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The Importance of Symptom Reduction for Functional Improvement after Cognitive Behavioral Therapy for Anxiety and Depression: A Causal Mediation Analysis

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Symptoms · Depression · Anxiety · Cognitive behavioral therapy · Functioning · Mediation · Prompt mental health care · Improving access to physiological therapies · Outcome monitoring

Abstract
Introduction: The temporal relationship between symptoms and functioning in the context of cognitive behavioral therapy (CBT) for anxiety and depression is not fully understood, and there are few high-quality studies that have examined to what extent late intervention effects of CBT on functioning are mediated by initial intervention effects on symptoms while accounting for the initial effects on functioning and vice versa. ***Objective:*** The aim of the study was to investigate whether intervention effects on symptoms and functioning at 12-month follow-up were mediated by intervention effects on these outcomes at 6-month follow-up. ***Methods:*** Participants with anxiety and/or mild-to-moderate depression were randomly assigned to a primary mental health care service (n = 463) or treatment-as-usual (n = 215). Main outcomes were depressive symptoms (Patient Health Questionnaire [PHQ-9]), anxiety (General Anxiety Disorder-7 [GAD-7]), and functioning (Work and Social Adjustment Scale [WSAS]). Direct/indirect effects were derived using the potential outcomes and counterfactual framework. ***Results:*** The intervention effect on functioning at 12 months was largely explained by intervention effects at 6 months on depressive symptoms (51%) and functioning (39%). The intervention effect on depressive symptoms at 12 months was largely explained by the intervention effect at 6 months on depressive symptoms (70%) but not by functioning at 6 months. The intervention effect on anxiety at 12 months was only partly accounted for by intervention effects at 6 months on anxiety (29%) and functioning (10%). ***Conclusions:*** The findings suggest that late intervention effects of CBT on functioning were to a substantial degree explained by initial intervention effects on depressive symptoms even after accounting for initial effects on functioning. Our results support the importance of symptoms as an outcome in the context of CBT delivered in primary health care.

Introduction

Anxiety and depression are among the most common mental disorders and are associated with substantial functional impairment [1]. A multitude of studies have shown

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that cognitive behavioral therapy (CBT) can be effective in treating these conditions [2–5]. To evaluate the efficacy/effectiveness of CBT, symptom measures and/or diagnosis have traditionally been used as endpoints, while the importance of including functioning as a complementary endpoint has become more acknowledged during the last decade [6, 7].

The temporal relationship between symptoms and functioning in the context of treatment for anxiety and depression is not fully understood, although it is often assumed that changes in functioning lag changes in symptoms (i.e., a serial process) [6]. Most of the work in this regard is based on treatment studies observing that intervention effects on functioning tend to occur later than intervention effects on symptoms [8–11]. On the other hand, prospective observational studies have provided evidence for a bidirectional relationship between both depressive and anxiety symptoms and functioning [12–15]. Causal interpretations based on these types of studies are, however, often limited by their nonexperimental design [16] and may very well vary by diagnosis, functional domain, or context [6].

Experimental studies with repeated measurements arguably provide the best design to determine how an intervention influences an outcome by means of causal mediation analysis [17]. Surprisingly, few such studies have been conducted regarding the temporal relationship between symptoms and functioning in patients receiving CBT for anxiety and/or depression. The relevant studies that we identified all found that intervention effects on functioning were at least partly mediated by effects on symptoms [18–20]. Common for all these studies was that only serial processes were considered and that the intervention effect on functioning at the measurement occasion of the mediator (i.e., symptoms) was not controlled for. Parallel processes, in which the intervention simultaneously influences symptoms and functioning, or a combination of serial and parallel processes, with unidirectional or bidirectional cross-lagged effects, were also not considered, despite being reasonably plausible (see Fig. 1). The aim of the present study was therefore to determine whether late intervention effects on symptoms and functioning at 12-month follow-up were mediated by initial effects on symptoms and/or functioning at 6-month follow-up.

Methods

For the current study, data from the randomized controlled trial of Prompt Mental Health Care (PMHC) were used [21]. PMHC is the Norwegian adaptation of the English program Improving Access to Psychological Therapies (IAPT) [22] and is a free-of-charge, low-threshold, primary health care program aimed at reaching adults with anxiety and mild-to-moderate levels of depression. We have previously shown that PMHC treatment, in comparison with a treatment-as-usual condition, is effective in terms of reducing symptom levels of anxiety and depression and improving functioning at both 6- and 12-month follow-up [21, 23]. Design, study setting, recruitment, randomization, and interventions were described in detail in an earlier article that presented the main findings of the trial [21]. Key aspects will be summarized below.

The trial was conducted within routine care at, and in close collaboration with, two PMHC sites: Kristiansand and Sandnes. To be eligible for PMHC service during the trial period, the patient had to present with anxiety and/or mild-to-moderate depression as determined by the staff during initial assessment. A randomized controlled design with parallel assignment was used. The participants were randomized (using a computerized random number generator) on a 70:30 ratio (PMHC vs. TAU) with simple randomization within each of the two sites and with no further constraints. In PMHC, CBT treatment is offered in both low-intensity (guided self-help, psycho-educational courses) and high-intensity (individual treatment) forms. The care is organized according to a type of matched-care model, in which information from the initial assessment and patient preferences is used to determine the choice of treatment. Treatment-as-usual included all ordinary services available to the target population. In Sandnes and Kristiansand, as many Norwegian municipalities, this usually included follow-up by the GP, alternatively by private psychologists or occupational health services.

Data Collection

Data from measurements at baseline, 6 months, and 12 months after baseline in both the PMHC and TAU group were used for the present study to derive the intervention effects of PMHC compared to TAU at 6- and 12-month follow-up on symptoms of depression, symptoms of anxiety, and functioning. At follow-up, participants were invited to fill out questionnaires through standardized e-mails with direct, secure links to the online questionnaires.

Participant Flow

A total of 463 patients were originally randomized to the PMHC condition, whereas 218 patients were randomized to the TAU condition. During the research project, four participants withdrew their informed consent in the PMHC group and three in the TAU group, resulting in a net allocation of 459 to the PMHC group and 215 to the TAU group. At 6-month follow-up, outcome data were available for 62.4% of the participants in the PMHC group (n = 289) and 45.0% of the participants in the TAU group (n = 98). At 12-month follow-up, these percentages were 51.2% in the PMHC group (n = 237) and 38.5% in the TAU group (n = 84).

Outcome Variables

Symptoms of depression were measured using the Patient Health Questionnaire (PHQ-9), tapping frequency of nine symptoms ("not at all" [0] to "nearly every day" [3]) in the last 2 weeks [24, 25]. A sum score ranging from 0 to 27 was created. The PHQ-9

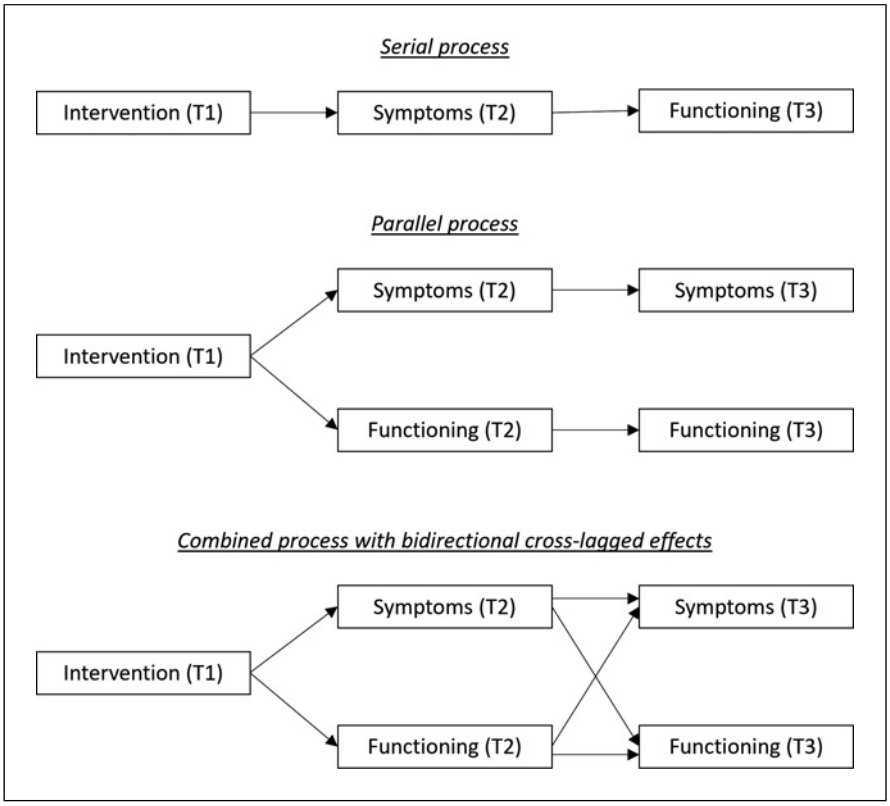


Fig. 1. Alternative models for the interrelationship between symptoms and functioning. Direct effects from T1 to T3 are not shown.

has been shown to have good reliability and validity for measuring major depressive disorder [24]. A total score ≥10 indicates clinically significant levels of depression.

Symptoms of anxiety (General Anxiety Disorder-7, GAD-7): symptoms of anxiety were measured using the GAD-7, including seven items with similar frequency ratings and time frame as PHQ-9 [25, 26]. A sum score ranging from 0 to 21 was created. GAD has displayed good reliability and validity for measuring generalized anxiety disorder [26] and satisfactory sensitivity and specificity for generalized anxiety and other anxiety disorders [27]. A total score ≥8 indicates clinically significant levels of anxiety.

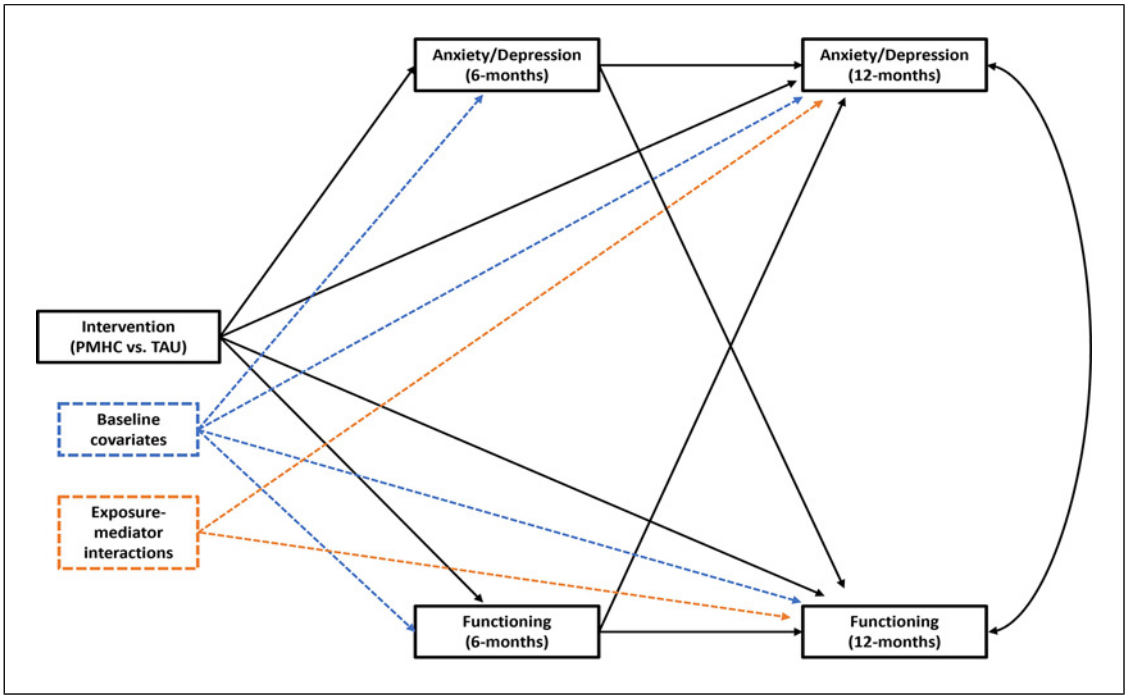
Functioning was measured using the Work and Social Adjustment Scale (WSAS) [28]. The WSAS contains 5 items, assessing impairment due to mental health problems during the last month in five domains (work/studies, home management, social leisure [activities together with others], private leisure [activities done alone], and personal or family relationships), all scored from 0 (not impaired) to 8 (severely impaired). A sum score ranging from 0 to 40 was created. The WSAS has been employed in previous evaluations of PMHC [29] and IAPT [30]. In this context, WSAS was found to have discriminant validity to, and comparable reliability and sensitivity to change as, the PHQ-9 and GAD-7 [31].

Baseline Covariates

Baseline values of the outcome variables and the following sociodemographic variables were included as covariates in all mediation analyses: sex (male/female), age, education (higher education [university/university college]: y/*n*), and marital status (married/cohabiting: y/*n*). Two questions, one multi-response item about current work status and one about sources of income, assessed employment status. Based on these, we determined whether participants were in full- or part-time regular work without receiving benefits (y) or not (*n*). To minimize the impact of potential mediator-outcome confounding, we did an exploratory search for theoretically relevant baseline variables (see [32] for an overview of available baseline variables) that would substantially correlate ($r > 0.2$) with symptoms of anxiety/depression and functioning at 6- and 12-month follow-up. Only self-control as measured by the Brief Self-Control Scale [33] fulfilled these criteria and was therefore included as an additional covariate.

Statistical Analyses

For each outcome (PHQ/GAD and WSAS at 12-month follow-up), we estimated the direct and indirect effects of the exposure (treatment) on the outcome variables for the included mediators (PHQ/GAD and WSAS at 6-month follow-up) while adjusting for potential confounders (sex, age, educational attainment, relationship status, self-control, and employment status). Continuous baseline variables were grand mean centered and included as covariates. As recommended, we included the exposure-mediator interactions in the model, as not doing so may lead to biased estimates and decreased statistical power to detect indirect effects [17]. For example, the model that examined whether



Color version available online

Fig. 2. Path diagram of the tested model (adjusted). The covariance between symptoms and functioning at 6 months is not displayed.

the intervention effects on depression and functioning at 12-month follow-up were explained by intervention effects on depression and functioning at 6-month follow-up included the exposure-mediator interactions "intervention × depression at 6 months" and "intervention × functioning at 6 months." See Figure 2 for an overview of the full model. Separate models were estimated for, respectively, symptoms of depression and functioning as outcomes and symptoms of anxiety and functioning as outcomes. Maximum likelihood estimation was used and is valid under the assumption of data missing at random. Bootstrapped standard errors and confidence intervals were obtained using 1,000 draws. All indirect/direct effects were derived using the potential outcomes and counterfactual framework, which enables proper definitions of indirect/direct effects when exposure-mediator interactions are included [17]. The practical interpretation of these effects is similar to that of the traditional product method used by Baron and Kenny [34].

Sensitivity analyses were carried out to examine whether the size of the (in)direct effect estimates was robust to missing data assumptions [35]. In this regard, a binary missing data indicator (1 = missing data at 12-month follow-up, 0 = not missing data at 12-month follow-up) was added to the model shown in Figure 2 and regressed on the outcome variables at 12-month follow-up. This mimics a Missing Not At Random scenario in which the probability of missing data on the outcome variables at a particular measurement occasion is related to the values of the outcomes at that same measurement occasion. Mplus version 8.7 was used for all analyses.

Results

Descriptive Statistics

The sample had a mean age of 34.8 years (SD = 12.3) and was predominantly female (66.6%). Over one-third had completed higher education (41.4%), more than half were married or cohabiting (56.5%), and 37.5% were in regular work without receiving benefits. The mean self-control score was 3.0 (SD = 0.6). We have previously shown that baseline characteristics were similar across treatment groups (PMHC vs. TAU) [21]. At baseline, 42.9% had clinically relevant levels of both symptoms of depression and anxiety, 37.9% had clinically relevant levels of depressive symptoms only, and 19.2% had clinically relevant levels of anxiety symptoms only.

Table 1 shows the observed PHQ, GAD, and WSAS scores at baseline, 6- and 12-month follow-up by treatment group. For all outcomes, the average improvement was greater for participants assigned to the PMHC group compared to those assigned to the TAU group. Formal effect estimates are presented elsewhere [21, 23].

Mediation Effects with Symptoms of Depression and Functioning as Outcomes

As shown in Table 2, the intervention effect on depressive symptoms at 12-month follow-up was

Table 1. Descriptive statistics for depression, anxiety, and functioning across time points

	PMHC		TAU		Total	
	n	mean (SD)	*n*	mean (SD)	*N*	mean (SD)
PHQ						
Baseline	459	14.9 (4.5)	215	15.0 (4.5)	674	14.9 (4.5)
6-month FU	289	7.1 (4.8)	98	10.5 (6.5)	387	8.0 (5.5)
12-month FU	237	6.8 (5.1)	84	9.8 (5.8)	321	7.6 (5.5)
GAD						
Baseline	459	12.1 (4.2)	215	11.9 (4.2)	674	12.0 (4.2)
6-month FU	289	5.6 (3.9)	98	7.6 (4.5)	387	6.1 (4.2)
12-month FU	235	5.3 (4.0)	84	7.5 (5.0)	319	5.9 (4.4)
WSAS						
Baseline	459	21.8 (7.7)	215	21.4 (8.1)	674	21.7 (7.8)
6-month FU	276	12.7 (9.4)	93	15.8 (10.4)	369	13.5 (9.7)
12-month FU	230	11.4 (10.3)	82	14.7 (10.2)	312	12.3 (10.3)

Table 2. Unstandardized total, direct, and indirect effect estimates of the mediation model with depression and functioning as outcomes

	Unadjusted, MAR Est. (95% CI)	**Adjusted, MAR** Est. (95% CI)	**Adjusted, MNAR** Est. (95% CI)
Outcome: PHQ-9 at 12-month FU			
Total effect	**−2.89 (−4.28, −1.52)**	**−3.24 (−4.89, −1.50)**	**−3.37 (−5.01, −1.62)**
Direct effect	−0.67 (−1.77, 0.53)	−1.15 (−2.91, 0.73)	−1.18 (−2.93, 0.67)
Total indirect effect	**−2.22 (−3.30, −1.27)**	**−2.08 (−3.20, −1.19)**	**−2.19 (−3.30, −1.29)**
Specific indirect effect (mediator=PHQ-9 at 6M FU)	**−2.02 (−3.06, −1.10)**	**−1.93 (−3.10, −1.04)**	**−2.08 (−3.31, −1.11)**
Specific indirect effect (mediator=WSAS at 6M FU)	−0.20 (−0.54, 0.02)	−0.16 (−0.52, 0.12)	−0.11 (−0.47, 0.17)
Outcome: WSAS at 12-month FU			
Total effect	**−3.03 (−5.46, −0.46)**	**−3.21 (−6.18, −0.20)**	−2.98 (−6.13, 0.56)
Direct effect	−0.12 (−2.39, 1.94)	−0.30 (−3.09, 2.62)	−0.34 (−3.37, 3.39)
Total indirect effect	**−2.90 (−4.70, −1.15)**	**−2.90 (−4.63, −1.45)**	**−2.63 (−4.46, −1.05)**
Specific indirect effect (mediator=PHQ-9 at 6M FU)	**−1.56 (−3.05, −0.48)**	**−1.64 (−3.34, −0.41)**	−1.17 (−2.94, 0.20)
Specific indirect effect (mediator=WSAS at 6M FU)	**−1.34 (−2.65, −0.27)**	**−1.26 (−2.58, −0.32)**	**−1.46 (−2.80, −0.42)**

Estimates in bold indicate $p < 0.05$. MAR, Missing At Random; MNAR, Missing Not At Random; 6M FU, 6-month follow-up.

largely explained by the intervention effect on depressive symptoms at 6-month follow-up (70.0%, adjusted analysis). In contrast, the intervention effect on functioning at 12-month follow-up was explained by both the intervention effect on functioning at 6-month follow-up and the intervention effect on depressive symptoms at 6-month follow-up. More precisely, functioning at 6-month follow-up explained 39.4% of the total effect on functioning at 12-month follow-up, and symptoms of depression at 6-month follow-up explained 51.2% of this effect (adjusted analysis). A sensitivity analysis regarding missing data assumptions did not substantially alter these findings (see Table 2).

Mediation Effects with Symptoms of Anxiety and Functioning as Outcomes

As shown in Table 3, the intervention effect on symptoms of anxiety at 12-month follow-up was only partly explained by the intervention effect on symptoms of anxiety at 6-month follow-up (28.9%) and functioning at 6-month follow-up (10.0%; adjusted analysis). That is, more than half of the intervention effect on symptoms of anxiety at 12-month follow-up remained unexplained. The intervention effect on functioning at 12-month follow-up was partly explained by functioning at 6-month follow-up (47.1%, adjusted analysis) but not at all by symptoms of anxiety at 6-month follow-up. A sensitivity analysis with regard to

Table 3. Unstandardized total, direct, and indirect effect estimates of the mediation model with anxiety and functioning as outcomes

	Unadjusted, MAR Est. (95% CI)	**Adjusted, MAR** Est. (95% CI)	**Adjusted, MNAR** Est. (95% CI)
Outcome: GAD-7 at 12-month FU			
Total effect	**−2.01 (−3.05, −0.81)**	**−2.49 (−3.85, −1.09)**	**−2.63 (−4.02, −1.24)**
Direct effect	−0.76 (−1.69, 0.25)	**−1.52 (−2.92, −0.14)**	**−1.61 (−2.93, −0.26)**
Total indirect effect	**−1.26 (−2.03, −0.60)**	**−0.97 (−1.53, −0.45)**	**−1.02 (−1.62, −0.49)**
Specific indirect effect (mediator=GAD-7 at 6M FU)	**−1.07 (−1.81, −0.53)**	**−0.72 (−1.30, −0.28)**	**−0.80 (−1.40, −0.31)**
Specific indirect effect (mediator=WSAS at 6M FU)	**−0.19 (−0.44, −0.00)**	**−0.25 (−0.57, −0.02)**	**−0.22 (−0.54, 0.00)**
Outcome: WSAS at 12-month FU			
Total effect	**−3.27 (−5.67, −0.63)**	**−3.46 (−6.31, −0.43)**	−2.79 (−6.13, 1.01)
Direct effect	−1.06 (−3.16, 1.14)	−1.29 (−4.05, 1.43)	−0.84 (−4.14, 2.93)
Total indirect effect	**−2.21 (−3.78, −0.62)**	**−2.17 (−3.63, −0.85)**	**−1.95 (−3.41, −0.58)**
Specific indirect effect (mediator=GAD-7 at 6M FU)	−0.29 (−1.04, 0.31)	−0.54 (−1.52, 0.25)	−0.14 (−1.14, 0.84)
Specific indirect effect (mediator=WSAS at 6M FU)	**−1.92 (−3.37, −0.53)**	**−1.63 (−2.94, −0.54)**	**−1.81 (−3.32, −0.61)**

Estimates in bold indicate $p < 0.05$. MAR, Missing At Random; MNAR, Missing Not At Random; 6M FU, 6-month follow-up.

missing data assumptions did not substantially alter these findings (see Table 3).

Post hoc Analyses

Anxiety did not contribute to explaining the intervention effect on functioning at 12-month follow-up, and we wondered whether this may have been due to the fact that on average the provided treatment was more focused on depression than it was on anxiety. We conducted a first post hoc analysis of the subsample that had clinically significant levels of anxiety at baseline without comorbid depressive symptoms to explore this hypothesis. The patterns were, however, similar to the findings based on the whole sample, though the subsample had become too small to draw firm conclusions.

It was also somewhat surprising that the intervention effect at 12-month follow-up on anxiety remained largely unexplained. One straightforward reason for this result could be that depressive symptoms at 6-month follow-up were not included as a mediator in the analyses with anxiety and functioning as outcomes (presented in Table 3). A second post hoc analysis, in which all three outcome variables were included simultaneously, showed that also after including depressive symptoms, the intervention effect on anxiety at 12-month follow-up remained largely unexplained. Further, the depressive symptoms did not significantly contribute to explaining the intervention effect on anxiety.

Discussion

The current study aimed to examine to what extent late intervention effects of CBT for depression and anxiety on symptoms and functioning at 12-month follow-up could be explained by initial intervention effects on these outcomes at 6-month follow-up. Our analyses showed that the intervention effect on functioning at the 12-month follow-up was largely explained by intervention effects at the 6-month follow-up on functioning (39%) and symptoms of depression (51%) but not at all by symptoms of anxiety. Furthermore, the intervention effect on symptoms of depression at 12-month follow-up was largely explained by the intervention effect at 6-month follow-up on symptoms of depression (70%), whereas the intervention effect on symptoms of anxiety at 12-month follow-up remained largely unexplained and was only partly accounted for by intervention effects at 6-month follow-up on symptoms of anxiety (29%) and functioning (10%).

Our finding that the intervention effect on functioning was to a substantial degree explained by effects on symptoms of depression was in line with findings from previous work [18–20] and emphasizes the importance of symptoms as an outcome. As argued and shown by Clark et al. [22], patient- and service-level symptom outcome monitoring is important with regard to service transparency but also yields important ways to improve patient outcomes and reduce cross-service variability. Our study adds to this by showing empirically that initial symptom improvements following treatment are likely to translate into later improvements in functioning, even after accounting for initial intervention effects on functioning. This is considered highly relevant not only from an individual but also from a societal and economic point of view. Mental disorders are estimated to be the costliest medical condition in

Norway, whereof more than half the costs are due to tax-based production loss, such as disability pension claims [36]. Furthermore, the indications of late effects on functioning, following symptom improvement, underscore the need for patience in clinical practice in expecting intervention effects on functioning as well as to include long enough follow-up time in clinical trials to enable recording of such effect. In the context of PMHC, this was particularly the case for symptoms of depression but not for symptoms of anxiety.

One possible explanation for the finding that the intervention effect on anxiety did not contribute to explain the later intervention effect on functioning could be that symptoms of anxiety are more volatile at the within-person level as compared to symptoms of depression. Higher volatility may lead to a lower autocorrelation between symptoms of anxiety at 6-month follow-up and symptoms of anxiety at 12-month follow-up, which in turn results in a lower indirect effect. Higher volatility does not necessarily impact the group-level mean of anxiety, which may explain why the intervention effect of PMHC on symptoms of anxiety remained relatively stable from 6-month follow-up to 12-month follow-up. A second explanation could be that on average the provided treatment was more focused on depression than it was on anxiety. The study sample was dominated by participants with depressive symptomology at baseline and consisted to a lesser degree of participants with specific anxiety problems [21]. However, a post hoc analysis of the subsample that had clinically significant levels of anxiety at baseline without comorbid depressive symptoms suggested that findings were comparable to those of the full sample. Moreover, PMHC therapists are trained to use clinical judgment in order to adapt treatment when anxiety and depression coexist, in line with recommendations by others [37], and we would therefore not expect that the mixed sample would impact the results to begin with.

Another interesting and somewhat surprising finding in our study was that the intervention effect at 12-month follow-up on anxiety remained largely unexplained. Our second post hoc analysis indicated that this was not due to the omission of the variable depression in the model. It is therefore likely that other mechanisms were involved, for example, operating through mediators like anxiety cognitions and avoidance behavior [38].

In line with this interpretation, the correlation and explained variance between symptoms of anxiety and functional impairment is found to be lower than between symptoms of depression and functional impairment [6, 7]. It could be that anxiety disorders affect the individual in a more complex way than depression. For instance, avoidance and in-situation safety behavior may mask the subjective experience of impairment and hence attenuate the association between symptoms and reported function [39]. Finally, there might be domain-specific impairment across various anxiety conditions/disorders [6]. For instance, there seems to be lower correlation between social anxiety disorder and social functioning [40] compared to other anxiety disorders. The addition of comorbid depression may complicate this matter even more [37]. We were not able to investigate such diagnosis- and/or domain-specific associations in this study.

The substantial intervention effect of PMHC compared to TAU on functioning, maintained at 12 months [23] and even further improved in the PMHC group at 24 and 36 months [41], is in itself worth mentioning and lends support for IAPT-like services as viable treatment alternatives for anxiety and depression. It should nonetheless be noted that the estimated intervention effects on symptoms were larger than the effect on functioning [21, 23]. This was the case at both 6- and 12-month follow-up and is in line with findings from previous studies, suggesting that CBT alone may not be sufficient to match improvements in functioning with improvements in symptoms [42, 43]. A more tailored approach regarding functioning may as such be required, for example, by work-focused CBT for those who struggle with work-related issues. Other promising approaches to better tailor treatment content to specific problems and to prevent relapse include staging in planning an intervention according to specific phases of a depressive disorder [37] or by sub-type of coexisting anxiety and depression [44, 45]. For instance, applying a sequential combination of pharmacotherapy and psychotherapy is associated with reduced risk of relapse in major depression [44] and should hence be considered for the more severe cases. PMHC treatment adopts a self-managing and well-being focus. Applying a well-being therapy approach could hence be a second step ingredient in the treatment for these patients, which may also yield lasting improvements both in symptoms and functioning [46–48].

Strengths and Limitations

The current study has several strengths, most notably the RCT design, the relatively large sample size, application of state-of-the-art mediation analysis, use of validated instruments, and the use of sensitivity analysis to test the robustness of missing data assumptions. Although this is not the first study that examines the mediating effect of symptoms on functioning in the context of CBT, this is one of the first

to simultaneously control for the parallel mediation of the lagged outcome variable, in our case functioning at 6-month follow-up. We believe that inclusion of such a lagged variable is necessary and increases the validity of the results of the present study.

A few weaknesses should also be mentioned. First, the study suffers from a high level of attrition at 6- and 12-month follow-up. Even though the sensitivity analyses indicated that the results were comparable under a "Missing Not At Random" scenario, this can by no means compensate for the uncertainty introduced by the current level of attrition, and results should therefore be interpreted with caution. A second weakness is that despite the RCT design and the inclusion of multiple baseline covariates, we cannot exclude the possibility of bias due to unobserved mediator-outcome confounding.

Conclusion

The current study shows that the interrelationship between symptoms and functioning is best represented as a combined parallel and serial process (see Fig. 1). The parallel process implies that intervention effects on symptoms observed at 6-month follow-up contribute to explain intervention effects on symptoms at 12-month follow-up. Similarly, intervention effects on functioning observed at 6-month follow-up contribute to explain intervention effects on functioning at 12-month follow-up. Additionally, we found evidence for a serial process with a unidirectional cross-lagged effect, in which the intervention effects on symptoms of depression contributed substantially to explain the intervention effects on functioning at 12-month follow-up.

We consider the latter the main finding of the present study, as it emphasizes the importance of symptoms as an outcome but also provides empirical support for the notion that the effects of CBT on symptoms may have a ripple effect on a broader range of outcomes, in our case on the socially important outcome functioning. In line with that, the results of our study also illustrate the relevance of IAPT-like services for society. In addition to being a key factor for sense of remission of anxiety and depression from the view of the individual [40], improved functioning has direct benefits in areas such as participation in social life and work life. From public health and health economic perspectives, it could therefore be beneficial if more countries made CBT accessible through IAPT-like initiatives.

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Statement of Ethics

The trial protocol was approved by the Regional Ethics Committee for Western Norway (REK-vest no. 2015/885) and the trial was reported according to the CONSORT statement and is registered at ClinicalTrials.gov (NCT03238872). No changes were made to primary and secondary outcomes after trial approval. All participants have given their written informed consent. All methods were carried out in accordance with relevant guidelines and regulations.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

O.R.F.S. contributed to the design of the study, performed the statistical analyses, and drafted the manuscript. O.R.F.S., L.E.A., and M.K. contributed to interpretation of the data, offered critical revisions of the draft, and read and approved the final manuscript.

Data Availability Statement

The datasets analyzed during the current study are not publicly available due to ethical restrictions and personal data protection but are available from the corresponding author on reasonable request.

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