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a randomized controlled trial with mediation analysis

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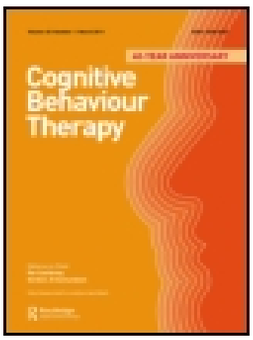
Published in:
Cognitive Behaviour Therapy

DOI:
10.1080/16506073.2021.1937695

2022

Document Version:
Publisher's PDF, also known as Version of record



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Cognitive Behaviour Therapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/sbeh20

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To cite this article: Tove Wahlund, Hugo Hesser, Sean Perrin, Sanna Johansson, Vilgot Huhn, Sara Sörhus, Severin Lindskog, Eva Serlachius, Erik Hedman-Lagerlöf, Brjánn Ljótsson & Erik Andersson (2021): Therapist-guided online metacognitive intervention for excessive worry: a randomized controlled trial with mediation analysis, Cognitive Behaviour Therapy, DOI: 10.1080/16506073.2021.1937695

To link to this article: https://doi.org/10.1080/16506073.2021.1937695

Published online: 20 Jul 2021.

COGNITIVE BEHAVIOUR THERAPY
https://doi.org/10.1080/16506073.2021.1937695

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Therapist-guided online metacognitive intervention for excessive worry: a randomized controlled trial with mediation analysis

Tove Wahlund[a,b], Hugo Hesser[c,d], Sean Perrin[e], Sanna Johansson[a], Vilgot Huhn[a], Sara Sörhus[a], Severin Lindskog[a], Eva Serlachius[a,b], Erik Hedman-Lagerlöf[a], Brjánn Ljótsson[a] and Erik Andersson[a]

[a]Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet; [b]Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden; [c]Department of Behavioural Sciences and Learning, Linköping University, Linköping, Sweden; [d]School of Law, Psychology and Social Work, Center for Health and Medical Psychology, Örebro University, Örebro, Sweden; [e]Department of Psychology, Lund University, Lund, Sweden

ABSTRACT

Previous studies have found an association between excessive worrying and negative beliefs about worry. It is unclear if change in these beliefs mediate worry reduction. This study aimed to examine (1) if a simplified online metacognitive intervention can reduce worry, (2) whether changes in negative beliefs about worry mediate changes in worry severity, and (3) moderated mediation, i.e., if the mediating effect is more pronounced in individuals with a high degree of negative beliefs about worry at baseline. Adult excessive worriers ($N = 108$) were randomized to 10-weeks of the online metacognitive intervention (MCI) aimed at reducing negative beliefs about worry, or to wait-list (WL). Outcomes, mediation, and moderated mediation were examined via growth curve modelling. Results indicated a significant reduction in the MCI group (d = 1.6). Reductions in negative beliefs about worry and depressive symptoms separately mediated changes in worry severity during the intervention, but in a multivariate test only the former remained significant. Sensitivity analysis indicated that the hypothesized mediation was robust to possible violations of mediator-outcome confounding. The moderated mediation hypothesis was not supported. The results from this randomized trial add to the growing literature suggesting that negative beliefs about worry play a key role in worry-related problems. *ClinicalTrials.gov Identifier: NCT03393156*

ARTICLE HISTORY
Received 6 May 2021
Accepted 28 May 2021

KEYWORDS
Negative beliefs about worry; worry; mediation; internet; metacognitions

Introduction

Excessive worry, usually defined as repetitive intrusive thoughts about future negative events, is a key feature of Generalized Anxiety Disorder (GAD) but is also a frequent complaint in individuals with other psychiatric disorders and chronic physical illnesses (American Psychiatric Association, 2013). Excessive worry is associated with a wide

CONTACT Erik Andersson erik.m.andersson@ki.se Department of Clinical Neuroscience, Division of Psychology, Karolinska Institutet, Solna 171 77, Sweden

range of negative health-related behaviors and outcomes. These include insomnia, alcohol and substance use, depressive symptoms, post-traumatic stress, prolonged grief, eating disorders, reduced working memory capacity, as well as increased somatic complaints and persecutory delusions (Butler et al., 1995; Davies et al., 2016; Eisma et al., 2017; Ferrer et al., 2013; Hayes et al., 2008; Hong, 2007; Jansson & Linton, 2006; Roussis & Wells, 2008; Sala & Levinson, 2016; Verkuil et al., 2012). Several psychological treatments (e.g., cognitive behavioral therapy, applied relaxation) have been found to be moderately effective in reducing the frequency and impact of excessive worry, primarily in individuals with GAD and other anxiety disorders (Cuijpers et al., 2014; Slee et al., 2019). One potential way to improve outcomes in psychological treatments for excessive worry is to investigate the mechanisms of change during treatment and how they relate to the underlying psychological model of excessive worry (Kraemer et al., 2002).

Numerous psychological models have been put forth over the years to explain the development and maintenance of excessive worry (Behar et al., 2009). This study primarily concerns itself with the relationship between excessive worrying and negative beliefs about worry, particularly their uncontrollability and dangerousness, as specified in the metacognitive model of excessive worry (Butler et al., 1995; Wells, 2009; Wells & Carter, 1999). Central to the model is the notion of a cognitive attentional syndrome (CAS) defined by perseverative thinking (worry, rumination) and dysfunctional coping strategies (thought suppression, procrastination, avoidance) to manage negative thoughts and emotions (Wells, 2009). The CAS arises from positive ("worrying helps me to solve problems") and negative ("I cannot control my worrying" or 'worrying is dangerous') beliefs about worry. The model specifies other cognitive factors, including a need to control one's thoughts generally, implicit procedural metacognitive processes (attentional control), and cognitive confidence. However, it is the negative beliefs about worry that are seen to play a primary role in the emergence of the CAS, which in turns increases the risk for perseverative thinking and a range of disorders (Wells, 1995, 2009; Wells & Carter, 1999).

There is a large evidence base finding an association between beliefs about worry and excessive worry. Studies typically show stronger associations between beliefs about the uncontrollability/dangerousness of worry and excessive worry, than between beliefs about the helpfulness of worrying and excessive worry (Fergus & Wheless, 2018; Ramos-Cejudo & Salguero, 2017; Ryum et al., 2017; Thielsch et al., 2015a, 2015b; Wells et al., 2010). There is also emerging evidence that metacognitive therapy is a highly efficacious treatment for worry-related problems with significantly larger effects than active comparators (Normann et al., 2014). However, it is unclear if reductions in negative beliefs about excessive worry specifically mediate change in excessive worry, as the metacognitive model stipulates. The present study was designed to address this gap in the literature. We used a randomized controlled design where 108 excessive worriers were randomized to an online metacognitive intervention (MCI), primarily aimed at reducing negative beliefs about worry, or to a waiting-list control group (WL). The main advantage of using an internet-based delivery format is that it is a scalable treatment that can recruit large sample of participants in a relatively short period of time. Our first hypothesis was that MCI would reduce worry severity and negative beliefs about worry compared to WL at post-intervention. Our second hypothesis was that reductions in negative beliefs about

worry would significantly mediate worry reduction relative to a comparator mediator (changes in depressive symptoms during treatment). Third, we hypothesized that the presence of more negative beliefs about worry at baseline would be associated with a stronger mediation effect (moderated mediation).

Method

Trial design

The study employed a randomized controlled design with two arms, 10 weeks of MCI or wait-list control group (WL). The initial power analyses indicated that a sample size of 140 participants would generate 90% power to detect a significant between-group effect size in the medium range (d = 0.50, alpha = .05) for the primary outcome variable (self-reported worry) at post-intervention/post-WL. The actual sample size was 108 participants. Participants were randomly assigned (1:1) to MCI or WL by an independent researcher who received a list of anonymous participant information and used a webpage (www.random.org) to allocate participants to the groups. All participants were randomized on the 5th of February 2018, with the experimental phase starting the following day. All outcome and mediator variables were assessed at pre- and post-intervention/WL assessment, and at 6-month and 12-month follow-ups. At the end of the 10-week waitlist, participants in the WL condition completed 10 weeks of MCI and were re-assessed at post-intervention. Their follow-up data are not included in this study. Consistent with recommendations for identifying possible treatment mechanisms (Kazdin, 2007), measures of worry severity (primary outcome), negative metacognitive beliefs (putative mediator) and depressive symptoms (comparator mediator) were administered weekly during the 10-week MCI/WL period. All participants provided informed consent to participate and the study protocol was approved by the Regional Ethics Board (Stockholm, Sweden). The study was prospectively registered with clinicaltrials.gov (NCT03393156), and all results are reported in accordance with the CONSORT statement (Boutron et al., 2008).

Participants

To be included, participants had to be at least 18 years of age, living in Sweden, with access to the internet, and to have high levels of self-reported worry as indexed by a total (raw) score of >56 out of a possible total score of 80 on the Penn State Worry Questionnaire (Meyer et al., 1990). This cutoff score was chosen based on the formula for uneven distributions between normal and clinical populations (Jacobson & Truax, 1991). For the purposes of this study, the normative data for the PSWQ were obtained from two previous studies involving normal and clinical populations (Brown et al., 1992; Gillis et al., 1995). A cut-off score of >56 on the PSWQ corresponds to an individual scoring at the upper end of the moderate worry range (40–59), or in the high worry range (60–80) according to the scale developers (Meyer et al., 1990). This cut-off has also been used in previous clinical studies of excessive worry (Andersson et al., 2017, 2020).

Exclusion criteria were as follows: (a) substance dependence during the last 6 months; (b) a diagnosis of post-traumatic stress disorder, bipolar disorder, or psychosis; (c)

symptoms better explained by autism or borderline personality disorder; (d) moderate to severe depression as indicated by a score of >25 on the self-report version of the Montgomery Åsberg Depression Rating Scale (Svanborg & Åsberg, 2001); (e) any change in dosage of psychotropic medication that could affect worry symptoms less than 2 months prior to study inclusion; and (f) having received metacognitive therapy for excessive worry during the last 2 years. During the 10-week MCI/WL period, participants had to agree to keep any psychotropic medication stable and not to seek any additional psychological treatments.

Recruitment and inclusion

Study information was spread through social media platforms and sent to mental health care providers across Sweden. Potential participants (N = 186) self-referred via an internet platform where study information was provided. On the platform, they completed online screening measures consisting of the PSWQ, MADRS-S, Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993), the Drug Use Disorders Identification Test (DUDIT; Berman et al., 2005), and general background information. Individuals who were initially assessed as eligible via the online screening (N = 132) were contacted by telephone by a member of the research team who provided further information about the study and then carried out an assessment of inclusion/exclusion criteria, including diagnostic status using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998).

All telephone assessments were conducted either by a licensed clinical psychologist or by a master's student in the last year of a five-year psychology program (details shown in the Online Supplement). Of the 110 eligible individuals who fulfilled all study criteria, 108 completed the baseline assessments, consented to participate, and were randomized to either MCI or WL. Figure 1 displays the study flow.

Intervention

MCI is comprised of eight consecutive modules (chapters), including written information (approximately 60 pages) and MP3-files with instructions for homework exercises. The MCI intervention is original work, written by the last author, and broadly follows the full metacognitive therapy outline which has been described in detail elsewhere (2009). However, it is important to stress that MCI is a simplified and condensed online version (written pre-defined descriptions and instructions) and lacks some elements done in face-to-face metacognitive therapy (for instance, a flexible Socratic dialogue between the patient and therapist as done in face-to-face metacognitive therapy). Thus, the current study is not an investigation of the full metacognitive therapy protocol but a test of whether a reduction in negative beliefs about worry mediates reductions in worry severity in individuals receiving a simplified, condensed, online metacognitive intervention.

The intervention is 10 weeks long and includes access to a therapist via written communications over a secure internet platform. The first two modules include psychoeducation about worry and a walkthrough of the metacognitive model of worry with case examples. The remaining modules engage participants in exercises specifically

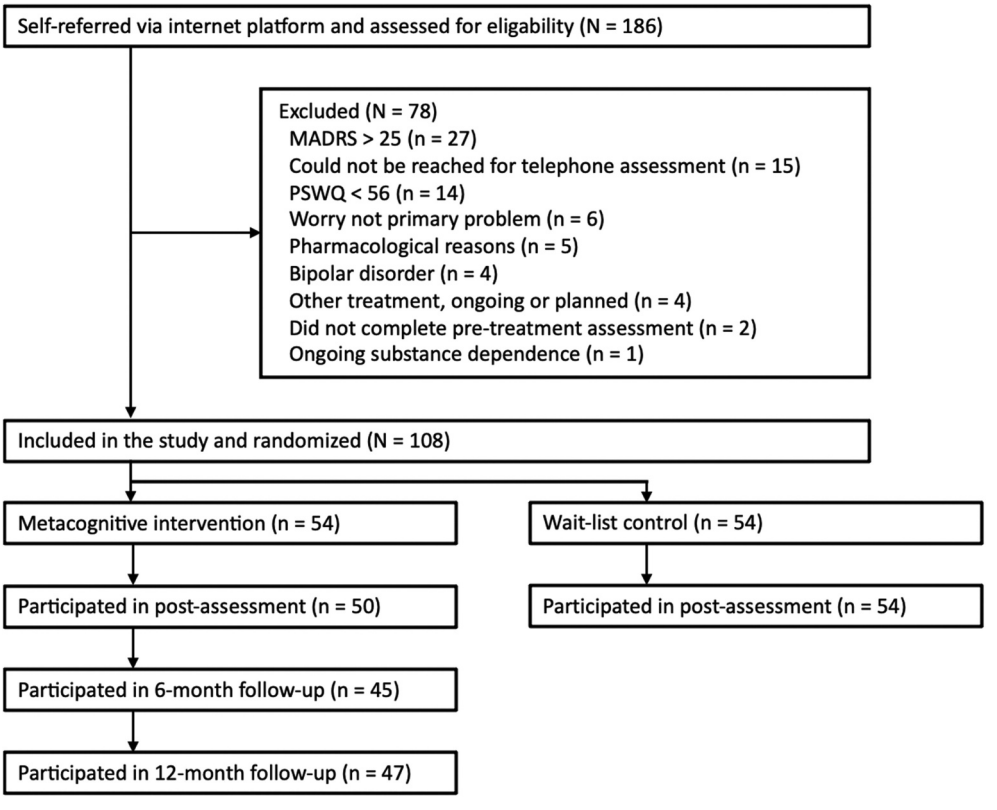

Figure 1. Flow of participants through each stage of the study. PSWQ = Penn State Worry Questionnaire. MADRS-S = Montgomery Åsberg Depression Rating Scale—Self report.

designed to modify any negative metacognitive beliefs about worry. These exercises include detached mindfulness and attention training (module 3), worry postponement (module 4), restructuring of negative metacognitive beliefs about worry (modules 3–8), restructuring of positive beliefs about worry (module 7), and behavioral experiments to modify metacognitive beliefs and dysfunctional worry-management strategies (modules 5–7). The final module (8) focuses on relapse prevention. After completing the first module, access to the next module required participants to inform their therapist about their homework exercises through the internet platform. All therapist support to participants was provided in written form via the internet platform. Further information about the intervention and the therapists is available in the Online Supplement.

Waiting-list control group (WL)

Participants randomized to the WL group were informed that they would be prompted by the internet platform to complete various questionnaires on a weekly basis, and at the end of the 10-week waiting period, they would be able to start the intervention. WL participants were provided with the telephone number to a clinician in the research team to contact if their symptoms worsened. No other information or type of support was provided to the WL group.

Measurements and assessment points

Primary outcome and mediator variables

The primary outcome was self-reported worry severity at post-intervention/WL, assessed with the 16-item PSWQ. Individual items are rated on a 1 (not at all typical of me) to 5 (very typical of me) scale; higher scores indicating higher levels of worry severity. The PSWQ has excellent psychometric properties, high levels of convergent and divergent validity, and a single factor structure in both clinical and non-clinical samples (Brown et al., 1992; Meyer et al., 1990). The putative mediator was negative beliefs about worry assessed with the 6-item, Negative Beliefs about Uncontrollability and Danger Subscale (MCQ-30-Neg) of the 30-item Metacognitions Questionnaire (Wells & Cartwright-Hatton, 2004). Individual items on the MCQ-30-Neg are scored on a 1 (do not agree) to 4 (highly agree) scale; higher scores indicating stronger negative beliefs about worry. The MCQ-30 possesses high levels of internal consistency (r = 0.91) and convergent and criterion validity (Wells & Cartwright-Hatton, 2004). The comparator mediator was assessed using the two-item, Patient Health Questionnaire-2 (PHQ-2; Arroll et al., 2010). The items on the PHQ-2 (little interest or pleasure in doing things; feeling down, depressed or hopeless) are rated on a 0 (not at all) to 3 (nearly every day) frequency scale, and in this study covering the past week. The PHQ-2 possesses high levels of internal reliability and is highly sensitive/specific to the presence of a diagnosis of Major Depression as assessed by clinical interview (Arroll et al., 2010). The outcome (PSWQ) and mediator measures (MCQ-30-Neg, PHQ-2) were administered weekly during MCI and WL.

Secondary outcomes

A number of secondary outcomes were assessed using validated self-report measures, which were administered at baseline, post-intervention/WL and at the 6- and 12-month follow-ups. The severity of depression symptoms was assessed using the 9-item MADRS-S (Svanborg & Åsberg, 2001). The strength of the other worry-related cognitive processes specified in Wells (1995) metacognitive model were assessed with the other four (6-item) subscales of the MCQ-30: cognitive confidence; positive beliefs about worry; cognitive self-consciousness; and the need to control thoughts. Cognitive avoidance was assessed with the 25-item Cognitive Avoidance Questionnaire (CAQ; Sexton & Dugas, 2008). The 30-item Contrast Avoidance Questionnaire—Worry (Llera & Newman, 2017) assessed the use of worry to avoid negative emotional shifts, to create and sustain negative emotions, and to create positive emotional contrasts.

Adverse events

Information about adverse events was obtained using a self-rating scale administered to participants at post-intervention and post-wait-list via the internet platform. In the event that an adverse event was reported, the participant was contacted via telephone by a member of the research team who asked additional questions about the intensity and duration of the adverse event(s).

Statistical analyses

The effects of intervention and the mediator, reflected by the total, direct and indirect effects, and conditional indirect effects (i.e., moderated mediation), were assessed using univariate and multivariate latent growth curve models (Bollen & Curran, 2006). The ability of growth models to provide parameter estimates for the growth trajectories for groups of participants (i.e., fixed effects) and for individual participants (i.e., random effects) as a function of observed covariates makes these models especially suitable for the study of mediation and moderation in clinical trials (Cheong et al., 2003; Hesser, 2015).

All models were fitted using full information maximum likelihood estimation with non-normality robust standard errors using version 8.1 of Mplus (L. K. Muthén & Muthén, 2017). All models were based on all available data from all randomized participants (intention-to-treat), yielding unbiased parameter estimates and standard errors, under the assumption of missing at random (Enders, 2010). Throughout, 95% confidence intervals were computed, with the Wald-statistics (estimate-null/standard error [SE]) used to test the null hypothesis; results were interpreted as statistically significant when $p < .05$ (i.e., $z > 1.96$). Model fit measures included the Comparative Fit Index (CFI), Tucker–Lewis Index (TLI), and Root Mean-Square Error of Approximation (RMSEA) (see, e.g., (Bollen & Curran, 2006)). A model was deemed to have an unacceptable fit if the CFI and TLI were <0.90 and the RMSEA was >0.10 (Bollen & Curran, 2006). When applicable, effect sizes in the form of standardized mean differences (Cohen's *d*) were computed using the model-implied, endpoint mean-difference and baseline standard deviation (equation 7; Feingold, 2009).

Analysis of controlled treatment effects

To address the first hypothesis, a univariate unconditional growth model was fitted using all weekly measurements to capture the functional form of change, mean rate of change (i.e., fixed effects), and individual differences of change (i.e., random effects) for the primary outcome and mediator variables. For all variables, linear growth models with correlated random intercepts and slope factors, and time-specific, uncorrelated residual terms were fitted to the data. Next, a conditional univariate growth model was estimated in which the treatment condition was included as a binary variable (1 = MCI, 0 = WL) in the linear growth model to examine whether individual growth rates varied as a function of treatment condition. For the secondary outcomes, the same analytic procedure and growth model was used to linear changes in outcomes between pre- and post-assessment as function of condition, with the exception that the slope was treated as a fixed rather than a random effect.

Mediation analysis

To test the second hypothesis, parallel process growth models for mediation were estimated (Cheong et al., 2003). This involves combining the univariate growth models for the mediator and outcome variables into a multivariate parallel process growth model, and examining whether (1) intervention condition (MCI vs WL) had an effect on the latent slope of the pre- to post-intervention scores on the measure of negative

beliefs about worry (MCQ-30-Neg; the mediator variable; a-path); and (2) individual changes on the mediator variable were correlated with individual changes in weekly scores on the measure of worry severity (PSWQ; the outcome variable; b-path). Following recommendations for multivariate growth models (Bollen & Curran, 2006), the time-specific residual terms at each time point and across constructs (i.e., mediator and outcome variable) were correlated in order not to inflate the regression among random effects (i.e., latent intercepts and slopes). To evaluate the mediated effect, the cross-product of the a-path (i.e., treatment condition effect on the mediator) and the b-path (effect of mediator on outcome) was computed, and a bias-corrected 95% confidence interval constructed using bootstrapping with 3000 samples drawn with replacement (MacKinnon et al., 2004). If the confidence interval did not include zero, the mediated effect was considered to be statistically significant different from zero (at the specified alpha level).

To test the robustness of the indirect (mediated) effect to violations of the sequential ignorability assumption (i.e., that there was no mediator-outcome confounding), sensitivity analyses were conducted for each mediator model (Imai et al., 2010; Muthén et al., 2017). In these sensitivity analyses, indirect effects were computed for different fixed values of the residual correlation between mediator and outcome (from $r = -.7$ to .7) to determine whether the indirect effect was significant when a certain degree of mediator-outcome confounding was allowed. If the indirect effect remained statistically significant (i.e., if the upper limit of the confidence interval did not contain zero), even in the presence of a high residual correlation, then the indirect effect was considered to be robust to unmeasured mediator-outcome confounders.

To test whether changes in negative beliefs about worry mediated change in worry severity relative to an (assumed) non-relevant comparator mediator (changes in depressive symptoms severity during treatment), a combined multiple mediator parallel process growth model was fitted. This model evaluates the effect of the putative mediator (change in negative beliefs about worry) on the outcome while holding constant the effect of the comparative mediator (change in depressive symptoms) in the model. The multiple mediator model also allowed us to test the difference in the product of the a- and b-paths.

Moderated mediation analysis

To test the third hypothesis that the indirect (mediated) effect depended upon the baseline scores of the mediator, a moderated-mediator model was specified following recommendations provided by Preacher et al. (model 2; Preacher et al., 2007). Specifically, parallel process growth modeling was used to test the conditional indirect effect with the random latent intercept of the mediator as the moderator. The random intercept was used instead of the observed scores on the mediator because the observed variable can be a fallible indicator of the true initial status (B. O. Muthén & Curran, 1997).

To evaluate whether the mediated effect was moderated by baseline scores of the mediator, we again estimated a parallel process growth model in which the interaction term between latent intercept factor (i.e., baseline score on the mediator) and the treatment condition variable was included in the model. The slopes of the mediator and outcome were regressed on the interaction term and the key parameter in the model

was the interaction effect on the slope of the mediator. The size of the conditional indirect effect depended on the extent to that this interaction term departed from zero (Preacher et al., 2007). If this interaction was significant, the moderator function was used to compute the conditional indirect effects for different values of the moderator (range from 2 SD above and 2 SD below the mean). The point estimate of the conditional indirect effect was plotted along with bootstrapped 95% confidence bands using the loop function in Mplus (L. K. Muthén & Muthén, 2017). The same approach to estimating a moderated-mediator model in a randomized controlled trial can be found in Hesser et al. (2018).

Analysis of long-term outcomes for treated participants

A series of piecewise growth models was employed to examine maintenance of gains throughout the follow-up period for those initially randomized to intervention. The first piece captured the change from pre- to post-assessment, and the second piece captured change from post- to follow-up assessments (6-month and 12-month).

Tests of model assumptions

The data were carefully screened to assess for possible violations of assumptions (e.g., skewed distributions, outliers) underlying the analytical model that could create spurious associations and invalid conclusions. Following visual inspection of histogram and box plots to screen for data problems, Cook's distance measure (D; Cook, 1977) and the log-likelihood contribution for each individual were computed and the statistics were plotted against key parameters in the model to detect prediction and model fit outliers (Weisberg, 2014). Cook's *D* above 1 were used as an indication of an extreme observation that might influence the model, given that values below 1 have been shown to be less likely to influence parameter estimates in ordinary regression (Weisberg, 2014). Extreme observations that were likely to influence model fit and/or parameter estimates were removed and the analyses rerun to evaluate whether the removed observations affected estimates and/or model fit statistics to a significant degree.

A few outliers were detected in each model that changed the estimates, SE and model fit statistics to varying degrees depending upon the model. It should be noted, however, that outliers did not change the qualitative interpretation of the results, with the exception for the analysis examining the conditional indirect effect of the putative mediator (MCQ-30-Neg). With the exception of this analysis, we present all the analyses with the full sample (N = 108).

Results

Table 1 presents the sociodemographic and clinical characteristics of the participants separately by intervention group at baseline. Data attrition was low at post-intervention (3.7%) and the two follow-ups (13–17%; Figure 1). Mean scores for the mediator and all outcome variables are available in Online Supplement. For participants initially randomized to MCI, 100% completed the first module and 20% the last module, with the mean number of completed modules being 5.6 out of 8 (SD = 2.0). At post-intervention, four

Table 1. Sociodemographic and clinical characteristics of all participants (N = 108) by intervention group.

	Intervention Group	
Variable	MCI (*n* = 54)	WL (*n* = 54)
Gender (*n*)		
Women	45	43
Men	9	11
Age (yr)		
Mean age (SD)	38 (11)	40 (12)
Min-Max	24–64	19–69
Education (*n*)		
Primary school	-	1
High school	9	15
University	41	35
Other	4	3
Comorbidity (*n*)		
Generalized Anxiety Disorder	39	45
Depression	7	5
Panic Disorder	5	6
Obsessive Compulsive Disorder	6	4
Social Anxiety Disorder	9	12
Agoraphobia	4	8
Binge Eating Disorder	–	1
ADHD	1	2
Autism Spectrum Disorder	1	1
Dermatillomania	1	-
Number of psychiatric diagnoses (*n*)		
None	7	6
One	30	27
Two	10	11
Three	3	8
Four	3	2
Psychotropic medication (*n*)		
Antidepressants (SSRI/SNRI)	10	13
Anxiolytics and/or sleep medicine	7	8
Neuroleptics and/or antiepileptics	–	1
Levothyroxine	1	4
Previous psychological treatment (*n*)		
Cognitive Behavior Therapy	24	22
Psychodynamic Therapy	9	12
Other, non-specified	22	25
None	12	10

MCI = Metacognitive intervention; WL = Waiting-list; ADHD = Attention Deficit Hyperactivity Disorder.

individuals (7.4%) in the MCI group and five (9.2%) in the WL-group reported adverse events, none of which were serious (Online Supplement). At the 6- and 12-month follow-ups, 10.2% and 12%, respectively, had sought additional treatment (Online Supplement).

Controlled effect of intervention on outcome and mediator variables

Table 2 presents the results of the univariate linear conditional growth models for the primary outcome, putative and comparator mediator variables (full fit statistics and mean scores are available in Online Supplement). Inspection of the *p*-values for the effect of intervention on slope (under *Fixed Effects* in Table 2) revealed statistically significant between-group differences for the average pre- to post-intervention change

Table 2. Results from the linear growth model examining the controlled effects of the intervention on the main outcome and mediator variables.

	Effect			Group difference at post	
Outcome/Predictor	Estimate	S.E.	*p*	Mean difference [95%CI]	Effect size
PSWQ					
Fixed effects					
Icept	64.778	0.916	<0.001		
Slope	0.108	0.061	0.077		
Tx on icept	0.845	1.382	0.541		
Tx on slope	−1.979	0.740	<0.001	−13.512 [−16.864, −10.161]	1.642
Random effects					
Var icept	46.548	5.865	<0.001		
Var slope	0.656	0.213	0.002		
Cov icept/slope	−1.979	0.740	0.007		
MCQ-30-Neg					
Fixed effects					
Icept	17.534	0.381	<0.001		
Slope	0.036	0.031	0.254		
Tx on icept	0.449	0.588	0.445		
Tx on slope	−0.652	0.073	<0.001	−6.072 [−7.505, −4.638]	1.654
Random effects					
Var icept	8.237	1.141	<0.001		
Var slope	0.108	0.024	<0.001		
Cov icept/slope	−0.308	0.149	0.038		
PHQ-2					
Fixed effects					
Icept	2.340	0.164	<0.001		
Slope	−0.018	0.016	0.240		
Tx on icept	0.10	0.254	0.694		
Tx on slope	−0.043	0.027	0.034	−0.510 [−1.104, 0.083]	0.332
Random effects					
Var icept	1.508	0.303	<0.001		
Var slope	0.015	0.005	0.001		
Cov icept/slope	−0.043	0.027	0.112		

Fixed effects describe the average effects, whereas random effects describe individual differences in intercepts and linear slopes. The unstandardized and standardized means (effect size) were derived from the parameter estimates. Tx = treatment variable; Icept = intercept; Var = variance; Cov = covariance; S.E = standard error; PSWQ = Penn State Worry Questionnaire; MCQ-30 = Metacognitions Questionnaire-30; PHQ-2 = Patient Health Questionnaire-2.

in worry severity, negative beliefs about worry, and depressive symptoms, favoring MCI relative to WL on all variables. The right hand side of Table 2 presents the mean difference and 95% confidence interval (95% CI) between MCI and WL at post-intervention and the effect size for this difference. Large effect size differences were observed between the two groups for the primary outcome (d = 1.6) and putative mediator (negative beliefs about worry), with a moderate effect size difference for the comparator mediator (depressive symptoms). Long-term follow-up results indicated sustained effects (Online Supplement). In all univariate conditional growth models examining effects on primary outcome and mediator variables, significant heterogeneity in the individual growth trajectories (random effects) remained unexplained after adjusting for (the fixed) intervention effects (all p's < .01). This made it possible to evaluate mediation using parallel process growth models with random effects.

Table 3 presents the results of univariate linear conditional growth models for the effect of intervention on all secondary outcomes. Again, MCI was more effective than WL in reducing depressive symptoms (MADRS-S), metacognitive beliefs and processes (total

Table 3. Results from the linear growth model examining the controlled effects on secondary outcomes.

	Effect			Group difference at post	
Outcome/Predictor	Estimate	S.E.	*p*	Mean difference [95%CI]	Effect size
MCQ-30					
Fixed effects					
Icept	69.685	1.444	<0.001		
Slope	1.259	1.035	0.224		
Tx on icept	4.833	2.176	0.026		
Tx on slope	−13.474	2.468	<0.001	−8.641 [−14.132, −3.149]	0.764
Random effects					
Var icept	88.637	18.057	<0.001		
MADRS					
Fixed effects					
Icept	15.111	0.871	<0.001		
Slope	0.630	0.668	0.346		
Tx on icept	0.667	1.189	0.575		
Tx on slope	−5.371	1.144	<0.001	−4.705 [−7.594, −1.816]	0.761
Random effects					
Var icept	30.768	4.634	<0.001		
CAQ					
Fixed effects					
Icept	67.259	2.237	<0.001		
Slope	0.111	1.870	0.953		
Tx on icept	4.296	3.411	0.208		
Tx on slope	−9.602	3.082	0.002	−5.306 [−12.771, 2.160]	0.299
Random effects					
Var icept	225.244	37.469	<0.001		
CAQ-W					
Fixed effects					
Icept	90.315	2.482	<0.001		
Slope	0.315	1.987	0.874		
Tx on icept	5.000	3.921	0.202		
Tx on slope	−15.396	4.259	<0.001	−10.396 [−19.093, −1.700]	0.510
Random effects					
Var icept	232.589	47.043	<0.001		

Fixed effects describe the average effects, whereas random effects describe individual differences in intercepts. The unstandardized and standardized mean difference (effect size) were derived from the parameter estimates. Tx = treatment variable; Icept = intercept; Var = variance; S.E. = standard error; MCQ-30 = Metacognitions Questionnaire-30; MADRS-S = Montgomery Åsberg Depression Rating Scale—Self report; CAQ = Cognitive Avoidance Questionnaire; CAQ-W = Contrast Avoidance Questionnaire—Worry.

score on the MCQ-30), general cognitive avoidance (CAQ), and use of worry as an emotion regulation strategy (CAQ-W). The right hand side of Table 3 presents the model-implied mean differences with 95% CI and the effect size for the difference. All model-implied between-group effect sizes were in the small to moderate range for the secondary outcomes (*d*'s = 0.29 to 0.76). Mean scores for all secondary outcome variables are presented in Online Supplement.

Mediation analysis

Figure 2 presents the results of the mediation analyses. As can be seen, intervention group (MCI vs WL) significantly predicted the slope of the mediator (a-path), and the slope of the mediator significantly correlated with the slope of the outcome (b-path) in the model where MCQ-30-Neg served as the mediator. For the model involving the

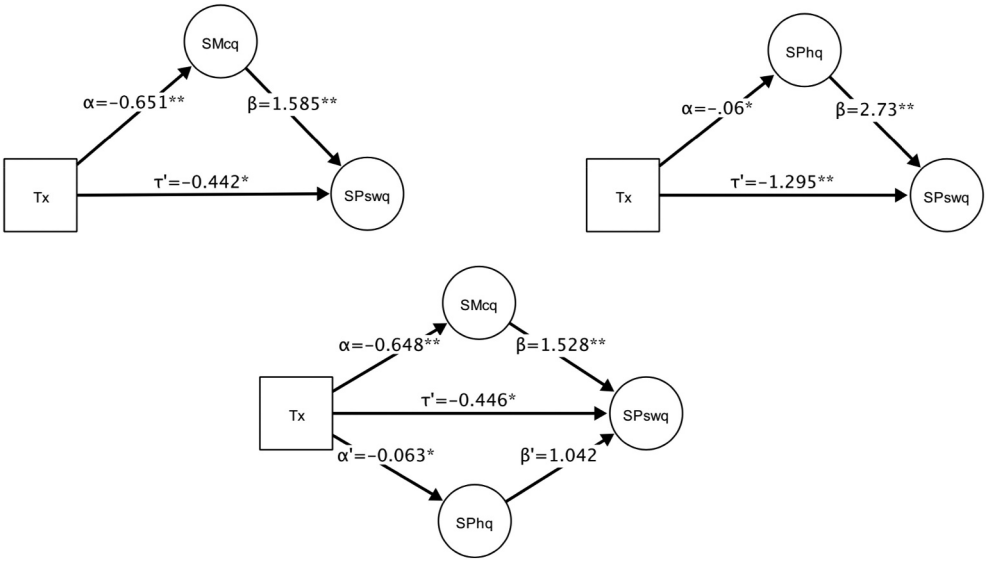

Figure 2. Mediation analysis. Parallel process growth models examining the intervention effect on the linear growth rate of the outcome (Penn State Worry Questionnaire; PSWQ) via the linear growth rates on the putative mediator variable (Negative Beliefs Subscale of the Metacognitions Questionnaire-30 [MCQ]) and comparator mediator variable (Patient Health Questionnaire-2 [PHQ-2]). The models are simplified and only key parameters of interest are shown for clarity. Unstandardized parameter estimates are shown. Tx = binary treatment variable (Metacognitive intervention) = 1, Wait-list control = 0); SPswq = latent growth rate factor for PSWQ; SMcq = latent growth rate factor for MCQ-30 Negative Beliefs Subscale; SPhq = latent growth rate factor for PHQ-2; *$p < .05$ **$p < .01$

comparator (non-relevant) mediator (depression scores assessed with the PHQ-2), intervention group again significantly predicted the slope of the mediator, and the correlation between mediator and outcome was significant (see Figure 2). The bootstrapped confidence interval for the ab-products indicated both the putative mediator (negative beliefs about worry) and the comparator mediator (depressive symptoms) were both statistically significant: MCQ-30-Neg, ab = −1.032, 95% CI [−1.655, −0.627]; and PHQ-2, ab = −0.164, 95% CI [−0.431, −0.014]. The relative influence of the two mediators is reported below.

Figure 2 also presents the results of the multiple mediator model that included the putative (negative beliefs about worry—MCQ-30-Neg) and comparative mediators (depressive symptoms—PHQ-2). In this model, changes in negative beliefs about worry continued to significantly mediate the effect of intervention group on worry severity (ab = −0.908, 95% CI [−1.537, −0.458]) whereas changes in depressive symptoms did not (ab = −0.063, 95% CI [−0.303, 0.005]). A direct test of the indirect effect difference indicated that the indirect effect of negative beliefs on worry was statistically significantly larger than the indirect effect of depressive symptoms on worry ($z = 2.991$, $p = .003$).

Figure 3 presents the results of the sensitivity analyses. As can be seen, the indirect effect of the putative mediator (negative beliefs about worry) on outcome (worry severity) was fairly robust to possible violations of mediator-outcome confounding, given that it

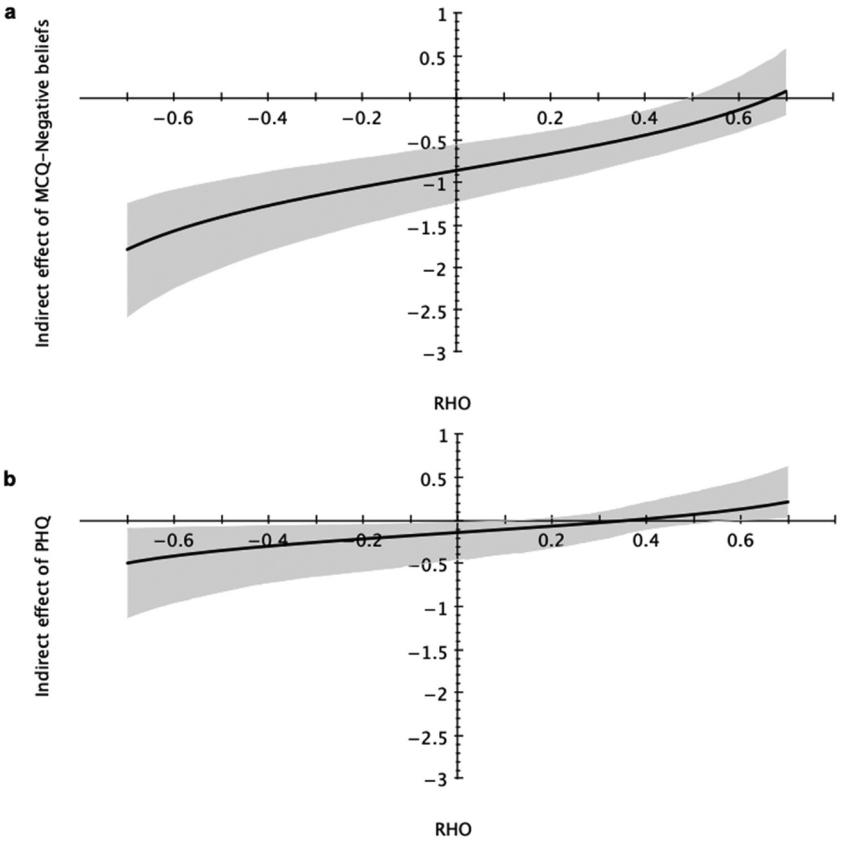

Figure 3. Sensitivity analysis. Sensitivity plots for the indirect effect of (a) Metacognitions Questionnaire-30 (MCQ-30) Negative Beliefs Subscale and (b) Patient Health Questionnaire-2 (PHQ-2). The x-axis represents the residual correlation (RHO), and the y-axis represents the indirect effect. The solid line represents the estimated indirect effect at different values of the residual correlation (range from −.7 to .7). The point at which the solid line crosses the y-axis represents the estimated indirect effect when the residual correlation is zero (i.e., no mediator-outcome confounder). The gray areas represent the 95% bootstrapped confidence interval for the indirect effects at each value of the residual correlation.

would require a residual correlation of .5 (or higher) between mediator and outcome in order for the confidence interval for the negative indirect effect to include zero. In respect of the sensitivity analysis for the comparator mediator (depressive symptoms), for residual correlations of .12 (or higher) the upper limit of the confidence interval included zero (see Figure 3), indicating that the indirect effect of depressive symptoms was considerably more sensitive to unmeasured mediator-outcome confounders than the indirect effect of negative metacognitive beliefs. In other words, and compared to the indirect effect of negative beliefs about worry, it would take a smaller unobserved confounder to reject the conclusion that changes in depressive symptoms mediated the effect of intervention on worry severity.

Moderated mediation

To determine whether the indirect (mediated) effect on the primary outcome variable (self-reported worry) was moderated by baseline values of the putative and comparator mediators, a parallel process growth model that included an interaction term for the relationship between the latent intercept and intervention group was estimated separately for negative beliefs about worry and depressive symptoms. The interactive effect of the intervention group and baseline values of the mediators on the slope of the mediators was non-significant for both mediators (both p's > .30).[1] Thus, contrary to expectation, the beneficial effect of changes in negative beliefs about worry on worry outcomes was not conditional upon the participant having higher levels of such beliefs at baseline. The same was true for the mediating effect of depressive symptoms on worry outcomes.

Analysis of long-term follow-up

Significant changes were observed during the 10-week treatment phase for all variables (p's < .001; Online Supplement). No further (significant) changes occurred between post-treatment and the 12-month follow-up for all variables (p's > .07) with one exception; scores on the CAQ-W continued to decline between post-treatment and follow-up (p = .021).

Discussion

The present study sought to investigate if a metacognitive intervention could reduce worry and if negative beliefs about worry—as specified in the theoretical model—mediated these reductions. A further aim was to assess whether changes in these negative beliefs about worry were more relevant to outcomes for participants with higher levels of these beliefs at baseline. Strengths of the current study were the randomized design, weekly measurements, inclusion of a parallel competing mediator, and sensitivity analyses where we investigated whether the hypothesized mediation was robust to possible violations of mediator-outcome confounding.

Results showed that the intervention had a large and clinically meaningful total effect in reducing excessive worry. In support of the metacognitive model (Wells, 1995; Wells & Carter, 1999), changes in negative beliefs about worry during the intervention significantly mediated pre- to post-intervention reductions in worry severity (primary outcome). The mediated effect of negative beliefs upon worry was significantly stronger than that of a hypothesized non-relevant comparator mediator (depressive symptoms), and when included in the same mediator model, only changes in negative beliefs remained a significant mediator of self-reported worry. Furthermore, the mediation effect for negative beliefs about worry was highly robust with regard to the influence of unmeasured variables that might also impact the effect of this variable on worry outcomes (i.e., mediator-outcome confounding). The same was not true for the comparator mediator. Altogether, the effects of changes in negative beliefs about worry on worry severity do not appear to be the result of another unmeasured variable. Thus, the present trial adds to

a growing literature suggesting that negative beliefs about worry may play a key role in excessive worry (McEvoy et al., 2015; McEvoy & Mahoney, 2013; McEvoy et al., 2013).

Contrary to expectation, the observed mediation effect was not dependent upon (moderated by) baseline strength of the participant's negative beliefs about worry. This is a curious finding because it is reasonable to assume that the benefits accrued from targeting such beliefs in therapy should be less when these beliefs are weaker. However, it is important to note that the participants in this trial had high levels of negative beliefs about worry at baseline and it is possible that a larger sample size would be needed to find a significant moderation-mediation effect.

While not assessed with the frequency necessary to estimate mediation effects in this study, we did observe significant pre- to post-intervention changes in other processes specified in the metacognitive model, as well as cognitive avoidance and use of worry as an emotion regulation strategy (measured, respectively, with the MCQ-30, CAQ and CAQ-W). Future studies should investigate whether these additional psychological processes mediate changes in worry, and in trials evaluating the full metacognitive therapy protocol. It is also important to note that mediators are not necessarily the same thing as causal treatment mechanisms, and inferences about causation require a number of different assumptions to be met and methodological features to be employed (Kazdin, 2007). Further trials designed to assess mediation effects that employ active treatment comparators, simultaneous and repeated measurement of multiple candidate mediators, isolation of particular interventions within the metacognitive therapy protocol, and N of 1 designs are therefore needed.

While the present trial benefitted from several methodological strengths, the findings should be viewed as preliminary given certain limitations. First, the primary outcome was a self-report measure (the PSWQ) and our results may have varied had we used an interview-based assessment. A meta-analysis (Cuijpers et al., 2014) found that effect sizes based on self-report measures for worry tend to be lower than for clinician-rated instruments. Consequently, it is possible that both the outcome and mediator effects in the present study were underestimated. Second, depressive symptoms were assessed using the PHQ-2, comprised of two items measuring low mood and anhedonia over the past week. The measure does not assess rumination, which according to the metacognitive model (Wells, 2009) is another form of perseverative thinking (like worry) that significantly contributes to the development and maintenance of anxiety and depression. Third, we did not investigate the impact of MCI on comorbid conditions beyond depressive symptoms. A recommendation for future research is therefore to investigate if reductions in negative metacognitive beliefs and/or excessive worry lead to cascade effects for other psychiatric symptoms, as shown by Freeman et al. (2015). Additionally, this trial excluded individuals who had moderate to severe depression and future trials should investigate if the results generalize to the larger population of high-worriers. Finally, the trial therapists had limited training in metacognitive therapy. Thus, while the risk of researcher allegiance to the intervention under test was minimized (Munder et al., 2013), it is possible that the effect sizes found in this trial could have been higher if the research team/therapists had received more expert supervision in metacognitive techniques (previous trials that have used trained face-to-face meta-cognitive therapists have generally obtained even larger reductions than found in this trial; Normann et al., 2014). Thus, the intervention tested in this study should not be regarded as equivalent to the full metacognitive therapy protocol.

In summary, the current study provides preliminary empirical support suggesting that reduction in negative beliefs about worry play an important role in outcomes for treatment of excessive worry. Results also add to the growing evidence-base for meta-cognitive interventions in the treatment of excessive worry.

Note

1. The analysis of the conditional indirect effect of the mediator (MCQ-30-Neg) approached significance in the full sample (N =108). However, a few outlying observations obtained from a small subset of participants (n = 6) altered the effect of the interaction between mediator and intervention group on the slope of the mediator in terms of the point estimate (−0.049 vs −0.012), SE (0.026 vs 0.034), and p-value (.057 vs .740).

Acknowledgments

This study was funded by Fredrik and Ingrid Thuring foundation. This work used the BASS platform from the eHealth Core Facility at Karolinska Institutet, which is supported by the Strategic Research Area Healthcare Science (SFO-V).

Declaration of interests

Drs. Ljótsson and Hedman-Lagerlöf reports personal fees from Pear Therapeutics Inc. outside the submitted work; In addition, Drs. Ljótsson and Hedman-Lagerlöf have copyright to an IBS self-help manual with royalties paid from Pear Therapeutics Inc. The authors have no additional conflicts of interest to declare.

ORCID

Tove Wahlund https://orcid.org/0000-0002-5123-2392
Hugo Hesser https://orcid.org/0000-0002-9736-8228
Sean Perrin https://orcid.org/0000-0002-5468-4706
Sanna Johansson https://orcid.org/0000-0003-4752-4744
Vilgot Huhn https://orcid.org/0000-0001-7443-3384
Sara Sörhus https://orcid.org/0000-0002-0781-7561
Severin Lindskog https://orcid.org/0000-0002-7250-4836
Eva Serlachius https://orcid.org/0000-0001-7115-6422
Erik Hedman-Lagerlöf https://orcid.org/0000-0002-7939-9848
Brjánn Ljótsson https://orcid.org/0000-0001-8086-1668
Erik Andersson https://orcid.org/0000-0003-0088-8719

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