial more severely underweight patients were included, too. Follow-up assessment in the Fairburn study[2] was conducted at 23 months and in the ANTOP study[3] at

22 months. In the Fairburn study[2], mean BMI change from baseline to follow-up was $1.7kg/m^2$, whereas in the ANTOP study[3] this was 1.64, 1.30, and $1.22 kg/m^2$ respectively for focal psychodynamic psychotherapy, CBT-E, and optimized treatment as usual. In our study, the BMI change was $2.25 kg/m^2$ for MANTRA and $2.16 kg/m^2$ for SSCM at 24 months. If one only looks at the MOSAIC sub-group with initial BMI below $17.5 kg/m^2$ (for easier comparison with the Fairburn study[2]), BMI change from baseline to 24 months is 2.5 and $2.0 kg/m^2$ for MANTRA and SSCM. Thus, compared to best available recent other studies our BMI outcomes at 24 months are excellent.

In our trial the dose of treatment was more modest and tailored to the illness severity of patients compared to these other two studies[2,3], where 40 sessions of treatment were routinely offered. However, this did not translate into greater need for hospitalization in our study compared to the ANTOP study where in focal psychodynamic therapy 19% of the patients required inpatient treatment, in CBT-E 29%, and in TAU-O 40%. In the Fairburn study[2], additional intensive treatment was needed in 13/50 (22.6%) of cases.

As previously reported, MANTRA was assessed as statistically significantly more acceptable and credible by patients at 12 months[6] and there were higher treatment completion rates and higher research assessment completion rates up to 24 months. Overall outcomes in both treatments were similar, and at least comparable to those of other recent trials, but MANTRA may have advantages for those with a more severe illness. Finally, a small number of SSCM patients experienced harms, whereas no harms were noted in MANTRA. In conclusion, both MANTRA and SSCM can be recommended as outpatient treatments for adults with AN.

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Figure 1. CONSORT flow diagram

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Figure 2. Predicted mean BMI at all three post-randomization time points (originating from observed mean at baseline). Covariates were fixed at mean baseline level of BMI (16.69), restrictive AN and no previous hospital admissions.

Online Appendix

Participants:

All available participants of the MOSAIC trial were contacted for participation in the follow-up study. Participants in this trial initially were recruited from consecutive new referrals to the outpatient services of four specialist UK Eating Disorders Services in London and Oxford, namely the South London and Maudsley National Health Service (NHS) Foundation Trust Specialist Eating Disorders Unit (n=84), the North East London Foundation Trust Eating Disorders Service (n=10), the Barnet, Enfield & Haringey Mental Health NHS Trust (n=21) and the Oxford Health NHS Foundation Trust (n=27).

Inclusion criteria of the MOSAIC trial were as follows: Male or female, aged between 18 and 60 years; with a BMI of 18.5 kg/m^2 or below; and a DSM-IV diagnosis of AN or Eating Disorder Not Otherwise Specified (EDNOS)[15], thus we used a broad definition of AN. Our definition of EDNOS included people who fulfilled all criteria of AN, except the weight criterion; those who fulfilled all criteria for AN but still had menses; those without a fat phobia; and those with partial AN (defined as having features of AN but missing at least two of the four diagnostic criteria)[16].

Exclusion criteria for the MOSAIC trial were: Life-threatening AN requiring immediate inpatient treatment as defined in the NICE guidelines[17]; insufficient knowledge of English to understand the treatment; learning disability; severe mental or physical illness which needed treatment in its own right (e.g. psychosis, diabetes mellitus); substance dependence or pregnancy. The trial did not exclude patients on antidepressants, provided they were on a stable dose, i.e. ≥four weeks.

Study Procedures:

Ethical approval for the MOSAIC Trial was obtained from Central London REC 4, National Research Ethics Service, Royal Free Hospital, London, NHS REC Reference: 10/H0714/9. This included ethical approval for the 24-month follow-up.

The trial was registered with Current Controlled Trials (ISRCTN67720902; URL:

http://www.controlled-trials.com/ISRCTN67720902).

Assessments:

Assessments took place at 24 months after randomization. Assessors were blind to patient treatment

allocation.

Measures:

The measures used at the 24 months assessment were the same as those at previous assessment points

(pre–treatment [baseline], post-treatment [6 months] and short-term follow up [12 months]).

Primary Outcome:

Body mass index: Patients' height had been recorded at baseline assessment. Patients' weight was

obtained at 24 months assessment.

Secondary Outcomes:

Eating Disorders Examination (EDE) global and subscale scores[18]. The EDE is a widely used, semi-

structured interview that generates four subscale scores: dietary restraint, eating concern, weight

concern and shape concern. These four subscales are used to create a global score. For patients

unwilling/unable to do the EDE interview, the questionnaire form of this assessment (EDE-Q) was

used. The EDE-Q has been found to have similar validity to the EDE interview[19].

Other psychopathology: We used the Depression, Anxiety and Stress Scale-21 (DASS-21)[20] and the Obsessive Compulsive Inventory-Revised (OCI-R)[21]. The DASS is a 21-item self-report measure that assesses mood state over the past seven days using a 4-point Likert scale. The total score can be used as a measure of general distress. The OCI-R is an 18-item questionnaire which uses a 5 point forced choice severity scale and provides a single global score (max score=72).

Psychosocial impairment: The Clinical Impairment Assessment (CIA)[22]. This is a self-report measure of global psychosocial impairment resulting from the individual's ED behaviors.

Neurocognitive and social-cognitive measures: The Wisconsin Card Sorting Task[23] and the Brixton Spatial Anticipation Task[24] assess cognitive flexibility (set-shifting ability). The Rey-Osterrieth Complex Figure Test[25,26] is a test of central coherence and evaluates ability to plan, organize and assemble complex information. Baron-Cohen's 'Reading the Mind in Film' task[27] assesses participants' Theory of Mind. The levels of missing data were too high at 24 months to include these following measures in analyses.

Service use: The number of MANTRA and SSCM sessions were recorded by therapists on a case record form. Patients completed the Client Services Receipt Inventory (CSRI)[28], a self-report measure of service use, adapted for the current study to cover a wide variety of hospital, mental health, and community-based services as well as medications, impact of employment and additional personal expenditure due to the ED. CSRI data will be reported separately. In addition, patients' electronic hospital records were used to obtain data on service utilization during the follow-up period.

Sample Size Calculation:

We estimated a 25% loss-to-follow up by 24 months and a resulting available sample size of 142*0.75/2=53 patients per group. With this sample size we would have 90% power to detect a standardized treatment effect of Cohen's d=0.64 and 80% power to detect an effect of d=0.55 or larger (two-sample t-test, 5% significance level). Assuming a standard deviation of weight gain of 4

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kgs, these effect sizes translate into additional weight gains of 2 kgs and 2.56 kgs under MANTRA respectively and we previously argued that extra weight gains in this range are both realistic and clinically significant (see MOSAIC protocol[5]).

Trial Interventions:

Although patients in the current follow-up study no longer received the MOSAIC trial interventions, for ease of reference we have included some information on the content and duration of these. Further details, e.g. regarding therapist training and supervision, can be found in the trial protocol paper[5].

Following randomization, patients were offered either 20 once-weekly sessions of MANTRA or SSCM followed by 4 once-monthly follow-up sessions. In addition, patients in both arms were offered up to 4 sessions with a dietician and 2 joint sessions with a carer/close other. Patients with a BMI of ≤ 15 kgs/m^2 were offered 30 weekly sessions of therapy and similar additional and follow-up sessions.

MANTRA: This is an AN-specific therapy that targets four factors, linked to underlying obsessional and anxious/avoidant personality traits, thought to maintain the illness and therefore addressed in treatment. These are: a thinking style characterized by inflexibility, attention to detail at the expense of the bigger picture and fear of making mistakes; impairments in the socio-emotional domain (such as avoidance of the experience and expression of emotions); pro-anorexia beliefs (positive beliefs the person has about the utility of AN in helping them manage their life, e.g. AN keeps me safe); and the often inadvertently unhelpful response of close others, including emotional over-involvement, avoidance or criticism/hostility.

MANTRA is centred around a patient-manual [unpublished], the use of which is tailored to the needs of the individual[9]. The therapist style is that of motivational interviewing, that is, reflective and collaborative. After an in-depth physical, psychological, neurocognitive and socio-emotional/relational assessment, a collaborative case formulation is developed. Feedback, for

example, about medical risk, and thinking style is used to build motivation to change. The principles

of behavioural change are used to guide people towards recovery. There is a clear hierarchy of

treatment procedures depending on the person's clinical profile and balancing treatment motivation,

level of medical risk, and personal resources and supports available.

SSCM: This treatment was developed as a comparison treatment in an RCT comparing CBT,

interpersonal therapy and SSCM[12-14]. SSCM is designed to be delivered by ED specialists and aims

'to mimic outpatient treatment that could be offered to individuals with AN in usual clinical practice'.

This treatment links features of clinical management and supportive psychotherapy. SSCM

emphasizes safe and appropriate patient management and care, including education and support, and a

positive and accepting therapeutic stance. The abnormal nutritional status and dietary patterns of AN

are seen as central to SSCM. The treatment emphasizes the resumption of normal eating and

restoration of weight and provides information on weight gain and weight maintenance strategies,

energy requirements and relearning to eat normally. The remaining therapy content is determined by

the patient. Further details of this treatment are described elsewhere[12,13]. There is also a manual for

therapists [McIntosh et al. unpublished], which contains psycho-educational handouts.

Statistical Analyses

All statistical analyses were based on the intention-to-treat principle using Stata 12[29]. All outcomes

were analyzed using linear mixed models and using the same model structures as in the primary

paper[6]. The dependent variable was the outcome at 24 months, and the (fixed) explanatory variable of

interest was trial arm. The models also included the baseline values of the variable under investigation

and the randomization stratifiers BMI, AN subtype, and previous ED inpatient admission[30,6] as further

explanatory variables. In addition, the model contained random effects for therapists in the two

treatment groups to allow for correlation in outcomes related to treatment being facilitated by the

same therapist. The variance of these random effects was allowed to vary between treatment groups

by including an interaction between therapist and treatment group.

Some missing values were present in the outcome variables. Following the approach laid out in Schmidt et al.[6], we empirically assessed whether a number of baseline variables were predictive of missing values in the outcome variables, and also checked whether nonadherence to treatment (coded "1" = completed at least 15 therapy sessions, "0" = did not complete intervention) was predictive of loss to follow up. Out of these, only nonadherence was found to be an empirical predictor (see the Results section). To allow for such a missing data generating process, multiple imputation (MI) using chained equations was implemented (Stata command *ice*[31]). The imputation step of the procedure used treatment group, baseline value, randomization stratifiers, outcome at other time points, adherence, and therapist dummy variables to predict missing post-randomization outcome values. Here, the benefit of MI lies in its ability to incorporate post-randomization variables that are not part of the analysis model (treatment nonadherence) in the imputation step, and so enables an analysis that is valid under a more realistic missing-at-random assumption[32]. To minimize Monte Carlo error, 50 imputations were used.

Subgroup analyses were used to assess the estimated treatment effects among study participants with a baseline BMI below 17.5kg/m^2, and among treatment completers.