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Whole-body Hyperthermia for Mild to Moderate Depressive Disorder – the HYPE 1 Randomized Controlled Trial

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Tables 1 to 4 are available in the Supplementary Files section.

Whole-body Hyperthermia for Mild to Moderate Depressive Disorder – the HYPE 1 Randomized Controlled Trial

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Declarations

- **Ethics approval and consent to participate**: The study was approved by the responsible ethics committee of the Medical Faculty of the University of Duisburg-Essen (Application 18-8439-BO) in accordance with the principles of the Declaration of Helsinki and local laws and regulations. All participants provided written informed consent.
- **Consent for publication**: Not applicable
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Abstract:

Background: About 30% of patients suffering from depression do not respond to antidepressants. In this randomized trial, we investigated antidepressant effects of repeated whole-body hyperthermia (WBH) in comparison to a waitlist group in non-treated patients with mild to moderate depression.

Method: The HYPE-I trial randomized 46 patients (48.04 years ± 13.74, 60.87% female) with mild to moderate depression and no current antidepressant treatment to either receive two WBH sessions or waiting for 6 weeks. The primary outcome was depression severity at week 6, measured by the Hamilton Rating Scale for Depression (HAMD-17). Secondary outcomes included the Beck Depression Inventory (BDI-II), Clinical Global Impression (CGI), Clinical Global Functioning (GAF), Fatigue (MFI), Stress (PSS), Quality of Live (SF-12) and adverse events. Intention-to-treat analyses with 95% confidence intervals (CI) were performed.

Results: No significant group differences were found for on the HAMD-17 at week 6 (-1.80, 95%CI: -5.56/1.96, p=.339). Secondary analyses showed significant group differences on the BDI-II at week 1 (-4.01, 95%CI: -7.08/-0.99, p=.011), on the GAF at week 3 (7.31, 95%CI: 1.33/13.29, p=.018), on the physical subscale of the MFI at week 1 and 3 (-1.19, 95%CI: -2.11/-0.28, p=.012; -2.38, 95%CI: -4.05/-0.72, p=.006) as well as on the mental subscale of the MFI week 3 (-1.24, 95%CI: -2.43/-0.52, p=.041). Response or remission rates did not show significant group differences. Minor adverse events were reported by 8 WBH patients, while no serious adverse events occurred.

Conclusions: Repeated WBH did not produce significant long-term effects after 6 weeks but might show short-term benefits in non-treated patients with depression.

Further studies are needed to identify subgroups that may benefit from hyperthermia. (Trial registration: ClinicalTrials.gov Number: NCT03906175, 5 April 2019).

Introduction

Unipolar depression is the most common psychiatric illness and has a worldwide prevalence of around 16% (Otte et al., 2016). According to the Global Burden of Diseases Study (GBD) 2021, depression is the second leading cause of disability-adjusted life years among mental disorders and has significant social and economic consequences (Ferrari et al., 2024) . Despite the frequency of depressive illnesses and the serious impact on the lives of those affected and on society as a whole, the exact pathophysiology of the illness is still largely unknown. This also applies to possible risk and resistance factors, about which only limited information is available. The currently established treatment strategies with pharmacotherapy and psychotherapy are associated with treatment response in slightly more than half of patients, while complete remission occurs in only 30 to 40% of patients (Pigott et al., 2023). Beside the problem of non-response to conventional antidepressant medication side effects and antidepressant discontinuation symptoms may limit pharmacological treatment (Kalfas et al., 2025; Pillinger et al., 2025). In certain subgroups, such as treatment-resistant depression, non-pharmacological methods are playing an increasingly important role (Saelens et al., 2025).

In addition to the classic neurotransmitter model, which describes changes in neurotransmitter levels and genetic and environmental factors as causative for the development of a depressive disorder, there has recently been increasing evidence that immunological processes and interactions with the central nervous system also have a strong impact on the development and course of affective disorders (Capuron

& Miller, 2011). These interactions between the immune system and the brain could play a significant role in the pathophysiology of depression and lead to the development of completely new treatment approaches for depressive disorders (Gaitonde & Nasrallah, 2025). In particular, an activated immune system is associated with psychological changes and may be linked to the onset or course of affective disorders or even reflect an inflammatory subtype of depression with the need of developing targeted treatment strategies (Miller, 2025; Miller & Raison, 2017). Moreover, accumulating evidence suggests that individuals with depressive disorders are also affected by altered thermoregulation, in particular by an increased core body temperature and a reduced ability to sweat (Raison et al., 2015).

Passive whole-body hyperthermia (WBH) is used as treatment in various fields of medicine, e.g. rheumatology, orthopedics, oncology and in the treatment of chronic pain (Heckel-Reusser, 2022). Early reports described antidepressant effects for hyperthermia treatment in patients with cancer (Koltyn et al., 1992). In recent years, different types of hyperthermia treatment are discussed to have mood-enhancing and antidepressant effects in patients with primary mood disorders (Gaitonde & Nasrallah, 2025). In a first randomized, double-blind and sham-controlled clinical trial Janssen and colleagues were able to demonstrate a significant, rapid and partially lasting reduction of depressive symptoms in unmedicated patients with MDD following a single WBH treatment with water-filtered infrared A (wIRA) (Janssen et al., 2016). To date, the study data has not been replicated and it remains unclear whether repeated WBH treatments using wIRA may be superior to a single treatment. Our prospective randomized controlled trial (HYPE-I) aimed to investigate antidepressant effects together with safety and tolerability data of repeated passive WBH in comparison to a waitlist group in non-treated patients with mild to moderate depression.

Methods

Trial design and registration

The trial was registered at ClinicalTrials.gov: NCT03906175 (5 April 2019) and carried out at a German hospital (Evang. Kliniken Essen-Mitte) between 2019 and 2024. The study was approved by the responsible ethics committee of the Medical Faculty of the University of Duisburg-Essen (Application 18-8439-BO) in accordance with the principles of the Declaration of Helsinki and local laws and regulations. All participants provided written informed consent. This study was conducted and is reported in accordance with the CONSORT guidelines. After baseline assessment, patients were randomized to either receive two WBH treatments within two weeks or wait for 12 weeks. Outcomes were assessed at weeks 1, 3 and 6. A follow-up was planned for week 12 after randomization but could not be realized because most patients missed the appointment due to the corona pandemia.

Eligibility criteria

Patients were enrolled at the department of Psychiatry and Psychotherapy at the Evang. Kliniken Essen-Mitte, Germany between 2019 and 2024. Participants were recruited via outpatient centers, print and online fliers. Patients between age of 18 and 75 years could be included in the HYPE-I trial if they had a diagnosis of unipolar depression with a current mild to moderate depressive episode (DSM-IV). Diagnosis was verified by diagnostic interview (M.I.N.I in Version 7.0.2. (Sheehan et al., 1998) Severity of depression was measured with the 17-item Hamilton-Depression Scale (HAMD-17) (Hamilton M., 1960). Patients had to show a score between 8-16 for diagnosis of mild depression and 17-23 for moderate (Zimmerman et al., 2013).

Exclusion criteria were current active psychotherapy, antidepressant drug treatment in the last 4 weeks before study inclusion or non-response to prior antidepressant drug

treatment, a history of electroconvulsive therapy or sleep deprivation, prior treatment with whole-body hyperthermia, acute suicidality and acute infections. We further excluded patients with contraindications to hyperthermia treatment, severe cardiovascular diseases (e.g. angina pectoris, heart failure, thrombosis, bleeding diathesis), severe gastrointestinal diseases (e.g. renal insufficiency, hepatitis, liver cirrhosis, peptic ulcer), severe neurological diseases (e.g. epilepsy, multiple sclerosis, cerebrovascular malformations or brain tumors), severe endocrine diseases (e.g. hyperthyroidism) or any oncological disease without remission. In addition, patients taking anti-inflammatory or immunosuppressive drugs (e.g. corticosteroids, alpha/beta agonists, immunosuppressants), women during pregnancy and breastfeeding, patients with severe psychiatric comorbidities (e.g. schizophrenia, schizoaffective disorder, bipolar-I-disorder, dementia, ADHD, obsessive-compulsive disorder, PTSD, alcohol or drug addiction) and patients lacking the ability to consent were excluded. At screening, all participants underwent routine hematological and biochemical laboratory testing, and pregnancy testing and received an electrocardiogram.

Randomization and blinding

Patients who met eligibility requirements and signed informed consent, were randomized either to two WBH treatment sessions within two weeks or to a waitlist control group. Randomization was carried out using block randomization with randomly varying block lengths. The randomization list was created by a biostatistician from the Department for Internal and Integrative Medicine, Evang. Kliniken Essen-Mitte, using Random Allocation Software (Saghaei, 2004). The list was password-secured, and neither the study physicians nor the therapists or data collectors were given insight before the randomization was completed. Based on these results, the sealed, sequentially numbered opaque envelopes containing the treatment assignments were

prepared. After obtaining written informed consent and baseline assessment, the study physician opened the lowest numbered envelope to reveal that patient's assignment.

Study Interventions

Whole-body hyperthermia

We used the Heckelbett HT-3000® (heckel Medizintechnik GmbH, Esslingen, Germany) for our study. Heat was generated by water-filtered infrared A-rays (wIRA®), which penetrate into the deeper layers of the skin with a light spectrum of 760 to 1400 nanometers, where they release energy in the form of heat to vascular convolutes and warm the blood flowing through them. By converting the heat chamber with flexible walls, the generation of evaporative cooling in the chamber is prevented. Hyperthermia therapy was started immediately after inclusion in the therapy group and making an appointment for the first treatment. The 2nd treatment took place 14 days after the first hyperthermia treatment.

The first phase of the treatment process consisted of a warm-up phase with the aim of reaching a core body temperature of 38.5°C. The time required to reach this target depended on the individual subject. During the warm-up phase, the test subjects were given fluids orally as desired. Some subjects received a cold washcloth on their forehead for support. After reaching a core body temperature of 38.5°C, the wIRA emitters were switched off and the flexible walls of the Heckel bed were detached from the superstructure, folded down and the test person wrapped up for one hour. Vital parameters were documented using the FebroData® program. At the end of the one-hour congestion phase, the treatment was completed and the test person was able to stand up and get dressed again. This course of treatment was easily reproducible.

Waitlist group

By being assigned to the waitlist group, patients were given a wait-and-see approach without therapeutic intervention which is in line with the Germen medical guidelines (Kassenärztliche Bundesvereinigung, 2022). The patients were informed that medical staff could be contacted at any time in the event of an acute deterioration in their state of health or imminent suicidal tendencies using the emergency number provided in the study information. For motivational reasons, patients in this group were offered to receive WBH after 12 weeks waiting time.

Outcome Measures

The a priori defined primary outcome measure was depression severity 6 weeks after randomization as assessed by the 17-item HAMD (Hamilton M., 1960). The severity in the HAMD-17 was classified into four levels: 0-7 = no depression, 8-16 = mild depression, 17-23 = moderate depression, ≥24 = severe depression (Zimmerman et al., 2013). Patients were rated before WBH as well as 1, 3, 6 and 12 weeks after randomization, with the ratings at weeks 1, 3, and 12 serving as secondary comparisons. Two trained raters and experienced psychiatrists blind to group assignment performed all HAMD-17 assessments as well as those for Clinical Global Impression of Severity (CGI-S) (Busner & Targum, 2007) and Global Assessment of Functioning (GAF) (Grootenboer et al., 2012; Hall, 1995). The CGI-S is rated on a 7-point scale from 1 = normal, not at all ill to 7 = among the most extremely ill patients. The GAF is rated on a 0-100 scale, with higher scores indicating better psychological, social, and occupational functioning.

Further secondary outcomes were patient-reported measures and were evaluated at the same time points. We used the Beck Depression Inventory II (BDI-II) as a self-

rating depression scale (Beck et al., 1996). In the BDI-II, scores between 14-19 are defined as mild depression, 20-28 as moderate and 29-63 as severe depression (Kuehner et al., 2023). The Multidimensional Fatigue Inventory (MFI) was used to assess existing fatigue symptoms across 20 items. Each of the 5 subscales can achieve a score ranging from 4 to 20 points (Goodchild et al., 2008; Smets et al., 1996). With the Perceived Stress Scale (PSS) patients rated their stress level on 10 items with a total stress score of up to 40 points (Cohen & Janicki-Deverts, 2012). We included the SF12 for self-assessment of physical and mental quality of life. The two subscales are standardized and range from 0 (lowest quality of life) to 100 (highest possible quality of life) (Jenkinson et al., 1997). Finally, the Treatment Credibility Scale (TCS) was used to rate “Expectation of possible improvement in depressive symptoms” at baseline numerically from “0 = not at all” to “10 = very strongly” (Devilly & Borkovec, 2000).

Safety was assessed by recording the total number of patients experiencing adverse events, along with the number and type of adverse events observed. Additionally received blood and immune parameters are still under investigation and will be published separately.

Sample size calculation and statistical analysis

A prior study on whole-body hyperthermia in patients with moderate depression served as the basis for the sample size calculation (Janssen et al., 2016). At week 6, this study found a mean HAMD-17 value of 12.40 ± 5.25 in the hyperthermia group (single treatment) and 17.21 ± 4.78 in the sham treatment control group, which corresponds to a mean effect size of Cohen’s d=-0.94. To be able to detect this effect with a power (1-b) of 0.80 and an α of 0.05, a two-sided t-test with a sample ratio of 1/1 requires an

N of 38 patients. Calculating a dropout rate of up to 15%, this corresponds to a final sample size of 46 patients in total (23 per group).

All analyses were based on the intention-to-treat (ITT) population. Missing at random values were imputed 50 times using fully conditional specification iterations, a multiple imputation technique based on multivariate regression models of group allocation, treatment expectation, prior depressive episodes, sociodemographic parameters (age, gender, education) and respective baseline values. The primary outcome was analyzed as a function of the treatment group (classified factor) and respective baseline values (linear covariate) using univariate analysis of covariance (ANCOVA). Between-group differences and 95% confidence intervals (CI) were estimated using 2-sided t-tests, and an alpha level of 5%. For the ANCOVAs of patient reported secondary outcomes, patients' expectations were added as an additional linear covariate to control for confounding placebo effects. In addition, responder analyses were calculated for patients who improved by at least 50% of their respective baseline values according to the HAMD-17 and BDI-II scales (response) and for those reporting values ≤ 7 in the HAMD-17 and ≤ 9 in the BDI-II (remission). Between-group differences for treatment response/remission were tested with chi^2 tests. To test influence of baseline antidepressant drug intake on changes of primary and secondary outcomes moderation analyses were calculated using PROCESS (release 4.2) macro for SPSS with bootstrapping of 5000 samples and 95%CIs.

Results

Patient flow

Of the 145 individuals screened for study participation, 100 were scheduled for an in-person eligibility assignment. Of those, 46 met eligibility criteria and were randomized

to one of the two groups. Of the 22 patients randomized to the WBH group, two patients dropped out before the first treatment because of loss of interest. All other patients received both of the WBH treatment. Complete outcome data were received from 18 to 19 of 22 WBH patients and 18 to 20 waiting-list patients. Reasons for missing data included loss of interest and no reply (Figure 1).

- Please insert figure 1 –

Sample characteristics at baseline

The mean age of the total study population was 48.04 ± 13.89 years. Twenty-eight (60.9%) of the patients were female (Table 1). The mean BMI was 25.17 kg/m^2. In the overall study population, the average number of depressive episodes was 5.08 ± 3.94 with a mean duration of all previous depressive episodes of 18.94 ± 16.43 weeks. A total of 17 (37%) subjects in the study reported that they had taken antidepressants as part of a former treatment: 11 (50%) in the treatment group and 6 (25%) in the waiting group. The average treatment expectation between the treatment group and the waiting group at bassline was comparable (6.00 ± 2.41 versus 5.95 ± 2.57). The mean baseline HAMD-17 score for subjects in the treatment group was 17.32 ± 3.85 and 15.96 ± 3.61 in the waiting group. The self-reported depression scores in the BDI-II showed a mean value of 23.91 ± 6.33 SD in the treatment group at baseline and 20.88 ± 7.79 in the waiting group. Both groups met the criteria for a clinically significant depressive episode (mild to moderate). The analysis of dropouts at week 6 did not

show significant differences in comparison to patients who completed the study (Table 2).

- Please insert Table 1 and Table 2-

Effects on the primary outcome

The ITT analysis on the primary outcome is shown in Figure 2 and Table 3. For depression severity 6 weeks after randomization, between-group differences on the HAMD-17 were found to be not statistically significant (Δ = 1.04, 95%CI = -2.38/4.48, p=.544).

- Please insert Figure 2 and Table 3 here -

Effects on secondary outcomes

For week 1 and week 3, between-group differences on the HAMD-17 were also not found to be statistically significant (table 3). BDI-II scores showed a statistically significant group difference at week 1, with a greater reduction in the treatment group (Δ = -4.04, 95%CI = -7,08/-0.99, p=.011) (Figure 2, Table 3). No significant group differences were found at week 3 (p=0.051) or at week 6 (p=0.32).

When comparing responder and patients who reached response or remission between groups, we had more responders after 1,3 and 6 weeks in the treatment group with the self-ratings (BDI-II scale) which was not seen with the HAMD17 scale which showed

better remissions after week 3 (Table 4). However, differences did not become significant.

- Please insert Table 4 here –

Secondary analyses of the Clinical Global Impression (CGI), Clinical Global functioning (GAF), Fatigue (MFI), Stress (PSS) and Quality of Live (SF-12) showed significantly greater improvements on GAF at week 3 (7.31, 95%CI: 1.33/13.29, p=.018), on the physical subscale of the MFI at week 1 and 3 (-1.19, 95%CI: -2.11/-0.28, p=.012; -2.38, 95%CI: -4.05/-0.72, p=.006), the motivational subscale at week 1 (-1.14, 95%CI: -2.11 -0.16, p=.024) as well as on the mental subscale at week 3 (-1.24, 95%CI: -2.43/-0.52, p=.041) (Table 3).

Moderation analyses on change in primary and secondary outcomes did not reveal a moderation effect of prior use of antidepressant treatment (data not shown).

Regarding safety and tolerability, no serious adverse events were observed. Side effects during WBH were reported in 36.4% of cases during the first session and in 27.3% during second treatment. Overall, 52% of participants needed support and motivation to finish the treatment during their first WBH, while this was only necessary for 38% during the second treatment. In about 65% of cases, the forehead had to be cooled during WBH. The most commonly observed side effects were mental restlessness (n=4, 20% during first and second treatment), physical restlessness and heat intolerance (n=4, 20% in first and n=3, 15% during second treatment), headache (n=3, 15% during first and n=2, 10% during second treatment) and hyperventilation (n=1,5% during second treatment). No patient reported dyspnoe or palpitation.

Discussion:

The primary objective of our clinical study was to evaluate the effectiveness of two passive whole-body hyperthermia treatments within 2 weeks for unmedicated patients with mild to moderate depression. From our knowledge, this is the first randomized prospective blinded trial treating patients with depression with repeated hyperthermia with water-filtered infrared A in patients without antidepressant medication. Within the 6-week treatment period, the treatment group received two passive whole-body hyperthermia treatments in the first 14 days. Regarding primary outcome with the 17-Item HAMD-17 scale, we did not observe significant group differences in the hyperthermia group compared to the waiting list group over time and at week 6. Also, the secondary outcome parameter BDI-II and other scales showed no significant group differences after 6 weeks. However, in the BDI-II the hyperthermia group showed a statistically significant higher early decline at week 1 post-treatment and a strong trend to a better outcome at week 3. However, both treatment and waiting group showed an improvement in their depression scores in the HAMD-17 and BDI up to week 6. We also investigated other clinically relevant parameter such as global functioning, fatigue, stress and Quality of Live. We found some early effects with significant group differences with greater improvements in global functioning after first treatment, less physical fatigue after first and second WBH, as well as better motivation after first and better mental fatigue after second WBH, but again those differences disappeared after 6 weeks.

Our results are in contrast to the study of Janssen and colleagues who could show in a first 6-week, randomized, double-blind study including 30 patients, that a single session of passive whole-body hyperthermia using wIRA in which core body temperature was elevated to 38.5 C produced a significant early and ongoing

antidepressant effect in people with major depressive disorders without antidepressants compared to those who received a sham control (Janssen et al., 2016). Improvements of depression severity were noticeable within one week after the start of treatment and persisted six weeks after the treatment. In addition, immunological changes were observed after WBH, followed by increased serum IL-6 after the treatment, which correlated with depression scores after 6 weeks (Flux et al., 2023). This could highlight the impact of immunological changes and a possible mechanism of action of WBH in depression. Results might also point out that the WBH treatment is especially suitable for subgroups with immunological changes, as is increasingly being discussed in cases of depression (Miller & Raison, 2017).

The study of Janssen and colleagues differed in some respects from our study. In our investigation, there were no sham conditions and a waiting list served as control group. Furthermore, we used a setting with repeated WBH treatments. From our perspective, a repeated sham treatment would not have been suitable for our design to ensure a double-blind setup. The most important point here is the significantly lower body temperature with a complete absence of fever, which the patient would have noticed at the latest by the second treatment.

Overall, we saw an improvement of depression scores in both groups. Our waiting group received a “wait and see setting” including diagnosis, information about the disease and symptom severity and support with regular appointments for rating. Furthermore, it was offered to receive WBH after 12 weeks waiting time. From psychiatric trials strong placebo affects are known in controlled trials, supporting therapeutic effects of any kind of psychiatric care, short interventions or even only information (Weimer et al., 2015). This is supported by meta-analytic data showing similar effects from control settings such as ultra short psychoeducation in bipolar

patients with cognitive behavioral therapy (Miklowitz et al., 2021). Especially major depressive disorders are known to show the highest responsiveness to placebo settings, even in neuromodulatory settings (Huneke et al., 2024). Taking together, our control group showed improvements in all used scales over time, supporting an unspecific therapeutic or placebo effect of the “wait and see” care.

An important reason why even clearer changes over time were not statistically significantly different is due to the high standard deviations in a group size that may have been too small for this purpose. Nevertheless, the main changes in HAMD-17 and BDI-II from baseline to T6 (6 weeks after the start of therapy) were more pronounced in the therapy group. This is supported by the observation, that especially with the BDI score we had more responders and patients with remission after 1, 3 and 6 weeks in the treatment group, but again without statistical significance.

Other reasons for small changes or improvements can be discussed. One possibility is that the HAMD-17 score as a measuring instrument is not sufficiently sensitive to detect the effects of hyperthermia. In fact, the HAMD-17 primarily measures the psychomotor and somatic dimensions of depression (Bagby et al., 2004). If the expected effects of hyperthermia treatment are based more on cognitive and affective changes, the HAMD-17 may not meet the criterion of being a sufficiently sensitive measuring instrument. However, this is contradicted by the fact that the HAMD-17 score was also used in the study by Janssen et al. and a significant change in the severity of depression was seen. In addition, we used various scales including CGI and BDI-II in this study without significant effects over time and after 6 weeks. However self-ratings showed more effects compared to the blinded ratings made by psychiatrist.

Furthermore, it is possible that our patient group was subject to increased preselection due to the exclusion criteria (no current treatment with antidepressants, no other current form of therapy), which led to a sample with a high chance of improvement even without active treatment. In fact, the German guideline for mild depression also includes active waiting as a possible therapeutic intervention (Kassenärztliche Bundesvereinigung, 2022). We cannot exclude that a subgroup of subjects had already completed other forms of therapy and were seeking an alternative treatment because they had been refractory to therapy. Thus, previous pharmacological treatment more than four weeks prior to the study, which was reported by a total of 11 subjects (50%) in the treatment and 6 (25%) in the waiting group, could also have influenced the treatment outcome by affecting the HPA axis, cytokines, and neurometabolism.

A recent review summarized trials using hyperthermia for treatment of depression (Gaitonde & Nasrallah, 2025). Different methods were used in order to reach increased body temperature of 38.5 °C followed by cool down periods. Beside us only in the study of Janssen and colleagues (Janssen et al., 2016) the whole-body hyperthermia treatment was performed under controlled conditions with water-filtered infrared A light in a Heckelbett HT-3000®, which always ensures the same conditions and enables continuous individual monitoring of core body temperature. Other studies used different methods of hyperthermia to improve mood, including infrared radiation, hyperthermic baths at 40°C to the point of discomfort, and hot yoga sessions combining 90 minutes at 40°C with a workout program. Overall, in most studies the interventions seemed to improve depressive symptoms. These effects appear to begin immediately after the end of treatment and can last up to six weeks thereafter. Thus, these trials indicate rather rapid and short term effects of hyperthermia on depressive mood changes, comparable to our results. Nevertheless, these studies have been limited by

small sample sizes, high dropout rates, and exclusion of subjects with either medical comorbidities or recent medication changes. In addition, the control groups for each of these studies also demonstrated heterogeneity.

In our trial WBH was well tolerated in most patients with or without antidepressant treatment. No serious adverse events were observed. Side effects were related to the physiological body cooling mechanism and the activation of the sympathetic stress system (reduced blood pressure, increase in heart rate, headache, increase in respiratory rate, restlessness and anxiety).

Our study has some important limitations. First, based on the available studies, the expected effect of the intervention may have been overestimated. This could have resulted in a sample size that was too small to detect any potential effects of the intervention. Second, for the reasons outlined, a sham intervention was not used, which means we cannot quantify the influence of possible contextual factors on the intervention's effect. Finally, data for Week 12 could not be meaningfully analyzed because too much data was missing due to pandemic conditions.

In conclusion we could not show ongoing antidepressant effects of repeated WBH in patients without antidepressant therapy over a 6 weeks period, but early effects on self-rated mood changes, global functioning and fatigue. However, whole-body hyperthermia might be a promising concept for a non-pharmacological treatment of possibly immunological subtypes of depression. Future controlled studies should improve sample size to detect clinical subgroups that may benefit particularly from hyperthermia treatment.

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Figures

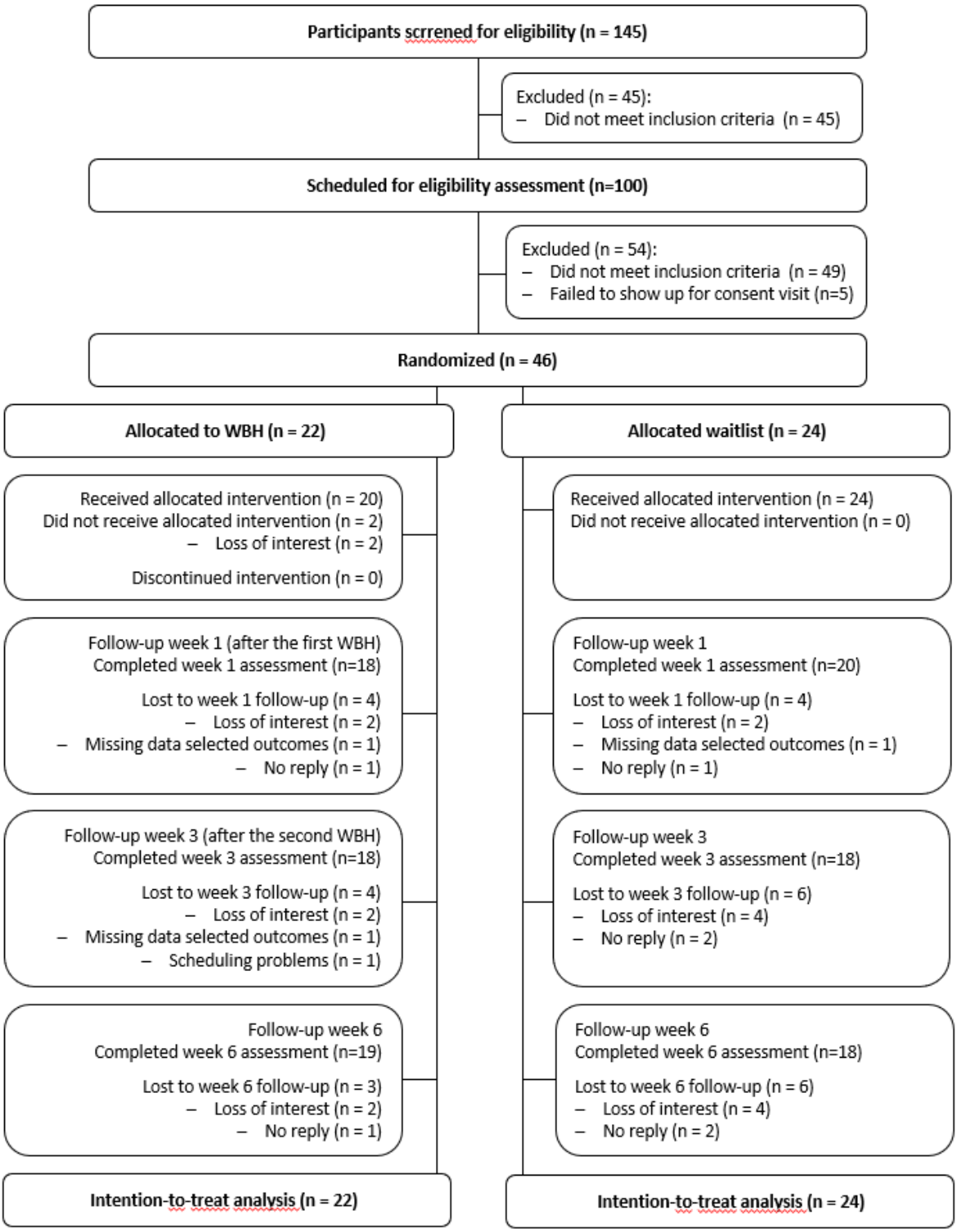

Figure 1

CONSORT Flow Diagram for Whole-Body Hyperthermia (WBH) and Waitlist Groups (Hype 1)

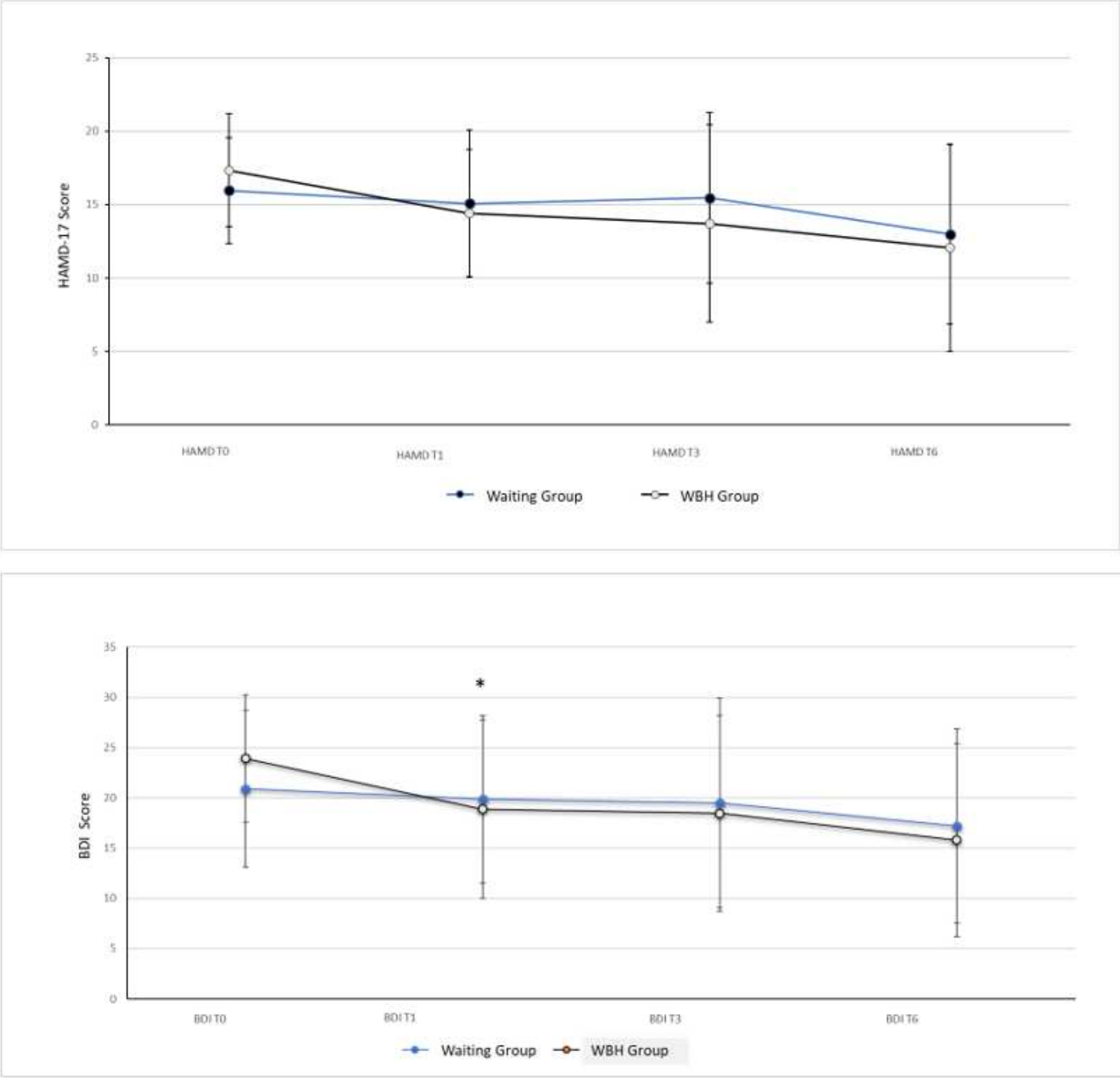

Figure 2

Effect of Whole-Body Hyperthermia (WBH) vs Waiting Group on 17-Item HAMD and BDI-II scale across the 6-Week Period

Abbr.: HAMD17 = 17 Items Hamilton Depression Rating Scale, BDII = Becks Depression Rating Scale II, T 1 = week 1, T3 = week 3, T 6 = week 6, * = $p < 0.05$

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1Hype1baselineend.docx
- Table2Hype1dropoutanalysisend.docx
- Table3Hype1analysesofoutcomesend.docx
- Table4Hype1ResponseRemission.docx