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Mediators during a Multimodal intervention for stress-induced exhaustion disorder

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ABSTRACT

Our understanding of the underlying psychological processes of development, maintenance, and treatments for stress-induced exhaustion disorder (ED) remains limited. Therefore, the current study aimed to explore whether sleep concerns, pathological worry, perfectionistic concerns, and psychological flexibility mediate change in exhaustion symptoms during a Multimodal intervention for ED based on Cognitive behavioral therapy principles. Participants ($N = 913$) were assessed at three time points, and mediation was explored using a two-criteria analytical model with linear mixed-effects models (criterion one) and random intercepts cross-lagged panel modeling (criterion 2). Criterion one for mediation was successfully met, as the findings indicated significant associations between time in treatment, with all suggested mediators, and exhaustion symptoms (significant ab-products). However, criterion two was not satisfied as changes in the mediators did not precede changes in exhaustion symptoms. Therefore, mediation could not be established. Instead, changes in the suggested mediators appeared to result from changes in exhaustion symptoms. Consequently, sleep concerns, pathological worry, perfectionistic concerns, and psychological flexibility appear to improve in conjunction with exhaustion symptoms during treatment, where improvement in exhaustion is indicated as the main driving factor, based on this exploratory analysis. The implications of these findings are contextualized within a broader framework of process-based therapy.

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Burnout; Exhaustion disorder; multimodal intervention; mediators; process of change

Introduction

The incidence of stress-related disorders is rising in the Western world, leading to increased sick leave, and reduced productivity (Cooper, 2009; Eurofound, 2018; European Agency for Safety and Health at Work et al., 2014). Considering these developments, exhaustion due to persistent non-traumatic stress has garnered increased

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public and academic attention (Parker & Tavella, 2022). There is currently no internationally accepted nomenclature for exhaustion due to persistent non-traumatic stress, and different terms are utilized; Clinical burnout, exhaustion disorder, job stress-related depression, and possibly neurasthenia (Wallensten et al., 2019). In Sweden, this condition is classified using the diagnosis of "stress-induced Exhaustion disorder" (ED; International Classification of Diseases, 10th Revision, code F43.8A; Kalliomäki & Brodda Jansen, 2021). ED is characterized by a debilitating state of exhaustion coupled with severe impairments in working memory and attention and is considered the end-stage of a severe burnout process that requires professional healthcare interventions (Grossi et al., 2015; van Dam, 2021). Numerous treatment studies for ED have been conducted, albeit with inconclusive results (Lindsäter et al., 2022). Hence, the current understanding of effective ED treatment, including what mechanisms should be the focus of clinical interventions, is limited.

Most research on the underlying mechanisms of ED has adopted a biological perspective, focusing on neuroimaging and potential biomarkers (Golkar et al., 2014; Hadrévi et al., 2019; Hansson et al., 2022; Lennartsson et al., 2015; Savic et al., 2018; Sjörs & Jonsdottir, 2015; Wallensten et al., 2016, 2021, 2021). These efforts have yet to yield any conclusive results (Lindsäter et al., 2022), and currently provide little insight into the underlying processes that give rise to and sustain ED, a knowledge gap hampering the development of effective clinical interventions. Meanwhile, the psychological processes of ED are still relatively unexplored, which is apparent in the published interventional research, where few studies describe a theory of ED processes and deploy interventions that target these processes specifically (van de Leur et al., 2023).

Current developments in psychological treatment research now call for treatment research to shift its focus towards treatments that (a) incorporate testable theories, (b) target specific evidence-based processes of change, and (c) cater to the unique needs of individual patients (Hayes & Hofmann, 2021; Hayes et al., 2019). Change processes refer to the specific variables through which a treatment exerts its influence on a targeted dependent variable (Kazdin, 2007). These processes should be theory-based, characterized by testable predictions, and are assumed to be dynamic and multilevel (Hofmann & Hayes, 2019). Conventionally, research into change processes has included the identification of mediators. Specifically, mediators are intermediate variables on the causal path from treatment to outcome (Kazdin, 2007; Kraemer et al., 2002).

Several variables that could mediate the treatment of ED have been identified. Prospective studies of patients with ED indicate that sleep is important in the recovery of ED (Ekstedt et al., 2009; Grossi et al., 2015; Söderström et al., 2012). A randomized controlled trial (RCT) of Cognitive behavioral therapy (CBT) for patients with adjustment disorder and ED considered insomnia, behavioral activation, perceived competence, and therapeutic alliance as potential mediators of exhaustion symptoms (Santoft et al., 2019). Positive changes in symptoms of exhaustion (measured with the Shirom Melamed Burnout Questionnaire) were partially mediated by improvements in insomnia and perceived competence. The importance of insomnia as a mediator of change in symptoms of exhaustion has later been corroborated in another RCT of Internet-CBT for ED and adjustment disorder (Lindsäter et al., 2021). However, there is some conceptual overlap between insomnia and ED, as sleep disturbance is a common symptom of ED. In fact, the

Karolinska Exhaustion Disorder Scale (KEDS), often used to measure ED symptoms, includes an item specifically related to sleep disturbances. To clarify the mediating role of insomnia further, the psychological component of insomnia, such as being concerned about and worrying about one's sleep, needs to be investigated.

In addition to insomnia, a recent theoretical review highlighted pathological worry and perfectionism as potential psychological change processes of ED (Almén, 2021). Worrying increases sympathetic activation and can interfere with sleep and relaxation (Brosschot et al., 2007; Ekstedt et al., 2009; Murnieks et al., 2020), which seems to be important in the treatment of ED (Almén, 2021). Furthermore, pathological worry has been highlighted as a potentially important transdiagnostic variable for understanding the development and maintenance of psychopathology in general (McLaughlin & Nolen-Hoeksema, 2011). Although various clinical trials of ED have described interventions targeting worry and rumination (van de Leur et al., 2023), to our knowledge, no study has yet explicitly focused on pathological worry as a potential change process in ED treatment.

Patients with ED often seem to struggle with high demands, perfectionism, and overcommitment (Avanzi et al., 2014; Gulin et al., 2021). While various definitions of perfectionism exist, most tend to converge on two higher-order dimensions: Perfectionistic strivings (which refer to high personal standards and self-oriented striving for perfection) and Perfectionistic concerns (which refer to the fear of making errors and worrying about being negatively evaluated by others). Of these dimensions, it is primarily perfectionistic concerns that have been linked to an increased risk of psychopathology (Limburg et al., 2017; Stoeber & Damian, 2014). As with pathological worry, perfectionism is suggested to be a transdiagnostic variable (Egan et al., 2011), and several published trials of ED treatment describe interventions targeting "performance-based-self-esteem" and perfectionistic behaviors (Gavelin et al., 2018; Lindsäter et al., 2018; van de Leur et al., 2020). However, to our knowledge, no prior study has explored the potential role of perfectionistic concerns as a mediator in the treatment of ED.

Other treatment components often described in clinical trials of ED are mindfulness exercises and the identification of core life values—methods usually associated with Acceptance and Commitment Therapy (ACT (Finnes et al., 2017; Lindsäter et al., 2018).; Psychological flexibility is a key concept in ACT as it is considered a core process critical in both the development and maintenance of psychopathology. It can be broadly defined as the ability to persist or change behavior in a way that includes conscious and open contact with internal experiences, together with an appreciation of what each situation entails with respect to one's values and goals (Hayes et al., 2006; Lundgren & Parling, 2016; McCracken & Morley, 2014). Despite being a target of many ED treatments, psychological flexibility has yet to be investigated as a potential process variable in the treatment of ED.

In light of what has been discussed above, the aim of the current study was to explore whether sleep concerns, pathological worry, perfectionistic concerns, and psychological flexibility mediate change in symptoms of exhaustion during treatment in a large sample of patients receiving a Multimodal intervention (MMI) for ED. Since data were analyzed within an exploratory framework, no *a priori* hypotheses were formulated.

Method

Study design

The present study uses data from an open clinical trial conducted at two units at a clinic (PBM Sweden AB) in Stockholm, Sweden, specializing in MMI for chronic pain and ED. Data collection was registered on Clinicaltrials.gov (Identifier: NCT03360136) and adhered to the ethical principles of the Declaration of Helsinki. It was approved by the Regional Ethical Review Board in Stockholm, Sweden (Approval Nr. 2016/1834–31/2). Other aspects of this sample, such as treatment outcomes, predictors of improvement and sub-groups, have previously been published (van de Leur et al., 2020, 2023, 2023).

Participants and recruitment procedure

Both units were part of a care program called "The health care choice for treatment of longstanding pain with or without comorbidity, and ED," on behalf of Health Care Services Stockholm County. Referrals came from general practitioners, primary health care, and various occupational health services.

Multi-professional teams comprising a licensed psychologist, a licensed physician, and a licensed physiotherapist evaluated all participants. A total of 1643 patients underwent assessment between September 2017 and March 2019. Of these, 472 did not meet the inclusion criteria, 73 were enrolled in a shorter treatment program, and 15 were offered rehabilitation for chronic pain instead. All patients at both units included in the standard 24-week MMI for ED were invited to participate. Out of the total 1083 patients invited to participate in the study, 151 declined to participate, and 17 withdrew before treatment commenced, leaving 915 patients. The variables assessed in the current study were unavailable for two participants, and as a result, they were excluded from the analysis, resulting in a final sample of 913.

Inclusion and exclusion criteria

Inclusion criteria for the study were: a) fulfilled the Swedish criteria for ED; b) described being severely limited in work and leisure time activities due to ED symptoms; c) > 4.5 on the Shirom-Melamed Burnout Questionnaire (SMBQ (Melamed et al., 1992); a cut-off stipulated by care program described above (see Participants and recruitment procedure); d) 18–65 years of age; e) suitable for group treatment.

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

Treatment

The treatment was administered by a multi-professional team comprising a licensed M. D., a licensed psychologist, a rehabilitation coordinator (occupational therapist, licensed nurse, or licensed psychologist), and a licensed physiotherapist. The MMI was group and

individually based and centered on CBT. In short, the intervention was based on functional analyses and included a range of established CBT components such as applied relaxation, mindfulness, valued action, behavioral activation, exposure, and assertiveness training, together with the promotion of physical exercise. A detailed account of the MMI has been provided previously (van de Leur et al., 2020).

Measurements

Demographic and psychological variables were collected during the assessment phase, at the start of treatment, mid-treatment (after 12 weeks), post-treatment (after 24 weeks), and at 12-month follow-up. In the current study, only measurements from treatment start, mid-treatment and post-treatment are utilized. All questionnaires were reliably administered digitally through a secure online login (Hedman et al., 2010). To reduce the risk of instrumentation bias, the order of the questionnaires was randomized with each dispatch.

Primary outcome measure

Exhaustion symptoms were measured using the Karolinska Exhaustion Disorder Scale (KEDS) (Besèr et al., 2014). KEDS consists of nine items, each corresponding to one of the diagnostic criteria of ED, rated on a numerical scale from 0–6. With a reported Cronbach's α of .94, KEDS has good internal consistency and can be utilized for tracking changes in symptoms during treatment (Besèr et al., 2014). In the current study, Cronbach's α for KEDS was .75.

Suggested mediators

Sleep concerns were measured by the Insomnia Severity Index (ISI). ISI has demonstrated good internal consistency and is considered a reliable measure of change in insomnia during treatment (Bastien et al., 2001). Cronbach's α for ISI in this study was .85. As mentioned earlier (see introduction), KEDS includes one item about sleeping difficulties. To investigate sleep concerns as a psychological process variable in relation to exhaustion symptoms rather than as an outcome, the following three questions of ISI were used: 4 (How satisfied/dissatisfied are you with your current sleep pattern?), 5 (How noticeable to others do you think your sleep problem is in terms of impairing the quality of your life?) and 7 (To what extent do you consider your sleep problem to interfere with your daily functioning—e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.- currently?). In a previous study, these three items, together with item 2 of ISI (difficulties staying asleep), have shown a Cronbach's α of .88 with good construct validity and to effectively assess insomnia in chronic pain patients (Wiklund et al., 2018). An exploratory factor analysis was performed on the current dataset to ensure the validity of ISI-3. This factor analysis, based on an eigenvalue greater than 1, revealed a one-factor solution explaining 71.4% of the variance, with a satisfactory factorability (Bartlett's test of sphericity: $\chi^2 = 1494$, $df = 3$, $p < .001$). Furthermore, ISI-3 showed a Cronbach's α of .88, indicating satisfactory reliability.

Pathological worry was measured by the Penn State Worry Questionnaire ultra-brief (PSWQ-brief) (Berle et al., 2011). PSWQ-brief consists of three items rated on a numerical rating scale from 1 (not at all typical for me) to 5 (very typical of me). The PSWQ-brief retains similar psychometric properties despite being substantially shorter than the original 16-item version, with a reported Cronbach's α = .85. Cronbach's α of the PSWQ-brief was .85 in the current study.

Perfectionistic concerns were measured by the subscale "perfectionistic concerns" from the Swedish Clinical Perfectionism Questionnaire (CPQ). The CPQ initially consisted of 12 items ranging on a numerical rating scale of 1 (not at all) to 4 (all of the time) and was created to measure the construct of clinical perfectionism (Egan et al., 2016). However, studies exploring the psychometric properties of CPQ have shown a two-factor structure; *perfectionistic strivings* and *perfectionistic concerns* (Dickie et al., 2012; Stoeber & Damian, 2014). In a recent publication, the Swedish version of CPQ was validated, showing an acceptable internal consistency (Cronbach's α = .72), and once the two reversed items in the original 12-item scale were removed, a confirmed two-factor structure (Parks et al., 2021). In the current study, the Cronbach's α of the Swedish 10-item version of the CPQ was .80, and 0.79 for the 5-item subscale *perfectionistic concerns*.

Psychological flexibility was measured by The Swedish Acceptance and Action Questionnaire (SAAQ) (Lundgren & Parling, 2016). The SAAQ contains six items rated on a numerical rating scale from 1 (never true) to 7 (always true) and has previously been shown to have good test-retest reliability and acceptable internal consistency (Cronbach's α = .85). In the current study, the Cronbach's α of the SAAQ was .86.

Statistics

Meditation was explored using two criteria; 1) There had to be an established effect of time in treatment on mediators, which in turn was associated with levels of exhaustion symptoms, and 2) within-individual change in the suggested mediators preceded the subsequent change in exhaustion symptoms. These criteria were explored using two statistical methods: linear mixed-effects models and random intercepts crossed-lagged panel modeling (RI-CLPM). All analyses were done in R version 4.1.3 (R Core Team, 2022).

Criteria one—effects of time in treatment on mediators

To establish criteria one, we utilized the mediation procedure by Baron and Kenny (1986) and Preacher and Hayes (2008) in four steps. First, three linear mixed-effects models were built for each mediator (M) of interest (sleep concerns, pathological worry, perfectionistic concerns, and psychological flexibility) to estimate the estimate a-, b-, c, c ´- and ab-paths connecting the independent variable (X), mediators (M), and the dependent variable (Y), here defined as exhaustion symptoms. Since there was no control group in the current study, X was defined as "time in treatment" (treatment start, mid-treatment, and post-treatment), assuming a linear change over time on mediators as well as symptoms of exhaustion, a procedure previously used in clinical trials (Bjureberg et al., 2017, 2018; Särnholm et al., 2021). The first mixed-effects model estimated the C-path. i.e. the relation between time in treatment (X) and exhaustion symptoms (Y), not

conditional on any of the mediators. The second mixed-effects model estimated the a-path between time in treatment (X) and the mediator (M). Finally, the third mixed-effects model estimated c' (c-prime)—change in the outcome not explained by the mediators—and b-path, i.e. the cross-sectional association between the mediator (M) and exhaustion symptoms (Y), when controlling for time in treatment (X). In this third model, sex, age, marital status, level of education, socioeconomic status, and "being on antidepressant medication pre-treatment" and "individual clinical psychologist during treatment" were also added as covariates. In the fourth step, the ab-path, i.e. the total mediated effect (or indirect effect), was calculated as the product of the a and b estimates, in accordance with the recommendations of Preacher and Hayes (2008). All three steps of the mixed-effects models for each mediator were bootstrapped 5000 times to obtain a 95% confidence interval (CI) around the ab-product to ensure statistical significance. The criterion for mediation was a CI not including zero.

Following the separate models for each mediator, a multiple mediator model was created to account for covariance between the four mediators (Preacher & Hayes, 2008), see Figure 1. This multiple mediator model was estimated using the same four steps described above. Here, the a-paths were calculated separately for each mediator, while the b-paths and c' were calculated using one model containing all mediators. Furthermore, the proportion of mediated change was calculated for the individual mediator models and the multiple mediator model, using the formula *ab/c* for each path, respectively (Preacher & Kelley, 2011).

Criteria two—within individual change and time precedence

RI-CLPM was utilized to explore if a within-individual change in the suggested mediators preceded the subsequent change in exhaustion symptoms or if a within-individual change in exhaustion symptoms preceded the subsequent change in the suggested mediators (Hamaker et al., 2015; Mulder & Hamaker, 2021). One model was built for each suggested mediator using lavaan 0.6–13 for R (Rosseel, 2012). Model fit was assessed using comparative fit index (CFI), Tucker-Lewis index (TLI), standardized root mean

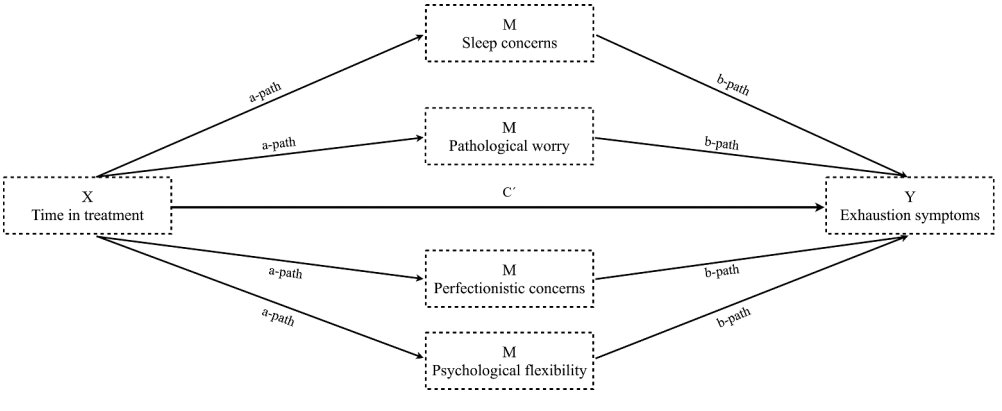

Figure 1. Model of all paths analyzed in multiple mediation analysis. X = independent variable. *M* = mediator. Y = dependent variable.

square residual (SRMR), and root mean squared error of approximation (RMSEA). To avoid problems with multicollinearity, all variables were mean-centered.

In a RI-CLPM, the variance is broken down into: 1) stable differences between persons (trait-like stability), represented by random intercepts (B-KEDSi and B-MEDi in Figure 2), and 2) with-in-unit fluctuation around the individual means (W-KEDSi and W-MEDi in Figure 2). The auto-regressive paths represent state-like stability over time at the with-in-person level. The cross-lagged paths between variables over time (β and γ in Figure 2) show whether a deviation from an individual's expected score (as determined by their random intercept) at one measurement point predicts a deviation from the expected score at the next measurement (Mulder & Hamaker, 2021). This procedure enables the investigation of whether the variables of interest predict each other over time and which variable is the dominant causal factor. In other words, utilizing RI-CLPM enabled us to investigate the direction of the b-path under criteria one; Whether a change in the suggested mediators led to a change in exhaustion symptoms over time at an individual level, or if it was the other way around.

Mirroring a procedure described by Axelsson et al. (2020), the temporal precedence of the suggested mediators in relation to exhaustion symptoms was evaluated in three steps. Firstly, we performed significance testing of the cross-lagged paths between the suggested mediators and succeeding exhaustion symptoms, and vice

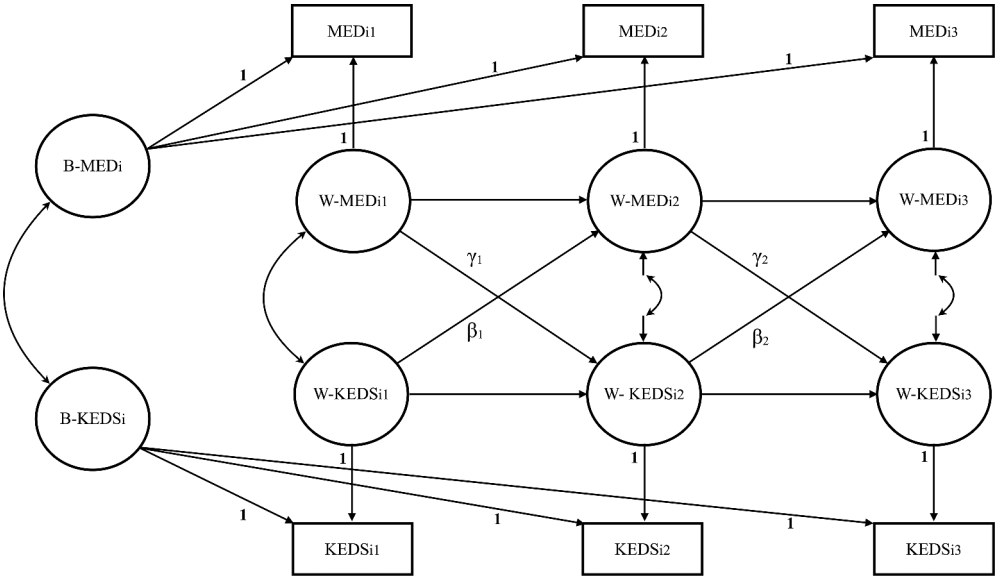

Figure 2. $KEDS_{it}$ denotes the observed exhaustion symptoms, and MED_{it} denotes the observed mediator of unit *i* at occasion *t*($n = 3$; 1 = treatment start, 2 = mid-treatment, 3 = post treatment). *B* denotes the between components of the model, i.e. random intercepts representing the stable difference between units over time. *W* represents the within components of the model, representing differences between a unit's observed score and the unit's expected score. γ represents the cross-lagged effects of deviations in the suggested mediator at occasion *t* on subsequent deviations on exhaustion symptoms at occasion t_{+1}. Conversely, β represents the cross-lagged effects of deviations in exhaustion symptoms at occasion *t* on the subsequent deviations in the suggested mediator at occasion t_{+1}.

versa (γ and β in Figure 2). Secondly, we compared the coefficients for these cross-lagged paths using the completely standardized solution, meaning all effects, including factor loadings, are standardized to facilitate scale-free comparison between effects within and between the models. Finally, we tested the statistical significance of the difference between the unstandardized coefficients for the cross-lagged paths (γ - β in Figure 2).

Participants had not received any treatment at the initial point of measurement (treatment start), and any changes observed at mid-treatment (represented by γ1 and β1 in Figure 2) could, therefore, not be attributed to treatment participation. As a result, when investigating the temporal precedence of the suggested mediators in relation to exhaustion symptoms, the cross-lagged paths between mid-treatment and post-treatment (γ2 and β2 in Figure 2) were prioritized.

Results

Attrition

Pretreatment characteristics of participants is presented in Table 1. Of the 913 patients, 97% completed treatment ($n = 888$), and 3% dropped out ($n = 25$). The response rate for each of the three measurement points was as follows: Treatment start 100% ($n = 910$); mid-treatment 98% ($n = 894$); post-treatment 95% ($n = 870$).

Criteria one of mediation—effects of time in treatment on mediators

Observed means and standard deviations across all three measurement points are presented in Table 2. There was a significant reduction of symptoms of exhaustion over time in treatment, in other words, a statistically significant c-path (estimate = −5.05 [95% CI −5.32; −4.81]). The results from the single mediator mixed-effects models are presented in Table 3. These analyses showed a significant reduction of all mediators over time in treatment (a-paths) and significant associations between the

Table 1. Pretreatment characteristics of participants.

	Total ($N = 913$)
Demographical variables	
Age, mean (SD)	42.98 (9.44)
Women, *n* (%)	788 (86)
Marital status, *n* (%)	
• Single or other	280 (31)
• Married/living together	569 (62)
• Partner (living apart)	63 (7)
Education, *n* (%)	
• Elementary school and/or secondary school	229 (25)
• University <3 years	142 (16)
• University ≥3 years	500 (55)
• Other	41 (4)
Socioeconomic status, *n* (%)	
• 0–250 000 SEK/year	76 (8)
• 250 000–500 000 SEK/year	308 (34)
• 500 000–1000 000 SEK/year	389 (43)
• >1000 000 SEK/year	140 (15)

Table 2. Observed means and standard deviations across all three measurement points.

	Treatment start M (SD)	Mid-treatment M (SD)	Post-treatment M (SD)
Exhaustion symptoms	32.85 (6.47)	27.24 (7.55)	22.72 (8.14)
Sleep concerns	7.27 (3.00)	5.58 (3.02)	4.57 (2.96)
Worry	9.72 (2.83)	8.59 (2.70)	7.30 (2.67)
Perfectionistic concerns	14.16 (3.41)	12.71 (3.45)	10.91 (3.53)
Psychological flexibility	22.58 (6.98)	21.22 (6.82)	17.87 (6.83)

Table 3. Results from the single and multiple mediator analyses.

Mediator	a-path (95% CI)	b-path (95% CI)	ab (95% CI)
Single mediator analyses			
Sleep concerns	−1.34 (−1.44; −1.23)*	1.11 (1.02; 1.21)*	−1.49 (−1.68; −1.32)*
Pathological worry	−1.20 (−1.21; −1.12)*	1.01 (0.90; 1.13)*	−1.22 (−1.39; −1.06)*
Perfectionistic concerns	−1.60 (−1.73; −1.49)*	0.62 (0.53; .71)*	−0.99 (−1.17; −0.83)*
Psychological flexibility	−2.35 (−2.57; −2.15)*	0.40 (0.35; 0.44)*	−0.93 (−1.09; −0.80)*
Multiple mediator analysis			
Sleep concerns	−1.34 (−1.44; −1.23)*	0.88 (0.79; 0.97)*	−1.18 (−1.35; −1.03)*
Pathological worry	−1.20 (−1.21; −1.12)*	0.45 (0.34; 0.56)*	−0.54 (−0.68; −0.40)*
Perfectionistic concerns	−1.60 (−1.73; −1.49)*	0.20 (0.12; 0.28)*	−0.32 (−0.45; −0.19)*
Psychological flexibility	−2.35 (−2.57; −2.15)*	0.16 (0.12; 0.20)*	−0.38 (−0.50; −0.27)*

Note. ab = mediated effect (indirect effect). CI = confidence interval. *Statistical significance established through bootstrapped CI not containing zero.

mediators and symptoms of exhaustion when controlling for the time in treatment (b-paths). The ab-products for all four mediators were also significant in the single mediator models, with a proportion of mediated change of 30% for sleep concerns, 24% for pathological worry, 20% for perfectionistic concerns, and 18% for psychological flexibility, respectively.

In the multiple mediator analysis (Table 3), all the a-paths, b-paths, and ab-paths remained significant. The proportion of mediated change was 48% in total, with sleep concerns accounting for 23%, Pathological worry 11%, perfectionistic concerns 6%, and psychological flexibility 8%. C´ was statistically significant (Estimate = −2.65 [95% CI −2.93; −2.38]), showing that 52% of the reduction in symptoms of exhaustion over time in treatment was unaccounted for by the suggested mediators.

Criteria two of mediation—within-individual change and time precedence

Four random intercepts crossed-lagged panel models were created, one for each suggested mediator, to explore whether a change in mediators preceded a change in exhaustion symptoms (Table 4). All models showed good fit indices with CFI and TLI values above 0.95, SRMR values below 0.01 and RMSEA values between 0.00–0.07. Overall, the cross-lagged paths from exhaustion symptoms at time t to the mediators at time $t + 1$ were stronger than the paths from mediators at time t to the exhaustion disorders at time $t + 1$. Sleep concerns and perfectionistic concerns at mid-treatment both showed a statistically significant association with exhaustion symptoms at post-treatment (γ_2 in Figure 2). However, when comparing differences in effect, there was a significantly larger effect from changes in exhaustion symptoms mid-treatment on changes in perfectionistic concerns posttreatment. For all suggested mediators except for

Table 4. Results from the random-intercepts cross-lagged panel models investigating within-individual change and time precedence in mediators and outcome.

	Effect of Exhaustion symptoms on the suggested mediator (β)		Effect of the suggested mediator on Exhaustion symptoms (γ)		Difference in effect (γ-β)
	est (95% CI)	css	est (95% CI)	css	z
Sleep concerns					
start-mid	0.08 (0.01–0.15)*	**0.15**	0.30 (−0.01–0.61)	0.12	−0,11
mid-post	0.09 (0.05–0.13)*	**0.23**	0.34 (0.09–0.59)*	0.12	−1,39
Pathological worry					
start-mid	0.04 (−0.02–0.19)	0.09	0.36 (−0.05–0.70)*	**0.12**	0,84
mid-post	0.15 (0.10–0.20)*	**0.51**	0.31 (−0.05–0.66)	0.08	−4,10*
Perfectionistic concerns					
start-mid	0.14 (0.07–0.20)*	**0.28**	0.12 (−0.20–0.44)	0.05	−3,27*
mid-post	0.12 (0.07–0.17)*	**0.29**	0.31 (0.08–0.53)*	0.11	−2,09*
Psychological flexibility					
start-mid	0.19 (0.08–0.31)*	**0.20**	0.09 (−0.06–0.23)	0.07	−2,10*
mid-post	0.23 (0.13–0.32)*	**0.29**	0.128 (−0.01–0.26)	0.09	−2,73*

Note. *Statistical significance established. Significant values for β indicate a within-individual change in ED symptoms temporally predicted subsequent change in the suggested mediator. Significant values for γ indicate a within-individual change in the suggested mediator temporally predicted subsequent change in ED symptoms. css = coefficient of the completely standardized solution (all effects, including factor loadings, are standardized to facilitate scale-free comparison between effects within and between the models). The highest css value between β and γ on each time point is highlighted in bold.

sleep concerns, the cross-lagged effect of exhaustion symptoms on the suggested mediator between mid-treatment and post-treatment was significantly larger than the suggested mediators' cross-lagged effect on symptoms of exhaustion.

Discussion

The current study explored sleep concerns, pathological worry, perfectionistic concerns, and psychological flexibility as mediators of change in exhaustion symptoms in ED patients participating in MMI. In the first step of the mediation analysis (criteria one), significant ab-products were identified for all suggested mediators using linear mixed-effects models. These ab-products remained significant in the multiple mediation analysis, with a 48% proportion of mediated change. A limitation of this first step is that the association between mediators and the outcome (the *b*-path) is cross-sectional, limiting the evidence that mediators had a causal effect on the outcome. The second analysis using RI-CLPM (criteria 2) failed to demonstrate that changes in the suggested mediators occurred prior to changes in exhaustion symptoms. As a result, this aspect of mediation between the suggested mediators and exhaustion symptoms could not be established. Instead, changes in symptoms of exhaustion appeared to precede changes in the suggested mediators.

The criteria one analysis showed significant ab-products, indicating a link between mediators and changes in exhaustion symptoms. The multiple mediation analysis revealed that sleep concerns accounted for the largest unique proportion of change (23%). Moreover, the cross-lagged path from sleep concerns at mid-treatment to exhaustion symptoms at post-treatment was statistically significant. However, the same was true for the effect of exhaustion symptoms at mid-treatment on sleep concerns at post-treatment, which was larger but with no significant difference between effects. These

findings corroborate previous studies identifying insomnia as a potential mediator in ED treatment (Lindsäter et al., 2021; Santoft et al., 2019). Notably, these studies focused on insomnia specifically rather than sleep concerns, and only one employed a statistical method that partially accounted for time precedence between sleep and exhaustion symptoms (a time-lagged correlation rather than a causal relationship; Santoft et al., 2019). Given the current study's results and previous research, sleep concerns appear to play a role in understanding ED as they seem to share a bi-directional association.

Regarding the other suggested mediators, the criteria two analysis demonstrated that the cross-lagged effects of exhaustion symptoms on the suggested mediators were significantly greater than that of the suggested mediators' effects on symptoms of exhaustion. These findings suggest that within-individual changes in pathological worry, perfectionistic concerns, and psychological flexibility are mediated by within-individual changes in exhaustion symptoms across time in treatment, rather than the other way around. Based on this interpretation, pathological worry, perfectionistic concerns, and psychological flexibility do not drive change in exhaustion symptoms. Instead, they would be considered secondary outcomes rather than processes of change.

Setting time precedence aside, the criteria two analysis does establish that changes in the suggested mediators and exhaustion symptoms are related to one another, warranting further investigation. A possible explanation for the lack of mediated effects is that the time frames addressed are too long, that there are individual differences in how the potential mediators operate, or that the relations between outcomes and potential mediators are more complex, such as bidirectional and nonlinear (Hofmann et al., 2020). Change in mediators and influence exerted on outcomes are likely to happen in a shorter time frame than the relatively lengthy intervals included here. Changes for some people may happen day to day or within a week or two, rather than over exactly the 12 and 24 weeks specified here. Likewise, a change in outcome may result from changes in unique sets of potential mediators for different people (MacKinnon et al., 2007). Sleep may not be the main factor for all, for example. Finally, a mediator might change and impact an outcome, which in turn impacts back on the mediator or other mediators, and rates of change may differ during different phases of treatment, and so on. Unfortunately, the analyses conducted here, even as sophisticated as they are, cannot accommodate potential mediators operating in these ways.

Furthermore, it is important to interpret the lack of mediating effects from the suggested mediators within the context of the limited research on ED treatment. As noted in the introduction, most published treatment studies lack an explicit theoretical framework or treatment rationale based on change processes (van de Leur et al., 2023). While the MMI in the current study had different components, most of the components were psychological. Therefore, suggested mediators primarily focused on psychological variables that were adapted from existing research, associated areas of cognitive-behavioral therapy, and clinical experience. However, they were not originally designed to understand ED specifically. Certainly, additional components within the MMI or alternative change processes could have influenced exhaustion symptoms as well, and their influence may not have been adequately captured by the suggested mediators in the current study. Therefore, future research should prioritize developing a theory about the processes of change that underlie and sustain ED, as well as creating measures that capture these processes. This

could potentially facilitate the development of more targeted and effective treatments for ED.

Finally, yet another possible explanation for the lack of mediated effects is that the MMI administered to the patients in the current study did not have enough effects on the suggested mediators. While the MMI did contain components aimed at the proposed mediators (see van de Leur et al., 2020) these were delivered alongside a range of concurrent interventions, which is typical for MMI. This may have led to a dilution of the effects of specific interventions. Thus, future research on ED treatment should focus on more targeted interventions with explicit components that address specific change processes. Such an approach would increase the likelihood of identifying the critical components for the success of ED treatment.

Limitations and strengths

The current study's strengths include a large sample size of 913 participants from a clinical setting with low attrition, resulting in high statistical power and good clinical applicability. Furthermore, the order of all questionnaires was randomized at each instance of administration to reduce the risk of instrumentation bias. Another strength is the selection of statistical methods, which allowed for examining time-precedence and intra-individual change. These aspects are often emphasized as crucial in mediation research but are not always adequately investigated. However, it should be noted that RI-CLPM are not without limitations. For example, while these models effectively distinguish between-person and within-person variation and attempt to account for time-invariant confounding, they do not address the potential impact of time-varying confounders (Mund et al., 2021). Time-varying confounders could include changes in other symptoms or processes that influence both ED symptoms and the suggested mediators.

A key limitation of the study is the absence of a control group, which precludes making any causal inferences regarding the relationship between the MMI and changes in the suggested mediators and symptoms of exhaustion. Although open clinical trials and cohort studies are not as conclusive as controlled studies, they can still yield valuable insights into potential change processes by allowing for the examination of real-world interventions (Kazdin, 2007; Maric et al., 2012). This may stimulate new ideas and hypotheses for future, more refined research designs. Another significant limitation is the few measurement points (three) utilized in the current design. Once again, the relationship between change processes and exhaustion symptoms is likely dynamic, reciprocal, and multifaceted, necessitating measurements with high granularity. Preferably, future research on mediators in ED should employ more frequent measurements than the current study on a weekly, if not daily, basis. This would enable a more comprehensive understanding of the temporal dynamics and potential causal pathways between change processes and symptoms of exhaustion. Ideally, such clinical designs would be enhanced by additional complementary experimental approaches.

Conclusion

In the current study, pathological worry, perfectionistic concerns, and psychological flexibility did not appear to mediate the changes in exhaustion symptoms among ED patients undergoing MMI. Instead, it was the other way around, where changes in exhaustion symptoms seemed to mediate changes in the suggested mediators. On the positive side, this study can inform future research by highlighting the potential importance of sleep concerns in ED treatment and establishing a link between exhaustion symptoms and pathological worry, perfectionistic concerns, and psychological flexibility. Given the explorative nature of the study, these results should be interpreted with caution. Nevertheless, we encourage future research on ED to focus on developing more focused interventions based on a theory of ED change processes, incorporating explicit components that address these processes, and employing high-granularity measurements. Such research will hopefully lead to more effective interventions and better outcomes for patients with ED.

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