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Predictors and sub-groups in the treatment of stress-induced exhaustion disorder

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ABSTRACT

Little is known about psychological interventions for stress-induced Exhaustion disorder (ED), and there is a need for more research to improve the outcomes obtained in treatments. The present study examines predictors of improvement, including sub-group responses, in a large sample of ED patients receiving a Multimodal intervention (MMI) based on Cognitive Behavior Therapy (N = 915). In step one, available variables were explored separately as predictors of improvement in ED symptoms. In step two, sub-groups were explored through Latent Class Analysis to reduce the heterogeneity observed in the larger group and to investigate whether combining the variables from step one predicted symptom improvement. Younger age, no previous sick leave due to ED, and scoring high on anxiety, depression, insomnia, perfectionism, and treatment credibility emerged as separate predictors of improvement. In the sub-group analyses, a sub-group including participants who were single and had a lower income showed less improvement. Overall, people with ED participating in MMI report symptom improvement regardless of characteristics before treatment. However, the present findings do have the potential to inform future treatments for ED, as they highlight perfectionism as a predictor of improvement and the importance of assessing treatment credibility during treatment.

Introduction

Ill health due to occupational stress is a growing concern in many western countries (Eurofound, 2018; Hewlett & Moran, 2014; International Labour Organization, 2016; OECD, 2012). When factoring in sickness absence and productivity loss, the total cost of work-related stress has been estimated to be 187 billion US dollars in the western world (Hassard et al., 2018). For many people, exposure to persistent non-traumatic stress leads
to a debilitating state of exhaustion characterized by extensive physical fatigue and
cognitive impairments, but not necessarily symptoms of depression (Grossi, Perski,
et al., 2015; van Dam, 2021). In Sweden, the diagnosis of “Exhaustion disorder” (ED;
ICD-code F43.8A) is used to classify this condition (Kalliomäki & Brodda Jansen,
2021). Similar international terms include work-related depression, stress-related exhaustion,
clinical burnout, and possibly neurasthenia (Wallensten et al., 2019). Additionally, recent
publications in the clinical treatment sciences indicate that ED is far from a unique
Swedish condition (Cléach, 2014; Dalgaard et al., 2017; Engebretsen & Bjorbækmo,
2019; Jensen et al., 2022; Kristiansen et al., 2019; Netterstrøm et al., 2013; Tylec et al.,
2021; van der Klink & van Dijk, 2003).

Little is still known about the treatment of ED (Lindsåter et al., 2022). Certainly, confusion
surrounding the terminology of ED does not help in this regard. While no specific treatment
is identified as the gold standard, people with ED participating in treatments based on
Cognitive Behavioral Therapy (CBT) report symptom improvement and improved return-to
work rates (Finnes et al., 2019; Lindegård et al., 2022; Lindsåter et al., 2018; Malmberg
Gavelin et al., 2018; Persson Asplund et al., 2018; Salomonsson et al., 2020; van de
Leur et al., 2020). At the same time, there is no consensus regarding psychological theory,
methods, or processes of change that should be the focus of interventions. Many treatments currently
offered to patients suffering from ED consist of large packages of multi-component inter-
ventions that appear to offer little clinical flexibility and lack specificity, making it difficult
to discern which components are crucial for treatment success and for whom. The need for
individualized interventions for ED has been highlighted since there is both high hetero-
genecity within the ED population and treatment responses vary widely (Malmberg
Gavelin et al., 2018; Norström et al., 2022). Consequently, work is needed to help to determine how to
focus and individualize psychological treatments for ED. Two ways to address this include
analyses of individual predictors of improvement during treatment or analyses of empirical
sub-groups of treatment participants who differ in treatment response. These are the aims of
the present paper.

Predictors are pretreatment variables associated with the strength and direction of
treatment outcome. Identifying determinants of treatment success can help with future
treatment assignments or identify modifiable targets for these treatments and answer
questions about what treatment works for whom (Kraemer et al., 2002). One previous
study has investigated sex, age, education, symptom duration, comorbid depression, use
of antidepressants, and sick leave as predictors of improvement in ED symptoms during
treatment (measured with the Shirom-Melamed Burnout Questionnaire) (Glise et al.,
2012). Symptom duration longer than one year before seeking specialist care predicted
less improvement in symptoms of exhaustion during treatment, but the other variables
did not predict outcome. To our knowledge, this is the only study previously published
on predictors of improvement during the treatment of ED.

In psychological treatment research, predictors of outcome are often divided into
three general classes to differentiate among them practically: Demographics (e.g. age, sex,
social status, living situation, education, socioeconomic status), clinical characteristics
(e.g. concurrent symptom burden, psychiatric comorbidity, comorbid persistent pain,
stable psychotropic medication), and treatment-related variables (e.g. treatment cred-
ibility) (Salomonsson et al., 2019). With other common mental health conditions,
treatment credibility at baseline has been shown to predict treatment success
(Constantino et al., 2019; Salomonsson et al., 2019), but it has not been examined in the treatment of ED.

While demographic variables and clinical characteristics can increase the understanding of differences in symptom progression and may help predict who benefits from treatment and who does not, they do not necessarily inform the focus of psychological treatment. To achieve such understanding, modifiable variables that can be targeted in treatment must be explored. Physical activity, for example, is often promoted in the treatment of ED, but it has yet to be explored as a predictor of change (Eskilsson et al., 2017; Gerber et al., 2015). It has previously been acknowledged that patients with ED often struggle with high demands, over-commitment, and perfectionism (Avanzi et al., 2014; Gulin et al., 2021). A recent theoretical paper highlighted perfectionism as a variable that can be targeted for change in treatment (Almén, 2021). This paper also underlined the importance of worrying as it increases sympathetic activation and can interfere with restorative behaviors such as sleep and relaxation, usually highlighted in ED treatment (Brosschot et al., 2007; Murnieks et al., 2020). The importance of sleep in developing and treating ED is also often highlighted in ED research (Ekstedt et al., 2009; Grossi, Jeding et al., 2015; Söderström et al., 2012), and changes in insomnia seem to mediate improvements in exhaustion symptoms during CBT for ED (Lindsåter et al., 2021; Santoft et al., 2019). Therefore, physical activity, perfectionism, worry, and insomnia appear worth further study as processes underlying symptoms and symptom change in ED.

Finally, while individual predictors may contribute to a better understanding of how patients respond to treatment, another practical way to address heterogeneity across a range of varying characteristics is by identifying sub-groups. Such sub-groups could potentially aid the tailoring of treatment to particular people’s needs. The need for studying potential sub-groups of ED patients participating in treatment has been frequently highlighted (Glise et al., 2020; Gulin et al., 2021; Norström et al., 2022; van de Leur et al., 2020), but to our knowledge, no such analysis has yet been made.

In summary, given the limited understanding of the progression of ED and its treatment, identifying predictors of improvement and sub-groups among patients with ED during treatment can potentially help improve focus and individualization of ED treatment. Therefore, the current study’s aim was twofold: Our first aim was to utilize a comprehensive approach to explore whether a wide range of demographic variables, clinical characteristics, and treatment-related variables at baseline individually predicted changes in symptoms of exhaustion in participants receiving a CBT-based Multimodal intervention (MMI) for ED. Our second aim was to explore the existence of sub-groups across the variables from the first aim and to understand whether these sub-groups predicted symptom improvement over time. Since data were analyzed within an exploratory framework, no a priori hypotheses were formulated.

**Method**

**Study design**

This large open clinical trial took place at two healthcare units (PBM Sweden AB) in Stockholm, Sweden, specializing in MMI for longstanding pain and ED. The
study was registered on Clinicaltrials.gov (Identifier: NCT03360136), approved by the Regional Ethical Review Board in Stockholm, Sweden (Approval Nr. 2016/1834–31/2) and followed the ethical principles of the Declaration of Helsinki. Symptoms trajectories during and after treatment for a subset of this sample \( n = 389 \) have been reported in a previous publication (van de Leur et al., 2020).

**Participants and recruitment procedure**

Both healthcare units were part of a specialized healthcare initiative called “The health care choice for treatment of longstanding pain with or without comorbidity, and ED” on behalf of Health Care Services Stockholm County. The clinics received referrals from primary healthcare, general practitioners, and occupational health services. After being referred for ED, the patients were assessed by a team of one licensed physician (45 minutes), one licensed psychologist (60 minutes), and one licensed physiotherapist (45 minutes). A total of 1643 patients underwent a multi-professional assessment between September 2017 and Mars 2019. Out of these, 472 did not fulfill the inclusion criteria for participation in the MMI, 15 patients were included in the rehabilitation program for longstanding pain, and 73 were offered a short version of the rehabilitation program for ED (12 or 16 weeks).

All ED patients at both units included in the standard 24-week MMI were asked to participate in the study. Of the 1083 patients included in the 24-week treatment, 17 independently dropped out before treatment started and were excluded from the data collection. Another 151 declined participation. A total of 915 patients were included in the study. A further 27 of these dropped out during the treatment. Consequently, 888 patients completed the 24-week MMI. Table 1 presents the pretreatment characteristics of patients.

**Inclusion and exclusion criteria**

Inclusion criteria for the study were: a) referred for ED, fulfilled the criteria for ED; b) scored > 4.5 on the Shirom-Melamed Burnout Questionnaire (SMBQ; Melamed et al., 1992), a cut-off determined by the Health Care Services Stockholm County for being accepted to the health care initiative mentioned above (see Participants and recruitment procedure); c) was considered suitable for group treatment; d) 18–65 years of age.

Exclusion criteria were: a) abuse of alcohol or drugs; b) participating in any other form of MMI; c) severe depression, moderate/high risk of suicide, psychosis, or untreated PTSD.

**Treatment**

The treatment was delivered by a multi-professional team consisting of one licensed psychologist, one licensed M.D., one licensed physiotherapist, and one rehabilitation coordinator (with the profession of an occupational therapist, licensed psychologist, or a licensed nurse). The treatment consisted of group and individual interventions based on CBT and has been described thoroughly in a previous publication (van de Leur et al., 2020).
Measurements

Demographics, clinical characteristics, and treatment-related variables were all collected during the assessment phase at baseline. In addition, the outcome was collected at baseline, at the start of rehabilitation, mid-treatment (12 weeks into treatment), post-treatment (24 weeks), and at 12-month follow-up (after finished treatment). In the current publication, we only use variables measured at baseline together with outcome over time, except for treatment credibility, which was collected at the start of treatment (since participants were given information about the treatment after the baseline measurements were taken). All questionnaires were administered digitally through a secure online login (Hedman et al., 2010). To decrease instrumentation bias, the order of the questionnaires was randomized at each dispatch.

Table 1. Pretreatment characteristics of patients.

<table>
<thead>
<tr>
<th>Demographical variables</th>
<th>Total (N = 915)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>42.96 (9.43)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>789 (86)</td>
</tr>
<tr>
<td>Marital status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Single or other</td>
<td>280 (31)</td>
</tr>
<tr>
<td>Married/living together</td>
<td>572 (63)</td>
</tr>
<tr>
<td>Partner (living apart)</td>
<td>63 (7)</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
</tr>
<tr>
<td>Elementary school and/or secondary school</td>
<td>232 (25)</td>
</tr>
<tr>
<td>University&lt;3 years</td>
<td>142 (16)</td>
</tr>
<tr>
<td>University≥3 years</td>
<td>500 (55)</td>
</tr>
<tr>
<td>Other</td>
<td>41 (4)</td>
</tr>
<tr>
<td>Socioeconomic status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0–250 000 SEK/year</td>
<td>76 (8)</td>
</tr>
<tr>
<td>250 000–500 000 SEK/year</td>
<td>308 (34)</td>
</tr>
<tr>
<td>500 000–1000 000 SEK/year</td>
<td>391 (43)</td>
</tr>
<tr>
<td>&gt; 1000 000 SEK/year</td>
<td>140 (15)</td>
</tr>
<tr>
<td>Child with a disability, n (%)</td>
<td>132 (14)</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
</tr>
<tr>
<td>Symptoms&gt;1 year before treatment, n (%)</td>
<td>643 (70)</td>
</tr>
<tr>
<td>Previous sick leave due to ED, n (%)</td>
<td>321 (35)</td>
</tr>
<tr>
<td>Psychiatric comorbidity, n (%)</td>
<td>332 (36)</td>
</tr>
<tr>
<td>Antidepressant medication, n (%)</td>
<td>349 (38)</td>
</tr>
<tr>
<td>Persistent pain, n (%)</td>
<td>128 (14)</td>
</tr>
<tr>
<td>Anxiety, mean (SD)</td>
<td>11.63 (4.03)</td>
</tr>
<tr>
<td>Depression, mean (SD)</td>
<td>11.26 (3.69)</td>
</tr>
<tr>
<td>Treatment-related variables</td>
<td></td>
</tr>
<tr>
<td>Insomnia, mean (SD)</td>
<td>16.06 (6.10)</td>
</tr>
<tr>
<td>Worry, mean (SD)</td>
<td>9.93 (3.04)</td>
</tr>
<tr>
<td>Perfectionism, mean (SD)</td>
<td>33.76 (6.26)</td>
</tr>
<tr>
<td>Physical activity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Nothing</td>
<td>282 (31)</td>
</tr>
<tr>
<td>Now and then</td>
<td>241 (26)</td>
</tr>
<tr>
<td>1–2 times/week</td>
<td>221 (24)</td>
</tr>
<tr>
<td>3–4 times/week</td>
<td>118 (13)</td>
</tr>
<tr>
<td>&gt;4 times/week</td>
<td>53 (6)</td>
</tr>
<tr>
<td>Treatment credibility</td>
<td>41 (6.14)</td>
</tr>
</tbody>
</table>
Outcome

Symptoms of ED were measured with the the Karolinska Exhaustion Disorder Scale (KEDS) (Besèr et al., 2014). KEDS consists of nine items rated on a 7-point numerical scale ranging from zero to six. Each item corresponds to one diagnostic criterion of ED. Severity definitions are presented at scores 0, 2, 4, and 6. KEDS has demonstrated good internal consistency with a reported Cronbach’s α of .94 and can be used for measuring changes during treatment (Besèr et al., 2014). Cronbach’s α for KEDS in this study was .75.

Predictors

Demographic variables

The following demographic variables were collected: age (continuous), gender (Male/ Female), marital status (Single or other, Married or living together, Partner living apart), education (Elementary school and/or secondary school, University < 3 years, University > 3 years, other). Socioeconomic status was measured with an ordinal scale ranging from 1 to 10 (1 = less than 100 000 SEK/year, 10 = > 2500 000 SEK/year) based on the recommendations of Diemer et al. (2013) (Diemer et al., 2013). Furthermore, patients were asked if they had a child living at home with a neuropsychiatric or developmental disorder (Yes/No).

For the sub-group analysis, age was categorized into four levels (18–30, 31–40, 41–50, > 50), and socioeconomic status into four levels (< 250 000 SEK/year, 250 000–500 000 SEK/year, 500 000–1000 000 SEK/year, and > 1000 000 SEK/year).

Clinical characteristics

The duration of symptoms before seeking help was measured by asking how many years, months, and days they had experienced symptoms of persistent stress before seeking healthcare for these specific symptoms. These answers were then dummy coded into 0 (< 12 months) or 1 (≥ 12 months).

Previous sick leave due to ED was measured by a yes/no question.

Psychiatric comorbidity was diagnosed during the initial team assessment. The existence of one or more psychiatric comorbid diagnoses were dummy coded into 0 (= no comorbidity) or 1 (= comorbid psychiatric diagnosis).

Persistent pain was measured by two yes/no questions: 1) If the patients regularly experienced pain, and 2) if this pain was periodically recurring or persistent (never free of pain), where answers were dummy coded into 0 (= no persistent pain) or 1 (= persistent pain).

Antidepressant medication was registered at the assessment phase and dummy coded into 0 (= no antidepressant medication) or 1 (= antidepressant medication).

The concurrent symptom burden of depression and anxiety was measured using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). HADS consists of 14 items rated on a 4-point Likert scale, ranging from zero to three. Each subscale (anxiety and depression) has a total score of 21, where a score of ≥ 11 indicates an ongoing mood or anxiety disorder. HADS has satisfactory internal consistency (Bjelland et al., 2002). The Cronbach’s α was .75 for the depression scale and .78 for
the anxiety scale in this study. For the sub-group analysis, answers in each sub-scale were categorized by the recommended HADS cut-off scores: normal/mild (0–10), moderate (11–14), and severe (15–21).

**Treatment-related variables**

*Insomnia* was measured using the Insomnia Severity Index (ISI). The ISI has demonstrated adequate internal consistency (Bastien et al., 2001). Cronbach’s $\alpha$ for ISI in this study was .85. For the sub-group analysis, answers were categorized by the recommended ISI cut-off scores: no/mild (0–14), moderate (15–20), and severe (21–28).

*Physical activity* (PA) was measured with three questions (frequency, intensity, and duration), in accordance with previous research on PA and ED (Lindegård et al., 2015), following the guidelines of the American College of Sports Medicine and the American Heart Association (Haskell et al., 2007). In the current paper, the first question about frequency of training during the previous month was utilized as a categorical variable to measure PA, rated between 1–5 (1 = nothing; 2 = now and then; 3 = 1–2 times/week; 4 = 3–4 times/week; 5 = ≥ 4 times/week).

*Pathological worry* was measured using the Penn State Worry Questionnaire ultra-brief (PSWQ-brief) (Berle et al., 2011). PSWQ-brief consists of three items rated on a Likert scale from 1 (not at all typical for me) to 5 (very typical of me). Despite being a considerably shorter version of the original 16-item version, the PSWQ-brief possesses similar psychometric properties and has shown good internal consistency (Cronbach’s $\alpha$ = .85; Berle et al., 2011). In the current study, Cronbach’s $\alpha$ of the PSWQ-brief was .85. No established cut-offs exist for PSWQ-brief. Therefore, a categorization of three levels was made for the sub-group analysis based on a tertile distribution of scores in the current sample: no/mild (0–9), moderate (10–12), and severe (13–15).

*Perfectionism* was measured using The Clinical Perfectionism Questionnaire (CPQ; 51). The CPQ consists of 12 items ranging on a Likert scale of 1 (not at all) to 4 (all of the time) and the internal consistency, Cronbach’s $\alpha$, is within the acceptable range (.71–.82 for the full self-report measure), depending on the study and sample (Parks et al., 2021). A 10-item version of the Swedish CPQ has been validated (Parks et al., 2021), but to benchmark the scores of CPQ in the current study with previously published treatment studies of clinical perfectionism, the original 12-item version was used. In the current study, Cronbach’s $\alpha$ of the CPQ was .78. No established cut-offs exist for CPQ. However, in a previous randomized controlled trial of clinical perfectionism (Rozental et al., 2017), the treatment group scored an average of 38.26 (SD = 4.63) before treatment. Based on these scores study, a categorization of three levels was made for the sub-group analysis: low (<35), moderate (35–39), and high (≥ 40).

The perceived treatment credibility of the MMI was measured using the Credibility/expectancy Questionnaire (CEQ). The CEQ was administered at the start of treatment, after receiving a thorough description of the treatment but before beginning the MMI. The CEQ consists of five items scored on a 10-point Likert scale and has demonstrated high internal consistency and good test-retest reliability (Devilly & Borkovec, 2000). Cronbach’s $\alpha$ for CEQ in this study was .84. No established cut-offs exist for CEQ. Therefore, a categorization of three levels was made for the sub-group analysis based on the tertile distribution of scores in the current sample: low (0–29), moderate (30–39), and high (≥ 40).
**Statistics**

**Predictor analysis**

All statistical analyses were performed in Jamovi 2.3.16.0 (The Jamovi Project [Computer Software], 2021). Predictors of improvement over time were explored in three steps: First, crude linear mixed-effects models were built separately for each predictor variable, using all five repeated measurements of KEDS (pre, start, mid, post, and 12-month follow-up) with time as a categorical variable and each predictor as fixed effects, and random intercepts for each subject. Interactions between the predictor and each time point were included in all models to let the growth curves vary over time depending on the predictor variable. ANOVA tests of the interaction coefficients between the predictor and time were performed to assess overall differences in growth curves across levels of the predictor variables. All data were analyzed using an intention-to-treat procedure, meaning all patients that started treatment were included in the analysis, irrespective of completion. Missing data were treated as missing at random and handled by the maximum likelihood estimation in the statistical models, assuming all covariates related to missingness were included in the model.

In the second step, separate models were built for each predictor, adjusting for demographic variables (including previous significant interactions). In a third step, one large model was built for the treatment-related variables, adjusting for all demographic variables and clinical characteristics (including previous significant interactions with time) to evaluate the relative contribution of each predictor in relation to one another. To avoid problems with multicollinearity, all continuous variables were mean-centered. The assumption of multivariate normally distributed residuals was evaluated by inspecting Q-Q plots. The homogeneity of the residuals was tested by plotting the residuals against the predicted values. Finally, multicollinearity was assessed using the variance inflation factor, where values < 5 were deemed adequate.

**Subgroup analysis**

Latent Class Analysis (LCA) was used to identify sub-groups using the snowRMM package in Jamovi (Seol, 2022). LCA is a statistical technique that utilizes responses to categorical variables to detect latent homogeneity in samples (Hagenaars & McCutcheon, 2002). Unlike cluster analyses, LCA does not identify cases with the most similar scores on multiple variables belonging to the same class. Instead, LCA is built upon the assumption that latent classes explain similarities of response patterns across different cases and is considered helpful for identifying subgroups of individuals who might benefit from treatment (Weller et al., 2020).

To identify latent classes at baseline, continuous variables were converted into categorical variables (see predictors above). We first estimated a two-class model and then added classes until the best model fit was achieved using both theoretical interpretability and three different statistical criteria: a) the Bayesian information criterion (BIC), b) the Akaike information criterion (AIC), and c) Entropy, with BIC given precedence in case of disagreement among the criteria, since many researchers consider this to be the most reliable and preferred fit indicator in LCA (Weller et al., 2020). Lower scores for BIC and AIC indicate a better fit, and an entropy score closer to 1 is desirable.

Finally, using the final solution of sub-groups from the LCA as a predictor, change over time was explored in a linear mixed-effects model using all five
repeated measurements of KEDS (pre, start, mid, post, and 12-month follow-up) with time and sub-groups as fixed effects, and random intercepts for each subject. Again, an interaction between sub-groups and time was included to model growth curves over time.

**Results**

**Attrition**

The response rate for each of the five measurements points were as follows: Pretreatment questionnaires 100% ($N = 915$); treatment start 99% ($n = 910$); mid-treatment 98% ($n = 894$); post-treatment 95% ($n = 870$); 12-month follow-up 86% ($n = 784$).

**Predictors of improvement over time**

**Demographic variables**

Age was the only demographic predictor that showed a significant interaction with time on KEDS, $F(4, 3454) = 6.52$, $p < .01$ (**Table 2**). The plot of the age*time interaction (**Figure 1**) shows that being older was associated with a lesser improvement in KEDS than being younger.

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>Crude</th>
<th>Adjustment 1</th>
<th>Adjustment 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Gender</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Marital status</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Education</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Child with disability</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms&gt;1 year</td>
<td>NS</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Previous sick leave due to ED</td>
<td>**</td>
<td>*</td>
<td>-</td>
</tr>
<tr>
<td>Psychiatric comorbidity</td>
<td>NS</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Antidepressant medication</td>
<td>NS</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Persistent pain</td>
<td>NS</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Anxiety</td>
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<tr>
<td>Depression</td>
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</tr>
<tr>
<td>Treatment-related variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Worry</td>
<td>NS</td>
<td>NS</td>
<td>*</td>
</tr>
<tr>
<td>Perfectionism</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Physical activity</td>
<td>**</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Treatment credibility</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
</tbody>
</table>

Adjustment 1: adjusted for all demographic variables, including significant interactions with time.  
Adjustment 2: adjusted for all demographic variables, clinical characteristics, and treatment-related variables, including all significant interactions with time.  
NS: non-significant interaction with time.  
*Significant interaction with time $p < 0.05$.  
**Significant interaction with time $p < 0.01$.  

**Table 2.** Demographic, clinical characteristics, and treatment-related variables and their association with differences in exhaustion symptom levels over time (i.e. interaction with time).
Figure 1. Graphs depicting the estimated mean values from all separate predictors of improvement showing a significant interaction with time on symptoms of exhaustion (crude models), measured with the Karolinska exhaustion disorder scale (KEDS).
**Clinical characteristics**

Of the clinical characteristics, “previously on sick leave due to ED” (F(4, 3451) = 4.24, p < .01), anxiety (F(4, 3447) = 5.84, p < .01) and depression (F(4, 3448) = 7.08, p < .01) showed significant interactions with time on KEDS. These interactions remained significant when adjusting for demographic variables (adjustment 1). The plot of the previously ED*time interaction (Figure 1) shows that patients previously being on sick leave due to ED improved less on KEDS during treatment than patients who had not.

The plot of the anxiety*time interaction (Figure 1) shows that patients with a high degree of anxiety reported more ED symptoms at the start of treatment compared to patients with lower degrees of anxiety. However, between pretreatment and treatment start differences in ED symptoms between high and low anxiety decrease and then continue to be parallel throughout and after treatment. The same pattern occurs in the depression*time interaction KEDS (Figure 1); At the start of treatment, patients with high degrees of depressive symptoms report higher degrees of ED symptoms, but as treatment starts, differences have decreased somewhat and remain parallel throughout and after treatment.

**Treatment-related variables**

Of the treatment-related variables insomnia (F(4, 3454) = 5.77, p < .01), perfectionism (F(4, 3438) = 8.92, p < .01), physical activity (F(16, 3441) = 2.03, p < .01) and treatment credibility (F(4, 3448) = 8.59, p < .01) showed significant interactions with time on KEDS. All these interactions remained significant when adjusting for demographic variables (adjustment 1) and demographic variables, clinical characteristics, and treatment-related variables (adjustment 2).

In the plot of the insomnia*time interaction (Figure 1), the same pattern seen in the interactions of depression and anxiety is repeated; a high degree of insomnia pretreatment is associated with higher ED symptoms compared to patients with lower degrees of insomnia. At treatment start, these differences in ED symptoms decreased somewhat and remain parallel throughout and after treatment.

Looking at the plot of perfectionism*time interaction (Figure 1), patients who reported high degrees of perfectionism at the start of treatment report higher degrees of ED symptoms than patients with a low degree of perfectionism. However, at the end of treatment, no difference remained in ED symptoms between patients with high and low perfectionism, indicating that patients with high degrees benefit more from treatment.

In the plot of physical activity*time interaction (Figure 1) it is difficult to discern a connection between levels of physical activity at the start of treatment and changes in ED symptoms over time. Overall, patients with no training reported more ED symptoms than those working out. As treatment progressed, differences in ED levels decreased, except for patients training “now and then,” whose trajectories muddies the interpretation.

Finally, the plot treatment credibility*time interaction (Figure 1) shows that patients reported the same amount of ED symptoms regardless of treatment credibility pretreatment. As treatment progressed, patients who perceived a high treatment credibility improved more than those who perceived low treatment credibility.
**Latent class analysis**

Results from the LCA supported the existence of sub-groups of ED patients at baseline before starting treatment. Table 3 presents the results of the latent class analysis’s five different class models. A three-class structure (Figure 2) of the class models explored was selected based on favorable BIC and model interpretability. However, it should be noted that the other fit criteria did not indicate a three-class solution.

Differences across the three sub-groups mainly concerned education, socioeconomic status, insomnia, depression, perfectionism, marital status, anxiety, and worry, with differences in education, marital status, socioeconomic status, anxiety, and worry being most pronounced. Based on differences in scores, the subgroups were named “partner

**Table 3.** Model fit and diagnostic criteria for latent class analyses.

<table>
<thead>
<tr>
<th>Models</th>
<th>LL</th>
<th>AIC</th>
<th>BIC</th>
<th>Entropy</th>
<th>SALCPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Class</td>
<td>−13549</td>
<td>27231</td>
<td>27554</td>
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<td>0.94</td>
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<td>27543</td>
<td>0.77</td>
<td>0.84</td>
</tr>
<tr>
<td>5 Class</td>
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<td>26929</td>
<td>27742</td>
<td>0.76</td>
<td>0.71</td>
</tr>
<tr>
<td>6 Class</td>
<td>−13222</td>
<td>26849</td>
<td>27827</td>
<td>0.76</td>
<td>0.74</td>
</tr>
</tbody>
</table>

LL = log-likelihood; AIC = Akaike information criterion; BIC = Bayesian information criterion; SALCPP = smallest average latent class posterior probability.

**Figure 2.** The final 3-class solution from the latent class analysis is depicted by the average score for each categorical variable explored across each identified latent class (sub-group).
high neuroticism” \((n = 253, 28\%)\), “single lower income” \((n = 252, 28\%)\), and “partner low neuroticism” \((n = 407, 44\%)\). The mixed effects model using the three-class solution as a predictor showed a significant interaction between the subgroups and time on KEDS \((F(8, 3438) = 3.28, p < .001\)).\) Looking at the plot of the subgroup*time interaction in Figure 3, there is an apparent main effect (parallel lines) between the three sub-groups. Over time, the improvement in the group “single lower income” stagnated, indicating a less beneficial trajectory than the other two sub-groups.

**Discussion**

The present study aimed to explore predictors of improvement during treatment in a large sample of ED patients \((N = 915)\). In step one, we separately explored demographic variables, clinical characteristics, and treatment-related variables as predictors of improvement in ED symptoms over time. In step two, the existence of sub-groups was explored using the variables from step one to investigate whether similarities across a combination of variables predicted improvement in ED symptoms over time.

Of all the variables explored, younger age, no previous sick leave due to ED and scoring high on anxiety, depression, insomnia, physical activity, perfectionism, and treatment credibility separately emerged as significant predictors of symptom
improvement. The sub-group analyses yielded a three-class structure with subgroups named “partner high neuroticism” (28%), “single lower income” (28%), and “partner low neuroticism” (44%). The mixed model using the suggested sub-groups as a predictor of change showed a significant interaction over time, indicating a less beneficial trajectory in the sub-group “single lower income”.

**Demographic variables and clinical characteristics**

In the current study, age was the only demographic variable that significantly predicted improvement in ED symptoms over time. Albeit a small effect (Figure 1), being younger seems to be associated with more improvement of ED symptoms during treatment. In the context of ED, younger age as a predictor of improvement is a novel finding since previous research has indicated that age is not important in understanding the progression of ED symptoms during treatment (Glise et al., 2012). However, previous studies of ED populations have been considerably smaller, so the lack of previous findings regarding younger age as a predictor of improvement could potentially be an issue of statistical power.

Regarding clinical characteristics, previous sick leave due to ED was associated with less improvement during treatment. This predictor remained significant when controlling for age, seeing that age was also a significant predictor, and older age is presumably linked to an increased chance of repeated ED episodes. The association between repeated ED episodes and worse progression is not unexpected, given our understanding of neighboring psychiatric disorders. For instance, similar patterns are seen in depressive disorders, where prior episodes increase the likelihood of subsequent episodes and lead to more rapid relapses (Burcusa & Iacono, 2007). Previous ED research has found symptom duration before seeking consultation to be a negative predictor of symptom development, which has been interpreted as an indication of the importance of recognizing early signs of ED (Glise et al., 2012). While this finding was not replicated, the current study further adds to the notion of clinically acknowledging symptoms of persistent stress early, as repeated illness episodes appear to be associated with somewhat less improvement in ED symptoms during treatment.

Reporting high levels of anxiety and depression was associated with greater improvement in ED symptoms between pre-measurement and treatment start. However, in Figure 1, the graphs of anxiety and depression clearly show the apparent main effects of depression and anxiety (parallel lines), indicating a higher degree of overall symptom burden before and after treatment. Thus, rather than being indicative of treatment gains, we interpret the results of anxiety and depression as an expression of a high correlation between anxiety, depression, and ED symptoms and that high levels of ED symptoms before treatment are associated with a larger room for improvement over time.

In summary, results demonstrating that age and previous sick leave due to ED are significant predictors of improvement during ED treatment are novel findings that are potentially scientifically interesting and warrant further research. However, individuals of older age or previous sick leave due to ED also describe large symptom improvements during treatment. Therefore, these findings have limited practical significance from a clinical standpoint due to the small effects demonstrated and the inherent inability to target these variables with treatment. Instead, based on the results from the current study, clinicians should probably avoid making assumptions about treatment efficacy based
solely on patient demographics or clinical characteristics, since patients with ED participating in MMI report improvements in their symptoms regardless of these variables.

**Treatment-related variables**

Of the treatment-related variables explored, all but one (worry) were significant predictors of improvement. When interpreting the patterns from the graphs of each growth model over time (Figure 1), treatment credibility and perfectionism stood out as potentially clinically relevant treatment-related variables, while physical activity and insomnia did not. For physical activity, it is hard to discern a connection between levels of physical activity at the start of treatment and changes in ED symptoms over time (Figure 1). So, although significant, no clear interpretation of the direction of physical activity as a predictor can be made.

In the plot of the insomnia*time interaction (Figure 1), the same pattern seen in the interactions of depression and anxiety is repeated; a high degree of insomnia at the pretreatment of treatment is associated with improvements in ED at the treatment start. However, the graph also depicts an apparent main effect (parallel lines), indicating that high levels of insomnia before treatment are associated with higher mean ED symptoms both before and after treatment. As with anxiety and depression, we interpret this as an expression of a high correlation between insomnia and ED symptoms and that a high level of ED symptoms pretreatment is associated with a larger room for improvement over time.

The patients scoring high on perfectionism before treatment reported higher degrees of ED symptoms and proportionally improved more during treatment. Compared to anxiety, depression, and insomnia, there does not seem to be a main effect, and all patients end at the same ED levels, regardless of levels of perfectionism before treatment. This pattern could be interpreted as 1) perfectionism is a possible risk factor in developing ED since high degrees of perfectionism are associated with higher scores of ED symptoms pretreatment and 2) patients with high perfectionism benefit more from treatment. Previous research has highlighted patients with ED struggling with high demands (Gulin et al., 2021), and perfectionistic concerns seem to be associated with the development of burnout (Hill & Curran, 2016). In the current study, participants rated an average of 33.76 (SD 6.26) on the CPQ, which is high considering previous populations in treatment studies of perfectionism range between 35.53–38.26 (Riley et al., 2007; Rozental et al., 2017). Challenging perfectionistic behaviors are common in ED treatment, and it is a component of the treatment delivered to the patients in the current study (van de Leur et al., 2020). It can therefore be suggested with some degree of justification that future research focus on the role of perfectionism in the development and maintenance of ED. Both these avenues should be further investigated since the risk factors for developing ED are not necessarily the same variables that should be the focus of treatment.

Finally, scoring high on treatment credibility at the start of treatment was associated with larger improvements in ED symptoms over time. These results further add to the evidence that patients who believe in treatment report more considerable treatment gains (Constantino et al., 2019; Salomonsson et al., 2019; Smeets et al., 2008; Wampold, 2015). Therefore, in treating ED, as with other forms of mental
illness, ensuring patients believe in the treatment rationale seems important in maximizing treatment results. Furthermore, the variables perfectionism and treatment credibility identified as predictors in the current study indicate that ED symptoms do not necessarily follow a determined progression identical for all individuals. Instead, the course of ED seems to be associated with other variables, variables that are possible to target in treatment. Due to the limited understanding of the progression of ED and its treatment, the current study utilized a comprehensive explorative approach. However, future research will probably benefit from a more theory-driven approach to further illuminate the role of treatment-related variables in understanding the development and maintenance of ED.

**Sub-group analysis**

In the mixed effects model using the three-class solution as a predictor, the subgroups of “partner low neuroticism” started at lower levels of ED symptoms and had the same trajectory as “partner high neuroticism, which started at a higher level. That scoring high across anxiety, worry, depression, insomnia, and perfectionism is associated with higher levels of ED symptoms does not come as a surprise. What stood out was the somewhat less beneficial trajectory of the “single lower income” sub-group. In treating depression, being married is a predictor of treatment success (Hamilton & Dobson, 2002). While being single and having a lower socioeconomic status are correlated, these factors likely limit one’s ability to make lifestyle changes that promote recovery over time. The current study, the trajectories are only measured over 18 months. Over time, however, these trajectories could be reinforced. So, while the three-class solution found in the current study has no clinical implications, future clinical research could investigate whether being single and having a lower income warrants further attention.

Additionally, it’s worth noting that while the LCA aimed to identify latent homogeneity across variables at baseline, it did not provide insights into the potential additive effects of multiple predictors on an individual level. For instance, it did not consider the potential cumulative effects of predictors such as being older and having prior sick leave due to ED on symptoms development during treatment. These cumulative effects could be a valuable area of investigation for future research.

**Limitations and strengths**

The strengths of the current study include the large sample from a clinical setting (N = 915) with low attrition, ensuring high power with good clinical applicability, and enabling the exploration of several different predictor variables simultaneously. The study’s generalizability and external validity are strengthened by several factors, including a large sample size, a rigorous assessment procedure involving three professionals, and inclusive criteria for comorbidity. Furthermore, data collection took place in two natural clinical settings, further enhancing the study’s external validity. Consequently, albeit restricted to one geographical area, given the sample size, we estimate the current study population to be representative of ED patients in general. Lastly, the order of all questionnaires was randomized at each instance of administration to reduce the risk of instrumentation bias.
The absence of a control group is a significant limitation of the current study, as it precludes the ability to infer causality between treatment and symptom improvement. The improvements described could result from spontaneous recovery or other confounding variables. Furthermore, the patterns of anxiety, depression, insomnia, and perfectionism could be an expression of regression to the mean, meaning extreme values tend to move towards the average when sampled repeatedly over time. However, this explanation seems less plausible for perfectionism due to the low correlation between perfectionism and ED symptoms pretreatment, identified through the absence of a main effect. Finally, while the three-step procedure used in the separate predictor analyses helped to account for shared variance among the predictors, it is worth noting that many of these constructs correlate. While this may reflect genuine associations, it could also be partly due to a lack of measurement specificity. No international agreement exists on how exhaustion due to persistent non-traumatic stress is diagnosed or measured and the specific symptom presentation of ED as well as its overlap with other psychiatric and somatic conditions, are not yet fully understood (Lindsäter et al., 2023). Consequently, we encourage future research to develop and use more refined measurements to elucidate better the relationships between, for example, anxiety, depression, and ED.

Due to the exploratory nature of the current study, the findings presented here need to be replicated, especially the LCA results, since this method is data-driven, and the models produced depend on particular data sets. That being said, exploratory studies followed by further conceptual work constitute critical steps in increasing the knowledge of subgroups and change processes (Kazdin, 2007) - especially in nascent research areas such as ED treatment, where the understanding of subgroups, risk factors, and treatment-related variables is still limited.

**Conclusions**

In the current study, we explored demographic variables, clinical characteristics, and treatment-related variables as predictors of improvement in ED symptoms during treatment, separately and across a range of variables in the form of subgroups. Younger age, no previous sick leave due to ED and scoring high on anxiety, depression, insomnia perfectionism, and treatment credibility separately emerged as predictors of symptom improvement. The sub-group “single lower income” was associated with less improvement. While the findings that being older, having previously been on sick leave due to ED, and the subgroup “single lower income” was associated with less improvement are potentially scientifically interesting, their clinical utility appears limited because their effects are minor and cannot be targeted in treatment. Instead, the overall impression is that ED patients participating in CBT-based MMI report symptom improvement regardless of demographic variables, clinical characteristics, treatment-related variables, or subgroup membership. The findings of perfectionism and treatment credibility do, on the other hand, have the potential to inform the treatment practices of ED. Perfectionism, as a predictor for symptom improvement in the current study, suggests perfectionism is potentially important in treating ED. Furthermore, efforts to ensure ED patients understand and believe in the treatment rationale should be encouraged, as high perceived treatment credibility seems to be associated with larger improvements in ED symptoms during treatment.
Disclosure statement

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