Statistical Analysis Plan

Online Cognitive Behavioral Therapy Targeting Cardiac Anxiety Following Myocardial Infarction (MI-CBT) -A Randomized Controlled Trial

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This is the statistical analysis plan for the study approved by the Regional Ethics Committee in Stockholm on September 9, 2022 (reg no 2022-04087-01).

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Analysis plan

Continuous Outcome Measures

The study protocol pre-specifies the use of linear mixed models for the analysis of the continuous outcome measures (i.e., all measures presented in the paper except for number of healthcare consumption and accelerometer measurement of physical activity and blood samples).

Analysis of between-group changes

Three measurement points will be available for analysis. Baseline (i.e., before randomization), post-treatment (post; i.e., immediately after treatment), and 3-month follow-up (3mfu) after post-treatment. The 3-month follow-up is the pre-determined primary endpoint. To utilize all available data, all three measurement points from all randomized patients will be included in the analysis. The model will include group, time, and group-by-time interaction effect as fixed effects. Time will be entered as a factor/categorical variable with three levels, baseline, post, and 3mfu, with baseline as the reference category. Thus, the model estimates separate interaction effects for post and 3mfu, allowing us to investigate the relative change from baseline between the groups at both post and 3mfu. Inference about treatment effect at the primary endpoint will be based on the p-value of the group-by-3mfu interaction effect, at a significance alpha-level of .05. The mixed models will also include a random intercept to account for the within-individual dependence between the individual observations over time.

Between group effect sizes (Cohen's d) will be calculated as the interaction effects (group-by-post and group-by-3mfu) divided by the baseline standard deviation for the respective measure. To obtain 95% confidence intervals for the effect sizes, we will bootstrap the mixed models analysis 5,000 times. The bootstrap sampling will be performed at the individual level, i.e., each sample included a random sampling (with replacement) of all randomized individuals. Each time an individual is selected, all their observations will be included with a new clustering identifier. For each bootstrap sample, the mixed models will rerun to obtain the interaction effects and the baseline standard deviation will be recalculated to obtain the post and 3mfu effect sizes. The 5,000 bootstrapped effect sizes are then used to obtain bias-corrected and accelerated 95% confidence intervals.

Analysis of within-group changes in the MI-CBT group

These analyses will be performed to investigate the long-term changes in the MI-CBT group compared to baseline. One long-term follow-up measurement points will be available at this point, 12 months after post-treatment (12mfu). To utilize all available data, we will also include the baseline, post, and 3mfu measurement points in the mixed-models analysis. Time will be entered as a factor/categorical variable with four levels, baseline, post, 3mfu, and 12mfu, with baseline as the reference category. Thus, the model estimated separate effects of time for post, 3mfu and 12mfu, allowing us to investigate the change from baseline in the MI-CBT group. The mixed models will also include a random intercept to account for the within-individual dependence between the individual observations over time.

Within-group effect sizes will be calculated by dividing the time effects by the baseline standard deviation and 95% confidence intervals are obtained by the same bootstrapping method used for the between-group effects.

Analysis of healthcare consumption

Regarding healthcare consumption data (i.e., the number of healthcare visits during the last three months), we expect that the distribution of scores will not be suitable for a linear mixed model as described above, since number of healthcare visits is a count variable. If appropriate, we will use statistical a model more suitable for skewed count data, generalized mixed model using the Poisson distribution with a log link function random intercept. Confidence intervals for fixed effects will be calculated based on the guidelines provided at https://stat.ethz.ch/pipermail/r-sig-mixed models/2011q1/015910.html. Effect sizes will not be calculated for this data and instead we will exponentiate the group-by-time interaction effects (between-groups analyses) and Time effects (within-group analyses) to get the percentage reduction in healthcare consumption. In other respects, between- and within group analyses will be performed with the same model specifications as the continuous outcomes.

Analysis of accelerometer data of physical activity and sleep

Regarding accelerometer data, each participant will contribute with values at the three timepoints (baseline, post, 3mfu). Data from the accelerometer (ActiGraph wGT3x-BT) will be processed as previously described (1) using appropriate thresholds to define different levels of intensity (e.g., Moderate-to-vigorous physical activity, MVPA). Daily average MVPA will be calculated as the weighted mean of weekdays and weekend days, that is, {([mean of weekdays × 5] + [mean of weekend days × 2])/7}. Data processing will be conducted by means of the software program R and the package GGIR.

Blood sample analysis

The blood samples are collected at three timepoints: pre-treatment, post-treatment and at the 3mfu. Regarding blood samples, descriptive statics and changes over time using appropriate (i.e., based on distribution) repeated measures statistics will be performed. Venous blood is collected for local analyses of fasting plasma glucose, HbA1c, plasma total cholesterol, LDL, HDL,triglycerides, hsCRP, creatinine.

Reference:

1. Sandborg J, Söderström E, Henriksson P, Bendtsen M, Henström M, Leppänen MH, Maddison R, Migueles JH, Blomberg M, Löf M. Effectiveness of a Smartphone App to Promote Healthy Weight Gain, Diet, and Physical Activity During Pregnancy (HealthyMoms): Randomized Controlled Trial. JMIR Mhealth Uhealth. 2021 Mar 11;9(3):e26091.