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Danksagung

Ein Handbuch entsteht aus den einzelnen Arbeiten
wie ein Mosaik aus vielen farbigen Steinchen:
durch Auswahl und geordnete Zusammenstellung.

Ludwik Fleck

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No one is an island.

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Abstract

Bodily distress refers to a spectrum of persistent and impairing physical symptoms often accompanied by maladaptive psychological responses. It serves as an umbrella-term encompassing somatoform disorders, newer diagnostic frameworks emphasizing psychobehavioral features (i.e., somatic symptom disorder and bodily distress disorder), and functional somatic syndromes such as chronic fatigue syndrome (CFS), irritable bowel syndrome, and fibromyalgia. Despite increasing recognition of their clinical relevance, the evidence base for psychotherapeutic interventions for bodily distress remains fragmented. Conventional cognitive behavioral therapy (CBT) has shown small to moderate efficacy in treating bodily distress. However, newer variations of cognitive behavioral interventions, focusing on acceptance and mindfulness – so-called “third wave” treatments – are hypothesized to be particularly effective in the treatment of this clinical domain. Yet, comprehensive evidence syntheses comparing these modalities are lacking, especially on relative effects between these treatment approaches. This dissertation evaluates the efficacy and acceptance of conventional cognitive behavioral interventions and “third wave” treatments for adults with bodily distress. Employing meta-analytical methods – including pairwise meta-analyses and network meta-analysis – this dissertation synthesizes randomized controlled trials across the sub-syndrome CFS and the whole spectrum of bodily distress.

Study 1 focuses on meta-analytic evidence syntheses of 15 trials with 2,015 participants on CBT for CFS, confirming its absolute efficacy in reducing fatigue and comorbid psychopathology compared to control groups while also showing high treatment acceptance, indicated by low rates of treatment refusal and premature termination in the treatment groups.

Study 2 investigates mindfulness- and acceptance-based therapies (mindfulness-based cognitive therapy, mindfulness-based stress reduction, and acceptance and commitment therapy) for bodily distress in adults. The meta-analysis, based on 16 trials with 1,288 participants, reveals that these “third wave” treatments significantly reduce somatic symptom severity and improve secondary outcomes, such as anxiety, depression, perceived health status, mindfulness, and psychological inflexibility compared to control conditions.

Study 3 employs a network meta-analysis to compare CBT and “third wave” treatments for bodily distress. Results based on a large dataset of 74 trials (with 8,277 participants) suggest comparable efficacy in reducing somatic symptoms, with “third wave” treatments providing additional benefits in alleviating anxiety and depression.

Overall, these findings affirm CBT as a well-established treatment, particularly for CFS, demonstrating high adherence and sustained long-term benefits. Furthermore, the findings support “third wave” treatments as promising alternatives to conventional CBT in the treatment of bodily distress and related disorders. The dissertation also underscores the methodological value of meta-analytical evidence synthesis as well as network meta-analysis in addressing research gaps by enabling indirect treatment comparisons. Despite promising results, limitations such as study heterogeneity and limited long-term follow-up data emphasize the need for further direct comparisons and research on treatment moderators and mechanisms. These findings support the integration of cognitive behavioral treatments in treatment guidelines while further aiming to optimize patient care.

Zusammenfassung

Körperlicher Distress bezeichnet das Spektrum anhaltender, beeinträchtigender körperlicher Symptome, die häufig im Zusammenhang mit maladaptiven psychischen Reaktionen auftreten. Körperlicher Distress dient als Oberbegriff für somatoforme Störungen, neuere diagnostische Klassifikationen, die psychobehaviorale Faktoren in den Fokus rücken, wie die somatische Belastungsstörung, aber auch für funktionelle somatische Syndrome, etwa das chronische Erschöpfungssyndrom (chronic fatigue syndrome, CFS), Reizdarmsyndrom und Fibromyalgie. Trotz der klinischen Relevanz ist die Evidenzbasis für psychotherapeutische Interventionen fragmentiert. Während die konventionelle kognitive Verhaltenstherapie (KVT) kleine bis mittlere Effekte in der Behandlung körperlichen Distresses zeigte, werden neuere Variationen kognitiv-behavioraler Interventionen, die auf Akzeptanz und Achtsamkeit basieren – so genannte „dritte Welle“-Verfahren – vermehrt als wirksam bei der Behandlung dieses Störungsbereichs gehandelt. Es fehlen jedoch umfassende Evidenzsynthesen in diesem Forschungsfeld, insbesondere zu relativen Effekten zwischen den Ansätzen. Diese Dissertation untersucht Wirksamkeit und Akzeptanz konventioneller KVT und Verfahren der „dritten Welle“ bei Erwachsenen mit körperlichem Distress. Unter Verwendung paarweiser und Netzwerk-meta-analytischer Methoden werden die Ergebnisse randomisierter kontrollierter Studien zum Subsyndrom CFS und zum gesamten Spektrum körperlichen Distresses zusammengefasst.

Studie 1 evaluiert den Einsatz von KVT bei CFS mithilfe meta-analytischer Evidenzsynthesen basierend auf 15 Studien mit 2015 Teilnehmenden und bestätigt die absolute Wirksamkeit von KVT in der Reduktion von Erschöpfungssymptomatik und komorbider Psychopathologie im Vergleich zu Kontrollgruppen; bei gleichzeitig hoher Behandlungsakzeptanz, die sich in niedrigen Raten von Behandlungsverweigerung und vorzeitigem Abbruch in den Behandlungsgruppen widerspiegelt.

Studie 2 untersucht achtsamkeits- und akzeptanzbasierte Therapien bei Erwachsenen mit körperlichem Distress. Die Meta-Analyse (16 Studien, 1288 Teilnehmende) zeigt, dass diese „dritte Welle“-Verfahren den Schweregrad somatischer Symptome signifikant reduzieren und sekundäre Outcomes wie Angst, Depression, der wahrgenommene Gesundheitsstatus, Achtsamkeit und Akzeptanz von Schmerzen im Vergleich zu Kontrollbedingungen verbessern.

In Studie 3 wird eine Netzwerk-Metaanalyse durchgeführt, um KVT und „dritte Welle“-Verfahren bei körperlichem Distress zu vergleichen. Die Ergebnisse basieren auf einer großen Datenbasis von 74 Studien (mit 8277 Teilnehmenden) und deuten auf eine vergleichbare Wirksamkeit bei der Reduktion somatischer Symptome hin, wobei die „dritte Welle“-Verfahren zusätzliche Vorteile bei der Reduktion von Angst und Depression aufweisen.

Insgesamt ist es auf Basis dieser Ergebnisse gerechtfertigt, KVT als gesichert wirksam zu bewerten, insbesondere für CFS, ausgezeichnet durch eine hohe Therapieadhärenz und nachhaltige Effekte. Zudem stützen die Ergebnisse die Behandlungen der „dritten Welle“ als vielversprechende Alternativen zur konventionellen CBT in der Behandlung körperlichen Distresses und verwandten Störungen. Die Dissertation unterstreicht auch den methodischen Nutzen der meta-analytischen Evidenzsynthese und der Netzwerk-Meta-Analyse, um Forschungslücken mithilfe indirekter Behandlungsvergleiche zu schließen. Trotz vielversprechender Ergebnisse weisen Limitationen wie die Heterogenität zwischen den Studien und die begrenzte Datenlage zu Langzeiteffekten auf die Notwendigkeit weiterer direkter Vergleiche und der Erforschung von Moderatoren und Mechanismen der Behandlung hin. Diese Ergebnisse unterstützen die Aufnahme kognitiv-behavioraler Interventionen in Behandlungsleitlinien und zeigen gleichzeitig auf, dass die Patientenversorgung noch Optimierung bedarf.

List of Abbreviations

Abbreviation	Explanation
ACT	Acceptance and commitment therapy
APA	American Psychiatric Association
CBT	Cognitive behavioral therapy
CFS	Chronic fatigue syndrome
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4 th edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5 th edition
EURONET-SOMA	European Research Network to Improve Diagnosis, Treatment and Health Care for Patients with Persistent Somatic Symptoms
FSS	Functional somatic syndromes
IBS	Irritable bowel syndrome
ICD-10	International Classification of Diseases, 10 th revision
ICD-11	International Classification of Diseases, 11 th revision
MBCT	Mindfulness-based cognitive therapy
MBSR	Mindfulness-based stress reduction
MBT	Mindfulness-based therapy
NCCMH	National Collaborating Centre for Mental Health
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OCEBM	Oxford Centre for Evidence-Based Medicine
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RCT	Randomized controlled trial
SSD	Somatic symptom disorder

1. Introduction

Somatic symptom disorder (SSD) and related conditions, including functional somatic syndromes (FSS) such as chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS), and fibromyalgia show substantial overlap (Fink & Schröder, 2010; van der Meulen et al., 2024) and can be subsumed under the umbrella-term *bodily distress*. These chronic and often disabling disorders are highly prevalent (Hiller et al., 2006; Rometsch et al., 2024; Wittchen et al., 2011) and are characterized by persistent physical symptoms, frequently accompanied by maladaptive cognitive, emotional, and behavioral responses (Basavarajappa et al., 2020). Despite their substantial burden (Henningsen et al., 2018), effective treatments in bodily distress remain limited. Psychological interventions are the most effective approach (Hausteiner-Wiehle et al., 2013; Kleinstäuber et al., 2014; Koelen et al., 2014; van Dessel et al., 2014; van Gils et al., 2016). The largest body of evidence is available for cognitive behavioral therapy (CBT; Ford et al., 2019; Glombiewski et al., 2010; van Dessel et al., 2014). Hence, CBT has been widely recognized as a first-line psychological treatment for bodily distress (Löwe et al., 2024). However, symptom improvement through psychotherapy remains moderate at best (Henningsen et al., 2018).

Especially in CFS, despite evidence for its efficacy (Castell et al., 2011; Kuut et al., 2023; Malouff et al., 2008; Price et al., 2008), treatments with a psychobehavioral rationale were currently questioned (e.g., Vink & Vink-Niese, 2022) since some even consider them harmful (Twisk & Maes, 2009). Therefore, engagement with CBT in CFS remains specifically challenging (Friedberg, 2016). That is, beyond estimating effect sizes, analyses should also assess treatment acceptability (Swift et al., 2017) as drop-out from psychotherapies is of interest to make assumptions on acceptance of interventions (Karekla et al., 2019). Furthermore, recognizing that psychological treatments for bodily distress could be further optimized, interventions other than CBT are increasingly being

explored. Emerging “third wave” approaches might offer valuable treatment alternatives for chronic bodily symptoms (Frostholm & Rask, 2019) through their mindfulness- and acceptance-based approaches. Despite growing interest in “third wave” treatments (Rief et al., 2022), quantitative evidence synthesis in the field of bodily distress remains scarce. Furthermore, evidence regarding their efficacy compared to traditional CBT remains limited, as direct comparisons with CBT are lacking (Frostholm & Rask, 2019).

This dissertation aims to contribute to the understanding of the efficacy of cognitive behavioral interventions, both conventional CBT and “third wave” approaches, in adults with bodily distress. Through the three distinct – yet interconnected – meta-analytical projects presented in this thesis, this work examines the efficacy of these interventions, offering insights into their absolute efficacy, potential differential effects, and a systematic approach to examine treatment acceptance. An essential focus of this work is assessing efficacy of interventions across the whole spectrum of bodily distress, considering both broad and sub-diagnostic levels. This includes evaluating the absolute efficacy of CBT in the sub-syndrome CFS where psychotherapy research remains particularly limited (*study 1*). Similarly, the absolute efficacy of “third wave” treatments in bodily distress compared to inactive and non-specific control groups will be examined to assess whether they could offer valuable treatment alternatives to CBT (*study 2*). Consequently, the efficacy of “third wave” treatments will also be examined in comparison to conventional CBT to better understand their relative efficacy (*study 3*). Concurrently, this work emphasizes that treatment acceptability is a crucial yet often overlooked factor. By addressing these dimensions, the dissertation aims to determine not only whether interventions are effective but also whether they are well-received within CFS (*study 1*), a relevant subset of the field. Each study is designed to address critical gaps in existing literature, providing, in the overall view, a comprehensive evaluation of the (cognitive behavioral) psychotherapeutic landscape for bodily distress.

2. Theoretical Background

2.1 Bodily Distress

The term bodily distress encompasses a range of conditions characterized by persistent and distressing physical symptoms (Henningesen et al., 2018). While symptoms like digestive issues, pain, dizziness, or fatigue are common in the general population, they do not necessarily constitute a psychological disorder. Most individuals experience transient bodily sensations that fluctuate over time (Hiller et al., 2006). However, when symptoms persist on most days for several months, causing substantial distress and impairment, they can be considered clinically relevant (Löwe et al., 2024). The concept of bodily distress unifies various related diagnoses and syndromes, characterized by persistent physical symptoms, under a single framework (Martin & Van den Bergh, 2020).

Diagnostics and Classification. Conditions classified under bodily distress tend to have longer symptom durations than other mental disorders (Claassen-van Dessel et al., 2018; van Dessel et al., 2014). This is due to bodily distress often remaining under-diagnosed, with individuals on average suffering 25 years without adequate treatment (Herzog et al., 2018). On the one hand, many patients with bodily symptoms are reluctant to engage with mental health services (Henningesen et al., 2018). On the other hand, many clinicians regard somatoform diagnoses unacceptable (Dimsdale, 2011), as they are reluctant to attribute psychological diagnoses to patients presenting with bodily symptoms (Fink, 2017). One of the main problems in the diagnostic process is the lack of a reliable biomarker (Ying-Chih et al., 2020). Consequently, many of the diagnoses in the field of bodily distress were historically consensus-based (Fink, 2017) and have changed considerably throughout the decades.

In psychodynamic theory, somatization, historically linked to bodily distress, refers to the expression of psychological distress through the conversion of emotional

conflicts into physical symptoms (Witthöft & Hiller, 2010). Classification manuals, moving away from the previous causal assumptions (e.g., DSM-IV, American Psychiatric Association, 1994; ICD-10, World Health Organization, 2009), opted for a descriptive form of diagnosis, characterizing somatization disorder by the presence of unclear or insufficiently explained symptoms (Hiller & Janca, 2003). However, this approach was not empirically supported and therefore criticized as overly restrictive (Rief et al., 2011). Patients were required to report a specific number and type of symptoms (either at least four pain symptoms, or two gastrointestinal, or one sexual, or one pseudoneurological symptom), although a simple symptom count is insufficient for diagnosis of a psychological disorder (Rief & Isaac, 2007). Moreover, the reliability of categorizing symptoms as medically explained versus unexplained is also low (Leiknes et al., 2006; Rief & Rojas, 2007), as this dichotomy is often artificial (Kroenke et al., 2002). Despite around one-third of physical symptoms are considered to be medically unexplained (Kroenke & Mangelsdorff, 1989; Marple et al., 1997), determining this status remains challenging (Kroenke et al., 2007).

Therefore, contemporary classifications rather incorporate psychological features, emphasizing the role of psychobehavioral factors in the exacerbation, maintenance, and perception of physical symptoms (Rief & Martin, 2014). Beyond somatic symptoms and mood disorders, these factors contribute significantly to disability and help identify patients at risk of chronification, as seen in pain disorders (Rief et al., 2010). Including psychological features aids in recognizing individuals in need of healthcare (Rief et al., 2011) and informs treatment options (Voigt et al., 2010). Reflecting this shift, the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association, 2013) eliminated the distinction between medically explained and unexplained symptoms, introducing somatic symptom disorder (SSD) to focus on excessive thoughts, feelings, or behaviors related to physical symptoms (Rief & Martin,

2014). Similarly, the eleventh revision of the International Classification of Diseases (ICD-11, World Health Organization, 2022) defines bodily distress disorder as one or more persistent and distressing physical symptoms – whether medically explained or unexplained – accompanied by excessive focus on these symptoms.

An additional category, functional somatic syndromes (FSS), describes complaints and functional limitations in certain areas of the body or bodily functions (Henningsen et al., 2018) that are not sufficiently explained by another medical condition (Fischer & Nater, 2014). They are either linked to a single organ system or describe a specific symptom cluster (Henningsen et al., 2018). However, these syndromes have been criticized for showing similar symptoms or mechanisms while receiving different classifications in various disciplines (Fink, 2017). Emphasizing these similarities, FSS are also proposed to be integrated in bodily distress as bodily distress captures almost all FSS-patients (Fink & Schröder, 2010). The most established FSS with well-defined diagnostic criteria are IBS, CFS, and fibromyalgia (van der Meulen et al., 2024).

A central debate in the field concerns whether these syndromes should be grouped into a single, unified disorder (*lumping*) or treated as distinct conditions (*splitting*; Chalder & Willis, 2017; Wessely et al., 1999). The case for *lumping* is supported by the overlap in case definitions, with some FSS criteria listing comparable symptoms (Fink & Schröder, 2010). Furthermore, there are significant epidemiological overlap rates between syndromes (van der Meulen et al., 2024), e.g., for chronic fatigue and somatization syndrome (Martin et al., 2007). Additionally, researchers identified several comparable risk factors (Löwe et al., 2024) and propose shared underlying mechanisms for different FSS (White, 2013). These similarities between syndromes could indicate an underlying phenomenon common to the entire spectrum of bodily distress, covering somatoform disorders and FSS. Consequently, the bodily distress framework moves beyond the concept of medically unexplained symptoms (Henningsen et al., 2018),

offering an overarching clinically useful approach as it is practically often challenging to determine whether an organic explanation is considered insufficient (Basavarajappa et al., 2020). However, *splitting* may be necessary to identify subtypes within bodily distress that respond differently to treatment, as seen in other conditions (e.g., sepsis and acute respiratory distress syndrome, Prescott et al., 2016). Given the inconclusive evidence on this issue (e.g., Lacourt et al., 2013), a nuanced approach integrating both perspectives could enhance diagnosis and treatment, capturing the common features while recognizing the unique aspects of individual conditions (Seaburn, 2002).

In conclusion, the validity of disorder categories must be balanced with clinical utility (Kendell & Jablensky, 2003): The concept of bodily distress includes somatoform disorders from the DSM-IV (American Psychiatric Association, 1994) and the ICD-10 (World Health Organization, 2009), SSD from the DSM-5 (American Psychiatric Association, 2013), bodily distress disorder from the ICD-11 (World Health Organization, 2022), and FSS, such as CFS, IBS, and fibromyalgia; all of which share transdiagnostic mechanisms (Löwe et al., 2024). While diagnostic frameworks differentiate between syndromes, a comprehensive approach to bodily distress as an overarching term for these related disorders offers a clinically valuable perspective, focusing on the comparable underlying mechanisms. Since no clear evidence supports distinct sub-disorders, the bodily distress category remains practical, though potential diversity within it should be acknowledged (White, 2013). Consequently, the dissertation will adhere to this definition of bodily distress in the following sections.

Epidemiology. The median 12-month prevalence of somatoform disorders in Europe is estimated at 6%, though an expert-based adjustment (excluding headache-related cases) suggests a slightly lower rate of 4.9%. Women are affected at twice the rate of men (Wittchen et al., 2011). In functional disorders, which are also subsumed under bodily distress, the point prevalence across Europe found in a meta-analysis was 8.78% (95%CI 7.61 to 10.10%). In specific subgroup analyses for the subtypes IBS (9.08%, 95%CI 7.31 to 11.22%) and chronic widespread pain (8.45%, 95%CI 5.40 to 12.97%), the rates were comparable to the overall results (Rometsch et al., 2024). Hence, considering the findings on somatoform disorders and functional disorders, bodily distress is a highly prevalent condition. As somatic complaints are associated with a vast number of impairments like lower quality of life, fatigue, anxiety as well as sleep problems (Hinz et al., 2017), bodily distress leads to significant emotional, social (Budtz-Lilly et al., 2015), and socioeconomic burdens; work absenteeism and disability further contribute to its impact (Rask et al., 2017). On a societal level, bodily distress patients' high utilization in the medical sector places significant demands on healthcare resources (Henningesen et al., 2018). Even after adjusting for psychological and organic comorbidities, patients with bodily distress use in- and outpatient care at twice the rate of those without the condition (Barsky et al., 2005). However, the frequent attendance in secondary care might not improve morbidity (Reid et al., 2003) as they often involve extensive diagnostic testing and treatment attempts, some of which may lead to iatrogenic effects (Fink, 1992; Rask et al., 2017). Additionally, indirect costs arise from lost work productivity due to absenteeism and therefore lost working years (Rask et al., 2017). Considering both direct and indirect costs, the burden of bodily distress is comparable to that of depression or anxiety (Jacobi et al., 2014). That is, bodily distress is common and debilitating to those affected.

Comorbidities. Bodily distress is frequently accompanied by comorbidity with mental disorders, most notably, depression and anxiety (e.g., Rosmalen et al., 2011), which are strongly correlated with somatic symptoms (Bekhuis et al., 2015). At least half of all patients with bodily distress, depression, or anxiety fulfil the criteria for at least one other of the other two disorders (Löwe et al., 2008). While depression and anxiety are considered risk factors (Löwe et al., 2024), neither can clearly be identified as reaction to bodily symptoms as some patients develop depression or anxiety before the bodily symptoms become clinically relevant (Henningesen et al., 2003). Patients with both somatic symptoms and comorbid depression or anxiety often experience greater functional impairment, leading to increased healthcare utilization, higher treatment costs (Barsky et al., 2005; Waal et al., 2004), and decreased treatment response (Sarter et al., 2021). Additionally, bodily distress is commonly associated with post-traumatic stress disorder (Andreski et al., 1998; Milligan-Saville et al., 2017). Furthermore, in more severe cases of bodily distress, personality disorders are common comorbidities (Garcia-Campayo et al., 2007) and patients are at a higher risk of suicide, with about a quarter of patients having active suicidal ideation (Wiborg et al., 2013). In summary, bodily distress is frequently accompanied by other psychological disorders.

Aetiology. A broad range of risk factors has been suggested as a conceptual framework for understanding the persistence of bodily symptoms (Löwe et al., 2024). The pattern of risk factors closely resembles the risk profile observed in depression and anxiety (Creed et al., 2012). One of the most important risk factors in the development of persisting bodily symptoms identified is childhood psychological abuse (Creed et al., 2012), which may alter the neuroendocrine system (Heim et al., 2009) and therefore contribute to bodily distress. Other risk factors include lower education levels, being of separated, divorced, or widowed marital status, general medical illness, anxiety, depression (Creed et al., 2012), female gender (Tomenson et al., 2013), and

neuroticism (Lahey, 2009). The more bodily symptoms a person experiences – whether medically explained or not – the greater the risk of symptoms persisting. Similarly, many of the other risk factors also exhibit a dose-response relationship, whereby an increased number of risk factors leads to a higher likelihood and intensity of somatic symptoms (Creed et al., 2012).

The triggering factors of acute symptoms are typically either acute biomedical incidents (e.g., infections) or adverse life events resulting in acute stress (Kitselaar et al., 2023). Whether symptoms persist depends on a combination of biomedical and psychosocial factors. Biomedical factors are pathophysiological features within the autonomic nervous, immune, metabolic, or microbiomic systems as well as persistent inflammation and epigenetic factors (Löwe et al., 2024). Some patients may experience negative unintended effects or be dissatisfied with the treatment they receive for their symptoms (Henningesen et al., 2018). For others, a lack of accessibility or other barriers, such as stigma, within the healthcare system may also factor in on the persistence of their symptoms (Löwe et al., 2022). Proposed psychosocial factors are both cognitive-perceptual and affective. Cognitive-perceptive factors, e.g., a focus on symptoms and interpreting these symptoms in a catastrophizing manner may lead to somatosensory amplification (Barsky, 1992). Furthermore, affective deficits might also increase the risk of persisting symptoms. Additionally, behavioral patterns, e.g., avoidance behavior, might aggravate physical inactivity leading to deconditioning. All these factors might play a role in the persistence of symptoms through a network of interplaying paths. That is, bodily distress can develop from complex combinations of various biopsychosocial risk factors (Löwe et al., 2024). Therefore, an appropriate form of treatment, addressing biopsychosocial aspects, is indicated.

2.2 Psychological Treatments

Therapeutic interventions must address multiple factors to effectively manage bodily distress (Kliem et al., 2014), incorporating multiple biopsychosocial factors. There are passive and active treatment approaches. Within the most prominent passive therapy approach, pharmacological treatments, primarily antidepressants are used to achieve short-term symptom relief (e.g., for sleep-related problems) or address pain syndromes as well as comorbidities with mental disorders. Patients also regularly utilize outpatient surgeries. However, with an increased risk of infection or treatment-attributable tissue damage (Schneider et al., 2021), this carries an increased risk of iatrogenic effects (Fink, 1992; Rask et al., 2017). While passive approaches primarily address the biological components, active forms of treatment are also increasingly taking psychosocial aspects into account. More active treatments include physiotherapeutic, behavioral, and, the most prominent form of non-pharmacological treatments, psychological treatments (van Dessel et al., 2014). In psychological treatments such as CBT, ACT, and psychodynamic psychotherapy, clients get access to psychological content through communication or other means (Cuijpers et al., 2008) which enables them to actively participate in coping with their symptoms (Henningesen et al., 2018).

Current guidelines for different disorders within bodily distress emphasize low-risk, cost-effective approaches, prioritizing reflective communication, coping-oriented therapy, and interdisciplinary collaboration for treating functional somatic symptoms (Roenneberg et al., 2019). Since psychological treatments focusing on reflective communication and coping usually carry a low-risk, they are consequently a core component of many recommended management approaches. Guidelines on psychotherapy for somatoform and associated disorders specifically recommend CBT for conditions such as somatization disorders, CFS, IBS, and fibromyalgia (Martin et al., 2013). Similarly, a synthesis of multiple National Institute for Health and Care Excellence

(NICE) guidelines (National Collaborating Centre for Mental Health [NCCMH], 2018) supports the use of CBT adapted for bodily symptoms. However, there are no comprehensive guidelines for treatments addressing the entire spectrum of bodily distress (Witthöft & Rief, 2024).

Furthermore, despite available recommendations for sub-syndromes, there is a gap between guidelines and real-world treatment practices (Kohlmann et al., 2018). However, even if patients with bodily distress receive adequate treatment, it often takes several years from the first development of symptoms till the start of psychological treatment (see also 2.1 Bodily Distress, Diagnostics and Classification). Moreover, psychotherapy remains particularly underutilized, partly due to low patient motivation (e.g., Martens et al., 2010) which is typically a requirement for psychotherapy (Ryan et al., 2011). Moreover, patients seem to prefer other interventions, and limited capacity in psychotherapy settings further restricts access (Roenneberg et al., 2019). Nonetheless, evidence suggests that interventions provided by psychotherapists lead to greater symptom reduction compared to general practitioners (Gerger et al., 2015). Therefore, further research regarding efficacy of different psychological treatments is warranted to enable patients to receive and engage in soundly evidence-based treatments. The most frequently evaluated psychological treatment for different variants of bodily distress is CBT (Swainston et al., 2022).

2.2.1 Cognitive Behavioral Therapy

Grounded in the cognitive behavioral model (Deary et al., 2007), CBT provides a structured approach to understanding how individual predisposing, triggering, and maintaining factors contribute to a patient's symptoms (van Dessel et al., 2014). Across sub-syndromes, individual adaptations of the cognitive behavioral model emphasize specific characteristics, e.g., all-or-nothing-behavior in IBS (Spence & Moss-Morris, 2007), unhelpful illness beliefs and disturbed sleep in CFS (Surawy et al., 1995), or

fear-avoidance in fibromyalgia (Vlaeyen et al., 2016). Nonetheless, there are notable similarities in maintaining processes over all conditions within bodily distress: In addition to predisposing factors (see also 2.1, Bodily Distress, Aetiology), the cognitive behavioral model identifies four factors that contribute to the persistence of symptoms: cognitive factors, physiological processes, behavioral patterns, and social influences (Deary et al., 2007). On the cognitive level, patients with bodily distress exhibit prolonged attention to bodily sensations, becoming excessively focused on them. Subsequently, patients tend to attribute (normal) somatic sensation as alarming or dangerous. This tendency to catastrophize symptoms, such as fearing that minor symptoms signal serious illness, typically leads to increased arousal, further amplifying symptoms and creating a vicious cycle of distress and symptom exacerbation (Barsky, 1992; Witthöft & Hiller, 2010). Furthermore, patients with bodily distress tend to ruminate more (Mazaheri et al., 2016), feel more helpless about their symptoms (L. Barth et al., 2025), and to perceive themselves as less resilient to stress (Rief et al., 1998). Physiological processes, such as dysregulation of the hypothalamic-pituitary-adrenal axis and prolonged physiological arousal, contribute to symptom maintenance and exacerbate the experience of distress (Deary et al., 2007). Behavioral responses also play a role in maintaining bodily distress. Patients usually avoid activities or actions that they associate with possible symptom exacerbation. In the long run, avoiding physical activity can lead to a decrease in patients' bodily constitution, which in turn increases fatigue and physical discomfort after physical activity, reinforcing the belief that activity is harmful (Witthöft & Hiller, 2010). Some patients also exhibit a pattern of excessive activity followed by prolonged rest, a cycle known as all-or-nothing behavior (Spence & Moss-Morris, 2007). Additionally, patients often engage in excessive medical consultations or self-monitoring of symptoms (Witthöft & Hiller, 2010). While seeking reassurance may temporarily reduce anxiety, it usually results in a recurring cycle of distress and further

reassurance-seeking behavior (Puri & Dimsdale, 2011). Social system variables like social support can also play a role in the maintenance of symptoms (Looper & Kirmayer, 2002). These interacting factors demonstrate how bodily distress is perpetuated. That is, the cognitive behavioral model is the basis for CBT, mainly targeting cognitive distortions, physiological dysregulation, and maladaptive behaviors.

Consequently, the focus of CBT is to identify and challenge dysfunctional cognitions (J. Barth et al., 2016) and behaviors (van Dessel et al., 2014) resulting from the processes presented above using techniques like cognitive restructuring or exposure exercises, e.g., exposure to movement or certain activities. While CBT is not explicitly rooted in a particular philosophical theory, it aligns most closely with critical rationalism. It promotes a scientific approach based on the principle of falsifiability, enabling patients to critically evaluate and adapt their belief systems. Using the Socratic method, therapists support patients in testing and modifying their dysfunctional beliefs through hypothesis falsification (Hofmann & Asmundson, 2008; Hofmann & Münch, 2013). Patients with bodily distress frequently exhibit maladaptive behaviors, such as avoidance behaviors, e.g., avoiding specific movements or physical exercise, and excessive reliance on pain medication. To address these maladaptive behaviors, CBT incorporates operant procedures such as behavioral activation. However, behavioral activation and other interventions may initially lead to an increase in symptoms (Martin & Rief, 2011), which can result in premature treatment termination. In order to mitigate this, a graded approach is advised to help patients gradually adjust to behavioral changes. Further, patients frequently consult (Reid et al., 2003) or change doctors (Zwaan & Müller, 2006), highlighting the need to replace dysfunctional reassurance-seeking with strategies that foster self-responsible coping (Martin et al., 2013). Additionally, homework assignments play a crucial role in most CBT treatment manuals, reinforcing learned techniques outside of therapy sessions (J. Barth et al., 2016).

Mechanisms. As mentioned above, CBT is not based on a particular philosophy, but falsification is inherent to the therapeutic process (Hofmann & Asmundson, 2008). That is, addressing and challenging maladaptive beliefs is central to treatment (Chalder et al., 2015; Christensen et al., 2015). Therefore, CBT-based treatment for bodily distress focuses on developing a personalized model of the disorder, reframing the understanding of symptoms from a purely organic explanation to a psychobiological perspective, challenging and modifying unhelpful beliefs about health and the body (Witthöft & Hiller, 2010) – i.e., changing illness perception (Christensen et al., 2015). This way, CBT aims to promote greater physical activity and decrease excessive attention to bodily sensations and symptoms, ultimately breaking the cycle of distress and maladaptive behaviors (Witthöft & Hiller, 2010).

Efficacy. CBT has been shown to be effective in treating several sub-syndromes and -diagnoses within the spectrum of bodily distress. Multiple studies have demonstrated that CBT can effectively reduce physical symptoms, psychological distress, and disability associated with somatization (Kroenke & Swindle, 2000). A recent meta-analysis found that CBT significantly alleviated somatic, anxiety, and depressive symptoms in somatoform disorders and medically unexplained physical symptoms, with benefits sustained during follow-up (Jing et al., 2019). For specific FSS such as IBS (Black et al., 2020) and fibromyalgia (Cojocararu et al., 2024; Kundakci et al., 2022), recent evidence syntheses have confirmed positive effects of CBT. Furthermore, an additional meta-analysis on insomnia in fibromyalgia (Climent-Sanz et al., 2022) demonstrated that CBT is also effective for managing this common symptom. Similarly, internet-based CBT has emerged as a promising approach, offering standardized treatment courses for chronic pain or FSS in general (Vugts et al., 2018) and fibromyalgia in particular (Bernardy et al., 2019). In contrast, for CFS, the evidence syntheses available are outdated (Castell et al., 2011; Malouff et al., 2008; Price et al., 2008) and need to be updated to incorporate more

recent evidence. Furthermore, existing meta-analyses in the field concentrate almost exclusively on efficacy outcomes, with limited consideration of other relevant domains such as adherence to therapy, which provides important insight into treatment acceptability (Swift et al., 2012).

In conclusion, while CBT effectively reduces symptoms, associated distress, and comorbid psychopathology across various sub-syndromes and -disorders (Swainston et al., 2022), the evidence base for CFS requires updating. Moreover, previous syntheses have focused predominantly on efficacy, without systematically incorporating indicators of treatment acceptability. Thus, comprehensive syntheses addressing both efficacy and acceptability for the sub-syndrome CFS as well as across the spectrum of bodily distress are still missing.

2.2.2 “Third Wave” Treatments

For several years, the so-called “third wave” of behavior therapy, also referred to as contextual CBT (Hayes et al., 2011) has gained prominence (Rief et al., 2022). The “third wave” is supposed to build upon conventional behavioral therapy (the “first wave”) and CBT (the “second wave”), expanding treatment approaches beyond symptom reduction to focus on fostering flexible and adaptive responses. “Third wave” treatments emphasize contextual and functional aspects of thoughts and behavior and integrate elements from humanistic, existential, analytical, and systemic frameworks (Hayes & Hofmann, 2021). The following approaches are commonly subsumed under the umbrella of “third wave” treatments: acceptance and commitment therapy (ACT), mindfulness-based therapy (MBT), mindfulness-based cognitive therapy (MBCT), mindfulness-based stress reduction (MBSR), metacognitive therapy, schema therapy, emotion regulation training, the unified protocol, compassion-focused therapy/compassionate mind training, well-being therapy, functional analytic psychotherapy, positive psychotherapy, dialectical behavior therapy, mindfulness-based relapse prevention, the cognitive-

behavioral analysis system of psychotherapy, integrative behavioral couples therapy, and mode deactivation therapy (Heidenreich & Michalak, 2013). Most of these “third wave” treatments are characterized by focusing on skills like mindfulness and acceptance (Hayes, 2004).

As these core skills are suggested to have transdiagnostic applicability, “third wave” treatments might be relevant across a range of psychological conditions, such as ACT, which is explicitly labeled a transdiagnostic therapy manual. Additionally, “third wave” treatments share conceptual similarities with non-CBT approaches in that they focus on how individuals relate to their experiences rather than on altering the experiences themselves (Hayes et al., 2011). That is, compared to conventional CBT, “third wave” approaches differ in their underlying theoretical rationale. While emotion regulation strategies in CBT are primarily antecedent-focused (e.g., modifying dysfunctional thoughts), most “third wave” treatments take a response-focused approach, emphasizing acceptance of emotions, whether adaptive or maladaptive, rather than altering them (Hofmann & Asmundson, 2008). Despite these differences, there is significant overlap in therapeutic techniques between “third wave” treatments and conventional CBT. While techniques such as acceptance and mindfulness are not used regularly in CBT, they are compatible with the CBT model (Hofmann & Münch, 2013).

The two most important approaches in the so-called “third wave” are mindfulness-based interventions and ACT. Mindfulness is based on meditation techniques and spiritual aspects rooted in Buddhism, which were then translated to intervention approaches (Frostholm & Rask, 2019). It is defined as a state of awareness in which individuals intentionally focus on the present moment with openness and non-judgment, allowing experiences to unfold naturally (Kabat-Zinn, 2003). The gold-standard mindfulness intervention is mindfulness-based stress reduction (Kabat-Zinn, 1982). Building on this, mindfulness-based cognitive therapy (Lakhan & Schofield, 2013)

integrates elements of conventional CBT with MBSR techniques (van Dam et al., 2018). ACT is based on relational frame theory and functional contextualism, wherein the validity of a patient's analysis is determined by its utility in achieving their goals. The primary aim of ACT is to enhance psychological flexibility, which is achieved through acceptance, mindfulness, cognitive defusion, recognizing that one's thoughts and feelings do not define the self, clarifying values, and committed action (Hayes et al., 2011). Within ACT, acceptance refers to the active, nonjudgmental openness to one's present-moment experience (Hayes, 2004). As illustrated by the similarity between the definitions of mindfulness and acceptance, these two constructs are very closely related.

Emerging evidence suggests that “third wave” treatments may be particularly well-suited for treatment in patients with bodily distress (Deary et al., 2007). Their emphasis on acceptance of inner experiences, including physical symptoms, and value-based action may provide a valuable complement to traditional CBT-based interventions.

Mechanisms. Coping with bodily symptoms requires psychological adjustments. In “third wave” treatments, acceptance of bodily symptoms and associated impairment is suggested as a possible adjustment to bodily distress. Acceptance is actively encouraged through mindfulness techniques, which may enhance patients' attention regulation, body awareness, and emotion regulation skills (Hölzel et al., 2011). By practicing non-judgmental acceptance, patients with bodily distress can cultivate a greater sense of detachment from distressing thoughts. This way, they can recognize that past or possible future states are merely conceptualizations rather than reflections of present reality (Frostholm & Rask, 2019). Another therapeutical goal is to reduce experiential avoidance, which refers to patients' tendency to avoid distressing inner experiences (Hofmann & Asmundson, 2008). This enables patients to take committed action that is congruent with their values, promoting engagement in meaningful activities despite ongoing symptoms (Hayes et al., 2011). Although it remains unclear whether “third wave” treatments affect

dysfunctional cognitions, improvement might be achieved through changes in avoidance behavior. Additionally, MBCT, originally developed for patients with recurrent depression, might also help to tackle depressive symptoms, addressing the high comorbidity with bodily distress (Frostholm & Rask, 2019).

Evidence. Despite growing interest in “third wave” treatments for bodily distress high quality evidence remains limited (Frostholm & Rask, 2019). Until a few years ago, research on mindfulness-based interventions was relatively limited in demonstrating their effectiveness within clinical practice (Dimidjian et al., 2016). Nonetheless, previous meta-analyses, based on small sets of studies, indicated that “third wave” treatments are effective in treating bodily distress, with small to moderate effect sizes in psychosomatic disorders (e.g., Lakhan & Schofield, 2013). These preliminary results are comparable to the effects observed in conventional CBT but smaller than those for anxiety and depressive disorders (Heidenreich & Michalak, 2015). Similarly, in the closely related – and partly overlapping – field of chronic pain, a recent overview of meta-analytic evidence syntheses showed consistent effects in symptom reduction for ACT (Martinez-Calderon et al., 2024).

In summary, “third wave” treatments could, in theory, offer valuable treatment options in bodily distress through their focus on nonjudgemental acceptance of bodily sensations, thoughts, and emotions. However, there is no quantitative synthesis of evidence in the field focusing on the whole spectrum of bodily distress.

3. Aims

Bodily distress, encompassing various clinical conditions from somatoform disorders and FSS, is highly prevalent (Rometsch et al., 2024) and incapacitating (Löwe et al., 2024). It contributes substantially to health care costs at both the individual (Rask et al., 2017) and societal levels (Henningsen et al., 2018). Since bodily distress is the result of a complex interplay of biopsychosocial factors, treatment approaches should address cognitive, physiological, behavioral, and social processes (Deary et al., 2007). CBT provides a structured intervention targeting these domains (van Dessel et al., 2014). However, its acceptability – particularly in CFS – has been questioned (e.g., Vink & Vink-Niese, 2022), effects are mostly small to moderate, and psychotherapeutic approaches generally remain underutilized in the treatment of bodily distress (Henningsen et al., 2018). In addition to CBT, “third wave” treatments target similar processes through different mechanisms. They have been proposed as promising treatment alternatives, providing an opportunity to advance current treatment strategies (Frostholt & Rask, 2019). However, to ensure patients receive evidence-based care, the efficacy of treatments has to be evaluated in clinical trials (Backmann, 2017). As individual clinical trials alone do not provide sufficient evidence to determine efficacy conclusively, meta-analytical integration of findings serves as a stronger foundation for evidence-based treatment guidelines (American Psychiatric Association [APA] Presidential Task Force on Evidence-Based Practice, 2006). As of now, there are no comprehensive guidelines covering treatments for the entire spectrum of bodily distress (Witthöft & Rief, 2024). Accordingly, the overarching aim of this dissertation is to systematically evaluate the efficacy of conventional CBT and “third wave” approaches for adults with bodily distress through three meta-analytic projects, assessing not only absolute efficacy but also differential effects and treatment acceptance – providing a comprehensive overview of the psychotherapeutic landscape.

While examining the full spectrum of bodily distress is valuable, exploring its specific sub-syndromes – especially those that are still not well understood – can provide important insights. The evidence on efficacy of psychological treatments, including CBT has recently been synthesized for IBS (Black et al., 2020) as well as for fibromyalgia (Cojocaru et al., 2024; Kundakci et al., 2022). However, only few systematic reviews are available for CFS (Henningsen et al., 2018) and the evidence has not been meta-analytically synthesized for over a decade (Castell et al., 2011; Malouff et al., 2008; Price et al., 2008). Particularly, since the benefit of CBT for CFS has recently been questioned (Flottorp et al., 2022; National Institute for Health and Care Excellence, 2021; Vink & Vink-Niese, 2022), it is of interest whether treatments are effective, but it is also important to consider the question of patient acceptance. Since, in practice, patients need to adhere to treatments in order to benefit from them (Swift et al., 2017), the *first* study focuses on evaluating the efficacy as well as treatment acceptability of CBT for CFS. It aims to assess the extent to which CBT impacts fatigue, depression, anxiety, and perceived health status in adults with CFS, as well as examining treatment adherence, as indicated by drop-out rates at different study stages.

While efficacy of CBT for various sub-syndromes of bodily distress is well-documented, its effects are generally small to moderate (Löwe et al., 2024), highlighting the need for more effective treatments (Martin & Van den Bergh, 2020). “Third wave” treatments (such as ACT, MBCT, and MBSR) have been proposed as promising alternatives (Frostholm & Rask, 2019). By emphasizing acceptance of internal experiences, including physical symptoms, and promoting value-driven actions, these interventions may serve as a valuable complement to traditional CBT (Deary et al., 2007). Nonetheless, evidence on the efficacy for “third wave” treatments has been synthesized less frequently (e.g., Lakhan & Schofield, 2013). Existing meta-analyses tend to focus on individual sub-diagnoses, e.g., medically unexplained symptoms (Billones et al., 2020)

and fibromyalgia (Haugmark et al., 2019). Given recent revisions in the classification of bodily distress, a comprehensive synthesis of the available evidence is lacking. To address these gaps, the *second* study evaluates the absolute efficacy of “third wave” treatments, namely, MBCT, MBSR, and ACT, for adults with bodily distress. It examines how these interventions impact somatic symptoms, depression, anxiety, perceived health status, and psychological skills such as acceptance and mindfulness compared to inactive and non-specific controls.

That is, the *first* and *second* study assess the efficacy of active treatments based on direct comparisons to inactive and non-specific control groups. Building on this, the *third* project will focus on relative efficacy between the treatment approaches. While “third wave” treatments are frequently proposed as promising alternatives to conventional CBT in bodily distress, no comprehensive evidence exists to determine whether any of these approaches are superior. Thus, evidence on relative effects remains scarce, and no comprehensive meta-analytic comparison between conventional CBT and “third wave” treatments in bodily distress has been conducted to date. Therefore, the study aims to explore the comparative efficacy of traditional CBT and “third wave” approaches in order to provide evidence-based guidance for clinical practice. Addressing this gap, a network meta-analysis (NMA) will be computed to evaluate the relative efficacy of CBT and “third wave” treatments in treating adults with bodily distress. Additionally, the absolute efficacy of both approaches will be compared to inactive and non-specific control groups. Incorporating these control groups further enables the estimation of differential influences of these controls on effect sizes. In summary, this dissertation – in three meta-analytic projects – synthesizes evidence from primary studies to evaluate CBT and newer modifications of these approaches for bodily distress. Collectively, these studies provide a broad evaluation of psychotherapeutic treatments for bodily distress, while extending the focus beyond assessing efficacy on somatic symptom severity.

4. Methods

Psychotherapy research aims to answer one of the most important questions in the field of clinical psychology “*What* treatment, by *whom*, is most effective for *this* individual with that specific problem, and under *which* set of circumstances?” (Paul, 1967, p. 111). That is, it is essential to assess treatments’ efficacy. However, individual clinical trials examining (psycho-)therapies may be limited in their accuracy due to small sample sizes, methodological differences, or contextual factors. Thus, an evidence-based evaluation is most accurate when it incorporates evidence from multiple relevant studies (APA Presidential Task Force on Evidence-Based Practice, 2006). This is the very premise upon which the field of meta-analytical psychotherapy research is founded (Cuijpers, 2016). Consequently, systematic reviews/meta-analyses of RCTs provide the highest level of evidence in examining treatment benefits (Oxford Centre for Evidence-Based Medicine [OCEBM] Levels of Evidence Working Group, 2011). That is, meta-analytic research provides a robust foundation for psychotherapy guidelines (APA Presidential Task Force on Evidence-Based Practice, 2006), allowing for well-informed clinical decisions based on the aggregation of study findings (Lasserson et al., 2021). Thus, ensuring clinical recommendations are informed by the most reliable and cumulative scientific evidence available (APA Presidential Task Force on Evidence-Based Practice, 2006).

To evaluate the efficacy of psychological treatments for bodily distress, this dissertation employed meta-analytical methods – both conventional meta-analyses and NMA – to synthesize evidence from multiple RCTs. Given the broad field of bodily distress, encompassing various conditions, a synthesis of the current research landscape is particularly valuable. Specifically, considering that psychological interventions for bodily distress show only small to moderate effects (Henningsen et al., 2018) and are underutilized (Roenneberg et al., 2019), it is critical to examine not only their efficacy on

core symptoms but also their impact on comorbid symptoms, the maintenance of treatment effects, and overall treatment acceptability. Within this dissertation, the individual projects focused either on adults with bodily distress or a specific sub-syndrome that is also included in the broader concept of bodily distress.

The analyses in the *first* and *second* study examined the efficacy of specific psychological treatment approaches in reducing symptoms compared to inactive and non-specific control groups, providing summary effect size estimates (Higgins et al., 2021). By integrating findings on different outcomes from multiple studies, the individual meta-analytic projects provided a comprehensive evaluation of treatment effects. While the primary outcome in each project focused on severity of the primary somatic symptoms (e.g., fatigue in CFS or pain in fibromyalgia), secondary outcomes were comorbid psychopathology (depression and anxiety) as well as the perceived health status, combining information on quality of life and impairment due to symptoms. In addition, the *second* study examined mindfulness, psychological inflexibility, and pain acceptance as proposed relevant constructs within “third wave” treatments. While all these outcomes on efficacy were analyzed at post-treatment, their maintenance was also examined analyzing follow-up data divided into short- and long-term intervals. Additionally, the *first* study systematically aggregated information on treatments’ acceptability to patients, providing a framework for a differentiated examination of treatment adherence. Furthermore, the consistency of treatment effects across studies was assessed through moderator and sensitivity analyses, e.g., to explore how outcomes may vary depending on treatment characteristics or sample characteristics. Consequently, the projects enhance the understanding of treatment efficacy and reliability of results on various domains.

While absolute effects, comparing treatments to inactive and non-specific control groups are informative about whether treatments in fact improve symptoms, comparisons between treatments help to investigate potential relative effects. Although newer

treatment approaches expand treatment options and may be preferable for some patients, scientific evidence for their superiority remains limited in most disorders (Voderholzer, 2019). Furthermore, since the number of available trials directly comparing active therapies is typically limited (Cuijpers, 2016), direct comparisons alone may not provide sufficiently robust conclusions regarding the efficacy of specific treatment formats when findings are synthesized using meta-analytic methods. Thus, the *third* project, using NMA methods (Schwarzer et al., 2015), allowed to draw comparisons based on direct as well as indirect comparisons of conditions (Tonin et al., 2017). That is, two or more treatments had to be compared to the same control condition (or conditions) in RCTs. Accordingly, a network of comparisons resulted. If there were no direct comparisons between two treatments that should be compared, information on the indirect comparisons was gathered from the network. Consequently, the common control condition linked the other treatments included in the network (Harrer et al., 2022). For example, if a treatment A was compared to a control condition and a treatment B was compared to the same control in another trial, one could gather indirect evidence from the trials (Schwarzer et al., 2015). This approach is particularly valuable in areas like bodily distress, where direct comparisons between interventions in primary trials are relatively scarce. Incorporating both direct and indirect comparisons in this project, enables a more comprehensive assessment of whether CBT and “third wave” treatments differ in their effects on somatic symptoms, depression, anxiety, or perceived health status.

As groundwork for all projects presented within this dissertation, a comprehensive database of RCTs on CBT or “third wave” treatments for adults with bodily distress was developed. The impetus for the projects was a database of RCTs in depression developed by Pim Cuijpers and colleagues (2008), which has served as a foundation for numerous meta-analyses in psychotherapy research (Cuijpers, 2017). For this project, in a similar manner, relevant RCTs were systematically identified through searches in bibliographic

databases, including PubMed (NCBI), PsycInfo (Ovid), the Cochrane Library (including the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews; Reviews and Protocols, and Cochrane Clinical Answers), and PSYNDEX (ZPID). Inclusion and exclusion criteria varied between studies, depending on the respective scope. Study selection followed a standardized procedure, described in detail in the publications. Only RCTs were included as eligible study designs. Additionally, in crossover trials, data from the first study phase, i.e., before treatment conditions were switched, were included as standard RCT data. For data extraction, a standardized template (Maas genannt Bermpohl et al., 2024) was used to ensure consistency across studies. To ensure comparability of the evidence syntheses, they were reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA; Page, McKenzie, et al., 2021).

In summary, this project helps building a comprehensive database following standardized procedures. To analyze the questions in the *first* and *second* study, conventional meta-analysis methods were used to synthesize the available evidence, whereas in the *third* study, with its focus on relative effects between CBT and “third wave” treatments, the NMA method was considered a particularly suitable aggregation method.

5. Study 1

5.1 Reference and Author Contributions

Title: Efficacy and Acceptance of Cognitive Behavioral Therapy in Adults with Chronic Fatigue Syndrome: A Meta-analysis

Authors: Frederic Maas genannt BERPohl, Ann-Cathrin Kucharczyk-Bodenburg, & Alexandra Martin

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Author contributions:

- Frederic Maas genannt BERPohl developed the research question, the outline, and conceptual background for this work under the supervision of Alexandra Martin.
- Frederic Maas genannt BERPohl and Ann-Cathrin Kucharczyk-Bodenburg, under the supervision of Alexandra Martin, completed the literature search, data extraction, and risk of bias assessment, building on initial work by two research assistants.
- Frederic Maas genannt BERPohl performed data analyses.
- Frederic Maas genannt BERPohl interpreted the results with contributions from Alexandra Martin; all authors discussed the results.
- Frederic Maas genannt BERPohl wrote the manuscript with contributions and revisions by Ann-Cathrin Kucharczyk-Bodenburg and Alexandra Martin.

Additional support:

- Tabea Gamers and Viola Bergfeld helped with study selection and data extraction

5.2 Submitted Manuscript

Efficacy and Acceptance of Cognitive Behavioral Therapy in Adults with Chronic Fatigue Syndrome: A Meta-analysis

Frederic Maas genannt BERPohl, Ann-Cathrin Kucharczyk-Bodenburg, & Alexandra Martin

Abstract

Background: The systematic aggregation of research on cognitive behavioral therapy (CBT) in chronic fatigue syndrome (CFS) needs an update. Although meta-analyses evaluating interventions typically focus on symptom reduction, they should also consider indicators of treatment acceptability, e.g., drop-out rates.

Methods: Randomized controlled trials (RCTs) investigating CBT in adults with CFS compared to inactive and non-specific control groups were included. First, efficacy was examined, considering fatigue, depression, anxiety, and perceived health. Secondly, drop-out rates through different trial stages were analyzed: Non-completion of all mandatory sessions, drop-out (primary study definition), treatment refusal (non-starters), and average of sessions completed.

Results: We included 15 RCTs with 2015 participants. CBT was more effective than controls in fatigue ($g = -0.52$, 95%CI -0.69 to -0.35), perceived health, depression, and anxiety at post-treatment. At long-term follow-up the effects were maintained for fatigue and anxiety. Rates of non-completion (22%, 95%CI 3-71), drop-out (15%, 95%CI 9-25), and treatment refusal (7%, 95%CI 3-15) were relatively low, with a high average proportion of sessions completed. Total time of therapy moderated the effect on fatigue, while the number of sessions moderated the effect on perceived health. Fatigue severity influenced adherence.

Conclusion: The results indicate that CBT for CFS is effective in reducing fatigue, fatigue related impairment, and severity of depression and anxiety. Conclusions on efficacy at follow-ups are still limited. However, adherence is high in CBT. The results may help to inform clinical

practice. Future research should focus on examining the maintenance of effects, while also emphasizing the importance of treatment acceptance.

Keywords: chronic fatigue syndrome; myalgic encephalomyelitis; treatment evaluation; adherence; drop-out.

Introduction

Chronic fatigue syndrome (CFS) is a debilitating disorder characterized by medically evaluated, unexplained, persistent or recurrent persistent fatigue that is not the result of current stress, not relieved by rest, results in significant activity limitations, and for which there is no clear organic explanation [1]. However, there is a broad array of possible diagnostic criteria that can be used for CFS. Hence, CFS according to the presented definition needs to be differentiated from newer classification approaches for myalgic encephalomyelitis/CFS [2]. While the etiology of CFS remains unclear, evidence suggests that not only biological but also psychosocial factors play an important role in the development and maintenance of the condition [3]. Cognitive behavioral therapy (CBT) derives from corresponding disorder models that assume interactions among biological/physical, psychological, and social factors [4]. CBT has been shown to be one of the most effective psychological treatments for CFS. In CFS, CBT is based on assumptions about the interaction of cognitive processes and behaviors, which contribute to the perpetuation of the ailments. It usually involves identifying the patient's negative thoughts, beliefs [5], and behaviors believed to contribute to the physical symptoms [6], most importantly, patients' focus on perceived symptoms of fatigue is decreased [7]. The therapist helps the patient develop altered and more realistic views on their illness, and coping skills to manage their symptoms [8]. Thus, patients experience reversibility of symptoms, which results in enhanced self-efficacy [9]. The goal is to help patients gradually increase their activity levels and thereby to decrease impairments (e.g., [8]). Previous studies indicate short-term efficacy of

CBT in reducing symptoms, enhancing quality of life, and improving physical functioning in patients with CFS. However, the evidence base for the long-term efficacy remains unclear [10].

Several previous meta-analyses have examined the efficacy of CBT in the treatment of CFS. Malouff et al.'s [11] meta-analysis ($k = 13$) found significant reductions in fatigue for CBT compared with inactive and non-specific control conditions ($d = 0.54$, 95%CI 0.26 to 0.81). Functioning was significantly reduced in subjective ($d = 0.45$, 95%CI 0.12 to 0.78) as well as objective measures ($d = 0.52$, 95%CI 0.28 to 0.76). However, not all evaluated interventions entailed cognitive components. The Cochrane review ($k = 15$) by Price et al. [8] resulted in small to moderate effects, e.g., for fatigue severity ($SMD = -0.39$, 95% CI -0.60 to -0.19), physical functioning ($SMD = 0.11$, 95%CI -0.32 to 0.54), depression ($SMD = -0.24$, 95%CI -0.53 to 0.05), and anxiety symptoms ($SMD = -0.30$, 95%CI -0.59 to -0.01) compared with inactive control conditions. Although meta-analytic results indicate significant efficacy in fatigue, functional impairment/quality of life, depression, and anxiety at short-term follow-up, long-term efficacy remains largely unclear [8, 12].

Despite these positive findings, the use of CBT as a treatment for CFS is controversial. The preceding version of the National Institute for Health and Care Excellence (NICE) guideline [13] recommended CBT for myalgic encephalomyelitis/CFS. However, the updated guideline published in 2021 [14] no longer recommends CBT as a curative, but only as an adjunctive treatment. This change has generated debate and criticism, in part due to the methods chosen by NICE to make the decision [15]. The debate highlights the need for up-to-date research on the efficacy of CBT in the treatment of CFS. Previous meta-analyses point to the short-term efficacy of CBT for CFS [8, 11, 12]. However, their publication dates back 10 to 15 years, so their results may now be outdated and not fully representative of the current state of research. A recent systematic review showed that several studies have been published since then, that could provide valuable information [16].

Furthermore, patient acceptance is an important factor in the evaluation of CFS treatment. In this context, patient acceptance of psychological treatments is of interest. If a treatment is not acceptable to patients despite demonstrated positive outcomes, it may not be effective in practice [17]. In research, drop-out might decrease the validity of the conclusions drawn from clinical trials. It is possible that it leads to a form of selection bias within randomized controlled trials [18], when people refuse to start or finish a therapy. Furthermore, psychotherapies might not work in full effect, when not adequately completed. Therefore, non-adherence can have negative consequences for patients and can increase health care costs [17]. For CFS, the review by Price et al. [8] reported an *odds ratio* of 1.77 (95%CI 1.13 to 2.75) for drop-out of the intervention arms compared to usual care. Malouff et al. [11] reported a mean CBT drop-out rate of 12% with a range of 0-42%. Castell et al. [12] found a median drop-out rate of 17% with a range of 0-46%. However, none of these meta-analyses differentiated between different stages of drop-out; they conferred to the authors' definitions of drop-out which are not necessarily pre-defined or uniform. Hence, the implications that can be drawn from these results are limited.

One reason for the lack of willingness to engage in psychological therapy could be the discrepancy between the subjective explanatory concepts of some people with CFS and CBT models. That is, patients that suffer from CFS often have their own explanations about the causes and nature of their illness. When these subjective explanatory models are primarily physical and not related to psychological processes (such as appraisals and dysfunctional coping behavior), they may be hesitant to engage in a therapy that emphasizes these aspects [19]. Furthermore, patient characteristics like fatigue severity or comorbid psychopathology could determine whether a patient is able and willing to participate in CBT (e.g., [20]). Other aspects of the treatment itself, such as format in individual or group intervention, might influence the acceptability of treatments for patients as well [8].

Therefore, an updated meta-analysis should examine not only the efficacy of CBT, but also its acceptability to patients. To address these questions, first, a meta-analysis of randomized controlled trials (RCTs) to evaluate the efficacy of CBT in adults with CFS was conducted. Our objective was to evaluate the outcomes fatigue, depression, anxiety, and functional impairment post-treatment and to determine whether these effects persist in the long term. Secondly, we analyzed acceptance of CBT in a very differentiated way, i.e., drop-out rates at different stages of the trials. Here, the primary outcomes were non-completion of all mandatory sessions, and drop-out according to the primary study definition. Additionally, treatment refusal (non-starters), and the average number of sessions completed were included. Besides, for both parts of the project, differentiated moderator analyses served to identify the impact of study design, treatment format and participant characteristics on treatment efficacy and acceptance, e.g., regarding the different diagnostic criteria and control groups used in the studies, intervention related variables (treatment intensity and therapy setting), and – for the acceptance analyses – clinical variables (fatigue severity and duration of fatigue symptoms).

Methods

The reporting of this meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [21]. A protocol for this project is available under: <https://osf.io/2je7u>. Furthermore, the data and R codes are available: <https://osf.io/wq4gj/>.

Eligibility Criteria

Studies were considered eligible for inclusion if they met the following criteria: (a) participants were adults (≥ 18 years old) diagnosed with CFS according to any of the recognized diagnostic criteria (e.g., Oxford criteria [22] or Fukuda definition [1]; see Supplement for a complete list of eligible diagnostic criteria) or a score above a certain threshold on a validated symptom scale; (b) the study was a randomized controlled trial that compared CBT to inactive or non-specific control groups; (c) each arm relevant to this project was $n \geq 10$ participants [23]; (d) the study was published in English or German.

Literature Search

A systematic literature search was conducted in six databases, including PubMed, PsycINFO, PSYINDEX, CENTRAL, CDSR, and CCA; the final search was on 1st of June 2022. Results were filtered for *randomized controlled trial*, *meta-analysis*, and *systematic review* in PubMed, and for *clinical trial*, *meta-analysis*, and *systematic review* in PsycINFO. The search in PSYINDEX was limited to articles published in *academic journals*; consequently, grey literature, i.e., unpublished reports, was not included. The search algorithm for PubMed in the Supplement provides an example for the search strategies used.

Study Selection

For study selection, abstracts were scanned for eligibility after the removal of duplicates by two independent researchers. Afterwards, the full articles of the reports that had not been excluded in the screening process were assessed for eligibility. During an additional backwards search, the references of meta-analyses and systematic reviews found during the first phase were searched for further eligible reports. The final selection was discussed between all authors. None of the independent researchers were blinded to any aspects of the studies at any time during the process.

Data Extraction

Data were extracted from eligible studies by two independent reviewers using a standardized sheet. The extracted data was then again checked by ACKB. A complete list of extracted variables is provided in the Supplement. When reported, results of intent-to-treat-analyses were preferred; as were validated measures, if multiple measures were used for the assessment of the same outcome. Furthermore, two independent researchers assessed the risk of bias (RoB) using the revised Cochrane risk of bias tool for randomized trials for the efficacy outcomes (RoB 2.0, [24]). As the tool was not developed for acceptance outcomes, we did not use it for these.

Outcome Variables and Data Analysis

We used a random effects model to estimate the effect sizes, and heterogeneity was assessed using the I^2 statistic. The primary analysis was a meta-analysis of the efficacy of CBT in the treatment of CFS. The primary outcome was *fatigue* (physical and mental). Secondary outcomes were *depression*, *anxiety*, and *perceived health status* (including functional disability and quality of life). Outcomes were examined for post-treatment assessment, for short-term (up to 3 months) and long-term follow-up assessments (3-12 months) [25], as well as any follow-up intervals over a year. The standardized mean difference was calculated using Hedges' g , with negative effects indicating a larger symptom reduction in treatment groups for fatigue, depression, and anxiety compared to the control groups; while positive effects on perceived health status suggest a larger improvement in treatment groups.

In the meta-analyses of the acceptance of CBT in CFS, we distinguished different forms of drop-out: The outcomes of interest were *non-completion* of all mandatory sessions, *drop-out* according to the primary study definition, *treatment refusal* (non-starters), and *average number of sessions completed*. On the one hand, non-completion was defined as all-cause discontinuation [26] after the treatment has been started, i.e., a unilateral termination of

treatment despite therapeutic need [27] and against therapeutic advice. Thus, non-completion can be considered as the proportion of participants who started the treatment and completed at least one treatment module, but did not complete all sessions: $(n \text{ participants not completing all sessions}) / (n \text{ participants starting intervention})$. On the other hand, treatment refusal was defined as the proportion of participants in each group that did not start the intervention after being allocated and thus did not complete any module: $(n \text{ participants not starting treatment}) / (n \text{ participants allocated to intervention group})$ [28].

In accordance with former meta-analyses examining acceptance, we also included the primary authors' definition of drop-out: $(n \text{ participants dropping out according to authors' definition}) / (n \text{ participants starting intervention})$. Lastly, the average proportions of sessions completed was examined to estimate the amount of therapy participants, who started therapy, received: $(\text{average number of sessions completed}) / (\text{total number of sessions})$.

The meta-analyses for non-completion, treatment refusal, and for the average proportion of sessions completed in the intervention groups was calculated using weighted rates. For studies in which a rate of non-completers or drop-outs was reported, but not the number of participants who started treatment, we "imputed" the number of participants, i.e., we used the number of participants allocated as an estimation of starters. Non-completion and drop-out were also assessed for the control groups, and compared to the intervention groups using Relative Risk (RR). However, distinguishing these forms of drop-out was not possible in most inactive control groups. Lastly, the reasons for discontinuations were extracted for all acceptance outcomes, if available.

Moderator Analyses

We conducted moderator analyses to explore the influence of study-related, intervention-related variables, and clinical variables on efficacy and acceptance of CBT in CFS: The choice of the control group was examined by comparing the effects of non-specific (TAU, psychological, and attention placebo groups) and inactive control groups (WL). Furthermore, the therapy setting, therapy dosage (i.e., total therapy time in minutes), number of sessions, and duration of treatment (in weeks) were examined as potential moderators to judge the effect of intervention characteristics. As in former meta-analyses, we planned to examine differences between study outcomes considering the diagnostic criteria used for inclusion. We also examined the influence of fatigue severity and the duration of fatigue symptoms at baseline on non-completion, drop-outs, and average proportion of sessions completed. Regarding the other outcomes this was not feasible. For both, meta-regressions and subgroup analyses, we used a mixed-effects model with a true overall effect for each subgroup and random effects within subgroups. Subgroups had to be at least $k \geq 3$ to be included in the analyses. Variables were dummy coded to dichotomize categories if necessary.

Sensitivity Analyses

First, outlier studies were identified and every study's individual influence on effect sizes and heterogeneity was analyzed. Further, to evaluate the use of the random effects model, results in the meta-analyses using fixed effect and random effects models were compared. Lastly, we recalculated the analyses excluding those studies for which we “imputed” the number of starters in the calculation of non-completion and drop-out rates.

Publication Bias

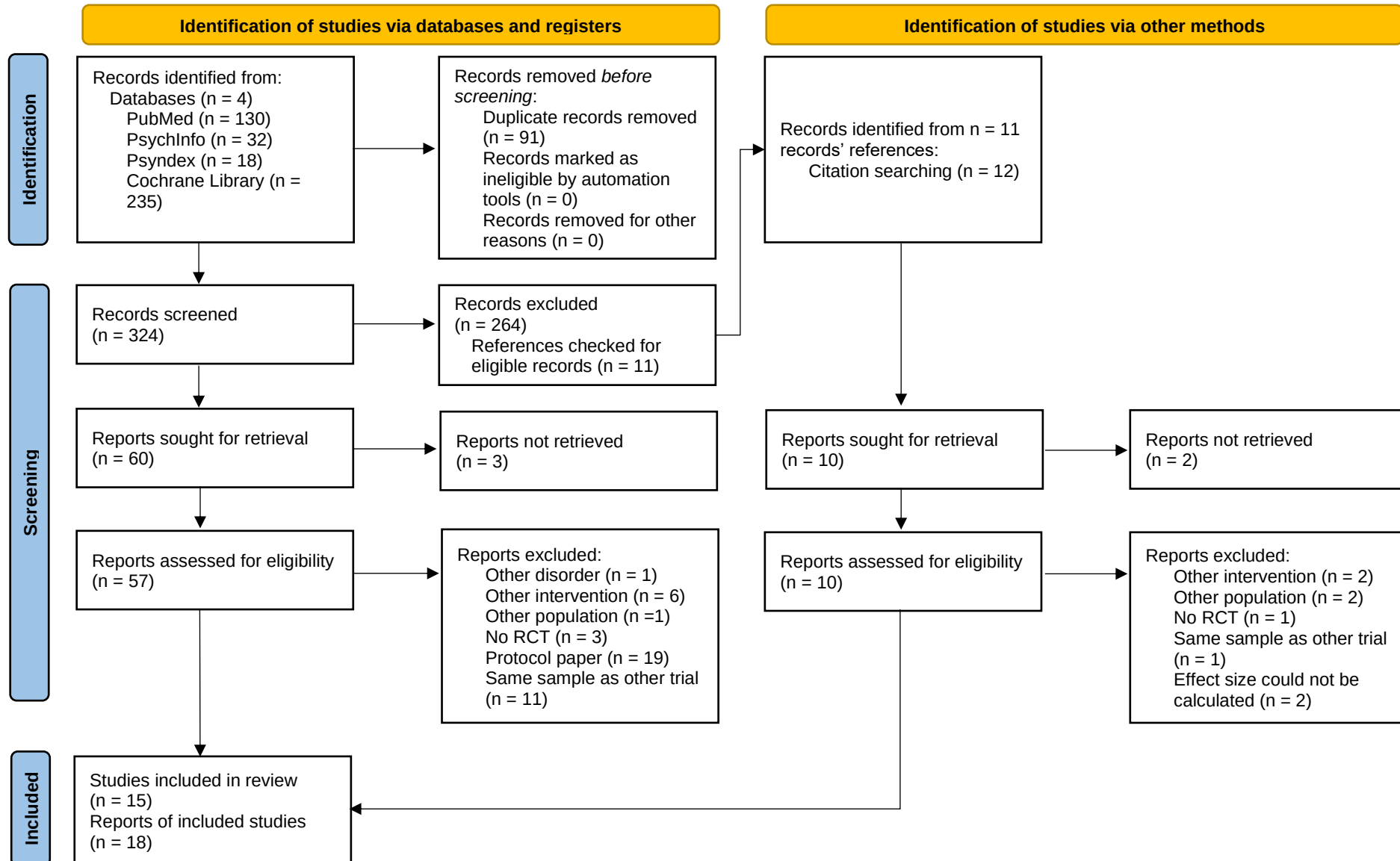
Publication bias was assessed for every efficacy outcome using contour-enhanced funnel plots and Egger's regression test. Furthermore, using the *p*-curve method the distribution of statistically significant *p*-values for anomalies was examined.

Results

Study Selection and Characteristics

The initial search yielded a total of 415 articles, of which 91 were duplicates. The remaining 324 articles' titles and abstracts were screened for eligibility, and 253 articles were excluded as they did not meet inclusion criteria (Fig. 1). The full texts of the remaining 57 articles were assessed for eligibility, and 41 studies were excluded. Through other methods, like backwards search, two relevant reports were identified. Finally, $k = 15$ studies with $n = 2015$ participants were included in the meta-analysis (with data reported in 18 manuscripts). There was no indication that eligible RCTs published in other languages were excluded during the course of the systematic literature search.

The included studies were conducted in Europe ($k = 6$ in Great Britain, $k = 5$ in the Netherlands, $k = 1$ in Norway) and US ($k = 3$); they were published between 1996 and 2021. Most studies ($k = 10$) used the international definition criteria (Centers for Disease Control and Prevention, [1]) for inclusion of CFS patients, while the other studies either used the Oxford criteria ([22], $k = 3$), or cut-off values ($k = 2$). The sample sizes of the studies ranged from 37 to 321 participants that were allocated to treatment arms. The duration of treatments varied from 8 to 36 weeks ($M = 18.85$, $SD = 8.52$), with a range of two to 17 sessions ($M = 10.71$, $SD = 4.83$), and a total time of direct contact from 2 to 28 hours ($M = 12.75$, $SD = 7.82$). One study used an internet-based self-help form of CBT [29], another used a video-telephone-based program [30], three studies implemented CBT in a group setting [31–33].

Fig. 1*PRISMA 2020 flow diagram (adapted from Page et al. [21])*

All studies compared CBT to inactive or non-specific control groups, namely $k = 5$ wait-list (WL), $k = 6$ treatment as usual (TAU), $k = 3$ psychological placebo (in the form of relaxation [34, 35] or a health promotion group [30]), and one study with an attention placebo control group (symptom monitoring [36]). That is, $k = 5$ studies used an inactive control group (WL), while the other $k = 10$ studies used non-specific controls (see Tables 1 and 2 for further study characteristics).

There were two stepped-care studies that built up on two included studies: [20] used the same sample as [37], while [38] recruited additional participants that were added to the sample in [29]. To avoid the problem of dependent samples, we did not include the second parts of these studies. Furthermore, [39] incorporated CBT in a multidisciplinary intervention, but graded exercise predominated. Therefore, we did not include the study in the analyses.

For studies with multiple arms we combined similar arms where possible: For [29] there were two similar internet-based CBT arms, one facilitated protocol-driven therapist feedback, in the other one, therapist feedback was provided on demand. In [33] the CBT conditions only differed in group sizes (either four participants and one therapist or eight participants and two therapists per group). For other studies, some additional arms could not be included in the analyses: The shorter CBT arm from [40] as well as the cognitive therapy arm from [35] relied on a different rationale than the elaborated CBT arms in both studies and were therefore excluded. Since the control groups in [36], i.e., the symptom monitoring support and TAU, were not comparable, TAU was excluded. Additionally, ineligible control groups were excluded: Anaerobic activity therapy [35], education and support [31], (active) guided support groups [41], graded exercise, and adaptive pacing [42].

Table 1*Study Characteristics*

Study	Conditions	<i>n1/n2</i>	Setting	Guidance	Criteria	Country	Specific Target Group	No. Sessions	Time total ^a	Duration of treatment (weeks)	Follow-ups ^b (weeks)
Deale et al., 1997	CBT/Psy plac	30/30	Individual		OC	GB	Adults	13	900	20	24, 240
Friedberg et al., 2013	CBT/Att plac	37/38	Individual	Para	CDC	US	Adults	2	120	14	48
Gotaas et al., 2021	CBT/WL	78/80	Individual	Psy	CDC	NO	Adults	17		17	36
Huibers et al., 2004	CBT/TAU	76/75	Individual	GP	Cut-Off	NL	Workers	6	180	16	16, 32, 176
Janse et al., 2018	CBT/WL	160 ^c /80	Individual	Psy	CDC	NL	Adults	7			
Jason et al., 2007	CBT/Psy plac	29/28	Individual	Para	CDC	US	Adults	13	585	26	48
Knoop et al., 2008	CBT/WL	85/86	Individual	Psy	CDC	NL	Adults				
Milrad et al., 2019	CBT/Psy plac	75/75	Individual		CDC	US	Couples	10	600	10	
O'Dowd et al., 2006	CBT/TAU	52/51	Group	Mixed	CDC	GB	Adults	8	960	16	32
O'Dowd et al., 2020	CBT/TAU	28/16	Individual	GP	Cut-Off	GB	Adults	4	120	10	14

Study	Conditions	n1/n2	Setting	Guidance	Criteria	Country	Specific Target Group	No. Sessions	Time total ^a	Duration of treatment (weeks)	Follow-ups ^b (weeks)
Prins et al., 2001	CBT/TAU	93/91	Individual	Mixed	CDC	NL	Adults	16	960	32	24
Rimes & Wingrove, 2013	MBCT/WL	18/19	Group	Psy	CDC	GB	Adults	9	1215	8	8
Sharpe et al., 1996	CBT/TAU	30/30	Individual	Psy	OC	GB	Adults	16	960	16	16, 32
White et al., 2011	CBT/TAU	161/160	Individual	Mixed	OC	GB	Adults	15	900	36	28, 96
Wiborg et al., 2015	CBT/WL	136/68	Group	Mixed	CDC	NL	Adults	14	1680	24	

Note. Att plac = attention placebo; CBT = cognitive behavioural therapy; CDC = international centers for disease control and prevention criteria; GB = United Kingdom; GP = general practitioner; MBCT = mindfulness-based cognitive therapy; Mixed = guidance provided by psychologist and psychiatrist; n1 = intervention group; n2 = control group; NL = Netherlands; NO = Norway; OC = oxford criteria; Para = paraprofessional (study nurses, trained students); Psy = trained clinician (licensed psychotherapist/trained psychologist); Psy plac = psychological placebo; TAU = treatment as usual; US = United States of America; WL = wait-list.

^aTotal time of direct contact in minutes (was not applicable for Janse et al., 2018 and Knoop et al., 2008)

^bAfter end of treatment (short-term follow-up = ≤ 12 weeks, long-term follow-up = 13 to 48 weeks, follow-up longer than 12 months = > 48 weeks)

^cTwo intervention groups (ICBT with feedback on demand & ICBT with protocol-driven feedback) were merged for conducting the analyses.

The primary outcome measure for the efficacy of CBT was fatigue, which was assessed in 14 of the trials. Most used either the Checklist Individual Strength – Fatigue subscale ($k = 5$), or the Chalder Fatigue Questionnaire ($k = 5$, one using an adapted version of the scale; see Supplement for more information on outcome measures). For [35] and [43] no means were reported at post-treatment, and for [44] no effect could be calculated as *SDs* were not reported. Depression was mostly assessed using the Hospital Anxiety and Depression Scale – depression subscale ($k = 6$), or the Beck Depression Inventory ($k = 2$). Anxiety was rated on the Hospital Anxiety and Depression Scale – anxiety subscale ($k = 6$) and the Beck Anxiety Inventory ($k = 2$). Perceived health status was mainly assessed using the Short Form Health Survey – physical functioning subscale ($k = 9$).

Efficacy of CBT

The meta-analytic results ($k = 11$) showed that CBT was significantly more effective in reducing fatigue than the control conditions at post-treatment $g = -0.52$ (95%CI -0.69 to -0.35; Fig. 2A). As only one study's follow-up met our criterion for short-term follow-up [32], no results could be aggregated for any outcome. At long-term follow-up ($k = 7$), with a mean follow-up duration of 31.14 weeks ($SD = 12.75$), the effect on fatigue was also significant: $g = -0.41$ (95%CI -0.65 to -0.18). The heterogeneity across the studies was $I^2 = 64.4\%$ (95%CI 32.1 to 81.3), indicating a moderate to high level of variability between the studies at post-treatment, and no to high heterogeneity at long-term follow-up ($I^2 = 57.9\%$, 95%CI 2.5 to 81.8). For follow-ups longer than 12 months post-treatment, two studies provided information on fatigue severity: [45] reported a ~3.5-year follow-up to [46] ($g = 0.12$, 95%CI -0.23 to 0.47), and [47] reported a two-year follow-up to [42] ($g = -0.21$, 95%CI -0.47 to 0.05).

Table 2*Additional information on acceptance outcomes*

Study	Conditions	<i>n1/n2</i>	Drop-out definition	Prop. drop-outs	Prop. treatment refusal ^a	Prop. non-completion ^a	Prop. average sessions completed
Deale et al., 1997	CBT/Psy plac	30/30				0.10 [0.02; 0.27]	
Friedberg et al., 2013	CBT/Att plac	37/38		0.23 [0.10; 0.42]		0.19 [0.08; 0.35]	
Gotaas et al., 2021	CBT/WL	78/80		0.21[0.12; 0.32]	0.01 [0.00; 0.07]	0.23 [0.82; 0.93]	
Huibers et al., 2004	CBT/TAU	76/75	Not completing CBT/ Not completing post assessment	0.28[0.18; 0.40]	0.06 [0.02; 0.15]		0.88 [0.39; 0.99]
Janse et al., 2018	CBT/WL	160 ^b /80	Opening all modules + emailing fortnightly/ Not completing post assessment	0.31 [0.24; 0.39]	0.06 [0.03; 0.11]	0.88 [0.82; 0.93]	
Jason et al., 2007	CBT/Psy plac	29/28	Completing < 4 sessions/ Completing < 4 sessions				0.77 [0.48; 0.92]
Knoop et al., 2008	CBT/WL	85/86			0.20 [0.12; 0.30]		
Milrad et al., 2019	CBT/Psy plac	75/75		0.05 [0.01; 0.13]			0.93 [0.54; 0.99]
O'Dowd et al., 2006	CBT/TAU	52/51					
O'Dowd et al., 2020	CBT/TAU	28/16			0.39 [0.22; 0.59]	0.41 [0.18; 0.67]	

Study	Conditions	<i>n1/n2</i>	Drop-out definition	Prop. drop-outs	Prop. treatment refusal ^a	Prop. non-completion ^a	Prop. average sessions completed
Prins et al., 2001	CBT/TAU	93/91	Formally withdrawing CBT/ Not attending assessments	0.28 [0.18; 0.39]	0.11 [0.05; 0.19]		
Rimes & Wingrove, 2013	MBCT/WL	18/19	“Discontinued MBCT”/ Not completing post assessment	0.06 [0.00; 0.29]	0.06 [0.00; 0.27]		0.81 [0.45; 0.96]
Sharpe et al., 1996	CBT/TAU	30/30	No drop-outs reported	0.00 [0.00; 0.12]	0.00 [0.00; 0.12]	0.00 [0.00; 0.12]	
White et al., 2011	CBT/TAU	161/160	Completing < 10 sessions/ Completing < 3 sessions	0.11 [0.06; 0.17]	0.02 [0.00; 0.05]		
Wiborg et al., 2015	CBT/WL	136/68	“Discontinued intervention”/ Not completing post assessment	0.15 [0.09; 0.22]	0.12 [0.07; 0.18]		

Note. Att plac = attention placebo; Average proportions of sessions completed = (average number of sessions completed) / (total number of sessions); CBT = cognitive behavioural therapy; Drop-outs = primary authors’ definition of drop-out: (*n* participants dropping out according to authors’ definition) / (*n* participants starting intervention); *n* = number of participants allocated to each group; *n1* = intervention group; *n2* = control group; Non-completion = prop. of participants who started treatment and completed at least one session: (*n* participants not completing all sessions) / (*n* participants starting intervention); Psy plac = psychological placebo; TAU = treatment as usual; WL = wait-list.

^aA table with additional information on reasons is provided in the supplement

^bTwo intervention groups (ICBT with feedback on demand & ICBT with protocol-driven feedback) were merged for conducting the analyses

For the secondary outcomes, CBT was significantly more effective in reducing depression and anxiety than the control conditions at post-treatment with small to moderate effects (Table 3). Furthermore, perceived health status was significantly improved in the CBT groups with a small effect. At long-term follow-up, neither the effects on perceived health status, nor on depression were significant (see Table 3; see Supplement for the forest plots). However, anxiety showed a significant small effect. It is to note, that the individual effects' 95%CI included 0, but the aggregated effect did not and was therefore significant. Of the secondary outcomes, only perceived health status was reported at follow-ups longer than a year post treatment: $g = -0.35$ (95%CI -0.7 to 0.0) for [46], and $g = 0.17$ (95%CI -0.08 to 0.43) for [42].

Acceptance of CBT

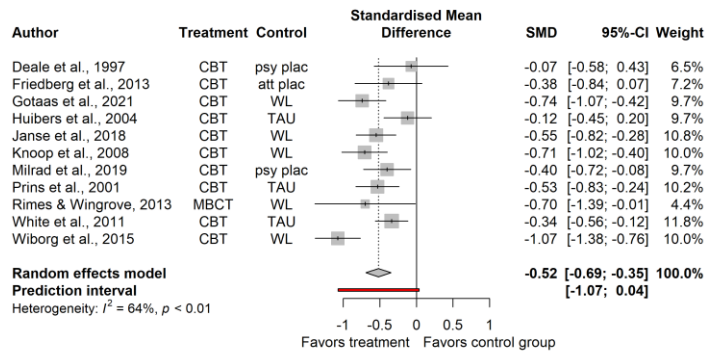
The results of the meta-analyses on acceptance showed that the non-completion in the CBT groups was 22% (0.22, 95%CI 0.03 to 0.71, Fig. 2B. Using each study's drop-out definition ($k = 10$), the overall weighted rate was 15% (0.15, 95%CI 0.09 to 0.25, Fig. 2C). Four studies reported the average numbers of sessions completed, and for those the average proportion of modules was 84% (0.84, 95%CI 0.56 to 0.96). Ten studies reported the numbers of participants who were allocated, but did not start CBT. The weighted rate of treatment refusal was 7% (0.07, 95%CI 0.03 to 0.15). Reasons for drop-out were rarely reported (see Supplement for a list of all reasons).

Relative Risks

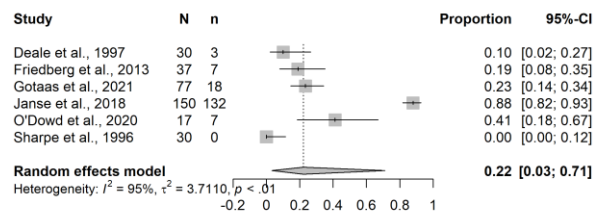
In the calculations of the *RR* in the acceptance outcomes, the *RR* for non-completion ($k = 5$) was $RR = 3.87$ (95%CI 0.30 to 49.63) with a heterogeneity of $I^2 = 89.2\%$ (95%CI 77.5 to 94.8). For drop-out ($k = 9$) the aggregated *RR* was 2.26 (95%CI 1.05 to 4.86; $I^2 = 67.6\%$, 95%CI 34.7 to 83.9). As one study [44] reported that there was neither drop-out nor non-completion in any group, it could not be incorporated in the analysis.

Figure 2

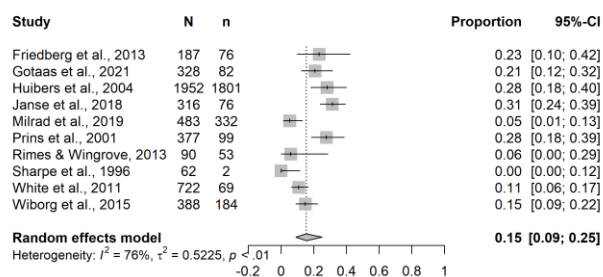
Forest plots for primary outcomes for fatigue, non-completion, and drop-out



(A)



(B)



(C)

Note. A: forest plot for fatigue (post-treatment); B: forest plot for non-completion in CBT groups; C: forest plot for drop-out in CBT groups.

Table 3

Additional information on treatment effects on outcomes at post-treatment, at follow-up, and for indicators of acceptance

Outcome	<i>k</i>	<i>n</i> ^a	Pooled effect ^b	95%CI	<i>p</i>	<i>I</i> ²	95%CI	95%PI
Post-treatment								
Fatigue	11	1727	-0.52	-0.69; -0.35	< 0.001	64.4%	32.1; 81.3	-1.07; 0.04
PHS	11	1679	0.29	0.11; 0.47	0.002	65.3%	34.2; 81.8	-0.30; 0.88
Depression	5	422	-0.36	-0.55; -0.17	< 0.001	0.0%	0.0%; 79.2%	-0.67; -0.05
Anxiety	3	212	-0.34	-0.62; -0.07	0.01	0.0%	0.0; 89.6	-2.11; 1.42
Long-term follow-up								
Fatigue	7	850	-0.41	-0.65; -0.18	< 0.001	57.9%	2.5; 81.8	-1.09; 0.26
PHS	8	1107	0.15	-0.18; 0.47	0.37	76.6%	53.5; 88.3	-0.93; 1.22
Depression	6	631	-0.15	-0.31; 0.00	0.06	0.0%	0.0; 74.6	-0.37; 0.07
Anxiety	5	571	-0.20	-0.36; -0.03	0.02	0.0%	0.0%; 79.2%	-0.46; 0.07

Outcome	<i>k</i>	<i>n</i> ^a	Pooled effect ^b	95%CI	<i>p</i>	<i>I</i> ²	95%CI	95%PI
Acceptance								
Non-completion	6	341	0.22	0.03; 0.71		95.4%	92.2; 97.2	0.00; 0.99
Drop-out	10	812	0.15	0.09; 0.25		75.7%	54.9; 86.9	0.03; 0.52
Treatment refusal	10	865	0.07	0.03; 0.15		80.3%	64.6; 89.0	0.01; 0.52
Ave. prop. sessions	4	198	0.84	0.56; 0.96		0.0%	0.0; 84.7	0.44; 0.97

Note. 95%CI = 95%confidence interval; 95%PI = 95% prediction interval; Ave. prop. sessions = (average number of sessions completed) / (total number of sessions); Drop-out = primary authors' definition of drop-out: (*n* participants dropping out according to authors' definition) / (*n* participants starting intervention); *g* = Hedges' *g*; *k* = number of studies; Long-term follow-up = 13 to 48 weeks after post-treatment; *n* = number of participants; Non-completion = prop. of participants who started treatment and completed at least one session: (*n* participants not completing all sessions) / (*n* participants starting intervention); PHS = perceived health status; Treatment refusal = prop. of participants that did not start the intervention: (*n* participants not starting treatment) - (*n* participants allocated to intervention group).

^aFor the acceptance outcomes, only the participants in the intervention groups were considered

^bHedges' *g* for efficacy outcomes, proportions for acceptance outcomes

Moderator Analyses

Moderator analyses were conducted to examine the effects of different variables on the efficacy and acceptance of CBT. The moderator analyses for efficacy outcomes were limited to post-treatment due to the small number of studies in the follow-up intervals. First, the subgroup analysis on control groups showed that the effects on fatigue between CBT and inactive control groups ($g = -0.76$, 95%CI -0.96; -0.56) were larger than the effects between CBT and non-specific control groups ($g = -0.34$, 95%CI -0.47; -0.21) at post-treatment (Table 4). There was no significant difference between subgroups for perceived health status or drop-out. Subgroups were too small for depression, anxiety, non-completion, and average proportion of sessions completed. The differences in therapy setting, i.e., individual and group setting, were not significant for perceived health status. The subgroups were too small to be analyzed for all other outcomes.

Therapy dosage was a significant moderator for fatigue ($R^2 = 91.17\%$, $p = 0.0003$), i.e., a higher dosage was associated with a greater reduction in fatigue. However, the meta-regressions for perceived health status, depression, anxiety, non-completion, drop-out, and average proportion of sessions completed were not significant. The meta-regression on number of sessions was significant for perceived health status ($R^2 = 49.21\%$, $p = 0.03$), indicating that more sessions are associated with a greater improvement in the perceived health status, but not significant for any other outcome. Duration of therapy in weeks was not a significant moderator for any outcome either. Subgroup analyses for diagnostic criteria ratings were not possible as there were not at least two groups with $k \geq 3$.

Fatigue severity was a significant moderator for non-completion and drop-out. That is, higher fatigue prior to treatment was associated with greater non-completion and higher drop-out. However, it was not significant for the average proportion of sessions completed. Duration of fatigue symptoms was neither a significant moderator for non-

completion nor for drop-out. As only two studies reported information on the average proportion of sessions completed and the duration of symptoms, no analysis was conducted for this outcome. The detailed results of the meta-regression analyses are presented in the Supplement.

Table 4*Moderator analyses – subgroup analyses*

Subgroup analysis	<i>k</i>	Pooled effect ^a	95%CI	τ^2	I^2	p_{subgroup}
<i>Control condition^b</i>						
Fatigue						0.0006
Non-specific	6	-0.34	-0.47; -0.21	0	0.0%	
Inactive	5	-0.76	-0.96; -0.56	0.02	36.7%	
Perceived Health Status						0.31
Non-specific	6	0.21	-0.09; 0.50	0.10	74.7%	
Inactive	5	0.39	0.20; 0.57	0.02	29.1%	
Drop-out						0.33
Non-specific	6	0.13	0.05; 0.31	0.82	77.8%	
Inactive	4	0.20	0.09; 0.37	0.17	76.2%	
<i>Therapy setting^c</i>						
Perceived Health Status						0.98
Individual	8	0.29	0.08; 0.50	0.06	68.3%	
Group	3	0.29	-0.15; 0.72	0.10	70.1%	

Note. Effects on efficacy outcomes at post-treatment.

^aHedges' *g* for efficacy outcomes, proportions for acceptance outcomes

^b*k* < 3 for depression, anxiety, non-completion, and average proportion of sessions completed

^c*k* < 3 for fatigue, depression, anxiety, non-completion, drop-out, treatment refusal, and average proportion of sessions completed

Sensitivity Analyses

We did not detect any outliers for depression, anxiety, drop-out, and the average proportion of sessions completed. For fatigue, there was one outlier [33] as well as for perceived health status [46], non-completion [29], and treatment refusal [43]. While the mean estimated effects did not change drastically after exclusion, heterogeneity decreased for all four outcomes.

When comparing the results using a random effects model (0.22, 95%CI 0.03 to 0.71) and a fixed effect model (0.49, 95%CI 0.44 to 0.54), there was only a difference in the estimate of the non-completion rate. Other than that, the confidence intervals tended to be wider in the analyses using a random effects model. The exclusion of the studies using the number of participants allocated to the intervention group when the number of treatment starters was not given, did not result in meaningful differences for non-completion or drop-out (see Supplement for detailed sensitivity analyses).

Risk of Bias

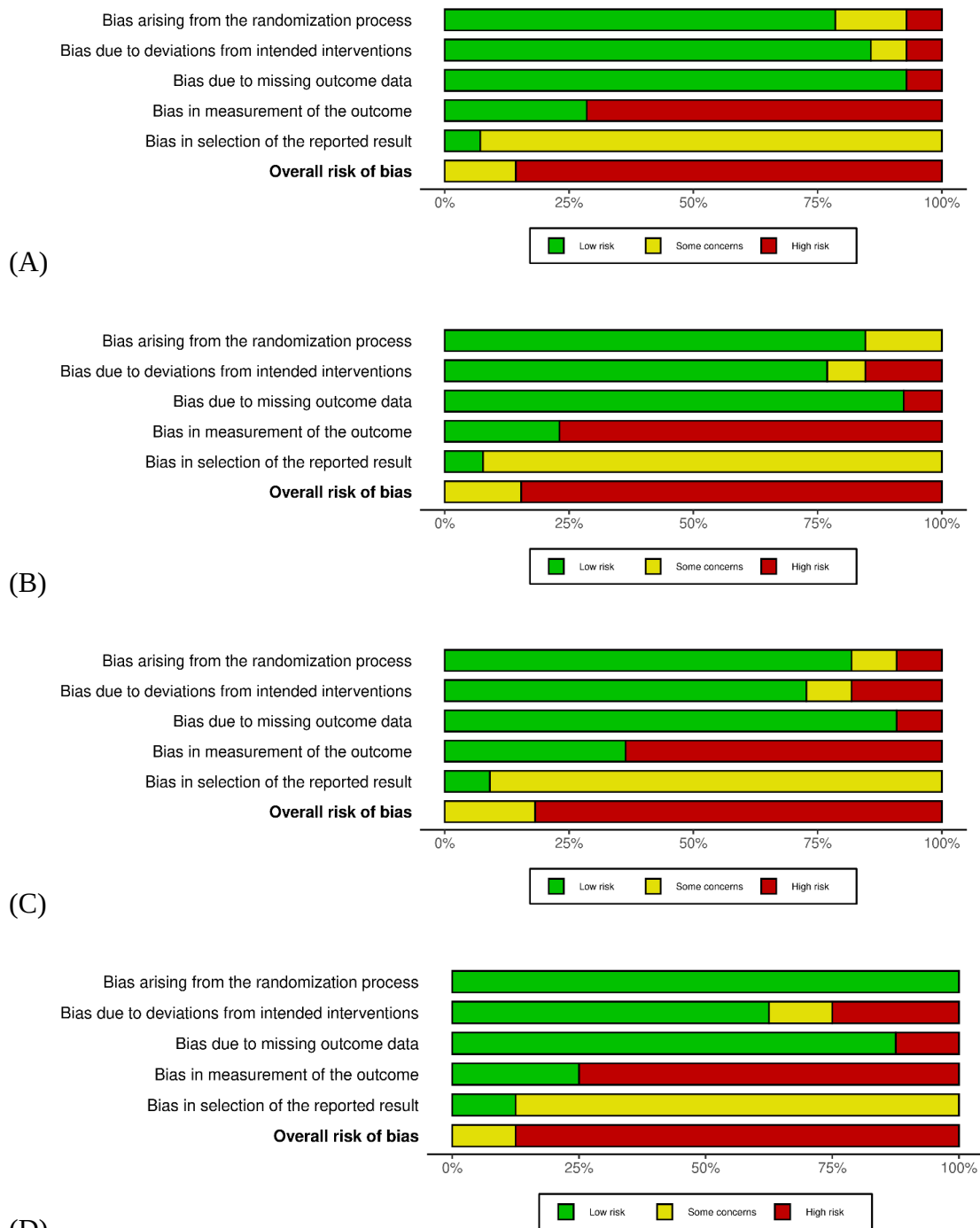
Overall RoB across all studies was either rated *high* or *some concerns* (Fig. 3). However, the RoB 2.0 tool might lead to higher ratings of conventional psychotherapeutic trial designs (cf. [48]).

Publication Bias

Egger's regression test did not indicate a possible publication bias in any of the efficacy outcomes at post treatment. While there was a significant result for anxiety at long-term follow-up, the test was solely based on five studies. The *p*-curve analyses indicated that the evidence on fatigue and perceived health status at post-treatment and for fatigue at long-term follow-up was based on evidential value. The funnel plots and *p*-curves are provided in the Supplement.

Figure 3

Risk of bias ratings for fatigue, perceived health status, depression, and anxiety at post-treatment



Note. **A** summary plot for fatigue; **B** summary plot for perceived health status, **C** summary plot for depression, **D** summary plot for anxiety. Additional information is provided in the Supplement.

Deviations from the Protocol

There resulted some deviations from the protocol: The outcomes *mental fatigue* and *physical fatigue* could not be aggregated separately because the studies did not report fatigue divided into these domains. Additionally, the outcomes *participation refusal* and *total drop-out rate* were excluded from the analysis. It was found that there was no consistent reporting of participation refusal in studies, which could be attributed to different recruitment methods used that led to differently defined participant pools between studies. Thus, an aggregated proportion of participation refusal would have been difficult to interpret. Furthermore, the reporting of *treatment refusal* (non-starters) and *drop-out* in studies was not always clearly distinguishable, possibly leading to overlaps and an overestimation of the total drop-out rate. In contrast to the protocol, an interrater reliability was not applicable as the chosen procedure in this project relied on consensus within the author group and therefore some decisions were revised after collective discussion. No sensitivity analysis for risk of bias values was carried out either, as most ratings were *high* and an analysis was therefore not feasible. Lastly, moderator analyses were streamlined to enhance clarity in reporting, i.e., we unified the moderator analyses for efficacy and acceptance outcomes.

Discussion

The results of this meta-analysis provide important insights into the efficacy and acceptance of CBT in the treatment of CFS in adults. Our findings confirm that CBT is an effective intervention for CFS. We found significant post-treatment effects of CBT on fatigue, depression, anxiety, and perceived health status. The effect on the primary efficacy outcome, fatigue, was moderate with a confidence interval ranging from small to moderate effects. The mean effects on the other efficacy outcomes were smaller, yet had wider confidence intervals. That is, there were small effects on depression, anxiety, and perceived health status in CBT

compared to inactive and non-specific control groups. The follow-up effects suggest a partial maintenance, while the data base is slightly smaller than for post-treatment. The effect on fatigue was small with the upper end of the 95%CI ranging into moderate effects. For the secondary outcomes, neither the effect on depression nor on perceived health status was significant at long-term follow-up. In contrast, there was a small significant overall effect on anxiety. All in all, these results are in line with previous research [8, 11, 12, 16, 49], indicating that CBT can alleviate CFS symptoms and improve patients' overall well-being. In fact, this analysis is based on a broader data base compared to previous meta-analyses. Yet, for some outcomes sample sizes are still relatively small. This is especially the case for depression and anxiety. Besides, this is the first project that provides meaningful aggregated long-term effects; in previous works, there were only short-term follow-up effects [8] or aggregation was not possible [12]. While there is a recently published individual patient data meta-analysis in CBT for CFS [49], the data base for that project was limited to a specific treatment-protocol (e.g., [50]) and therefore less generalizable.

In the light of the latest NICE guidelines [14], this meta-analysis sheds light on the acceptance of CBT in the treatment of CFS, which is an important aspect of treatment evaluation. The results showed that non-adherence rates in the CBT group were generally low, indicating that CBT was acceptable to patients. Over all studies, only 7% of participants refused participation after randomization. Of those who started the interventions, a mean of 15% dropped out of the treatment groups, and 22% did not complete all mandatory modules. That is, most participants completed all mandatory modules and even more received an adequate amount of treatment according to the individual study authors' definitions. In line with this, some studies that reported the average proportion of sessions completed, and the aggregated rates indicate that patients on average complete most sessions. Although some clinicians argue that some patients

discontinue treatment due to major improvements already made during the current path of treatment, this is rather unlikely [51]. While cases of clinically relevant worsening of symptoms due to CBT are rather rare in CFS [16], they might still have an increased risk of dropping out of treatment. In general, about one fifth of participants drop out of psychotherapy trials [28, 52]. That is, the findings on drop-out in this project are comparable to general reviews on drop-out in psychotherapy studies. Furthermore, the results on treatment refusal are comparable to treatment refusal rates in individual therapies for various psychological disorders as well [28].

In non-completion, the *RR* was not significant between intervention and control groups, but the confidence interval was wide, and heterogeneity was considerable. In contrast, the *RR* for drop-out was significantly larger in intervention groups, i.e., participants were more than twice as likely to drop-out of the intervention groups compared to the controls. Heterogeneity was moderate to considerable. However, in the non-specific, and especially in the inactive control groups, the definitions of dropping out of the control group and non-completion in the control group were not always clearly defined. Moreover, in most control groups, participation was low-threshold due to the inactive nature. Hence, the *RRs* cannot be adequately interpreted as they are most likely biased by this methodological artifact.

The reported analyses on efficacy and acceptance provide average effects, thereby complementing another recent review [16] that reported the proportion of clinically improved or worsened cases. Furthermore, the results of most analyses in this project showed a relevant amount of heterogeneity. This suggests that not every patient benefits from CBT, which is why an array of moderators was examined: Using moderator and sensitivity analyses, the effects on fatigue were larger when only compared to inactive control groups (moderate to large effect). However, the effects were still small to moderate, if CBT was compared to an intervention that controls for some factors such as therapist support, attention, or expectancy variables. Within

the subgroup analyses, the 95%CI of both groups did not overlap and heterogeneity was drastically reduced in both groups. There was a similar pattern for perceived health status, as the effect was only significant for inactive control groups, but not for non-specific control groups with a larger 95%CI for the latter (from no effect to a moderate effect). Yet, the subgroups did not differ significantly. For perceived health status, the therapy setting (group vs. individual) did not affect the outcome, but its potential impact on other outcomes could not be evaluated. Although it was not possible to calculate subgroup analyses based on the different diagnostic criteria used for inclusion of CFS patients, most included studies used well-established criteria [2]. For the two studies that used cut-off values as inclusion criteria, sensitivity analyses did not indicate a significant impact on results.

Furthermore, the influence of three variables of treatment intensity was examined: treatment dosage (total time in minutes), the number of sessions, and the duration of treatments in weeks. There was an effect of treatment dosage, as expected, for fatigue (higher dosage predicts a higher symptom reduction), and the moderator accounted for almost all heterogeneity ($R^2 = 91.17\%$). Although the included studies evaluated relatively short therapies with a range from 2 to 17 sessions, the number of sessions was a significant moderator for the effect in perceived health status. Duration of treatment (in weeks) neither affected efficacy nor acceptance. That is, treatment intensity may be a relevant moderator in CFS. Consequently, two indicators of treatment intensity each showed a relevant association with one of the two most frequently studied efficacy outcome measures. In contrast, they were not associated with the measures of treatment acceptance. Fatigue severity was associated with a higher non-completion rate – that is, if the mean on the fatigue scale rises one point, the proportion of non-completion rises 0.1. This was also true for drop-out, but to a lesser extent. That is, some individuals might not deem themselves able to participate in regular sessions due to their severe fatigue symptoms. Duration

of symptoms at baseline neither moderated non-completion nor drop-out. The differentiated sensitivity analyses, which considered the meta-analytic model choice and the influence of specific studies indicated that the project's results are robust. Additionally, there was no substantial indication of publication bias for the efficacy outcomes.

Limitations and Future Directions

As this project's focus was on investigating the absolute efficacy of CBT, which allows for a more accurate assessment of the efficacy and acceptance of the intervention [53], the interpretation of results is limited to this pool of studies. Consequently, the statements made apply primarily to CFS according to the Oxford criteria [22] and Centers for Disease Control and Prevention (CDC) definition [1], but not for myalgic encephalomyelitis/CFS according to the definition by the NICE guidelines [14]. However, a recently published individual patient data meta-analysis did not find evidence suggesting that patients meeting different case definitions or reporting additional symptoms benefited less from CBT [49]. Nonetheless, the selection of studies might have led to an overestimation of effects as effects are usually larger when compared to inactive and non-specific control groups [54]. Additionally, in line with Kim et al.'s [55] findings on measures used in CFS trials, the measures of fatigue and perceived health status are self-report ratings. This has partly been criticized [56]. However, this line of argument neglects the fact that those affected primarily report subjective suffering. The assessment of self-ratings is in line with the recommendations by the EURONET-SOMA group [57]. The same applies to comorbid psychopathology, which can be a predictor [58], a concomitant factor or a consequence of CFS [12]. Therefore, subjective experienced fatigue, comorbid psychopathology, and resulting disabilities have been chosen as key outcome measures. However, post-exertional malaise – which has been proposed as a cardinal symptom for myalgic encephalomyelitis/CFS in the latest NICE-guidelines [14] – could not be

systematically aggregated as it was seldom assessed and not uniformly reported [29, 35, 42]. Future studies should take this into account. Furthermore, this project – as previous meta-analyses in the field – can neither answer which components of CBT are effective nor does it allow for therapy comparisons. Since, studies were considered here if they were based on a cognitive-behavioral rational rather than a purely behavioral rational, we cannot draw conclusions on differences between behavioral and cognitive components or the like.

Since the overall RoB was rated at least *some concerns*, but mostly *high* for the included studies, this should be taken into account when interpreting the results. Nonetheless, the high rating can partly be explained by the nature of conventional psychotherapeutic trial designs used for these studies. This does not imply that these designs are without flaw, however, these ratings do not render the results irrelevant. For example, one major criticism of psychotherapy trials in CFS is a lack of blinding [56]. However, this overemphasizes the assumed effect of blinding in trials, which is not reflected in clinical data [59].

Furthermore, there might be a form of selection bias in the examined sample since the included studies were conducted mainly in Europe and the US, which may limit the generalizability of the findings to other regions. More importantly, the included participants in the studies already agreed to participate in a RCT on CBT for CFS. That is, participants who are not willing to partake in CBT might simply refuse participation. Moreover, as most studies included at least some face-to-face contact, it might disadvantage those CFS patients who, due to their pronounced symptom severity, are housebound [16]. Therefore, conclusions on this subset of CFS patients cannot be drawn. Thus, it remains an open question as to which treatments or forms of treatment are appropriate for patients who are this severely impaired. Future studies should continue to systematically assess the reported efficacy outcomes, and should additionally be supplemented with objective measurement instruments. Thus, other observable

indicators would also be of interest, such as behavior changes and sickness leave days. In particular, the catamnestic effects in CBT should be further investigated in large-scale trials. Currently, in study reports, specific forms of drop-out rates are seldom reported [17], and a consistent definition of drop-out is lacking [28]. While it is understandable that authors define an adequate amount of treatment received as the main indicator of acceptance, this leads to a certain amount of variance between studies' definitions of adequate treatment. However, it is noticeable that across all studies, only a small proportion of studies reported uptake and discontinuation; which could indicate attrition bias [16]. Especially, the (non-)completion of all mandatory modules and information on the mandatory modules completed were only reported in some studies. In line with former meta-analyses on adherence, treatment refusal (e.g., [28]), and drop-outs (e.g., [17]) have been systematically aggregated here. Additionally, in this project, the analysis of non-completion and the average proportion of mandatory modules provided a new perspective on and operationalized measures of adherence and hence acceptance. Differentiated information on adherence is essential. Preferably, future studies should report the described variants of acceptance outcomes. Although there is now a broader database compared with the meta-analyses from 10 to 15 years ago, the subgroup analyses and, especially, the regression analyses to identify possible moderators of efficacy and acceptance require further primary studies.

Conclusion

In conclusion, this meta-analysis provides further evidence for the efficacy of CBT in the treatment of CFS in adults and maintenance of the effects, while also highlighting the importance of considering the acceptance of treatments. Acceptance of CBT in CFS does not seem to be lower when compared with other patient groups with various mental disorders – this also applies if the stricter criterion of non-completion is taken into account. The results may

help inform clinical practice and future research in this area. Hence, this project contributes to a better understanding of the potential benefits and limitations of CBT in the treatment of CFS and supports clinical decision-making. One reason why some people with CFS are reluctant to undergo psychological therapy could be the lack of willingness to engage in psychological therapy among people with CFS. This may stem from a mismatch between their personal beliefs about their condition and the foundational principles of therapies like CBT. Recognizing and addressing this disconnect is crucial for providing effective support and treatment for individuals with CFS, potentially by tailoring therapy to their unique needs and perspectives. Considering that initial fatigue severity was associated with a slightly increased risk of discontinuation of treatment, one could consider acceptance facilitating interventions – as shown in pain [60]. Similarly, stepped-care approaches might be promising in the field of CFS: first, the participants receive low-threshold intervention (e.g., internet-based self-help program), and then, if needed, a more intense face-to-face therapy [20].

Supplementary Information

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Author Contributions

FMgB and AM developed the research question and conceptual background for this work. FMgB developed the outline. Two research assistants independently performed the literature search, data extraction, and risk of bias assessment, which was then checked by ACKB and discussed with FMgB. AM took part in the final decisions on inclusion. FMgB performed data analyses. AM regularly provided feedback on the progress and results. FMgB and AM prepared the final manuscript for publication while ACKB provided feedback on the manuscript.

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Data Availability

The data that support the findings of this project are openly available in OSF at <https://osf.io/wq4gj>, <https://doi.org/10.17605/OSF.IO/WQ4GJ>.

Declarations

Ethical Approval

The investigators of the primary trials report positive ethics votes for these studies, and there are no ethical requirements that this meta-analysis would violate.

Informed Consent

The participants gave their informed consent to the investigators of the primary trials. **Research**

Involving Human Participants and/or Animals

Not applicable, as this project is based on published reports.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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6. Study 2

6.1 Reference and Author Contributions

Title: Efficacy of mindfulness- and acceptance-based cognitive-behavioral therapies for bodily distress in adults: a meta-analysis

Authors: Frederic Maas genannt BERPohl, Lea Hülsmann, & Alexandra Martin

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Author contributions:

- Frederic Maas genannt BERPohl developed the research question and conceptual background for this work under the supervision of Alexandra Martin.
- Frederic Maas genannt BERPohl developed the outline, formulated the search terms, and independently performed the literature search, data extraction, and risk of bias assessment in collaboration with Lea Hülsmann under the supervision of Alexandra Martin.
- Frederic Maas genannt BERPohl performed the data analyses.
- Frederic Maas genannt BERPohl interpreted the results with contributions from Lea Hülsmann and Alexandra Martin; all authors discussed the results.
- Frederic Maas genannt BERPohl wrote the manuscript with contributions and revisions by Lea Hülsmann and Alexandra Martin.

Additional support:

- Ann-Cathrin Kucharczyk-Bodenburg helped with the literature search, data extraction and risk of bias assessment.

6.2 Submitted Manuscript

Efficacy of mindfulness- and acceptance-based cognitive-behavioural therapies for bodily distress in adults: a meta-analysis

Frederic Maas genannt BERPpohl, Lea Hülsmann, Alexandra Martin

Abstract

Objective: Bodily distress, i.e., somatoform disorders and associated functional somatic syndromes, is highly prevalent, often persistent and highly disabling. It has been proposed that “third wave” therapies may be beneficial variants of cognitive behavioural treatments. However, evidence on their efficacy is scarce. This meta-analysis examines the efficacy of “third wave” psychotherapies (mindfulness-based cognitive therapy [MBCT], mindfulness-based stress reduction [MBSR], and acceptance and commitment therapy [ACT]) in adults with bodily distress.

Method: We included randomized controlled trials (RCTs) treating adults with bodily distress using MBCT, MBSR, and ACT compared to inactive and non-specific control groups. A random effects model was used. The primary outcome was somatic symptom severity. Secondary outcomes were degrees of depression and of anxiety, health anxiety, perceived health status, mindfulness, psychological inflexibility, and pain acceptance.

Results: Sixteen RCTs with 1288 participants were included in the analysis ($k = 4$ MBCT, $k = 7$ MBSR, $k = 5$ ACT; $k = 7$ fibromyalgia, $k = 5$ irritable bowel syndrome, $k = 1$ chronic fatigue syndrome, $k = 2$ bodily distress, $k = 1$ medically unexplained symptoms). However, not all studies provided data for each of the relevant outcomes. The analyses revealed that “third wave” therapies were more effective than control conditions in reducing somatic symptom severity ($k = 15$, $n = 1100$, $g = -0.51$, 95%CI -0.69; -0.32). Heterogeneity was moderate ($I^2 = 52.8\%$, 95%CI 15.1 to 73.8). Effects for secondary

outcomes were small to moderate with varying degrees of heterogeneity. We did not find differences between the different therapy approaches (mindfulness- vs. acceptance-based therapies); neither therapy dosis (i.e., total duration of therapy sessions) nor number of sessions were significant moderators of efficacy.

Conclusions: The therapies addressing mindfulness and acceptance proved to be more effective than control conditions. Hence, they are promising treatment approaches for bodily distress. However, there is still need for research on which patient groups may benefit from these psychological approaches.

Systematic review registration: <https://osf.io/g7hby>, identifier: 10.17605/OSF.IO/4RZGC.

Keywords: persistent physical symptoms, somatoform disorders [MeSH], Somatic Symptom Disorder, treatment evaluation, efficacy.

1. Introduction

Incapacitating, persistent physical symptoms, i.e., functional and somatoform bodily complaints, are highly prevalent. Due to an increased use of healthcare services and frequent work absenteeism these complaints are often associated with increased costs for the health care system (1). Several psychological therapies are considered well-established in the treatment of persistent physical symptoms; with the largest body of evidence available for cognitive behavioural therapy (CBT, 2). However, symptoms are at best moderately improved by psychotherapy (1). Hence, there is need for more effective treatments (3). So-called “third wave” therapies may represent promising new approaches in this context. They may hold the potential to improve management of bodily distress emphasizing mindfulness and acceptance as important change mechanisms (4). The most prominent “third wave” therapies are mindfulness-based cognitive therapy (MBCT), mindfulness-based stress reduction (MBSR), and acceptance and commitment therapy (ACT).

MBCT combines CBT techniques with mindfulness practices. Therefore, it helps individuals to observe their experiences including thoughts, physical sensations and emotions in a non-judgmental way, leading to greater acceptance of inner experiences (5). In its mindfulness practices, it is based on MBSR. MBSR combines mindfulness practices with yoga and body awareness techniques to help individuals manage stress, pain, and illness. The goal of MBSR is to help individuals enhance their self-awareness (6). Mindfulness, as a supposed key mechanism of MBCT and MBSR, may help patients to interrupt rumination processes, and as a consequence interpret bodily symptoms less negatively by shifting their attentional focus away from the negative appraisal of their symptoms. Consequently, mindfulness could indirectly lead to a more accepting attitude towards bodily sensations. ACT focuses on accepting difficult thoughts and emotions while working toward one's values and goals. The goal in ACT is to help individuals develop psychological flexibility and become more effective in their actions and relationships. To that effect, ACT rather aims at reducing avoidance behaviours and uses a more direct approach on acceptance of inner experiences including somatic symptoms, emphasizing mindfulness and values clarification as key components for psychological flexibility and well-being (7). Hence, all of these three “third wave” therapies could have a positive impact on emotion regulation processes and interrupt patients' reinforcement processes related to their symptoms (8), thus also reducing comorbid depression and anxiety (4). Efficacy of these therapies has already been shown for some specific functional somatic syndromes or symptoms (e.g., 9, 10). However, no meta-analysis in the field provides sufficient evidence for “third wave” therapies taking into account recent changes in classification. Due to these changes, the focus in defining bodily distress is no longer primarily on the strict distinction between medically unexplained symptoms and medically explained symptoms, but on considering excessive psychobehavioral characteristics in relation to the physical symptoms. Hence, several different diagnoses can now be subsumed under the concept of bodily distress, such as medically unexplained symptoms, somatoform disorders, Bodily Distress

Disorder, Somatic Symptom Disorder (and its predecessors in previous editions of the DSM). Functional somatic syndromes, such as irritable bowel syndrome, chronic fatigue syndrome, and fibromyalgia are also included here (3).

The research base for “third wave” therapies has improved in recent years (11). Two recent reviews, one systematic review on mindfulness-based therapies in medically unexplained symptoms (9) and one narrative review on “third wave” therapies in bodily distress and health anxiety (4), yield promising results. However, effect sizes were not statistically aggregated.

The last meta-analysis focussing on the efficacy of mindfulness-based therapies, including MBCT, MBSR, and unspecified mindfulness training for bodily distress (12), incorporated 13 trials; one of them quasi-randomized. Effects were small to moderate on pain, symptom severity, quality of life, depression, and anxiety, favouring the mindfulness-based therapies. However, this meta-analytic aggregation needs to be updated due to the growing body of literature in this field in recent years. Whereas the research base for “third wave” therapies in fibromyalgia has been recently meta-analytically examined (10) based on 8 RCTs and one quasi-randomized controlled trial. Again, the effects were small to moderate, e.g., for pain, health-related quality of life, depression, and anxiety. However, the meta-analysis was limited to a single functional somatic syndrome.

As there is no current quantitative integration of findings for the efficacy of MBCT, MBSR, and ACT for the full scope of bodily distress, the aim of this meta-analysis is to examine the efficacy of these “third wave” therapies in adults with bodily distress. Hence, we examine the immediate efficacy and maintenance after completion of these treatments in comparison to inactive and non-specific control groups. The primary outcome is somatic symptom severity. However, a comprehensive evaluation should not be limited to somatic symptoms alone (13). Therefore, we also examine the effects on

perceived health status, comorbid psychopathologies as well as mechanisms that are considered central to the “third wave” therapies.

2. Methods

2.1 Protocol and openness

The project is reported according to the PRISMA 2020 statement (14) and was registered on OSF (Registration DOI: 10.17605/OSF.IO/G7HBY). All analyses were computed in R version 4.2.1 (15). A complete list of packages used can be found in the supplement. The data (within an R environment) and the full R code are available on OSF (<https://osf.io/an6zy/>).

The investigators of the primary trials report positive ethics votes for these studies, and there are no ethical requirements that this meta-analysis would violate.

2.2 Eligibility criteria

Study participants needed to be adults (≥ 18 years old) and fulfil the criteria for bodily distress (a complete list of included diagnoses can be found in the Supplementary material). Although there is a considerable overlap between hypochondriasis/illness anxiety and bodily distress, studies solely focussing on these diagnoses will be excluded as well as studies on body dysmorphic disorder. The assessment of bodily distress should either be based on a diagnostic interview, or scores above a certain threshold on a validated symptom scale. Eligible therapies were MBCT, MBSR, and ACT, while studies examining conventional CBT were not included. Any of these “third wave” therapies had to be compared to an inactive control arm or unspecific treatment within the study, i.e., no treatment, wait-list (WL), treatment-as-usual (TAU), enhanced care (EC, e.g., TAU with additional psychoeducation or counselling) or attention/psychological/pill placebo. Furthermore, only RCTs and (results of the first

part of) cross-over trials were selected if they entailed $n \geq 10$ participants per arm (16). Additionally, reports had to be published in English or German.

2.3 Search strategies and study selection

PubMed, PsycInfo, Psynindex, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database for Systematic Reviews (CDSR) were last searched on 01st of October 2021. The complete search algorithms can be found in the Supplementary Material.

For study selection, abstracts were scanned for eligibility after the removal of duplicates. Subsets of the reports were each selected by two independent researchers and disagreements were resolved by discussion. Afterwards, the full articles of the reports that had not been excluded in the screening process were assessed for eligibility. During an additional backwards search, the references of meta-analyses and systematic reviews found during the first phase were searched for further eligible reports. None of the independent researchers (FMgB and LH) were blinded to any aspects of the studies at any time during the process.

2.4 Data extraction

For each report, two researchers (FMgB and LH; FMgB and a research assistant for the studies identified in the final search update) extracted data independently using a previously prepared Microsoft Excel-sheet (17) (see Supplementary material for a complete list of extracted variables). If reported, results of intent-to-treat (ITT)-analyses were extracted. Otherwise, per-protocol (PP) data were assessed. If multiple measures were used for the assessment of similar outcomes, validated measures were preferred. If multiple or none of the measures were validated, FMgB, LH, and a research assistant decided which measure was more suitable. AM supervised these decisions while being blinded to the results. The decision-making process was documented (see Supplementary material). If

multiple publications were based on one dataset, the publications were considered as a single study. If data could not be extracted from the published paper (or Supplementary material), e.g., if it was not possible to calculate effect sizes, the original authors were contacted and asked to provide the relevant data.

2.5 Risk of bias assessment

The risk of bias (RoB) was assessed with the revised Cochrane risk of bias tool for randomized trials (RoB 2.0) (18) by two independent researchers (in the same constellations mentioned above).

2.6 Outcome measures

Outcomes were examined for post-treatment assessment as well as for short-term (up to 3 months) and long-term follow-up assessments (> 3 months) (19). If multiple follow-up assessments were provided all of which fell into either the short-term or the long-term category, the longest of these follow-up periods was included.

The primary outcome was somatic symptom severity. Secondary outcomes were perceived health status (PHS), depressive symptoms, anxiety symptoms, and health anxiety; PHS included quality of life, and health-related quality of life measures as well as impairment due to illness (20). Additionally, some exploratory analyses were performed for relevant constructs in the included treatments: mindfulness, psychological inflexibility, and pain acceptance. On the one hand, mindfulness is considered a core mechanism of MBCT as well as MBSR and is also used in ACT. On the other hand, tackling psychological inflexibility is the main focus in ACT (7). To achieve an increased psychological flexibility, ACT aims at pain acceptance, i.e., acceptance of symptoms, in patients with bodily distress to reduce avoidance behaviours (4).

2.7 Data analyses

Since different scales were used to assess the outcomes of interest throughout the included studies, standardized mean difference (SMD) was chosen as summary statistic for all outcomes. More precisely, Hedges' g was calculated. Especially, as the number of participants was expected to be small in some groups, Hedges' g holds the benefit that it is adjusted for small sample bias (21). If no total score but scores from several subscales were available for an outcome, we combined the subscales into one total score using a method for integrating dependent effect sizes (22), if applicable (see Supplementary material for formulas). The values extracted for PHS scales on which higher scores indicate higher impairment were multiplied by (-1) to ensure all scales pointed in the same direction (23). Consequently, for PHS and mindfulness positive effects indicate an improvement favouring the treatment condition. For all other outcomes negative effects indicate a reduction of symptoms favouring the treatment condition.

A random effects model was used in this analysis as the aim of this analysis is to draw statistical inferences on the underlying universe based on the study results (24). The recommendation to use the restricted maximum likelihood (REML) estimator for τ^2 for continuous data was followed (25). The I^2 -statistic was calculated to quantify heterogeneity (23).

2.8 Moderator analyses

Several subgroup analyses were conducted using a mixed-effects model, presuming each subgroup containing an individual true overall effect and random effects within subgroups (26). In order to compute the analyses with dichotomized categories, we dummy coded the groups. We only calculated subgroup analyses for subgroups with $k \geq 3$. For the meta-regressions we used a mixed-effects model as well.

First, despite their parallels, the different therapies differ in their foci which could influence outcome. Thus, we examined whether the mindfulness-based (MBCT/MBSR) and the acceptance-based (ACT) approaches differ in their efficacy. Additionally, we planned to compare therapies that were delivered in a face-to-face setting to internet-based interventions. Since the choice of control group typically influences the effect size (27), another subgroup analysis was computed to investigate the impact of control group conditions. We dichotomized the control groups into non-specific and inactive control groups. While we considered WL inactive comparisons, we classified psychological or attention placebos, TAU, and enhanced care (e.g., TAU combined with regular counselling or psychoeducation) as non-specific control groups. Besides, we conducted subgroup analyses for the different diagnoses (i.e., disorders) included as recommended by Lakhan and Shofield (12). Additionally, we examined the influence of treatment intensity as low-intensity treatments usually result in smaller effects (e.g., 2). Hence, a subgroup analysis was performed comparing low- and high-intensity psychotherapy (28), i.e., manuals with less than eight sessions versus manuals with eight or more sessions. In line with this, we performed an explorative meta-regression on number of sessions. Another meta-regression was conducted on therapy dosis, i.e., total time of therapy sessions in minutes. We deviated from the registered moderator analyses: We dichotomized some moderators to be able to form larger subgroups. Further, no analyses on type of assessment were conducted. Lastly, we were not able to conduct useful analyses on baseline scores, neither on somatic symptom severity nor on comorbidities (see Supplementary material for details on these deviations from registered protocol).

2.9 Sensitivity analyses

A sensitivity analysis was performed to evaluate the use of the random effects model, comparing results in the meta-analyses using fixed effect and random effects models. In addition, based on outlier analyses, we computed influence analyses (leave one out-method) as well as Graphic Displays of

Heterogeneity (GOSH plots) to display study heterogeneity graphically (29). Lastly, another sensitivity analysis was conducted to examine whether the selection of scales in PHS due to our prioritization influenced results.

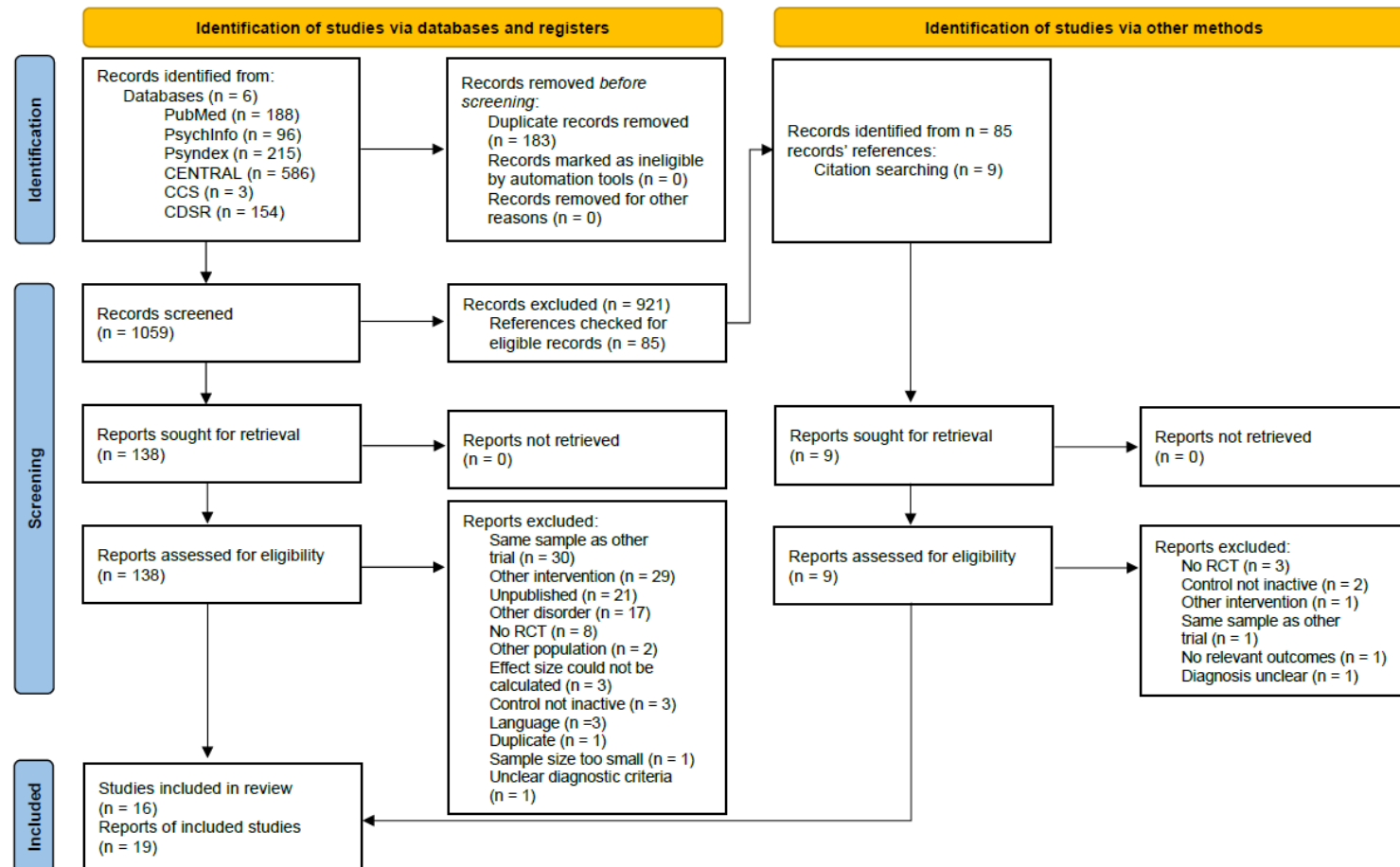
2.10 Publication bias

To examine possible publication bias, contour-enhanced funnel plots were created and examined for asymmetry for every outcome at post-treatment. Moreover, we computed Egger's regression test to statistically assess asymmetry (30). Furthermore, we used the *p*-curve method, focussing on the distribution of statistically significant *p*-values (31).

3. Results

3.1 Study selection

For study selection 1,242 reports were retrieved from the databases. After deduplication 1,059 reports were screened. During screening, 921 reports were excluded. Therefore, 138 full-texts were retrieved and assessed for eligibility; 119 of which were excluded after full-text assessment, e.g., thirty reports were excluded as they were based on the same sample as another and did not provide additional relevant data for this project. Finally, we included $k = 16$ studies (with information gathered from 19 reports) including $n = 1288$ participants randomized (see Figure 1). We gathered additional data from Weissbecker et al. (32), and Cash et al. (33) for the study by Sephton et al. (34), and from Wicksell et al. (35) for Jensen et al. (36). Interrater agreement for study selection was $\kappa = 0.85$, i.e., almost perfect (37).

Figure 1*PRISMA 2020 flow diagram (adapted from Page et al., 2021)*

3.2 Study characteristics

All included studies focused on adults, one of which explicitly focused on a student population (38). While five studies solely examined women, participants were predominantly female in all other studies. Of the included studies, seven focused on fibromyalgia (36, 39–42, 34, 43), five on irritable bowel syndrome (44–46, 38, 47), one on chronic fatigue syndrome (48), two on bodily distress syndrome (49, 50), and one on medically unexplained symptoms (51). Four of the included studies implemented MBCT, seven studies MBSR, and five studies ACT. Only two of the included studies combined either MBCT (51) or MBSR (50) with methods from conventional CBT. Most studies implemented the therapies in a group setting; only one study (43) was internet-based and therefore patients participated in an individual setting; another study (38) consisted of a self-help approach following a group workshop. One study (49) consisted of more than two potentially relevant arms: extended ACT, brief ACT, and EC. We decided to include the extended ACT arm as well as the EC condition and excluded the brief ACT approach from the analyses. Control groups involved WL ($k = 7$), TAU ($k = 5$), EC ($k = 3$), and psychological placebo (a social support group, $k = 1$). TAU conditions were defined as continuation of current treatment (40, 43, 47), continued medication (41, 45). All studies but one (45) that was set in Iran took place in OECD countries. Further study characteristics are provided in the supplement. For data extraction all disagreements in the independently extracted data were resolved through discussion in a consensus meeting.

3.3 Risk of Bias

Overall RoB was high across all studies; details on the ratings of individual studies are provided in the supplement. Three domains were predominantly responsible for the high ratings: In the domain “RoB in measurement of the outcome”, we rated the risk of bias as high for all studies except for one. As blinding is rather difficult in psychotherapy trials, and almost impossible in the included designs (e.g.,

WL vs. psychotherapy), we assumed that the assessors for self-report measures (i.e., the participants themselves) were probably aware of the therapy they received. Only in Gaylord et al. (44) we rated RoB as low as participants perceived the support group as credible as the intervention group. The evaluation of “RoB in selection of reported results” required the availability of a study protocol. Although nine studies provided a protocol, these did not entail information on the planned analyses. In accordance with the RoB tool 2.0, for the domain “RoB due to missing outcome data”, we rated all intention-to-treat methods as adequate that allowed inclusion of all participants for whom data were available.

Due to the initially low interrater reliability ($\kappa = 0.59$ for the five domains; $\kappa = 1$ for overall RoB judgement) between FMgB and LH, an additional research assistant independently rated all studies with disagreement between the raters and studies identified in the final search update. This improved interrater reliability for these studies ($\kappa = 0.76$; $\kappa = 1$ for overall RoB judgement).

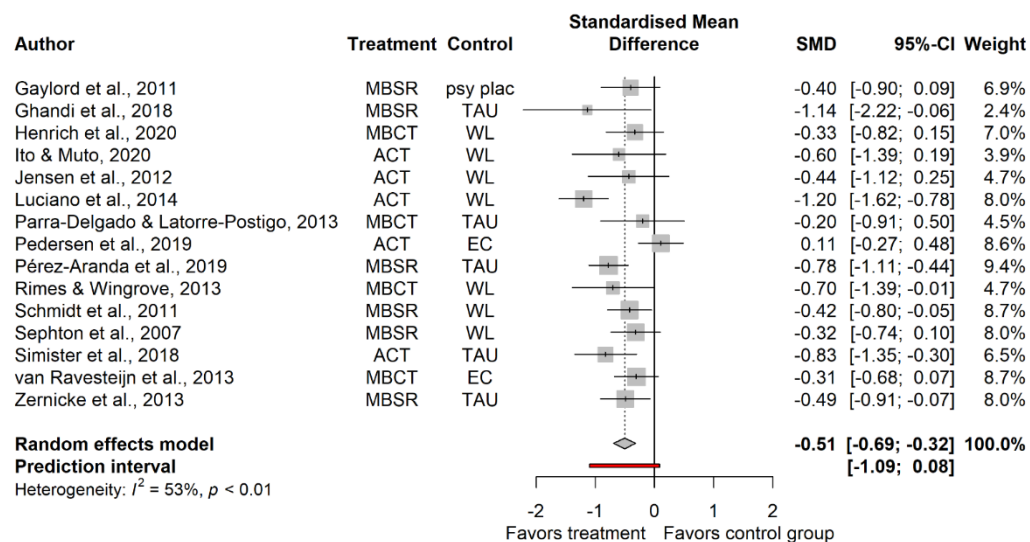
3.4 Treatment effects – post-treatment

For the primary outcome, somatic symptom severity, 15 studies provided data at post-treatment ($n = 1100$). Results showed a significant effect in favour of the “third wave” therapies compared to inactive and non-specific control conditions ($g = -0.51$, 95%CI -0.69 to -0.32; see Figure 2 for a forest plot and Table 1 for more detailed results on all outcomes). Heterogeneity was 52.8% (95%CI 15.1 to 73.8). All studies reported a measure of PHS ($n = 1221$). The aggregated effect size was $g = 0.41$ (95%CI 0.11 to 0.72; forest plots for all secondary outcomes are provided in the supplement). Heterogeneity was considerable (83.7%, 95%CI 74.8 to 89.4). For the comorbid psychopathologies the symptoms scores were also reduced in the treatment groups compared to the control groups at post-treatment. Results on depression of 13 studies, based on $n = 980$ participants, were aggregated to an effect of $g = -0.52$ (95%CI -0.82 to -0.23). Anxiety scores were provided in nine studies ($n = 687$) at post-treatment,

leading to an effect of $g = -0.38$ (95%CI -0.65 to -0.11). For both comorbid psychopathologies, heterogeneity was substantial (depression: 79.8%, anxiety: 67.4%). The outcomes measures focussing on mechanisms in the “third wave” therapies, i.e., mindfulness ($k = 8$, $n = 603$, $g = 0.49$, 95%CI 0.33 to 0.65), and psychological inflexibility ($k = 3$, $n = 216$, $g = -0.47$, 95%CI, -0.93 to -0.02) improved significantly. While the mean heterogeneity indicated that it might not be of importance or only moderate, the respective 95%CIs were very wide (see Table 1). For health anxiety and pain acceptance, the effects were not aggregated as only two studies reported measures of each construct.

Figure 2

Forest plot for somatic symptom severity (post-treatment)



3.5 Treatment effects – short-term follow-up

For the short-term follow-up period (up to 3 months post treatment), somatic symptom severity was significantly reduced compared to the control conditions ($k = 9$, $n = 500$). The “third wave” therapies reduced somatic symptom severity in participants ($g = -0.45$, 95%CI -0.72 to -0.19). PHS was again reported in all studies that entailed a short-term follow-up ($k = 10$, $n = 554$). PHS improved significantly in the therapy arms compared to the control conditions ($g = 0.40$, 95%CI 0.09 to 0.71). The improvements in depression ($k = 9$, $n = 508$, $g = -0.40$, 95%CI -0.59 to -0.21), and anxiety ($k = 6$, $n = 326$, $g = -0.27$, 95%CI -0.49 to -0.05) were maintained at short-term follow-up. The additional outcome mindfulness was reported in $k = 6$ studies ($n = 333$); the aggregated effect was $g = 0.32$ (95%CI 0.10 to 0.54) at short-term follow-up. The estimates on quantified heterogeneity had rather wide 95%CIs for all outcomes (see Table 1). Health anxiety was not reported in any study at short-term follow-up; psychological inflexibility ($k = 2$) and pain acceptance ($k = 1$) were too rarely reported at short-term follow-up to be aggregated.

3.6 Treatment effects - long-term follow-up

Only six ($n = 591$) studies reported the primary outcome, somatic symptom severity, at follow-up periods longer than 3 months (mean follow-up period was ~ 9.57 months, $SD = 3.55$). Nonetheless, for these studies the aggregated effect was significant ($g = -0.40$, 95%CI -0.79 to -0.002). However, we could not find a significant effect at long-term follow-up for PHS ($k = 6$, $n = 635$; $g = 0.44$, 95%CI -0.19 to 1.08). While we found a significant effect for anxiety ($k = 3$, $n = 346$, $g = -0.62$, 95%CI -1.12 to -0.11), the effect on depression ($k = 4$, $n = 453$, $g = -0.47$, 95%CI -1.08 to 0.14) was not significant at long-term follow-up anymore. For the exploratory outcome mindfulness, only three studies ($n = 309$) reported results at follow-ups longer than 3 months after end of treatment. These findings did not result in a significant aggregated effect ($g = 0.37$, 95%CI -0.06 to 0.81). For all outcomes, heterogeneity was

substantial to considerable. Only two studies reported health anxiety and only one study each reported psychological inflexibility and pain acceptance at follow-up. Hence, effects were not aggregated for these outcomes.

3.7 Moderator analyses

When comparing acceptance-based therapies (ACT) with the mindfulness-based therapies (MBCT and MBSR) we did not find a significant group difference for somatic symptom severity ($p_{subgroup} = 0.658$). For the acceptance-based therapies ($k = 5$) the effect was $g = -0.59$ (95%CI -1.07 to -0.10) and for mindfulness-based therapies ($k = 10$) it was $g = -0.47$ (95%CI -0.62 to -0.33). However, heterogeneity was larger in acceptance-based therapies ($I^2 = 81.8\%$) than in mindfulness-based therapies ($I^2 = 0.00\%$). We did not find a significant effect of *type of treatment* in any other outcome, either (more detailed results on all moderator analyses can be found in the Supplementary material). As we only identified one study that implemented an internet-based intervention, we did not perform a subgroup analysis for *modus of treatment* (face-to-face vs. internet-based). When dichotomising control groups into *inactive and non-specific control conditions*, we did not find significant subgroup differences for any outcome, either. Regarding subgroup analyses for the different *diagnoses* (i.e., disorders) included, we could only examine differences between the subgroups of irritable bowel syndrome and fibromyalgia as all other subgroups did not hold enough studies ($k < 3$). Here, we did not find significant subgroup differences for any outcome. *Therapy dosis* (i.e., total duration of therapy sessions) was not a significant moderator for any outcome, neither was the *number of sessions*. We did not find significant subgroup differences between *low- and high-intensity treatments* for any outcome. We did not examine moderators for follow-up periods as we only found little studies for these intervals.

Table 1*Treatment effects*

Outcome	<i>k</i>	<i>n</i>	<i>g</i>	95%CI	<i>p</i>	<i>I</i> ²	95%CI	95%PI
Post-treatment								
Somatic Symptom Severity	15	1100	-0.51	-0.69; -0.32	< 0.001	52.8%	15.1; 73.8	-1.09; 0.08
PHS	16	1221	0.41	0.11; 0.72	0.008	83.7%	74.8; 89.4	-0.85; 1.67
Depression	13	980	-0.52	-0.82; -0.23	< 0.001	79.8%	66.2; 87.9	-1.61; 0.57
Anxiety	9	687	-0.38	-0.65; -0.11	0.006	67.4%	34.2; 83.8	-1.20; 0.44
Mindfulness	8	603	0.49	0.33; 0.65	< 0.001	0.0%	0.0; 67.6	0.29; 0.69
Psychological inflexibility	3	216	-0.47	-0.93; -0.02	0.043	49.7%	0.0; 85.4	-5.16; 4.21
Short-term follow-up								
Somatic Symptom Severity	9	500	-0.45	-0.72; -0.19	< 0.001	53.7%	1.8; 78.2	-1.16; 0.26
PHS	10	554	0.40	0.09; 0.7	0.012	65.1%	31.6; 82.2	-0.60; 1.40
Depression	9	508	-0.40	-0.59; -0.21	< 0.001	26.7%	0.0; 65.8	-0.72; -0.09
Anxiety	6	326	-0.27	-0.49; -0.05	0.017	0.0%	0.0; 74.6	-0.58; 0.04
Mindfulness	6	333	0.32	0.10; 0.54	0.004	0.0%	0.0; 74.6	0.01; 0.63
Long-term follow-up								
Somatic Symptom Severity	6	591	-0.40	-0.79; -0.002	0.049	82.3%	62.4; 91.6	-1.74; 0.95
PHS	6	635	0.44	-0.19; 1.08	0.171	91.9%	85.2; 95.6	-1.87; 2.75
Depression	4	453	-0.47	-1.08; 0.14	0.133	88.6%	73.4; 95.1	-3.35; 2.4
Anxiety	3	346	-0.62	-1.12; -0.11	0.016	79.2%	33.7; 93.5	-6.65; 5.42
Mindfulness	3	309	0.37	-0.06; 0.81	0.095	66.4%	0.0; 90.3	-4.62; 5.37

Note. 95%CI = 95% confidence interval; 95%PI = 95% prediction interval; *g* = Hedges' *g*; *k* = number of studies; *n* = number of participants; PHS = perceived health status.

3.8 Sensitivity analyses

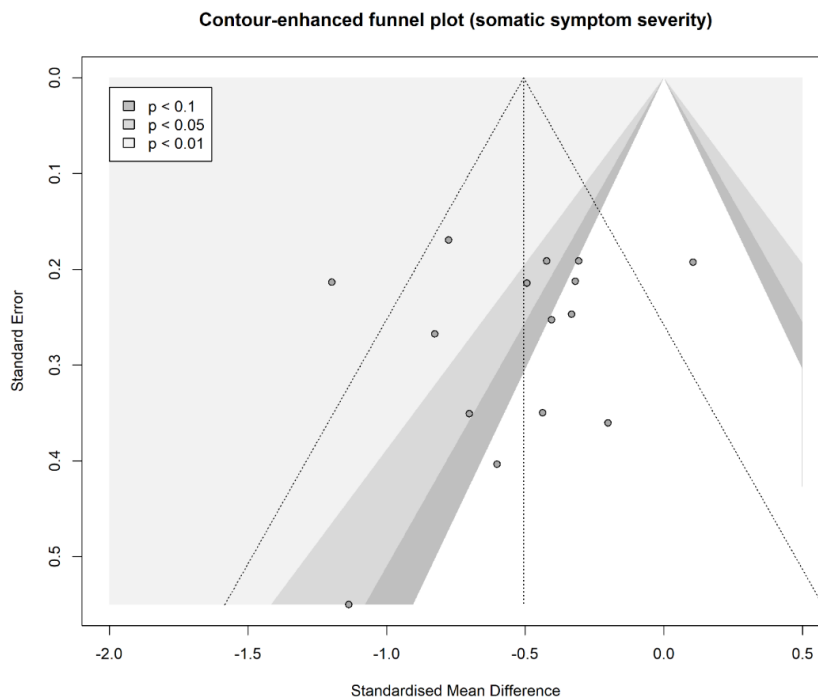
The sensitivity analysis comparing use of the random effects model to the *fixed effect model* did not reveal major differences. As expected, the 95%CI's were larger in the meta-analyses based on the random effects model. The sensitivity analyses concerning the *choice of PHS scales* did not result in meaningful differences. In the *outlier analyses*, we identified two outliers for somatic symptom severity (39, 49), as well as for PHS (39, 51), and one outlier for depression (39) at post-treatment. After excluding the outliers, the effect sizes decreased for all three outcomes. That is, the lower end of the 95%CI's of all outliers was above the upper end of the 95%CI for the respective pooled effect. Furthermore, the mean I^2 values decreased when the outliers were excluded from the analyses. However, the 95%CI's for the heterogeneity in the analyses with outliers and without outliers still overlapped. We did not identify any outliers for anxiety or mindfulness at post-treatment. Details on the sensitivity analyses can be found in the Supplementary material.

3.9 Publication Bias

Eggers' test did not indicate the presence of funnel plot asymmetry for any outcome at post-treatment (see Figure 3 for the contour-enhanced funnel plot for somatic symptom severity at post-treatment; details and funnel plots for all other outcomes are provided in the supplement). However, for anxiety as well as for mindfulness, power might not have been adequate to detect a potential bias. Furthermore, for health anxiety, psychological inflexibility, and pain acceptance we did not analyse publication bias due to the small number of studies. In the p -curve analyses, we found that evidential value was present for all outcomes at post-treatment as far as it was possible to determine (p -curves are depicted in the supplement). However, it was not possible to examine anxiety or psychological inflexibility due to sample size restrictions.

Figure 3

Contour-enhanced funnel plot for somatic symptom severity (post-treatment)



4. Discussion

For adults with bodily distress, the effects of the included “third wave” therapies (ACT, MBCT, and MBSR) at post-treatment indicate a reduction in somatic symptom severity, and of comorbid symptoms of depression and anxiety. Further, results suggest an improvement related to PHS, reflected by an increased (health-related) quality of life and a reduction of impairments due to illness. The effects at short-term follow-up (up to 3 months) suggest maintenance of the effects in somatic symptom severity. The effects on PHS, depression, and anxiety were maintained as well. However, the effects at long-term follow-up on somatic symptom severity and anxiety were small; the effects on PHS and depression were insignificant.

At post-treatment and short-term follow-up, we found small to medium effect sizes. On the long run, effects on somatic symptom severity and anxiety were small. That is, the mindfulness- and acceptance based therapies are more effective than inactive and non-specific control conditions. However, there was a significant amount of heterogeneity. While one might deem the broad definition in PHS accountable for the amount of the substantial heterogeneity in the effects on this measure, we want to point out that we also found a large amount of heterogeneity in depression. The latter was straightforwardly operationalised in the included studies by using established self-report depression scales for assessment.

All in all, the effects are in line with previous research. In comparison to former meta-analyses in the field, the data base for this meta-analysis was considerably improved. A certain overlap ($k = 6$) with Lakhan and Schofield's (12) meta-analysis was given. That is, half of their included trials were incorporated in our analyses, too. Six of the nine total studies included in the latest meta-analysis on "third wave" therapies in fibromyalgia (10) were also identified in the present meta-analysis. However, these former projects included not only a quasi-randomised controlled trial (52), but also trials that did not solely rely on established "third wave" therapy manuals. Findings here included short-term maintenance of treatment effects and, in some outcomes, over the longer follow-up. In a previous work (12) the reported outcomes were descriptively smaller. Still, the 95%CIs overlapped. The overlap of confidence intervals does not necessarily imply that the results are comparable, however, it can be an indicator that they are. In Haugmark et al. (10), the effect on health-related quality of life was larger than our effect on PHS which might be attributed to differences in operationalisation decisions. However, the 95%CIs overlapped here as well. Lakhan and Schofield (12) did not aggregate follow-up effects meta-analytically.

Although the effects are only small to moderate, ACT, MBCT, and MBSR may be clinically useful, as the main goal in psychotherapy approaches for bodily distress is not a full remission, but to enable patients to adaptively cope with their symptoms (53). While the “third wave” therapies and conventional CBT were not directly compared, the effect sizes we found are comparable to those of conventional CBT (1). This means that mindfulness- and acceptance-based therapies could possibly pose an effective treatment alternative for patients suffering from bodily distress.

While some patients might benefit more from these “third wave” therapies than from CBT, specific predictors still have to be identified. Hence, we included measures of potential change mechanisms as exploratory outcomes. Mindfulness, central to MBCT and MBSR, improved significantly at post-treatment, and this effect was maintained at short-term follow-up. However, at long-term follow-up the effect was no longer significant. Psychological inflexibility was lower at post-treatment in the groups that received “third wave” therapies, indicating that ACT in fact tackles psychological inflexibility. Overall, the number of follow-up studies on mechanism variables is very small, and no data could be integrated for psychological inflexibility or pain acceptance due to lack of studies. It also remains unclear whether these effects are associated with the changes in clinical outcomes, as it was not possible to examine this relationship in this meta-analysis.

The moderator analyses did not identify relevant sources of heterogeneity. That is, e.g., the effect on somatic symptom severity seems to be independent of the specific type of treatment and treatment intensity or dosis. However, subgroup and moderator analyses usually lack power (54). Consequently, non-significant results do not necessarily indicate that there is no effect. Generally, for the outcomes that were seldomly reported, the 95%CIs were larger due to limited accuracy. As the number of studies decreased for the follow-up periods, the confidence intervals grew larger for the other outcomes, too. Same goes for the accuracy of the heterogeneity measure. Therefore, we advise researchers to comply

to the core domains of bodily distress recommended by the EURONET-SOMA group (13), as conclusions could not be drawn for all of them.

Furthermore, almost all studies evaluated treatments in a group setting, including the studies on ACT – which is not a group program per se. Thus, the efficacy of ACT, MBCT, and MBSR as individual therapy cannot be assessed (we also did not find evidence that the study implementing ACT in an individual (internet-based) setting (43) had a substantial impact on the results). Individual therapy may have the advantage of being better tailored to the individual problem and treatment goal (4). However, treatments with group format could have the advantage of being more cost-efficient. Nonetheless, except for the social support group condition in one trial (44), all control groups in the included studies were individual-focused rather than group therapy-focused. Therefore, we cannot determine whether the effects of the included “third wave” therapies may have been influenced by the group component. It is possible, for example, that certain desirable effects result from the social support in groups alone (55).

A factor limiting generalization of results to the wide scope of bodily distress is that most included studies were on functional somatic syndromes and only three on other conditions within the category of somatoform disorders. It is noteworthy that so far there is no study that investigated the efficacy of “third wave” therapies in Somatic Symptom Disorder or bodily distress disorder, i.e., recently introduced classification approaches predominantly focussing on the excessive psychobehavioral components of bodily distress. Mindfulness-based or acceptance and commitment therapy might be especially useful for these disorders as they could help in reducing excessive psychobehavioral symptoms such as excessive symptom related preoccupation and worries as well as experiential avoidance.

The results need to be interpreted in the light of potential biases. RoB ratings were rather high for the included studies. Some domains lead to high RoB ratings when studies were designed according to conventions in psychotherapy trials in bodily distress. For example, all outcome scores relied on self-reports increasing RoB scores in the domain “RoB in measurement of the outcome”. That is, we considered the patients as outcome assessors which were probably not blinded due to a lack of convincing (placebo-)control groups (56). In the “RoB in the selection of reported results” most studies were rated high for the majority of outcomes. However, selective reporting of analyses could not be examined in most registrations (e.g., on clinicaltrials.gov) as the templates lack options to provide information on analysis plans.

Our analysis had several strengths. We complied with current guidelines on conducting, analysing, and reporting meta-analytic results. Based on a preregistered rationale, we examined efficacy on various manifestations of bodily distress. Furthermore, we integrated follow-up effects of the included “third wave” therapies, for which aggregated data for the entire field of bodily distress was previously lacking (e.g., 12).

However, there were some conceptual limitations to this study. First and foremost, the definition for “third wave” therapies that was used in this study solely entailed MBCT, MBSR, and ACT. Subsequently, this project allows statements regarding the efficacy of these three therapies, which have now been the subject of a number of studies in bodily distress. However, an assessment regarding the efficacy of other “third wave” approaches (like meta-cognitive therapy) is currently not possible, yet. Apart from that, only inactive and non-specific control groups were taken into account which could result in an overestimation of the effect sizes (27). No conclusions can be drawn regarding the efficacy of “third wave” therapies in comparison to other active treatments, especially evidence-based treatments.

Lastly, we did not include grey literature, i.e., unpublished reports. Nonetheless, there was no indication of publication bias.

4.1 Prospects

Future updates of this meta-analysis would be a useful tool to include new findings in the field of psychotherapy in adults with bodily distress; ideally incorporating all core outcome domains in bodily distress as well as more long-term follow-ups. Moreover, it might be useful to collect individual patient data, i.e., primary data from RCTs, and combine them into one dataset to enable researchers to identify mediators and moderators of effects in “third wave” therapies. Nonetheless, larger trials are needed, preferably RCTs that help to identify mechanisms in symptom reduction. Future RCTs should also implement control groups that control for unspecific effects in the intervention examined, e.g., peer-support as a group component in group therapy. Considering the distribution of diagnoses within our sample, more studies on Somatic Symptom Disorder and bodily distress disorder would be especially beneficial to the field.

4.2 Conclusions and implications

The results of this meta-analysis suggest that ACT, MBCT, and MBSR can be beneficial treatment approaches for bodily distress in adults, showing improvements in somatic symptom severity, comorbid psychopathology, and perceived health status. This meta-analysis provides a good summary of the current state of research of the included “third wave” therapies’ efficacy in bodily distress using an enlarged data base due to the focus on bodily distress and not solely focussing on a single syndrome or symptom. All in all, these results could form the basis for these “third wave” therapies to be included in treatment guidelines, while acknowledging that more research is needed to reliably draw conclusions on the efficacy in all relevant domains of bodily distress – especially in the long run.

Data Availability Statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author Contributions

FMgB and AM developed the research question and conceptual background for this work and prepared the final manuscript for publication. FMgB and LH developed the outline, formulated the search terms, and independently performed the literature search, data extraction, and risk of bias assessment (with the help of a research assistant). FMgB performed data analyses and provided feedback on the manuscript. AM regularly provided feedback on the progress and results. All authors contributed to the article and approved the submitted version.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at:

<https://www.frontiersin.org/articles/10.3389/fpsy.2023.1160908/full#supplementary-material>

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7. Study 3

7.1 Reference and Author Contributions

Title: Efficacy of cognitive behavioral therapy and acceptance- and mindfulness-based treatments in adults with bodily distress – a network-meta-analysis

Authors: Frederic Maas genannt BERPohl & Alexandra Martin

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Author contributions:

- Frederic Maas genannt BERPohl developed the research question and conceptual background for this work under the supervision of Alexandra Martin.
- Frederic Maas genannt BERPohl, with the help of research assistants, developed the outline, formulated the search terms, and performed the literature search, data extraction, and risk of bias assessment (the latter for a subset of the included studies) under the supervision of Alexandra Martin.
- Frederic Maas genannt BERPohl performed data analyses.
- Frederic Maas genannt BERPohl interpreted the results with contributions from Alexandra Martin; all authors discussed the results.
- Frederic Maas genannt BERPohl wrote the manuscript with contributions and revisions by Alexandra Martin.

Additional support:

- Ann-Cathrin Kucharczyk-Bodenburg helped with study selection, data management, and risk of bias assessment.

7.2 Submitted Manuscript

Efficacy of cognitive behavioral therapy and acceptance- and mindfulness-based treatments in adults with bodily distress – a network-meta-analysis

Frederic Maas genannt Bermpohl, Alexandra Martin

Abstract

Introduction: Many physical complaints cause long-term *bodily distress*. Meta-analyses show that cognitive behavioral therapy (CBT) and acceptance- and mindfulness-based treatments (AMBT) reduce somatic symptom severity, but evidence on differential efficacy is limited. This study evaluates the efficacy of CBT and AMBT for bodily distress (e.g., somatoform disorders, functional somatic syndromes, and related disorders).

Methods: A network meta-analysis of randomized controlled trials on adults with bodily distress compared CBT and AMBT either directly or with non-specific control groups. Cohen's *d* based on between-group effect sizes was aggregated using a random effects model. Primary outcome was somatic symptom severity; secondary outcomes included depression, anxiety, and perceived health status.

Results: Based on 74 studies ($N = 8,277$), CBT ($d = -0.50$, 95%CI -0.70 to -0.29; between-group effect sizes vs. wait-list) and AMBT ($d = -0.55$, 95%CI -1.06 to -0.23; between-group effect sizes vs. wait-list) were equally effective in reducing somatic symptoms at posttreatment. AMBT were more effective than CBT in reducing depression ($d = -0.31$, 95%CI -0.58 to -0.04; between-group effect sizes) and anxiety ($d = -0.42$, 95%CI -0.73 to -0.11; between-group effect sizes) posttreatment. At long-term follow-up, effects were partly maintained; AMBT remained more effective than CBT for anxiety, with no differential effects for other outcomes.

Conclusions: Both treatments showed benefits compared to various controls. Evidence suggests potential differential treatment effects, indicating some patient groups may benefit more from AMBT. Clinicians should view CBT as foundational but remain open to variations, especially for comorbid pathology.

Keywords: persistent physical symptoms; somatoform disorder; somatic symptom disorder; psychological treatments; treatment evaluation

Introduction

Many persistent physical symptoms are chronic and impose a significant burden [1]. They are highly prevalent [2] and often lead to frequent medical consultations [1]. The disorders characterized by persistent physical symptoms can be subsumed under the label *bodily distress* [3], moving beyond the dichotomy of medically unexplained and explained symptoms [4]. This category includes *somatization disorder* (ICD-10 [5], DSM-IV [6] or precursor versions), newer classifications like *somatic symptom disorder* (DSM-5 [7]), *bodily distress disorder* (ICD-11 [8]), and *functional somatic syndromes*, such as irritable bowel syndrome, chronic fatigue syndrome, and fibromyalgia [9], since they share transdiagnostic mechanisms [4].

Several psychological interventions have been proposed for managing bodily distress, with cognitive behavioral therapy (CBT) being the most studied. Meta-analyses demonstrate small to moderate effects for CBT in individual functional somatic syndromes (e.g., [10] for chronic fatigue syndrome, [11] for irritable bowel syndrome, and [12] for fibromyalgia) and multiple medically unexplained symptoms [13]. However, no evidence synthesis exists for the efficacy of CBT in bodily distress across all syndromes and diagnoses. Alternatively, acceptance- and mindfulness-based treatments (AMBT), often referred to as “third wave” treatments [14], emphasize *acceptance*, *mindfulness*, and *values* in the treatment [15]. Prominent approaches include Acceptance

and Commitment Therapy (ACT [15]), mindfulness-based cognitive therapy (MBCT [16]), and mindfulness-based stress reduction (MBSR [17]). These treatments aim to help patients accept bodily sensations and foster values-driven actions to improve coping and well-being. A recent meta-analysis [18] reported beneficial outcomes for AMBT in bodily distress compared to non-specific control groups for, inter alia, somatic symptom severity ($g = -0.51$, 95%CI -0.69 to -0.32), depression and anxiety. Evidence does not suggest that mindfulness-based treatments are superior to acceptance-based treatments. Assessing absolute efficacy is crucial to determine patient benefit, while comparing relative efficacy offers insight into differential treatment effects [19]. However, evidence on differential efficacy between conventional CBT and AMBT for bodily distress is lacking.

Hence, this network meta-analysis (NMA) updates on the absolute efficacy of CBT, but also to estimate the relative efficacy of conventional CBT and AMBT. The NMA will include comparisons of treatments and inactive control groups as well as direct comparisons of treatments [20] in reducing bodily distress in adults. It focuses on immediate reductions in somatic symptoms while considering short- and long-term follow-up effects, comorbid psychopathologies (depression and anxiety), and perceived health improvement. Sensitivity analyses will assess the robustness of results. The role of non-specific factors [21] due to control group influences in randomized controlled trial (RCT) outcomes [22] will also be examined.

Methods

The network meta-analysis was pre-registered on PROSPERO (*CRD42021249468*; see online suppl. S4 for deviations from the protocol; for all online suppl. material, see <https://doi.org/10.1159/000544825>), analyses were computed in R version 4.3.4 ([23], see online suppl. S5 for a list of packages used), the corresponding code is available on OSF [24]. The results will be reported according to the PRISMA 2020 statement ([25], see online suppl. S16 for the PRISMA 2020 checklist).

Eligibility Criteria

For a study to be included, the participants needed to be adults (≥ 18 years old). Moreover, the participants need to fulfil the criteria for one of the conditions considered bodily distress, which are characterized by persistent physical symptoms sharing transdiagnostic mechanisms [4]: e.g., somatic symptom disorder, somatoform disorder, medically unexplained symptoms, chronic fatigue syndrome, fibromyalgia/chronic widespread pain, irritable bowel syndrome or an according research diagnosis (see online suppl. S1.1 for a complete list of included syndromes and diagnoses). The diagnostic assessment should either rely on a diagnostic interview or scores within a pre-defined range on a validated syndrome scale [26]. Only studies that provided conventional CBT, cognitive therapy or AMBT with a focus on bodily distress were included. As for AMBT, several therapies that are mostly characterized by a focus on skills like mindfulness and acceptance [15] were included (see online suppl. S1.2 for eligible treatments). Combinations of CBT and AMBT approaches were included as well and labelled accordingly. Treatments that only relied on behavioral components, e.g., behavioral activation, biofeedback, or relaxation techniques, were excluded.

Only RCTs with $n \geq 10$ per arm/group [27] that were published in English were selected. Within these RCTs, conventional CBT and an AMBT approach were compared directly, or either one of the approaches was compared to an inactive or unspecific control arm. Wait-list (WL) was considered an inactive control group. Attention/psychological/pill placebo conditions were expected to control for unspecific factors within the study design [19]. If both, the therapist as well as the participants were inactive during the placebo-phase, it was considered as attention placebo, e.g., symptom monitoring. However, if the participants were active during this phase, it was considered as psychological placebo [13], e.g., using internet forums. Treatment-as-usual (TAU) and enhanced care (EC, e.g., TAU with additional psychoeducation or counselling) were also included, although the definitions might differ between countries. As participants in TAU conditions often receive no scheduled intervention at all, *no treatment*-arms were consequently classified as TAU as well [28].

Search Strategies and Study Selection

PubMed (NCBI), PsycInfo (Ovid), CENTRAL (Cochrane Central Register of Controlled Trials), CDSR (Cochrane Database of Systematic Reviews; Reviews and Protocols), CCA (Cochrane Clinical Answers), and PSYNDEX (ZPID) were last searched on April 5th, 2024; additionally, Web of Science was searched on January 8th, 2025 (see online suppl. S1.4 for more detail and online suppl. S1.5 for search algorithms). For each electronic database search, results were exported to Zotero (Version 6.0.27-beta) and deduplicated using the built-in deduplication function. Then, titles and abstracts were scanned for eligibility (see online suppl. 1.3 for prioritization of exclusion criteria). Two independent researchers selected reports for full-text assessment and disagreements were resolved by discussion. FMgB screened all reports, while subsets of the reports were each independently scanned by research assistants. During an additional backwards search, the

references of meta-analyses, systematic reviews as well as eligible reports found during the first phase were searched for further possibly eligible reports. None of the independent researchers were blinded to any aspect of the studies at any time during the process.

Data Extraction

If there were multiple comparisons in one study, all arms that met inclusion criteria were included. Similar arms were then synthesized into one set of values [29] (see online suppl. 1.6 for more detail). If multiple measures were used for the assessment of similar outcomes, validated measures were preferred. If multiple or none of the measures were validated, FMgB and a research assistant decided which measure was selected (see online suppl. S2.4 for details). If multiple publications were based on one dataset, the most recent publication was included as far as the results are redundant. Otherwise, the publications were considered as a single study [26]. If data could not be extracted from the published paper (or online suppl. material), the original authors were contacted and asked to provide the relevant data.

Risk of Bias Assessment

The risk of bias (RoB) was assessed with the revised Cochrane risk of bias tool for parallel-group trials (RoB 2.0; [30]) by a trained research assistant, while subsets were independently assessed by FMgB to reconcile ratings and align rating procedures.

Outcome Measures

The outcomes were chosen in accordance with the EURONET-SOMA core outcome domains [31]. These recommendations provide a standardized set of key domains for measuring outcomes in clinical research regarding bodily distress, ensuring consistency and comparability across studies: Somatic symptom severity was the primary outcome. Depressive symptoms, anxiety symptoms, and the perceived health status were secondary

outcomes. The perceived health status combines measures of physical functioning, impairment, quality of life, health-related quality of life, and health status [32]. That is, for somatic symptom severity, depression, and anxiety, negative effect sizes indicate a reduction of symptoms, while for perceived health status, a positive effect size indicates improvement of perceived health status [18]. For all outcomes, if possible, the NMA was computed for posttreatment effects, short-term (up to 3 months after end of treatment), and long-term follow-up assessments (3 to 12 months after end of treatment; [33]). Follow-ups longer than 12 months were examined separately.

Data Analyses

The whole NMA was based on a frequentist approach [34]. A random effects model was used in this analysis to draw statistical inferences on the underlying universe based on the study results [35]. Although Hedges' g holds the benefit that it is adjusted for small sample bias [36], we used a specific form of Cohen's d [37] as summary statistic which is more consistent in multi-arm studies [38]. This method addresses systematic differences by utilizing all available evidence, thus enhancing the precision and robustness of the effect estimates [39]. Within the process, it provides a comprehensive method for comparing multiple treatments, enabling the estimation of both pooled and indirect effects, thereby offering a more complete understanding of the absolute and relative efficacy of different treatments. All CBT-based interventions were combined in one node in the network, the AMBT in another. Hence, this approach allows for an estimation of relative effects between CBT and AMBT. What is more, it also individually compares the relative effects of several control groups that might control for different unspecific factors in psychotherapy trials [40]. In the same line, it offers a differentiated presentation of various outcomes at several assessment points, also considering maintenance effects without limiting the inclusion of studies using a range of control

conditions. The proportion of direct and indirect comparisons that contribute to the respective estimates [41] are visualized with a direct evidence plot [29]. It is further possible to rank the efficacy of the included conditions in NMA based on P-scores [41]. The higher the P-score (0 to 1), the more solid the presented results are [42]. To assess the amount of heterogeneity/transitivity in this network, the between study variance will be given by τ^2 . Moreover, the I^2 -statistic and its 95%CIs will be calculated [43]. All comparisons that were estimated by combining direct and indirect evidence in the network were additionally tested for indifference between direct and indirect estimates to check for loop-inconsistency. Furthermore, each design's contribution to an estimate within the network as well as to the network inconsistency were examined [34].

Sensitivity Analyses

In the first sensitivity analysis, acceptance-based treatments and mindfulness-based treatments were analyzed as independent nodes in the network. Additionally, the analyses were computed separately for different psychotherapy settings: Since high-intensity treatments are usually more effective [13], low-intensity psychotherapy (i.e., < 8 sessions, [44]) and high-intensity psychotherapy (i.e., ≥ 8 sessions) were examined separately. An additional analysis focused exclusively on face-to-face interventions to assess whether the inclusion of self-guided or digital treatments (e.g., computer-, internet-, or app-based) influenced the outcomes. Furthermore, another sensitivity analysis examined all studies on somatic symptom and related disorders (e.g., bodily distress syndrome, medically unexplained symptoms, somatization disorder), while separately assessing the studies on functional somatic syndromes (e.g., irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome). An additional analysis examined only those studies that used clinical interviews or medical examinations to ensure inclusion diagnoses, in order to examine the influence of studies that relied on a cut-off score from a symptom scale. The selection

of follow-up intervals was also investigated: The longest available follow-up of every study was considered, irrespective of classification as short- or long-term follow-up (see above). Finally, the meta-analytic model choice was tested in a sensitivity analysis, comparing the results using the random effects model to the same analyses based on the fixed effect model. All sensitivity analyses (except the analysis on the longest-available follow-up) were computed for posttreatment effects.

Publication Bias

Multiple methods were implemented to detect possible meta-biases. To assess possible publication bias, a comparison-adjusted funnel plot [41] was conducted for all comparisons in addition to Egger's Test, in which a significant result indicates publication bias [29].

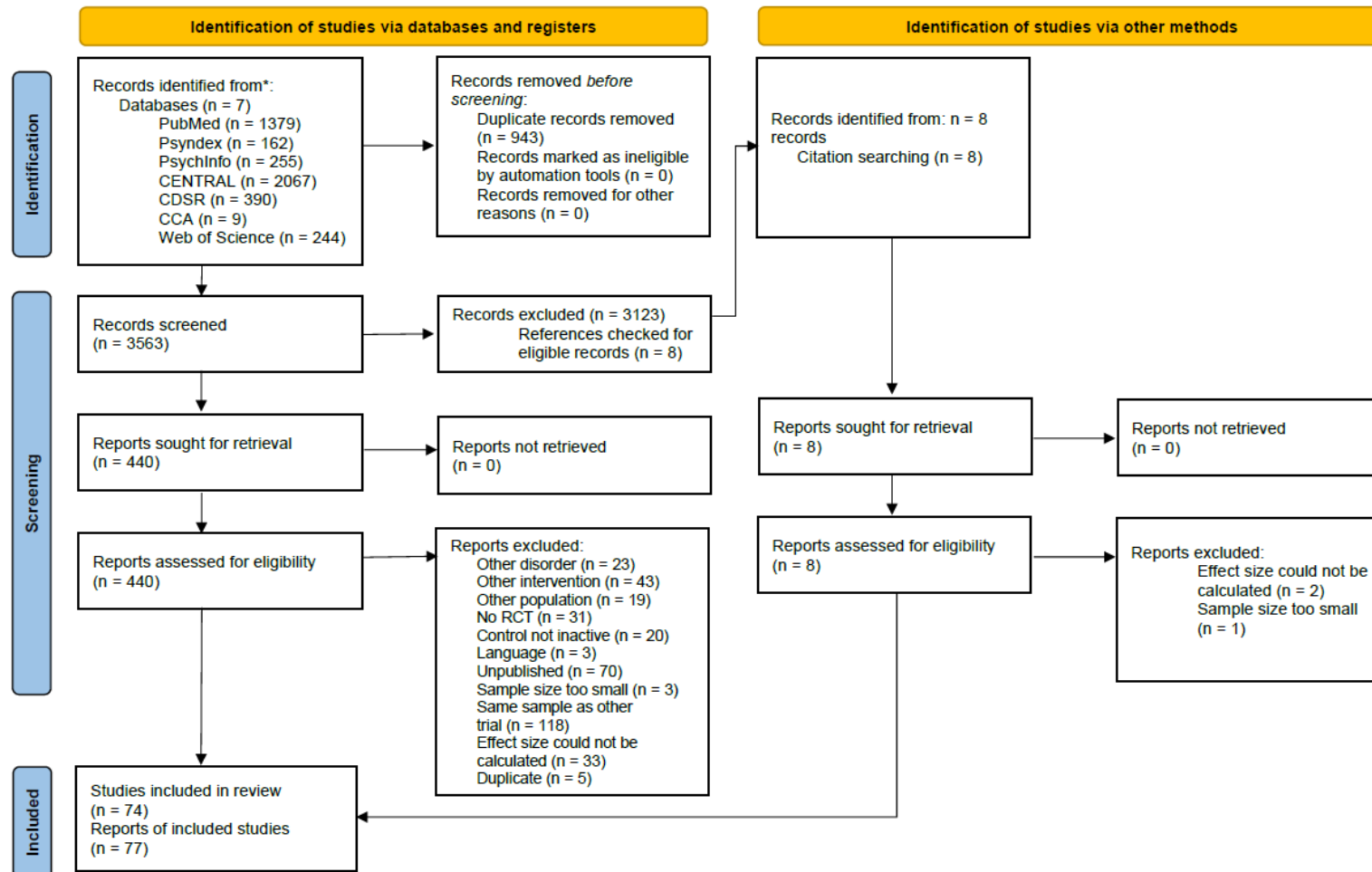
Results

Study Selection

For study selection, 4,506 records were retrieved (shown in Fig. 1). After removing 943 duplicates, 3,563 abstracts were screened, excluding 3,123 studies that did not meet criteria. Next, 440 full-text reports were assessed; after excluding 368 reports, leaving 72 included. Additionally, through backwards searching and experts in the field 5 reports were identified. Hence, a total of 77 reports of 74 studies were included for analysis (for [45], [46] provided additional information; [47] and [48] were also based on the same study; [49] provided follow-up data on [50]).

Figure 1

PRISMA 2020 flow diagram (adapted from Page et al. [25])



Study Characteristics

The included studies were published between 1994 and 2024. While not all studies provided information on age and sex distribution, in those that did, participants were on average 43.40 years old ($SD = 7.47$) and were mostly female (approximately 82.46%, $SD = 0.18$). In total, $k = 74$ studies with $N = 8,277$ participants, containing 8 conditions (see in Fig. 2), were included in the analysis (see online suppl. S2.2 for excluded study arms). Of these, four studies contained multiple (> 2) arms that were included in the analyses [51–54]. The majority of studies focused on the treatment of functional somatic syndromes, i.e., fibromyalgia or chronic widespread pain ($k = 25$), irritable bowel syndrome ($k = 23$), and chronic fatigue syndrome ($k = 13$). Most studies ($k = 53$) implemented CBT [50–53, 55–103], whereas $k = 16$ used an AMBT [45, 47, 54, 104–116], i.e., ACT ($k = 5$), MBSR ($k = 6$), MBCT ($k = 3$), Unified Protocol ($k = 1$), and positive psychotherapy ($k = 1$). Six studies used a combination of both approaches [76, 117–121]. Thirty-three of the included studies provided the treatments in a group setting, while $k = 36$ used an individual setting, and $k = 3$ studies mixed individual and group settings ([58] had one session that was provided individually, while all other sessions were in a group setting; [107] had a group workshop followed by a self-help program; [83] provided their program in individual and group setting, depending on how many patients came in on the respective day); for [85] and [99] the individual and group interventions were combined for the analysis in this project. Some studies ($k = 13$) implemented internet-based or app-based delivery formats; [75] shifted from face-to-face setting to an internet-based format in response to the COVID-19 pandemic; for [63] the telephone-delivered and web-delivered arms were combined. Within the included studies, the average number of sessions was 9.16 ($SD = 4.53$) with a range from a minimum of 1 session to a maximum of 24 sessions. The average treatment duration was 11.15 weeks ($SD = 6.42$) with a range from 1 week to a maximum of 36 weeks. Inactive and non-

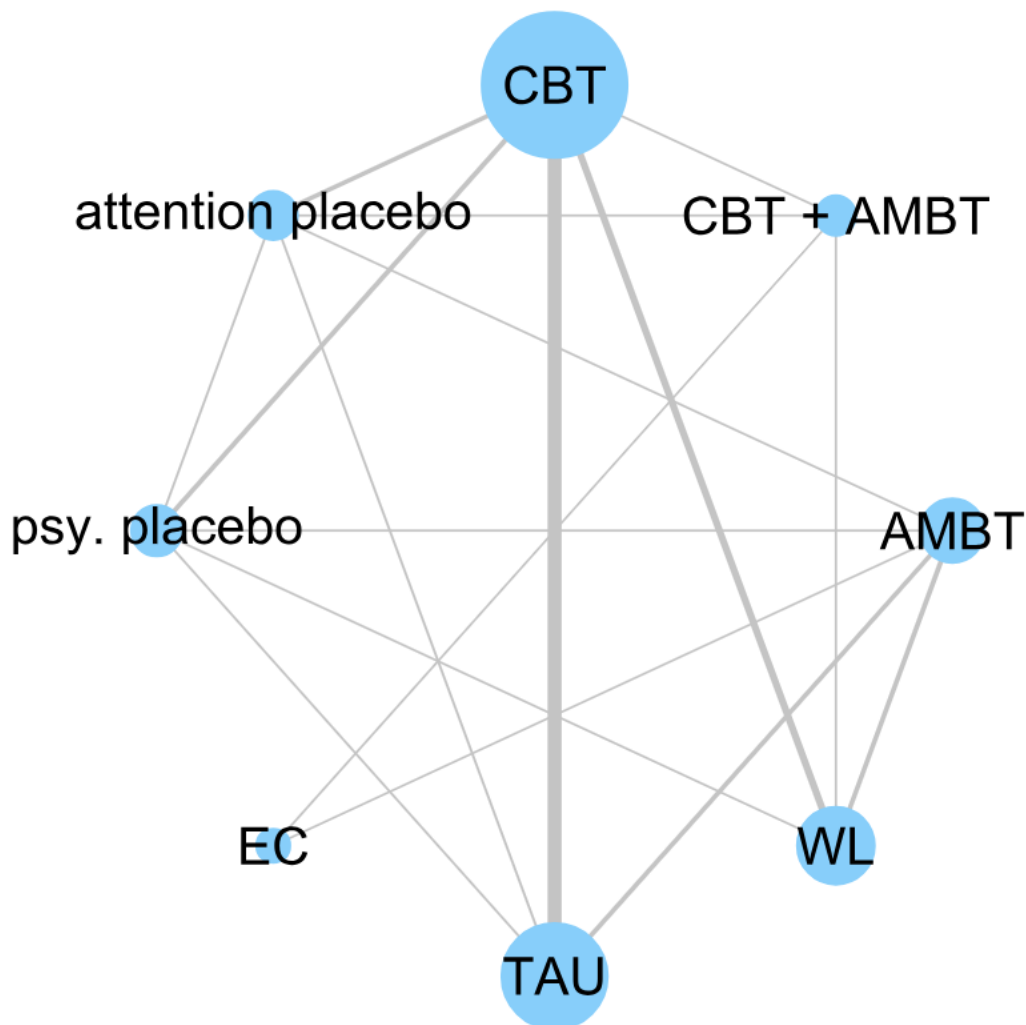
specific control groups were TAU ($k = 35$), WL ($k = 22$), psychological placebo ($k = 8$), attention placebo ($k = 8$), and EC ($k = 4$). In the TAU conditions, TAU ranged from no treatment to pharmacological treatment (cf. online suppl. S2.1 for details).

Network

Figure 2 shows that the overall network is well connected, with CBT and TAU being the most frequently compared treatments. Both, WL and TAU were connected to CBT and to AMBT, while the active treatments were generally connected to control groups. However, CBT was not connected to EC, and the treatment combinations of CBT and AMBT were not connected to TAU or psychological placebo. Additionally, CBT and AMBT had not been directly compared in the trials, although the combination of CBT and AMBT had been compared to CBT. The networks for the individual outcomes differed as not all studies provided data on all outcomes or for all assessment points (see online suppl. 2.3 for an overview; graphs are provided in the online suppl. S6).

Figure 2

Network plot for the overall-network at posttreatment



Note. Each node represents a treatment, with edges indicating direct comparisons between treatments found in the included studies. Edge thickness is proportional to the number of comparisons, and node size reflects the number of direct comparisons involving that node. AMBT = acceptance- and mindfulness-based treatments; CBT = cognitive behavioural therapy; CBT + AMBT = combination of CBT and AMBT; EC = enhanced care; psy placebo = psychological placebo; TAU = treatment as usual; WL = wait-list.

Risk of Bias

The RoB evaluation revealed that most studies had a high RoB, with only a few rated as having *some concerns* regarding RoB ($k = 2$ for somatic symptom severity, $k = 3$ for depression, $k = 3$ for anxiety, $k = 2$ for perceived health status): These studies solely exhibited potential issues in the domain *bias in the selection of reported results* (see online suppl. S3 for details on individual ratings of studies).

Treatment Effects – Posttreatment

The efficacy in reducing somatic symptom severity was examined in $k = 63$ studies (comprising a total of $n = 6,658$ participants) through $m = 71$ pairwise comparisons, across 17 different designs. Conventional CBT, AMBT, and their combination were significantly more effective in reducing somatic symptom severity compared to WL (Fig. 3a). All three active treatments also outperformed TAU, psychological placebo, and attention placebo, though they were not significantly more effective than EC ($k = 2$ studies). No significant differences were found between any combinations of active treatments. Similarly, no inactive or non-specific control group was superior to the others. Estimated and pooled treatment effects from direct comparisons were mostly comparable (cf. Table 1). Based on P-value rankings, AMBT (0.80), CBT (0.72), and their combination (0.87) were the most effective for reducing somatic symptom severity, followed by EC (0.71), psychological placebo (0.32), attention placebo (0.23), WL (0.20), and TAU (0.15; see online suppl. S9 for rankings on all outcomes). The quantified total heterogeneity/inconsistency in the network was $I^2 = 73\%$ (95%CI 65.3 to 79) with a between study variance of $\tau^2 = 0.12$. The remaining between designs inconsistency, based on the assumption of a full design-by-treatment interaction random effects model, was not significant ($Q_{between} = 9.62$, $df = 14$, $p = 0.79$; see online suppl. S10–13 for more detailed analyses on all outcomes).

Table 1*Treatment comparison estimates for somatic symptom severity at post-treatment*

AMBT	-	-	0.11 (-0.66; 0.87)	-0.76 (-1.11; -0.40)	-0.24 (-0.81; 0.32)	0.03 (-0.76; 0.82)	-0.58 (-0.90; -0.25)
-0.05 (-0.30; 0.19)	CBT	0.08 (-0.64; 0.80)	-	-0.50 (-0.66; -0.34)	-0.47 (-0.83; -0.12)	-0.45 (-0.84; -0.06)	-0.54 (-0.78; -0.30)
0.09 (-0.34; 0.52)	0.14 (-0.26; 0.54)	CBT + AMBT	-0.31 (-1.07; 0.46)	-	-	-1.01 (-1.59; -0.42)	0.15 (-0.64; 0.94)
-0.06 (-0.64; 0.53)	-0.00 (-0.60; 0.60)	-0.15 (-0.73; 0.44)	EC	-	-	-	-
-0.58 (-0.84; -0.33)	-0.53 (-0.68; -0.38)	-0.67 (-1.09; -0.26)	-0.53 (-1.13; 0.08)	TAU	-0.03 (-0.76; 0.70)	0.05 (-0.76; 0.86)	-
-0.47 (-0.80; -0.13)	-0.41 (-0.70; -0.12)	-0.55 (-1.03; -0.08)	-0.41 (-1.05; 0.24)	0.12 (-0.19; 0.43)	Psychological placebo	0.07 (-0.73; 0.86)	-0.29 (-1.05; 0.47)
-0.53 (-0.89; -0.17)	-0.48 (-0.79; -0.17)	-0.62 (-1.04; -0.21)	-0.48 (-1.11; 0.15)	0.05 (-0.28; 0.38)	-0.07 (-0.46; 0.33)	Attention placebo	-
-0.55 (-0.80; -0.30)	-0.50 (-0.70; -0.29)	-0.64 (-1.06; -0.23)	-0.50 (-1.10; 0.11)	0.03 (-0.21; 0.27)	-0.09 (-0.42; 0.24)	-0.02 (-0.37; 0.33)	WL

Note. $k = 63$, $m = 71$, $n = 6658$; effect size: Cohen's d (between-group effects after end of treatment); diagonal gives the treatments that were examined; upper triangle displays the pooled effect sizes of the direct comparisons available with 95% CIs; lower triangle contains the network meta-analysis effect sizes for each comparison with 95% CIs. AMBT = acceptance- and mindfulness-based treatments; CBT = cognitive behavioural therapy; CBT + AMBT = combination of CBT and AMBT; EC = enhanced care; TAU = treatment as usual; WL = wait-list

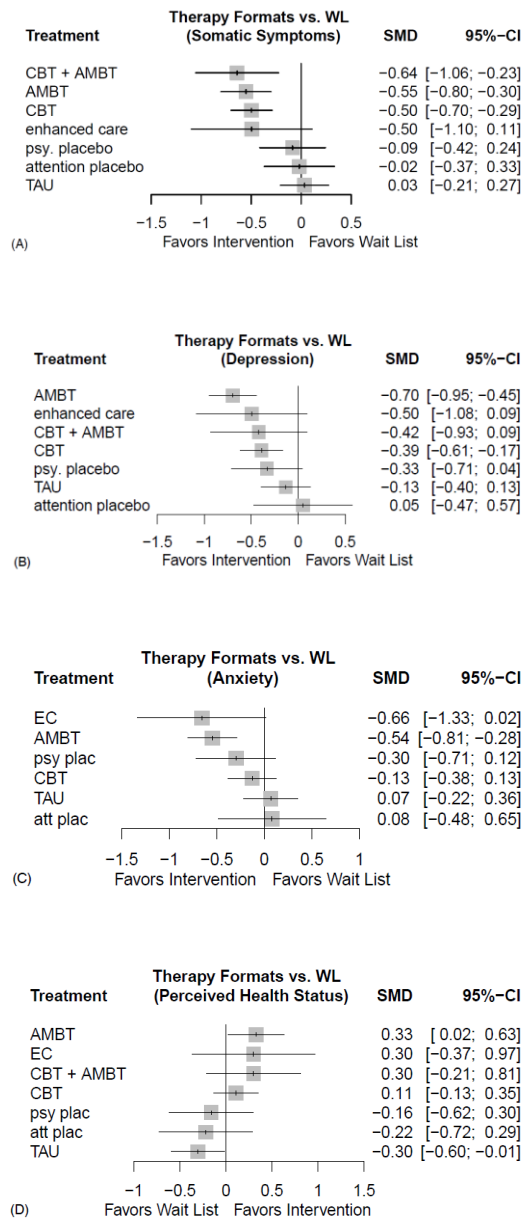
In depressive symptoms ($k = 44$, $n = 3,893$, $m = 48$), CBT and AMBT significantly reduced symptom severity compared to WL (Fig. 3b) and TAU; in contrast, their combination did not. However, CBT did not show greater efficacy compared to EC, psychological placebo, attention placebo, or the combination of CBT and AMBT. When compared with CBT, AMBT treatments showed a small effect size. No significant difference was found between AMBT and their combination with CBT. Among control groups, no significant differences were observed (cf. Table 2). Heterogeneity/inconsistency was $I^2 = 64.3\%$ (95%CI 50.1 to 74.5; $\tau^2 = 0.09$; full design-by-treatment interaction random effects model: $Q_{between} = 10.50$, $df = 8$, $p = 0.23$).

Regarding anxiety symptom severity ($k = 31$, $n = 2,795$, $m = 35$), AMBT significantly outperformed WL (Fig. 3c). In contrast, CBT did not show a significant effect compared to WL, psychological placebo, or attention placebo. However, CBT and AMBT were more effective than TAU. Further, AMBT had a small significant effect compared to CBT. EC showed a significant effect compared to TAU, other than that, no inactive or non-specific control group was significantly superior to the others (cf. Table 3). Heterogeneity/inconsistency was $I^2 = 56.3\%$ (95%CI 33.2 to 71.3; $\tau^2 = 0.06$; full design-by-treatment interaction random effects model: $Q_{between} = 5.25$, $df = 6$, $p = 0.51$).

For improving perceived health status ($k = 60$, $n = 6,366$, $m = 66$), AMBT demonstrated a significant positive impact compared to WL. However, neither CBT nor the combined interventions significantly enhanced perceived health status compared to WL (Fig. 3d). All active treatments were more effective than TAU, but CBT was not superior to psychological or attention placebo. Among control groups, there was only one significant difference: WL showed a significant effect compared to TAU. No significant effects were found between active treatments (cf. Table 4). Heterogeneity/inconsistency was $I^2 = 82.6\%$ (95%CI 78.0 to 86.2; $\tau^2 = 0.20$; full design-by-treatment interaction random effects model: $Q_{between} = 6.84$, $df = 12$, $p = 0.87$).

Figure 3

Forest plots – Posttreatment effects for somatic symptom severity, depression, anxiety, and perceived health status (as compared to waitlist)



Note. For perceived health status positive effects indicate efficacy of the treatments, for all other outcomes negative effects indicate efficacy of the treatments. AMBT = acceptance- and mindfulness-based treatments; att plac = attention placebo; CBT = cognitive behavioural therapy; CBT + AMBT = combination of CBT and AMBT; EC = enhanced care; psy plac = psychological placebo; TAU = treatment as usual; WL = wait-list.

Table 2*Treatment comparison estimates for depression at post-treatment*

AMBT	-	-	-0.08 (-0.78; 0.63)	-0.80 (-1.19; -0.41)	0.11 (-0.40; 0.62)	-	-0.67 (-0.98; -0.37)
-0.31 (-0.58; -0.04)	CBT	-0.04 (-0.70; 0.61)	-	-0.20 (-0.39; -0.01)	-0.39 (-0.88; 0.09)	-0.51 (-1.12; 0.11)	-0.38 (-0.64; -0.12)
-0.28 (-0.79; 0.24)	0.03 (-0.44; 0.51)	CBT + AMBT	-0.05 (-0.75; 0.66)	-	-	-0.43 (-1.16; 0.30)	-
-0.20 (-0.76; 0.36)	0.11 (-0.47; 0.68)	0.08 (-0.48; 0.63)	EC	-	-	-	-
-0.57 (-0.84; -0.29)	-0.26 (-0.43; -0.08)	-0.29 (-0.78; 0.21)	-0.36 (-0.95; 0.22)	TAU	-	-0.02 (-0.77; 0.73)	-
-0.36 (-0.74; 0.01)	-0.06 (-0.42; 0.30)	-0.09 (-0.67; 0.50)	-0.16 (-0.81; 0.49)	0.20 (-0.18; 0.59)	Psychological placebo	-	-0.34 (-1.04; 0.35)
-0.75 (-1.28; -0.22)	-0.44 (-0.92; 0.04)	-0.47 (-1.01; 0.07)	-0.55 (-1.23; 0.14)	-0.18 (-0.67; 0.31)	-0.38 (-0.97; 0.21)	Attention placebo	-
-0.70 (-0.95; -0.45)	-0.39 (-0.61; -0.17)	-0.42 (-0.93; 0.09)	-0.50 (-1.08; 0.09)	-0.13 (-0.40; 0.13)	-0.33 (-0.71; 0.04)	0.05 (-0.47; 0.57)	WL

Note. $k = 44$, $m = 48$, $n = 3893$; effect size: Cohen's d (between-group effects after end of treatment); diagonal gives the treatments that were examined; upper triangle displays the pooled effect sizes of the direct comparisons available with 95% CIs; lower triangle contains the network meta-analysis effect sizes for each comparison with 95% CIs. AMBT = acceptance- and mindfulness-based treatments; CBT = cognitive behavioural therapy; CBT + AMBT = combination of CBT and AMBT; EC = enhanced care; TAU = treatment as usual; WL = wait-list.

Table 3*Treatment comparison estimates for anxiety at post-treatment*

AMBT	-	0.11 (-0.51; 0.73)	-0.92 (-1.38; -0.46)	-0.12 (-0.58; 0.34)	-	-0.42 (-0.72; -0.12)
-0.42 (-0.73; -0.11)	CBT	-	-0.15 (-0.33; 0.02)	0.19 (-0.76; 1.15)	-0.25 (-0.81; 0.31)	-0.25 (-0.55; 0.04)
0.11 (-0.51; 0.73)	0.53 (-0.16; 1.22)	EC	-	-	-	-
-0.61 (-0.93; -0.30)	-0.20 (-0.36; -0.03)	-0.73 (-1.42; -0.03)	TAU	-	0.00 (-0.67; 0.67)	-
-0.25 (-0.64; 0.15)	0.17 (-0.27; 0.61)	-0.36 (-1.10; 0.38)	0.37 (-0.09; 0.82)	Psychological placebo	-	-0.04 (-0.66; 0.57)
-0.63 (-1.21; -0.04)	-0.21 (-0.72; 0.30)	-0.74 (-1.59; 0.11)	-0.01 (-0.53; 0.50)	-0.38 (-1.05; 0.29)	Attention placebo	-
-0.54 (-0.81; -0.28)	-0.13 (-0.38; 0.13)	-0.66 (-1.33; 0.02)	0.07 (-0.22; 0.36)	-0.30 (-0.71; 0.12)	0.08 (-0.48; 0.65)	WL

Note. $k = 31$, $m = 35$, $n = 2795$; effect size: Cohen's d (between-group effects after end of treatment); diagonal gives the treatments that were examined; upper triangle displays the pooled effect sizes of the direct comparisons available with 95% CIs; lower triangle contains the network meta-analysis effect sizes for each comparison with 95% CIs. AMBT = acceptance- and mindfulness-based treatments; CBT = cognitive behavioural therapy; EC = enhanced care; TAU = treatment as usual; WL = wait-list.

Table 4*Treatment comparison estimates for perceived health status at post-treatment*

AMBT	-	-	0.09 (-0.86; 1.04)	0.65 (0.18; 1.12)	0.08 (-0.60; 0.77)	0.00 (-0.97; 0.97)	0.49 (0.10; 0.88)
0.22 (-0.10; 0.53)	CBT	-0.03 (-0.94; 0.89)	-	0.42 (0.21; 0.62)	0.59 (0.01; 1.18)	0.26 (-0.44; 0.95)	0.03 (-0.24; 0.31)
0.03 (-0.50; 0.56)	-0.19 (-0.69; 0.31)	CBT + AMBT	-0.03 (-0.71; 0.64)	-	-	0.89 (0.18; 1.59)	-0.15 (-1.13; 0.82)
0.03 (-0.62; 0.68)	-0.19 (-0.85; 0.47)	-0.00 (-0.58; 0.58)	EC	-	-	-	-
0.63 (0.31; 0.95)	0.41 (0.22; 0.61)	0.60 (0.08; 1.13)	0.60 (-0.07; 1.28)	TAU	0.04 (-0.88; 0.96)	-0.09 (-1.08; 0.89)	-
0.49 (0.03; 0.95)	0.27 (-0.16; 0.70)	0.46 (-0.18; 1.10)	0.46 (-0.30; 1.22)	-0.14 (-0.59; 0.31)	Psychological placebo	-	0.33 (-0.62; 1.28)
0.55 (0.04; 1.05)	0.33 (-0.15; 0.80)	0.52 (-0.01; 1.05)	0.52 (-0.20; 1.23)	-0.09 (-0.58; 0.41)	0.06 (-0.56; 0.68)	Attention placebo	-
0.33 (0.02; 0.63)	0.11 (-0.13; 0.35)	0.30 (-0.21; 0.81)	0.30 (-0.37; 0.97)	-0.30 (-0.60; -0.01)	-0.16 (-0.62; 0.30)	-0.22 (-0.72; 0.29)	WL

Note. $k = 60$, $m = 66$, $n = 6366$; effect size: Cohen's d (between-group effects after end of treatment); diagonal gives the treatments that were examined; upper triangle displays the pooled effect sizes of the direct comparisons available with 95% CIs; lower triangle contains the network meta-analysis effect sizes for each comparison with 95% CIs. AMBT = acceptance- and mindfulness-based treatments; CBT = cognitive behavioural therapy; CBT + AMBT = combination of CBT and AMBT; EC = enhanced care; TAU = treatment as usual; WL = wait-list.

Treatment Effects – Follow-Ups

For the short-term follow-up (up to 3 months posttreatment, mean duration of follow-up: 9.37 weeks, *SD*: 2.61), only a small subset of studies reported data, and the combination of CBT and AMBT could not be examined. CBT was not significantly more effective than WL in reducing somatic symptom severity ($k = 12$, $n = 763$, $m = 14$; $d = -0.39$, 95%CI -1.55 to 0.77) or depressive symptoms ($k = 12$, $n = 690$, $m = 14$, $d = -0.29$, 95%CI -0.95 to 0.37). AMBT did not significantly reduce somatic symptom severity compared to WL ($d = -0.43$, 95%CI -0.97 to 0.10), but were more effective than WL for depressive symptoms ($d = -0.55$, 95%CI -0.93 to -0.17). No significant effects were found for anxiety ($k = 8$, $n = 476$, $m = 10$). For perceived health status ($k = 15$, $n = 990$, $m = 17$), CBT ($d = -0.31$, 95%CI -1.05 to 0.43) and AMBT ($d = 0.14$, 95%CI -0.27; 0.56) were more effective than TAU but not WL (see online suppl. S7 for forest plots).

For the long-term follow-up (between 3 and 12 months posttreatment; mean duration of follow-up: 24.13 weeks, *SD*: 8.84), no treatment significantly reduced somatic symptom severity compared to WL ($k = 20$, $n = 2,627$, $m = 22$), though the data on direct comparisons to WL was limited ($k = 3$). However, both AMBT and CBT were more effective than TAU ($k = 14$). No significant differences were found between the active treatments, nonetheless, the combination of CBT and AMBT was not more effective than any control group ($k = 3$). None of the control groups was superior to any other control group (cf. online suppl. S8 for effect size tables at long-term follow-up), whereas attention placebo was not examined in any study providing long-term follow-up data. For depressive symptoms at long-term follow-up ($k = 15$, $n = 1,695$, $m = 15$), AMBT and CBT were both more effective than WL, but their combination was not. No control group was superior to others, while psychological and attention placebo were not included in the network. For anxiety ($k = 12$, $n = 1,528$, $m = 12$), only AMBT were more effective than WL, showing a large effect size. Additionally, AMBT were moderately superior to

CBT. The combination of both approaches as well as psychological and attention placebo were not analyzed due to insufficient data. For perceived health status at long-term follow-up ($k = 20$, $n = 2,646$, $m = 22$), both CBT and AMBT were more effective than WL, TAU, and psychological placebo, but not EC ($k = 2$). Attention placebo was not included in the network. There was no indication of differential treatment efficacy and none of the control groups were superior to one another.

For follow-ups longer than a year after end of treatment (mean duration of follow-up: 53.22 weeks, SD : 13.93), only $k = 11$ studies reported outcomes ($k = 10$ for somatic symptom severity, $k = 5$ for depression, $k = 5$ for anxiety, and $k = 10$ for perceived health status). Due to limited data and unconnected networks, these were not analyzed.

Sensitivity Analyses

When *treatment manuals* were *split*, for somatic symptoms, all active treatments (CBT, ACT, mindfulness-based treatments, and the combination of CBT and AMBT methods) were superior to WL for somatic symptoms, with no significant differences among them (smaller nodes like the unified protocol and positive psychology, as well as EC were excluded; see online suppl. S14.1). For depression, all active treatments were superior to WL, with ACT more effective than CBT ($d = -0.86$, 95%CI -1.27 to -0.45), MBT ($d = -0.84$, 95%CI -1.31 to -0.38), and the CBT-AMBT combination ($d = -0.89$, 95%CI -1.51 to -0.28). For anxiety, ACT ($d = -0.73$, 95%CI -1.17 to -0.30) and MBT ($d = -0.37$, 95%CI -0.69 to -0.04) were superior to WL. ACT was also more effective than CBT ($d = -0.59$, 95%CI -1.10 to -0.08). CBT was only superior to TAU ($d = -0.19$, 95%CI -0.35 to -0.02). Regarding perceived health status, ACT was more effective than WL, CBT ($d = 0.59$, 95%CI 0.07 to 1.10), and all control groups, with no difference between ACT and MBT or the CBT-AMBT combination.

Only 20 studies included low-intensity treatments (< 8 sessions), therefore, these were not analyzed separately. For *high-intensity treatments* (≥ 8 sessions), AMBT were no longer superior to CBT in treating depression ($d = -0.29$, 95%CI -0.60 to 0.03), but remained more effective for anxiety ($d = -0.48$, 95%CI -0.81 to -0.16). No condition was superior to WL for perceived health status (see online suppl. S14.2).

The sensitivity analysis only analyzing *face-to-face interventions*, i.e., excluding the self-guided or digital interventions (computer-/internet-/app-based treatments), showed no major differences overall (see online suppl. S14.3).

When only examining *somatic symptom disorder and related disorders*, the database was too small to carry out the network meta-analysis and receive meaningful results, while for the analyses examining the studies on *functional somatic syndromes*, the results were comparable to the results from the main analyses on all outcomes (see online suppl. S14.4).

Focusing on the studies that based inclusion on *clinical interviews or medical examinations* rather than cut-off scores, for somatic symptom severity, effects were descriptively slightly smaller on average, though no meaningful differences emerged. For depression, similar trends were observed, with a slightly lower number of effects appearing smaller on average than for somatic symptom severity. Anxiety outcomes were comparable to the main analysis, while perceived health status showed the most notable difference: the average effect for the comparison CBT vs. wait-list nearly doubled, though it remained statistically non-significant (see online suppl. S14.5).

For the sensitivity analysis using the *longest available follow-up* periods (mean duration of follow-up: 26.34 weeks, SD : 18.13), some differences to the long-term follow-up results arose: For somatic symptom severity ($k = 41$, $n = 4,456$), both CBT and AMBT were superior to WL. For anxiety ($k = 23$, $n = 2,070$), AMBT were no longer superior to

CBT. For perceived health status ($k = 43$, $n = 4,590$), only AMBT remained superior to WL, whereas CBT no longer showed superiority (see online suppl. S14.6).

The sensitivity analysis *comparing random effects vs. fixed effect model* for this NMA showed on average 1.5 to 2.5 larger standard errors for the random effects model (see online suppl. S14.7 for details).

Publication Bias

For somatic symptom severity at posttreatment, in the comparison-adjusted funnel plot (see online suppl. S15), the effect sizes of the comparisons seem to be symmetrically distributed. Further, Egger's test was not significant ($p = 0.35$), i.e., not indicating publication bias for the whole network. Similarly, the Egger's tests for the other outcomes at posttreatment were not significant either.

Discussion

The present study utilizes an extensive dataset, enabling a thorough analysis of the effects of various psychological treatments across multiple patient outcomes and time points. Compared to previous meta-analyses in the field, it draws on a significantly larger database. By applying a network meta-analytic approach, which integrates evidence from numerous studies, it allows for a more comprehensive comparison of treatment efficacy. This method combines direct comparisons from head-to-head trials with indirect comparisons across the broader network of studies, offering a more complete picture of available evidence. Additionally, this analysis covers a wider range of CBT-based treatments, with a particular focus on conventional CBT and acceptance- and mindfulness-based approaches, expanding upon the scope of prior meta-analyses [18, 122]. Our findings underscore the robust efficacy of CBT, which was more effective than most inactive and non-specific controls in reducing somatic symptom severity at posttreatment, showing moderate effects. For anxiety and perceived health status, CBT

was only more effective than TAU, but it outperformed both WL and TAU in treating depression. When comparing the estimated effect sizes from the network meta-analysis with pooled direct comparisons, the results were largely consistent.

AMBT were more effective than most control groups on all outcomes at posttreatment. While there were no direct comparisons between these treatments and CBT, indirect comparisons revealed no significant differences in reducing somatic symptoms, indicating similar efficacy. However, for comorbid psychopathology, AMBT showed a slight advantage over CBT in reducing depression and anxiety, though these effects were small and not consistent across sensitivity analyses. This study also found varying impacts on perceived health status: while CBT had a small effect over TAU but not WL, AMBT demonstrated moderate improvements compared to both control conditions. These findings align with a recent meta-analysis that reported significant effects on somatic symptom severity and depression, but no effects on anxiety, while the effects on perceived health status were not examined [122]. An earlier Cochrane review on non-pharmacological therapies for medically unexplained symptoms [13] found effects on somatic symptoms and (measures comparable to) perceived health, though it did not report benefits for depression or anxiety. Notably, this project's larger dataset, due to broader inclusion criteria concerning bodily distress and inclusion of recent clinical trials, provides more robust insights.

These findings suggest that CBT remains a highly effective treatment, particularly for somatic symptom severity. Its moderate effects in reducing somatic symptoms highlight its value as a core therapeutic option for bodily distress. It should be prioritized as a first-line intervention. However, its limited advantage for depression and anxiety may indicate the need for supplementing CBT with other therapeutic strategies, such as AMBT, which may enhance outcomes in these areas.

This project found no consistent differences between inactive and non-specific control groups. However, all active treatments were significant compared to TAU for all outcomes at posttreatment, unlike other control groups. No active treatment was significantly more effective than EC, but this was likely due to the limited data on EC ($k = 1$ to 3) and the corresponding wide confidence intervals, so these results should be interpreted with caution.

There are now several studies on the maintenance of treatment outcomes, particularly on somatic symptom severity and perceived health status. However, as few studies provide short-term follow-up data (up to 3 months), these results should be interpreted cautiously. Long-term follow-up results suggest sustained effects in several comparisons for both CBT and AMBT. While CBT was only superior to TAU in improving perceived health status at posttreatment, it showed superiority over multiple control groups in the long-term for this outcome. AMBT remained effective for depression, anxiety, and perceived health status at long-term follow-up, and continued to surpass CBT for anxiety. Additionally, AMBT consistently outperformed TAU and psychological placebo (while psychological placebo data were not available for depression and anxiety). Overall, both treatments maintained their efficacy compared to various control groups that account for more factors than WL alone [40]. That is, clinicians should consider both the long-term efficacy of CBT and the advantages of AMBT. The latter might be particularly useful for anxiety-focused treatment.

The treatments that combined conventional CBT manuals with acceptance or mindfulness – or supplemented AMBT with cognitive techniques – outperformed TAU at posttreatment in somatic symptom severity and perceived health status. These combination treatments were as effective as the other active interventions in the network for somatic symptom severity, depression, and perceived health status at posttreatment.

However, sensitivity analyses revealed that the effects of these combined treatments were not consistently robust, likely due to the limited data set ($k = 6$) and variations in treatment approaches and intensities. While acceptance and mindfulness techniques are not regularly used in CBT, they are compatible with the CBT framework, as evidenced by the studies in this project. That is, both CBT and AMBT share many common components and non-specific factors, differing mainly in their therapeutic emphasis [123]. Hence, the integration of CBT with acceptance- and mindfulness-based techniques appears promising. Clinicians should therefore consider CBT as a foundational treatment but remain open to integrating or augmenting it for anxiety where results for CBT may be less robust.

When dissecting the effects of AMBT, the mindfulness-based treatments and CBT showed comparable efficacy, which aligns with findings in depression research [124]. In contrast to results from a conventional meta-analysis on AMBT [18], in this network meta-analysis, ACT emerged as more effective than mindfulness-based treatments, particularly in reducing comorbid depression symptoms. This suggests that ACT may be the key driver behind the observed superiority of acceptance- and mindfulness-based approaches over conventional CBT for comorbid conditions. Additionally, ACT significantly improved patients' perceived health status compared to CBT, while AMBT as a whole did not show this advantage. This might also be attributable to ACT's transdiagnostic approach [125], which addresses core psychological processes that are common across various mental health conditions [126], including bodily distress, depression, and anxiety. Given the high rates of comorbidity among patients with bodily distress [127], ACT's focus on processes like experiential avoidance and cognitive fusion likely helps alleviate symptoms across multiple conditions simultaneously, improving overall treatment outcomes. By targeting both comorbid anxiety and depression, ACT enhances patients' quality of life, enabling them to engage more in meaningful activities

and improve their functional capacity, which is often compromised by chronic bodily distress. ACT's emphasis on emotionality and pursuing positive life goals [128] may further contribute to its efficacy, pointing to its potential in improving patients' perceived well-being. The differences between ACT and CBT in these outcomes might highlight potential gaps in conventional CBT manuals.

Limitations

There was a considerable variability in how interventions were delivered, particularly in terms of duration and intensity, which could influence outcomes and complicate the aggregation of results in the network meta-analysis. However, this issue was examined in various sensitivity analyses, which did not indicate major influences on the results, e.g., through inclusion of internet-based treatments in the analyses. Moreover, the studies' inconsistent definitions of control conditions could distort the relative efficacy of the interventions. This variability was particularly evident in the wide range of definitions for TAU, EC, and psychological placebo. Additionally, most studies focused on posttreatment outcomes, which may not fully capture the long-term efficacy of treatments. As a result, the findings may overestimate the benefits of treatments that produce rapid improvements but fail to sustain these gains over time. Especially, the findings on the short-term follow-up are limited due to a reduced data base. However, the current findings at least suggest that the positive effects of the therapies are largely long-lasting.

The high prevalence of RoB across most studies suggests a limited reliability of the findings. Studies classified as having *some concerns* present a moderate risk, indicating that while their results might be less biased than those with a *high risk*, caution is still warranted when interpreting their outcomes. This assessment underscores the need for careful consideration of RoB in evaluating the included studies. These findings align with

previous research in the field [10, 18], where conventional psychotherapeutic trials often receive higher RoB ratings due to a lack of blinding, particularly when subjective outcome measures are used. In these trials, participants, who serve as raters, cannot be blinded to the treatments when the control condition differs significantly from the active intervention. Furthermore, less than half of the studies was preregistered, with some preregistered only retrospectively. Hence, selective reporting of outcomes could not be assessed in most cases.

When comparing the potential benefits of treatments, it is essential to interpret the findings with caution given the current state of research. The evidence base for ACT is considerably smaller than for conventional CBT, which has been extensively studied over several decades, resulting in a substantial body of evidence supporting its efficacy across various conditions [129], as also seen in this project. That is, ACT, as a newer approach, has fewer studies and less longitudinal data available. This disparity may contribute to publication bias and researcher allegiance, potentially inflating ACT's effect sizes [130]. Despite the promising findings in this project, potential overestimation of effects should be considered. While Egger's test did not indicate publication bias, unpublished null or negative results may exist and grey literature was not systematically included [131]. Furthermore, there were no studies that based their inclusion on the most recent classifications in the field, like somatic symptom disorder or bodily distress disorder. That is, generalization to these disorders needs to be tested in future research.

Future Research

Future research should focus on core outcome domains and examine the equivalence between CBT and acceptance- and mindfulness-based interventions, building on existing work. Investigating the mechanisms of action can unveil the processes driving therapeutic effects [132]. With larger data sets, meta-analyses could employ more precise classification of interventions, such as component network meta-analyses [133]. Additionally, exploring predictors and moderators through individual patient data network meta-analysis [134] could inform personalized interventions for bodily distress. Future RCTs should prioritize comparing treatments in sufficiently powered trials [135] while advancing the understanding of psychotherapy mechanisms, incorporating nuanced outcome measures, that reflect the multifaceted nature of bodily distress and patient experiences [31]. Moreover, non-specific control groups (e.g., attention placebo, supportive therapy) should be used to better isolate the specific effects of the therapeutic interventions from nonspecific factors like therapeutic attention and placebo effects [40]; here, the implementation of improved rationales, such as sham-mindfulness interventions could also help to enable double-blinding in psychotherapy trials [136]. Long-term follow-up assessments are necessary to improve the understanding of sustained treatment efficacy, and attrition rates should be systematically analyzed to gauge treatment acceptability. For example, while CBT has been shown to be acceptable in a subset of patients with chronic fatigue syndrome [10], it is important to examine acceptability across a broader range of syndromes within bodily distress.

Conclusion

This project contributes to the existing literature by providing a comprehensive assessment of the absolute and relative efficacy of CBT and AMBT for bodily distress. Hence, the findings can inform evidence-based practice, shape treatment guidelines, and guide the selection of appropriate interventions for adults experiencing bodily distress. Both CBT and AMBT are effective in addressing bodily distress symptoms. While mindfulness-based treatments and CBT show comparable efficacy, ACT may offer superior benefits in reducing comorbid anxiety and depression, as well as enhancing perceived health status in these patients. Overall, these findings suggest that CBT is highly effective for reducing somatic symptoms and should be prioritized as a first-line treatment, but AMBT present promising treatment approaches, potentially offering particular advantages for certain patient groups. Especially, for comorbid depression and anxiety, implementing ACT or integrating or augmenting CBT with acceptance-based therapies may enhance outcomes.

Statements

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature. That is, the investigators of the primary trials report positive ethics votes for these studies and the participants gave their informed consent to the investigators of the primary trials. Consequently, there are no ethical requirements that this network meta-analysis would violate.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

F.M.B. and A.M. developed the research question and conceptual background for this work and formulated the search terms. F.M.B. performed the literature search and data extraction (with the help of research assistants) while A.M. was consulted to resolve disagreement if necessary. F.M.B. performed data analyses and developed the outline. F.M.B. drafted the manuscript for publication with input from A.M.; A.M. provided regular feedback on the progress and results. Both are responsible for the content of the publication.

Data Availability Statement

The data that support the findings of this project are openly available in OSF at <https://osf.io/zhk3s/> (DOI: 10.17605/OSF.IO/ZHK3S).

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8. Discussion

8.1 Summary and Interpretation of the Findings

This dissertation aimed to systematically evaluate the efficacy of conventional CBT and “third wave” approaches for adults with bodily distress through three meta-analytic projects. By employing both conventional meta-analysis and NMA, it provides a comprehensive overview of the psychotherapeutic landscape, examining not only absolute efficacy but also differential effects and treatment acceptability. Together, the three sub-projects offer an integrative assessment of treatment efficacy across the broader spectrum of bodily distress, with a specific focus on the sub-syndrome of CFS.

The *first* study confirmed that cognitive behavioral approaches for CFS – a particularly controversial treatment for this condition (Vink & Vink-Niese, 2022) – remain effective, particularly in reducing fatigue and associated psychological distress. Furthermore, high treatment adherence rates suggest that patients generally tolerate and complete CBT interventions once initiated. These findings support previous meta-analytic (Castell et al., 2011; Kuut et al., 2023; Malouff et al., 2008; Price et al., 2008) and naturalistic (Adamson et al., 2020) research positioning CBT as one of the most established treatments for CFS, although future studies should further investigate its long-term efficacy. Furthermore, moderator analyses indicated that CBT showed stronger effects on fatigue when compared to inactive rather than non-specific controls. Higher therapy dosage and greater number of sessions were associated with larger improvements in fatigue and perceived health status, respectively, whereas neither therapy setting nor treatment duration were significant moderators. Baseline fatigue severity predicted higher non-completion and dropout rates, but other patient characteristics did not moderate adherence outcomes.

The *second* study expanded the diagnostic scope to bodily distress while redirecting the intervention focus toward “third wave” treatments. Consequently, it

demonstrated that “third wave” treatments – namely, MBCT, MBSR, and ACT – effectively reduce somatic symptom severity in adults with bodily distress. The therapies also improved secondary outcomes such as depression, anxiety, perceived health status, mindfulness, and psychological flexibility. Further, moderator analyses did not reveal significant differences in efficacy between mindfulness- and acceptance-based treatments, nor across inactive versus non-specific controls, sub-syndromes, treatment intensity, therapy dose, or number of sessions. This corroborates the overall results from the main analyses. Thus, the findings align with growing evidence that “third wave” treatments enhance psychological flexibility and mindfulness skills, which may alleviate the burden of somatic symptoms (Frostholm & Rask, 2019). Hence, these interventions represent promising avenues for clinical practice.

Building on this, the *third* study found that CBT and “third wave” treatments (specifically acceptance- and mindfulness-based treatments) are equally effective in reducing somatic symptoms, while “third wave” treatments may have greater effects on anxiety and depression at post-treatment. At short-term follow-up, evidence was limited across outcomes. At long-term follow-up, however, both CBT and “third wave” treatments were more effective than TAU in reducing somatic symptom severity, while only “third wave” treatments significantly reduced anxiety and outperformed CBT on this outcome. Data beyond one year were too sparse to allow firm conclusions. Sensitivity analyses showed that individually analyzing the effect of the included “third wave” treatments revealed advantages of ACT over CBT for depression, anxiety, and perceived health status, while mindfulness-based treatments demonstrated smaller but consistent effects. Only focusing on high-intensity treatments attenuated some differences, and restricting analyses by delivery format, diagnosis, or diagnostic method did not alter the overall results. These findings provide an important contribution to the literature by enabling indirect comparisons between treatment types, something not yet addressed in

head-to-head trials in the field of bodily distress. Although neither a project in mental and somatic disorders (or stress reactions; Öst, 2014), nor a recent NMA in depression research (Schefft et al., 2023) found differential effects between CBT and “third wave” treatments, the findings from this NMA project suggest a potential advantage for “third wave” approaches. Especially using ACT rationales within treatment may help more effectively address comorbid psychopathology in addition to reducing somatic symptom severity.

The main aim of this dissertation was to systematically evaluate CBT and “third wave” approaches for adults with bodily distress. Across the three meta-analytic projects, the findings demonstrate that both approaches are effective compared to control conditions, with largely comparable outcomes, while also providing insights into moderators of efficacy and patterns of treatment acceptance. That is, the projects provide a deeper understanding of treatment efficacy in bodily distress, addressing the question raised by Paul (1967) on which therapeutic approach works best for a given individual under specific conditions. In summary, both CBT and “third wave” treatments are effective from sub-syndromes like CFS to the broad spectrum of bodily distress incorporating various conditions. The consistency of effects across various analyses within the projects supports their general efficacy and applicability in improving patient outcomes. Both CBT and “third wave” approaches demonstrated small to moderate effects, which, while modest in size, are clinically meaningful given the chronicity and burden of bodily distress syndromes. Importantly, these effects were observed consistently across multiple domains, including somatic symptoms, psychological comorbidities, and perceived health status, indicating broad therapeutic benefits rather than isolated improvements. Considering that many of the included interventions were relatively brief in duration, these findings suggest that even time-limited psychotherapies can yield significant gains for patients, underscoring their practical value in routine care.

Positioning “Third Wave” Treatments within the Cognitive Behavioral Tradition.

Building on the findings summarized above, the broader question arises whether “third wave” approaches represent a true paradigm shift in psychotherapy or simply an evolution of existing behavioral treatments. Although “third wave” treatments introduce novel therapeutic emphases – particularly on mindfulness and acceptance – their efficacy profiles appear largely continuous with those of conventional CBT. The largely comparable efficacy of both treatment families, as demonstrated in the NMA, supports the notion that these approaches differ more in focus and technique than in fundamental function. While differences between conventional CBT and “third wave” treatments are sometimes overemphasized (Arch & Craske, 2008), there is a substantial overlap in techniques used in both approaches (Hofmann & Münch, 2013). Many of the strategies employed in “third wave” treatments, such as acceptance and mindfulness, are not regularly used in conventional CBT but are compatible with its broader theoretical framework. Particularly, ACT, dialectical behavior therapy, and metacognitive therapy are closely related to CBT (Hofmann & Asmundson, 2008; van Dam et al., 2018), suggesting that these approaches may be more complementary than fundamentally distinct. From a conceptual standpoint, the evidence from this dissertation aligns with findings that challenge the notion of discrete “waves” in cognitive behavioral psychotherapy. The distinctions between conventional CBT and “third wave” treatments are still being debated, as there is no clear-cut definition of what constitutes the latter. Accordingly, the approaches grouped under this label constitute a heterogeneous family of interventions, with different models of psychopathology and mechanisms of change. Some developers of therapies classified as “third wave” (such as metacognitive therapy and dialectical behavior therapy) have even questioned the validity of this classification (Hofmann & Asmundson, 2008). While others argue that the “third wave” constitutes a revolution in psychotherapy (Hayes, 2004), the findings from the NMA support that

“third wave” treatments are an extension of prior cognitive behavioral approaches (Heidenreich & Michalak, 2013) rather than a paradigm shift (Hofmann & Asmundson, 2008). That is, “third wave” interventions seem to reflect an adaptive evolution of CBT principles (Heidenreich & Michalak, 2013), broadening the scope of behavioral and cognitive techniques to target experiential avoidance, metacognitive awareness, and context sensitivity (Hayes, 2004).

Nonetheless, the concept of “third wave” provided a useful framework for capturing recent therapeutic developments and integrating them into the present analyses, even though some approaches commonly included under this label – such as dialectical behavior therapy and metacognitive therapy – have not yet been systematically evaluated in RCTs for bodily distress. In summary, it may be appropriate to view CBT as a family of interventions that includes both traditional techniques and newer adaptations, such as ACT and mindfulness-based treatments (Hofmann & Asmundson, 2008). This perspective underscores the potential for an integrative approach to psychotherapy, where clinicians can flexibly draw from both conventional cognitive behavioral, acceptance-, and mindfulness-based techniques to tailor treatment to individual patient needs.

8.2 Critical Evaluation and Limitations

The projects in this dissertation build the foundation for a rigorous comprehensive, transparent, and reliable database of psychotherapy trials for bodily distress: all included studies met stringent methodological criteria, with each project preregistered and both data and analytical code openly available. Due to the shared conceptual frameworks across the three projects, some RCTs were included in more than one analysis (see Appendix A). To reduce selection bias, facilitate future research, and support the ongoing advancement of evidence-based psychological interventions, the data collected within the dissertational projects will be publicly accessible via a meta-analytic

database of psychotherapy trials (www.metapsy.org), where it can be interactively analyzed (Cuijpers et al., 2022).

Basing the analyses on RCT data ensured the highest level of evidence for evaluating treatment efficacy (Hariton & Locascio, 2018). Although RCTs are sometimes considered less reflective of routine clinical practice (Mulder et al., 2018), this approach allowed to incorporate pragmatic designs examining diverse patient populations that enhance the results' applicability to real-world settings. The geographic coverage of included studies further enriched global relevance, though most originated from high-income Western countries, reflecting a common regional bias (e.g., in depression, Cuijpers et al., 2018). The array of settings employed in the studies underscores the adaptability of mental health interventions. Moreover, RCTs remain the gold standard for establishing treatment effects (Hariton & Locascio, 2018), with their practical relevance underestimated when held to overly stringent standards (Backmann, 2017).

Notwithstanding the extensive nature of the database created, a key outcome of systematic reviews and meta-analytic integration is not only to evaluate the evidence base – what has been studied, how rigorously, and how robust effects are across different variables – but also to identify the limitations of the existing data and highlight areas for further research and improvement at multiple levels: Despite considerable efforts to identify all relevant primary studies, the risk remains that the efficacy of treatments is somewhat overestimated as not all RCTs from the field could be included in the projects. Several studies were excluded because effect sizes could not be calculated, despite otherwise meeting eligibility criteria (up to $k = 33$ in the *third* project when $k = 74$ were included). Although primary authors were contacted to provide relevant data, not all responded, particularly for older trials. However, some of these trials exhibited indications of unreliable data handling (van Noorden, 2023), such as reporting means that

exceeded the maximum possible score on a given scale. As a result, these studies would have been excluded regardless of data availability.

Additionally, the number of studies providing direct comparisons between certain conditions was limited. In particular, some crucial nodes – such as CBT and “third wave” treatments – were not compared directly in any of the included studies. While the NMA approach was chosen to address this gap by allowing for indirect comparisons, the resulting effect size estimations may be less precise (Glenny et al., 2005).

Moreover, short- and long-term follow-up data were not consistently assessed across the included studies. This constrains the ability to assess the sustainability of treatment effects over time (Kline et al., 2018), including the potential for delayed symptom improvement. The ability to track long-term benefits would be particularly useful for understanding whether certain interventions yield more durable outcomes. Similarly, although the meta-analytic techniques applied attempted to account for variability, the lack of standardized outcome measures remains a challenge. Future studies employing more consistent measures, e.g., consistently applying the recommendations for the field by the *European research network to improve diagnosis, treatment and health care for patients with persistent somatic symptoms* (EURONET-SOMA, Rief et al., 2017), would help strengthen the evidence base. Additionally, outcomes measuring intervention-specific processes like mindfulness, psychological inflexibility or acceptance are not assessed by default in CBT trials. Therefore, these outcomes cannot be analyzed beyond “third wave” treatment approaches. That is, based on the available evidence, it remains unclear whether “third wave” treatments work through specific factors that other approaches like conventional CBT do not tackle. Other potentially relevant outcomes, such as unwanted negative treatment effects, could not be analyzed at all due to insufficient data reported in primary studies. This is a crucial limitation, as psychotherapy – while generally beneficial – is not

without side effects, including symptom deterioration or the emergence of new problems (Forand et al., 2013).

To ensure that the database is as comprehensive as possible but also entails comparable trials that can reasonably be used as a basis for aggregation, some studies were not incorporated into the analyses due to their lack of comparability with purely psychological treatments: ten RCTs included psychotherapy within multidisciplinary treatment settings, such as combinations of psychotherapy and physiotherapy. This exclusion, while methodologically necessary, might also limit the breadth of insights gained from the projects.

Although inclusion was limited to psychological treatments, the overall observed heterogeneity between studies possibly challenges the generalizability of findings. While the synthesis of diverse studies generally enhances the generalizability of findings, it also introduces variability that may affect the interpretation of results. That is, differences in the psychotherapy setting – such as individual versus group formats, delivery by specialized versus general practitioners, or variations in treatment duration – could act as confounding variables influencing treatment outcomes that could not be examined using the available methods for aggregate-level data for any project. For example, the psychotherapy setting may act as a confounding factor, as “third wave” interventions were predominantly delivered in group formats, whereas regarding treatment durations, particularly brief interventions like the included one-session-treatments were more often based on CBT. Further complicating the interpretation of results is the potential for treatment overlap. Some CBT interventions may have included mindfulness components, and vice versa, making it difficult to delineate the unique effects of each approach (cf. Sverre et al., 2022). Additionally, relying on aggregate data prevented an examination of potential collider bias within the trials (Lamp & MacKinnon, 2024). For instance, patients with bodily distress who volunteer for psychotherapy trials may represent a

selective subgroup of the broader population with bodily distress. As a result, the findings may be less generalizable to individuals who do not seek or qualify for participation in such studies. Furthermore, the studies encompassed different conceptualizations of bodily distress, ranging from organ system-specific syndromes (e.g., IBS) to categories like medically unexplained symptoms, which are not limited to a specific organ system. Therefore, the generalizability across different types of bodily distress might also be limited. That is, despite the rigorous inclusion criteria regarding study designs, the different eligible delivery formats and disorders might have introduced between-study heterogeneity. Although moderator analyses were not feasible in the NMA due to statistical constraints – limiting the assessment of potential moderators that might have explained heterogeneity – sensitivity analyses across all three projects did not identify any single factor as responsible for the observed heterogeneity.

Moreover, most included studies had a high risk of bias, which is mostly attributable to the increased level of difficulty with regard to the blinding of trials in psychotherapy research (Gold et al., 2017). However, after finalization of the projects presented in this dissertation, an adapted version of the risk of bias tool 2.0 was developed to adjust the ratings in psychotherapy research to the methodological specifics and challenges in psychotherapy research (The Metapsy Collaboration, 2025). This might improve the overall risk of bias assessment for the included methodologically rigorous studies conducted in line with established conventions of psychotherapy research. That is, this new approach could result in a clearer distinction between well-conducted studies and those with methodological limitations that might compromise the validity of their findings.

Another potential bias in psychotherapy research, not covered by the risk of bias assessment, is researcher allegiance: studies conducted by proponents of a specific therapeutic approach may unintentionally introduce bias in study design, implementation,

and interpretation, leading to inflated effect sizes (Leykin & DeRubeis, 2009). Over time, as treatments are examined in more diverse and rigorously controlled studies, effect sizes often decrease (Ioannidis, 1998). In the projects presented, while the findings are promising, the evidence base for “third wave” treatments was relatively small. While there were no indications of publication bias in any of the projects, this does not eliminate the possibility that null or negative findings remain unpublished and could therefore not be included in this project (Page, Sterne, et al., 2021). Ultimately, while ACT demonstrates promise and offers unique benefits for treating bodily distress, these findings should be interpreted with caution. The smaller and potentially biased evidence base necessitates further rigorous research to validate early positive results and to determine how “third wave” treatments compare to conventional CBT over the long term to ensure that potentially resulting clinical recommendations are based on the most comprehensive and robust evidence available.

In sum, both CBT and “third wave” approaches show positive effects in the treatment of bodily distress. The presented findings are not solely reflected by the aggregated effects themselves but the results were also scrutinized through systematic consideration of publication bias, risk of bias, and heterogeneity rather than by reporting mean effects alone. Nevertheless, some methodological aspects remain to be improved, and future work may benefit from advancements, such as adapting the risk of bias assessment to psychotherapy research and excluding low-quality studies.

8.3 Practical Implications

The results of this dissertation have several practical implications for the treatment of bodily distress. By advancing evidence on the efficacy of different therapeutic approaches, this contributes to the ongoing efforts to improve the management and well-being of individuals with bodily distress. While newer therapeutic approaches continue to emerge, the results reaffirm that CBT remains an effective and widely applicable

treatment option for bodily distress. Cognitive behavioral interventions for bodily distress have been adapted to address the diverse manifestations of these syndromes, yet they share several common features. These include addressing maladaptive symptom beliefs and illness-related anxiety, reducing functional impairment, and managing frequent comorbidities, all within a biopsychosocial treatment framework (Löwe et al., 2024). Notably, the included treatments in these projects were relatively brief, with an average duration of approximately 9 sessions ($SD = 4.53$), which underscores their feasibility in clinical practice. Current evidence suggests that CBT can be delivered in different formats (e.g., individual, group, or guided self-help), though further research is needed to determine the comparative efficacy and sustainability of these modalities.

Clinicians should particularly pay attention to the sustained efficacy of CBT, not only for bodily distress as a broad category but also for specific sub-syndromes such as CFS. Despite ongoing debates regarding the appropriateness of CBT for CFS (e.g., Vink & Vink-Niese, 2022), its demonstrated efficacy and relatively high adherence rates suggest that it should continue to be considered a valuable treatment option. Clinicians should continue to offer CBT as a viable treatment option for CFS, recognizing its high acceptability and capacity to support symptom management. Guidelines should reflect the current evidence base and, rather than downgrading CBT as in the recent NICE update (Flottorp et al., 2022), acknowledge it as the most consistently supported intervention for improving patient symptoms and functioning. Nonetheless, guidelines should also take into account that more severely impaired CFS patients may be more likely to discontinue treatment. Given that higher treatment intensity was associated with greater symptom improvement, these patients might benefit from extended or more intensive therapeutic formats, possibly in combination with acceptance facilitating or motivational interventions to enhance engagement (Baumeister et al., 2015).

For the whole spectrum of bodily distress, findings on CBT highlight that treatment effects, although modest in size, are consistent and clinically relevant across a range of conditions. This consistency strengthens the empirical foundation for recommending CBT as a core component of multidisciplinary treatment strategies, in alignment with current international standards of care (e.g., Hausteiner-Wiehle et al., 2013; NCCMH, 2018; Roenneberg et al., 2019).

At the same time, given the demonstrated efficacy of “third wave” approaches, clinicians should consider integrating therapies such as ACT and mindfulness-based treatments into treatment protocols for patients with bodily distress. These therapies have shown reliable absolute effects when compared to inactive and non-specific controls, suggesting their efficacy. That is, these results may warrant inclusion of acceptance- and mindfulness-based treatments in treatment guidelines, as has already begun to occur in some contexts (e.g., Roenneberg et al., 2019).

While both “third wave” and conventional CBT, are effective for treating bodily distress, ACT may be beneficial for patients who struggle with comorbidities like anxiety and depression, as findings indicate they may provide more robust outcomes in this regard compared to CBT. ACT might offer unique benefits through its focus on acceptance, mindfulness, psychological flexibility, values-driven action, and reduction of experiential avoidance. While CBT might enhance acceptance in CFS (Brooks et al., 2011), it was implemented as disorder-specific treatments in most included studies. However, ACT’s transdiagnostic rationale may explain its larger efficacy regarding comorbid psychopathology. Moving to transdiagnostic approaches to mental health problems could therefore help patients (Dalglish et al., 2020). Looking at bodily distress from a transdiagnostic perspective emphasizes focusing on the common features across its different nuances, rather than treating each condition separately. This might also support

a more unified treatment approach, in line with the *lumping* approach to classification (Chalder & Willis, 2017).

In conclusion, the “third wave” may not supplant CBT but rather enrich its clinical repertoire, particularly in treating patients with high psychological comorbidity or entrenched patterns of experiential avoidance. Hence, it is recommended that future guidelines incorporate this aspect to ensure optimal patient care.

8.4 Prospects

The findings of this dissertation highlight several important directions for future research. Future studies should incorporate direct head-to-head comparisons of active treatments and extended follow-up periods to assess the durability of treatment effects. Furthermore, future studies should systematically employ comprehensive assessment strategies that capture the various facets targeted and influenced by psychotherapeutic interventions (Rief et al., 2017). In the same line, the innovative approach on operationalizing treatment adherence at different stages within clinical trials, introduced in the *first* study, could be beneficial to compare results between different approaches, across meta-analytic projects. To facilitate this, future studies should report treatment refusal, premature treatment termination, and the average number of sessions completed in a transparent and standardized format.

Furthermore, understanding the factors that enhance or limit treatment efficacy is essential for refining interventions and tailoring them to individual patient needs (van der Feltz-Cornelis et al., 2018). Examining whether core features of “third wave” treatments – such as mindfulness and psychological flexibility – are also influenced by other treatments like CBT could clarify whether these outcomes are unique to “third wave” approaches or reflect shared therapeutic mechanisms. Conversely, studying cognitive and behavioral processes, such as catastrophizing or illness beliefs, within “third wave” interventions can help situate their effects within established

cognitive-behavioral models. Overall, future research should strive to investigate the mechanisms through which both CBT and “third wave” treatments reduce bodily distress, considering both treatment-specific and common factors (Cuijpers et al., 2019). While the meta-analytic findings suggest an average efficacy for patients, the precise pathways through which they reduce somatic and psychological symptoms or improve adherence remain underexplored. Examining these factors could help optimize treatments and inform the debate between a transdiagnostic (*lumping*) approach, such as ACT, versus more tailored (*splitting*) interventions, clarifying whether streamlined or subtype-specific strategies are most effective for bodily distress. Information on tailoring interventions to individual patient profiles could not only be gathered from large clinical trials but also using individual patient data meta-analyses (Riley & Fisher, 2021). To translate these findings into clinical practice, it is crucial to develop and test implementation strategies that can make these treatments more accessible and adaptable to different healthcare settings.

Finally, expanding meta-analytic methods beyond CBT and “third wave” treatments to include psychodynamic and pharmacological treatments would provide a more comprehensive understanding of their relative efficacy, ultimately informing more nuanced and effective treatment guidelines. By addressing these research gaps, future studies can contribute to the ongoing improvement of psychological interventions for bodily distress, ensuring that treatment approaches continue to evolve in both efficacy and acceptability. Consequently, the data resulting from the presented projects are designed as living meta-analytical database that will be regularly updated with an expanding thematic scope, which is planned to be incorporated into a meta-analytical research domain (Cuijpers et al., 2022; Maas genannt Bermpohl & Martin, 2026).

8.5 Conclusions

This dissertation provides a comprehensive meta-analytical evaluation of CBT and “third wave” treatments for adults with bodily distress. The key findings suggest that both conventional CBT and “third wave” treatments (ACT, MBCT, and MBSR) are effective in reducing somatic symptom burden while also improving mental health outcomes. These results reinforce the potential for psychological interventions to provide meaningful relief for patients with bodily distress, addressing both somatic symptoms and comorbid psychological symptoms.

CBT remains a cornerstone treatment for conditions like CFS, showing robust effects in reducing fatigue and comorbid psychopathology while improving the perceived health status, with high levels of treatment adherence. At the same time, “third wave” treatments emerge as promising alternatives, particularly for addressing comorbid depression and anxiety, where they may offer unique advantages. While both treatment modalities are supported by evidence, the findings highlight the importance of tailoring interventions to individual patient needs to optimize treatment outcomes.

This dissertation also underscores the importance of meta-analytical methods in synthesizing evidence from existing research, offering a more comprehensive perspective on treatment efficacy. The use of NMA allowed for indirect comparisons between CBT and “third wave” treatments, generating insights not yet available from direct comparison trials. By bridging these gaps in research, this methodological approach provides clinicians and researchers with nuanced guidance on which therapies may be best suited for different patient populations. Despite these contributions, certain limitations such as high heterogeneity and the lack of long-term follow-up data highlight the need for future research. Direct comparative trials between CBT and “third wave” treatments, as well as studies examining the long-term sustainability of treatment effects, are essential for refining these treatment approaches. Additionally, a deeper exploration of the

mechanisms underlying the psychological treatment of bodily distress and the development of personalized treatment approaches will be crucial for advancing the field.

In conclusion, this dissertation contributes to the growing body of evidence supporting psychological treatments for bodily distress and emphasizes the value of integrating diverse therapeutic approaches to address these conditions. By focusing on both efficacy and acceptability, this work helps guide clinicians in making informed, evidence-based decisions that can enhance patient outcomes in bodily distress.

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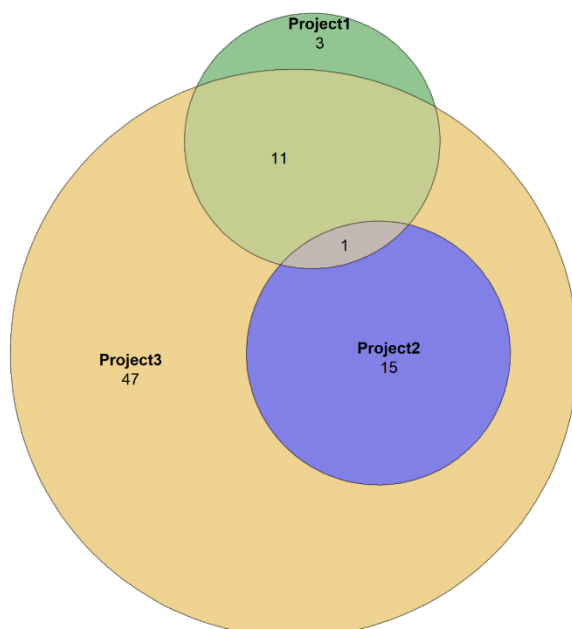
Appendix A

Study Overlap between Projects

Twelve studies from *project 1* as well as all studies from *project 2* were also incorporated into *project 3*. One study (Rimes & Wingrove, 2013) was included in all projects, as it examined MBCT for CFS – an intervention classified as “third wave” treatment but incorporating numerous CBT techniques. However, three studies from *project 1* were not fully aligned with the other projects. Sharpe et al. (1996) only provided data on the acceptance outcomes and was therefore excluded from the NMA on efficacy, while Deale et al. (1997) and Jason et al. (2007) utilized relaxation groups that were not included in the other projects. These discrepancies arose from the specific focus of *project 1* on acceptance of treatments, which primarily assessed the intervention groups rather than control groups. Hence, the inclusion criteria for control groups were slightly broadened in this project.

Figure S1

Study-overlap between the projects



Note. Project1 = meta-analysis on CBT in chronic fatigue syndrome; Project2 = meta-analysis on “third wave” treatments in bodily distress; Project3 = network meta-analysis on CBT and “third wave” treatments in bodily distress.

Appendix B

Appendix – Study 1

1. Eligible Diagnostic Criteria

The following criteria were considered eligible for inclusion:

- Holmes Criteria [1]
- Oxford criteria [2]
- Fukuda definition/Centers for Disease Control and Prevention (CDC) definition [3]
- Canadian consensus criteria [4]
- international consensus criteria [5]
- NICE guidelines [6]
- ICD-10 [7]: Neurasthenia (F48.0), unspecified Chronic fatigue (R53.82), ME/postviral fatigue syndrome (G.93.3)
- Systemic Exertion Intolerance Disease [8, 9]

2. Search Strategy

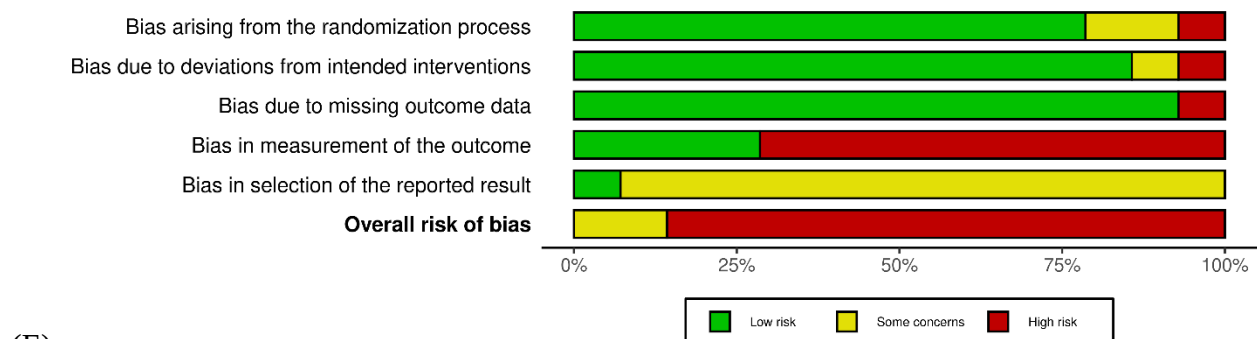
Exemplary search algorithm for PubMed:

("fatigue syndrome, chronic" [MeSH] OR "chronic fatigue syndrome" [All Fields] OR "fatigue syndrome*" [All Fields] OR CFS [All Fields] OR "ME/CFS" [All Fields] OR "CFS/ME" [All Fields] OR "psychogenic fatigue" [All Fields] OR "myalgic encephalomyelitis" [All Fields] OR "myalgic encephalopath*" [All Fields] OR "encephalopath*" [All Fields] OR "benign myalgic encephalomyelitis" [All Fields] OR "postviral fatigue syndrome*" [All Fields] OR "unspecified chronic fatigue" [All Fields] OR "post-infectious fatigue syndrome*" [All Fields] OR "chronic fatigue immune dysfunction syndrome*" [All Fields] OR "neurasthenia" [All Fields] OR "psychasthenia" [All Fields] OR "systemic exertion intolerance*" [All Fields] OR "post-exertional malaise"[All Fields]) AND (cbt [All Fields] OR "cognitive behavioral therap*" [All Fields] OR "cognitive behavioural therap*" [All Fields] OR "cognitive behavioral treatment*" [All Fields] OR "cognitive behavioural treatment*" [All Fields] OR "cognition therap*" [All Fields] OR "cognition treatment*" [All Fields] OR "cognitive therap*" [All Fields] OR "cognitive treatment*" [All Fields] OR "cognitive restructuring" [All Fields] OR (cognitive AND "perceptual change*") OR "cognitive reappraisal" [All Fields] OR "exposure therap*" [All Fields] OR "behavior modification*" OR "behaviour modification*" OR "resource activation" [All Fields] OR ("problem?solving" AND (therap* OR treatment*)) OR "behavioral activation" [All Fields] OR "behavioural activation" [All Fields] OR "behavioral activation therap*" [All Fields] OR "behavioural activation therap*" [All Fields] OR ("third wave" AND (therap* OR treatment*)) OR mindful* [All Fields] OR MBT [All Fields] OR MBCT [All Fields] OR MBSR [All Fields] OR (acceptance AND commitment) OR (dialectic* AND (behavioural OR behavioral)) OR DBT [All Fields] OR "metacognitive therap*" [All Fields] OR "metacognitive treatment*" [All Fields] OR "meta?cognitive therap*" [All Fields] OR "meta?cognitive treatment*" [All Fields] OR MCT [All Fields] OR ((Schematherap* OR "schema therap*") AND Young) OR "emotion?regulation skills training*" [All Fields] OR "emotion?regulation training*" [All Fields] OR "unified protocol*" OR "compassion focused therap*" [All Fields] OR "compassionate mind training*" [All Fields] OR "well-being therap*" [All Fields] OR "functional analytic psychotherap*" [All Fields] OR "positive psychotherap*" [All Fields] OR "integrative behavioural couples therap*" [All Fields] OR "integrative behavioural couple therap*" [All Fields] OR "mode deactivation therap*" [All Fields] OR "assertiveness training" [All Fields] OR ("compassion-focused" [All Fields] OR "compassion-focussed" [All Fields]) AND (therapy [SH] OR therapies [All Fields] OR therapy [All Fields] OR therap*[All Fields] OR therapis*[All Fields] OR Therapeutics [All Fields] OR treatment*[All Fields])) OR "solution-focused therap*" [All Fields] OR "self-control therap*" [All Fields] OR "self-control training*" [All Fields] OR "self control therap*" [All Fields] OR "self control training*" [All Fields])

3. Risk of Bias Assessment

Figure S1

Risk of bias ratings for fatigue at post-treatment



(E)

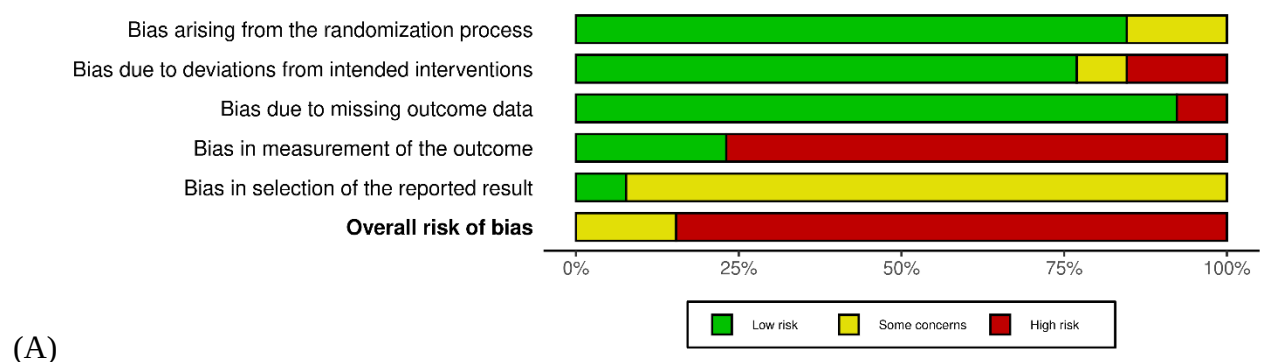
		Risk of bias domains					Overall
		D1	D2	D3	D4	D5	
Study	Deale et al., 1997	+	+	+	+	-	-
	Friedberg et al., 2013	+	+	+	+	-	-
	Gotaas et al., 2021	+	+	+	×	-	×
	Huibers et al., 2004	+	+	+	×	-	×
	Janse et al., 2018	-	+	+	×	-	×
	Jason et al., 2007	+	×	×	+	-	×
	Knoop et al., 2008	+	+	+	×	-	×
	Milrad et al., 2019	×	+	+	+	-	×
	O'Dowd et al., 2020	+	+	+	×	-	×
	Prins et al., 2001	+	+	+	×	-	×
	Rimes & Wingrove, 2013	+	-	+	×	-	×
	Sharpe et al., 1996	+	+	+	×	-	×
	White et al., 2011	+	+	+	×	+	×
	Wiborg et al., 2015	-	+	+	×	-	×

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
High
Some concerns
Low

(F)

Note. A: summary plot; B: traffic light plot.

Figure S2*Risk of bias ratings for perceived health status at post-treatment*

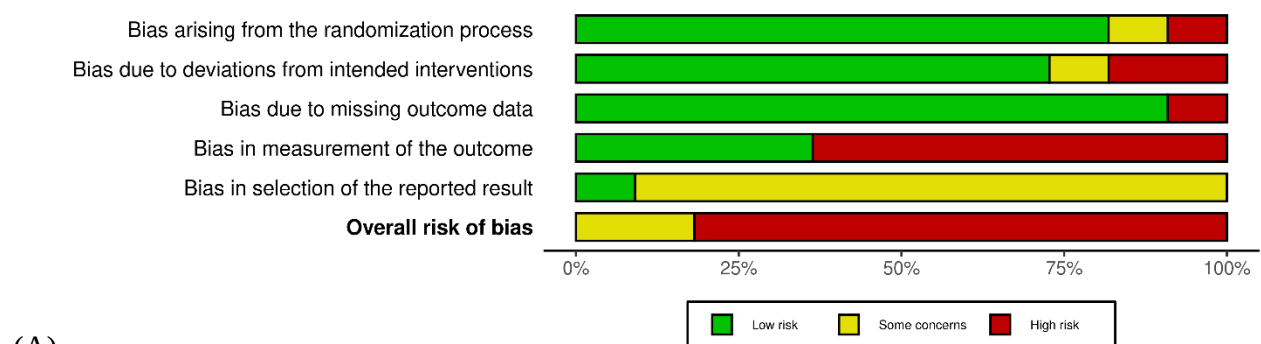
(B)

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
study	Deale et al., 1997	+	+	+	+	-	-
	Friedberg et al., 2013	+	+	+	+	-	-
	Gotaas et al., 2021	+	+	+	×	-	×
	Huibers et al., 2004	+	+	+	×	-	×
	Janse et al., 2018	-	+	+	×	-	×
	Jason et al., 2007	+	×	×	+	-	×
	Knoop et al., 2008	+	+	+	×	-	×
	O'Dowd et al., 2006	+	×	+	×	-	×
	O'Dowd et al., 2020	+	+	+	×	-	×
	Prins et al., 2001	+	+	+	×	-	×
	Rimes & Wingrove, 2013	+	-	+	×	-	×
	White et al., 2011	+	+	+	×	+	×
	Wiborg et al., 2015	-	+	+	×	-	×

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
High (red X)
Some concerns (yellow -)
Low (green +)

Note. A: summary plot; B: traffic light plot.

Figure S3*Risk of bias ratings for depression at post-treatment*

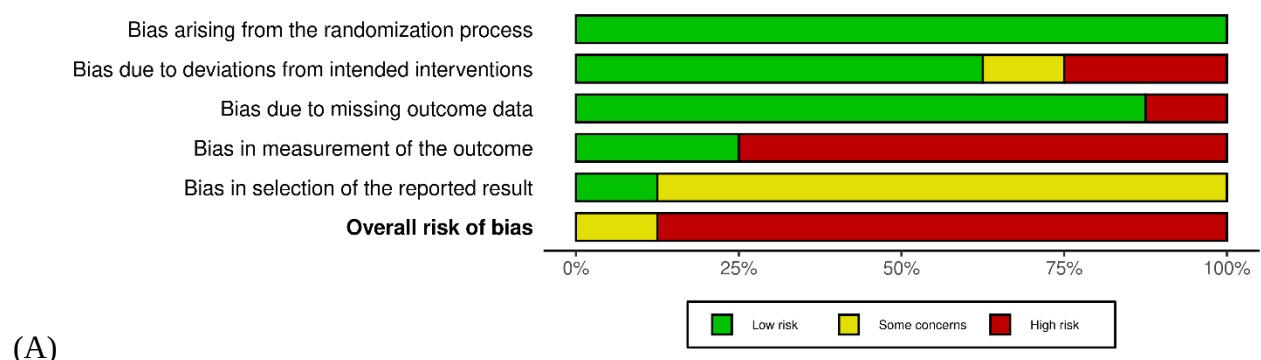
(B)

Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Deale et al., 1997	+	+	+	+	-	-
Friedberg et al., 2013	+	+	+	+	-	-
Gotaas et al., 2021	+	+	+	×	-	×
Jason et al., 2007	+	×	×	+	-	×
Milrad et al., 2019	×	+	+	+	-	×
O'Dowd et al., 2006	+	×	+	×	-	×
O'Dowd et al., 2020	+	+	+	×	-	×
Rimes & Wingrove, 2013	+	-	+	×	-	×
Sharpe et al., 1996	+	+	+	×	-	×
White et al., 2011	+	+	+	×	+	×
Wiborg et al., 2015	-	+	+	×	-	×

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement:
High (red X)
Some concerns (yellow -)
Low (green +)

Note. A: summary plot; B: traffic light plot.

Figure S4*Risk of bias ratings for anxiety at post-treatment*

(B)

	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Friedberg et al., 2013	+	+	+	+	-	-
Gotaas et al., 2021	+	+	+	×	-	×
Jason et al., 2007	+	×	×	+	-	×
O'Dowd et al., 2006	+	×	+	×	-	×
O'Dowd et al., 2020	+	+	+	×	-	×
Rimes & Wingrove, 2013	+	-	+	×	-	×
Sharpe et al., 1996	+	+	+	×	-	×
White et al., 2011	+	+	+	×	+	×

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
High
Some concerns
Low

Note. A: summary plot; B: traffic light plot.

4. R Packages

We used the packages {meta} [10], {metafor} [11], and {dmetar} [12] to aggregate effect sizes and compute associated analyses, and {tidyverse} [13] to visualize data in R version 4.2.1 [14]. For additional functions, we used the packages {esc} [15], and {car} [16]. Furthermore, data was imported using {readxl} [17]. To depict the risk of bias assessment, the package {robvis} [18] as well as the corresponding web application (<https://mcguinlu.shinyapps.io/robvis/>) were utilized.

5. Study Characteristics

Table S1

Study Characteristics regarding acceptance

Study	Con- ditions	<i>n</i>	Drop-out definition	Prop. drop- outs	Prop. treatment refusal	Reasons treatment refusal	Prop. non- completion	Reasons non-completion	Prop. average sessions completed
Deale et al., 1997	CBT	30					0.10 [0.02; 0.27]	Found it ineffective (<i>n</i> = 3), felt too ill to attend as an outpatient (<i>n</i> = 1), improved and wanted no further treatment (<i>n</i> = 1)	
	Psy plac	30						Too ill to continue attending (<i>n</i> = 1), no reason (<i>n</i> = 1), found the relaxation exercises overly tiring (<i>n</i> = 2)	
Friedberg et al., 2013	CBT	37		0.23 [0.10; 0.42]			0.19 [0.08; 0.35]	Too much work to do in study, didn't feel that the type of treatment was appropriate, no longer interested, "unknown" for those who did not return phone calls	
	Att plac	38							
Gotaas et al., 2021	CBT	78		0.21 [0.12; 0.32]	0.01 [0.00; 0.07]		0.23 [0.82; 0.93]	Due to fatigue (<i>n</i> = 3), poor economy (<i>n</i> = 2), psychosocial strain (<i>n</i> = 2), long distance to treatment centre (<i>n</i> = 2), lack of motivation for the treatment (<i>n</i> = 4), change of therapist (<i>n</i> = 1), current infection (<i>n</i> = 1), need of further psychiatric evaluation (<i>n</i> = 1)	
	WL	80							

Study	Con- ditions	<i>n</i>	Drop-out definition	Prop. drop- outs	Prop. treatment refusal	Reasons treatment refusal	Prop. non- completion	Reasons non-completion	Prop. average sessions completed
Huibers et al., 2004	CBT	76	Not completing CBT	0.28 [0.18; 0.40]	0.06 [0.02; 0.15]			Too busy/ work resumption (<i>n</i> = 6), not satisfied (<i>n</i> = 5), psychiatric complications (<i>n</i> = 2), unknown reason (<i>n</i> = 7)	0.88 [0.39; 0.99]
	TAU	75	Not completing post assessment						
Janse et al., 2018	CBT	160 ^a	Opening all modules + emailing fortnightly	0.31 [0.24; 0.39]	0.06 [0.03; 0.11]		0.88 [0.82; 0.93]		
	WL	80	Not completing post assessment						
Jason et al., 2007	CBT	29	Completing < 4 sessions						0.77 [0.48; 0.92]
	Psy plac	28	Completing < 4 sessions						
Knoop et al., 2008	CBT	85			0.20 [0.12; 0.30]				
	WL	86							
Milrad et al., 2019	CBT	75		0.05 [0.01; 0.13]					0.93 [0.54; 0.99]
	Psy plac	75							
O'Dowd et al., 2006	CBT	52						Moved away (<i>n</i> = 2), work pressures (<i>n</i> = 1), dropped out following an argument (<i>n</i> = 1), transport problems (<i>n</i> = 1), unable to attend owing to a bereavement (<i>n</i> = 2)	
	TAU	51						Withdrew from the study (<i>n</i> = 3), on holiday (<i>n</i> = 1), unable to attend (<i>n</i> = 1)	

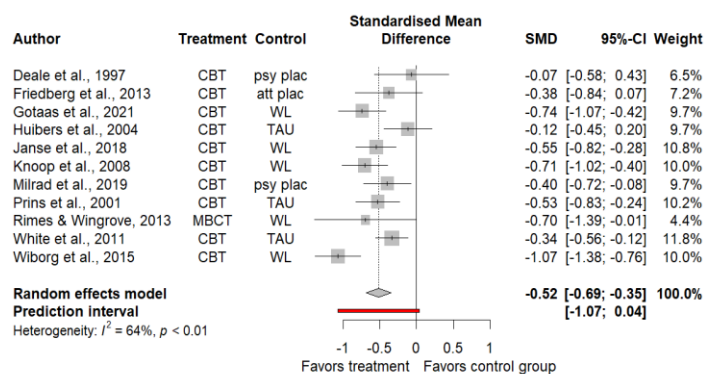
Study	Con- ditions	<i>n</i>	Drop-out definition	Prop. drop- outs	Prop. treatment refusal	Reasons treatment refusal	Prop. non- completion	Reasons non-completion	Prop. average sessions completed
O'Dowd et al., 2020	CBT	28			0.39 [0.22; 0.59]		0.41 [0.18; 0.67]	Did not relate to the therapeutic model, disliked telephone consultations, found the concept of self-reflection challenging	
Prins et al., 2001	TAU	16							
	CBT	93	Formally withdrawing CBT	0.28 [0.18; 0.39]	0.11 [0.05; 0.19]				
	TAU	91	Not attending assessments						
Rimes & Wingrove, 2013	MBCT	18	“Discontinued MBCT”	0.06 [0.00; 0.29]	0.06 [0.00; 0.27]	Withdrew due to family illness (<i>n</i> = 1)		Did not like group nature of MBCT (<i>n</i> = 1)	0.81 [0.45; 0.96]
	WL	19	Not completing post assessment						
Sharpe et al., 1996	CBT	30	No dropouts reported	0.00 [0.00; 0.12]	0.00 [0.00; 0.12]		0.00 [0.00; 0.12]		
	TAU	30							
White et al., 2011	CBT	161	Completing < 10 sessions	0.11 [0.06; 0.17]	0.02 [0.00; 0.05]				
	TAU	160	Completing < 3 sessions						
Wiborg et al., 2015	CBT	136	“Discontinued intervention”	0.15 [0.09; 0.22]	0.12 [0.07; 0.18]				
	WL	68	Not completing post assessment						

Note. Att plac = attention placebo; Average proportions of sessions completed = (average number of sessions completed) / (total number of sessions); CBT = cognitive behavioural therapy; Drop-Outs = primary authors' definition of drop-out: (*n* participants dropping out according to authors' definition) / (*n* participants starting intervention); *n* = number of participants allocated to each group; Non-completion = prop. of participants who started treatment and completed at least one session: (*n* participants not completing all sessions) / (*n* participants starting intervention); Psy plac = psychological placebo; TAU = treatment as usual; WL = wait-list.

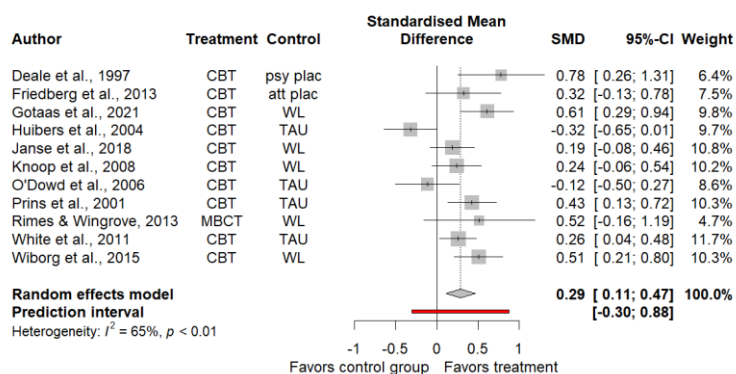
^a two intervention groups (ICBT with feedback on demand & ICBT with protocol-driven feedback) were merged for conducting the analyses.

Figure S5

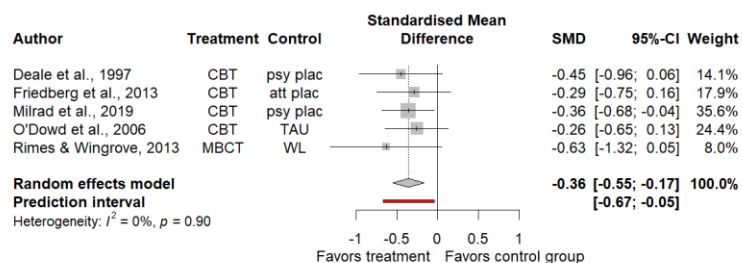
Forest plots – Post-treatment



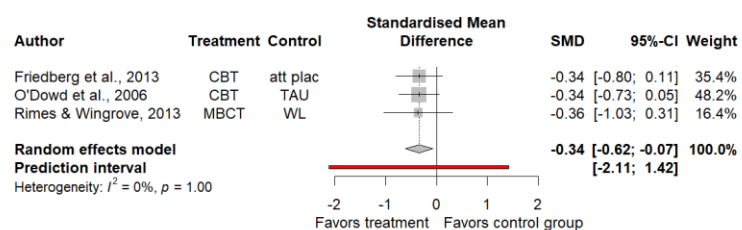
(A)



(B)

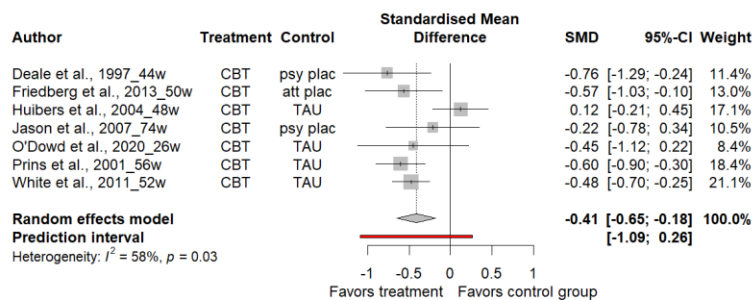


(C)

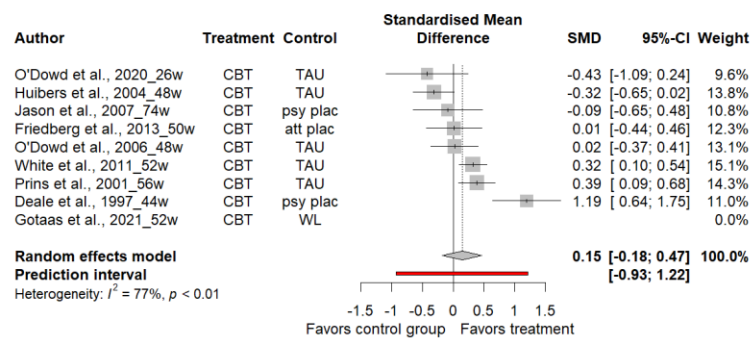


(D)

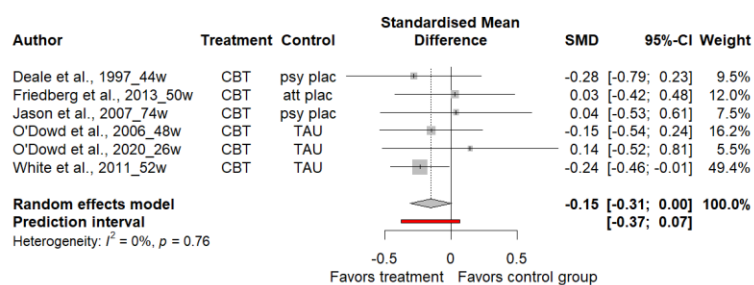
Note. A: fatigue at post-treatment; B: perceived health status at post-treatment; C: depression at post-treatment; D: anxiety at post-treatment. Note: For perceived health status positive effects indicate efficacy of the treatments, for all other outcomes negative effects indicate efficacy of the treatments

Figure S6*Forest plots – Long-term follow-up*

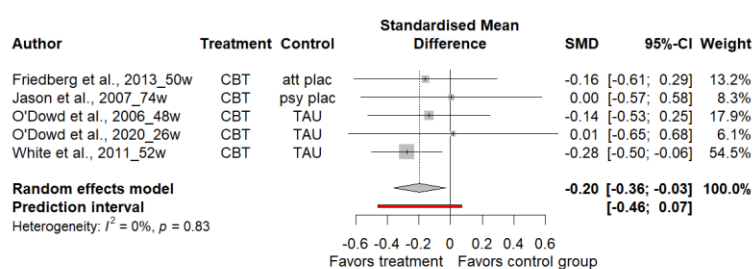
(A)



(B)

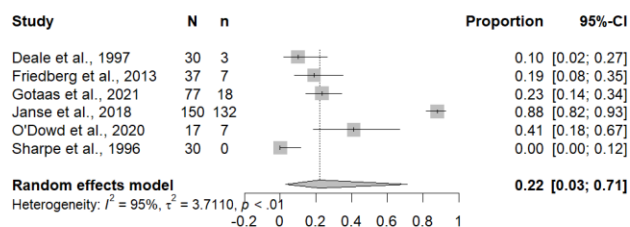


(C)

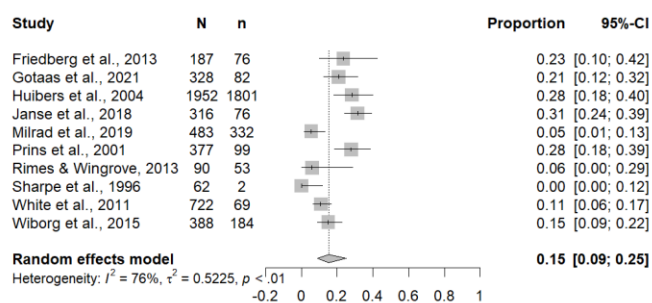


(D)

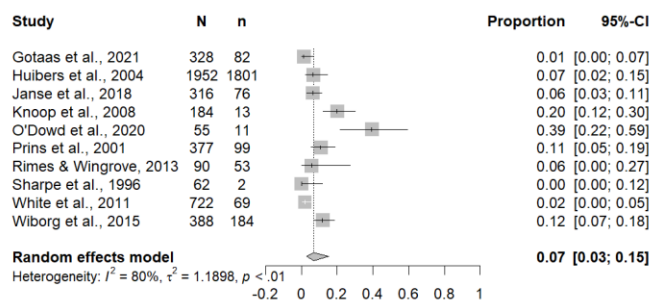
Note. A: fatigue at long-term follow-up; B: perceived health status at long-term follow-up; C: depression at long-term follow-up; D: anxiety at long-term follow-up. Note: For perceived health status positive effects indicate efficacy of the treatments, for all other outcomes negative effects indicate efficacy of the treatments.

Figure S7*Forest plots – Acceptance (proportions in intervention groups)*

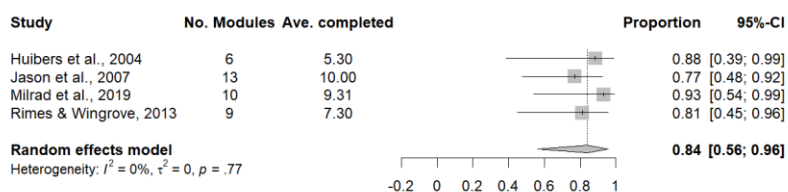
(A)



(B)

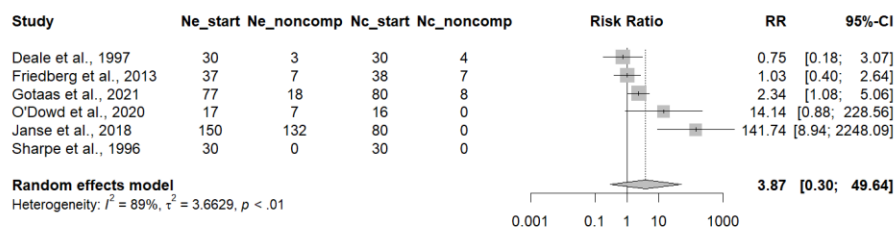


(C)

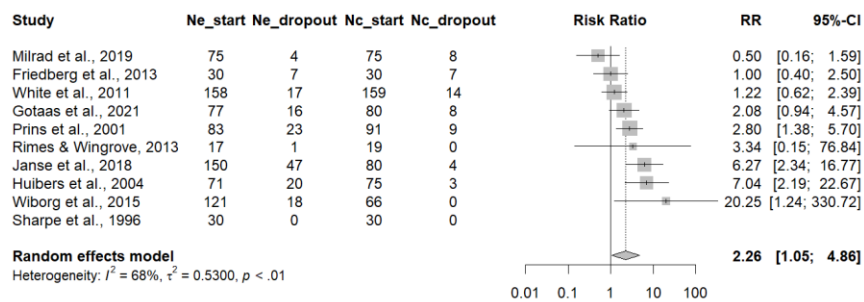


(D)

Note. A: non-completion; B: drop-out; C: treatment refusal; D: average proportion of sessions completed.

Figure S8*Forest plots – Acceptance (relative risks)*

(A)



(B)

Note. A: non-completion; B: drop-out.

6. Outcome Measures

Table S2

List of outcome measures

Study	Fatigue	Depression	Anxiety	Perceived Health Status
Deale et al., 1997	CFQ/CFS	BDI		MOS
Friedberg et al., 2013	FSS	BDI	BAI	SF-36-PF
Gotaas et al., 2021	CFQ/CFS	HADS-D ^a	HADS-A ^a	SF-36-PF
Huibers et al., 2004	CIS			SF-36-PF
Janse et al., 2018	CIS			SF-36-PF
Jason et al., 2007	FSS ^a	BDI-II ^a	BAI ^a	MOS ^a
Knoop et al., 2008	CIS			SF-36-PF
Milrad et al., 2019	FSI	CES-D		
O'Dowd et al., 2006		HADS-D	HADS-A	SF-36-PF
O'Dowd et al., 2020	CFQ/CFS ^a	HADS-D ^a	HADS-A ^a	SF-36-PF ^a
Prins et al., 2001	CIS			EQ-5D
Rimes & Wingrove, 2013	CFQ/CFS	HADS-D	HADS-A	PF-10
Sharpe et al., 1996	NRS ^a	HADS-D ^a	HADS-A ^a	
White et al., 2011	CFQ/CFS	HADS-D ^a	HADS-A ^a	SF-36-PF
Wiborg et al., 2015	CIS			SF-36-PF

Note. BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; BDI-II = Beck Depression Inventory-II; CES-D = Center for Epidemiologic Studies Depression Scale; CFQ/CFS = Chalder Fatigue Scale; CIS = Checklist Individual Strength – Fatigue subscale; EQ-5D = EuroQol Five-Dimensional Questionnaire; FSI = Fatigue Symptom Inventory; FSS = Fatigue Severity Scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety; HADS-D = Hospital Anxiety and Depression Scale – Depression; MOS = Medical Outcomes Study Short-Form General Health Survey physical functioning scale (previous version of the SF-36); PF-10 = Physical Functioning scale; SF-36-PF = Short Form Health Survey – Physical Functioning Subscale.

^a no effect sizes could be calculated at post-treatment due to missing values

7. Results Moderator Analyses – Meta-regressions

Table S3

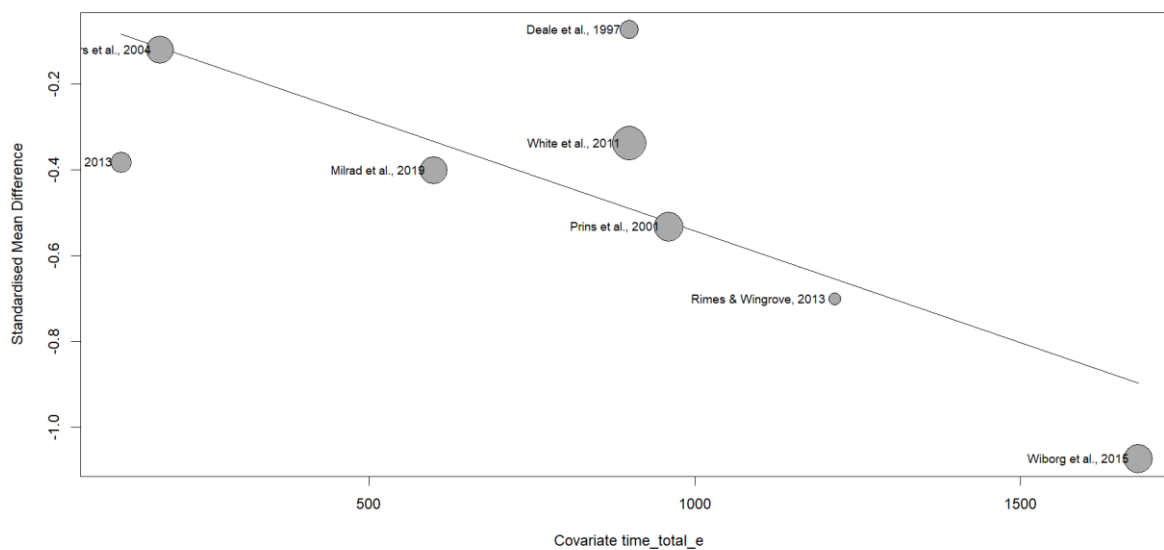
Meta-regression analyses for therapy dosage

Outcome	$\tau_{unexplained}^2$	I^2	R^2	$p_{moderator}$	Regression weight	Intercept
Fatigue	0.01	17.37%	91.17%	0.0003	-0.0005	-0.02
Perceived Health Status	0.06	63.91%	33.38%	0.10	0.0004	-0.05
Depression	0	0.00%	0.00%	0.66	-0.0001	-0.27
Anxiety	0	0.00%	0.00%	0.99	-0.00	-0.34
Non-completion	0.12	25.55%		0.13	-0.0025	-0.68
Drop-out	0.52	79.51%		0.40	-0.0005	-1.47
Ave. prop. sessions	0	0.00%		0.77	-0.0004	1.96

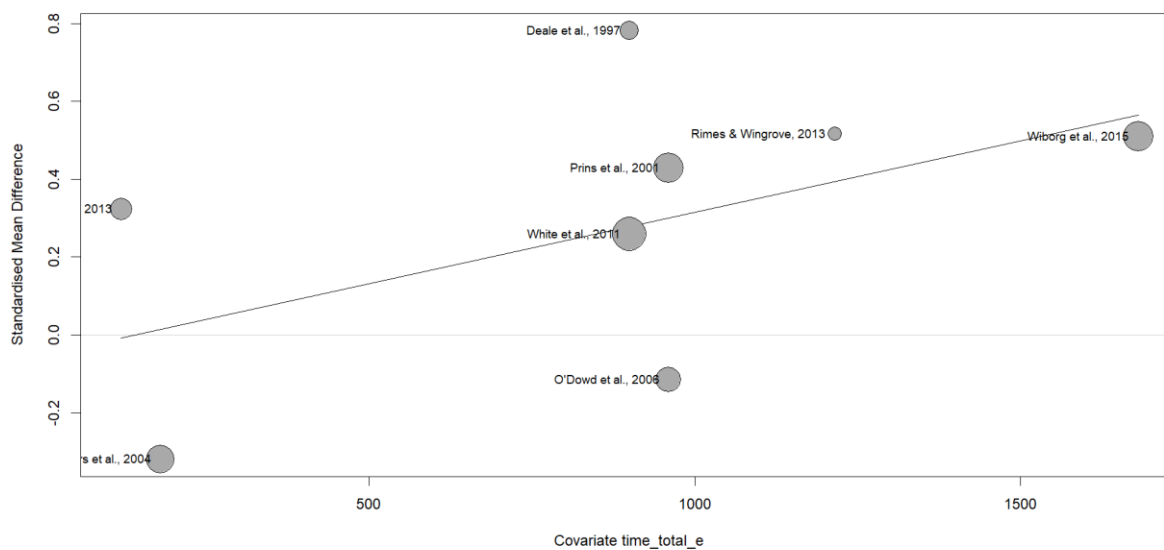
Note. Effect on efficacy outcomes at post-treatment; $\tau_{unexplained}^2$ = estimated amount of residual heterogeneity; I^2 = residual heterogeneity/unaccounted variability; R^2 = amount of heterogeneity accounted for (could only be calculated for efficacy outcomes)

Figure S9

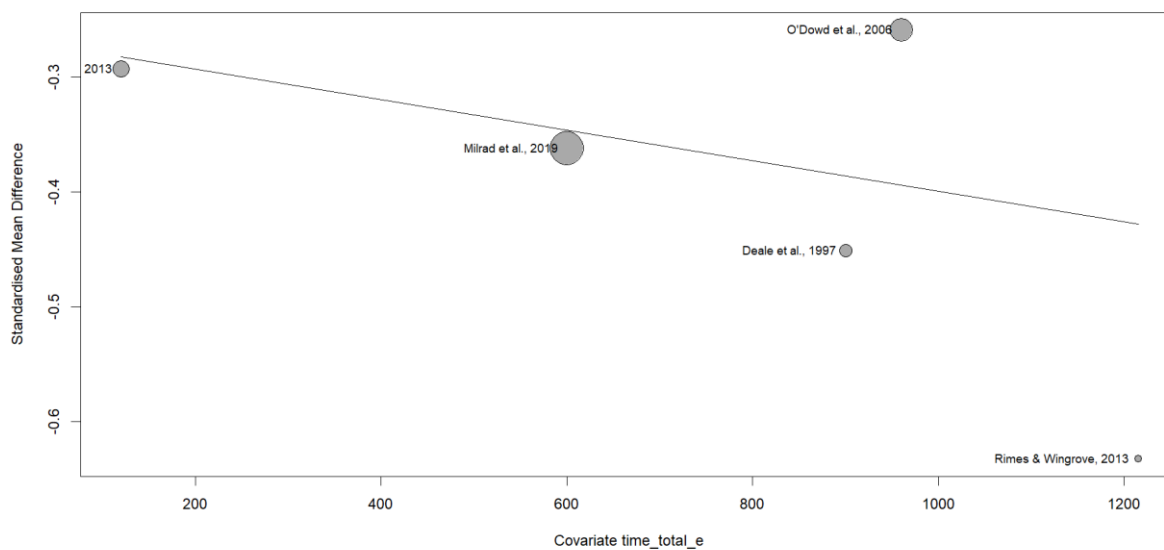
Bubble plots – meta-regression analysis for therapy dosage (total time of therapy in minutes)



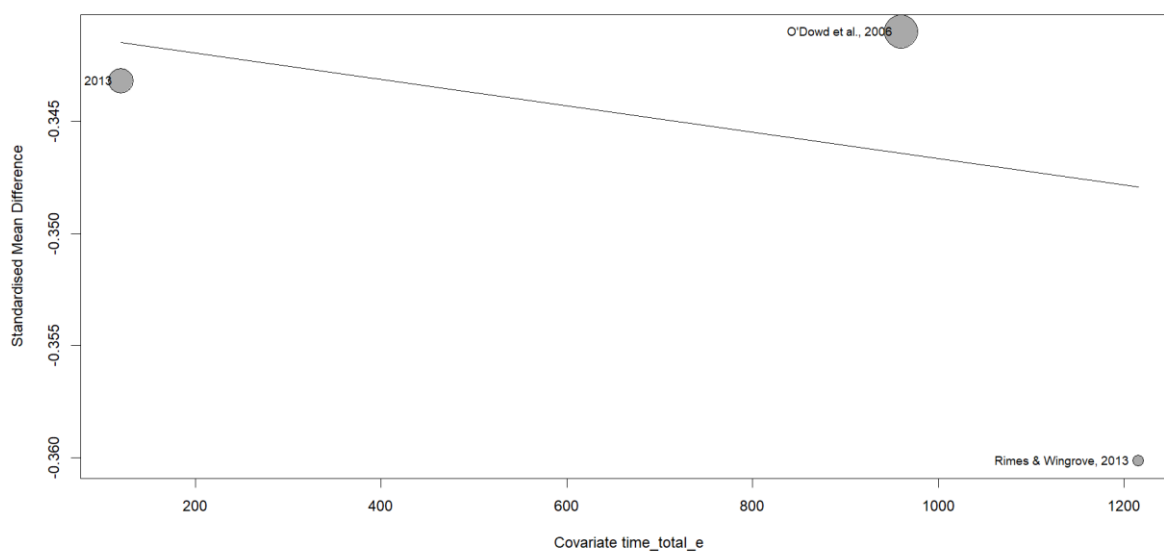
(A)



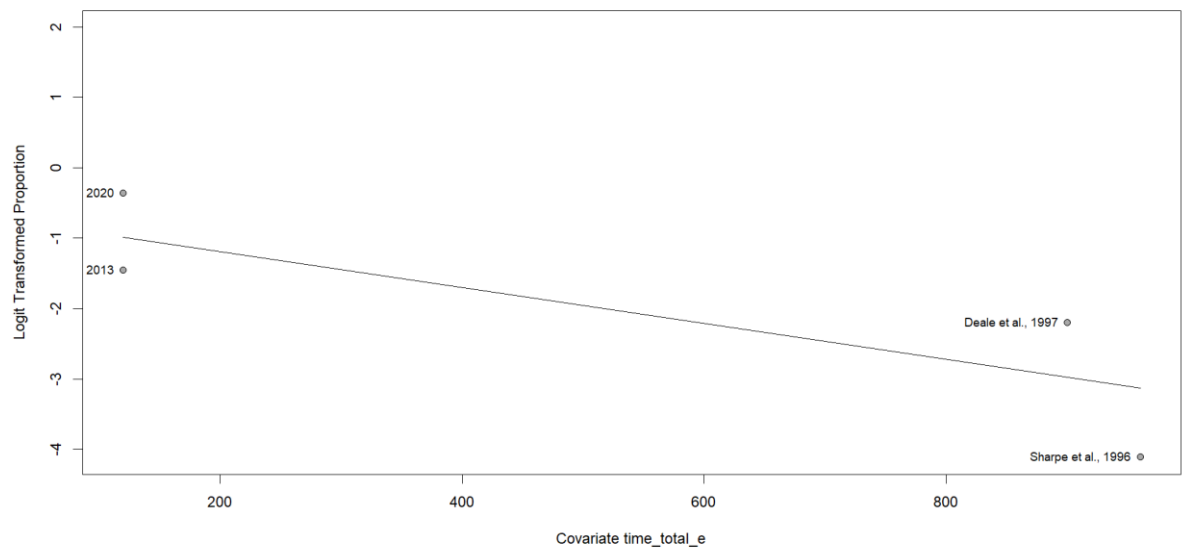
(B)



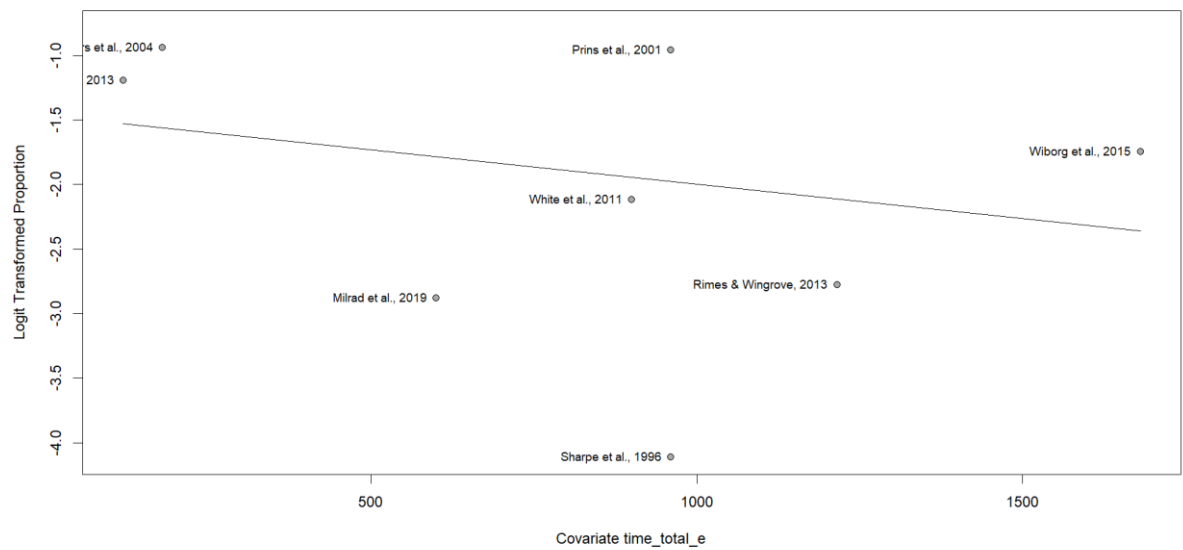
(C)



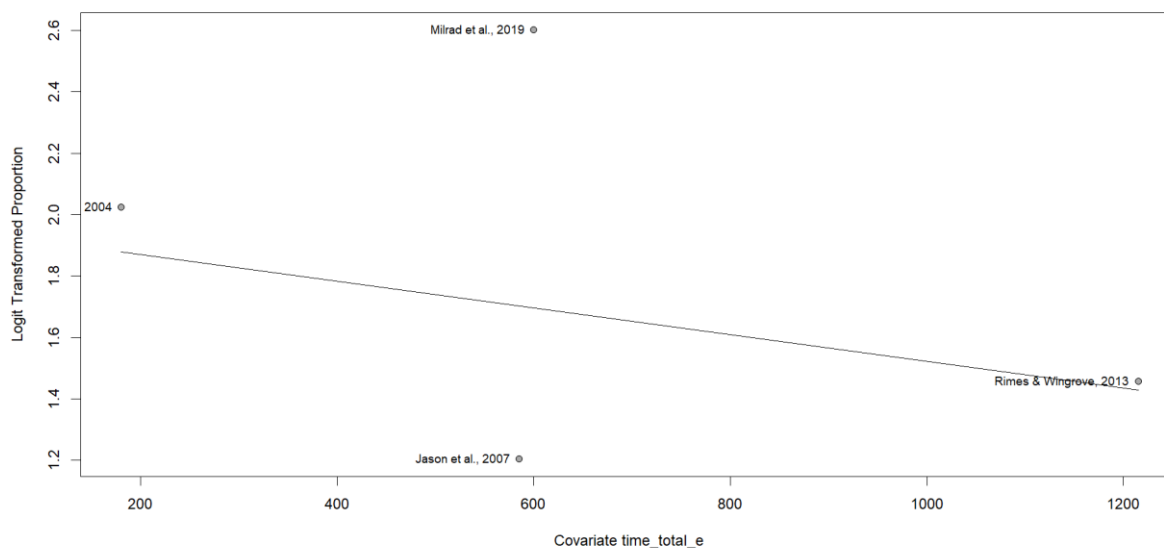
(D)



(E)



(F)



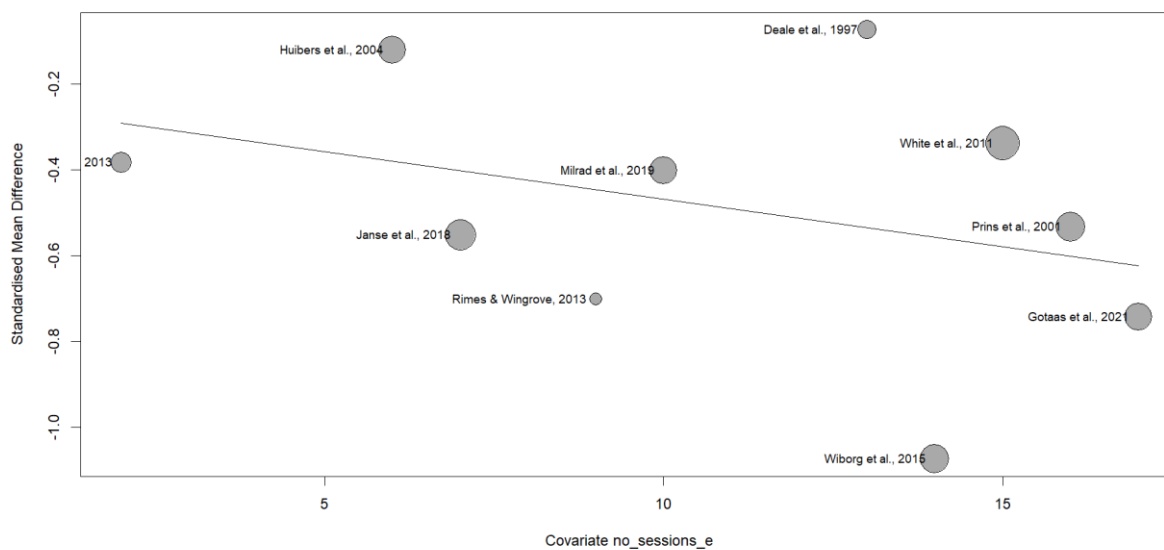
(G)

Note. A: bubble plot for the effect of therapy dosage on fatigue at post-treatment; B: bubble plot for the effect of therapy dosage on perceived health status at post-treatment; C: bubble plot for the effect of therapy dosage on depression at post-treatment; D: bubble plot for the effect of therapy dosage on anxiety at post-treatment; E: bubble plot for the effect of therapy dosage on non-completion; F: bubble plot for the effect of therapy dosage on drop-out; G: bubble plot for the effect of therapy dosage on the average proportion of sessions completed.

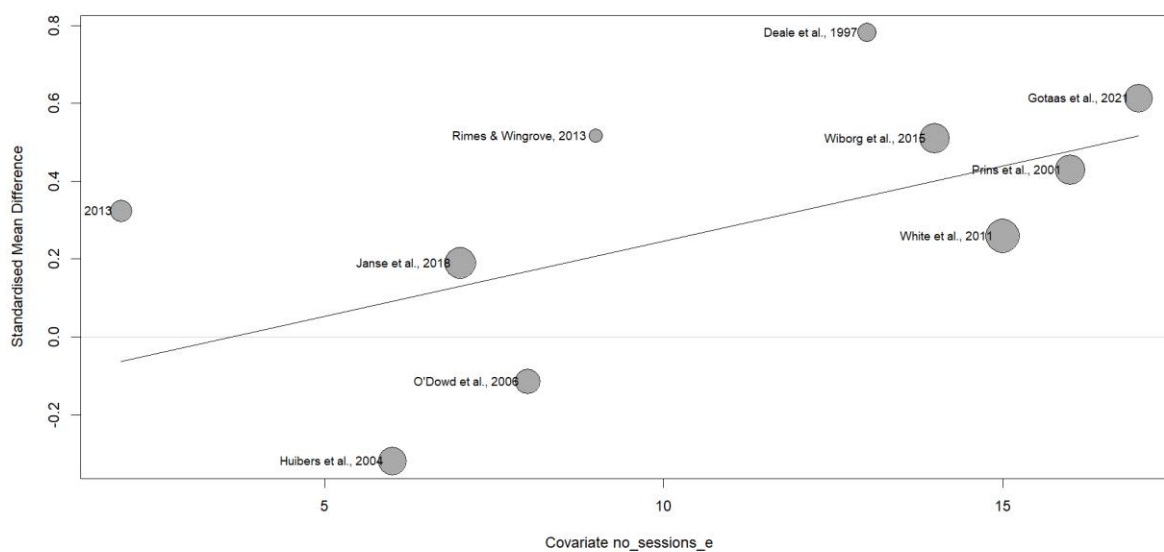
Table S4*Meta-regression analyses for number of sessions*

Outcome	$\tau_{unexplained}^2$	I^2	R^2	$p_{moderator}$	Regression weight	Intercept
Fatigue	0.05	65.44%	5.11%	0.27	-0.0222	-0.25
Perceived Health Status	0.04	55.37%	49.21%	0.03	0.0387	-0.14
Depression	0	0.00%	0.00%	0.63	-0.0142	-0.24
Anxiety	0	0.00%	0.00%	0.99	-0.0007	-0.34
Non-completion	2.88	93.61%		0.26	-0.1704	0.41
Drop-out	0.45	81.95%		0.32	-0.0529	-1.09
Ave. prop. sessions	0	0.00%		0.59	-0.1241	2.95

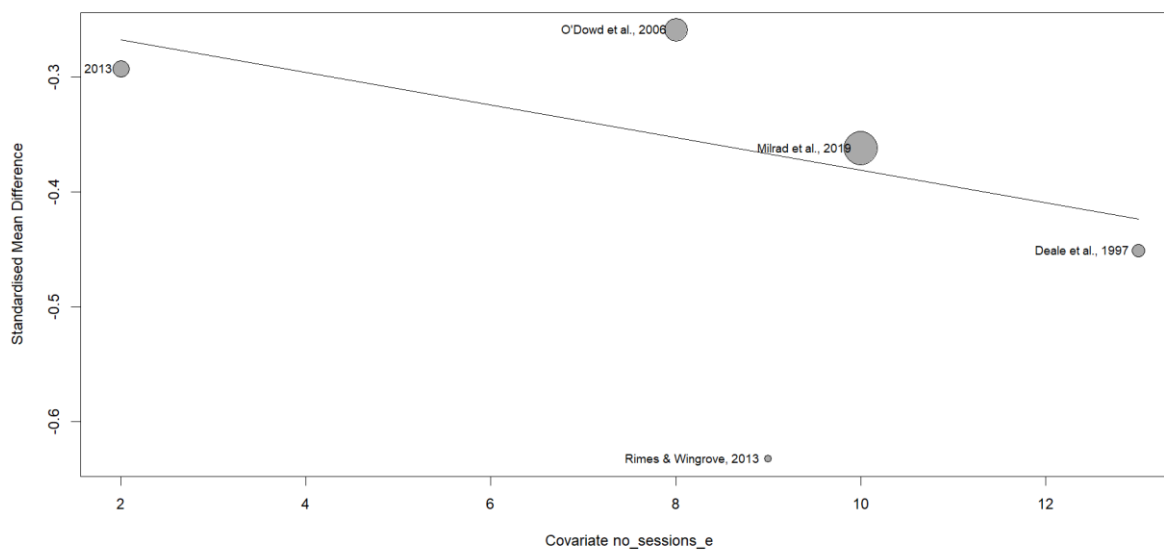
Note. Effect on efficacy outcomes at post-treatment; $\tau_{unexplained}^2$ = estimated amount of residual heterogeneity; I^2 = residual heterogeneity/unaccounted variability; R^2 = amount of heterogeneity accounted for (could only be calculated for efficacy outcomes)

Figure S10*Bubble plots – meta-regression analysis for number of sessions*

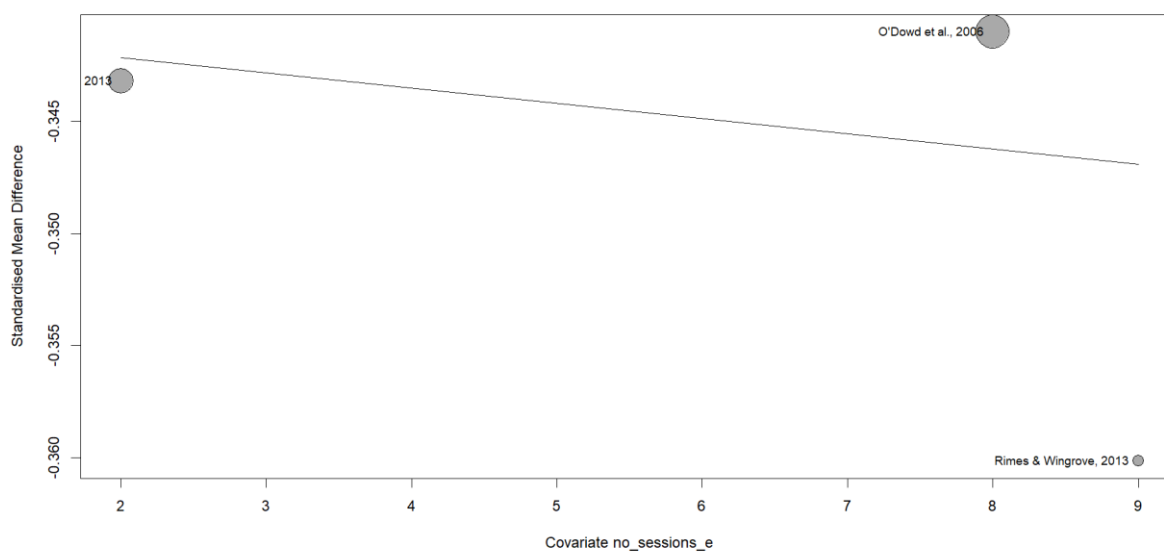
(A)



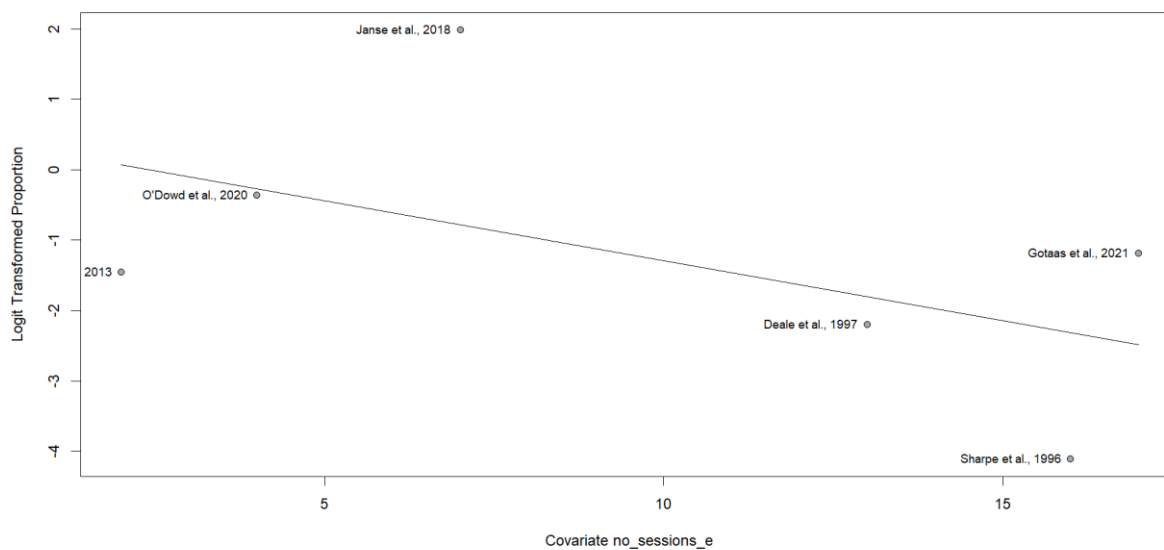
(B)



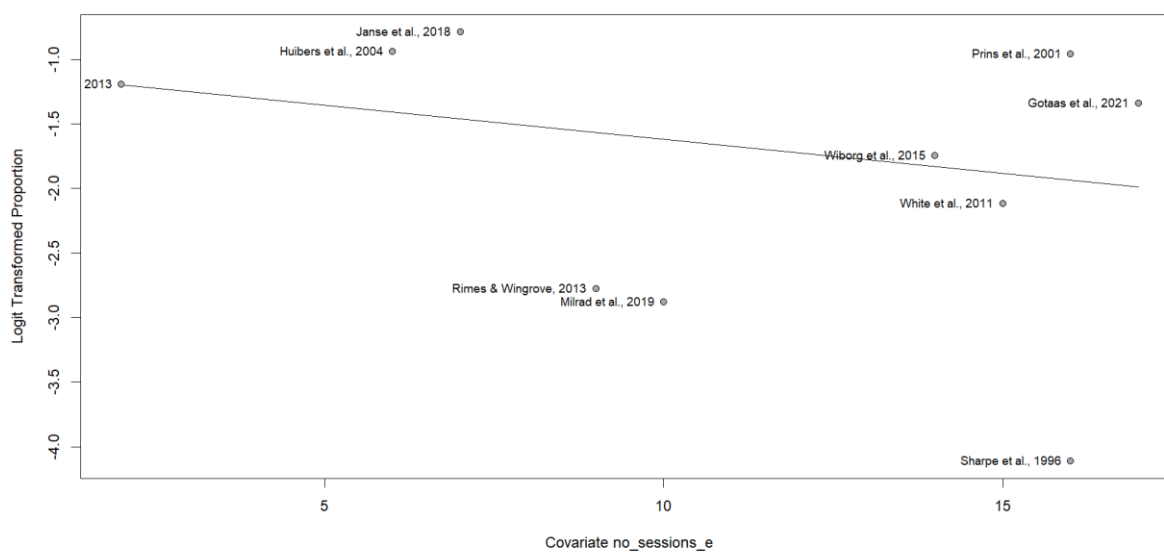
(C)



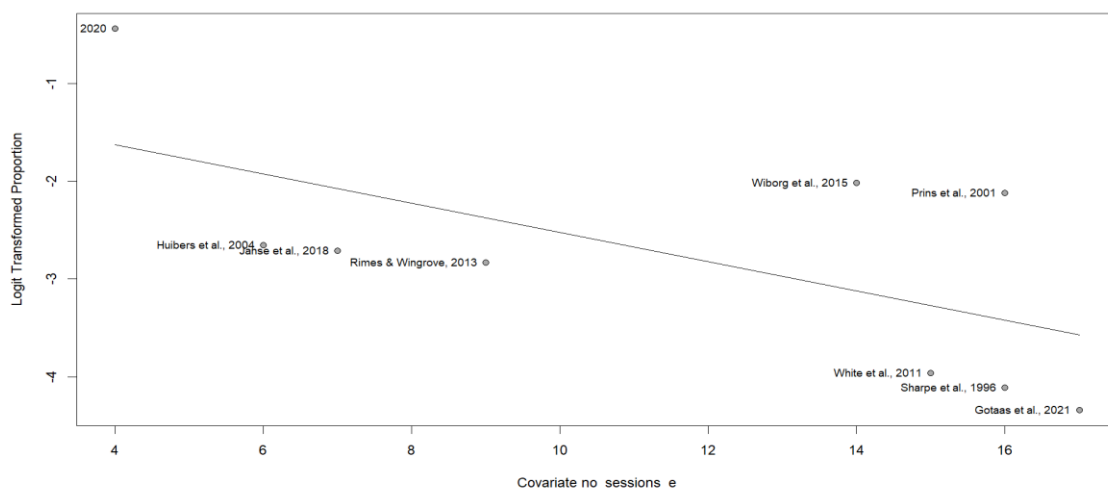
(D)



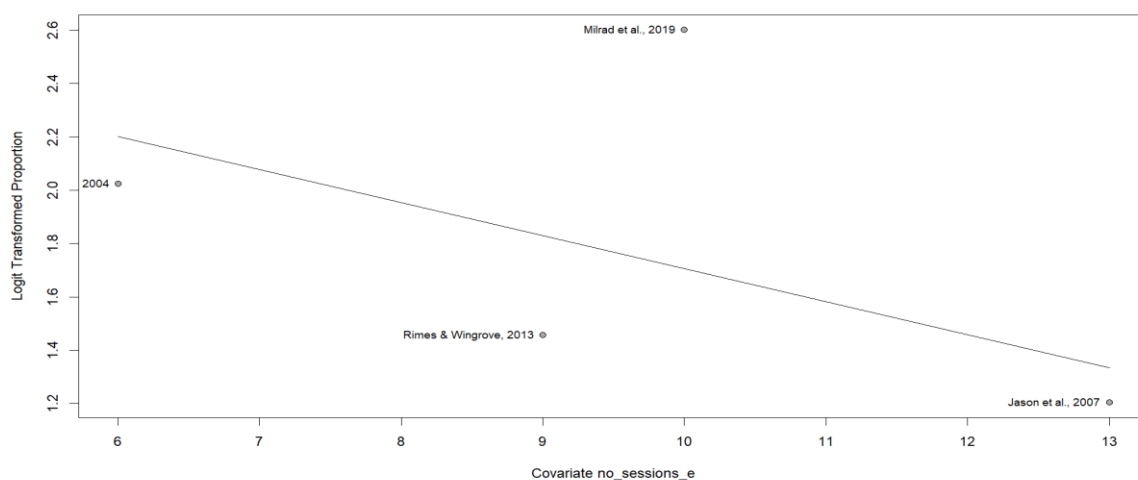
(E)



(F)



(G)



(H)

Note. A: bubble plot for the effect of number of sessions on fatigue at post-treatment; B: bubble plot for the effect of number of sessions on perceived health status at post-treatment; C: bubble plot for the effect of number of sessions on depression at post-treatment; D: bubble plot for the effect of number of sessions on anxiety at post-treatment; E: bubble plot for the effect of number of sessions on non-completion; F: bubble plot for the effect of number of sessions on drop-out; G: bubble plot for the effect of number of sessions on treatment refusal; H: bubble plot for the effect of number of sessions on the average proportion of sessions completed.

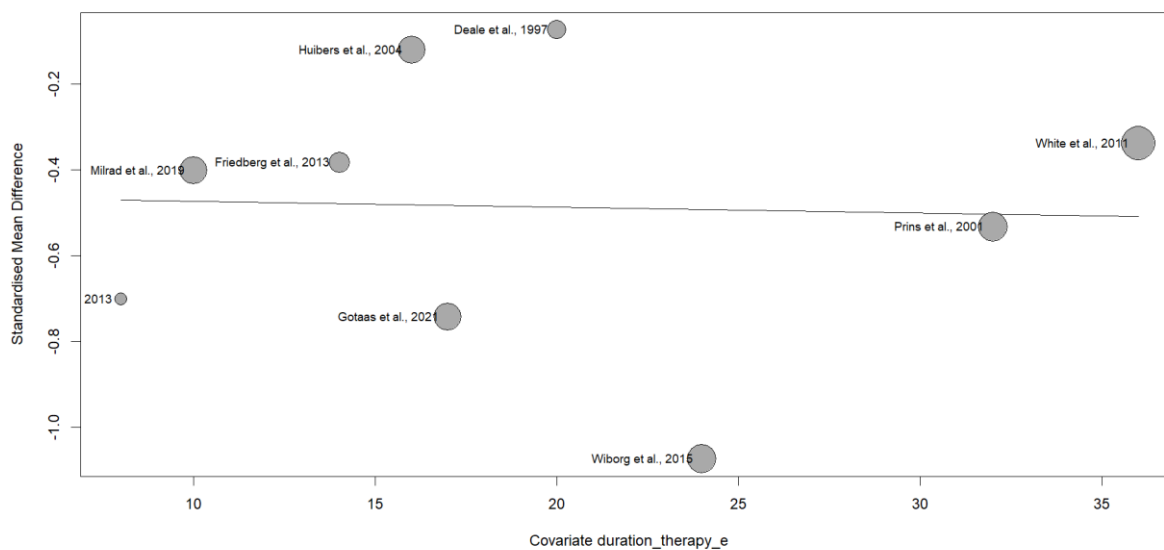
Table S5*Meta-regression analyses for duration of therapy in weeks*

Outcome	$\tau_{unexplained}^2$	I^2	R^2	$p_{moderator}$	Regression weight	Intercept
Fatigue	0.08	72.29%	0.00%	0.92	-0.0013	-0.46
Perceived Health Status	0.10	75.19%	0.00%	0.73	0.005	0.21
Depression	0	0.00%	0.00%	0.78	0.0074	-0.46
Anxiety	0	0.00%	0.00%	0.96	0.0024	-0.38
Non-completion	0.39	61.53%		0.21	-0.1795	1.11
Drop-out	0.46	79.48%		0.42	0.0257	-2.35
Ave. prop. sessions	0	0.00%		0.55	-0.0409	2.34

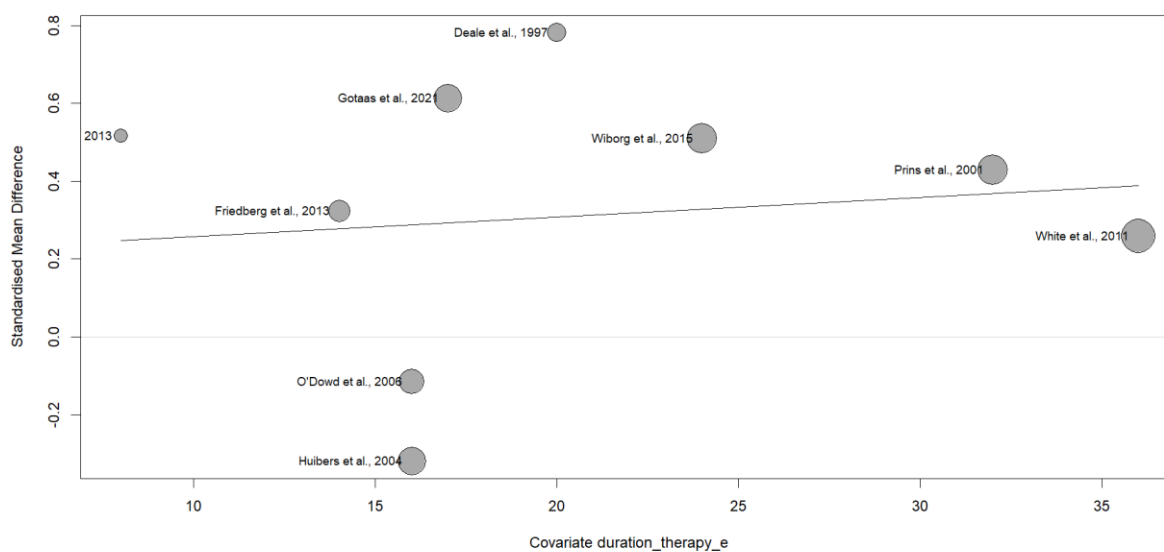
Note. Effect on efficacy outcomes at post-treatment; $\tau_{unexplained}^2$ = estimated amount of residual heterogeneity; I^2 = residual heterogeneity/unaccounted variability; R^2 = amount of heterogeneity accounted for (could only be calculated for efficacy outcomes)

Figure S11

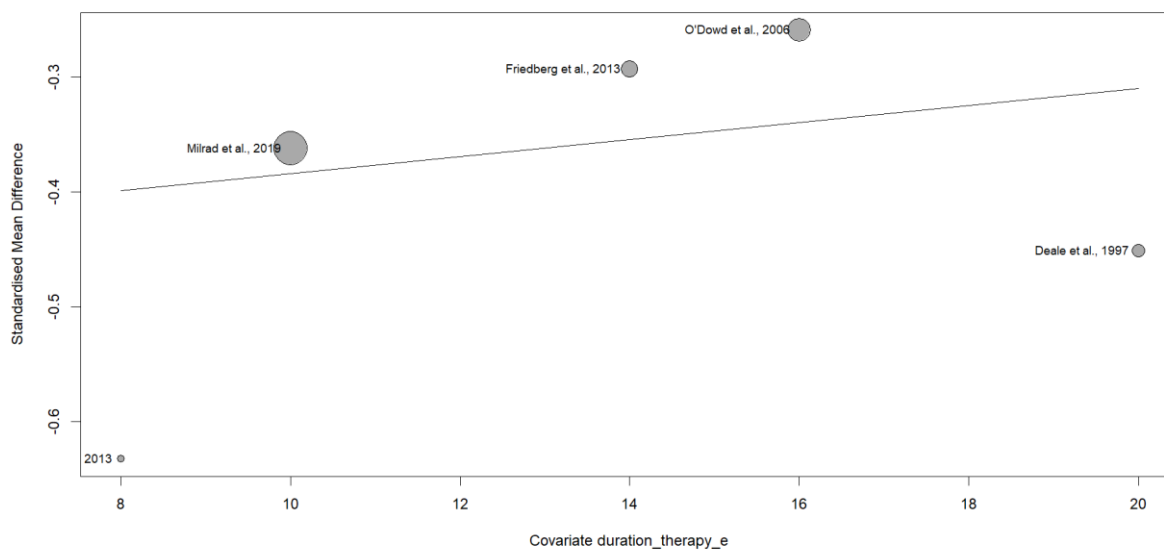
Bubble plots – meta-regression analysis for duration of therapy (weeks)



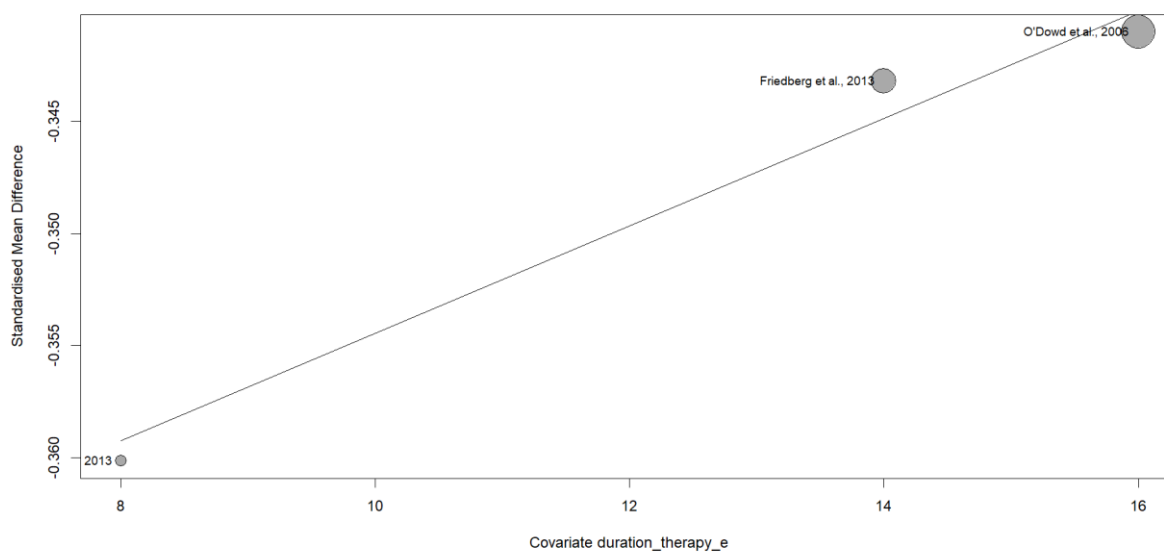
(A)



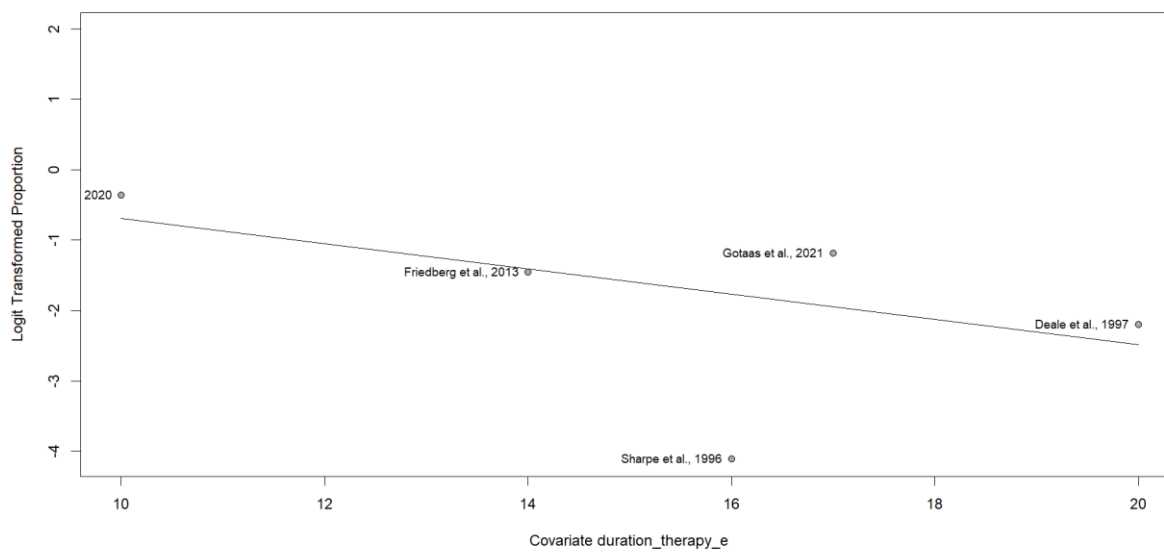
(B)



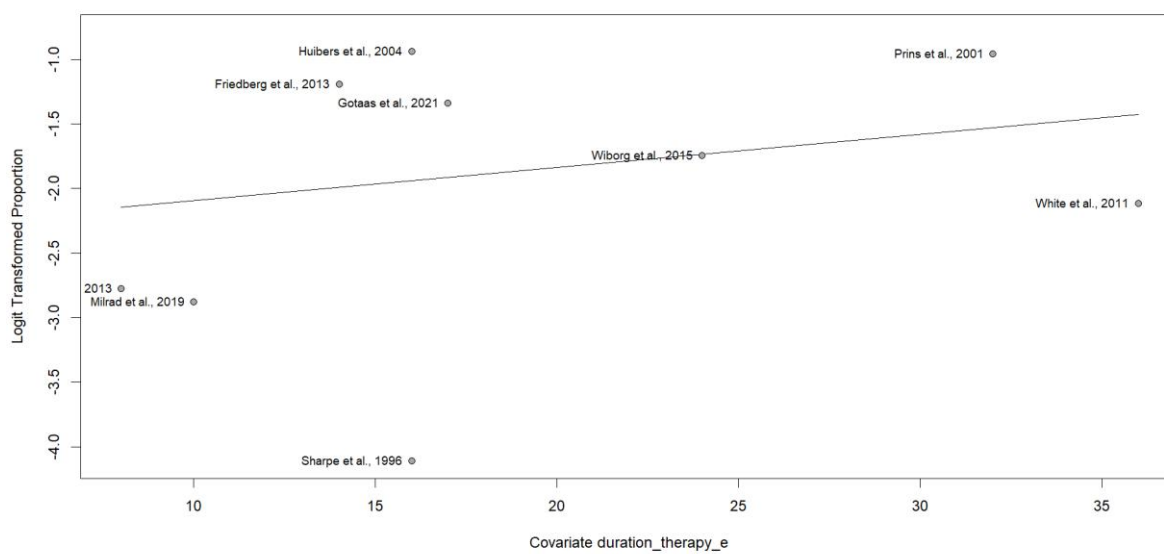
(C)



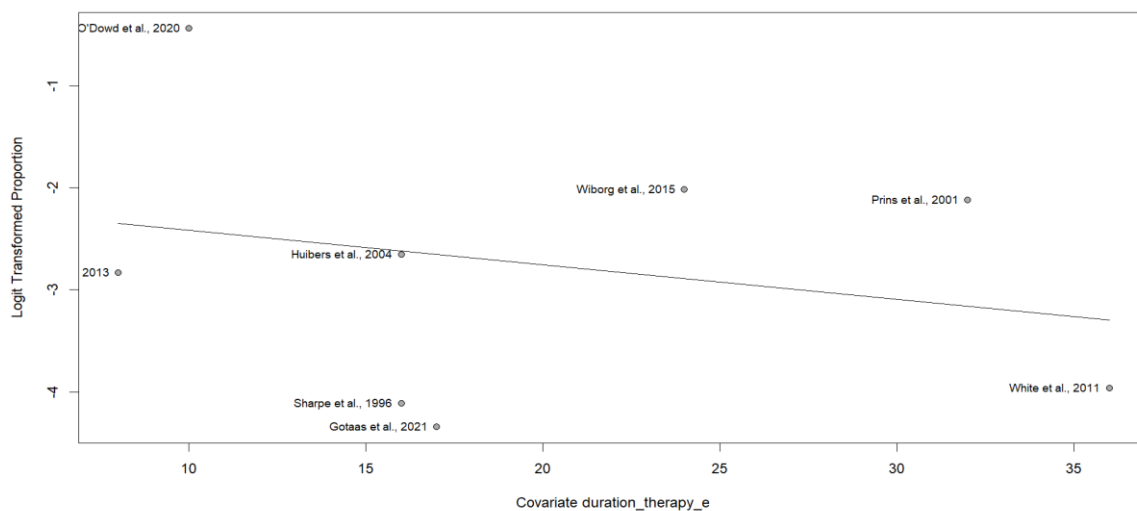
(D)



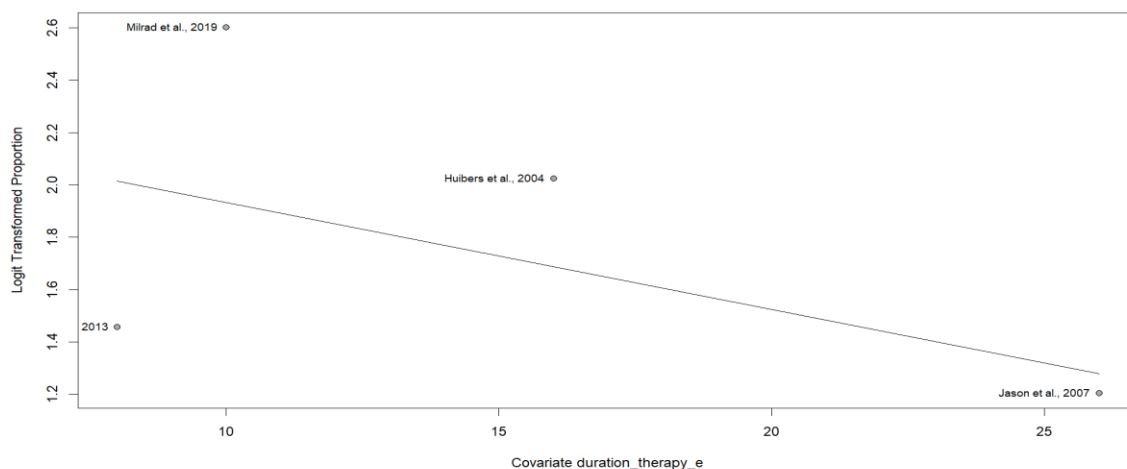
(E)



(F)



(G)



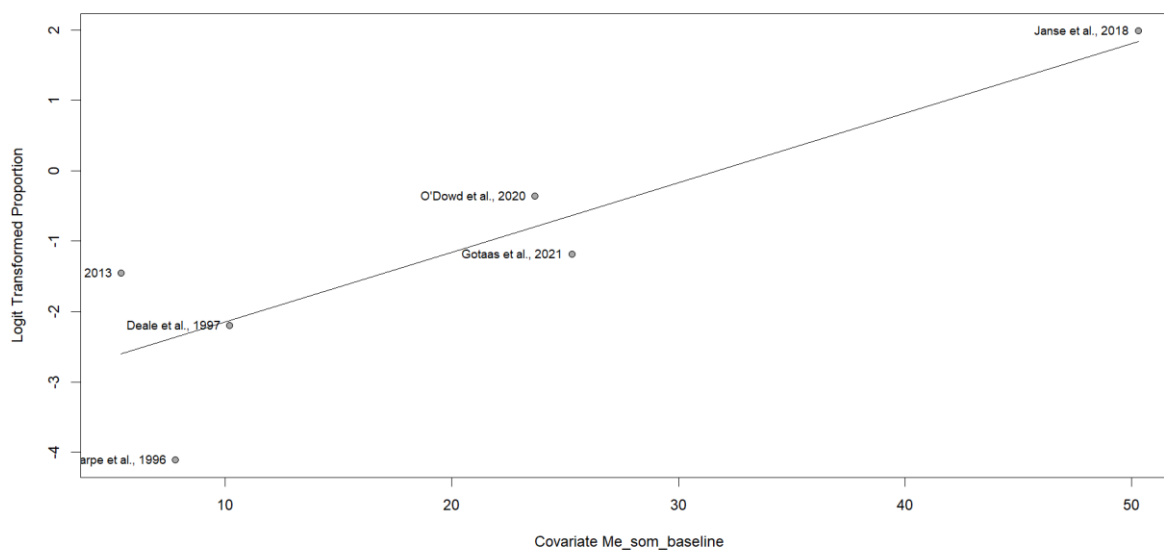
(H)

Note. A: bubble plot for the effect of duration of therapy on fatigue at post-treatment; B: bubble plot for the effect of duration of therapy on perceived health status at post-treatment; C: bubble plot for the effect of duration of therapy on depression at post-treatment; D: bubble plot for the effect of duration of therapy on anxiety at post-treatment; E: bubble plot for the effect of duration of therapy on non-completion; F: bubble plot for the effect of duration of therapy on drop-out; G: bubble plot for the effect of duration of therapy on treatment refusal; H: bubble plot for the effect of duration of therapy on the average proportion of sessions completed.

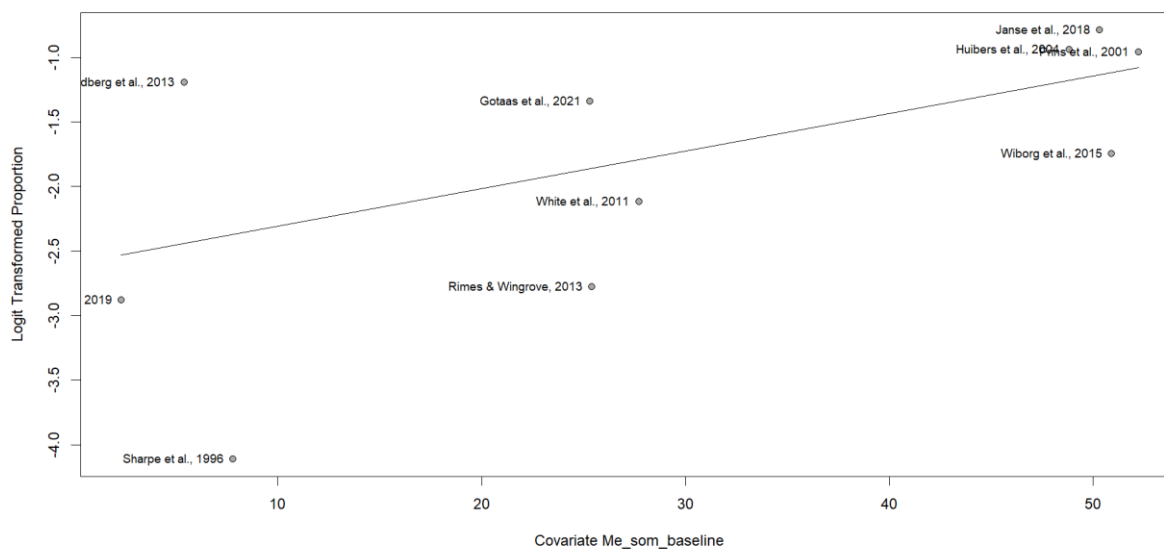
Table S6*Meta-regression analyses for fatigue severity at baseline*

Outcome	$\tau_{unexplained}^2$	I^2	$p_{moderator}$	Regression weight	Intercept
Non-completion	0.26	56.58%	0.005	0.0988	-3.13
Drop-out	0.17	64.30%	0.02	0.0290	-2.60
Ave. prop. sessions	0	0.00%	0.95	0.002	1.62

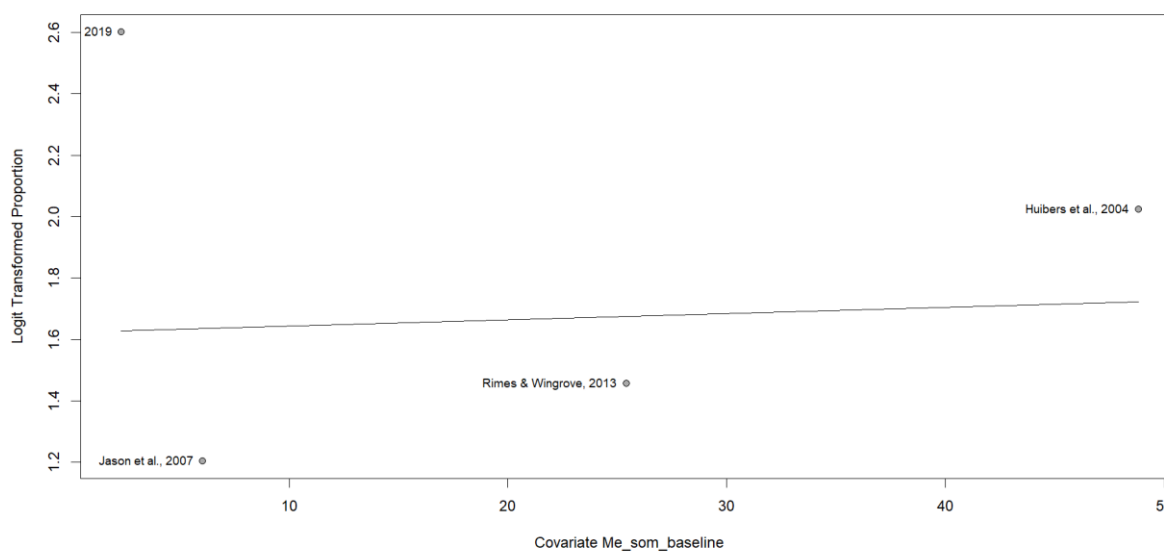
Note. $\tau_{unexplained}^2$ = estimated amount of residual heterogeneity; I^2 = residual heterogeneity/unaccounted variability

Figure S12*Bubble plots – meta-regression analysis for fatigue severity*

(A)



(B)



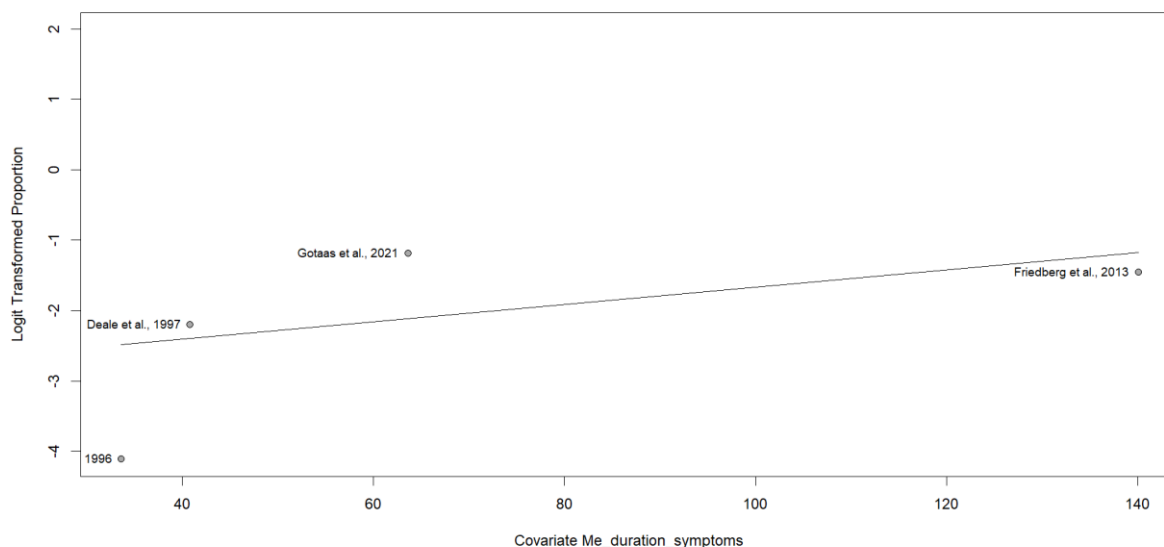
(C)

Note. A: bubble plot for the effect of fatigue severity on non-completion; B: bubble plot for the effect of fatigue severity on drop-out; C: bubble plot for the effect of fatigue severity on the average proportion of sessions completed.

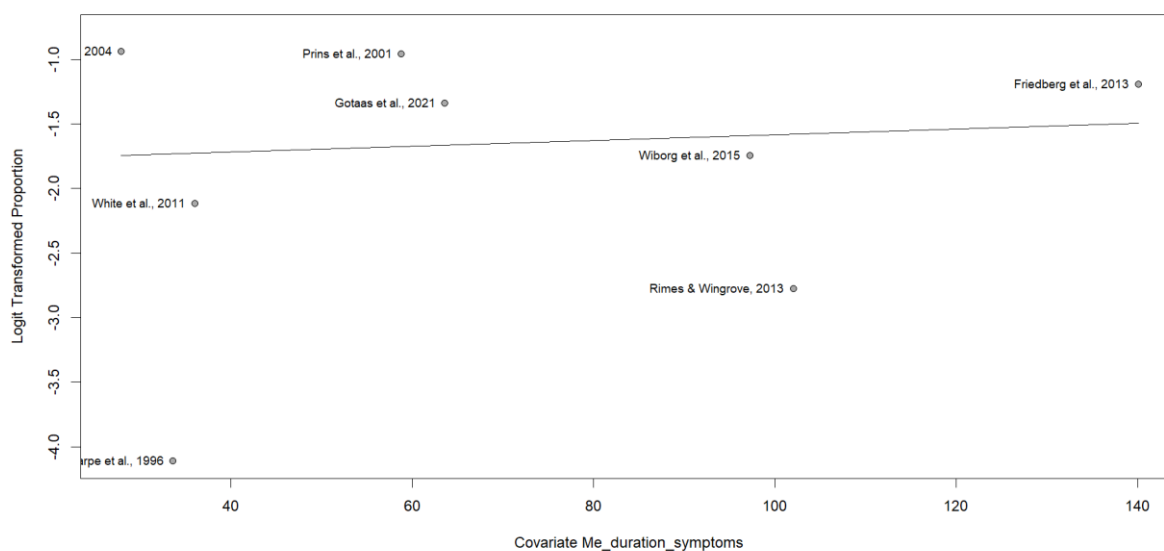
Table S7*Meta-regression analyses for duration of fatigue symptoms up to baseline*

Outcome	$\tau_{unexplained}^2$	I^2	$p_{moderator}$	Regression weight	Intercept
Non-completion	0.43	58.04%	0.37	0.0123	-2.90
Drop-out	0.32	74.72%	0.76	0.0022	-1.80

Note. $\tau_{unexplained}^2$ = estimated amount of residual heterogeneity; I^2 = residual heterogeneity/unaccounted variability; only $k = 2$ studies reported information on the average proportion of sessions completed and the duration of symptoms

Figure S13

(A)



(B)

Note. A: bubble plot for the effect of duration of fatigue symptoms on non-completion; B: bubble plot for the effect of duration of fatigue symptoms on drop-out.

8. Results Sensitivity Analyses

Table S8

Sensitivity analyses comparing fixed effect and random effects models

Outcome	<i>k</i>	Model	Pooled effect ^a	95%CI
Fatigue	11	Random effects	-0.52	-0.69; -0.35
		Fixed effect	-0.52	-0.62; -0.42
Perceived health status	11	Random effects	0.29	0.11; 0.47
		Fixed effect	0.28	0.18; 0.38
Depression	5	Random effects	-0.36	-0.55; -0.17
		Fixed effect	-0.36	-0.55; -0.17
Anxiety	3	Random effects	-0.34	-0.62; -0.07
		Fixed effect	-0.34	-0.62; -0.07
Non-completion	6	Random effects	0.22	0.03; 0.71
		Fixed effect	0.49	0.44; 0.54
Drop-out	10	Random effects	0.15	0.09; 0.25
		Fixed effect	0.19	0.16; 0.22
Treatment refusal	10	Random effects	0.07	0.03; 0.15
		Fixed effect	0.09	0.07; 0.11
Average proportion of sessions completed	4	Random effects	0.84	0.56; 0.96
		Fixed effect	0.84	0.69; 0.93

Note. Effect on efficacy outcomes at post-treatment; *k* = number of studies.

^a Hedges' *g* for efficacy outcomes, proportions for acceptance outcomes

Table S9*“Imputed” starters*

Outcome	Sample	k	Proportion	95%CI ^a	I^2	95%CI ^b
Non-completion	With imputation	6	0.22	0.03; 0.71	95.4%	92.2; 97.2
	Without imputation	4	0.26	0.01; 0.96	96.1%	92.7; 97.9
Drop-out	With imputation	10	0.15	0.09; 0.25	75.7%	54.9; 86.9
	Without imputation	8	0.17	0.09; 0.28	74.3%	47.9; 87.3

^a 95%CI for the proportion, ^b 95%CI for I^2

Table S10*Outlier analyses*

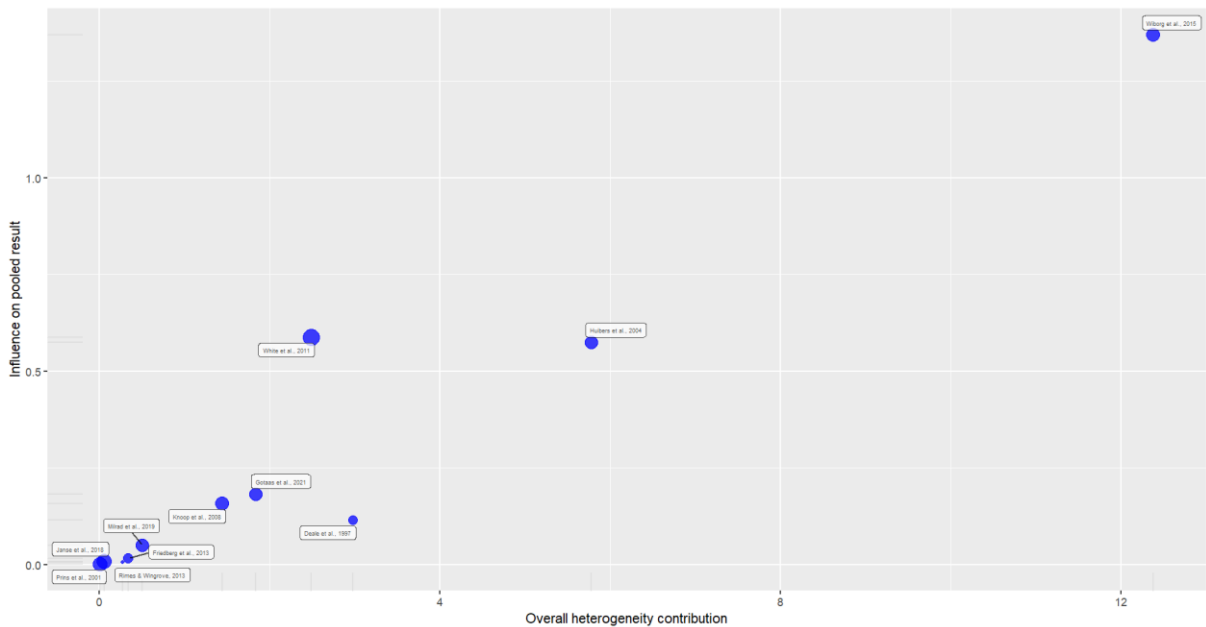
	<i>k</i>	Pooled effect ^a	95%CI ^b	<i>I</i> ²	95%CI ^c	95%PI
Fatigue						
With outliers	11	-0.52	-0.69; -0.35	64.4%	32.1; 81.3	-1.07; 0.04
Without outliers	10	-0.46	-0.59; -0.32	37.2%	0.0; 70.1	-0.80; -0.12
Perceived Health Status						
With outliers	11	0.29	0.11; 0.47	65.3%	34.2; 81.8	-0.30; 0.88
Without outliers	10	0.35	0.21; 0.48	38.9%	0.0; 70.9	0.01; 0.69
Non-completion						
With outliers	6	0.22	0.03; 0.71	95.4%	92.2; 97.2	0.00; 0.99
Without outliers	5	0.15	0.04; 0.42	33.1%	0.0; 74.6	0.01; 0.85
Treatment refusal						
With outliers	10	0.07	0.03; 0.15	80.3%	64.6; 89.0	0.01; 0.52
Without outliers	9	0.06	0.03; 0.12	70.4%	41.2; 85.1	0.01; 0.34

^a Hedges' *g* for efficacy outcomes, proportions for acceptance outcomes, ^b 95%CI for the proportion,

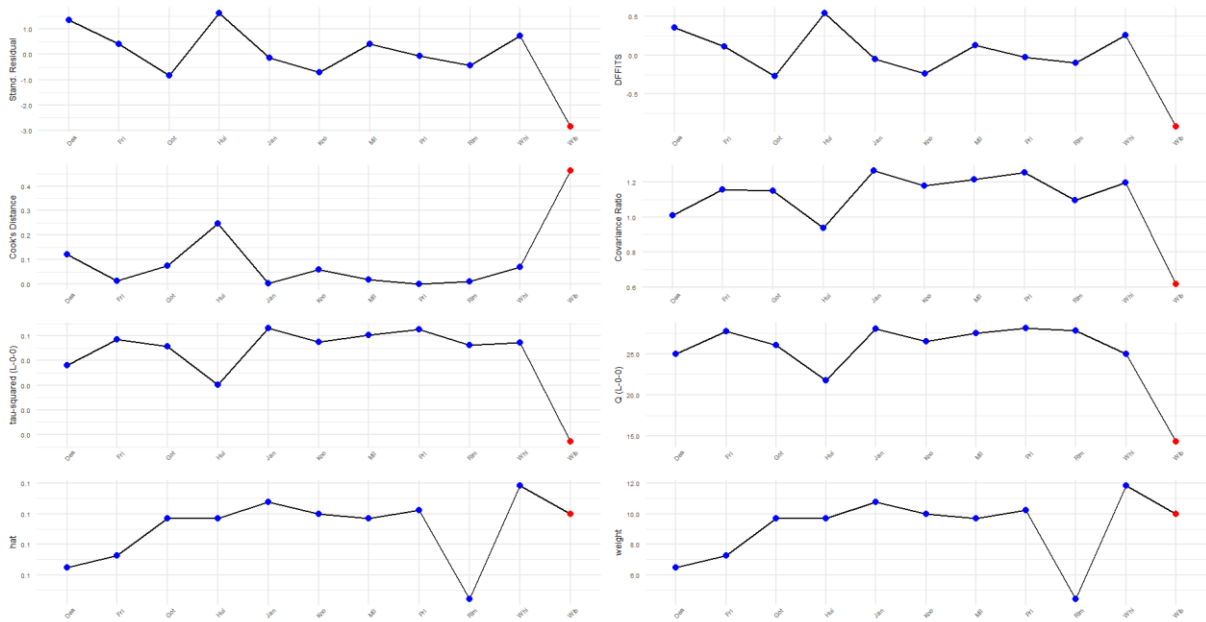
^c 95%CI for *I*²

Figure S14

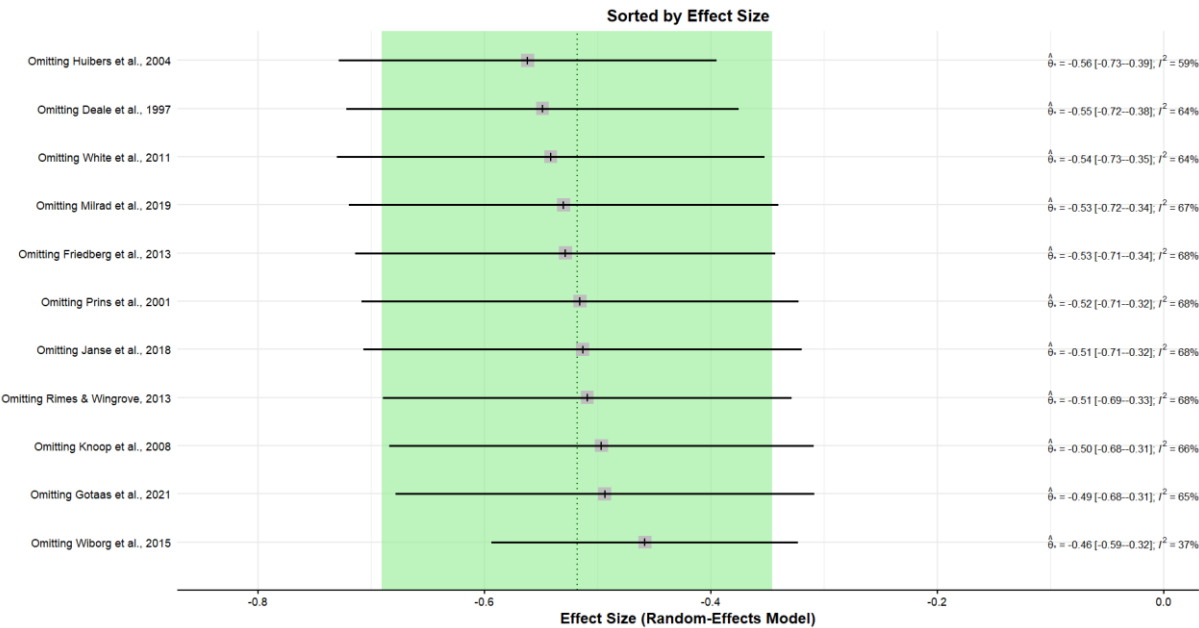
Results for the influence analyses for fatigue at post-treatment



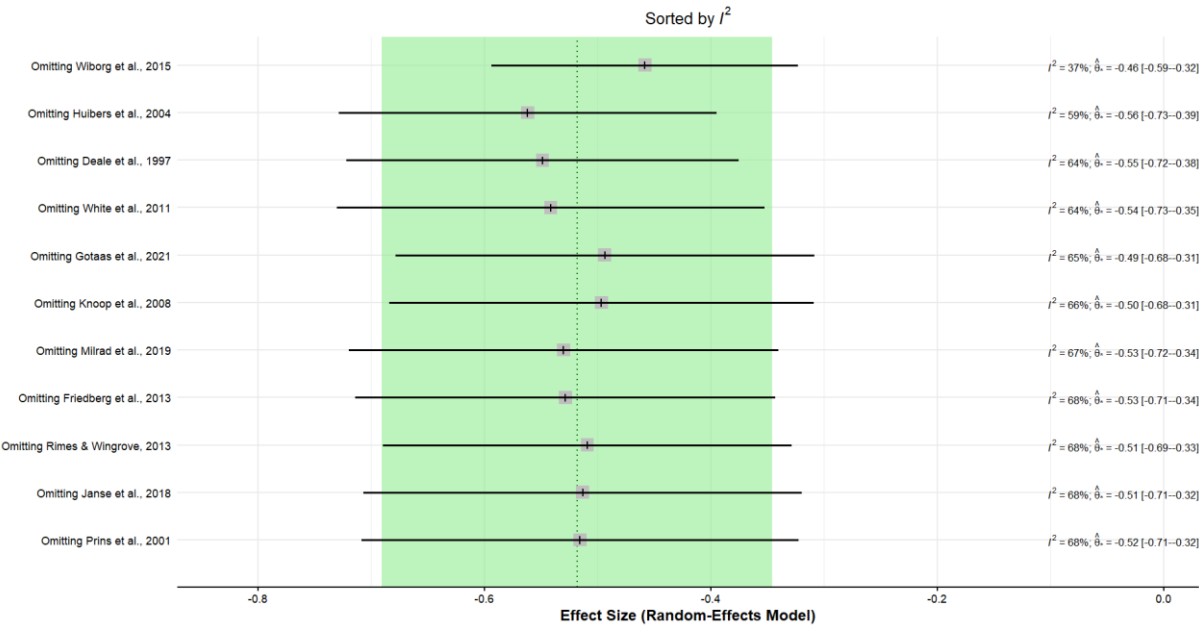
(A)



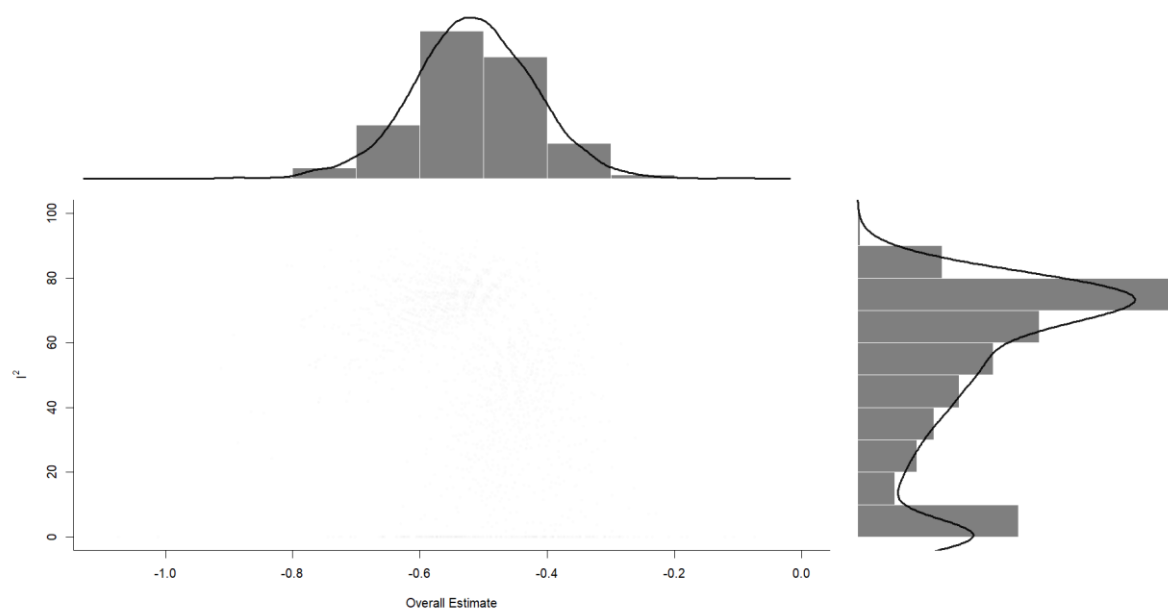
(B)



(C)



(D)



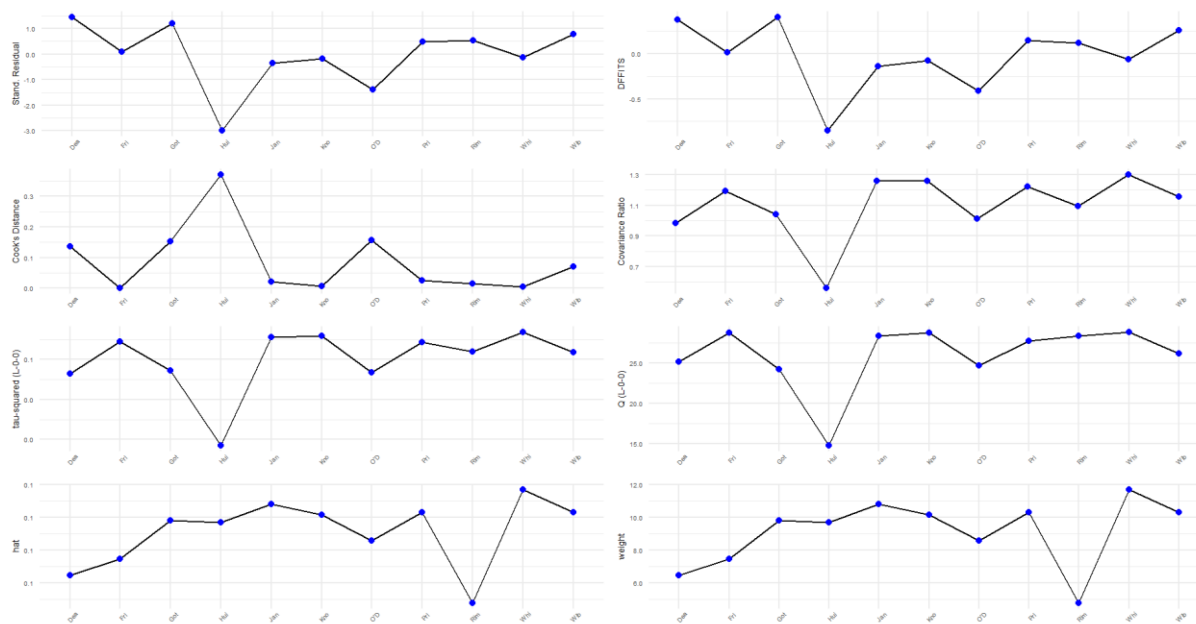
(E)

Note. A: Baujat plot; B: influence plot; C: leave one out method, influence on effect size; D: leave one out method, influence on heterogeneity; E: Graphic Display of Heterogeneity (GOSH) plot.

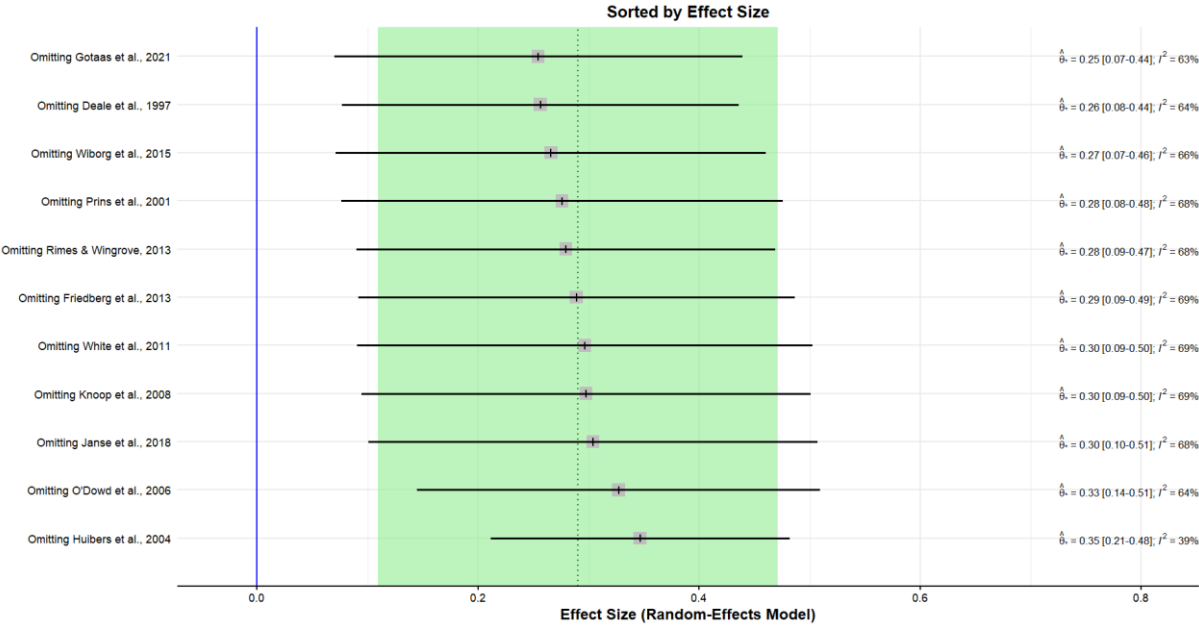
Figure S15

Results for the influence analyses for perceived health status at post-treatment

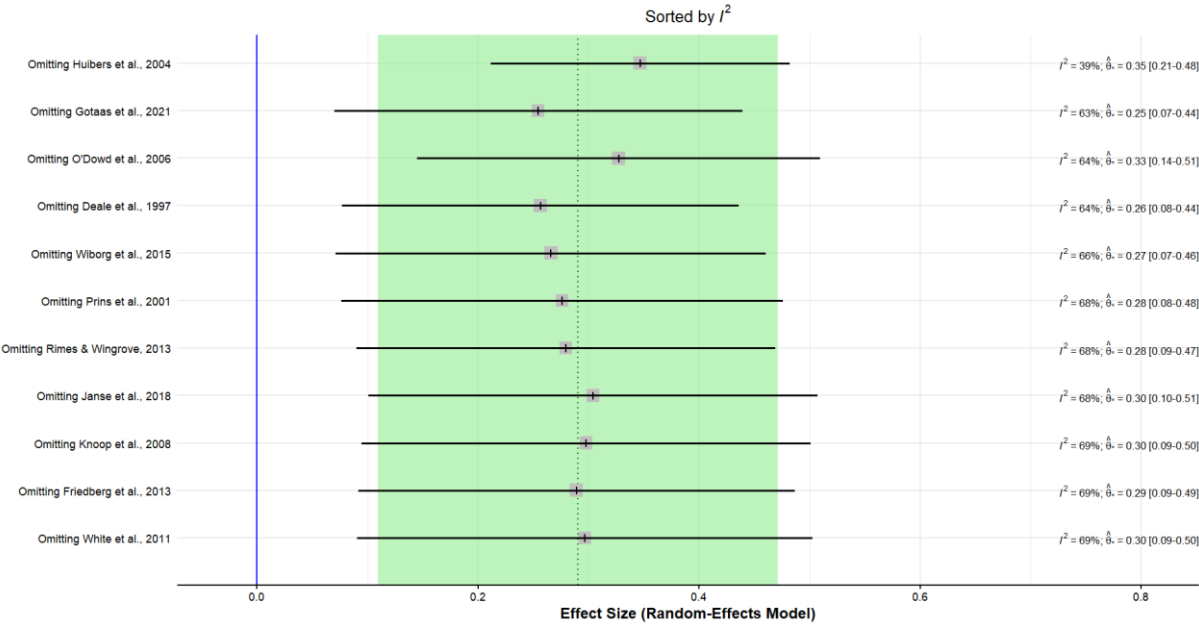
(A)



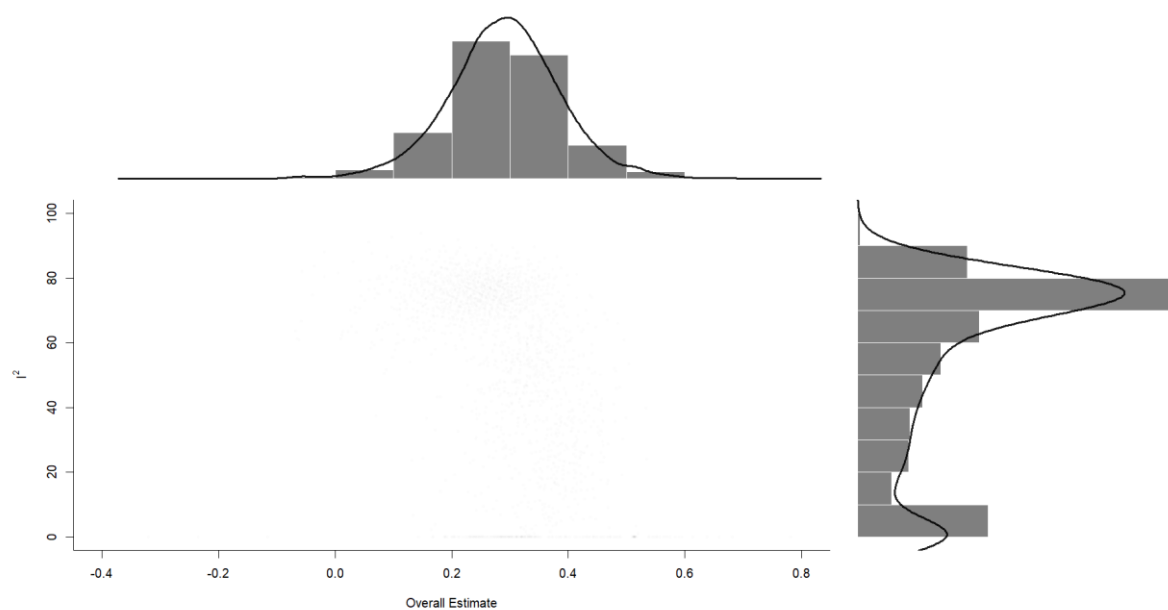
(B)



(C)

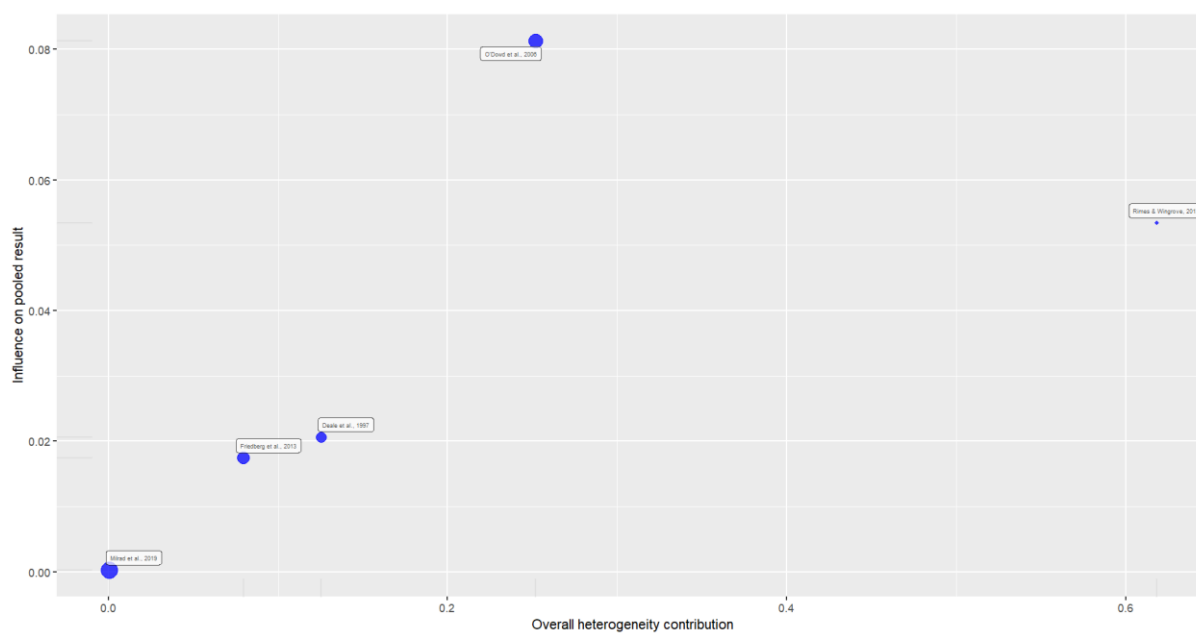
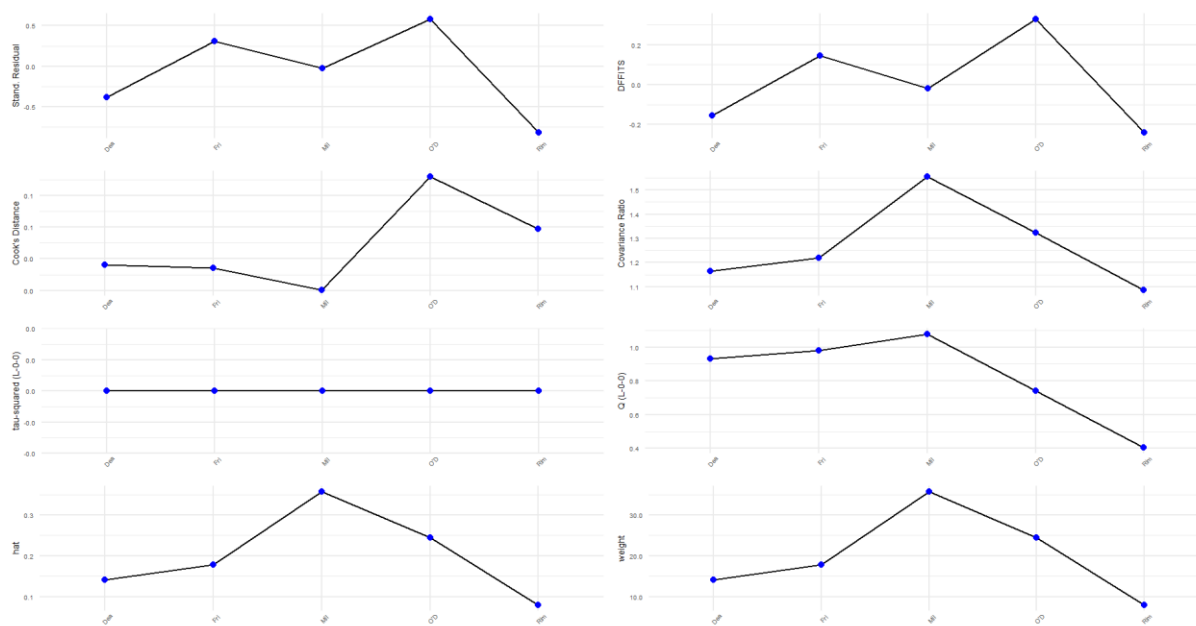


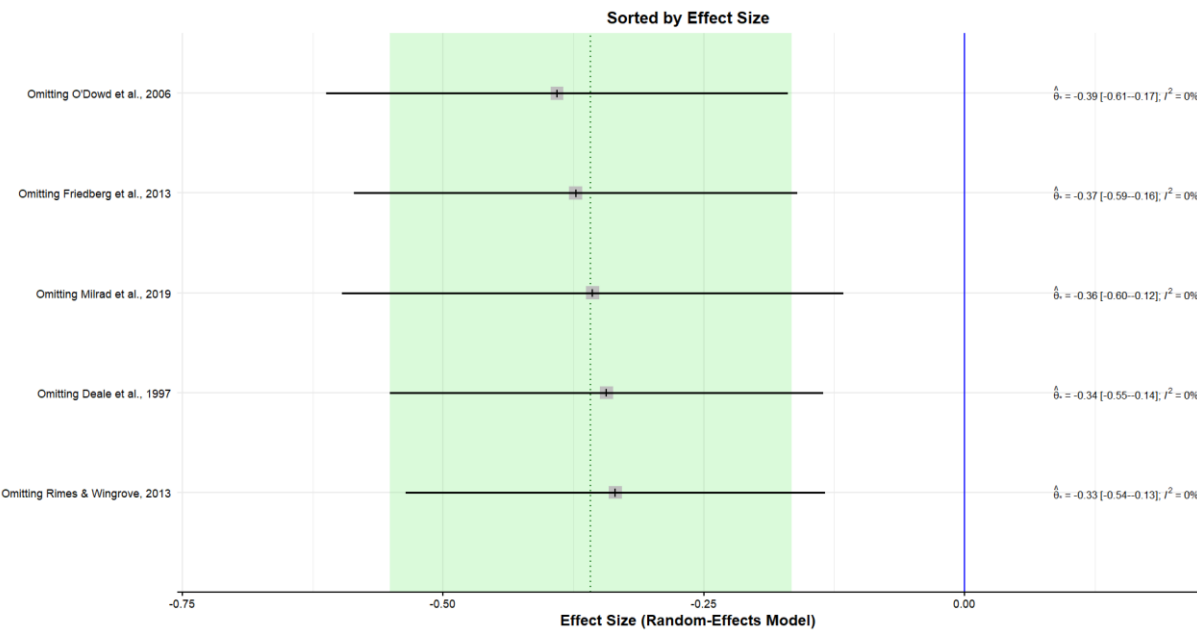
(D)



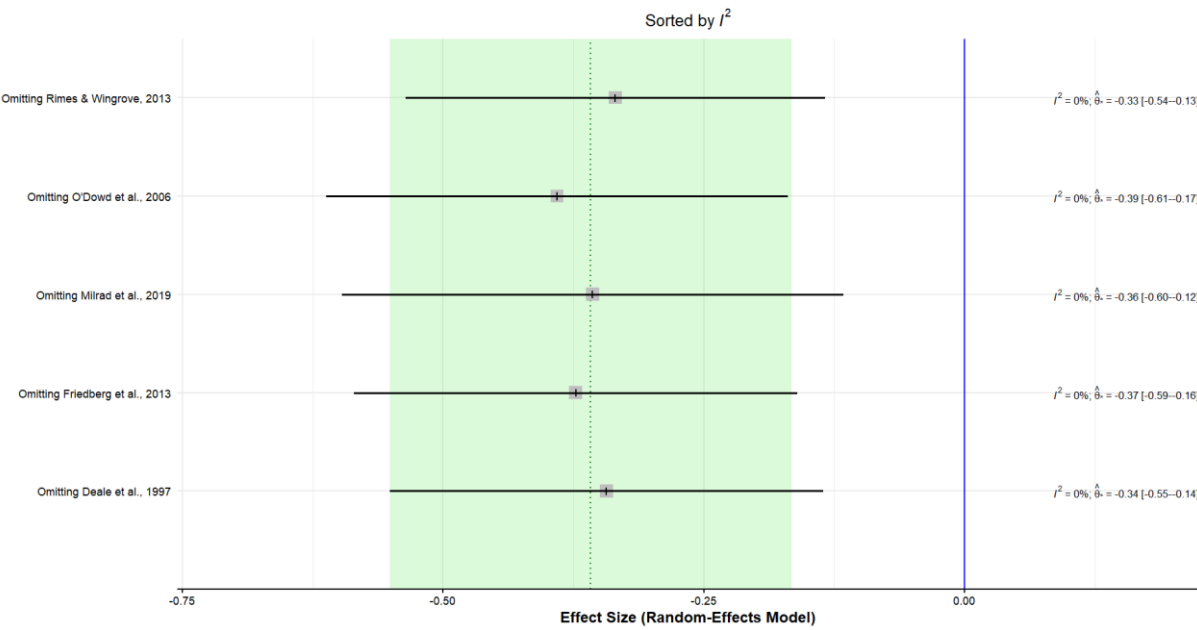
(E)

Note. A: Baujat plot; B: influence plot; C: leave one out method, influence on effect size; D: leave one out method, influence on heterogeneity; E: Graphic Display of Heterogeneity (GOSH) plot.

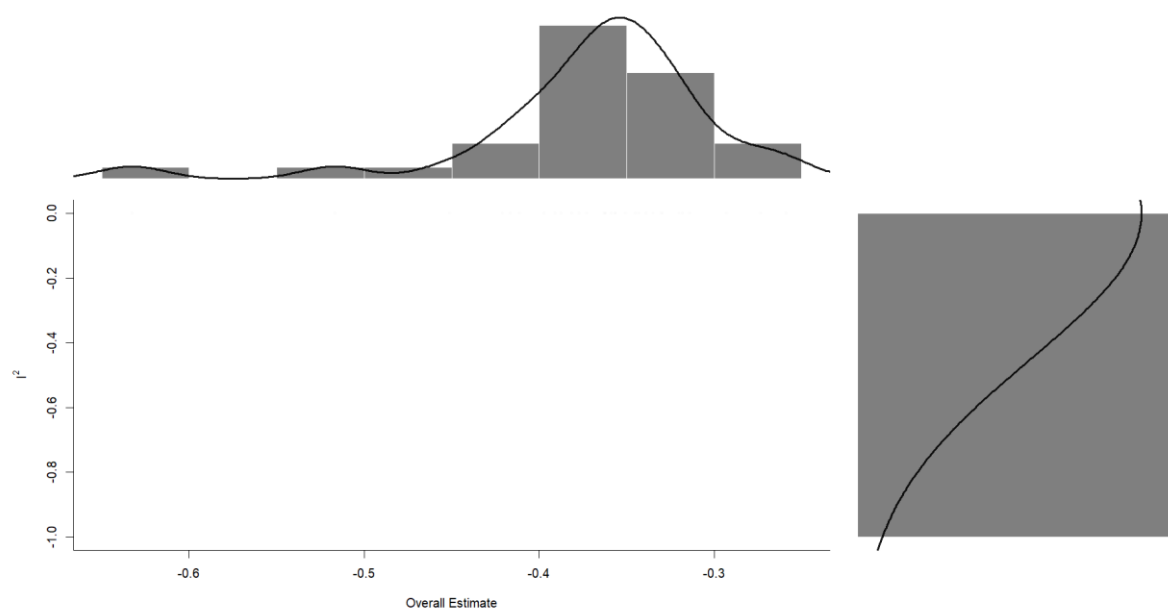
Figure S16*Results for the influence analyses for depression at post-treatment***(A)****(B)**



(C)



(D)

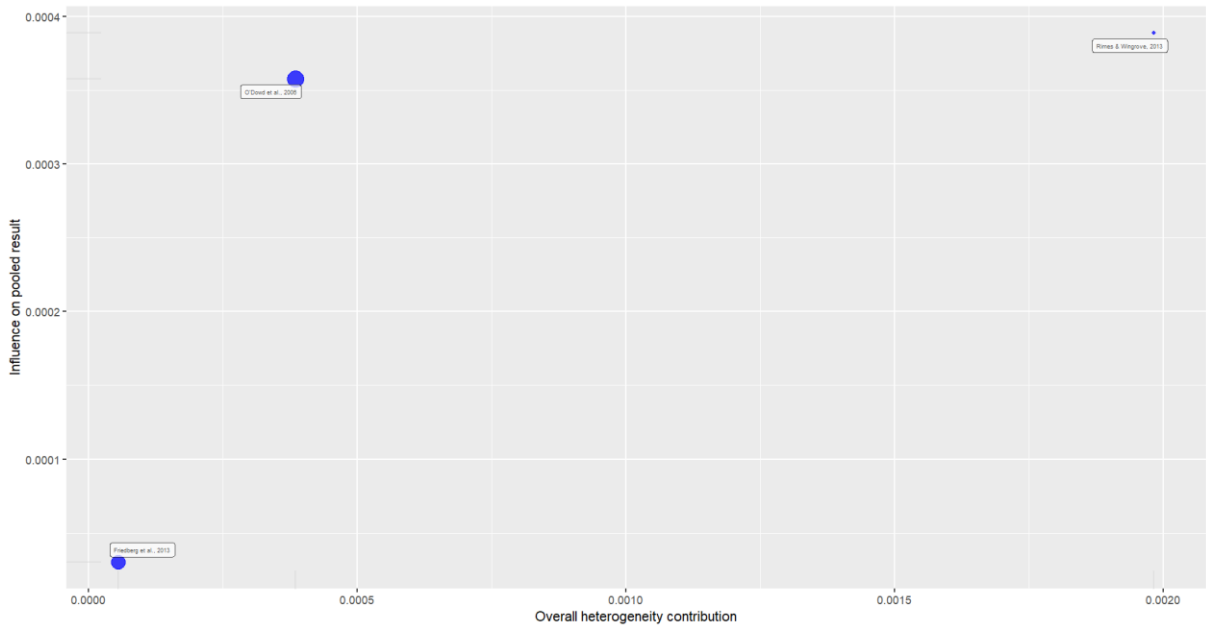


(E)

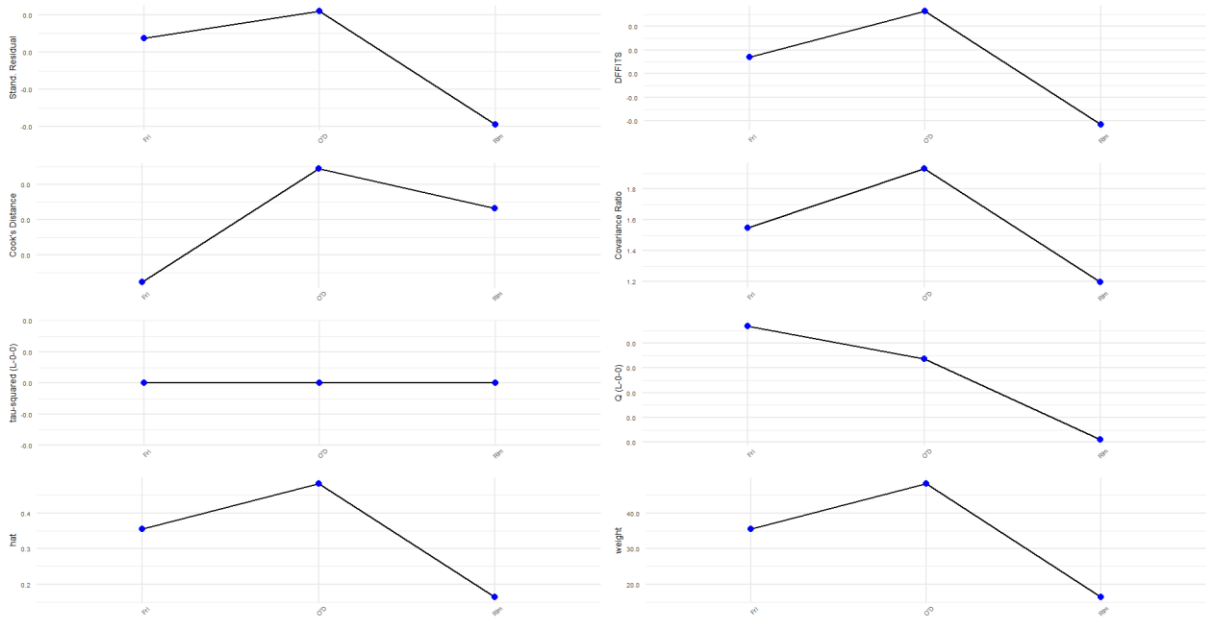
Note. A: Baujat plot; B: influence plot; C: leave one out method, influence on effect size; D: leave one out method, influence on heterogeneity; E: Graphic Display of Heterogeneity (GOSH) plot.

Figure S17

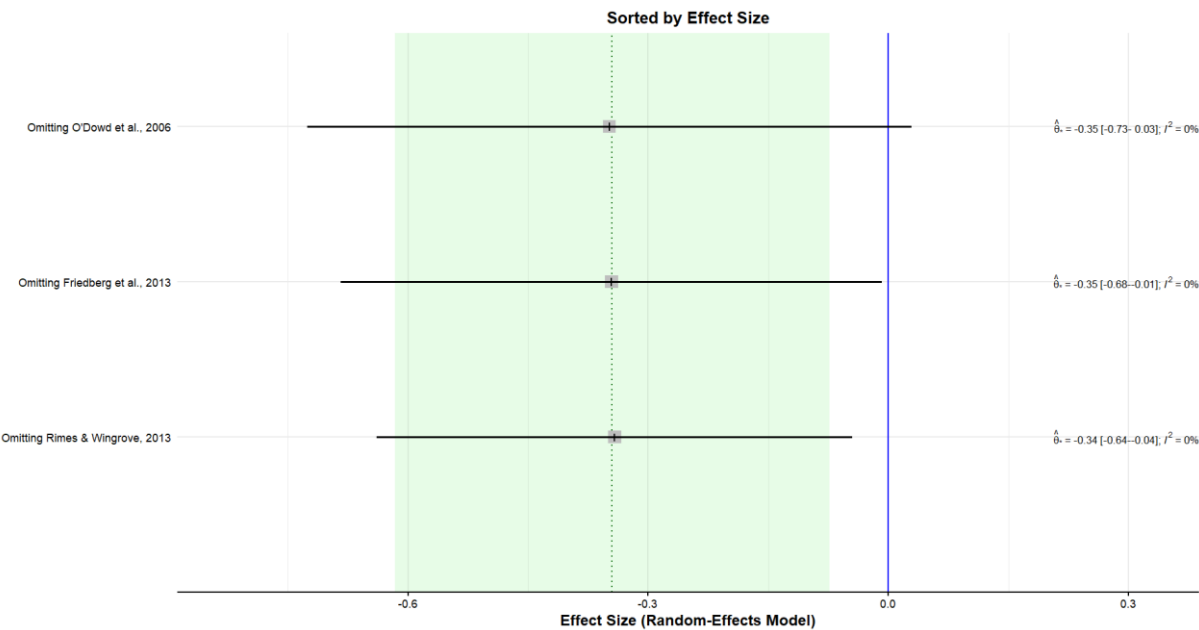
Results for the influence analyses for anxiety at post-treatment



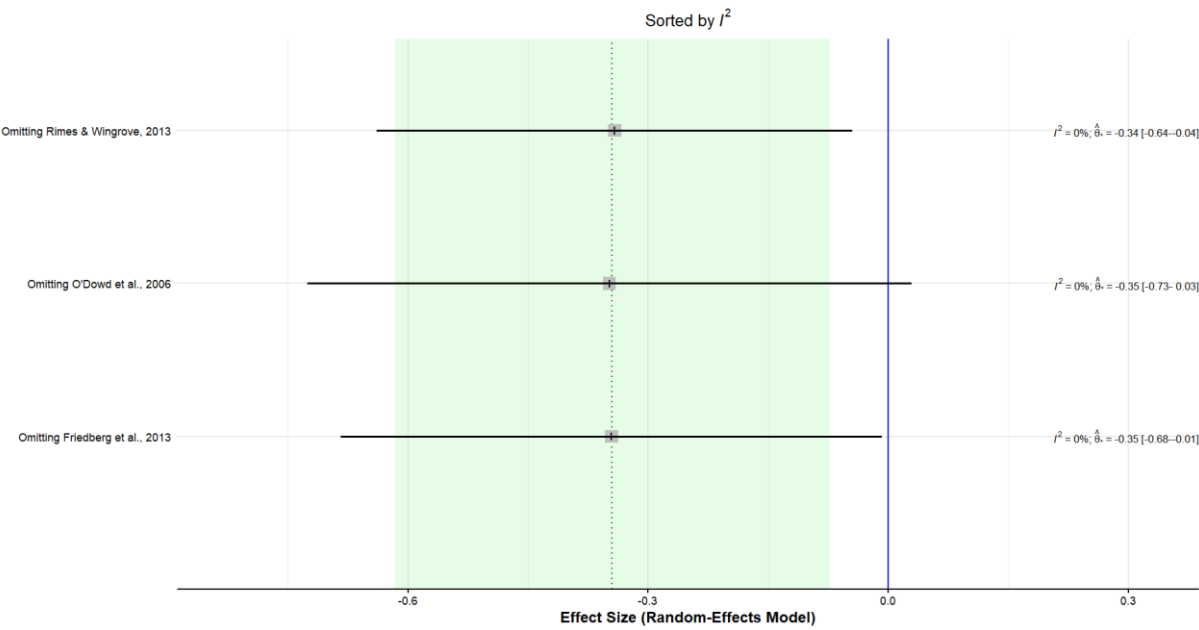
(A)



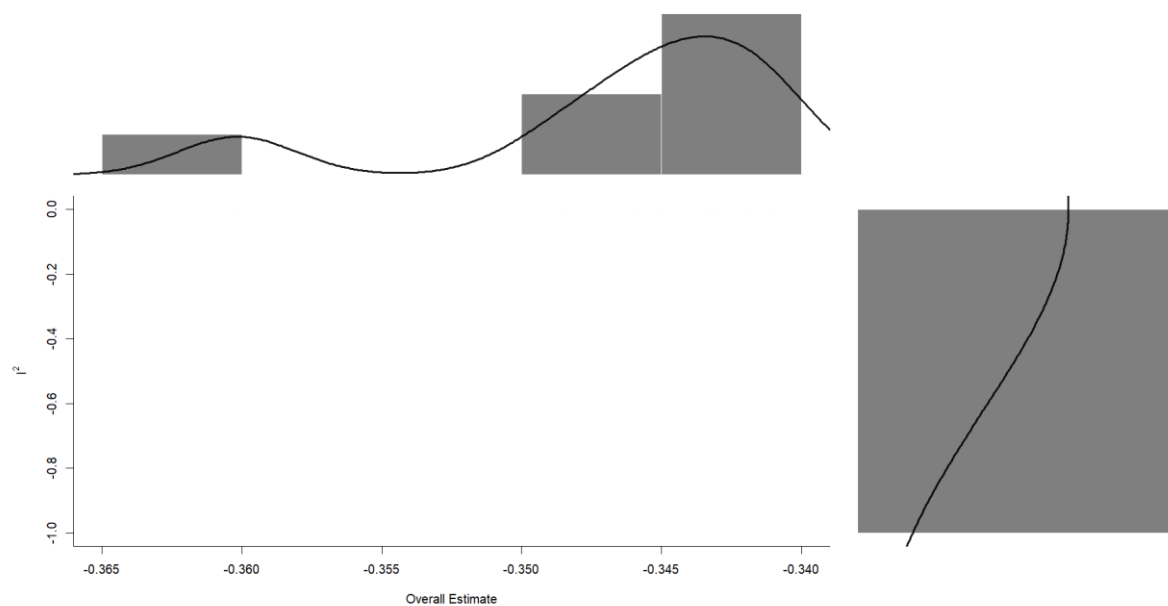
(B)



(C)

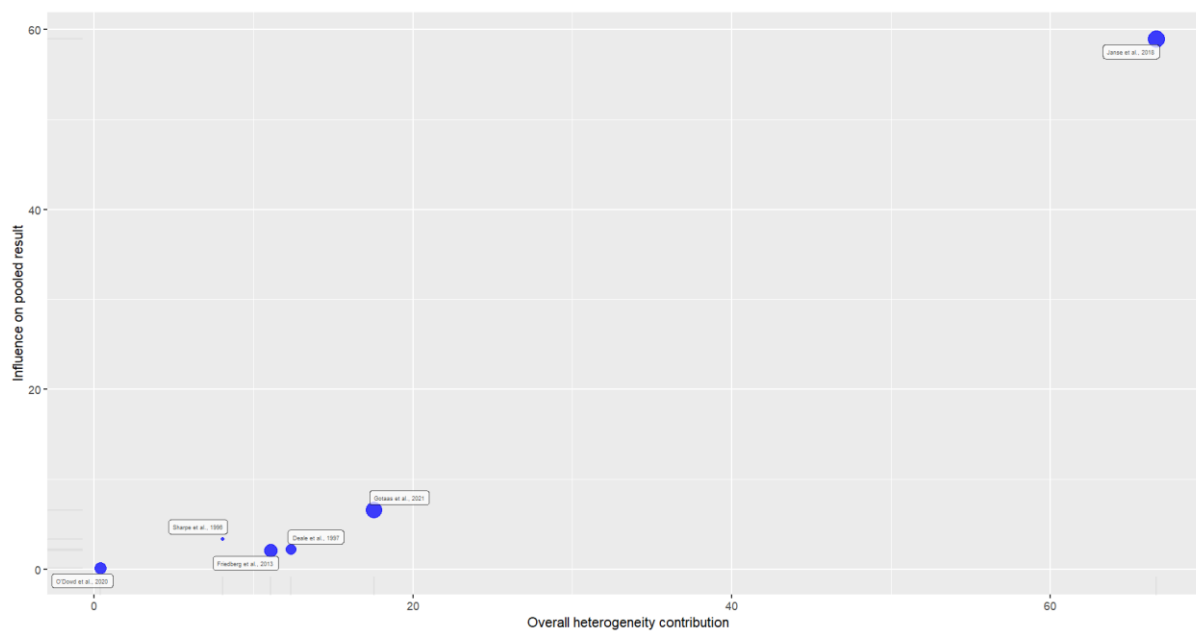
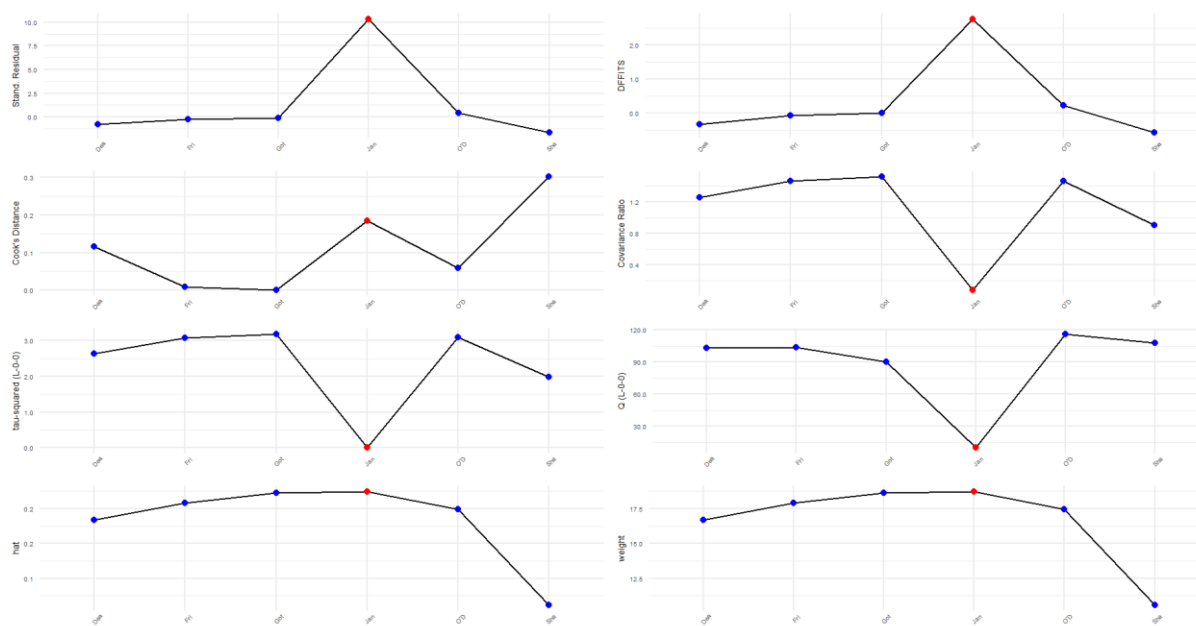


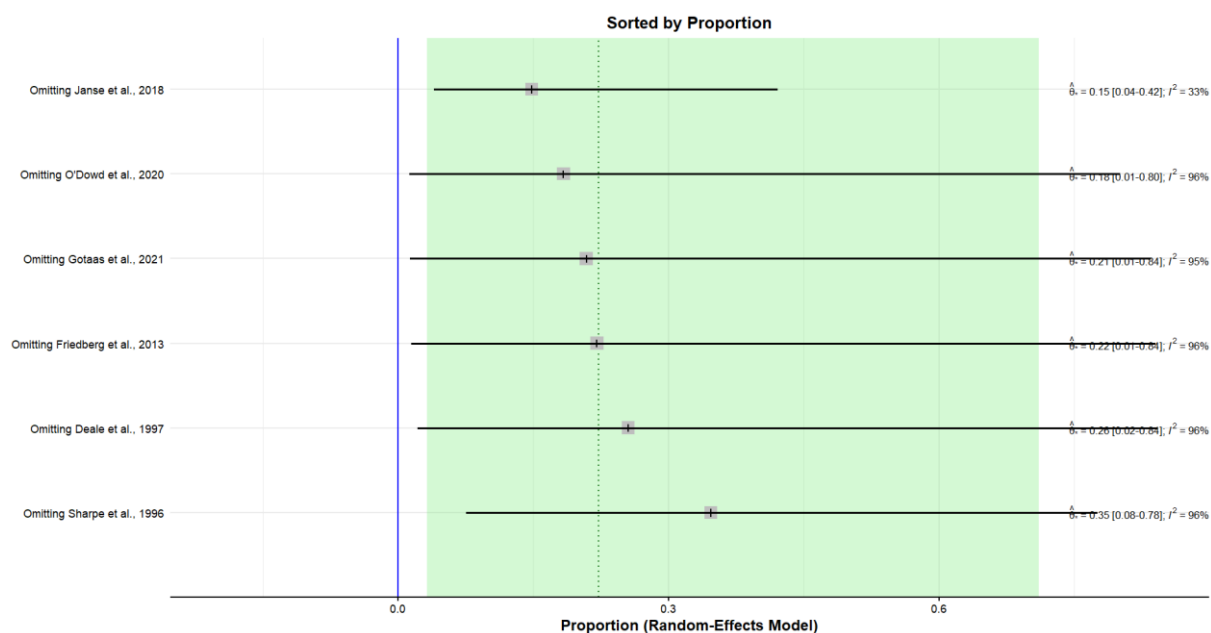
(D)



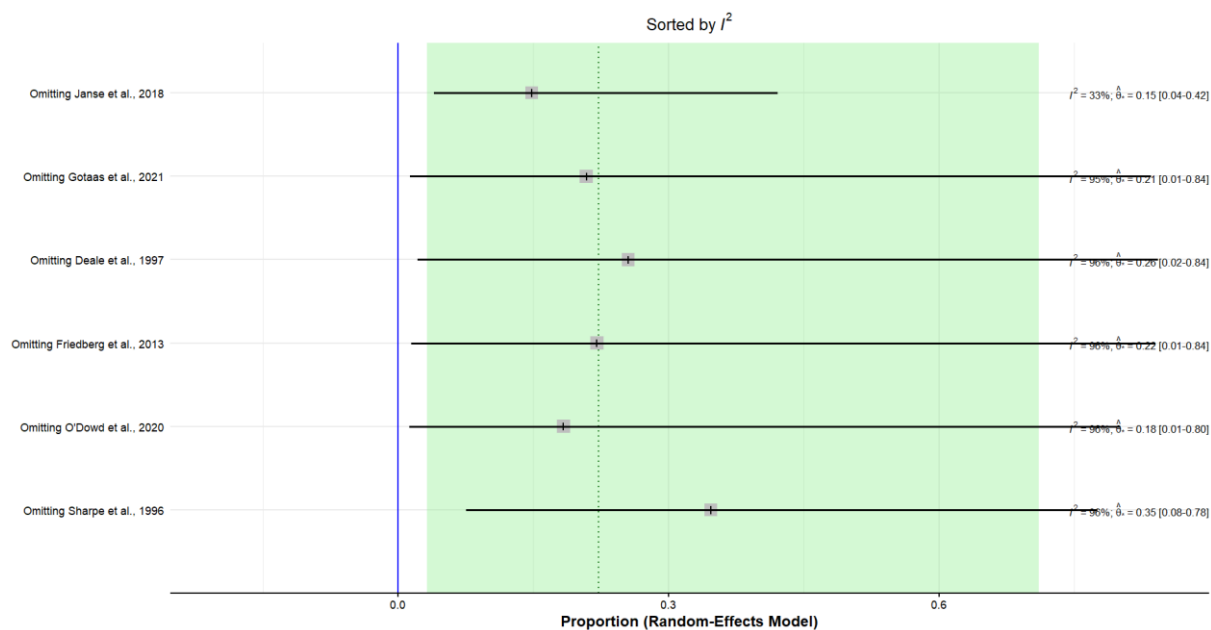
(E)

Note. A: Baujat plot; B: influence plot; C: leave one out method, influence on effect size; D: leave one out method, influence on heterogeneity; E: Graphic Display of Heterogeneity (GOSH) plot.

Figure S18*Results for the influence analyses for non-completion***(A)****(B)**

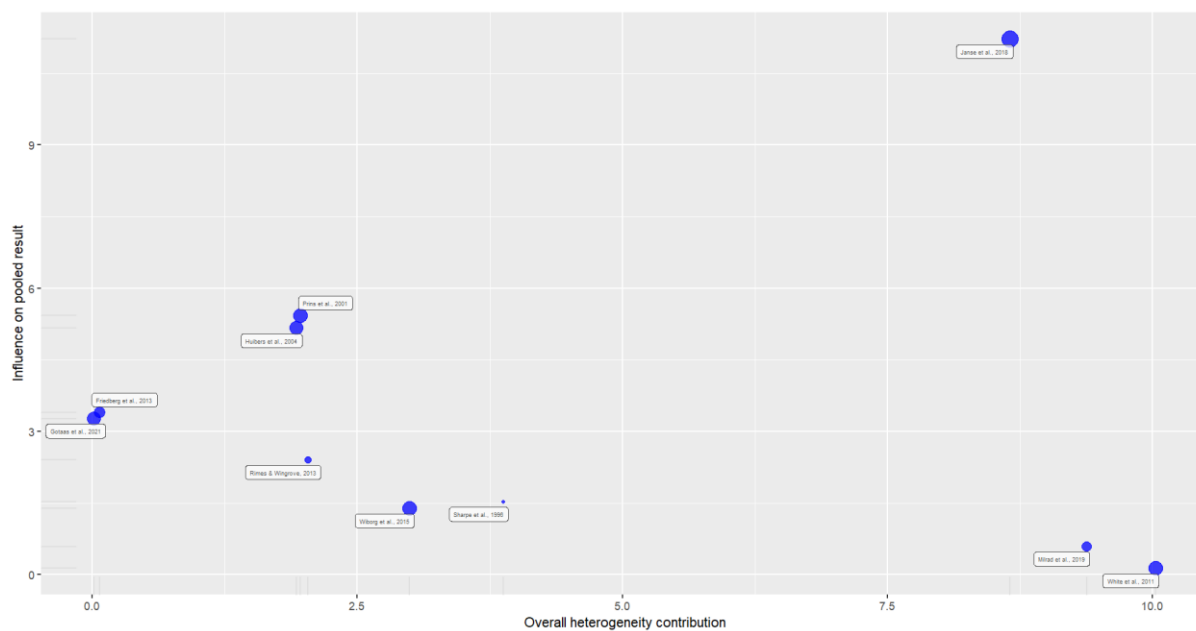
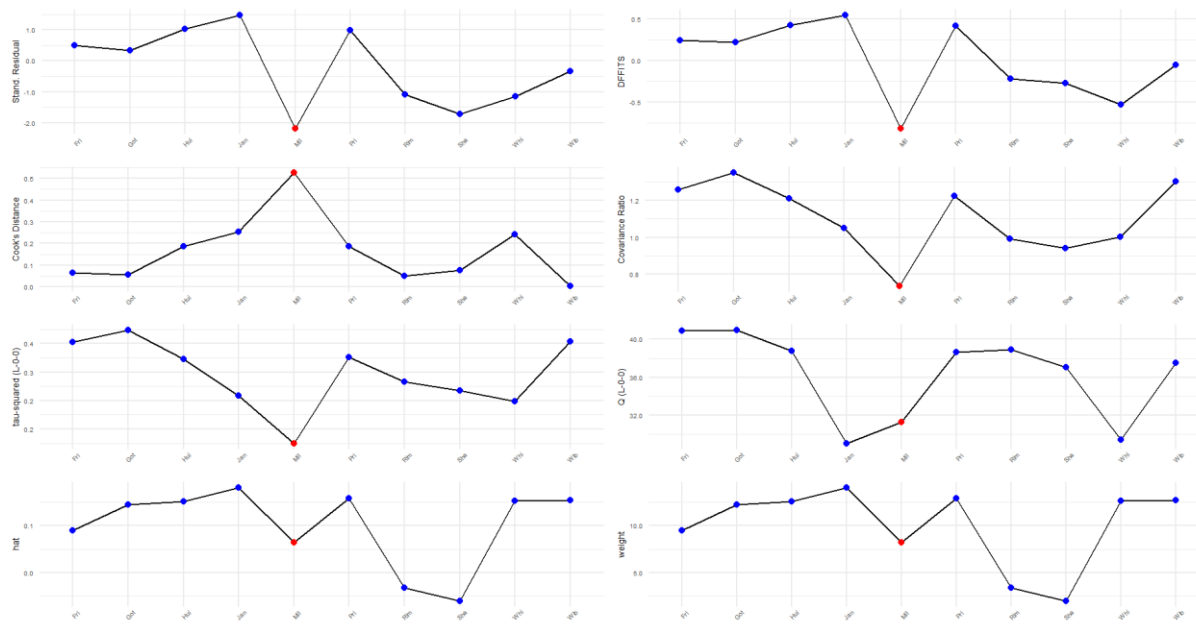


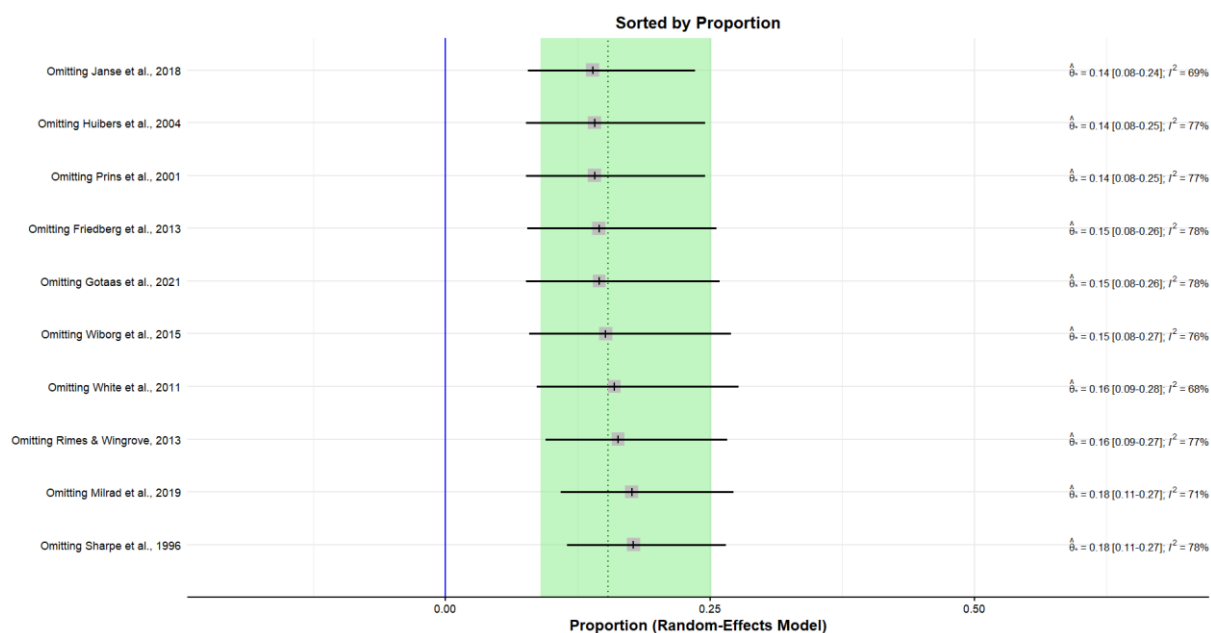
(C)



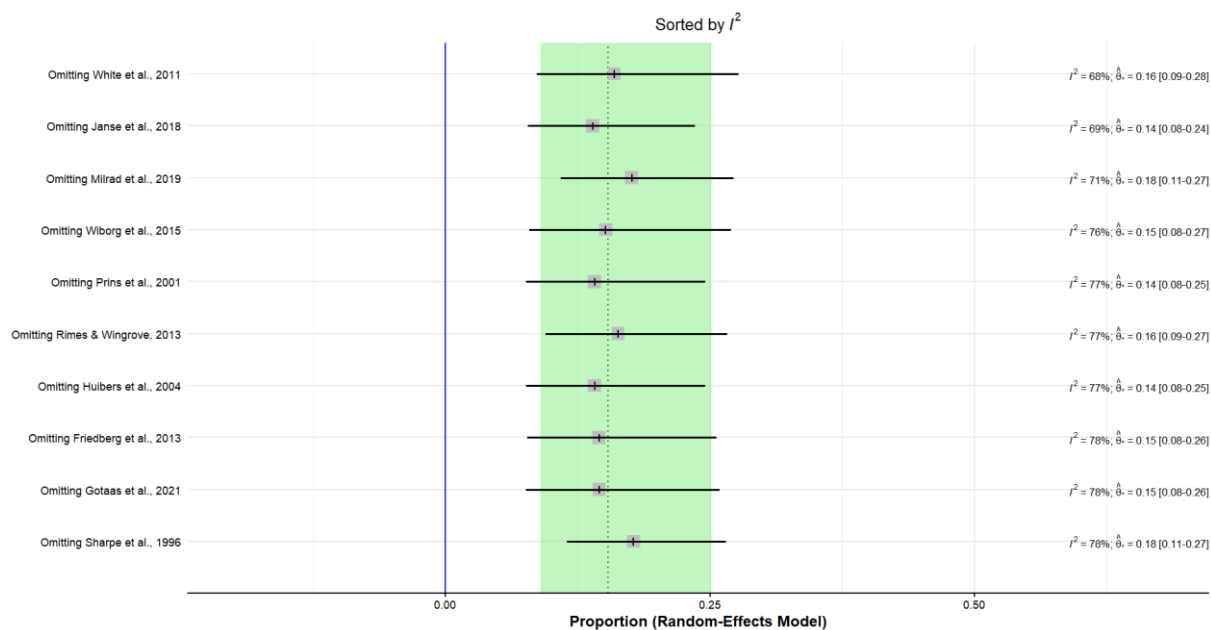
(D)

Note. A: Baujat plot; B: influence plot; C: leave one out method, influence on effect size; D: leave one out method, influence on heterogeneity.

Figure S19*Results for the influence analyses for drop-out***(A)****(B)**



(C)

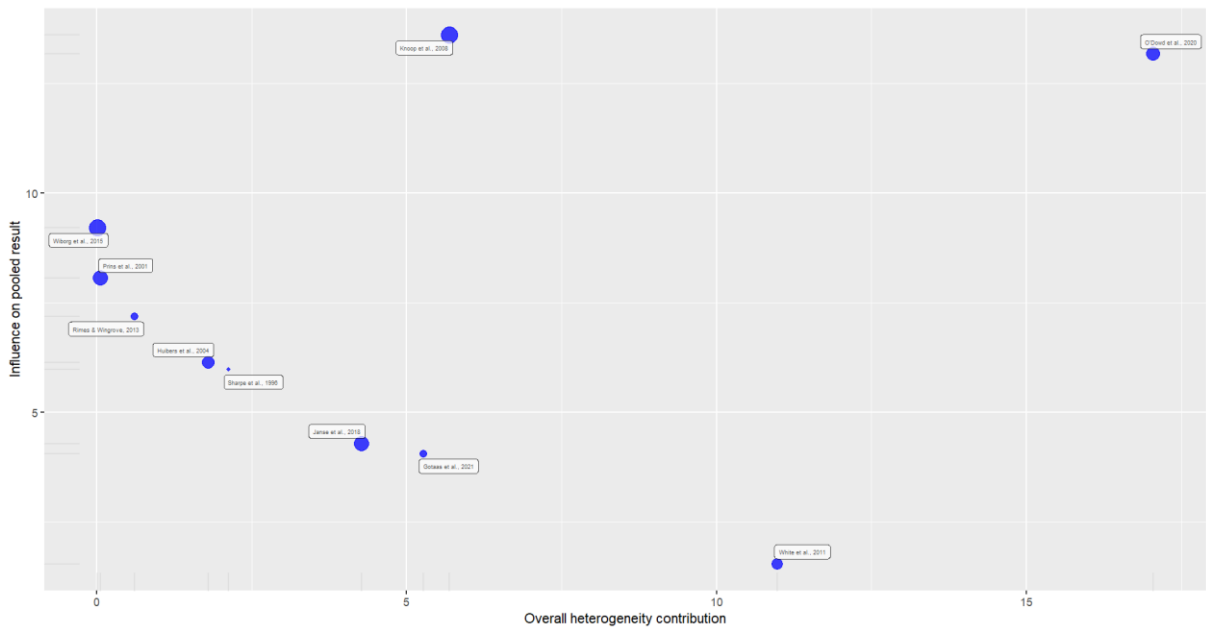


(D)

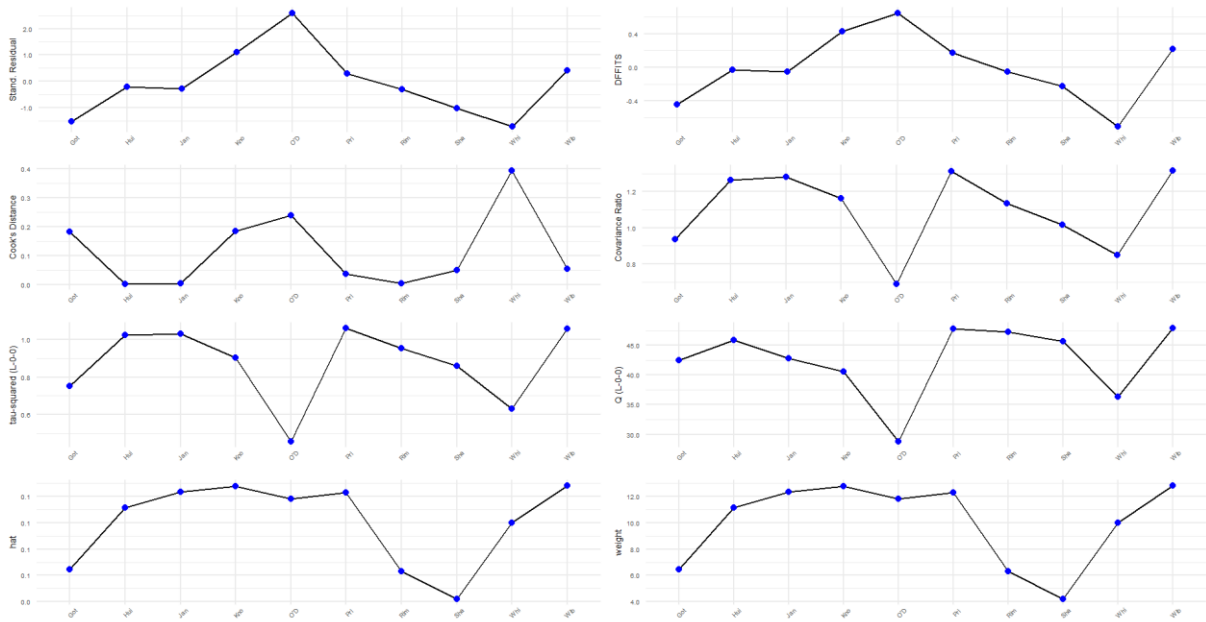
Note. A: Baujat plot; B: influence plot; C: leave one out method, influence on effect size; D: leave one out method, influence on heterogeneity.

Figure S20

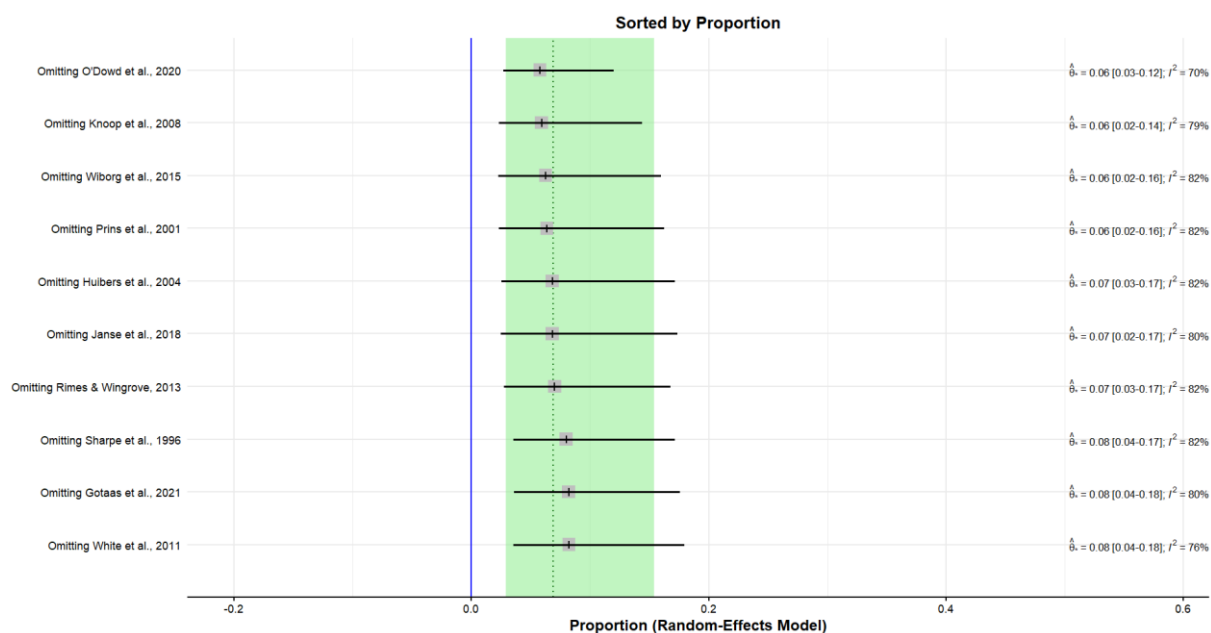
Results for the influence analyses for treatment refusal



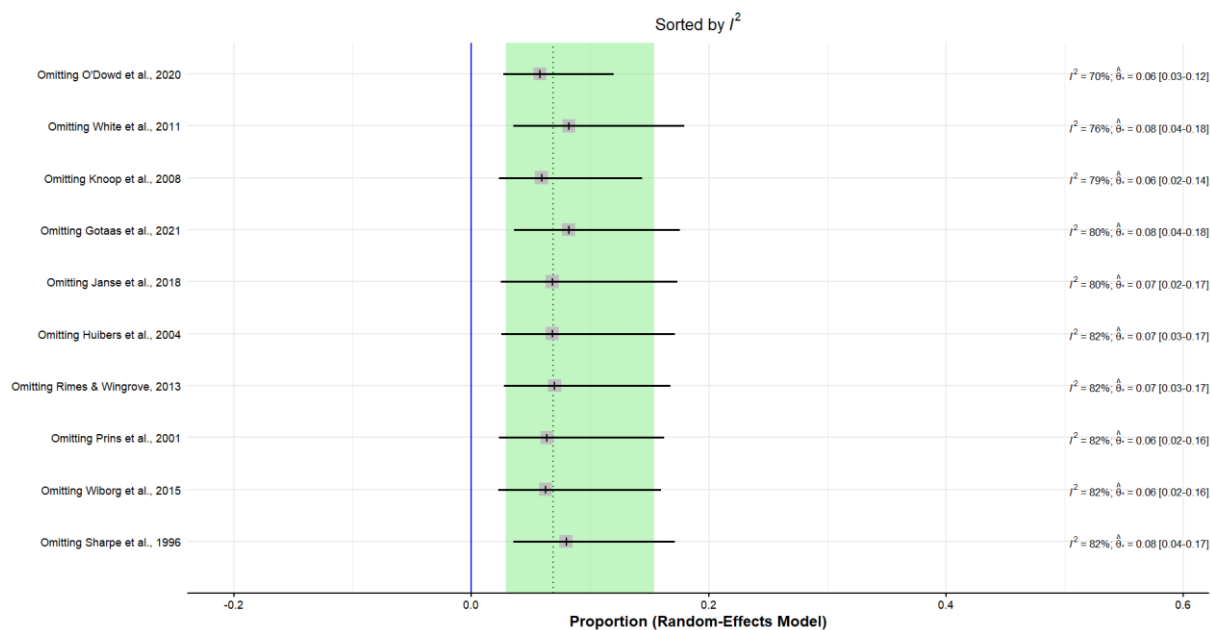
(A)



(B)



(C)

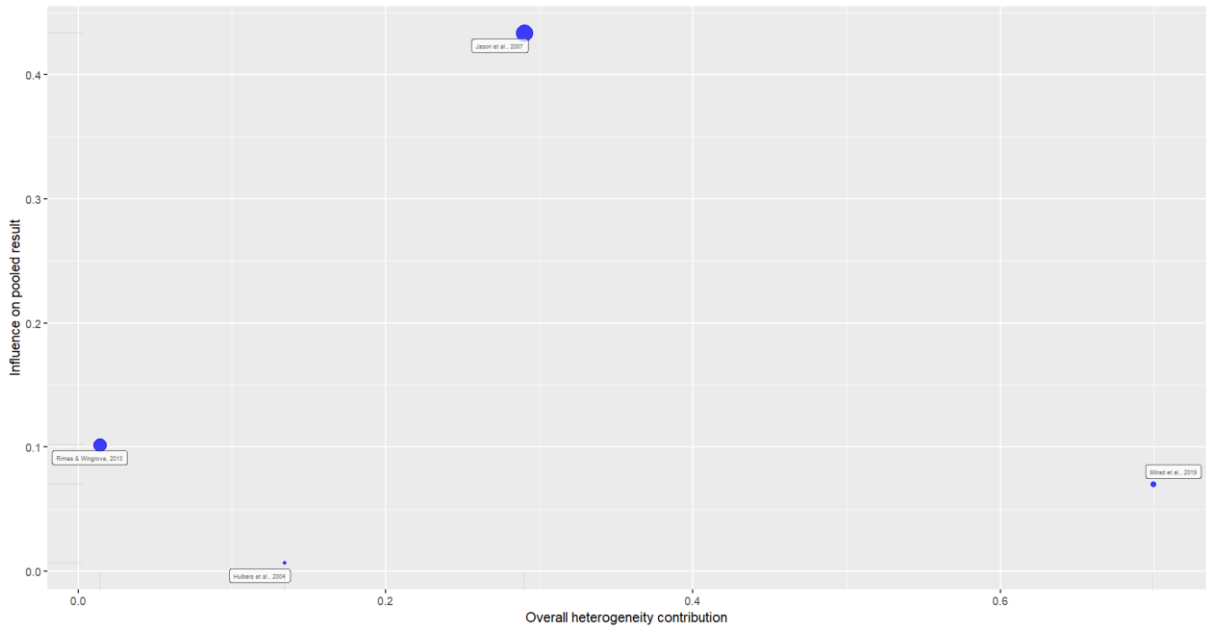


(D)

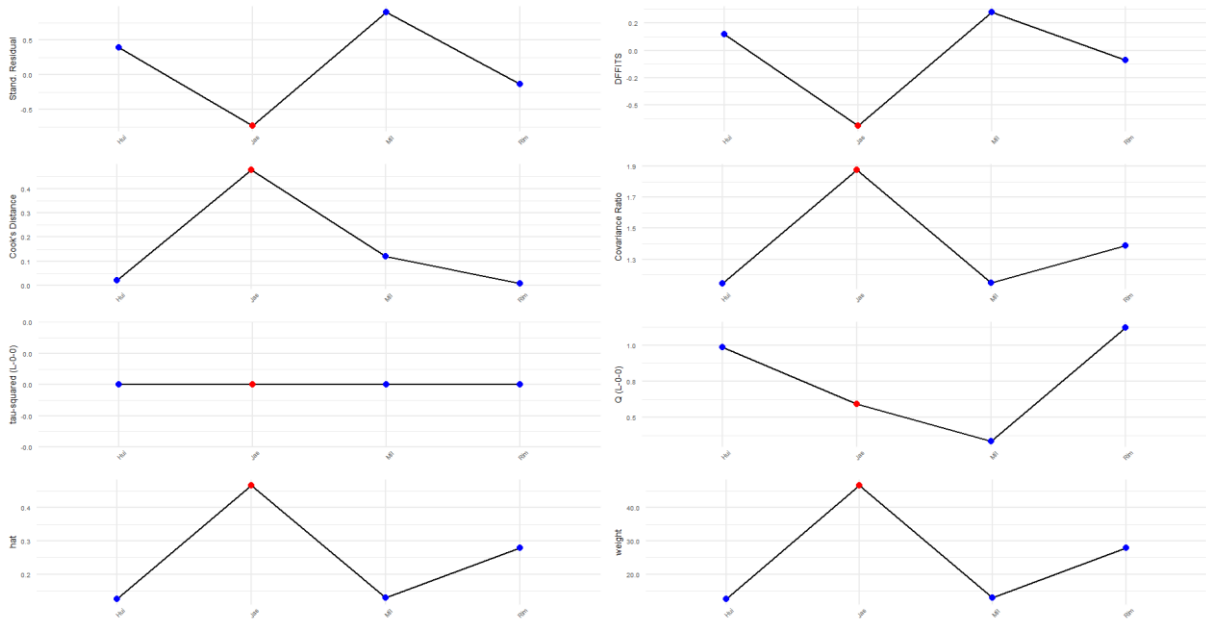
Note. A: Baujat plot; B: influence plot; C: leave one out method, influence on effect size; D: leave one out method, influence on heterogeneity.

Figure S21

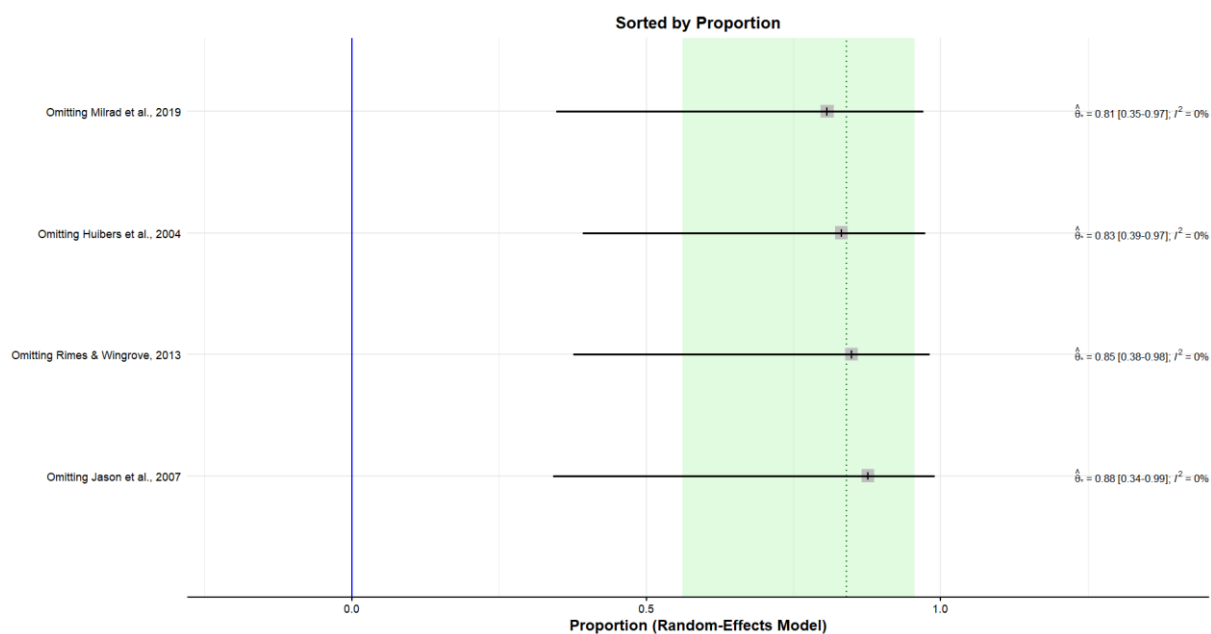
Results for the influence analyses for average proportion of session completed



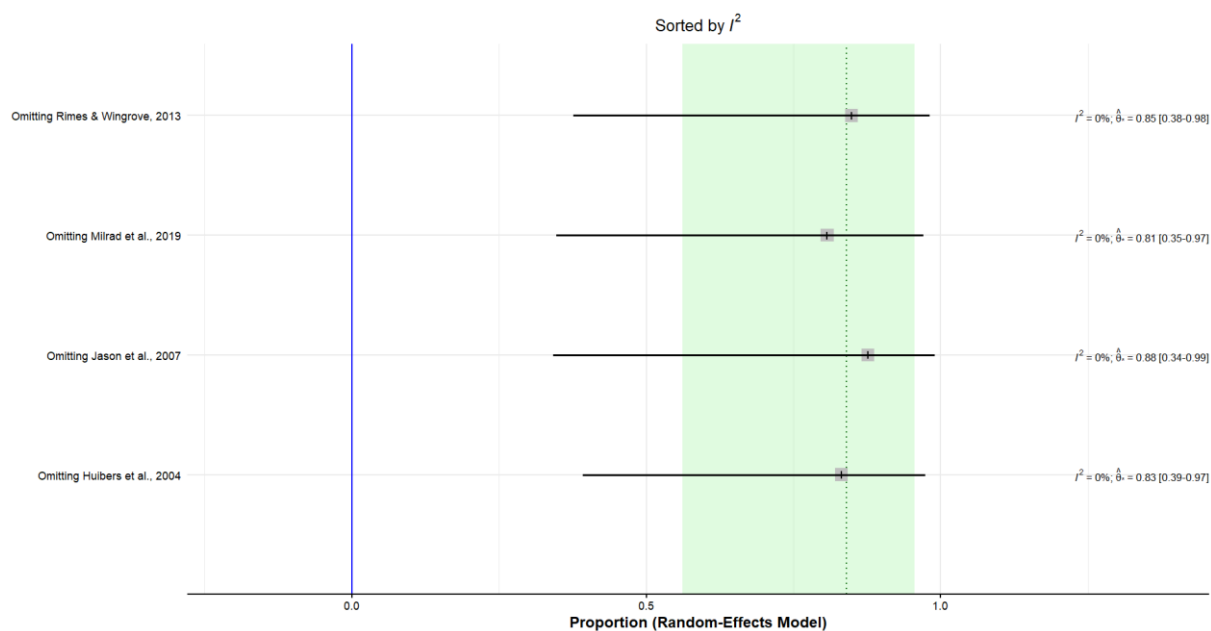
(A)



(B)



(C)



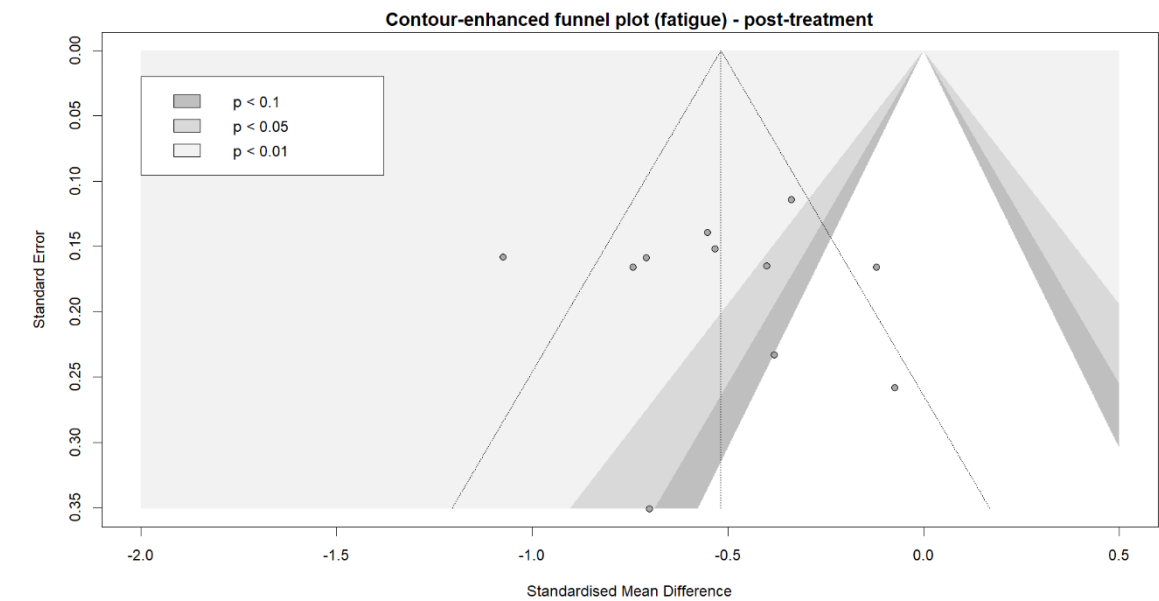
(D)

Note. A: Baujat plot; B: influence plot; C: leave one out method, influence on effect size; D: leave one out method, influence on heterogeneity.

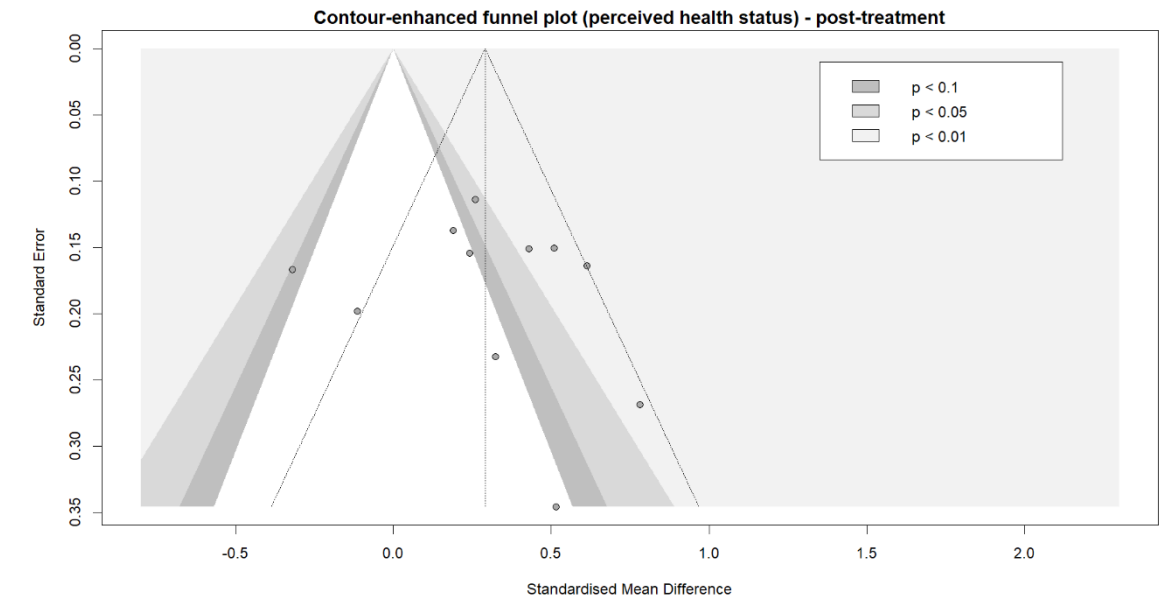
9. Publication Bias

Figure S22

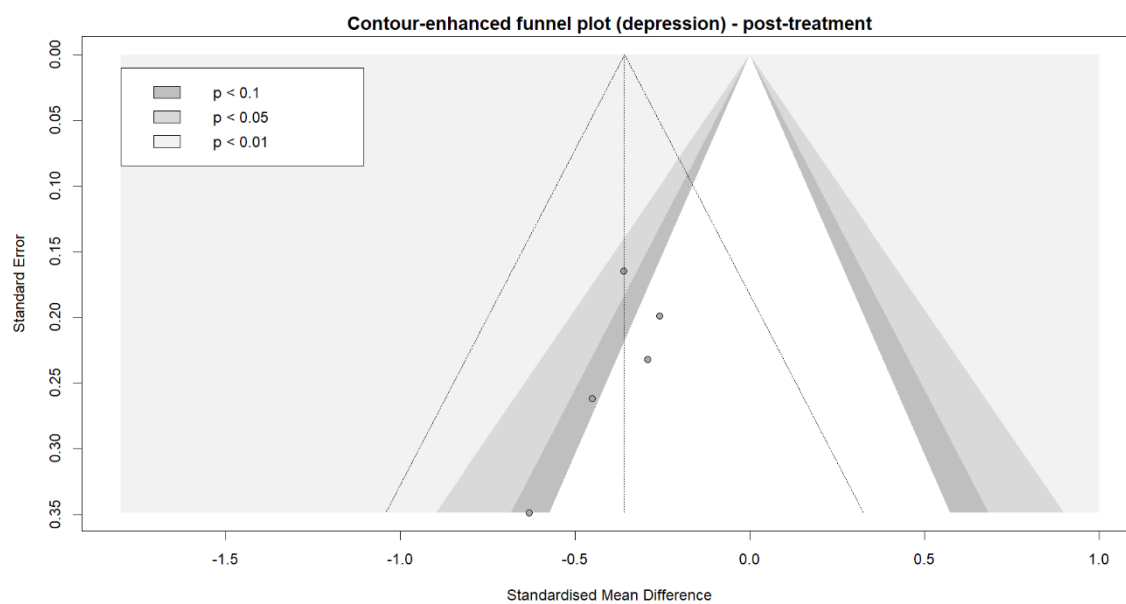
Publication bias



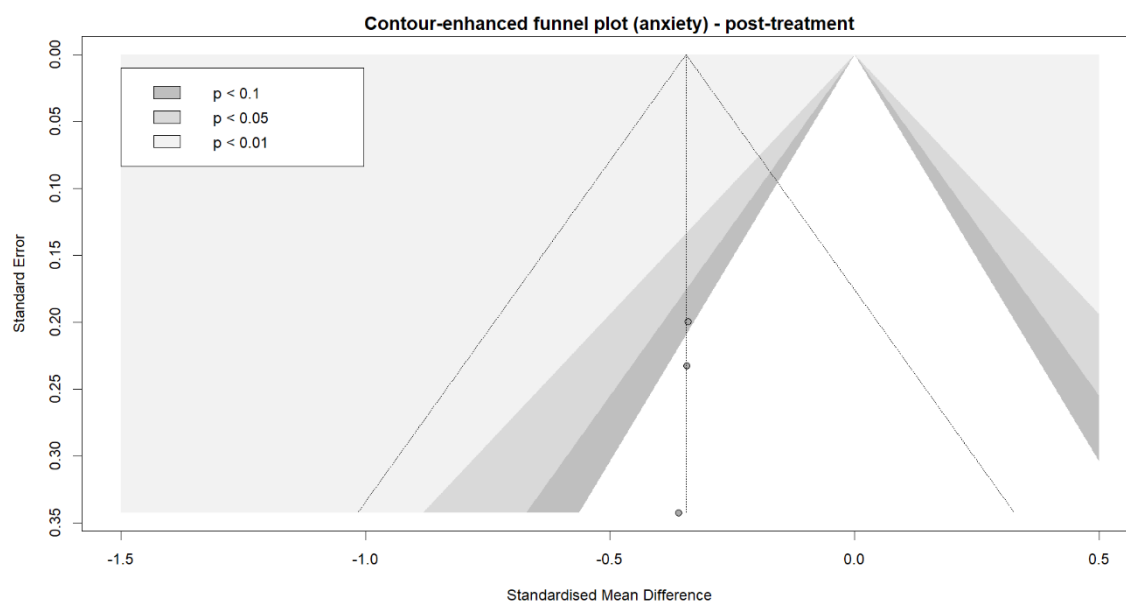
(A)



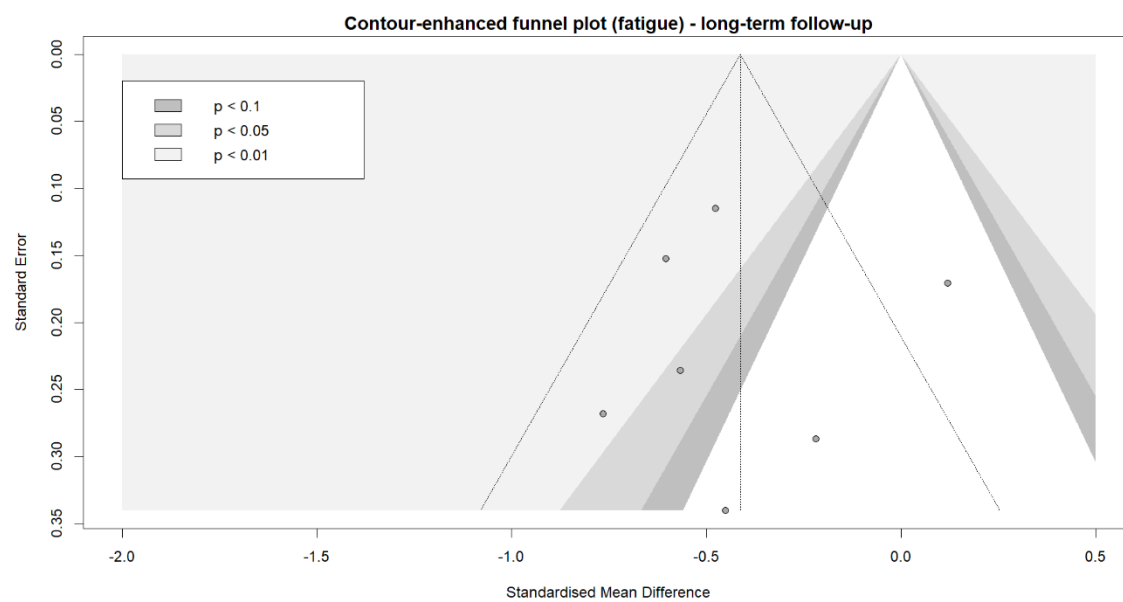
(B)



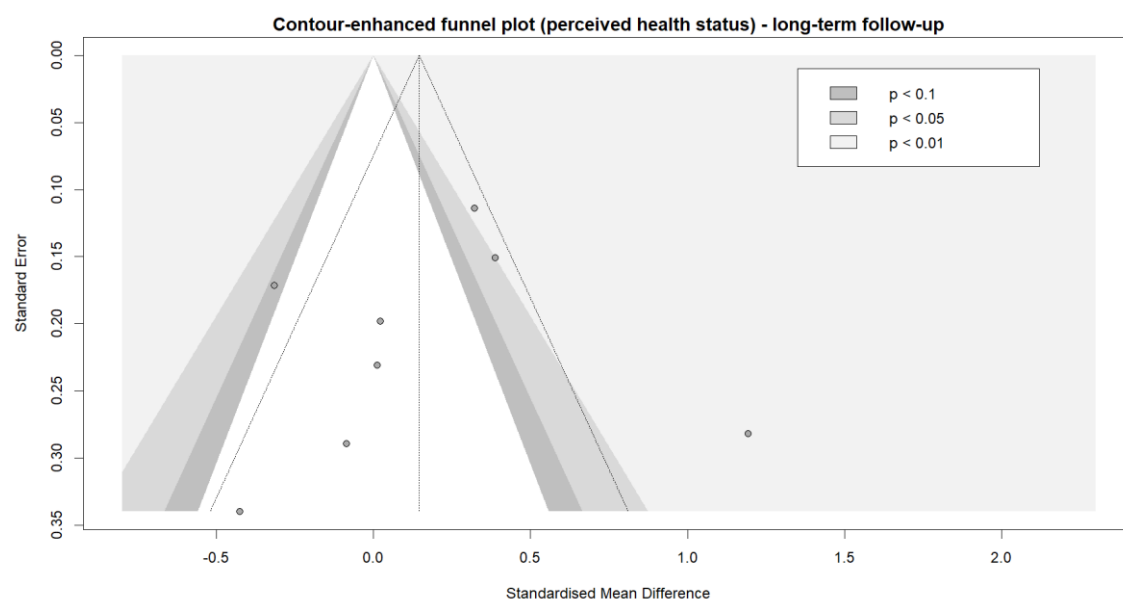
(C)



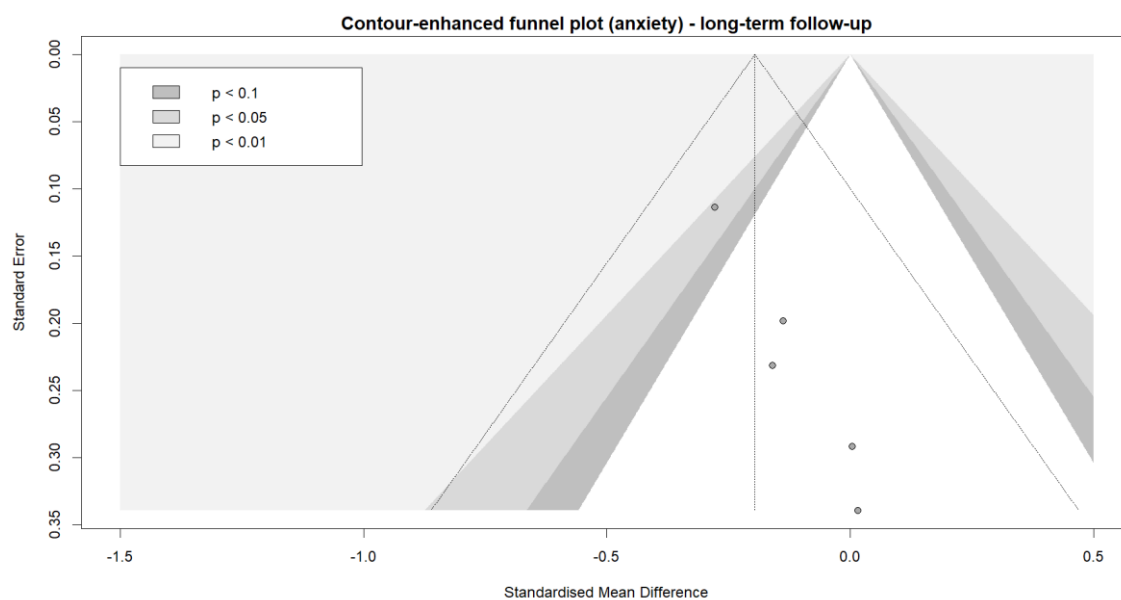
(D)



(E)



(F)



(G)

Note. A: fatigue at post-treatment; B: perceived health status at post-treatment; C: depression at post-treatment; D: anxiety at post-treatment; E: fatigue at long-term follow-up; F: perceived health status at long-term follow-up; G: anxiety at long-term follow-up.

Table S11*Results of Egger's regression tests*

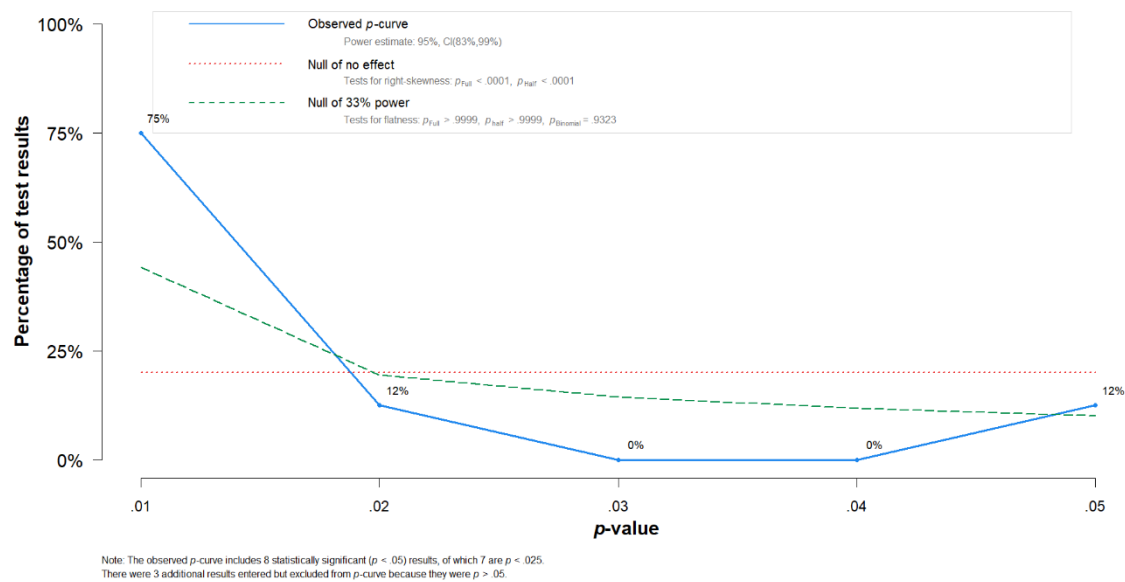
Outcome	Intercept	<i>t</i>	<i>p</i>
Post-treatment			
Fatigue	0.10	0.05	0.96
Perceived Health Status	0.94	0.47	0.65
Depression ^a	-1.33	-1.62	0.20
Anxiety ^a	-0.14	-6.26	0.10
Long-term follow-up			
Fatigue ^a	-0.03	-0.02	0.99
Perceived Health Status ^a	-1.04	-0.46	0.66
Depression ^a	1.30	2.24	0.09
Anxiety ^a	1.37	7.87	0.01

^a $k < 10$

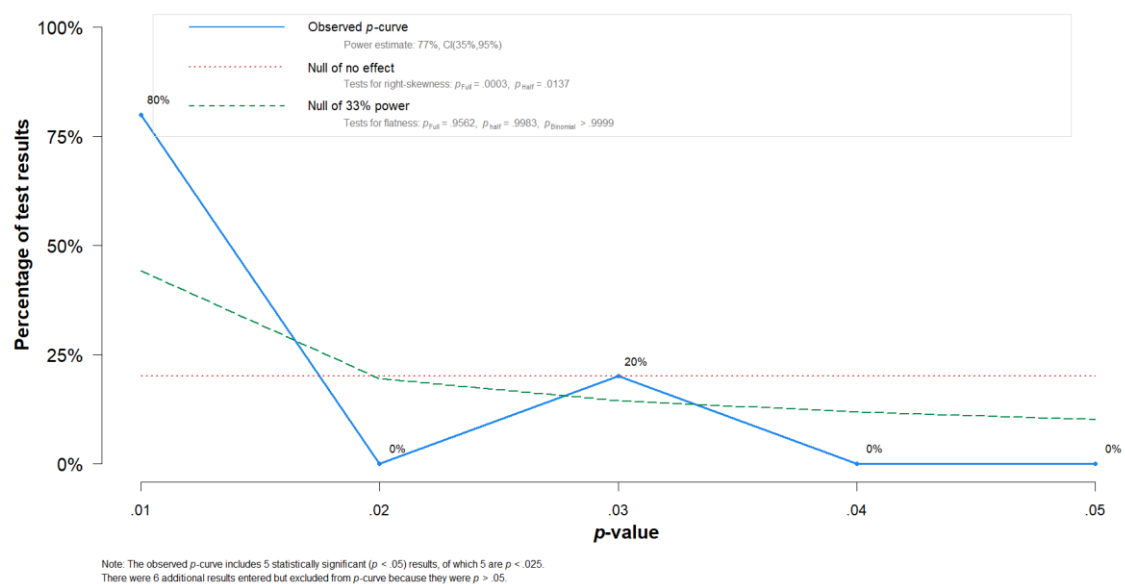
10. P-curve Analyses

Figure S23

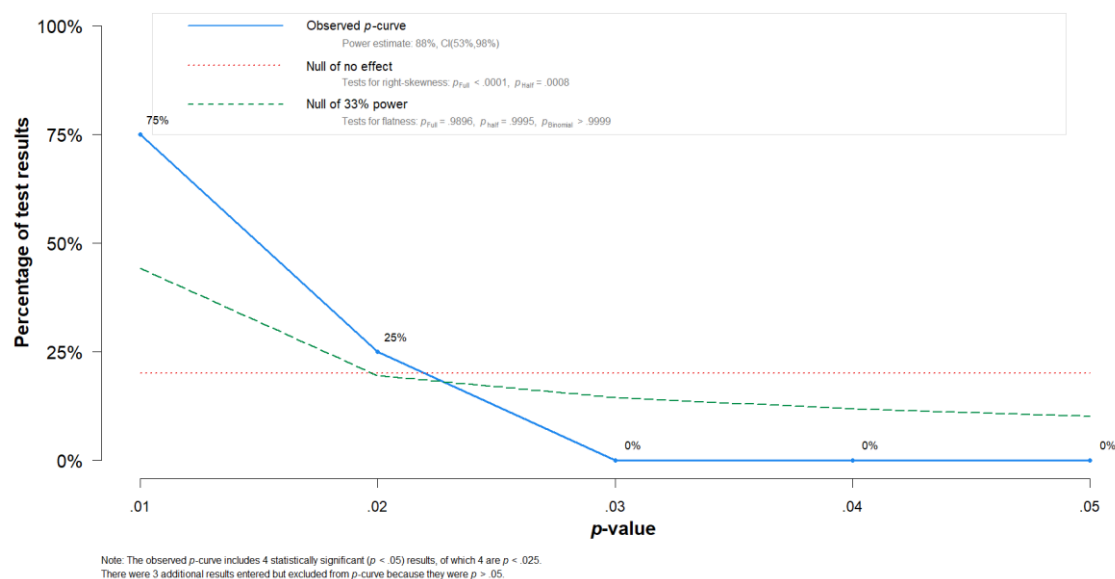
P-curve analyses



(A)



(B)



(C)

Note. A: p -curve for somatic symptom severity at post-treatment; B: p -curve for perceived health status at post-treatment; C: p -curve for somatic symptom severity at long-term follow-up. Note: p -curve could not be conducted for depression and anxiety at post-treatment and long-term follow-up as two or less significant ($p < 0.05$) effect sizes were detected; p -curve could not be conducted for perceived health status at long-term follow-up due to missing values.

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4. Carruthers BM, Jain AK, Meirleir KL de, et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. *J. Chronic Fatigue Syndr.* 2003;11:7–115. doi:10.1300/J092v11n01_02.

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Appendix C

Appendix – Study 2

1. Eligible syndromes and diagnoses

- ICD-10 (1):
 - Somatization disorder (F45.0)
 - Undifferentiated somatoform disorder (F45.1)
 - Dissociative (conversion) disorders (F44.)
 - Persistent somatoform pain disorder (F45.4)
 - Somatoform autonomic dysfunction (F45.3)
 - Other somatoform disorders (F45.8)
 - Somatoform disorder unspecified (F45.9)
 - Neurasthenia (in other neurotic disorders category; F.48.0)
- ICD-11 (2): Bodily Distress Disorder (6C40)
- DSM-IV (3):
 - Somatization Disorder (300.81) (4)
 - Undifferentiated somatoform disorder (300.81)
 - Conversion disorder (300.11)
 - Pain disorder (307.80)
 - Somatoform disorder not otherwise specified (300.81)
- DSM-5 (5): Somatic Symptom Disorder (300.82) (6)
- Bodily Distress Syndrome (7)
- Multisomatoform Disorder (8)
- Abridged Somatization (SSI-4/6; somatic symptom index) (9)
- Physical Symptom Disorder (10)
- Polysymptomatic Distress Disorder (4)
- Complex Somatic Symptom Disorder (11)
- Medically unexplained symptoms (MUS, 12)
- Functional Somatic Disorders (13)
- multi-symptom Functional Somatic Syndromes
 - IBS
 - Rome-I to -IV (14)
 - German consensus guidelines (15),
 - ICD-10 (1): K85.
 - CFS and myalgic encephalomyelitis (ME) will be combined under the term CFS
 - Holmes Criteria (16)
 - Oxford criteria (17)
 - Fukuda definition/Centers for Disease Control and Prevention (CDC) definition (18)
 - Canadian consensus criteria (19)
 - international consensus criteria (20)
 - NICE guidelines (21)
 - ICD-10 (1): Neurasthenia (F48.0), unspecified Chronic fatigue (R53.82), ME/postviral fatigue syndrome (G.93.3)
 - Systemic Exertion Intolerance Disease (22, 23)
 - FM/Fibromyalgia syndrome (FMS)
 - American College of Rheumatology (ACR) 1990 Criteria (24), ACR 2010 preliminary diagnostic criteria (25), 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria (26)
 - ICD-10 (1): M79.7
 - Chronic Widespread Pain: Defining feature of FM, although not pathognomonic (27)

2. Prioritization of exclusion criteria

Reasons for exclusion were prioritized as follows: focus is not on bodily distress; treatment is not CBT or a third wave treatment; focus is not on human adults (e.g., children, adolescents, animals); the study is not an RCT; neither control group is inactive, CBT or a third wave treatment; the report was not published in English or German.

3. Excluded studies

There are several studies we excluded but that might appear to meet our inclusion criteria:

- Amutio et al. (28): no clear definition as for how the diagnosis of FM was assessed
- Andrés-Rodríguez et al. : same sample as Pérez-Aranda et al. (29, subset)
- Givehki et al. (30): they assessed relevant outcomes but did not report them; authors did not answer inquiries
- Mirsharifa et al. (31): no clear definition as for how the diagnosis of IBS was assessed; authors did not answer inquiries
- Mohamadi et al. (32): reporting of relevant outcomes was considered faulty; authors did not answer inquiries
- Zomorodi et al. (33): only PHS was assessed of the relevant outcomes; its reporting is considered faulty; authors did not answer inquiries
- Ljótsson et al. (34, 35): exposure therapies with additional mindfulness elements
- Kleinstäuber et al. (36) : the intervention mainly contained conventional CBT with additional 3rd Wave methods

4. Search strategies

Search strategy PubMed

((“Somatoform disorders” [MeSH Terms] OR somatization disorder [MeSH Terms] OR somatization disorder [MeSH Terms] OR Neurasthenia [MeSH Terms] OR “conversion disorder” [MeSH Terms] OR psychophysiological disorder [MeSH Terms] OR “Psychosomatic medicine” [MeSH Terms] OR Fibromyalgia [MeSH Terms] OR “Fatigue Syndrome, Chronic” [MeSH Terms] OR “Irritable Bowel Syndrome” [MeSH Terms] OR “Colonic diseases, Functional” [MeSH Terms] OR briquet syndrome [MeSH Terms] OR

“somatoform disorder*” [All Fields] OR somatoform [All Fields] OR somatiz* [All Fields] OR somatis* [All Fields] OR “somatic symptom disorder*” [All Fields] OR (somatic NEAR symptom*) OR (pain NEXT disorder) OR “psychophysiological disorder*” [All Fields] OR “psychophysiologic disorder*” [All Fields] OR psychosomat* [All Fields] OR “persistent physical symptom*” [All Fields] OR “persistent somatic symptom*” [All Fields] OR “bodily distress” [All Fields] OR “body distress” [All Fields] OR “Physical Symptom Disorder” [All Fields] OR “pain disorder*” [All Fields] OR multisomat* [All Fields] OR “multi?somat*” [All Fields] OR polysymptom* [All Fields] OR “poly?symptom*” [All Fields] OR (multiple AND (“physical symptom*” OR “symptom diagnos*”)) OR

„frequent attend*” [Title/Abstract] OR „high utilis*” [Title/Abstract] OR „high utiliz*” [Title/Abstract]

OR “medically unexplain*” [All Fields] OR “organically unexplain*” [All Fields] OR MUS [All Fields] OR MUPS [All Fields] OR “unexplained medical*” [All Fields] OR “unexplained symptom*” [All Fields] OR “unexplained syndrom*” [All Fields] OR “unexplained illness*” [All Fields] OR nonorganic [All Fields] OR “non?organic” [All Fields] OR

“non?specific complain*” [All Fields] OR “non?specific symptom*” [All Fields] OR “psychosomatic syndrom*” [All Fields] OR

FSS [All Fields] OR "functional somatic syndrome*" [All Fields] OR "functional somatic disorder*" [All Fields] OR "functional symptom" [All Fields] OR "functional disorder*" [All Fields] OR "functional syndrome*" [All Fields] OR "functional somatic" [All Fields] OR "functional illness*" [All Fields] OR ((irritable OR functional) AND (bowel* OR colon*)) OR “functional gastrointestinal*” [All Fields] OR IBS [All Fields] OR fibromyalgia* [All Fields] OR fibrositis [All Fields] OR FM [All Fields] OR fibromyositis [All Fields] OR myofibrositis [All Fields] OR “chronic widespread pain*” [All Fields] OR “widespread musculoskeletal pain*” [All Fields] OR “myofascial pain*” [All Fields] OR “persistent pain*” [All Fields] OR “chronic intractable benign pain*” [All Fields] OR “fatigue syndrome*” [All Fields] OR “psychogenic fatigue” [All Fields] OR “systemic exertion intolerance” [All Fields] OR “myalgic encephalomyelitis*” [All Fields] OR “myalgic encephalopath*” [All Fields] OR CFS [All Fields] OR “CFS/ME” [All Fields] OR “postviral fatigue syndrome*” [All Fields] OR “systemic exertion intolerance*” [All Fields]))

AND

((“third wave” AND (therap* OR treatment*)) OR mindful* [All Fields] OR MBT [All Fields] OR MBCT [All Fields] OR MBSR [All Fields] OR (acceptance AND commitment) OR "mindfulness based stress reduction"[All Fields] OR "mindfulness based cognitive therapy"[All Fields] OR "acceptance and commitment therapy"[All Fields])

Filters: Randomized Controlled Trial, Meta-Analysis, Systematic Review

Search strategy Cochrane Library

ID Search

#1 MeSH descriptor: [Conversion Disorder] explode all trees

#2 MeSH descriptor: [Somatoform Disorder] explode all trees

#3 MeSH descriptor: [Somatoform Disorders] explode all trees

#4 MeSH descriptor: [Neurasthenia] explode all trees

#5 MeSH descriptor: [Psychophysiologic Disorders] explode all trees

#6 MeSH descriptor: [Psychosomatic Medicine] explode all trees

#7 MeSH descriptor: [Fibromyalgia] explode all trees

#8 MeSH descriptor: [Fatigue Syndrome, Chronic] explode all trees

#9 MeSH descriptor: [Irritable Bowel Syndrome] explode all trees

#10 MeSH descriptor: [Colonic Diseases, Functional] explode all trees

#11 “somatoform disorder*” OR somatoform OR somatiz* OR somatis* OR “somatic symptom disorder*” OR (somatic AND symptom*) OR (pain NEXT disorder) OR “psychophysiological disorder*” OR “psychophysiologic disorder*” OR psychosomat* OR “persistent physical symptom*” OR “persistent somatic symptom*” OR “bodily distress” OR "body distress" OR “Physical Symptom Disorder” OR “pain disorder*”

#12 **multisomat*** OR **"multi?somat*"** OR **polysymptom*** OR **"poly?symptom*"** OR **(multiple AND ("physical symptom*" OR "symptom diagnos*"))**

#13 **"medically unexplain*"** OR **"organically unexplain*"** OR **MUS** OR **MUPS** OR **"unexplained medical*"** OR **"unexplained symptom*"** OR **"unexplained syndrom*"** OR **"unexplained illness*"**

#14 **nonorganic** OR **"non?organic"** OR **"non?specific complain*"** OR **"non?specific symptom*"**

#15 **"psychosomatic syndrom*"**

#16 **FSS** OR **"functional somatic syndrome*"** OR **"functional somatic disorder*"** OR **"functional symptom"** OR **"functional disorder*"** OR **"functional syndrome*"** OR **"functional somatic"** OR **"functional illness*"**

#17 **((irritable OR functional) AND (bowel* OR colon*))** OR **"functional gastrointestinal*"** OR **IBS**

#18 **fibromyalgia*** OR **fibrositis** OR **FM** OR **fibromyositis** OR **myofibrositis**

#19 **"chronic widespread pain*"** OR **"widespread musculoskeletal pain*"** OR **"myofascial pain*"** OR **"persistent pain*"** OR **"chronic intractable benign pain*"**

#20 **"fatigue syndrome*"** OR **"psychogenic fatigue"** OR **"systemic exertion intolerance"** OR **"myalgic encephalomyelitis*"** OR **"myalgic encephalopath*"** OR **CFS** OR **"postviral fatigue syndrome*"** OR **"systemic exertion intolerance*"**

#21 **("third wave" AND (therap*OR treatment*))**

#22 **mindful*** OR **MBT** OR **MBCT** OR **MBSR**

#23 **(acceptance AND commitment)**

#24 **#1** OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7** OR **#8** OR **#9** OR **#10** OR **#11** OR **#12** OR **#13** OR **#15** OR **#16** OR **#17** OR **#18** OR **#19** OR **#20**

#25 **#21** OR **#22** OR **#23**

#26 **#24** AND **#25**

Search strategy PsycInfo

(("somatoform disorder*" OR somatoform OR somatiz* OR somatis* OR "somatic symptom disorder*" OR (somatic AND symptom*) OR "psychophysiological disorder*" OR "psychophysiologic disorder*" OR psychosomat* OR "persistent physical symptom*" OR "persistent somatic symptom*" OR "bodily distress" OR "body distress" OR "Physical Symptom Disorder" OR "pain disorder*" OR multisomat* OR "multi?somat*" OR polysymptom* OR "poly?symptom*" OR (multiple AND ("physical symptom*" OR "symptom diagnos*")) OR „frequent attend*" OR „high utilis*" OR „high utiliz*" OR "medically unexplain*" OR "organically unexplain*" OR MUS OR MUPS OR "unexplained medical*" OR "unexplained symptom*" OR "unexplained syndrom*" OR "unexplained illness*" OR nonorganic OR "non?organic" OR "non?specific complain*" OR "non?specific symptom*" OR "psychosomatic syndrom*" OR FSS OR "functional somatic syndrome*" OR "functional somatic disorder*" OR "functional symptom" OR "functional disorder*" OR "functional syndrome*" OR "functional somatic" OR "functional illness*" OR ((irritable OR functional) AND (bowel* OR colon*)) OR "functional gastrointestinal*" OR IBS OR fibromyalgia* OR fibrositis OR FM OR fibromyositis OR myofibrositis OR "chronic widespread pain*" OR "widespread

musculoskeletal pain*" OR "myofascial pain*" OR "persistent pain*" OR "chronic intractable benign pain*" OR "fatigue syndrome*" OR "psychogenic fatigue" OR "systemic exertion intolerance" OR "myalgic encephalomyelitis*" OR "myalgic encephalopath*" OR CFS OR "CFS/ME" OR "postviral fatigue syndrome*" OR "systemic exertion intolerance*")

AND

((("third wave" AND (therap* OR treatment*)) OR mindful* OR MBT OR MBCT OR MBSR OR (acceptance AND commitment))

AND

("double-blind" OR "random* assigned" OR control)

Methodology: Clinical trial, systematic review, meta-analysis

Search strategy Psyndex

(„somatisch* Belastung*“ OR „somatisch* Syndrom*“ OR „somatoform*“ OR „somatisier*“ OR „anhaltend* Körperbeschwerde*“ OR „Neurasthenie*“ OR „Konversionsstörung*“ OR „psychophysiologisch*“ OR „psychosomati*“ OR „Briquet Syndrom*“ OR „Schmerzstörung*“ OR (((„nicht spezifisch*“ OR „unspezifisch*“ OR „unklar*“ OR „medizinisch unerklärt*“ OR „organisch unerklärt*“ OR „nicht erklärt*“) AND („Symptom*“ OR „Syndrom*“)) OR „funktionell* Syndrom*“ OR „funktionell* Störung*“ OR „Reizdarm*“ OR „funktionell* gastrointestinal*“ OR „fibromyalgi*“ OR „fibrositis“ OR „fibromyositis“ OR „myofibrositis“ OR (“myofascial*” AND “Schmerz*”) OR “chronisch* Ganzkörperschmerz*” OR („Chronisch*“ OR „psychogen*“) AND („Müdigkeit*“ OR „Erschöpfung*“) OR „myalgic encephalomyelitis*“ OR „myalgic encephalopath*” OR “postviral* Erschöpfung*”)

AND

((„dritte Welle“ AND („Intervention*“ OR „Behandlung*“ OR „Therapie*”)) OR „achtsamkeit*“ OR („akzeptanz*“ OR “acceptance”) AND “commitment*”))

5. Study characteristics

Table S1

Study Characteristics

Study	Conditions	<i>n</i> allocated	Program Name	Guidance	Diag.	Specific Target Group	Country	No. sessions	Time total ^a	Follow-ups ^b (weeks)
Fjorback et al., 2013	MBSR	60	MBSR + CBT elements	Psychiatrist	BDS	Adults	DK	9	1890	24, 48
	EC	60								
Gaylord et al., 2011	MBSR	36	MBSR	Para	IBS	Women	US	9	1200	12, 24
	Psy. placebo	39								
Ghandi et al., 2018	MBSR	15	MBSR	Psy	IBS	Adults	IR	8	720	8
	TAU	19								
Henrich et al., 2019	MBCT	36	MBCT-IBS	Psy	IBS	Women	GB	6	720	6
	WL	31								
Ito & Muto, 2020	ACT	14	ACT for IBS	Psy	IBS	Students	JP	1	300	8
	WL	12								
Jensen et al., 2012; Wicksell et al., 2013	ACT	25	ACT for chronic pain	Psy	FM	Women	SE	12	1080	12
	WL	18								
Luciano et al., 2014	ACT	51	ACT adapted to FM	Psy	FM	Adults	ES	8	1200	16
	WL	53								
Parra-Delgado & Latorre-Postigo, 2013	MBCT	17	MBCT	Psy	FM	Adults	ES	8	1200	12
	TAU	16								
Pedersen et al., 2019	ACT	59	ACT	Mixed	BDS	Adults	DK	9	1695	32, 56
	EC	60								
Pérez-Aranda et al., 2019	MBSR	75	MBSR adapted for FM	Psy	FM	Adults	ES	8	960	40
	TAU	75								
Rimes & Wingrove, 2013	MBCT	17	MBCT	Psy	CFS/ ME	Adults	GB	9	1215	8
	WL	19								

Study	Conditions	n allocated	Program Name	Guidance	Diag.	Specific Target Group	Country	No. sessions	Time total ^a	Follow-ups ^b (weeks)
Schmidt et al., 2011	MBSR	58	MBSR	Para	FM	Women	GER	11	1740	8
	WL	59								
Sephton et al., 2007; Cash et al., 2015; Weissbecker et al., 2002	MBSR	51	MBSR	Psy	FM	Women	US	9	1650	8
	WL	40								
Simister et al., 2018	ACT	33	Online ACT protocol	Psy	FM	Adults	CA	7		12
	TAU	34								
van Ravesteijn et al., 2013	MBCT	61	MBCT + cognitive techniques	Para	MUS	Adults	NL	8	1560	36
	EC	56								
Zernicke et al., 2013	MBSR	43	MBSR	Para	IBS	Adults	CA	8	900	24
	WL	47								

Note. ACT = Acceptance and Commitment Therapy; BDS = bodily distress syndrome; CBT = cognitive behavioural therapy; CFS/ME = chronic fatigue syndrome/myalgic encephalomyelitis; CA = Canada; DK = Denmark; FM = fibromyalgia; EC = enhanced care; ES = Spain; GB = United Kingdom; GER = Germany; IBS = irritable bowel syndrome; IR = Iran; JP = Japan; MBCT = mindfulness-based cognitive therapy; MBSR = mindfulness-based stress reduction; Mixed = guidance provided by psychologist and psychiatrist; NL = Netherlands; Para = paraprofessional (study nurses, trained students); Psy = trained clinician (licensed psychotherapist/trained psychologist); Psy. placebo = psychological placebo; SE = Sweden; TAU = treatment as usual; US = United States of America; WL = wait-list.

^a total time of direct contact in minutes (was not applicable for Simister et al., 2018); ^b after end of treatment.

Table S2*Outcome measures*

Study	Somatic symptom severity	Depression	Anxiety	Health Anxiety	Perceived Health Status	Mindfulness	Psychological Inflexibility	Pain acceptance
Fjorback et al., 2013	SCL-90 (Somatization subscale) ^a	SCL-8 ^a	SCL-8 ^a	WI ^a	SF-36 (Physical)			
Gaylord et al., 2011	IBS-SSS	BSI-18 Depression	BSI-18 anxiety		IBS-QOL	FFMQ		
Ghandi et al., 2018	IBS-SSS				IBS-QOL-34			
Henrich et al., 2019	GSRS-IBS	DASS-21 (Depression subscale)	DASS-21 (Anxiety subscale)		IBS-QOL	FFMQ		
Ito & Muto, 2020	IBSSI	BDI-II	STAI (State)		SF-36 (Physical); IBS-QOL	FFMQ	CFQ	
Jensen et al., 2012; Wicksell et al., 2013	VAS	BDI	STAI (State)		SF-36 (Physical); FIQ		PIPS	
Luciano et al., 2014	VAS	HADS-D	HADS-A		FIQ; EQ-5D (VAS)			CPAQ

Study	Somatic symptom severity	Depression	Anxiety	Health Anxiety	Perceived Health Status	Mindfulness	Psychological Inflexibility	Pain acceptance
Parra-Delgado & Latorre-Postigo, 2013	VAS	BDI			FIQ			
Pedersen et al., 2019	BDS checklist	SCL-92 (Depression score)	SCL-92 (Anxiety score)	WI-7	SF-36 (Physical); WHO-DAS II			
Pérez-Aranda et al., 2019	FSDC	HADS-D	HADS-A		FIQ-R	FFMQ	PIPS	
Rimes & Wingrove, 2013	CFS	HADS-D	HADS-A		PF-10	FFMQ		
Schmidt et al., 2011	GBB-24	CES-D	STAI (Trait)		PLC; FIQ	FMI		
Sephton et al., 2007; Cash et al., 2015; Weissbecker et al., 2002	VAS	BDI			FIQ			
Simister et al., 2018	SF-MPQ	CES-D			FIQ-R	FFMQ		CPAQ-R
van Ravesteijn et al., 2013	PHQ-15	PHQ-9		WI	SF-36 (Physical); EQ-5D (VAS)	FFMQ		
Zernicke et al., 2013	IBS-SSS				IBS-QOL			

Note. BDI = Beck Depression Inventory; BDI-II = Beck Depression Inventory-II; BDS checklist = Bodily distress syndrome checklist; BSI-18 = Brief Symptom Inventory (short-form); CES-D = Center for Epidemiologic Studies Depression Scale; CFS = Chalder Fatigue Scale; CFQ = Cognitive Fusion Questionnaire; CPAQ = Chronic Pain Acceptance Questionnaire; CPAQ-R = Chronic Pain Acceptance Questionnaire-Revised; DASS-21 = Depressions-Angst-Stress-Skalen [Depression–Anxiety–Stress Scale]; EQ-5D = EuroQol Five-Dimensional Questionnaire; FFMQ = Five-Facet Mindfulness Questionnaire; FIQ = Fibromyalgia Impact Questionnaire; FIQ-R = Fibromyalgia Impact Questionnaire-Revised; FMI = Freiburg Mindfulness Inventory; FSDC = Fibromyalgia Survey Diagnostic Criteria; GBB-24 = Giessener Beschwerdebogen (Giessen Subjective Complaints List); GSRS-IBS = Gastrointestinal Symptom Rating Scale for IBS; HADS-A = Hospital Anxiety and Depression Scale – Anxiety; HADS-D = Hospital Anxiety and Depression Scale – Depression; IBS-QOL = Irritable Bowel Syndrome Quality of Life survey; IBSSI = Irritable Bowel Syndrome Severity Index; IBS-SSS = Irritable Bowel Syndrome-Symptom Severity Scale; PF-10 = Physical Functioning scale; PHQ-9 = Patient Health Questionnaire-9; PHQ-15 = Patient Health Questionnaire-15; PLC = Quality of Life Profile for the Chronically Ill; PIPS = Psychological Inflexibility in Pain Scale; SCL-8 = eight-item version of the Symptoms Check List; SCL-90 = Symptom Checklist-90; SCL-92 = 92-item version of the Symptom Checklist; SF-36 = Short Form Health Survey; SF-MPQ = McGill Pain Questionnaire-short form; STAI = State-Trait Anxiety Scale; VAS = Visual analogue scale; WI = Whiteley-Index; WI-7 = 7-Item Whiteley-Index; WHO-DAS II = WHO Disability Assessment Schedule 2.0.

^a data were not extractable or provided by authors.

6. List of extracted data

The following variables, grouped into four categories, were extracted.

Study characteristics:

- Author(s); Year of publication
- Citation (according to APA)
- Protocol: register + registration code/number; link to protocol; name of protocol file (and where to find it)
- Recruitment method
- Incentive provided for completing the treatment/control group & if so, which one
- Number of people assessed for eligibility
- Number of participants who declined to participate
- Number of participants randomized (for all groups)
- Number of persons allocated that completed at least one module in the treatment or participated in the control group (for all groups, if possible)
- Number of participants completing all modules as advised (for all groups, if possible)
- Post-assessment: duration from baseline to post-treatment assessment (done accordingly for follow-up assessments)

Clinical variables:

- Diagnosis assessment
- Diagnosis assessed
- Specific diagnosis/inclusion criteria regarding symptomology; how was this assessed
- Average and standard deviation (*SD*) for number as well as duration of symptoms (all groups)
- Exclusion of participants with comorbid disorders. If applicable, specify criterion.
- Average and *SD* for severity of somatic symptoms as well as how it was assessed
 - The data for post-treatment and respective follow-up assessments will be extracted.
 - The corresponding means of somatic symptom scores and *SDs* at baseline and post-treatment assessment will be extracted for the treatment group(s) and the control group(s), respectively.
 - Hedges' *g* and the *Standard Error (SE)* will be calculated if the mean and *SD* are not reported, but other measures that allow us to estimate the effect (e.g., 37). This will be done accordingly, for depressive and anxiety symptoms.

Intervention-related variables (for all included interventions):

- Form of treatment(s)
- Manual used. If so, name of the program/manual used
- Form of guidance
- Setting (group vs. individual therapy; internet-/computer-/app-based)
- Form of control group(s)
 - When a TAU-group was given access to the program after the trial was completed – i.e., TAU was combined with WL – it will be considered as TAU. When a group received no treatment, it will be administered as TAU too as it is considered as congruent to what patients received if they did not participate in the study (38).
- Assessment of consumer satisfaction and negative effects assessed and if so, how
- Number of sessions (per week)
- Duration of treatment
- Average proportion of modules completed
- Reasons for dropping out of treatment/control

Sociodemographic variables:

- Target group
- Mean age and *SD* (all groups)
- Proportion of female participants (all groups)
- Country the trial was conducted in

Combining subscales

We combined multiple subscales to a total score using a method for integrating dependent effect sizes (39, 37). Thus, we averaged means: $d = \frac{dx+dy}{2}$ (respectively $d = \frac{dx+dy+dz+da+db+dc+dd}{7}$ for 40). However, variances were assumed to be highly dependent (41). Rustenbach's (39) approach was applied as this approach additionally integrated the covariance between subscales, resulting in the following formula: $s^2_{(\frac{dx+dy}{2})} = \frac{1}{4}(s^2_{dx} + s^2_{dy} + 2 * cov_{dx dy})$ (39, p.118f). In order to calculate the covariance, the correlation between the subscales (e.g., r_{xy}) was not reported. Hence, we estimated a correlation of $r = 0.5$ between subscales (see for instance in 42). While this method is not optimal, it is preferred to naïve-methods (e.g. assuming a zero correlation, 41). The calculations were documented in the R Script which is provided online (<https://osf.io/an6zy/>).

Prioritization of outcome measures (PHS)

Six studies included more than one measure that we considered relevant for the outcome perceived health status. While we prioritized validated scales, some studies included two validated scales. Here, the decision was made according to the prioritisation of scales, favouring scales that rather assessed a global level of PHS over disorder-specific scales and more elaborate scales: The decision was made in favour of the physical component summary of the SF-36 (vs. FIQ) for Jensen et al. (43) as well as (vs. IBS-QoL) for Ito & Muto (44), (vs. WHO-DAS II) for Pedersen et al. (45), and we decided in favour of the global Scale Quality of Life Profile for the Chronically Ill (vs. FIQ) for Schmidt et al. (46). Furthermore, we decided to prioritize more elaborate scales over single item scales. Hence, we favoured the FIQ (vs. the visual analogue scale, VAS, of the EQ-5D) for van Ravesteijn et al. (47), and (vs. the VAS of the EQ-5D) for Luciano et al. (48).

7. Deviations from preregistration

We did not contact other relevant authors in the field about relevant studies additionally to our strategic literature search. However, we are planning to contact the EURONET-SOMA group regarding relevant studies to create a database on RCTs on all forms of psychotherapies in bodily distress.

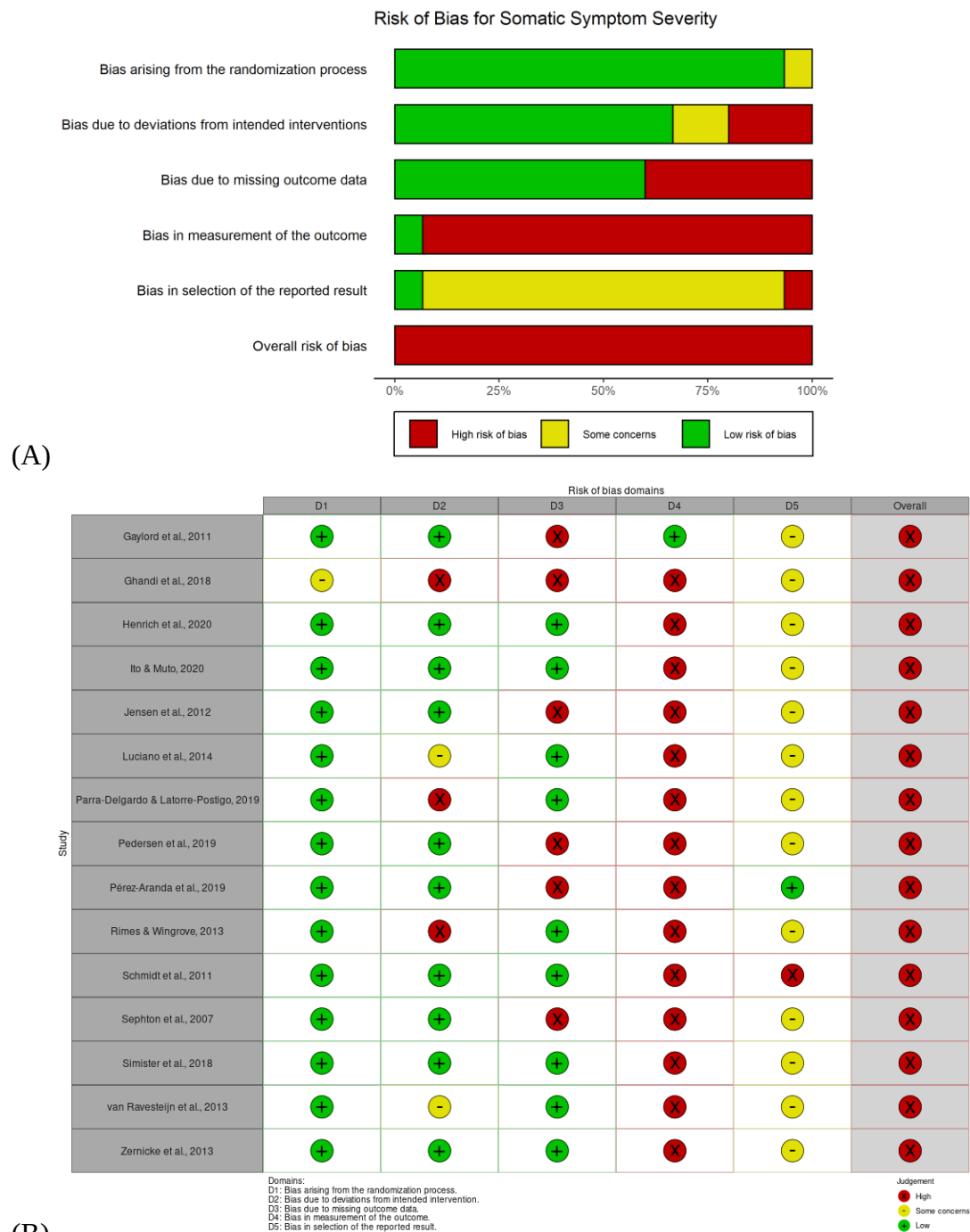
Deviations in moderator analyses were as follows: In the protocol we did not specify that we will compare MBCT and MBSR as a combined group against ACT. Furthermore, we chose a different form of dichotomisation for the control groups into inactive and non-specific as wait-list condition is the one eligible control condition possibly leading to the most inflated effect sizes (49). Another deviation from the protocol is that we did not perform a subgroup analysis for the type of assessment as we agreed that it would yield a sufficient benefit in a reassessment in a consensus meeting on the moderator analyses. Lastly, since the effect size (Hedges' g) is based on values from both groups, meta-regressions on symptom severity and comorbidity (depression/anxiety) were not possible as the values we extracted were only referring to one of the groups each.

All other deviations are mentioned in the main paper.

8. Risk of bias assessment

Figure S1

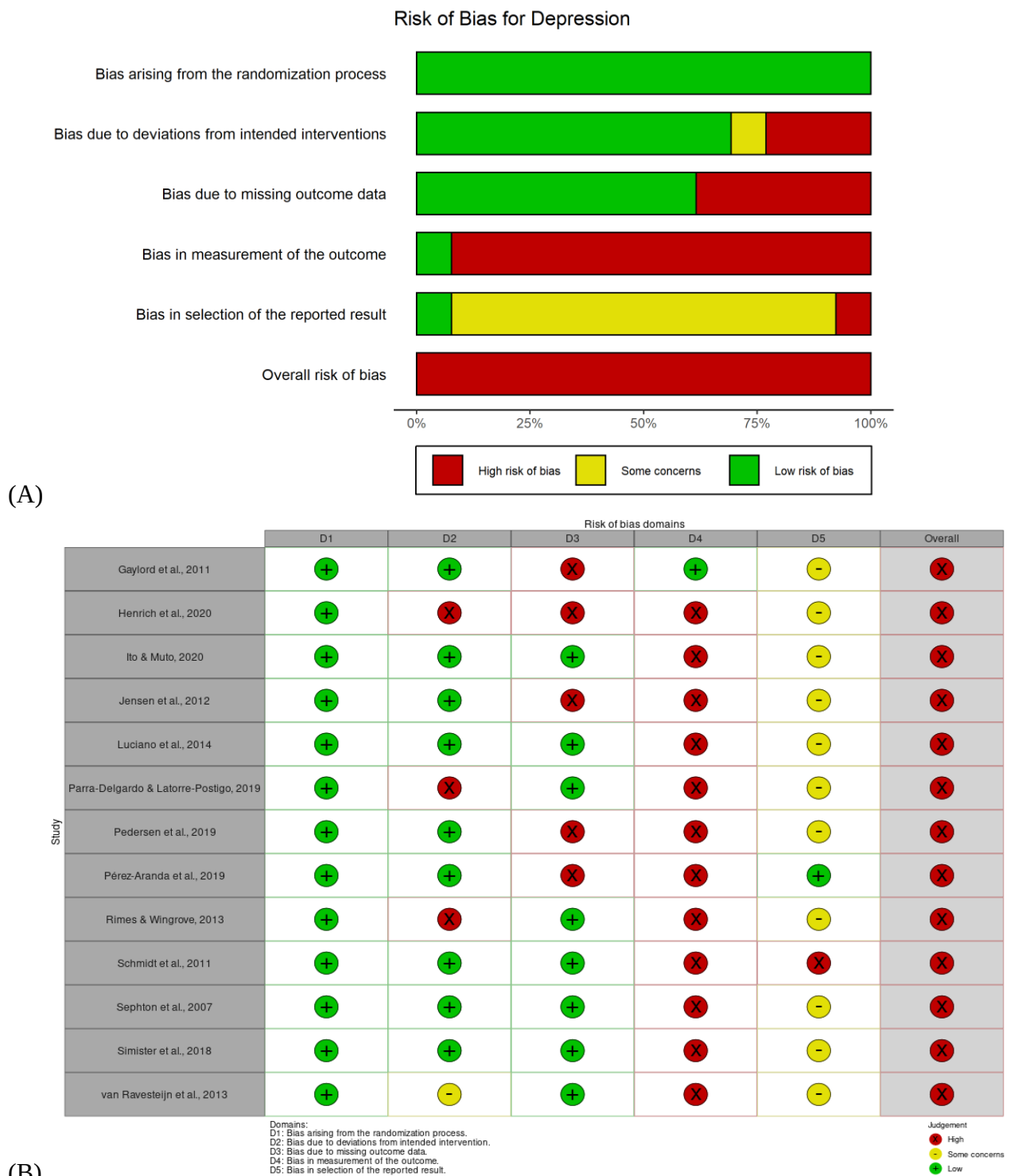
Risk of bias ratings for somatic symptom severity at post-treatment



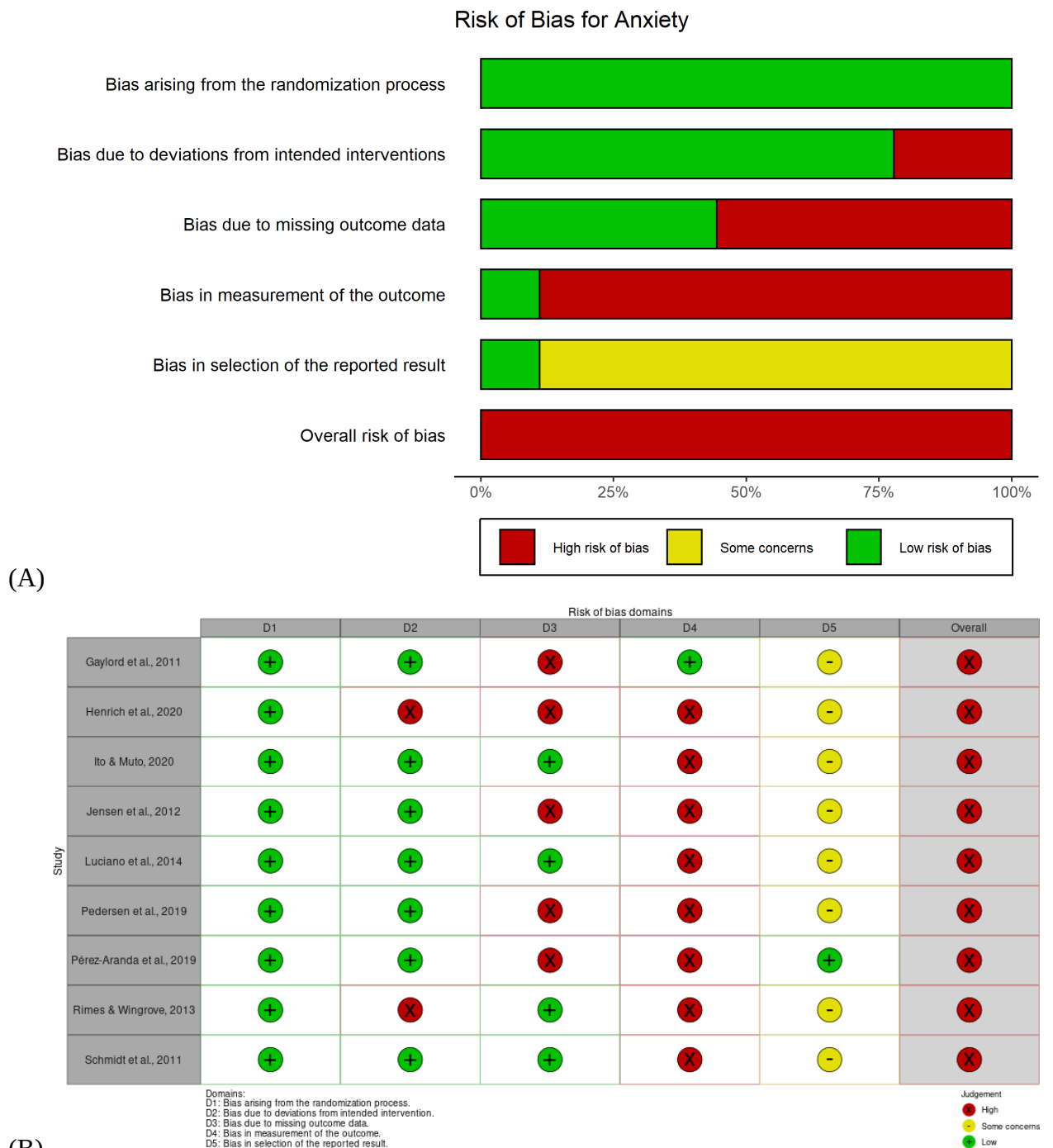
Note. A: summary plot; B: traffic light plot.

Figure S2*Risk of bias ratings for perceived health status at post-treatment*

Note. A: summary plot; B: traffic light plot.

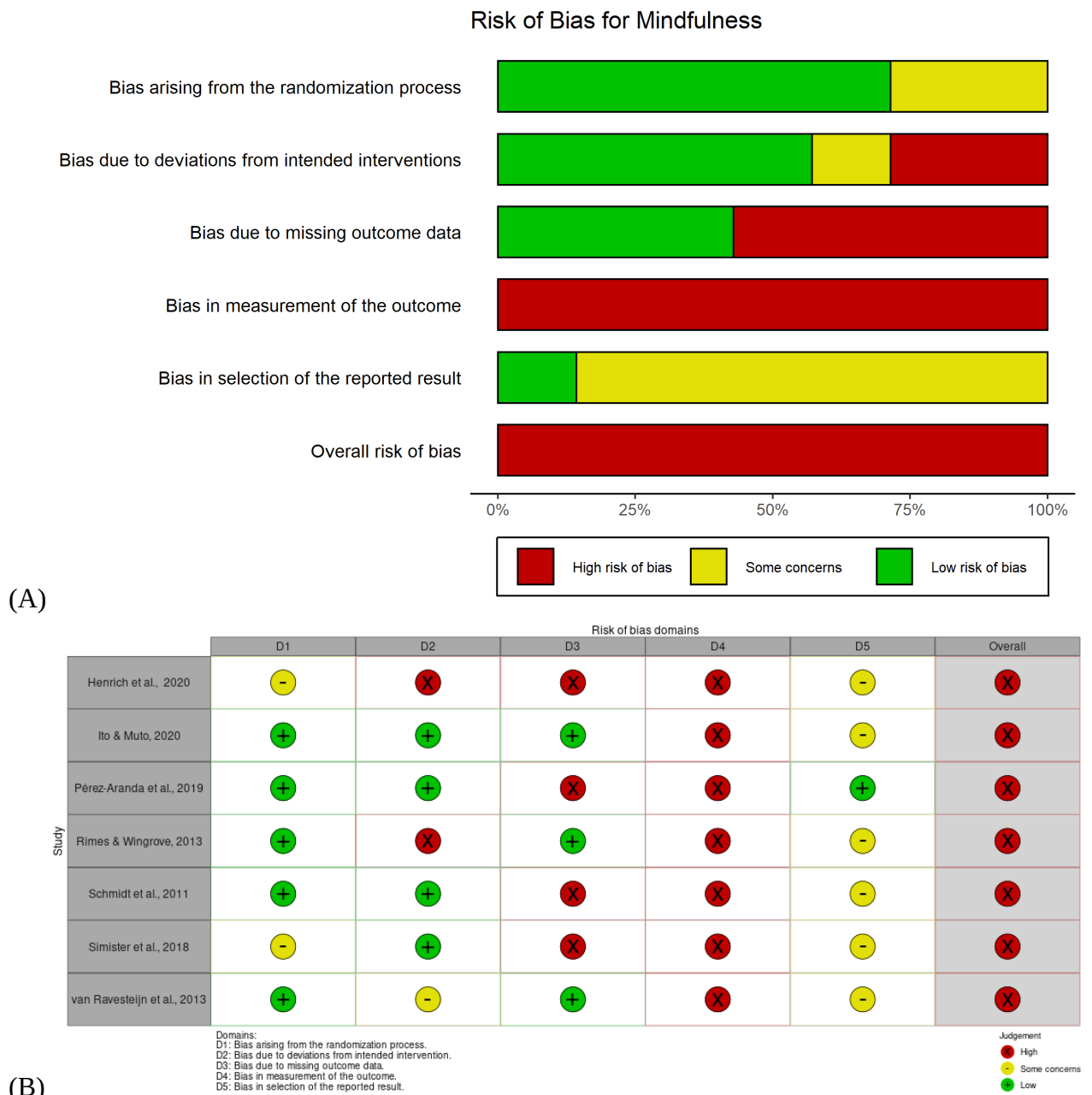
Figure S3*Risk of bias ratings for depression at post-treatment*

Note. A: summary plot; B: traffic light plot.

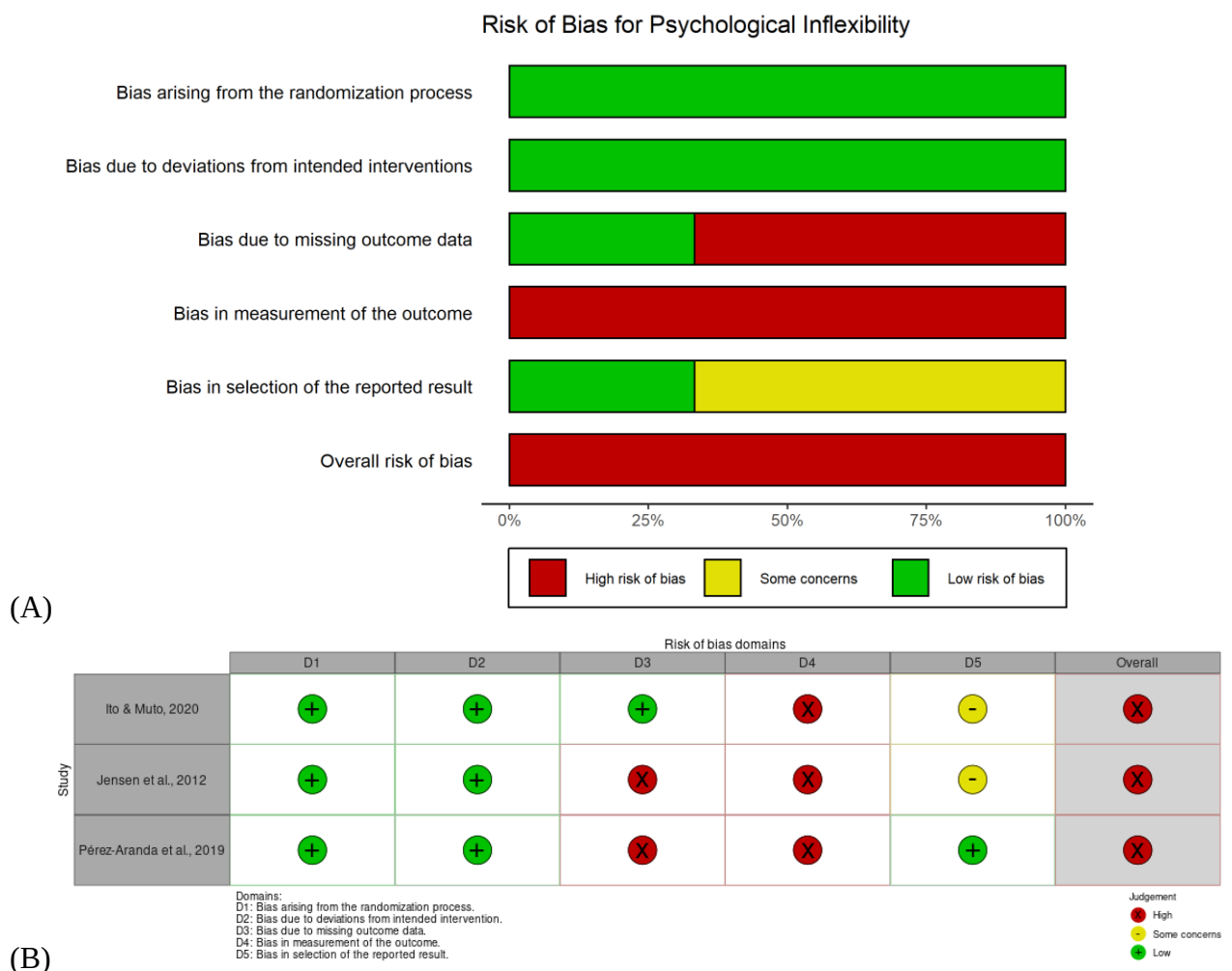
Figure S4*Risk of bias ratings for anxiety at post-treatment*

(B)

Note. A: summary plot; B: traffic light plot.

Figure S5*Risk of bias ratings for mindfulness at post-treatment*

Note. A: summary plot; B: traffic light plot.

Figure S6*Risk of bias ratings for psychological inflexibility at post-treatment*

Note. A: summary plot; B: traffic light plot.

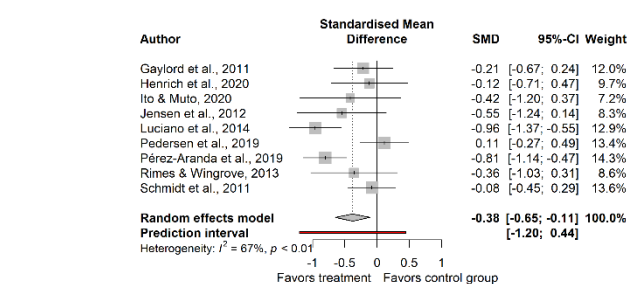
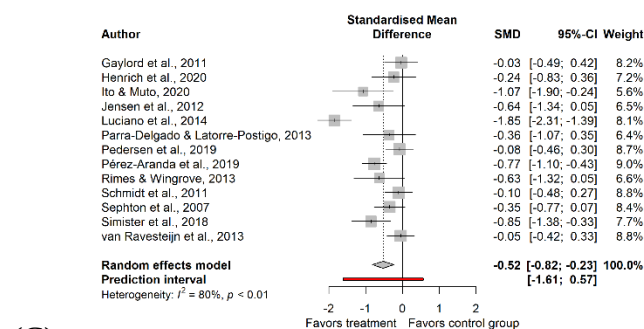
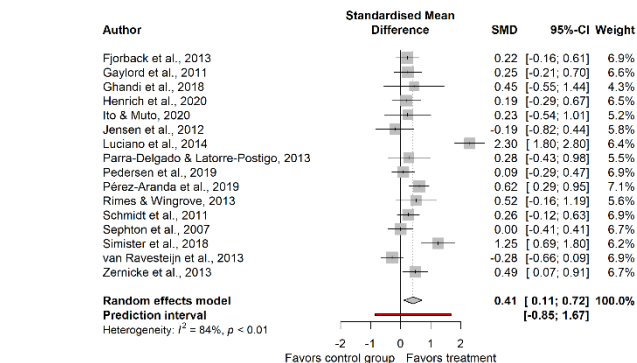
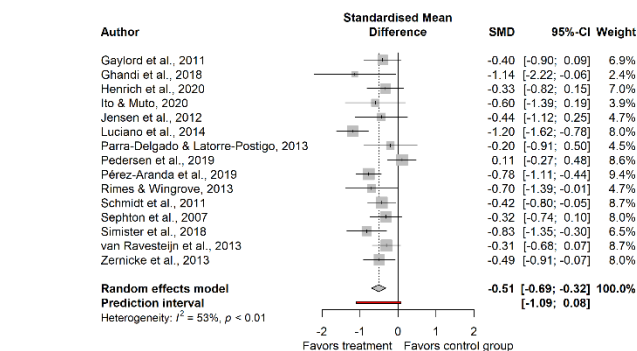
9. R packages

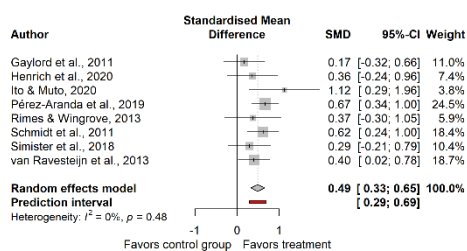
In R version 4.2.1 (50) we used the packages {meta} (51), {metafor} (52), and {dmetar} (53) to perform the effect size aggregation and associated analyses. The package {tidyverse} (54) provided good functions to visualize data. Additionally, we imported {esc} (55), and {car} (56). Furthermore, we used the packages {readxl} (57) to import the data that we prepared in Microsoft Excel (58) sheets. Additionally, we used the package {robvis} (59) as well as the corresponding web application (<https://mcguinlu.shinyapps.io/robvis/>) to depict the risk of bias assessment. Lastly, we used {irr} (60) to calculate interrater reliabilities.

10. Additional information on treatment effects

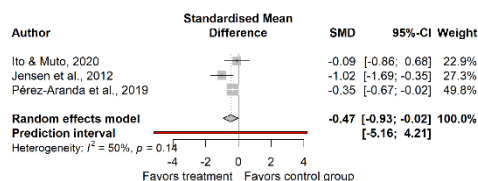
Figure S7

Forest plots – Post-treatment



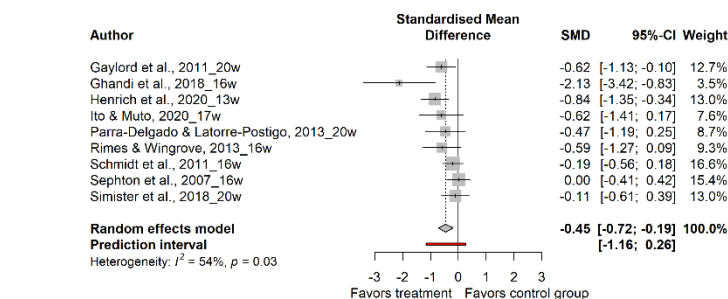


(E)

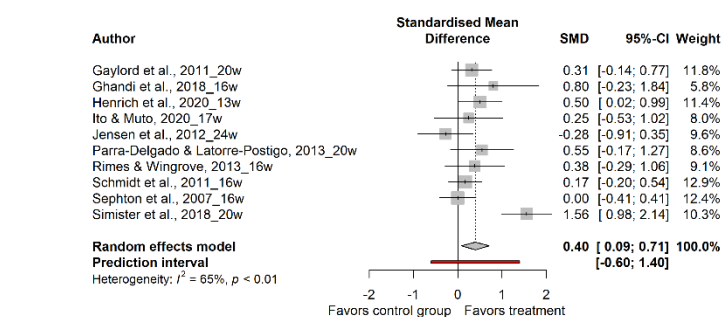


(F)

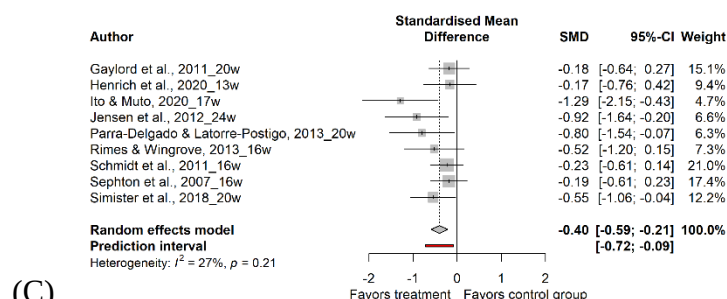
Note. A: somatic symptom severity at post-treatment; B: perceived health status at post-treatment; C: depression at post-treatment; D: anxiety at post-treatment; E: mindfulness at post-treatment; F: psychological inflexibility at post-treatment. Note: For PHS and mindfulness positive effects indicate efficacy of the treatments, for all other outcomes negative effects indicate efficacy of the treatments.

Figure S8*Forest plots – Short-term follow-up*

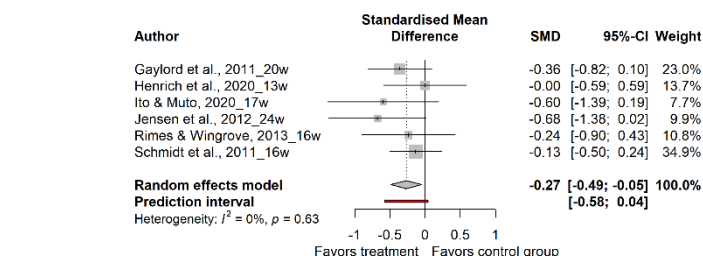
(A)



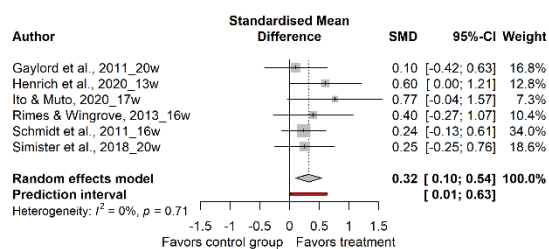
(B)



(C)



(D)

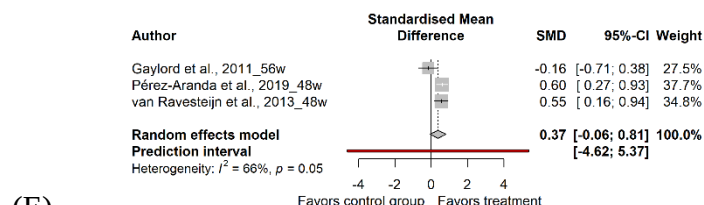
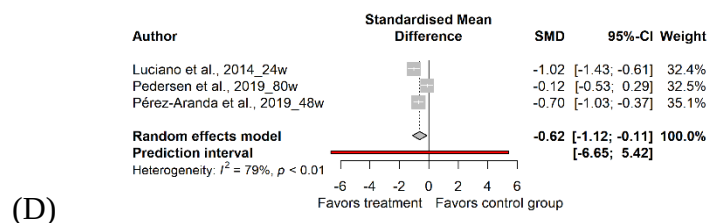
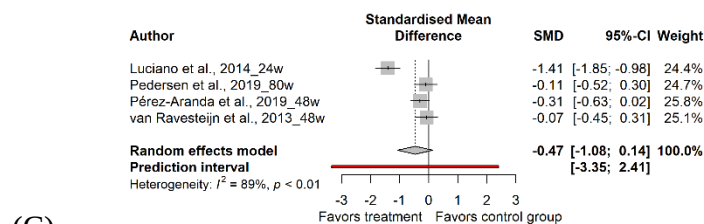
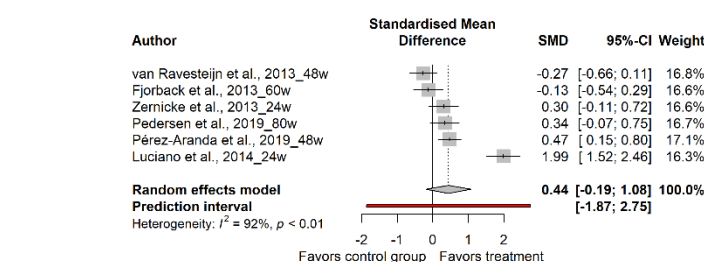
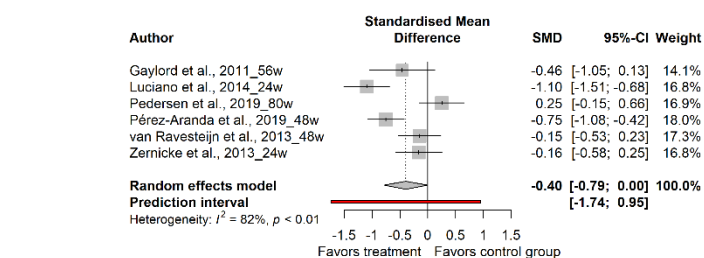


(E)

Note. A: somatic symptom severity at short-term follow-up; B: perceived health status at short-term follow-up; C: depression at short-term follow-up; D: anxiety at short-term follow-up; E: mindfulness at short-term follow-up. Note: For PHS and mindfulness positive effects indicate efficacy of the treatments, for all other outcomes negative effects indicate efficacy of the treatments.

Figure S9

Forest plots – Long-term follow-up



Note. A: somatic symptom severity at long-term follow-up; B: perceived health status at long-term follow-up; C: depression at long-term follow-up; D: anxiety at long-term follow-up; E: mindfulness at long-term follow-up. Note: For PHS and mindfulness positive effects indicate efficacy of the treatments, for all other outcomes negative effects indicate efficacy of the treatments.

Descriptive effects for outcomes that were not aggregated**Table S3***Health anxiety (post-treatment)*

Study	Instrument	<i>Ne</i>	<i>Nc</i>	Hedges' <i>g</i>	<i>SE</i>
Pedersen et al., 2019	WI-7	53	54	0.08	0.19
van Ravesteijn et al., 2013	WI-14	58	53	-0.14	0.19

Note. WI-7 = Whitely Index with 7 items; WI-14 = Whitely Index with 14 items; *Ne* = number of participants in the experimental group; *Nc* = number of participants in the control group; *SE* = standard error.

Table S4*Pain acceptance (post-treatment)*

Study	Instrument	<i>Ne</i>	<i>Nc</i>	Hedges' <i>g</i>	<i>SE</i>
Luciano et al., 2014	CPAQ	51	53	1.52	0.22
Simister et al., 2018	CPAQ-R	30	31	0.82	0.27

Note. CPAQ = chronic pain catastrophizing scale; CPAQ-R = chronic pain catastrophizing scale revised; *Ne* = number of participants in the experimental group; *Nc* = number of participants in the control group; *SE* = standard error.

11. Results moderator analyses

Table S5

Subgroup analyses for type of treatment (post-treatment)

	<i>k</i>	Hedges' <i>g</i>	95%CI	τ^2	<i>I</i> ²	<i>p</i> _{subgroup}
Somatic Symptom Severity						0.658
MBCT/MBSR	10	-0.47	-0.62; -0.33	0.0006	0.0%	
ACT	5	-0.59	-1.07; -0.10	0.22	81.8%	
Perceived Health Status						0.294
MBCT/MBSR	11	0.25	0.07; 0.43	0.04	38.2%	
ACT	5	0.75	-0.17; 1.66	1.00	93.6%	
Depression						0.079
MBCT/MBSR	8	-0.31	-0.53; -0.08	0.04	45.0%	
ACT	5	-0.89	-1.51; -0.28	0.40	88.4%	
Anxiety						0.729
MBCT/MBSR	5	-0.34	-0.65; -0.03	0.07	60.3%	
ACT	4	-0.45	-0.96; 0.07	0.19	79.2%	

Note. $k < 3$ for one of the subgroups for mindfulness, and psychological inflexibility.

Table S6*Subgroup analyses for control condition (post-treatment)*

	<i>k</i>	Hedges' <i>g</i>	95%CI	τ^2	<i>I</i> ²	<i>p</i> _{subgroup}
Somatic Symptom Severity						0.523
Non-specific	8	-0.45	-0.71; -0.20	0.07	58.0%	
Inactive	7	-0.57	-0.85; -0.30	0.07	49.2%	
Perceived Health Status						0.720
Non-specific	9	0.35	0.07; 0.63	0.12	69.8%	
Inactive	7	0.48	-0.15; 1.11	0.65	90.6%	
Depression						0.245
Non-specific	6	-0.35	-0.66; -0.03	0.10	68.7%	
Inactive	7	-0.69	-1.16; -0.21	0.33	84.7%	
Anxiety						0.737
Non-specific	3	-0.31	-0.85; 0.23	0.44	84.9%	
Inactive	6	-0.42	-0.75; -0.09	0.29	55.1%	
Mindfulness						0.425
Non-specific	4	0.43	0.20; 0.66	0.01	11.3%	
Inactive	4	0.58	0.30; 0.85	<0.001	0.0%	

Note. $k < 3$ for one of the subgroups for psychological inflexibility; inactive = wait-list; non-specific = EC, psychological placebo, TAU.

Table S7*Subgroup analyses for diagnosis (post-treatment)*

	<i>k</i>	Hedges' <i>g</i>	95%CI	τ^2	I^2	p_{subgroup}
Somatic Symptom Severity						0.396
IBS	5	-0.47	-0.72; -0.23	0.00	0.0%	
FM	7	-0.63	-0.89; -0.37	0.07	54.9%	
Perceived Health Status						0.349
IBS	5	0.32	0.08; 0.56	0.00	0.0%	
FM	7	0.65	0.008; 1.29	0.68	91.2%	
Depression						0.327
IBS	3	-0.36	-0.90; 0.19	0.13	56.7%	
FM	7	-0.71	-1.15; -0.27	0.28	84.2%	
Anxiety						0.156
IBS	3	-0.22	-0.55; 0.11	0.00	0.0%	
FM	4	-0.60	-1.01; -0.19	0.13	75.1%	
Mindfulness						0.657
IBS	3	0.45	-0.03; 0.94	0.08	46.6%	
FM	3	0.58	0.35; 0.80	0.00	0.0%	

Note. $k < 3$ for one of the subgroups for psychological inflexibility.

Table S8*Subgroup analyses for therapy intensity (post-treatment)*

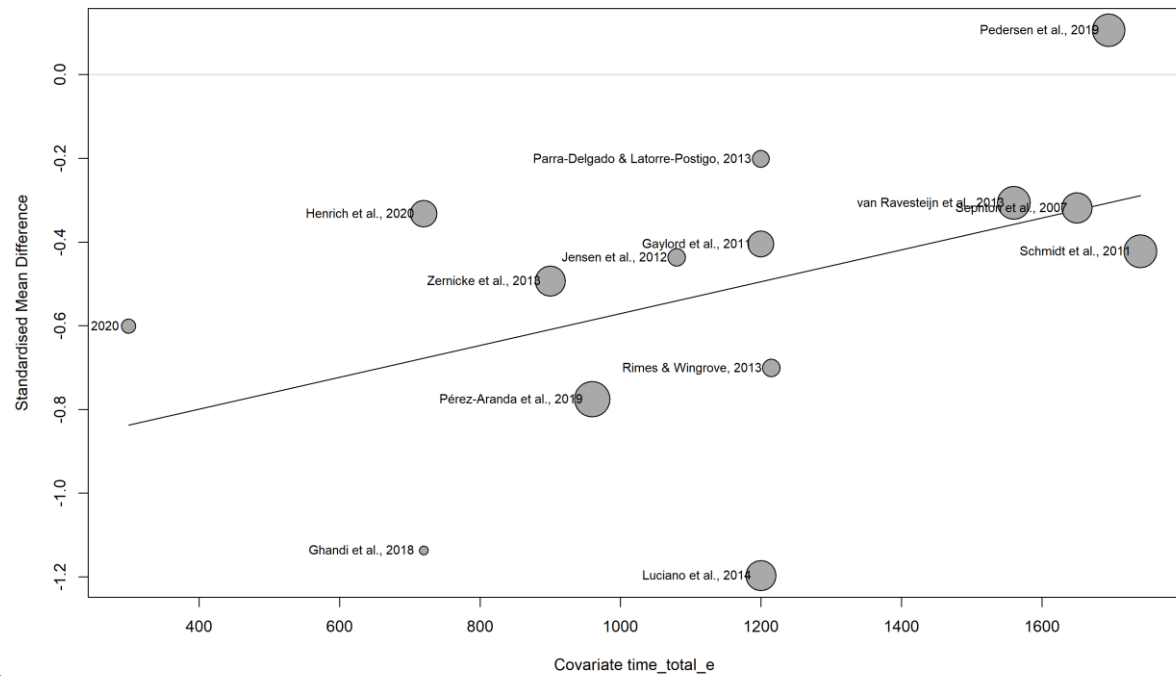
	<i>k</i>	Hedges' <i>g</i>	95%CI	τ^2	I^2	p_{subgroup}
Somatic Symptom Severity						0.712
High intensity	12	-0.49	-0.71; -0.28	0.08	60.1%	
Low intensity	3	-0.57	-0.92; -0.22	0.01	0.0%	
Perceived Health Status						0.634
High intensity	13	0.38	0.03; 0.73	0.35	85.3%	
Low intensity	3	0.57	-0.13; 1.27	0.28	77.5%	
Depression						0.496
High intensity	10	-0.48	-0.83; -0.12	0.26	83.5%	
Low intensity	3	-0.68	-1.16; -0.21	0.07	41.3%	
Mindfulness						0.911
High intensity	5	0.50	0.32; 0.68	0.00	0.0%	
Low intensity	3	0.48	0.09; 0.86	0.02	32.4%	

Note. $k < 3$ for one of the subgroups for anxiety, and psychological inflexibility.

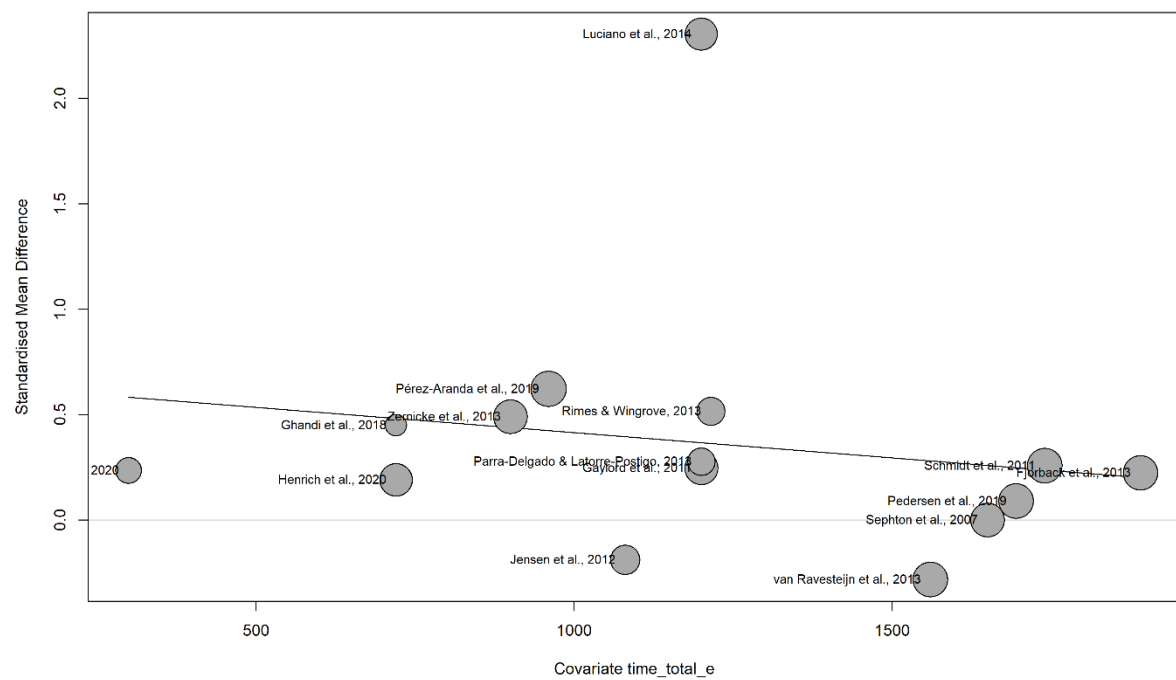
Table S9*Meta-regression analyses for therapy dosis (effect on outcomes at post-treatment)*

Outcome	$\tau_{unexplained}^2$	I^2	R^2	$p_{moderator}$	Regression weight	Intercept
Somatic Symptom Severity	0.05	46.69%	22.58%	0.109	0.0004	-0.95
Perceived Health Status	0.31	84.58%	0.00%	0.526	0.65	-0.0002
Depression	0.20	77.66%	14.51%	0.126	-1.23	0.0006
Anxiety	0.08	58.82%	18.93%	0.22	-0.85	0.0004
Mindfulness	0.0009	1.57%	0.00%	0.481	0.71	-0.0002

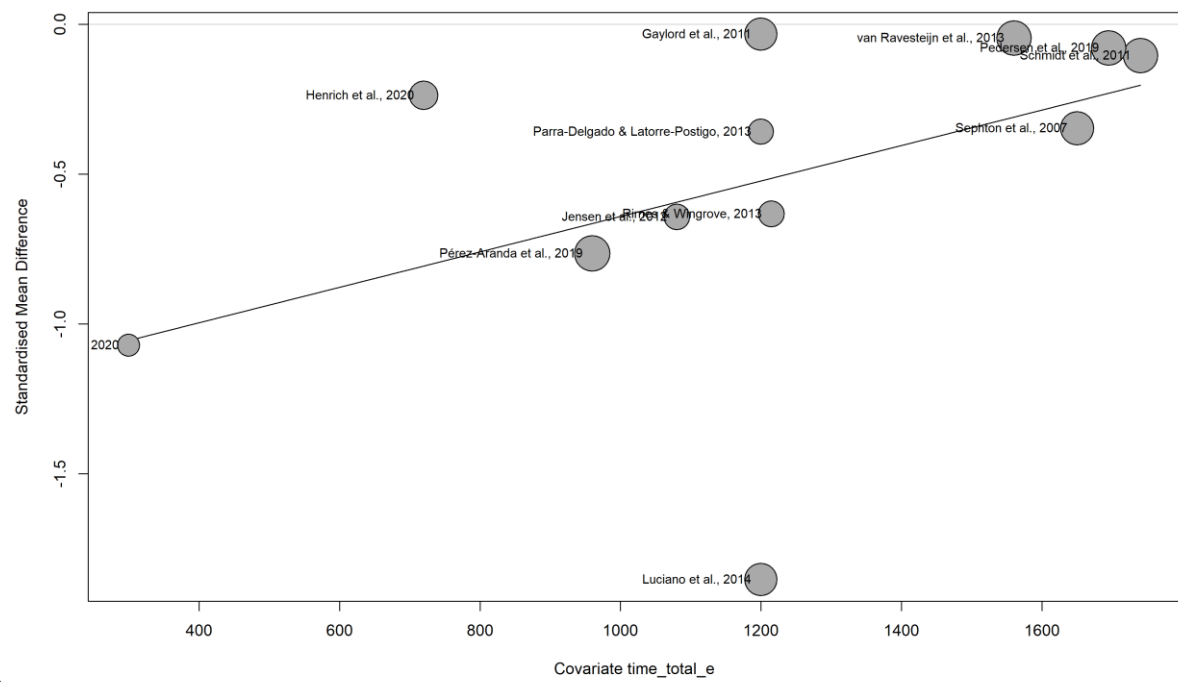
Note. $\tau_{unexplained}^2$ = estimated amount of residual heterogeneity; I^2 = residual heterogeneity/unaccounted variability; R^2 = amount of heterogeneity accounted for

Figure S10*Bubble plots – meta-regression analysis for therapy dosis*

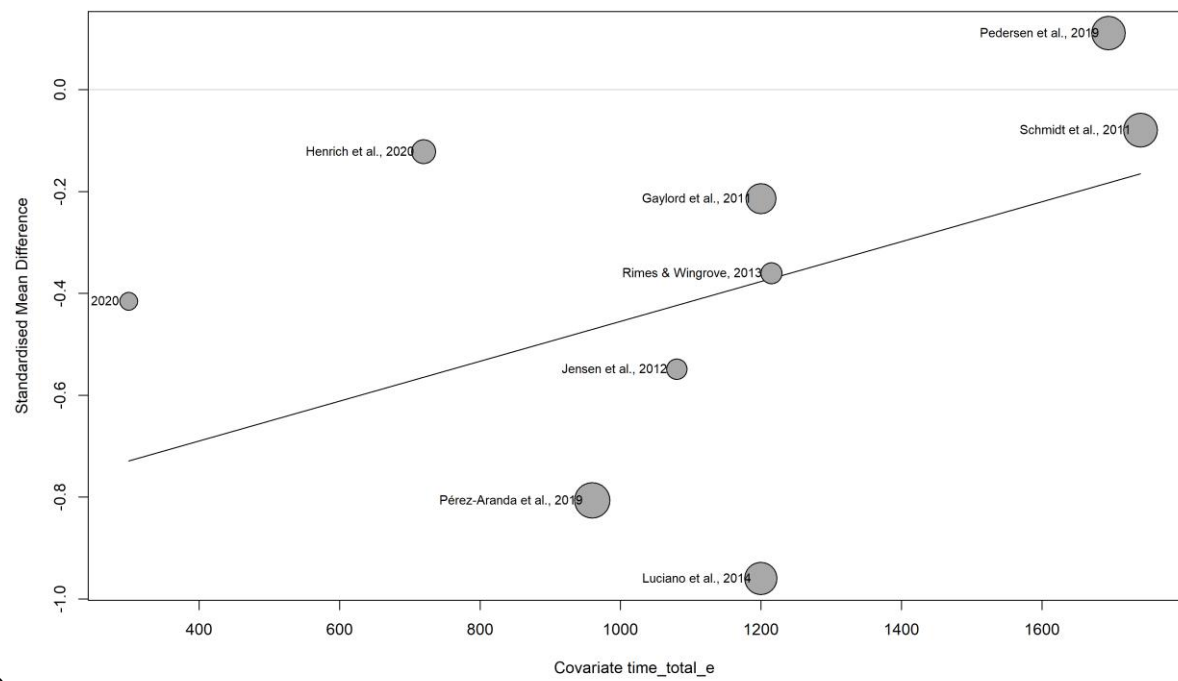
(A)



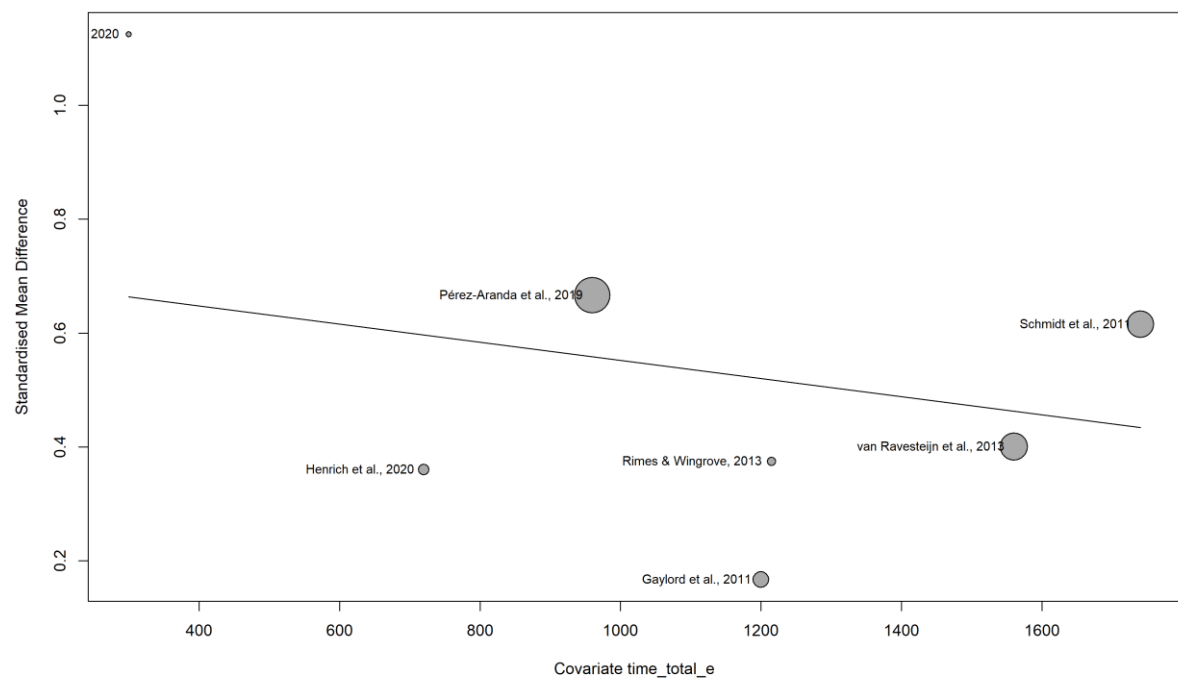
(B)



(C)



(D)



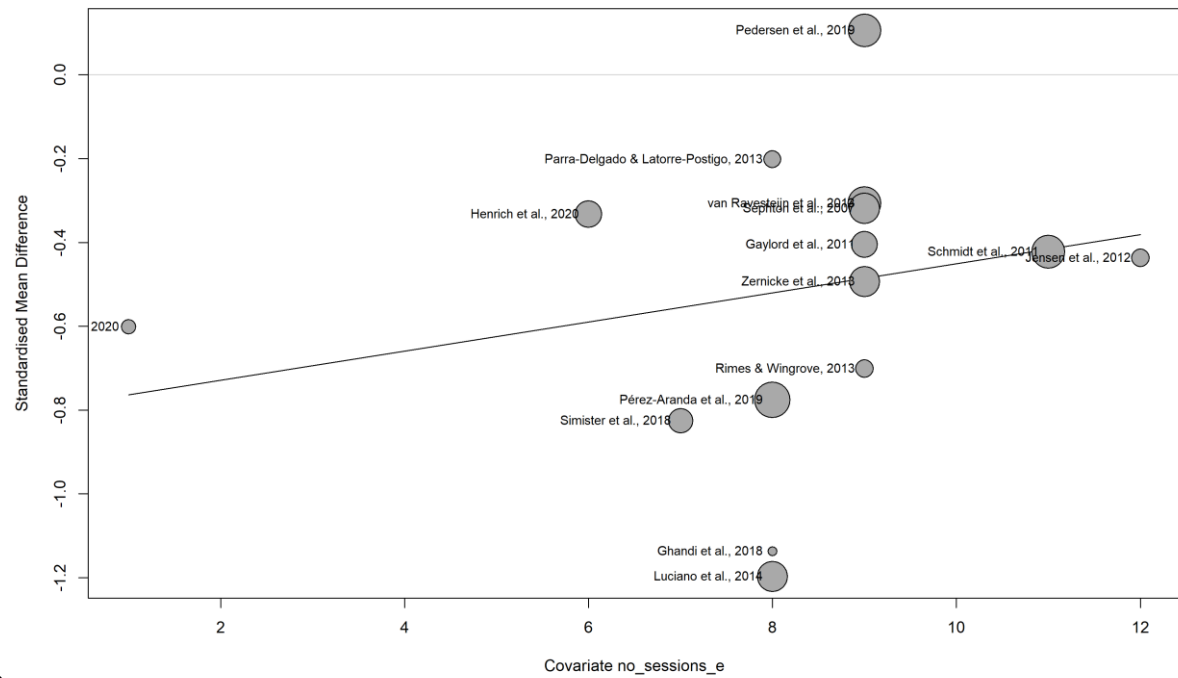
(E)

Note. A: bubble plot for the effect of psychotherapy dosis on somatic symptom severity at post-treatment; B: bubble plot for the effect of psychotherapy dosis on perceived health status at post-treatment; C: bubble plot for the effect of psychotherapy dosis on depression at post-treatment; D: bubble plot for the effect of psychotherapy dosis on anxiety at post-treatment; E: bubble plot for the effect of psychotherapy dosis on mindfulness at post-treatment. Note: Simister et al. (61) was not included as time_total_e could not be calculated.

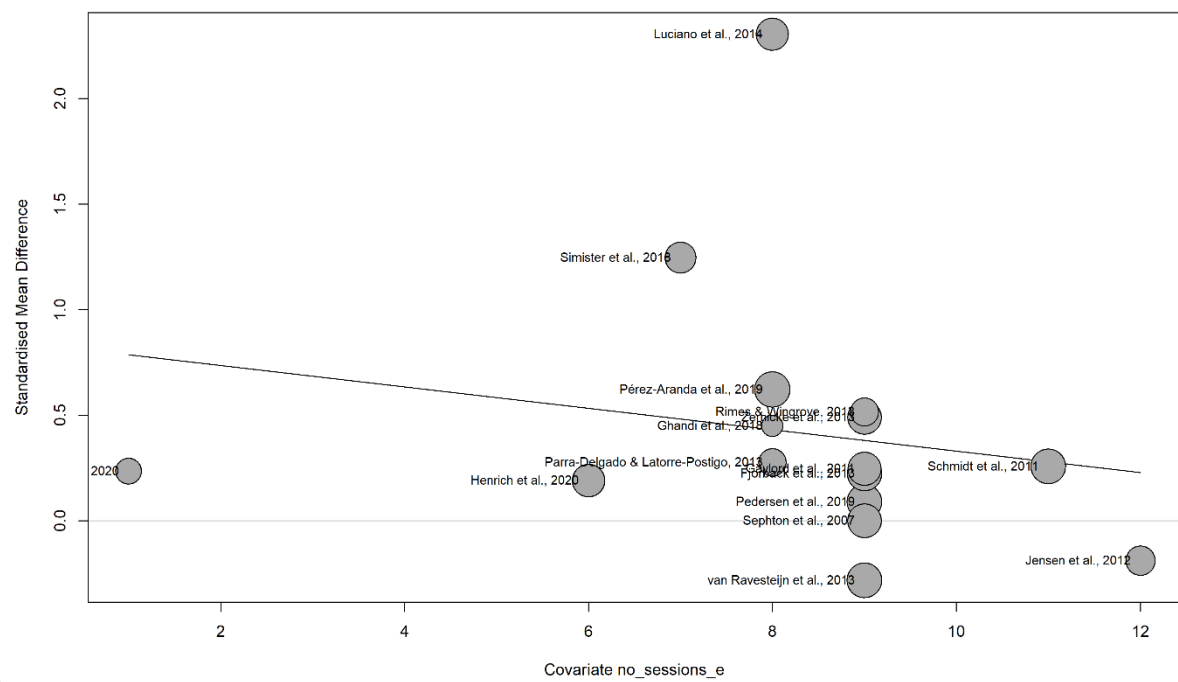
Table S10*Meta-regression analyses for number of sessions (effect on outcomes at post-treatment)*

Outcome	$\tau_{unexplained}^2$	I^2	R^2	$p_{moderator}$	Regression weight	Intercept
Somatic Symptom Severity	0.07	53.36%	0.00%	0.458	-0.80	0.03
Perceived Health Status	0.33	85.51%	0.00%	0.485	0.84	-0.05
Depression	0.21	78.58%	6.77%	0.225	-1.17	0.08
Anxiety	0.11	67.30%	0.00%	0.746	-0.53	0.02
Mindfulness	0.003	4.28%	0.00%	0.478	0.74	-0.03

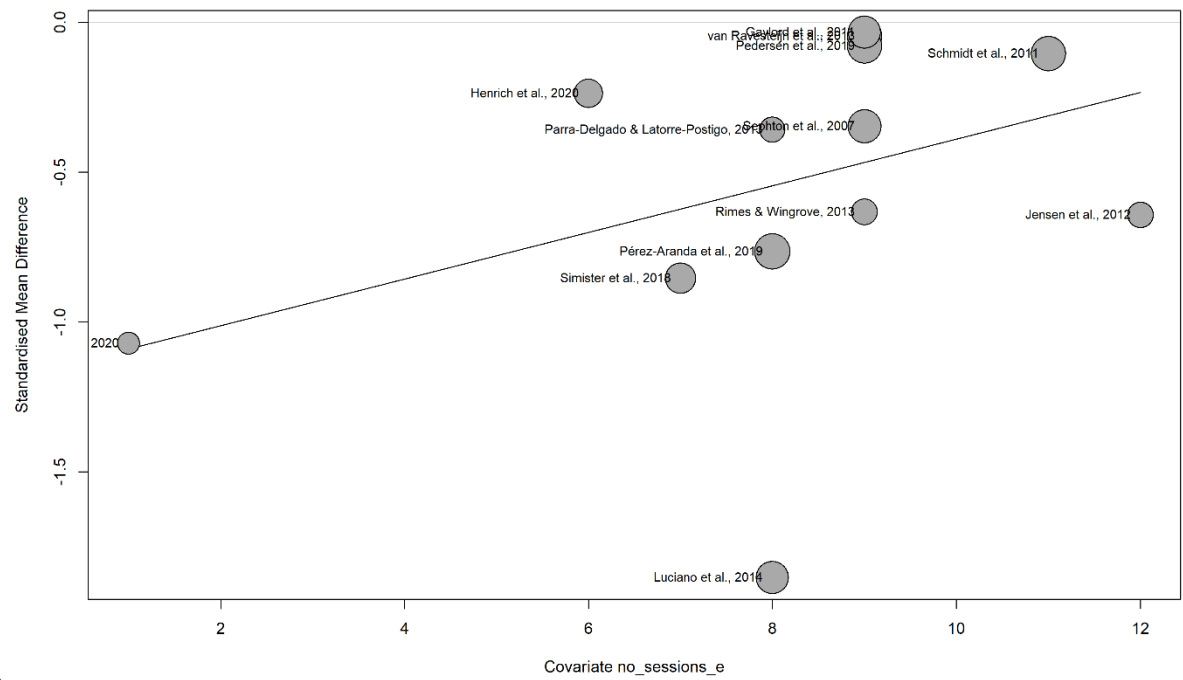
Note: $\tau_{unexplained}^2$ = estimated amount of residual heterogeneity; I^2 = residual heterogeneity/unaccounted variability; R^2 = amount of heterogeneity accounted for.

Figure S11*Bubble plots – meta-regression analysis for number of sessions*

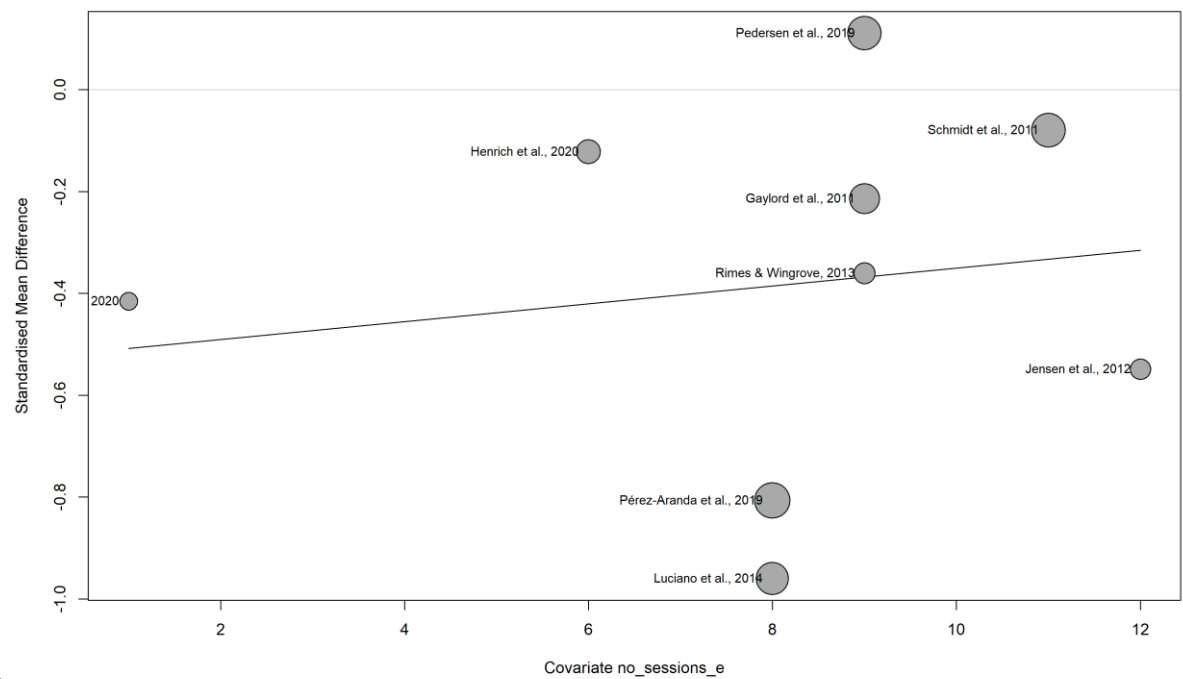
(A)



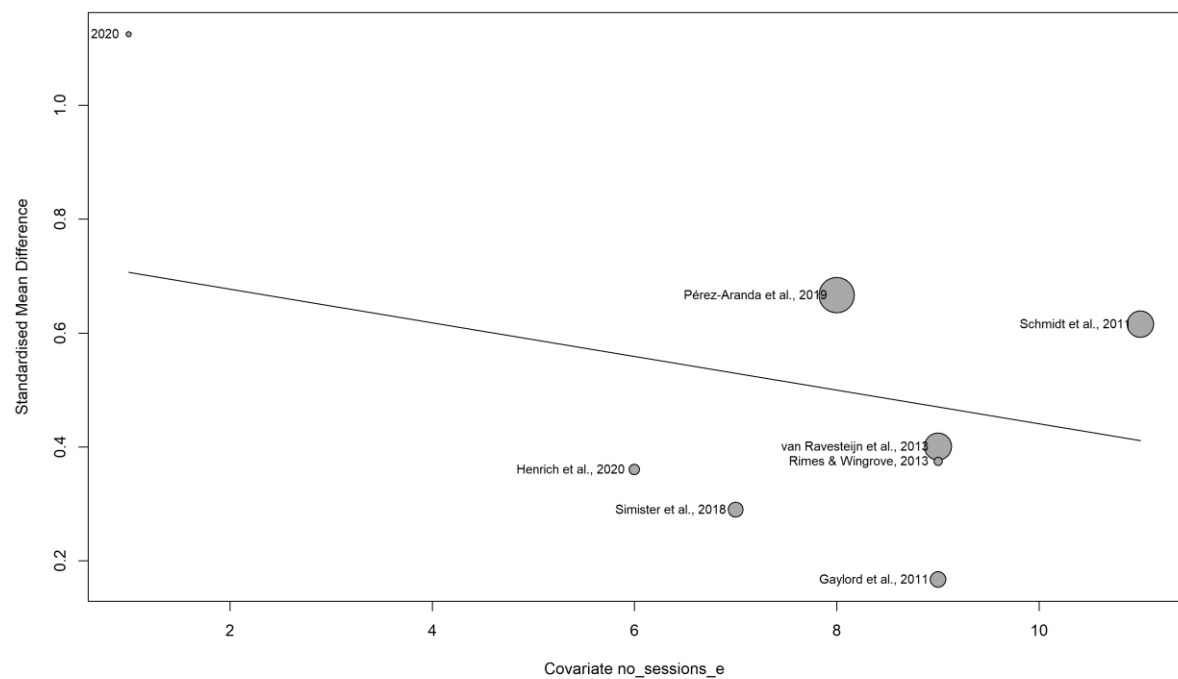
(B)



(C)



(D)



(E)

Note. A: bubble plot for the effect of number of sessions on somatic symptom severity at post-treatment; B: bubble plot for the effect of number of sessions on perceived health status at post-treatment; C: bubble plot for the effect of number of sessions on depression at post-treatment; D: bubble plot for the effect of number of sessions on anxiety at post-treatment; E: bubble plot for the effect of number of sessions on mindfulness at post-treatment. Note: Simister et al. (61) was not included as time_total_e could not be calculated.

12. Results sensitivity analyses

Table S11

Sensitivity analyses comparing fixed effect and random effects models (post-treatment)

Outcome	<i>k</i>	Model	Hedges' <i>g</i>	95%CI
Somatic symptom severity	15	Random effects	-0.51	-0.69; -0.32
		Fixed effect	-0.50	-0.62; -0.37
Perceived Health status	16	Random effects	0.41	0.11; 0.72
		Fixed effect	0.37	0.26; 0.49
Depression	13	Random effects	-0.52	-0.82; -0.23
		Fixed effect	-0.47	-0.60; -0.34
Anxiety	9	Random effects	-0.38	-0.65; -0.11
		Fixed effect	-0.39	-0.55; -0.24
Mindfulness	8	Random effects	0.49	0.33; 0.65
		Fixed effect	0.49	0.33; 0.65
Psychological inflexibility	3	Random effects	-0.47	-0.93; -0.02
		Fixed effect	-0.43	-0.70; -0.15

Note. *k* = number of studies.

Table S12

Sensitivity analyses comparing PHS with the prioritized measures and the alternative measures

Outcome	<i>k</i>	PHS Measures	Hedges' <i>g</i>	95%CI	<i>I</i> ²	95%CI
Post treatment	16	Prioritized	0.41	0.11; 0.72	83.7%	74.8; 89.4
		Alternative measures	0.42	0.20; 0.65	72.0%	53.8; 83.1
Short-term follow-up	10	Prioritized	0.40	0.09; 0.71	65.1%	31.6; 82.2
		Alternative measures	0.49	0.19; 0.79	63.5%	27.8; 81.5
Long-term follow-up	6	Prioritized	0.44	-0.19; 1.08	91.9%	85.2; 95.6
		Alternative measures	0.22	-0.19; 0.63	84.1%	67.1; 92.4

Note. *k* = number of studies.

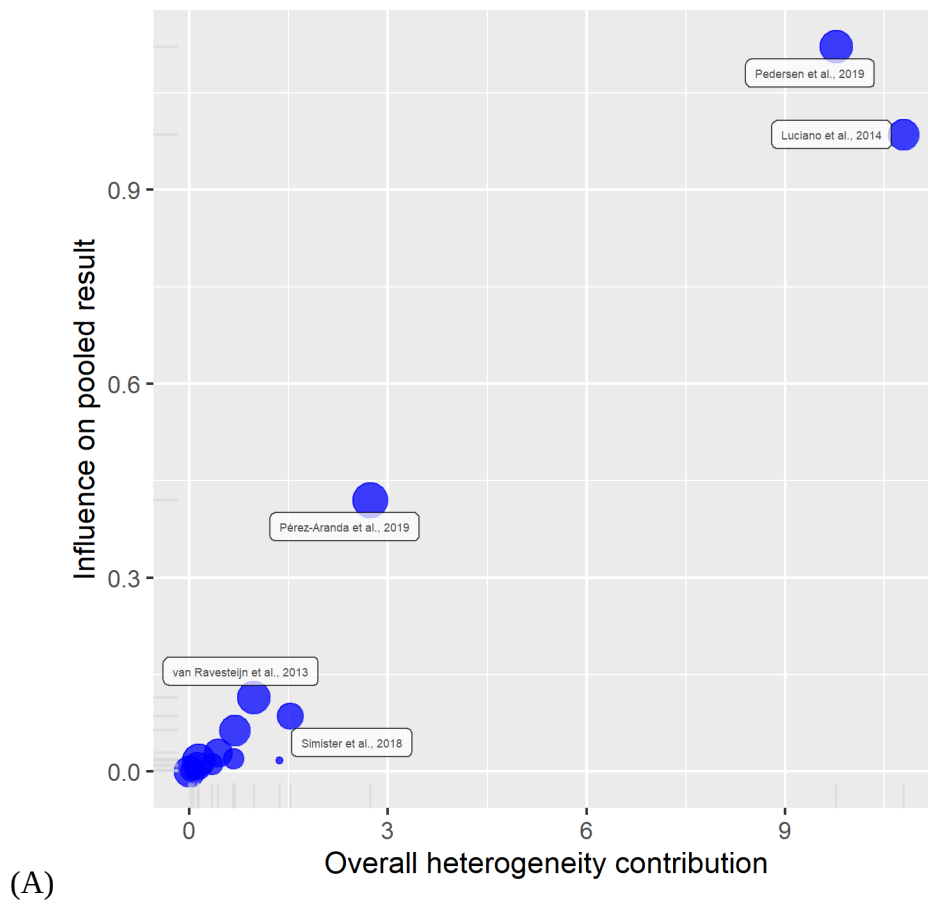
Table S13*Outlier analyses*

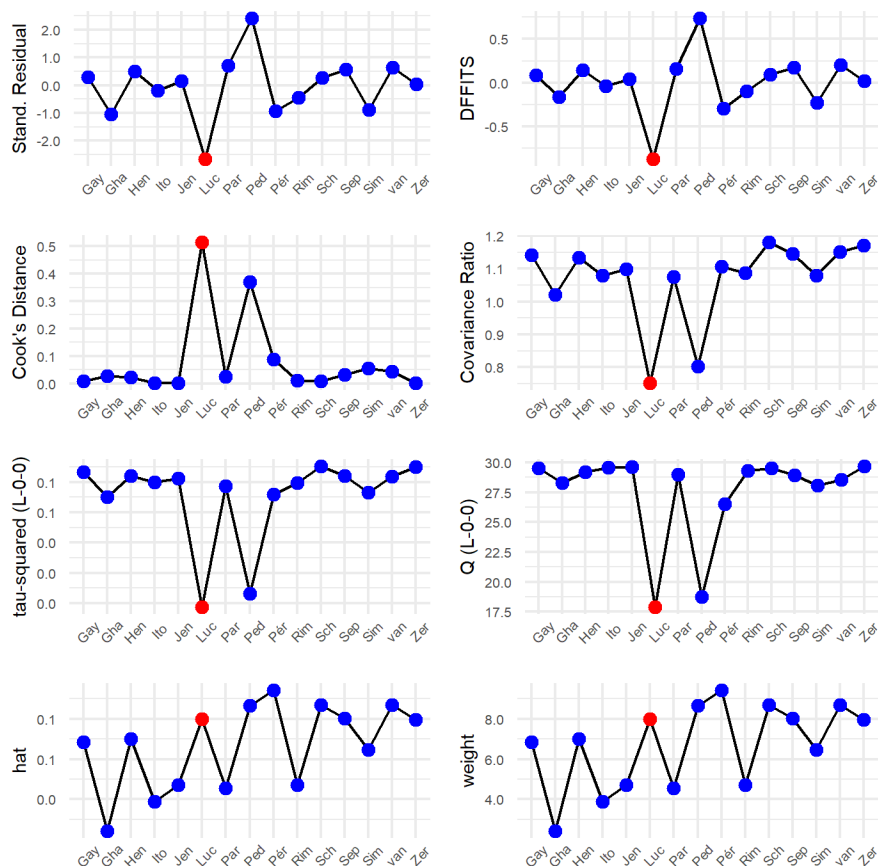
	<i>k</i>	Hedges' <i>g</i>	95%CI	<i>I</i> ²	95%CI	95%PI
Somatic Symptom Severity						
With outliers	15	-0.51	-0.69; -0.32	52.8%	15.1; 73.8	-1.09; 0.08
Without outliers	13	-0.50	-0.63; -0.37	0.0%	0.0; 56.6	-0.65; -0.35
Perceived Health Status						
With outliers	16	0.41	0.11; 0.72	83.7%	74.8; 89.4	-0.85; 1.67
Without outliers	14	0.33	0.15; 0.50	41.2%	0.0; 68.7	-0.17; 0.82
Depression						
With outliers	13	-0.52	-0.82; -0.23	79.8%	66.2; 87.9	-1.61; 0.57
Without outliers	12	-0.38	-0.57; -0.18	50.0%	3.0; 74.2	-0.95; 0.20

Note. *k* = number of studies.

Figure S12

Results for the influence analyses for somatic symptom severity at post-treatment

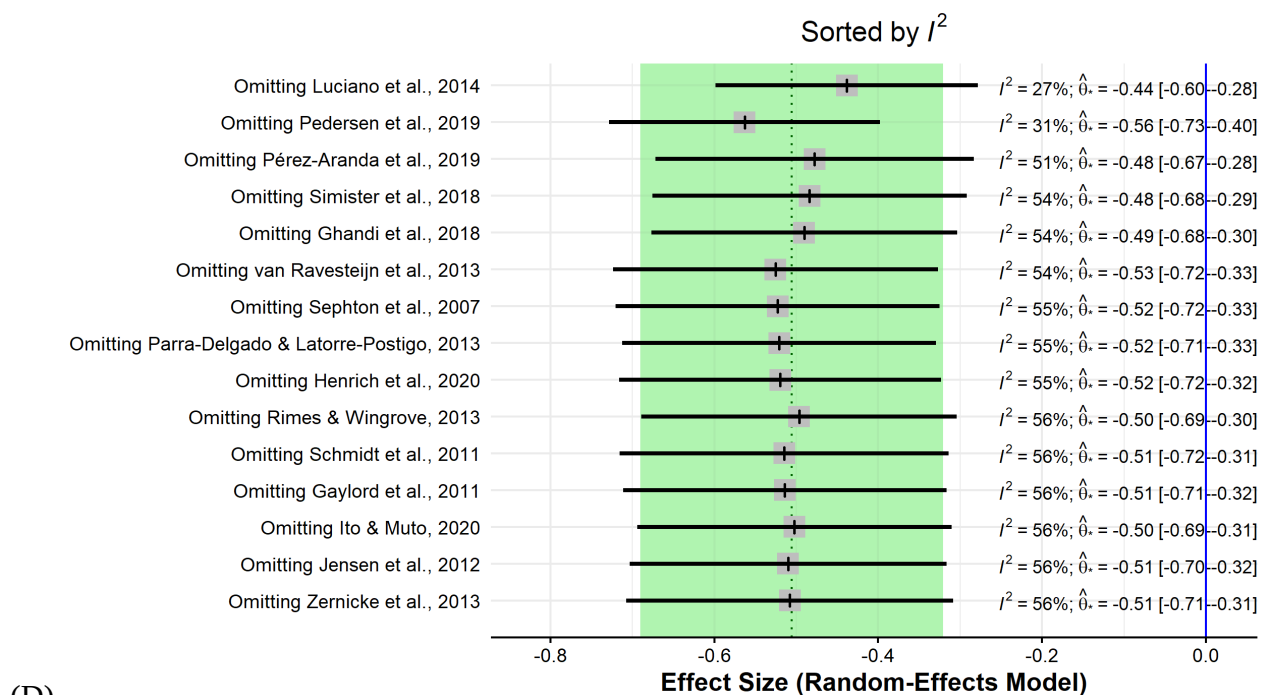




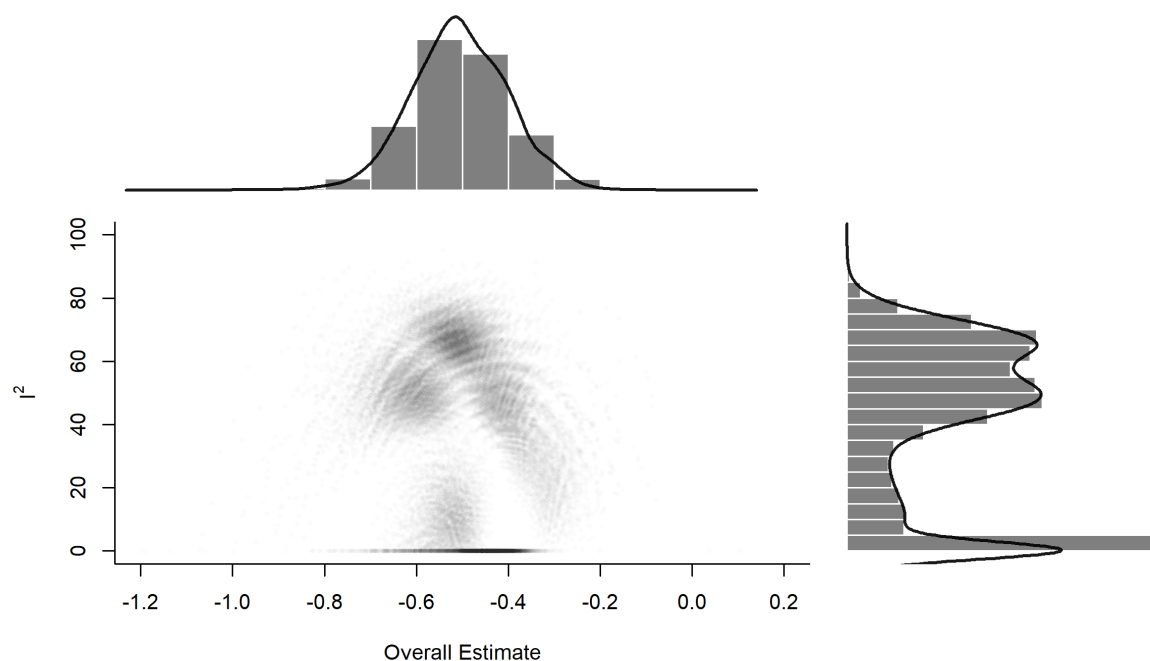
(B)



(C)



(D)



(E)

Note. A: Baujat plot; B: influence plot; C: leave one out method, influence on effect size; D: leave one out method, influence on heterogeneity; E: Graphic Display of Heterogeneity (GOSH) plot.

Information on how to interpret these plots:

Baujat plot: This plot helps to identify studies that excessively contribute to heterogeneity. It displays a study's impact on both the overall heterogeneity (measured by Cochran's Q) and the pooled effect size, determined using the leave-one-out method.

Influence plot: The studies' values on several influence measures are presented.

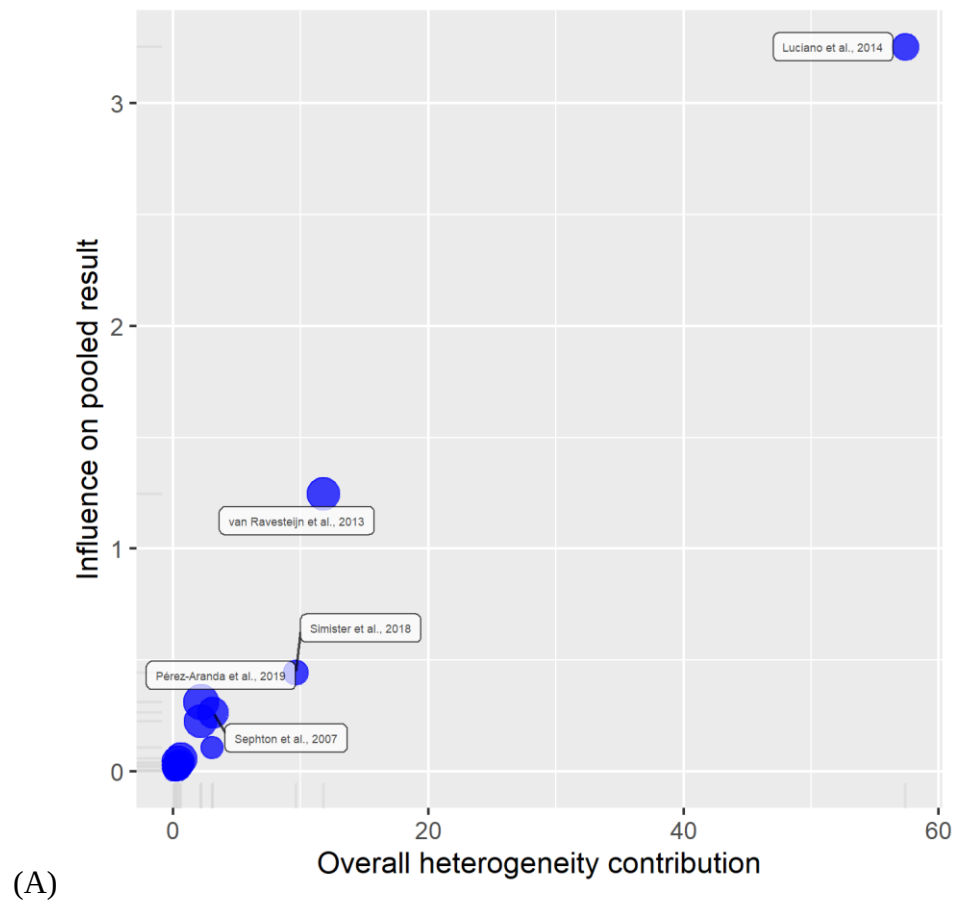
Leave one out method, influence on effect size: This plot visualizes the results from the Leave-one-out-analyses, it indicates the standardized difference in the overall effect when the study is included versus when it is excluded.

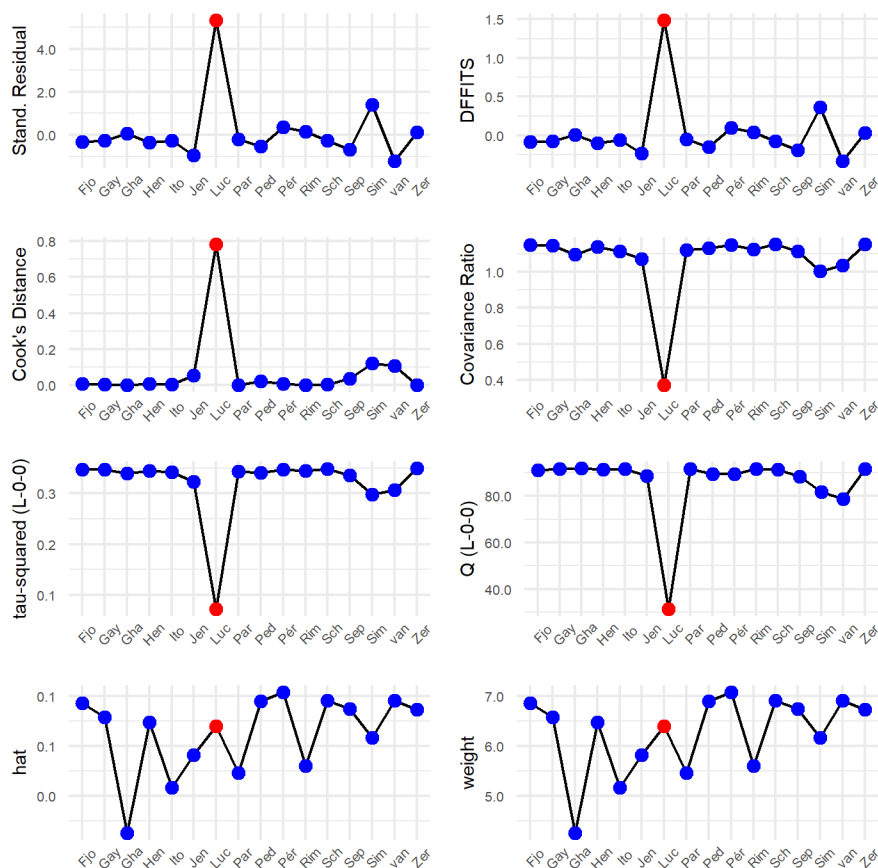
Leave one out method, influence on heterogeneity: This plot visualizes the results from the Leave-one-out-analyses, it indicates the standardized difference in the heterogeneity when the study is included versus when it is excluded.

Graphic Display of Heterogeneity (GOSH) plot: The plot shows the pooled effect size of all 2^{k-1} possible study combinations along the x-axis and the between-study heterogeneity on the y-axis. If the plot displays multiple distinct clusters, indicates the likelihood of multiple populations of effect sizes, calling for a subgroup analysis. Conversely, if the effect sizes are consistent, the GOSH plot will exhibit a uniform and symmetrical distribution.

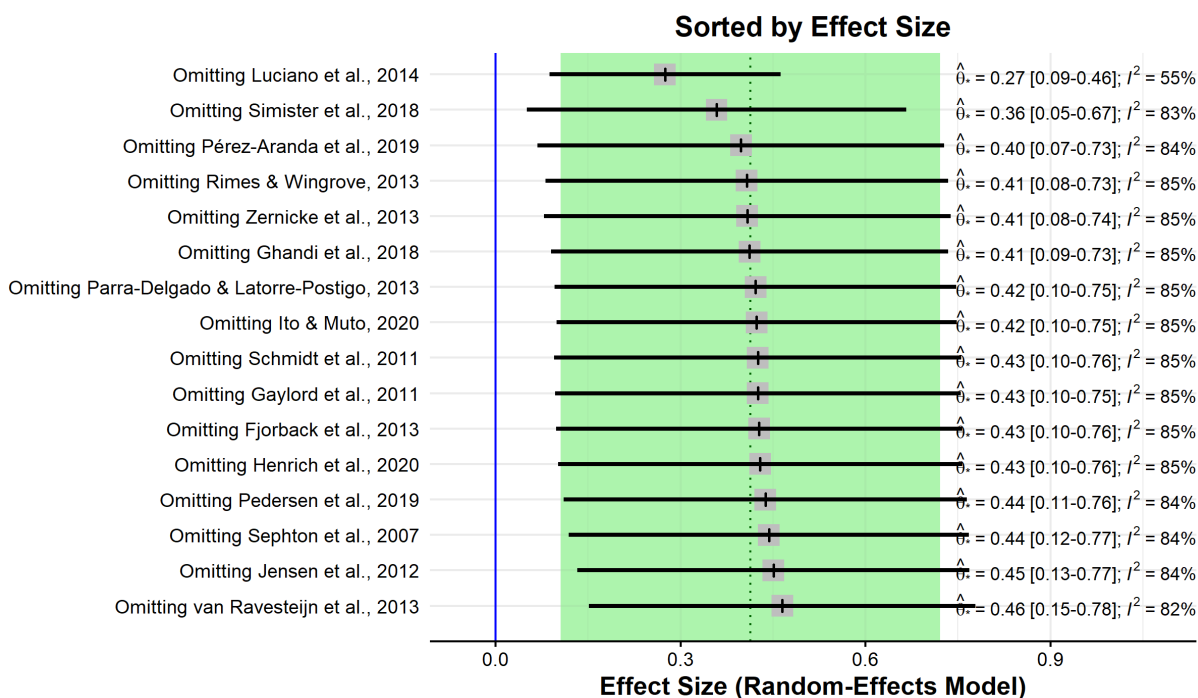
Figure S13

Results for the influence analyses for perceived health status at post-treatment

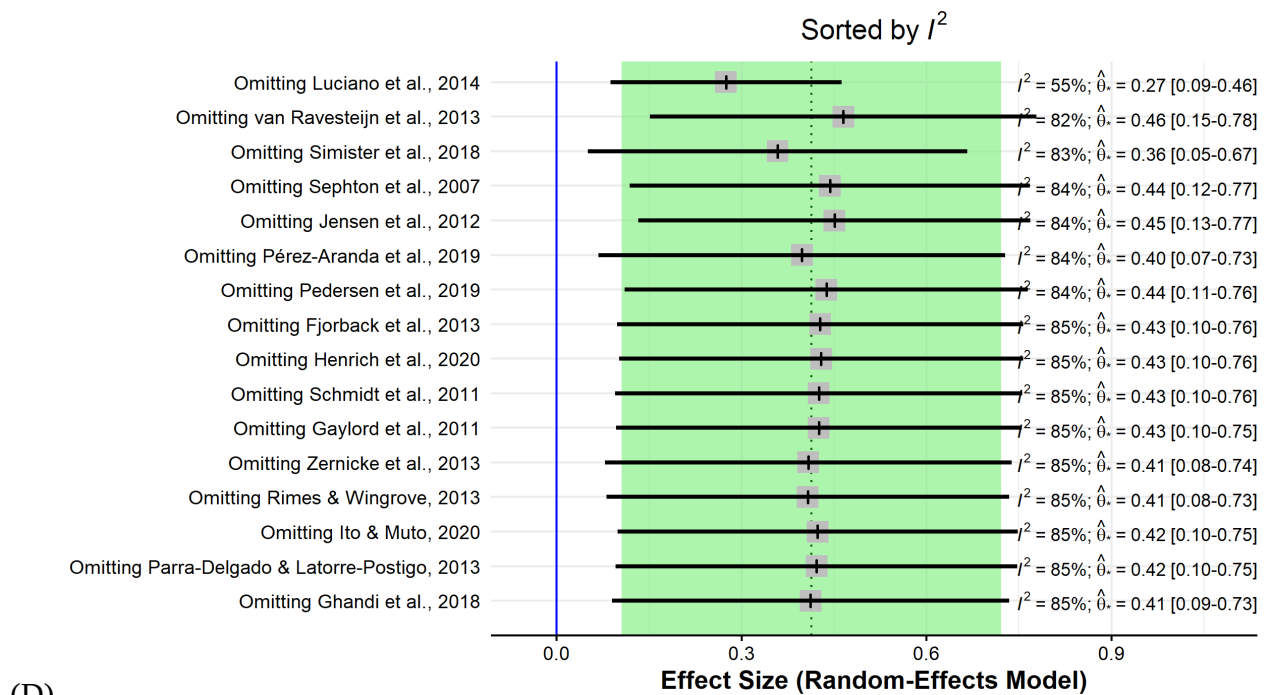




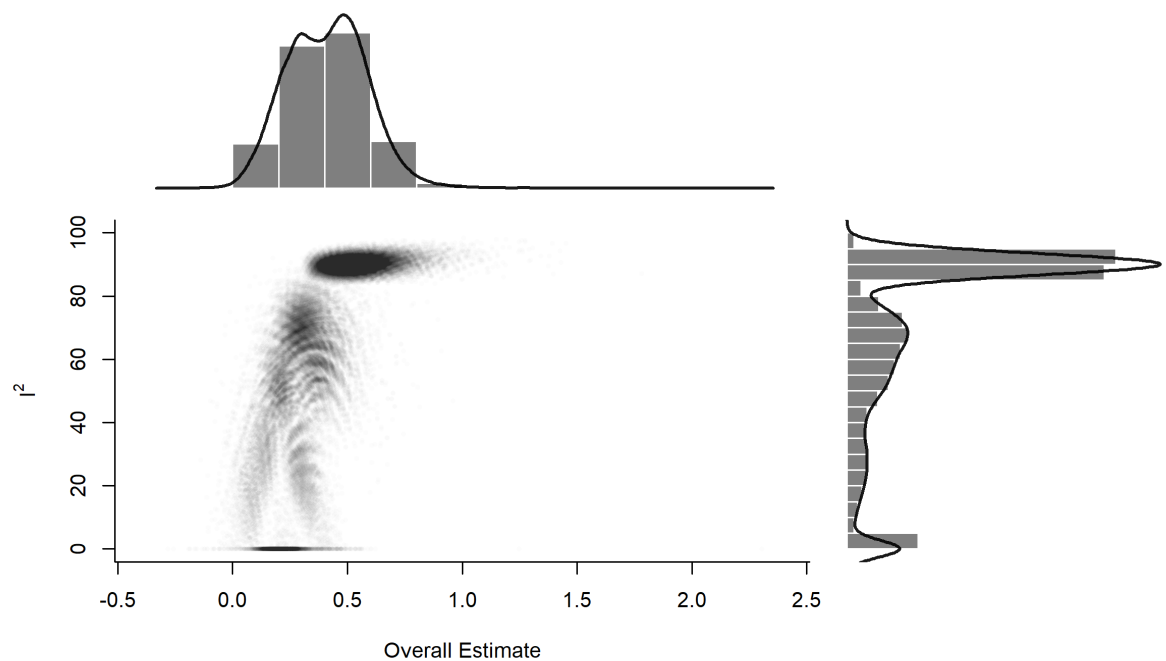
(B)



(C)



(D)

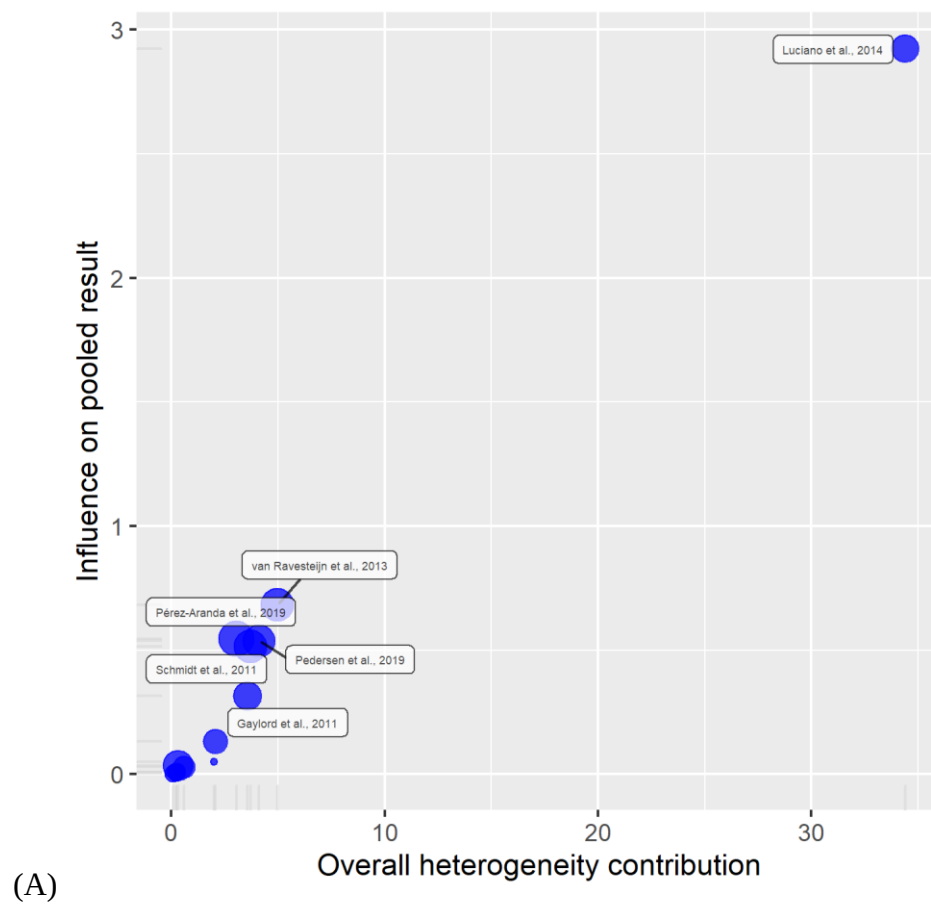


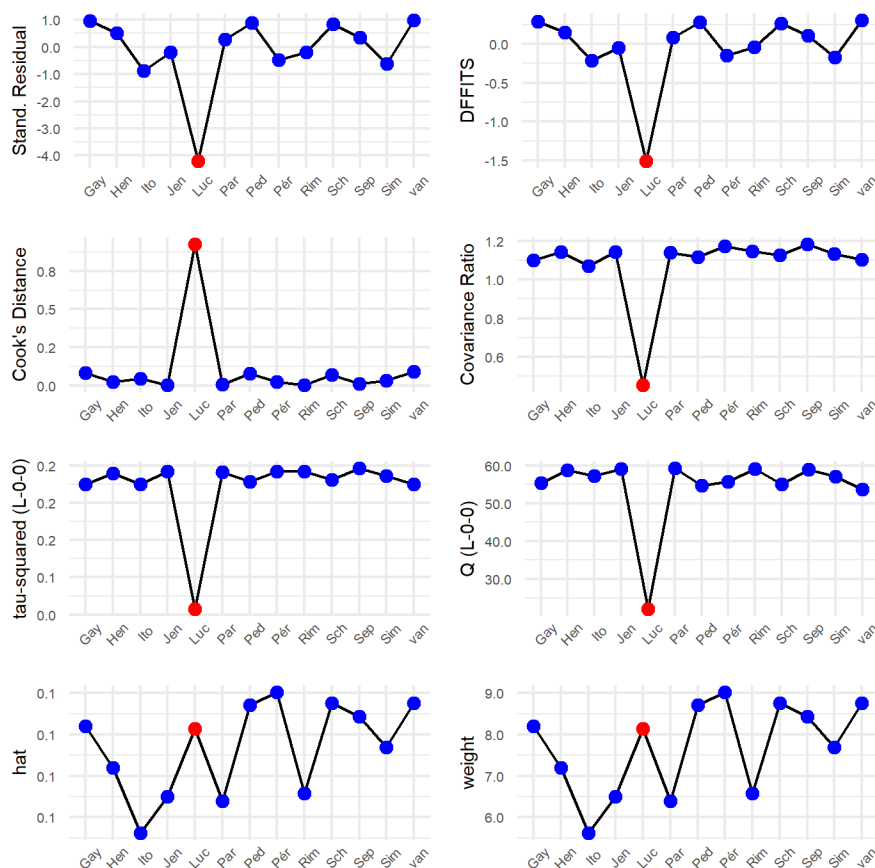
(E)

Note. A: Baujat plot; B: influence plot; C: leave one out method, influence on effect size; D: leave one out method, influence on heterogeneity; E: Graphic Display of Heterogeneity (GOSH) plot. Note: For more information on how to interpret these plots see below Figure S12.

Figure S14

Results for the influence analyses for depression at post-treatment

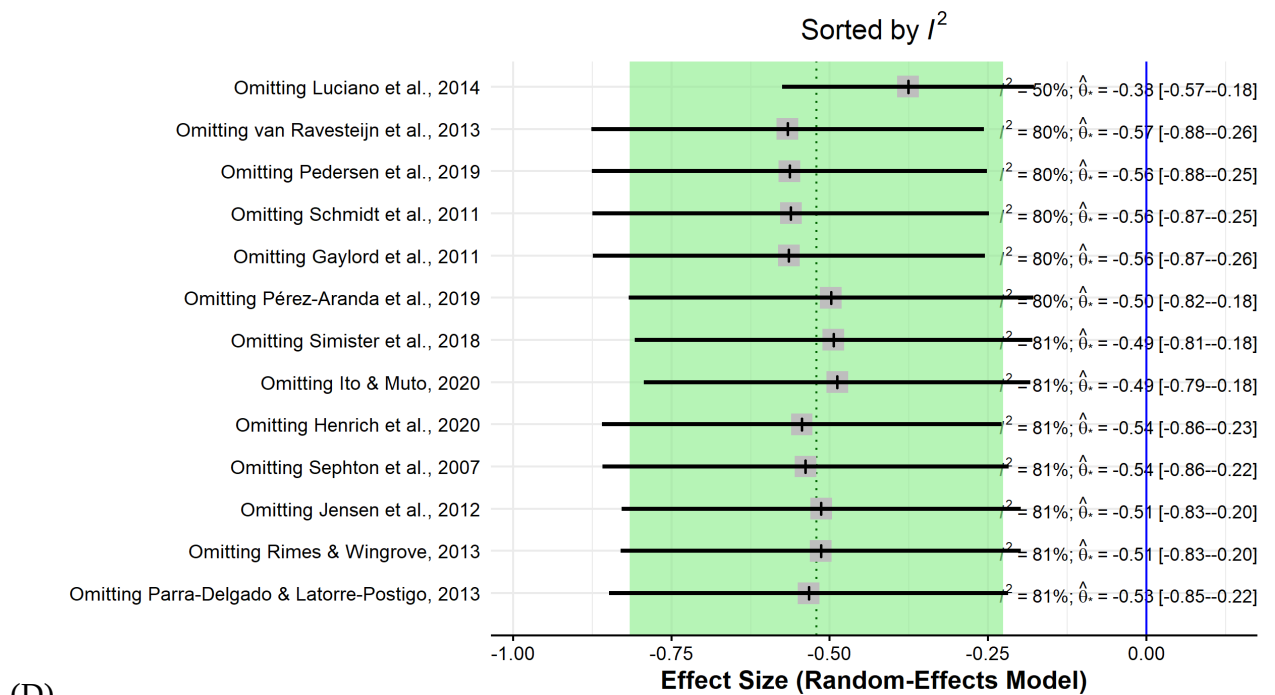




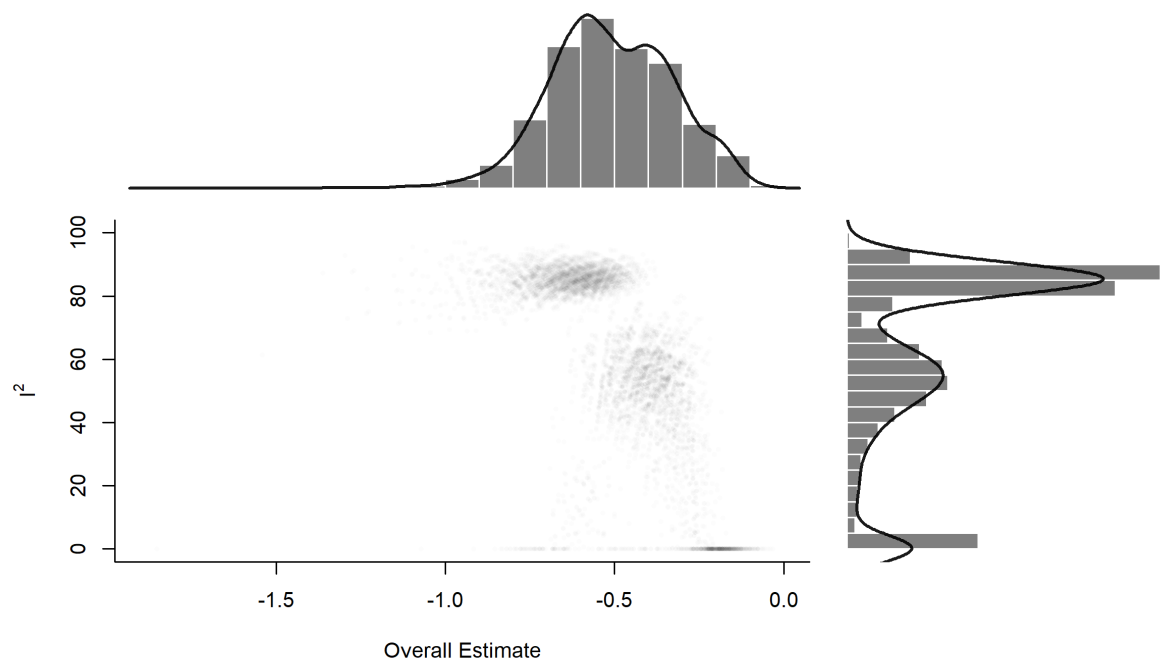
(B)



(C)



(D)



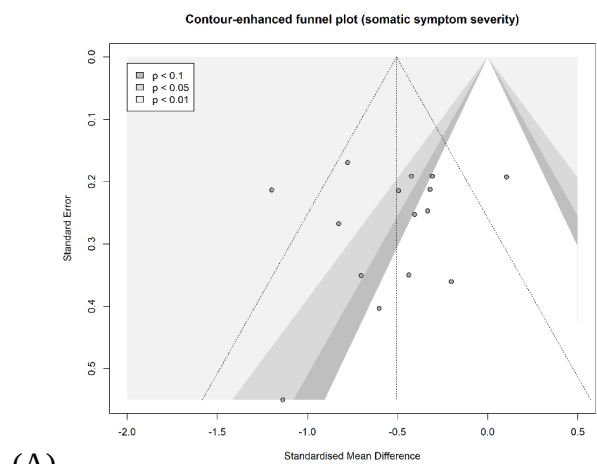
(E)

Note. A: Baujat plot; B: influence plot; C: leave one out method, influence on effect size; D: leave one out method, influence on heterogeneity; E: Graphic Display of Heterogeneity (GOSH) plot. Note: For more information on how to interpret these plots see below Figure S12.

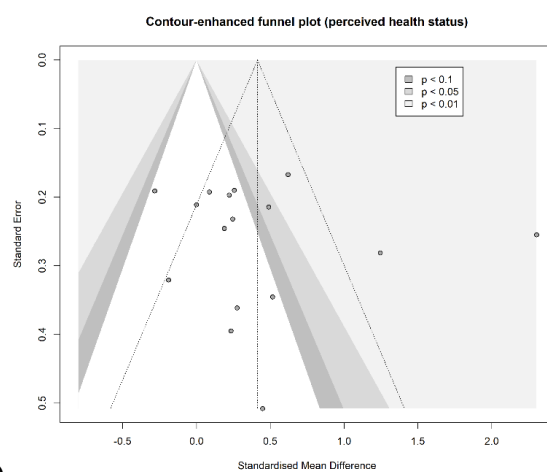
13. Publication Bias

Figure S15

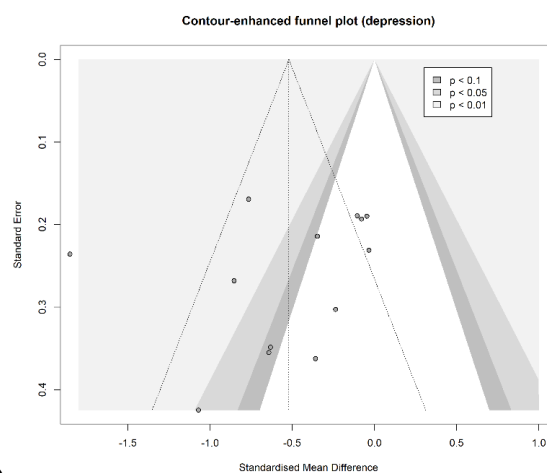
Publication bias – post-treatment



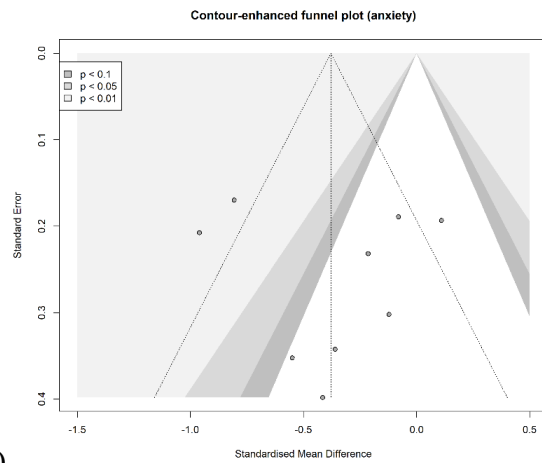
(A)



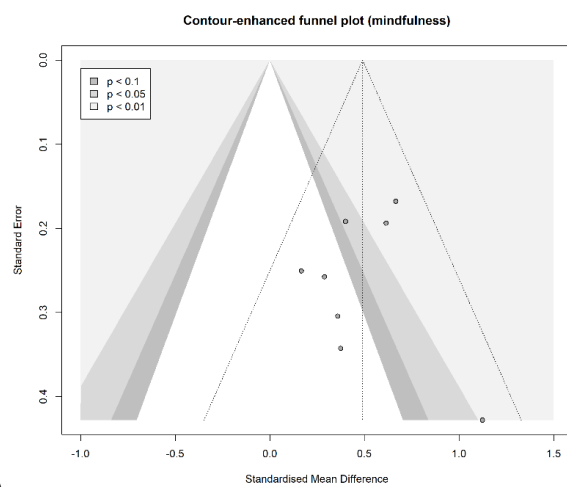
(B)



(C)



(D)

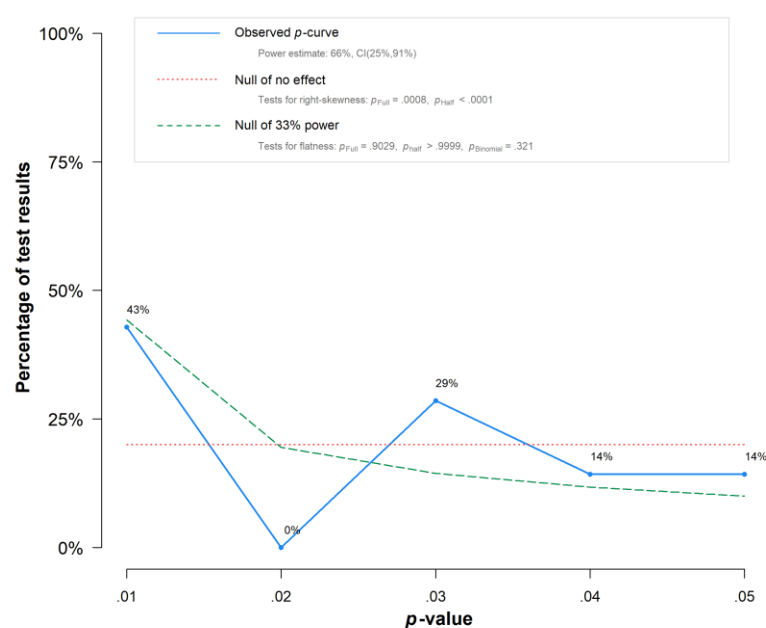


(E)

Note. A: somatic symptom severity at post-treatment; B: perceived health status at post-treatment; C: depression at post-treatment; D: anxiety at post-treatment; E: mindfulness at post-treatment; F: psychological inflexibility at post-treatment

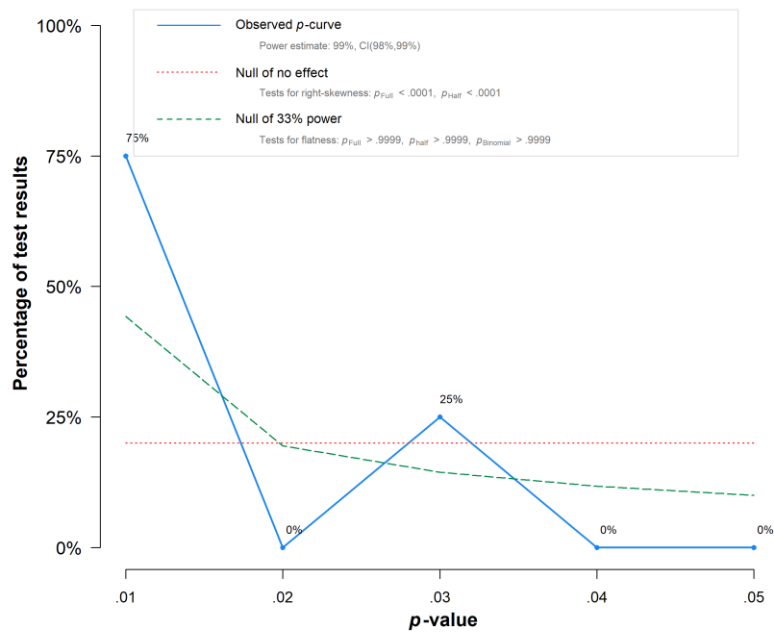
Table S14*Results of Egger's regression tests at post-treatment*

Outcome	Intercept	<i>t</i>	<i>p</i>
Somatic Symptom Severity	-0.71	-0.52	0.612
Perceived Health Status	1.34	0.56	0.579
Depression	-1.85	-0.78	0.449
Anxiety ^a	0.56	0.25	0.811
Mindfulness ^a	-0.22	-0.17	0.873

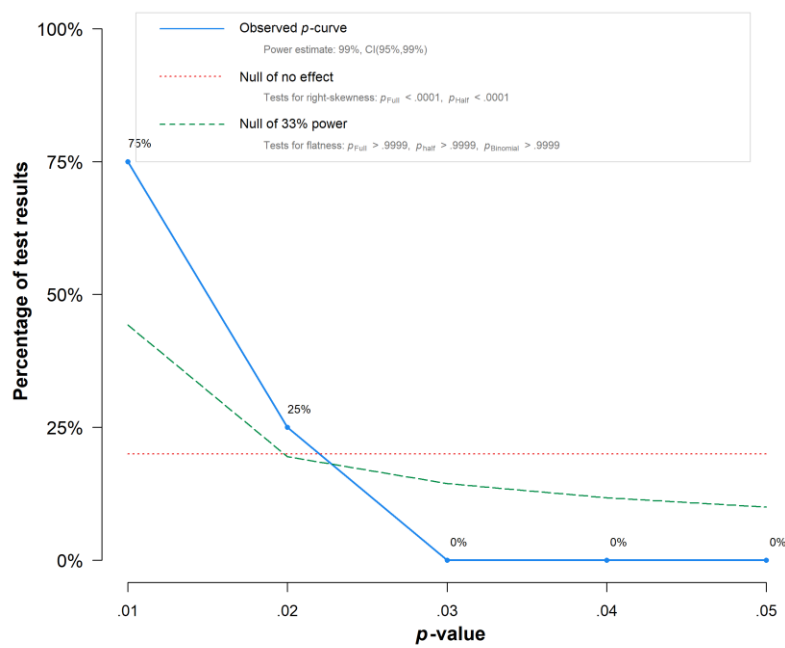
^a $k < 10$ **P-curve analyses****Figure S16***P-curve analyses*

(A)

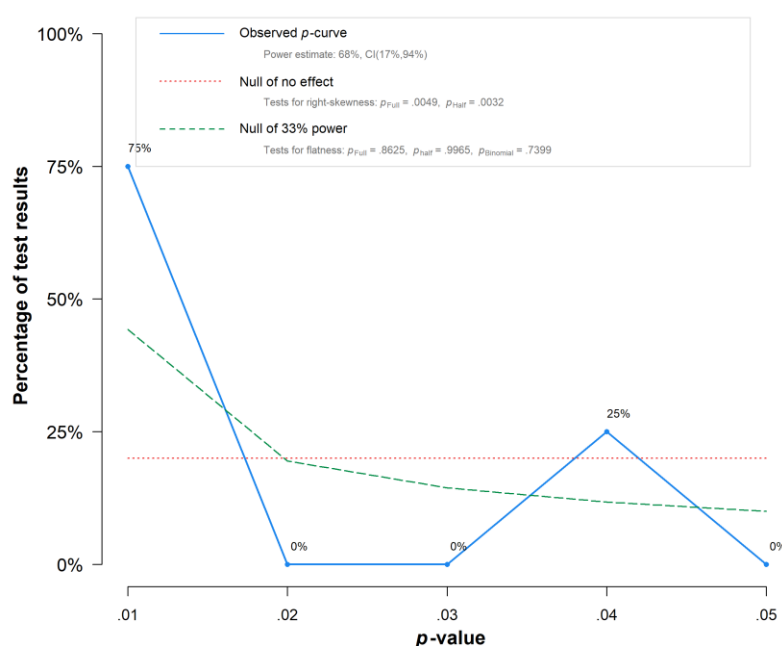
Note: The observed *p*-curve includes 7 statistically significant ($p < .05$) results, of which 4 are $p < .025$. There were 8 additional results entered but excluded from *p*-curve because they were $p > .05$.



(B)



(C)



Note: The observed p-curve includes 4 statistically significant ($p < .05$) results, of which 3 are $p < .025$. There were 4 additional results entered but excluded from p-curve because they were $p > .05$.

(D)

Note. A: p -curve for somatic symptom severity at post-treatment; B: p -curve for perceived health status at post-treatment; C: p -curve for depression at post-treatment; D: p -curve for mindfulness at post-treatment. Note: p -curve could not be conducted for anxiety and psychological inflexibility as two or less significant ($p < 0.05$) effect sizes were detected.

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Appendix D

Appendix – Study 3

S1 Inclusion and exclusion of studies

S1.1 Eligible syndromes and diagnoses

- ICD-10 [1]:
 - Somatization disorder (F45.0)
 - Undifferentiated somatoform disorder (F45.1)
 - Dissociative (conversion) disorders (F44.)
 - Persistent somatoform pain disorder (F45.4)
 - Somatoform autonomic dysfunction (F45.3)
 - Other somatoform disorders (F45.8)
 - Somatoform disorder unspecified (F45.9)
 - Neurasthenia (in other neurotic disorders category; F.48.0)
- ICD-11 [2]: Bodily Distress Disorder (6C40)
- DSM-IV [3]:
 - Somatization Disorder (300.81) [4]
 - Undifferentiated somatoform disorder (300.81)
 - Conversion disorder (300.11)
 - Pain disorder (307.80)
 - Somatoform disorder not otherwise specified (300.81)
- DSM-5 [5]: Somatic Symptom Disorder (300.82) [6]
- Bodily Distress Syndrome [7]
- Multisomatoform Disorder [8]
- Abridged Somatization (SSI-4/6; somatic symptom index) [9]
- Physical Symptom Disorder [10]
- Polysymptomatic Distress Disorder [4]
- Complex Somatic Symptom Disorder [11]
- Medically unexplained symptoms (MUS, [12])
- Functional Somatic Disorders [13]
- Clear-cut Functional Somatic Syndromes
 - IBS
 - Rome-I to -IV [14]
 - German consensus guidelines [15],
 - ICD-10 [1]: K85.
 - CFS and myalgic encephalomyelitis (ME) will be combined under the term CFS
 - Holmes Criteria [16]
 - Oxford criteria [17]
 - Fukuda definition/Centers for Disease Control and Prevention (CDC) definition [18]
 - Canadian consensus criteria [19]
 - international consensus criteria [20]
 - NICE guidelines [21]
 - ICD-10 [1]: Neurasthenia (F48.0), unspecified Chronic fatigue (R53.82), ME/postviral fatigue syndrome (G.93.3)
 - Systemic Exertion Intolerance Disease [22, 23]
 - FM/Fibromyalgia syndrome (FMS)
 - American College of Rheumatology (ACR) 1990 Criteria [24], ACR 2010 preliminary diagnostic criteria [25], 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria [26]
 - ICD-10 [1]: M79.7
 - Chronic Widespread Pain: Defining feature of FM, although not pathognomonic [27]

Exclusion

Although there is a considerable overlap between hypochondriasis/illness anxiety and bodily distress, studies solely focusing on these diagnoses will be excluded as well as studies on body dysmorphic disorder.

S1.2 Eligible treatments

- Cognitive behavioral therapy (CBT): CBT was considered as psychotherapies that focus on identifying misconceptions, exposure, and encouraging behavior changes [28]. To achieve this, techniques from cognitive therapy, e.g., cognitive restructuring, or behavior modules (from behavior therapy) like behavioral activation might be combined.
- Cognitive therapy (CT)
- Problem-solving therapy (PST) and its respective subtypes [specific forms of CBT [29]]
- Acceptance and commitment therapy (ACT)
- Mindfulness-based therapy (MBT)
- Mindfulness-based cognitive therapy (MBCT)
- Mindfulness-based stress reduction (MBSR)
- Metacognitive therapy (MCT)
- Schema therapy (according to Young)
- Emotion regulation (skills) training (according to Berking)
- Unified protocol (according to Barlow)
- Compassion focused therapy (CFT)/compassionate mind training (CMT)
- Well-being therapy (according to Fava)
- Functional analytic psychotherapy (FAP)
- Positive psychotherapy (PPT)
- Dialectical behavioral therapy (DBT)
- Mindfulness-based relapse prevention (MBRP)
- Cognitive-behavioral analysis system of psychotherapy (CBASP)
- Integrative behavioral couples therapy (IBCT)
- Mode deactivation therapy (MDT)

S1.3 Prioritization of exclusion criteria

Reasons for exclusion were prioritized as follows: focus is not on bodily distress; treatment is not CBT or an AMBT; focus is not on human adults (e.g., children, adolescents, animals); the study is not an RCT; neither control group is inactive, CBT, or an AMBT; the report was not published in English.

S1.4 Data base searches

PubMed was chosen as it yields reports from the medical field, whereas PsycInfo offers psychological reports. Both fields are relevant to our research topic. The Cochrane Library (CENTRAL, CDSR,

CCA) was additionally searched to complement the former two data bases. Furthermore, PSYNDEX was chosen to supplement the search for German studies. The search was further supplemented by a search in Web of Science. Although it has been hypothesized that the incorporation of grey literature may assist in addressing publication bias, unpublished papers are neither peer-reviewed nor can one systematically search for them, resulting in another form of bias [30]. Therefore, grey literature was not included. Consequently, dissertations and congress abstracts were only considered if they were additionally published as a journal article.

S1.5 Search strategies

PubMed

(„Somatoform disorders” [MeSH Terms] OR „somatization disorder” [MeSH Terms] OR „somatisation disorder” [MeSH Terms] OR Neurasthenia [MeSH Terms] OR „conversion disorder” [MeSH Terms] OR „psychophysiological disorder” [MeSH Terms] OR „Psychosomatic medicine” [MeSH Terms] OR Fibromyalgia [MeSH Terms] OR „Fatigue Syndrome, Chronic” [MeSH Terms] OR „Irritable Bowel Syndrome” [MeSH Terms] OR „Colonic diseases, Functional” [MeSH Terms] OR „briquet syndrome” [MeSH Terms] OR

„somatoform disorder*” [All Fields] OR somatoform [All Fields] OR somatiz* [All Fields] OR somatis* [All Fields] OR „somatic symptom disorder*” [All Fields] OR (somatic AND symptom*) OR „psychophysiological disorder*” [All Fields] OR „psychophysiologic disorder*” [All Fields] OR psychosomat* [All Fields] OR „persistent physical symptom*” [All Fields] OR „persistent somatic symptom*” [All Fields] OR „bodily distress” [All Fields] OR „body distress” [All Fields] OR „Physical Symptom Disorder*” [All Fields] OR „pain disorder*” [All Fields] OR

multisomat* [All Fields] OR „multi?somat*” [All Fields] OR polysymptom* [All Fields] OR „poly?symptom*” [All Fields] OR (multiple AND („physical symptom*” OR „symptom diagnos*”)) OR

„frequent attend*” [Title/Abstract] OR „high utilis*” [Title/Abstract] OR „high utiliz*” [Title/Abstract] OR

„medically unexplain*” [All Fields] OR „organically unexplain*” [All Fields] OR MUS [All Fields] OR MUPS [All Fields] OR „unexplained medical*” [All Fields] OR „unexplained symptom*” [All Fields] OR „unexplained syndrom*” [All Fields] OR „unexplained illness*” [All Fields] OR

nonorganic [All Fields] OR „non?organic” [All Fields] OR „non?specific complain*” [All Fields] OR „non?specific symptom*” [All Fields] OR

„psychosomatic syndrom*” [All Fields] OR

FSS [All Fields] OR „functional somatic syndrome*” [All Fields] OR „functional somatic disorder*” [All Fields] OR „functional symptom*” [All Fields] OR „functional disorder*” [All Fields] OR „functional syndrome*” [All Fields] OR „functional somatic*” [All Fields] OR „functional illness*” [All Fields] OR

((irritable OR functional) AND (bowel* OR colon*)) OR „functional gastrointestinal*” [All Fields] OR IBS [All Fields] OR

fibromyalgi* [All Fields] OR fibrositis [All Fields] OR FM [All Fields] OR fibromyositis [All Fields] OR myofibrositis [All Fields] OR

„chronic widespread pain*” [All Fields] OR „widespread musculoskeletal pain*” [All Fields] OR „myofascial pain*” [All Fields] OR „persistent pain*” [All Fields] OR „chronic intractable benign pain*” [All Fields] OR

„fatigue syndrome*” [All Fields] OR „psychogenic fatigue” [All Fields] OR „myalgic encephalomyelitis*” [All Fields] OR „myalgic encephalopath*” [All Fields] OR CFS [All Fields] OR „CFS/ME” [All Fields] OR „postviral fatigue syndrome*” [All Fields] OR „systemic exertion intolerance*” [All Fields] OR „post-exertional malaise” [All Fields]

AND

(cbt [All Fields] OR „cognitive behavioral therap*” [All Fields] OR „cognitive behavioural therap*” [All Fields] OR „cognitive behavioral treatment*” [All Fields] OR „cognitive behavioural treatment*” [All Fields] OR „cognition therap*” [All Fields])

[All Fields] OR „cognition treatment*“ [All Fields] OR „cognitive therap*“ [All Fields] OR „cognitive treatment*“ [All Fields] OR

„cognitive restructuring“ [All Fields] OR (cognitive AND „perceptual change*“) OR „cognitive reappraisal“ [All Fields] OR „exposure therap*“ [All Fields] OR „behavior modification*“ OR „behaviour modification*“ OR

(„problem?solving“ AND (therap* OR treatment*)) OR

(„third wave“ AND (therap* OR treatment*)) OR

mindful* [All Fields] OR MBT [All Fields] OR MBCT [All Fields] OR MBSR [All Fields] OR

(acceptance AND commitment) OR

(dialectic* AND (behavioural OR behavioral)) OR DBT [All Fields] OR

„metacognitive therap*“ [All Fields] OR „metacognitive treatment*“ [All Fields] OR „meta?cognitive therap*“ [All Fields] OR „meta?cognitive treatment*“ [All Fields] OR MCT [All Fields] OR

((Schematherap* OR „schema therap*“) AND Young) OR

„emotion?regulation skills training*“ [All Fields] OR „emotion?regulation training*“ [All Fields] OR

„unified protocol*“ OR

„compassion focused therap*“ [All Fields] OR „compassionate mind training*“ [All Fields] OR

„well-being therap*“ [All Fields] OR

„functional analytic psychotherap*“ [All Fields] OR

„positive psychotherap*“ [All Fields] OR

„integrative behavioural couple* therap*“ [All Fields] OR „integrative behavioral couple* therap*“ [All Fields] OR

„mode deactivation therap*“ [All Fields]

Filters: Randomized Controlled Trial, Meta-analysis, Systematic Review

PsycInfo

(„somatoform disorder*“ OR somatoform OR somatiz* OR somatis* OR „somatic symptom disorder*“ OR (somatic AND symptom*) OR „psychophysiological disorder*“ OR „psychophysiologic disorder*“ OR psychosomat* OR „persistent physical symptom*“ OR „persistent somatic symptom*“ OR „bodily distress“ OR „body distress“ OR „Physical Symptom Disorder“ OR „pain disorder*“ OR

multisomat* OR „multi?somat*“ OR polysymptom* OR „poly?symptom*“ OR (multiple AND („physical symptom*“ OR „symptom diagnos*“)) OR

„frequent attend*“ OR „high utilis*“ OR „high utiliz*“ OR

„medically unexplain*“ OR „organically unexplain*“ OR MUS OR MUPS OR „unexplained medical*“ OR „unexplained symptom*“ OR „unexplained syndrom*“ OR „unexplained illness*“ OR

nonorganic OR „non?organic“ OR „non?specific complain*“ OR „non?specific symptom*“ OR

„psychosomatic syndrom*“ OR

FSS OR „functional somatic syndrome*“ OR „functional somatic disorder*“ OR „functional symptom“ OR „functional disorder*“ OR „functional syndrome*“ OR „functional somatic“ OR „functional illness*“ OR

((irritable OR functional) AND (bowel* OR colon*)) OR „functional gastrointestinal*“ OR IBS OR

fibromyalgia* OR fibrositis OR FM OR fibromyositis OR myofibrositis OR

„chronic widespread pain*” OR „widespread musculoskeletal pain*” OR „myofascial pain*” OR „persistent pain*” OR „chronic intractable benign pain*” OR

„fatigue syndrome*” OR „psychogenic fatigue” OR „systemic exertion intolerance” OR „myalgic encephalomyelitis*” OR „myalgic encephalopath*” OR CFS OR „CFS/ME” OR „postviral fatigue syndrome*” OR „systemic exertion intolerance*” OR „post-exertional malaise”)

AND

(cbt OR „cognitive behavioral therap*” OR „cognitive behavioural therap*” OR „cognitive behavioral treatment*” OR „cognitive behavioural treatment*” OR „cognition therap*” OR „cognition treatment*” OR „cognitive therap*” OR „cognitive treatment*” OR

„cognitive restructuring” OR (cognitive AND „perceptual change”) OR „cognitive reappraisal” OR „exposure therap*” OR „behavior modification*” OR „behaviour modification*” OR

(„problem?solving” AND (therap* OR treatment*)) OR

(„third wave” AND (therap*OR treatment*)) OR

mindful* OR MBT OR MBCT OR MBSR OR (acceptance AND commitment) OR (dialectic* AND (behavioural OR behavioral)) OR DBT OR „metacognitive therap*” OR „metacognitive treatment*” OR „meta?cognitive therap*” OR „meta?cognitive treatment*” OR MCT OR

((Schematherap*OR „schema therap”) AND Young) OR

„emotion?regulation skills training*” OR „emotion?regulation training*” OR

„unified protocol*” OR „compassion focused therap*” OR „compassionate mind training*” OR

„well-being therap*” OR „functional analytic psychotherap*” OR

„positive psychotherap*” OR „integrative behavioural couples therap*” OR „integrative behavioural couple therap*” OR

„mode deactivation therap*”)

AND

(„double-blind” OR „random* assigned” OR control)

Methodology: Clinical trial, systematic review, meta-analysis

Psyndex

(„somatisch* Belastung*” OR „somatisch* Syndrom*” OR „somatoform*” OR „somatisier*” OR

„anhaltend* Körperbeschwerde*” OR „Neurasthenie*” OR „Konversionsstörung*” OR „psychophysiologisch*” OR „psychosomati*” OR „Briquet Syndrom*” OR „Schmerzstörung*” OR

((„nicht spezifisch*” OR „unspezifisch*” OR „unklar*” OR „medizinisch unerklärt*” OR „organisch unerklärt*” OR „nicht erklärt”) AND („Symptom*” OR „Syndrom*”)) OR

„funktionell* Syndrom*” OR „funktionell* Störung*” OR

„Reizdarm*” OR „funktionell* gastrointestinal*” OR

„fibromyalgi*” OR „fibrositis” OR „fibromyositis” OR „myofibrositis” OR („myofascial*” AND „Schmerz*”) OR „chronisch* Ganzkörperschmerz*” OR

((„Chronisch*” OR „psychogen*”) AND („Müdigkeit*” OR „Erschöpfung*”) OR „myalgic encephalomyelitis*” OR „myalgic encephalopath*” OR „postviral* Erschöpfung*”)

AND

((„kognitiv*“ AND („Intervention*“ OR „Behandlung*“ OR „Verhaltenstherapie“ OR „Therapie*” OR „Umstrukturierung*“ OR „Umbewertung*“)) OR („kognitiv?behavioral*“ AND („Intervention*“ OR „Behandlung*“ OR „Therapie*”)) OR

„Exposition*“ OR „Verhaltensmodifikation*“ OR „Verhaltensänderung*“ OR

„Problemlösetherapie*“ OR

(„dritte Welle“ AND („Intervention*“ OR „Behandlung*“ OR „Therapie*”)) OR

„achtsamkeit*“ OR ((„akzeptanz*“ OR „acceptance”) AND „commitment*”) OR

(„dialectic*” AND („behavioural” OR „behavioral”)) OR

„metakognitiv“ OR „meta?kognitiv“ OR

((Schematherap* OR „schema therap*”) AND Young) OR

„Emotionsregulationstraining*“ OR „Training emotionaler Kompetenz*” OR

„unified protocol*” OR „compassion focused therap*” OR „compassionate mind training*” OR

„well-being therap*” OR „functional analytic psychotherap*” OR

„positive psychotherap*” OR „integrative behavioural couples therap*” OR „integrative behavioural couple therap*” OR

„mode deactivation therap*”))

Source type: academic journals.

Cochrane Library

- #1 MeSH descriptor: [Conversion Disorder] explode all trees
- #2 MeSH descriptor: [Somatoform Disorders] explode all trees
- #3 MeSH descriptor: [Neurasthenia] explode all trees
- #4 MeSH descriptor: [Psychophysiologic Disorders] explode all trees
- #5 MeSH descriptor: [Psychosomatic Medicine] explode all trees
- #6 MeSH descriptor: [Fibromyalgia] explode all trees
- #7 MeSH descriptor: [Fatigue Syndrome, Chronic] explode all trees
- #8 MeSH descriptor: [Irritable Bowel Syndrome] explode all trees
- #9 MeSH descriptor: [Colonic Diseases, Functional] explode all trees
- #10 „somatoform disorder*” OR somatoform OR somatiz* OR somatis* OR „somatic symptom disorder*” OR (somatic AND symptom*) OR (pain NEXT disorder) OR „psychophysiological disorder*” OR „psychophysiologic disorder*” OR psychosomat* OR „persistent physical symptom*” OR „persistent somatic symptom*” OR „bodily distress” OR „body distress“ OR „Physical Symptom Disorder” OR „pain disorder*”
- #11 multisomat* OR „multi?somat*“ OR polysymptom* OR „poly?symptom*“ OR (multiple AND („physical symptom*” OR „symptom diagnos*”))
- #12 „frequent attend*” OR „high utilis*” OR „high utiliz*”
- #13 „medically unexplain*” OR „organically unexplain*” OR MUS OR MUPS OR „unexplained medical*” OR „unexplained symptom*“ OR „unexplained syndrom*“ OR „unexplained illness*“

- #14 nonorganic OR „non?organic” OR „non?specific complain*” OR „non?specific symptom*”
- #15 „psychosomatic syndrom*”
- #16 FSS OR „functional somatic syndrome*” OR „functional somatic disorder*” OR „functional symptom” OR „functional disorder*” OR „functional syndrome*” OR „functional somatic” OR „functional illness*”
- #17 ((irritable OR functional) AND (bowel* OR colon*)) OR „functional gastrointestinal*” OR IBS
- #18 fibromyalgia* OR fibrositis OR FM OR fibromyositis OR myofibrositis
- #19 „chronic widespread pain*” OR „widespread musculoskeletal pain*” OR „myofascial pain*” OR „persistent pain*” OR „chronic intractable benign pain*”
- #20 „fatigue syndrome*” OR „psychogenic fatigue” OR „systemic exertion intolerance” OR „myalgic encephalomyelitis*” OR „myalgic encephalopath*” OR CFS OR „postviral fatigue syndrome*” OR „systemic exertion intolerance*” OR „post-exertional malaise”
- #21 cbt OR „cognitive behavioral therap*” OR „cognitive behavioural therap*” OR „cognitive behavioral treatment*” OR „cognitive behavioural treatment*” OR „cognition therap*” OR „cognition treatment*” OR „cognitive therap*” OR „cognitive treatment*”
- #22 „cognitive restructuring” OR „cognitive perceptual change*” OR „cognitive reappraisal” OR „exposure therap*” OR „behavior modification*” OR „behaviour modification*”
- #23 („problem?solving” AND (therap* OR treatment*))
- #24 („third wave” AND (therap*OR treatment*))
- #25 mindful* OR MBT OR MBCT OR MBSR
- #26 (acceptance AND commitment)
- #27 (dialectic* AND (behavioural OR behavioral)) OR DBT
- #28 „metacognitive therap*” OR „metacognitive treatment*” OR „meta?cognitive therap*” OR „meta?cognitive treatment*” OR MCT
- #29 ((Schematherap*OR „schema therap*”) AND Young)
- #30 „emotion?regulation skills training*” OR „emotion?regulation training*”
- #31 „unified protocol*”
- #32 „compassion focused therap*” OR „compassionate mind training*”
- #33 „well-being therap*”
- #34 „functional analytic psychotherap*”
- #35 „positive psychotherap*”
- #36 „integrative behavioral coupl* therap*” OR „integrative behavioural coupl* therap*” OR „mode deactivation therap*”
- #37 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
- #38 #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
- #39 #37 AND #38

Web of Science

- #1 TI=(random* AND trial)
- #2 ALL=("third wave therapy" OR "third wave treatment*" OR MBSR OR MBCT OR (acceptance AND commitment) OR (dialectic* AND (behavioural OR behavioral)))
- #3 ALL=("cognitive behavioral therap*" OR "cognitive behavioural therap*" OR "cognitive behavioral treatment*" OR "cognitive behavioural treatment*")
- #4 #2 OR #3
- #5 ALL=("irritable bowel syndrome*" OR "functional gastrointestinal*" OR fibromyalgi* OR "chronic widespread pain*" OR "widespread musculoskeletal pain*" OR "chronic fatigue syndrome*" OR "myalgic encephalomyelitis*" OR "postviral fatigue syndrome*")
- #6 ALL=("psychosomatic syndrom*" OR "functional somatic syndrome*" OR "functional somatic disorder*")
- #7 ALL=(nonorganic OR "non?organic" OR "non?specific complain*" OR "non?specific symptom*")
- #8 ALL=("medically unexplained" OR "organically unexplained")
- #9 TI=("frequent attend*" OR "high utilis*" OR "high utiliz*")
- #10 ALL=("somatoform disorder" OR somatization OR somatisation OR "somatic symptom disorder*" OR "persistent physical symptom*" OR "bodily distress")
- #11 #5 OR #6 OR #7 OR #8 OR #9 OR #10
- #12 „#1 AND #4 AND #11
- #13 #12 and Article (Document Types) and English (Languages)

S1.6 Data selection

Similar arms were synthesized into one set of values, e.g., two control conditions that are considered as TAU. For synthesizing, combined means and standard deviations (*SDs*) were calculated, and the numbers of participants in the respective arms were combined. If available, the number of allocated participants and the scores of the ITT-analysis was used. Otherwise, per-protocol (PP) data were assessed.

List of extracted data

Study characteristics:

- Author(s); Year of publication
- Citation (according to APA)
- Protocol: register + registration code/number; link to protocol; name of protocol file (and where to find it)
- Recruitment method
- Incentive provided for completing the treatment/control group & if so, which one
- Number of people assessed for eligibility
- Number of participants who declined to participate
- Number of participants randomized (for all groups)
- Number of persons allocated that completed at least one module in the treatment or participated in the control group (for all groups, if possible)
- Number of participants completing all modules as advised (for all groups, if possible)
- Post-assessment: duration from baseline to post-treatment assessment (or follow-up assessments)

Clinical variables:

- Diagnosis assessment
- Diagnosis assessed
- Specific diagnosis/inclusion criteria regarding symptomology; how was this assessed
- Average and standard deviation (*SD*) for number as well as duration of symptoms (all groups)
- Exclusion of participants with comorbid disorders. If applicable, specify criterion.
- Average and *SD* for severity of outcomes as well as how it was assessed
 - The data for post-treatment and respective follow-up assessments will be extracted.
 - The corresponding means of somatic symptom scores and *SDs* at baseline and post-treatment assessment will be extracted for the treatment group(s) and the control group(s), respectively.
 - Hedges' *g* and the *Standard Error (SE)* will be calculated if the mean and *SD* are not reported, but other measures that allow us to estimate the effect (e.g., [31]).

Intervention-related variables (for all included interventions):

- Form of treatment(s)
- Manual used. If so, name of the program/manual used
- Form of guidance
- Setting (group vs. individual treatments; internet-/computer-/app-based)
- Form of control group(s)
 - When a TAU-group was given access to the program after the trial was completed – i.e., TAU was combined with WL – it will be considered as TAU. When a group received no treatment, it will be administered as TAU too as it is considered as congruent to what patients received if they did not participate in the study [32].
- Assessment of consumer satisfaction and negative effects assessed and if so, how
- Number of sessions (per week)
- Duration of treatment
- Average proportion of modules completed
- Reasons for dropping out of treatment/control

Sociodemographic variables:

- Target group
- Mean age and *SD* (all groups)
- Proportion of female participants (all groups)
- Country the trial was conducted in

S2 Study characteristics**Table S1***Study Characteristics*

Study	Conditions	<i>n</i>	Diagnosis	Setting	Guidance	Country	No. Sessions	Time total ^a	Duration of treatment (weeks)	Follow-ups ^b (weeks)
Alda et al., 2011	CBT TAU	57 56	FM	Group	Psy	ES	10	900	10	24
Allen et al., 2006	CBT TAU CT	43 41 120	SD (DSM-IV)	Individual	Psy	US	10	600	12	
Blanchard et al., 2007	Att Plac Psy Plac	44 46	IBS	Group	Psy	US	10	900	10	
Boyce et al., 2003	CBT TAU	35 34	IBS	Individual	Psy	AU	8	480	8	26,52
Castel et al., 2012	CBT TAU	34 30	FM	Mixed		ES	14	1680	14	12,24
Castel et al., 2013	CBT TAU	81 74	FM	Group	Psy	ES	24	2880	12	12,24,48
Chalder et al., 2021	TDT-CBT TAU	161 163	MUS	Individual		GB	8	480	22	20,32
Edinger et al., 2005	CBT TAU	18 11	FM	Individual	Psy	US	6	165	6	24

Study	Conditions	<i>n</i>	Diagnosis	Setting	Guidance	Country	No. Sessions	Time total ^a	Duration of treatment (weeks)	Follow-ups ^b (weeks)
Escobar et al., 2007	CBT	87	SSI	Individual	Psy	US	10	540	12	24
	TAU	85								
Everitt et al., 2019	CBT ^c	371	IBS	Individual	Psy	GB	6	360	9	12,36
	TAU	187								
Falcão et al., 2008	CBT	30	FM	Group	Psy	BR	10	1800	10	12
	TAU	30								
Fjorback et al., 2013	MBSR	59	BDS	Group	Psych-iatrist	DK	9	1890	8	24,48
	EC	60								
Friedberg et al., 2013	CBT	37	CFS/ME	Individual	Para	US	2	120	14	48
	Att Plac	37								
	TAU	38								
Friedberg et al., 2016	CBT ^c	89	CFS/ME	Individual	Self-Guided	US				36
	TAU	48								
Friesen et al., 2017	CBT	30	FM	Individual	Para	CA	5		8	
	WL	30								
Gaylord et al., 2011	MBSR	36	IBS	Group	Para	US	9	1200	8	12,24,48
	Psy Plac	39								
Ghandi et al., 2018	MBSR	15	IBS	Group	Psy	IR	8	720	8	8
	TAU	19								
Gotaas et al., 2021	CBT	78	CFS/ME	Individual	Psy	NO	17		17	36
	WL	80								

Study	Conditions	<i>n</i>	Diagnosis	Setting	Guidance	Country	No. Sessions	Time total ^a	Duration of treatment (weeks)	Follow-ups ^b (weeks)
Greene & Blanchard, 1994	CT	10	IBS	Individual	Psy	US	100	600	8	
	Att Plac	10								
Haghighayegh et al., 2011	CBT	16	IBS	Group	Psy	IR	8		8	8
	WL	16								
Henrich et al., 2020	MBCT	36	IBS	Group	Psy	GB	6	720	7	6
	WL	31								
Huibers et al., 2004	CBT	76	CFS/ME	Individual	GP	NL	6	180	16	32, 56
	TAU	75								
Hunt et al., 2021	CBT	43	IBS	Individual	Self-Guided	US	10		8	
	WL	48								
Ito & Muto, 2020 ^d	ACT	14	IBS	Mixed	Psy	JP	1	300	8	8
	WL	12								
Jang et al., 2014 ^d	CBT	45	IBS	Group	Mixed	KR	8	640	8	8,16
	Psy Plac	45								
Janse et al., 2018	CBT	160 ^c	CFS/ME	Individual	Psy	NL	7			
	WL	80								
Jensen et al., 2012; Wicksell et al., 2013	ACT	25	FM	Group	Psy	SE	12	1080	12	12
	WL	18								
Karlsson et al., 2015	CBT	24	FM	Group	Psy	SE	20	3600	24	
	WL	24								

Study	Conditions	<i>n</i>	Diagnosis	Setting	Guidance	Country	No. Sessions	Time total ^a	Duration of treatment (weeks)	Follow-ups ^b (weeks)
Kikuchi et al., 2022	CBT TAU	54 60	IBS	Group	Mixed	JP	100	900	10	
Kleinstäuber et al., 2019	CBT + ER CBT	127 128	MUS	Individual	Psy	DE	20	1000	20	24
Knoop et al., 2008	CBT WL	85 86	CFS/ME	Individual	Psy	NL				
Kristjánisdóttir et al., 2013	ACT WL	70 70	CWP	Individual	Self-Guided	NO	1	60	4	20
Lami et al., 2018	CBT ^c TAU	84 42	FM	Group	Psy	ES	9	810	9	12
Ljótsson et al., 2010	CBT + Mindfulness Att Plac	43 43	IBS	Individual	Para	SE	5		10	
Ljótsson et al., 2011	CBT + Mindfulness Att Plac	30 31	IBS	Individual	Para	SE	5		10	
Luciano et al., 2014	ACT WL	51 53	FM	Group	Psy	ES	8	1200	8	16
Martin et al., 2007	CBT TAU	70 70	MUS	Group	Psy	DE	1	240	1	20
McBeth et al., 2012	CBT TAU	112 109	CWP	Individual	Psy	GB	9	337,5	24	12
McCrae et al., 2019	CBT ^c WL	76 37	FM	Individual	Para	US	8	400	8	24
Menga et al., 2014	CBT TAU	28 28	FM	Individual	Self-guided	US	5		6	6

Study	Conditions	<i>n</i>	Diagnosis	Setting	Guidance	Country	No. Sessions	Time total ^a	Duration of treatment (weeks)	Follow-ups ^b (weeks)
Menon et al., 2017	CBT	41	MUS	Mixed	Psychiatrist	IN	1	30	1	
	TAU	35								
Milrad et al., 2019 ^d	CBT	75	CFS/ME	Individual		US	10	600	10	
	Psy Plac	75								
Mohsenabadi et al., 2018	UP	32	IBS	Individual	Psy	IR	12	1440	12	
	TAU	32								
Moreno et al., 2013	CBT ^c	120	SSI	Mixed	Psy	ES	10	900	10	24,48
	TAU	48								
Moss-Morris et al., 2010	CBT	31	IBS	Individual	Psy	NZ	3	180	7,5	12,24
	TAU	33								
Nhu et al., 2024	CBT	17	FM	Individual	Psy	TW	6	720	6	
	TAU	18								
O'Dowd et al., 2006	CBT	52	CFS/ME	Group	Mixed	GB	8	960	16	32
	TAU	51								
O'Dowd et al., 2020	CBT	28	CFS/ME	Individual	GP	GB	4	120	10	14
	TAU	16								
Ong et al., 2023 ^d	PPT	49	FM	Individual	Self-guided	US	5		5	4
	Att Plac	46								
Owusu et al., 2021	CBT	25	IBS	Individual	Self-guided	US	8		12	
	TAU	11								
Parra-Delgado & Latorre-Postigo, 2013	MBCT	15	FM	Group	Psy	ES	8	1200	8	12
	TAU	16								
Payne & Blanchard, 1995	CT	12	IBS	Individual	Psy	US	10	480	8	12
	Psy Plac	10								
Pedersen et al., 2019	ACT	59	BDS	Group	Mixed	DK	9	1695	12	32,56
	EC	60								
Pérez-Aranda et al., 2019	MBSR	75	FM	Group	Psy	ES	8	960	8	40
	TAU	75								

Study	Conditions	<i>n</i>	Diagnosis	Setting	Guidance	Country	No. Sessions	Time total ^a	Duration of treatment (weeks)	Follow-ups ^b (weeks)
Prins et al., 2001	CBT	93	CFS/ME	Individual	Mixed	NL	16	960	32	24
	Psy Plac	90								
	TAU	91								
Rimes & Wingrove, 2013	MBCT	17	CFS/ME	Group	Psy	GB	9	1215	8	8
	WL	19								
Sanders et al., 2007	CBT	17	IBS	Individual	Self-guided	US	5		8	
	WL	11								
Schmidt et al., 2011	MBSR	58	FM	Group	Psy	DE	11	1740	8	8
	WL	59								
	Psy Plac	59								
Schröder et al., 2013	CBT	49	MUS	Group	Psy	DE	8	720	8	
	WL	44								
Sephton et al., 2007; Cash et al., 2015	MBSR	51	FM	Group	Psy	US	9	1650	8	8
	WL	40								
Simister et al., 2018	ACT	33	FM	Individual	Psy	CA	7		8	12
	TAU	34								
Speckens et al., 1995	CBT	39	MUS	Individual	Psy	NL	12	720	24	24
	EC	40								
Thieme et al., 2006	CBT	42	FM	Group	Mixed	DE	15	1800	15	24,48
	Att Plac	40								
Tkachuk et al., 2003	CBT		IBS	Group	Psy	CA	10	900	9	
	Psy Plac									
Vallejo et al., 2015	CBT	20	FM	Group	Psy	ES	10	1200	10	12,24,96
	WL	20								
van Ravesteijn et al., 2013	MBCT	61	MUS	Group	Para	NL	9	1560	8	36
	EC	58								
Vlaeyen et al., 1996	CBT	49	FM	Group	Psy	NL	12	1080	6	
	WL	43								

Study	Conditions	<i>n</i>	Diagnosis	Setting	Guidance	Country	No. Sessions	Time total ^a	Duration of treatment (weeks)	Follow-ups ^b (weeks)
Vollmer & Blanchard, 1998	CBT ^c	22	IBS	Mixed	Psy	US	10	750	10	
White et al., 2011; Sharpe et al., 2015	Att Plac	10								
	CBT	161								
	TAU	160	CFS/ME	Individual	Mixed	GB	15	900	36	28, 96
Wiborg et al., 2015	CBT ^c	136	CFS/ME	Group	Mixed	NL	14	1680	24	
	WL	68								
Williams et al., 2010	CBT	59	FM	Individual	Self-guided	US	13		24	
	TAU	59								
Yang & Jun, 2022 ^d	CBT	30	IBS	Group	Psy	KR	4	360	4	12
	TAU	30								
Zernicke et al., 2013	MBSR	43	IBS	Group	Para	CA	9	900	8	24
	TAU	47								
Zonneveld et al., 2012	CBT	81	USD	Group	Psy	NL	13	1560	13	
	WL	78	(DSM-IV)							

Note. AMBT = acceptance- and mindfulness-based treatments; AU = Australia; Att Plac = attention placebo; BDS = bodily distress syndrome; BR = Brazil; CA = Canada; CBT = cognitive behavioural therapy; CWP = chronic widespread pain; DK = Denmark; EC = enhanced care; ES = Spain; GB = Great Britain; GP = general practitioner; IN = India; IR = Iran; JP = Japan; KR = South Korea; MBCT = mindfulness-based cognitive therapy; MBSR = mindfulness-based stress reduction; Mixed = guidance provided by psychologist and psychiatrist; MUS = medically unexplained symptoms; NL = Netherlands; NO = Norway; NZ = New Zealand; Para = paraprofessional (study nurses, trained students); PPT = positive psychotherapy; Psy = trained clinician (licensed psychotherapist/trained psychologist); Psy Plac = psychological placebo; SE = Sweden; SSI = abridged somatization; TAU = treatment as usual; TW = Taiwan; US = United States of America; UP = unified protocol (Barlow); USD (DSM-IV) = undifferentiated somatoform disorder; WL = wait-list.

^a total time of direct contact in minutes (was not applicable for Friedberg et al., 2016, Friesen et al., 2017, Gotaas et al., 2021, Haghayegh et al., 2011, Hunt et al., 2021, Janse et al., 2018, Knoop et al., 2008, Ljótsson et al., 2010, Ljótsson et al., 2011, Menga et al., 2014, Ong et al., 2023, Owusu et al., 2021, Sanders et al., 2007, Simister et al., 2018, and Williams et al., 2010); ^b after end of treatment (short-term follow-up ≤ 12 weeks, long-term follow-up = 13 to 48 weeks, follow-up longer than 12 months > 48 weeks) ^c two intervention groups were merged for conducting the analyses; ^d Milrad et al., 2015 was specifically focused on couples, Ong et al., 2023 was focused on older adults, Jang et al., 2014, Ito & Muto et al., 2020, and Yang & Jun, 2022 were focused on students, and Huibers et al., 2004 focused on workers.

S2.1 Characteristics of Control Groups

Treatment-as-usual

- **Alda et al., 2011:** TAU offered by GP (pharmacological treatment + doctor visits management) + consultation letter ('Guide for the Treatment of Fibromyalgia in Primary Care')
- **Allen et al., 2006:** Standard medical care + psychiatric consultation intervention
- **Boyce et al., 2003:** Two additional gastroenterologist sessions (15-30 min.) + dietary information booklet + high fiber diet
- **Castel et al., 2012:** Pharmacological treatment
- **Castel et al., 2013:** Pharmacological treatment
- **Chalder et al., 2021:** No treatment
- **Edinger et al., 2005:** Weekly meetings to provide sleep log/actigraphy data and to complete questionnaires + continuing medical care + WL
- **Escobar et al., 2007:** Consultation letter
- **Everitt et al., 2019:** Continuing medical care + consultation letter
- **Falcão et al., 2008:** Routine weekly medical visits
- **Friedberg et al., 2013:** No treatment
- **Friedberg et al., 2016:** No treatment
- **Ghandi et al., 2018:** Pharmacological treatment
- **Huibers et al., 2004:** No treatment
- **Kikuchi et al., 2022:** 30 min. group education + diary + WL
- **Lami et al., 2018:** "Usual medical care" [not elaborated]
- **Martin et al., 2007:** Standard medical care + WL
- **McBeth et al., 2012:** No treatment
- **Menga et al., 2014:** No treatment ("stable pharmacological treatment")
- **Menon et al., 2017:** Brief psychoeducation
- **Mohsenabadi et al., 2018:** No treatment + WL
- **Moreno et al., 2013:** Consultation letter (with Smith's norms)
- **Moss-Morris et al., 2010:** IBS fact sheet
- **Nhu et al., 2024:** No treatment
- **O'Dowd et al., 2006:** No treatment
- **O'Dowd et al., 2020:** Investigation (by GP) for other causes of fatigue (including blood screen), pharmacology + referral to specialist services
- **Owusu et al., 2021:** No treatment
- **Parra-Delgado & Latorre-Postigo, 2013:** Treatment as usual [not elaborated]
- **Pérez-Aranda et al., 2019:** No treatment + WL
- **Prins et al., 2001:** No treatment
- **Simister et al., 2018:** No treatment + WL
- **White et al., 2011:** Information leaflet + education, advice on self-help + pharmacotherapy
- **Williams et al., 2010:** No treatment
- **Yang & Jun, 2022:** No treatment
- **Zernicke et al., 2013:** No treatment + WL

Enhanced care

- **Fjorback et al., 2013:** Two hours specialist medical care and brief CBT for bodily distress syndrome
- **Speckens et al., 1995:** Optimised medical care + basic training in the detection and management of psychiatric disorders (90 min./3 months)
- **Pedersen et al., 2019:** One manualised follow-up consultation with a physician 1–2 weeks after randomisation (1–1½ h): understanding of diagnosis, optimising further treatment, awareness of stress factors, motivation for lifestyle changes + letter to GP
- **van Ravesteijn et al., 2013:** No treatment + WL

Psychological placebo

- **Blanchard et al., 2007:** Educational support group – topics introduced by therapist, emphasizing open sharing of views and experiences among members while refraining from giving direct recommendations or prescribing behavioral changes
- **Gaylord et al., 2011:** Social support group led by social workers to control for expectations and amount of group contact. 8 weekly sessions + one half-day session
- **Jang et al., 2014:** Educational information, nonmedical symptom management in groups led by investigator at pre-treatment and 8 weeks
- **Milrad et al., 2019:** Health Promotion - equal amounts of attention and contact time focused on providing health behavior information without any active treatment being given
- **Payne & Blanchard, 1995:** Symptom monitoring with supportive therapist contact
- **Prins et al., 2001:** Guided support groups led by social workers with emphasis on mutual understanding and recognition by means of exchanging experiences. 11 sessions/ 90 min. over 8 months
- **Schmidt et al., 2011:** Group intervention to control for nonspecific aspects of MBSR with educational discussions
- **Tkachuk et al., 2003:** Symptom monitoring with supportive therapist contact

Attention placebo

- **Blanchard et al., 2007:** Symptom monitoring
- **Friedberg et al., 2013:** Symptom monitoring with emotional support
- **Greene & Blanchard, 1994:** Symptom monitoring
- **Ljótsson et al., 2010:** Online discussion forum
- **Ljótsson et al., 2011:** Online discussion forum
- **Ong et al., 2023:** Daily emotion reporting
- **Thieme et al., 2006:** General discussions among patients
- **Vollmer & Blanchard, 1998:** Symptom monitoring

S2.2 Excluded arms of included studies

For $k = 8$ studies arms were combined for analysis, while for $k = 4$ studies arms were excluded. The combined arms were comparable intervention arms: In [33] the internet-based and the self-management intervention provided comparable content and only differed in terms of psychotherapist contact; in [34] the self-management arms were identical but used different forms of instrumentation; in [35] the combined CBT arms utilized different forms of therapist feedback; in [36] one of the two CBT arms additionally focused on pain management; similarly, in [37] one CBT arm focused on insomnia, the other one on pain; in [38] and [39] the CBT arms were implemented in different settings, i.e., individual and group. In most of the excluded arms, a condensed form of the original program was provided [40, 41]. For [42] the two intervention arms provided similar content, but the modalities (internet-based vs. face-to-face) were not comparable. Therefore, only the face-to-face group CBT arm was included.

S2.3 Outcome measures

Table S2

List of selected outcome measures

Study	Somatic symptom severity	Depression	Anxiety	Perceived Health Status
Alda et al., 2011	VAS (Pain)	HAM-D	HARS	FIQ
Allen et al., 2006	Severity of Somatic Symptoms Scale			SF-36 (Physical functioning subscale)
Blanchard et al., 2007	Physician global ratings BSSS (Frequency subscale)	HADS-D	HADS-A	SF-36 (Physical functioning subscale)
Boyce et al., 2003	NRS			FIQ
Castel et al., 2012	NRS			FIQ
Castel et al., 2013	PHQ-15	PHQ-9	GAD-7	WSAS
Chalder et al., 2021	MPQ			SF-36 (Physical functioning subscale)
Edinger et al., 2005	PHQ-15	HRSD	HAM-A	MOS-10
Escobar et al., 2007	IBS-SSS	HADS-D	HADS-A	WSAS
Everitt et al., 2019	VAS (Pain)	BDI	STAI (State subscale)	FIQ
Falcão et al., 2008				SF-36 (Physical functioning subscale)
Fjorback et al., 2013		SCL-8		SF-36 (Physical functioning subscale)
Friedberg et al., 2013	FSS	BDI	BAI	SF-36 (Physical functioning subscale)
Friedberg et al., 2016		BDI	BAI	SF-36 (Physical functioning subscale)
Friesen et al., 2017	BPI (Symptom severity subscale)	PHQ-9	GAD-7	SF-12
Gaylord et al., 2011	IBS-SS	BSI-18 (Depression subscale)	BSI-18 (Anxiety subscale)	IBS-QoL
Ghandi et al., 2018	IBS-SSS			IBS-QoL-34
Gotaas et al., 2021	CFQ			SF-36 (Physical functioning subscale)
Greene & Blanchard, 1994	Gastrointestinal Symptom Scores	BDI	STAI (State subscale)	

Study	Somatic symptom severity	Depression	Anxiety	Perceived Health Status
Haghighyegh et al., 2011		BDI		IBS-QoL
Henrich et al., 2020	GSRS-IBS	DASS-21 (Depression subscale)	DASS-21 (Anxiety subscale)	IBS-QoL
Huibers et al., 2004	CIS			SF-36 (Physical functioning subscale)
Hunt et al., 2021	GSRS-IBS	DASS-21 (Depression subscale)	DASS-21 (Anxiety subscale)	IBS-QoL
Ito & Muto, 2020	IBSSI (Japanese version)	BDI-II	STAI (State subscale)	IBS-QoL
Jang et al., 2014	BSSS			IBS-QoL
Janse et al., 2018	CIS			SF-36 (Physical functioning subscale)
Jensen et al., 2012; Wicksell et al., 2013	VAS	BDI	STAI (State subscale)	SF-36 (Physical functioning subscale)
Karlsson et al., 2015	MPI-1 (Symptom severity subscale)	MADRS-S		MPI-1 (Interference subscale)
Kikuchi et al., 2022	IBS-SSS	PHQ-9	GAD-7	IBS-QoL
Kleinstäuber et al., 2019	PHQ-15	BDI-II		EQ-5D
Knoop et al., 2008	CIS (Fatigue severity subscale)			SF-36 (Physical functioning subscale)
Kristjánssdóttir et al., 2013	VAS (Pain)			SF-8 (Physical subscale)
Lami et al., 2018	VAS (of MPQ-SF)	SCL-90-R (Depression subscale)	SCL-90-R (Anxiety subscale)	FIQ
Ljótsson et al., 2010	GSRS-IBS	MADRS-S		IBS-QoL
Ljótsson et al., 2011	GSRS-IBS			IBS-QoL
Luciano et al., 2014	VAS (Pain)	HADS-D	HADS-A	FIQ
Martin et al., 2007	BSI-6	BDI		
McBeth et al., 2012				SF-36 (Physical component scale)
McCrae et al., 2019	MPQ	BDI-II	STAI-Y1	PDI
Menga et al., 2014				FIQ
Menon et al., 2017	PHQ-15	PHQ-9	GAD-7	
Milrad et al., 2019	FSI	CES-D		
Mohsenabadi et al., 2018	GSRS-IBS	DASS-42 (Depression subscale)	DASS-42 (Anxiety subscale)	
Moreno et al., 2013	SOMS	HRSD	HAM-A	

Study	Somatic symptom severity	Depression	Anxiety	Perceived Health Status
Moss-Morris et al., 2010	IBS-SSS	HADS-D	HADS-A	
Nhu et al., 2024	BPI severity	BDI-II	BAI	FIQ-R
O'Dowd et al., 2006		HADS-D	HADS-A	SF-36 (Physical functioning subscale)
O'Dowd et al., 2020	CFQ	HADS-D	HADS-A	SF-36 (Physical functioning subscale)
Ong et al., 2023	PROMIS-SI			PROMIS-PF
Owusu et al., 2021	IBS-SSS	PHQ-9	GAD-7	
Parra-Delgado & Latorre-Postigo, 2013	VAS (Combined subscales)	BDI		FIQ
Payne & Blanchard, 1995		BDI	STAI (State subscale)	
Pedersen et al., 2019	BDS	SCL-92 (Depression Score)	SCL-92 (Anxiety Score)	SF-36 (Physical functioning subscale)
Pérez-Aranda et al., 2019	FSDC	HADS-D	HADS-A	FIQ-R
Prins et al., 2001	CIS			SIP
Rimes & Wingrove, 2013	CFQ	HADS-D	HADS-A	PF-10
Sanders et al., 2007	Gastrointestinal Symptom Diary			IBS-QoL
Schmidt et al., 2011	GCQ	CES-D	STAI (Trait subscale)	PLC
Schröder et al., 2013	SOMS-7	HADS-D	HADS-A	SF-12
Sephton et al., 2007; Cash et al., 2015	VAS (Pain)	BDI		FIQ
Simister et al., 2018	SF-MPQ	CES-D		FIQ-R
Speckens et al., 1995	NRS (Intensity)	HADS-D	HADS-A	VAS (Functional impairment)
Thieme et al., 2006	MPI (Pain intensity)			FIQ
Tkachuk et al., 2003	GI-Scale (Pain)	BDI-II	STAI (Trait subscale)	SF-36 (Physical component scale)
Vallejo et al., 2015		BDI		FIQ
van Ravesteijn et al., 2013	PHQ-15	PHQ-9		SF-36 (Physical functioning subscale)
Vlaeyen et al., 1996		BDI-II		
Vollmer & Blanchard, 1998	Gastrointestinal Symptom Diary			

Study	Somatic symptom severity	Depression	Anxiety	Perceived Health Status
White et al., 2011; Sharpe et al., 2015	CFQ	HADS-D	HADS-A	SF-36 (Physical functioning subscale)
Wiborg et al., 2015	CIS (Fatigue severity)			SF-36 (Physical functioning subscale)
Williams et al., 2010	BPI (Pain severity)	CES-D	STPI (State subscale)	SF-36 (Physical functioning subscale)
Yang & Jun, 2022	IBS-SSS			IBS-QoL
Zernicke et al., 2013	IBS-SSS			IBS-QoL
Zonneveld et al., 2012	SCL-90 (Somatization subscale)	SOM-90-R (Depression subscale)	SCL-90-R (Anxiety subscale)	SF-36 (Physical component scale)

Note. BAI = Beck Anxiety Scale; BDI = Beck Depression Scale; BPI = Brief Pain Inventory; BSI-18 = Brief Symptom Inventory-18; BSSS = ; CES-D = Center for Epidemiological Studies Depression Inventory; CFQ = Chalder Fatigue Questionnaire; CIS = Checklist Individual Strength; DASS = Depression Anxiety Stress Scales; FIQ(-R) = Fibromyalgia Impact Questionnaire (Revised); FSDC = Fibromyalgia Survey Diagnostic Criteria; FSS = Fatigue Severity Scale; GAD-7 = Generalized Anxiety Disorder 7; GCQ = Giessen Complaint Questionnaire; GI-Scale = Gastrointestinal Symptom Rating Scale; GSRS-IBS = Gastrointestinal Symptom Rating Scale for Irritable Bowel Syndrome; HADS-A = Hospital Anxiety and Depression Scale-Anxiety; HADS-D = Hospital Anxiety and Depression Scale- Depression; HAM-D = Hamilton Depression Rating Scale; HARS = Hamilton Anxiety Rating Scale; IBS-QoL = Irritable Bowel Syndrome Quality of Life; IBS-SSS = Irritable Bowel Syndrome Symptom Severity Scale; MADRS-S = Montgomery-Åsberg Depression Rating Scale-Self-report; MOS-10 = Medical Outcomes Study 10-Item Scale; MPQ = McGill Pain Questionnaire; NRS = Numeric Rating Scale; PF-10 = Physical Functioning Scale-10; PHQ-15 = Patient Health Questionnaire-15; PHQ-9 = Patient Health Questionnaire-9; PLC = Quality of Life Profile for the Chronically Ill; PROMIS-PF = Patient Reported Outcomes Measurement Information System- Physical Function; PROMIS-SI = Patient Reported Outcomes Measurement Information System – Pain intensity; SCL-8 = Symptom Checklist-8; SCL-90 = Symptom Checklist-90; SF-36 = Short Form Health Survey-36; SIP = Sickness Impact Profile; SOM-90-R = Somatization Inventory-90-Revised; SOMS = Screening for Somatoform Symptoms; STAI = State-Trait Anxiety Inventory; STPI = State-Trait Personality Inventory; VAS = Visual Analog Scale; WSAS = Work and Social Adjustment Scale.

S2.4 Selection of Measurement Instruments for Outcomes (first choice versus alternative measures)

Somatic symptom severity:

- Edinger et al.: MPQ vs. BPI
- Gaylord et al.: IBS-SS vs. BSI-18
- Nhu et al.: BPI severity vs NRS
- Pedersen et al.: BDS vs. SCL-92 (somatic symptom score)

Anxiety:

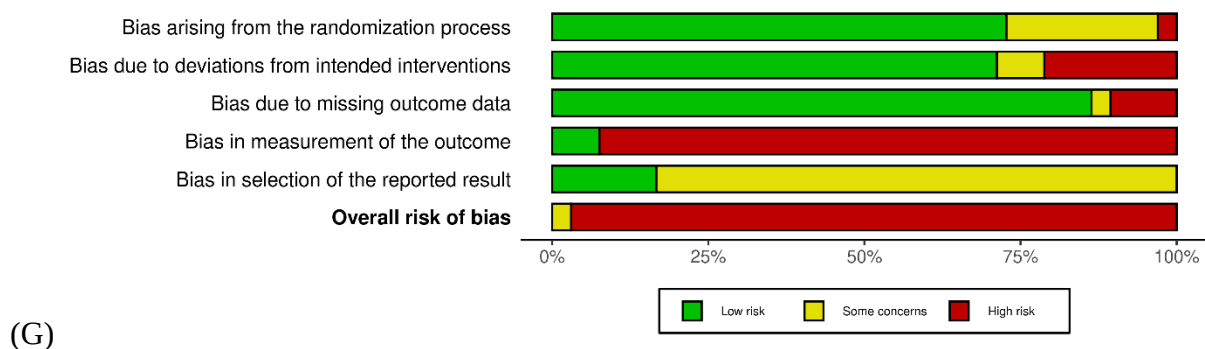
- Friesen et al.: GAD-7 vs. HADS-A

Depression:

- Friesen et al.: PHQ-9 vs. HADS-D

Perceived Health Status:

- Alda et al.: FIQ vs. VAS (EQ-5D)
- Friesen et al.: SF-12 vs. FIQ
- Ito & Muto: IBS-QoL vs. SF-36 PCS
- Jang et al.: IBS-QoL vs. BSSS-Disability
- Jensen et al.: SF-36 vs. FIQ
- Luciano et al.: FIQ vs. VAS (EQ-5D)
- O'Dowd et al., 2020: SF-36 vs. EQ-5D-5L
- Ong et al.: PROMIS-PF vs. PI
- Nhu et al.: FIQ-R vs. BPI interference
- Pedersen et al.: SF-36 vs. WHO-DAS II
- Schmidt et al.: PLC vs. FIQ

S3 Risk of bias**Figure S1***Risk of bias ratings for somatic symptom severity at post-treatment*

Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Aida et al., 2011	●	●	●	●	●	●
Allen et al., 2005	●	●	●	●	●	●
Blanchard et al., 2007	●	●	●	●	●	●
Boyce et al., 2003	●	●	●	●	●	●
Caskei et al., 2012	●	●	●	●	●	●
Caskei et al., 2013	●	●	●	●	●	●
Chalder et al., 2021	●	●	●	●	●	●
Edinger et al., 2005	●	●	●	●	●	●
Elcosh et al., 2007	●	●	●	●	●	●
Eventt et al., 2019	●	●	●	●	●	●
Falcão et al., 2008	●	●	●	●	●	●
Friedberg et al., 2013	●	●	●	●	●	●
Flassen et al., 2017	●	●	●	●	●	●
Gayford et al., 2011	●	●	●	●	●	●
Ghazali et al., 2018	●	●	●	●	●	●
Gutao et al., 2021	●	●	●	●	●	●
Greene & Blanchard, 1994	●	●	●	●	●	●
Henrich et al., 2020	●	●	●	●	●	●
Hubers et al., 2004	●	●	●	●	●	●
Hunt et al., 2021	●	●	●	●	●	●
Ito & Muto, 2020	●	●	●	●	●	●
Jang et al., 2014	●	●	●	●	●	●
Jansz et al., 2018	●	●	●	●	●	●
Jensen et al., 2012	●	●	●	●	●	●
Karlsson et al., 2015	●	●	●	●	●	●
Kiluchi et al., 2022	●	●	●	●	●	●
Kirchsteuber et al., 2019	●	●	●	●	●	●
Knoop et al., 2008	●	●	●	●	●	●
Krijgsdijk et al., 2013	●	●	●	●	●	●
Lami et al., 2018	●	●	●	●	●	●
Ljótsson et al., 2010	●	●	●	●	●	●
Ljótsson, Andersson et al., 2010	●	●	●	●	●	●
Luciano et al., 2014	●	●	●	●	●	●
Martin et al., 2007	●	●	●	●	●	●
McCrae et al., 2019	●	●	●	●	●	●
Ménon et al., 2017	●	●	●	●	●	●
Mirad et al., 2019	●	●	●	●	●	●
Mohsenabadi et al., 2018	●	●	●	●	●	●
Moreno et al., 2013	●	●	●	●	●	●
Moss-Morris et al., 2010	●	●	●	●	●	●
Nhu et al., 2024	●	●	●	●	●	●
Niher et al., 2011	●	●	●	●	●	●
O'Dward et al., 2020	●	●	●	●	●	●
Org et al., 2023	●	●	●	●	●	●
Owusu et al., 2021	●	●	●	●	●	●
Parrs-Dalgado & Labore-Pesigo, 2013	●	●	●	●	●	●
Pedersen et al., 2019	●	●	●	●	●	●
Perez-Artanda et al., 2019	●	●	●	●	●	●
Prins et al., 2001	●	●	●	●	●	●
Primes & Wingrove, 2013	●	●	●	●	●	●
Sanders et al., 2007	●	●	●	●	●	●
Schmidt et al., 2011	●	●	●	●	●	●
Schöder et al., 2013	●	●	●	●	●	●
Segnion et al., 2007	●	●	●	●	●	●
Simister et al., 2018	●	●	●	●	●	●
Speckers et al., 1995	●	●	●	●	●	●
Thieme et al., 2006	●	●	●	●	●	●
Thachuk et al., 2003	●	●	●	●	●	●
van Rensdijn et al., 2013	●	●	●	●	●	●
Vlaayen et al., 1996	●	●	●	●	●	●
Volmer & Blanchard, 1998	●	●	●	●	●	●
White et al., 2011	●	●	●	●	●	●
Wilberg et al., 2015	●	●	●	●	●	●
Williams et al., 2010	●	●	●	●	●	●
Yang & Yun, 2022	●	●	●	●	●	●
Zernicke et al., 2013	●	●	●	●	●	●

D1: Bias arising from the randomization process.
 D2: Bias due to deviations from intended intervention.
 D3: Bias due to missing outcome data.
 D4: Bias in measurement of the outcome.
 D5: Bias in selection of the reported result.

Judgment
 ● High
 ● Some concerns
 ● Low

(H)

Note. A: summary plot; B: traffic light plot.

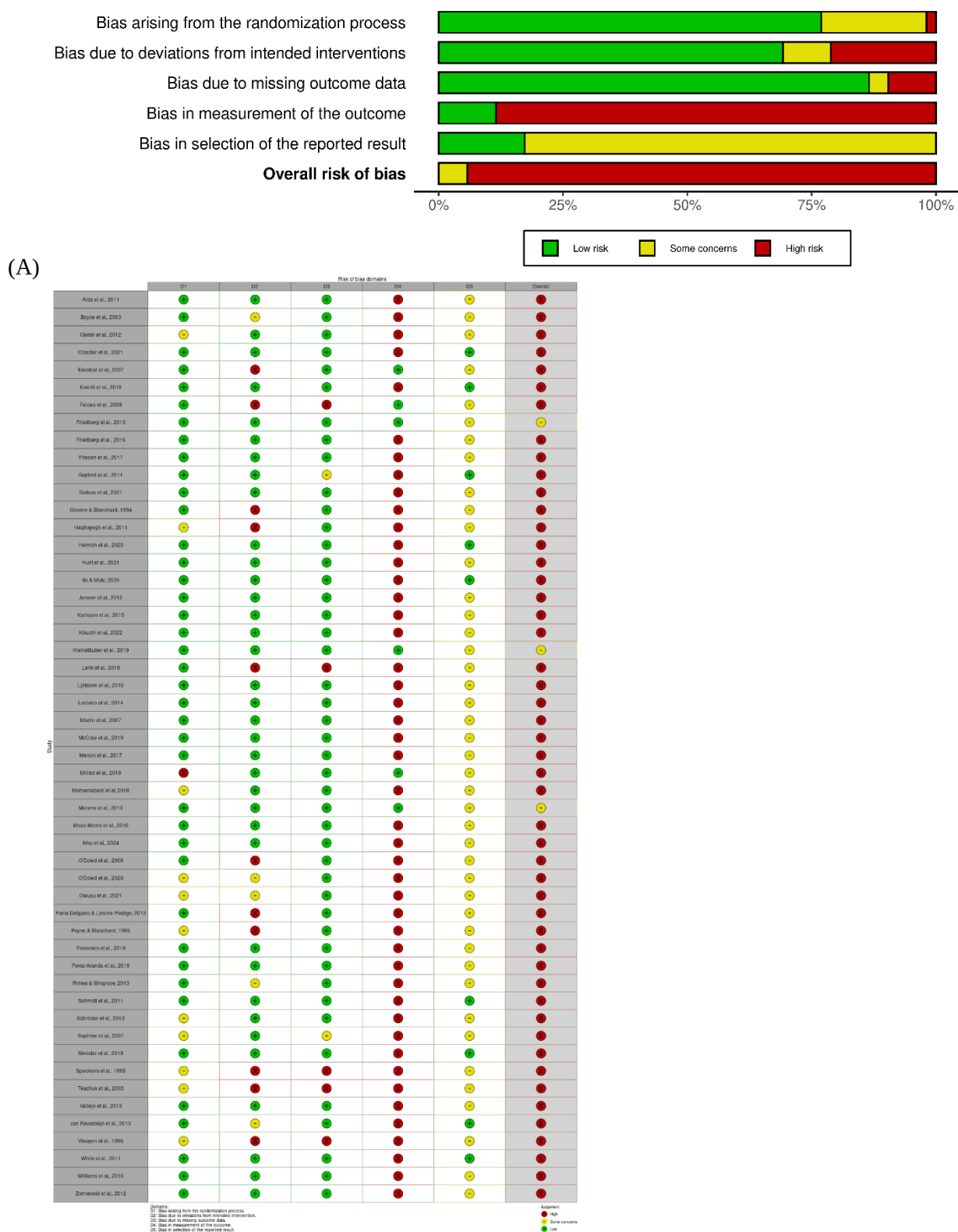
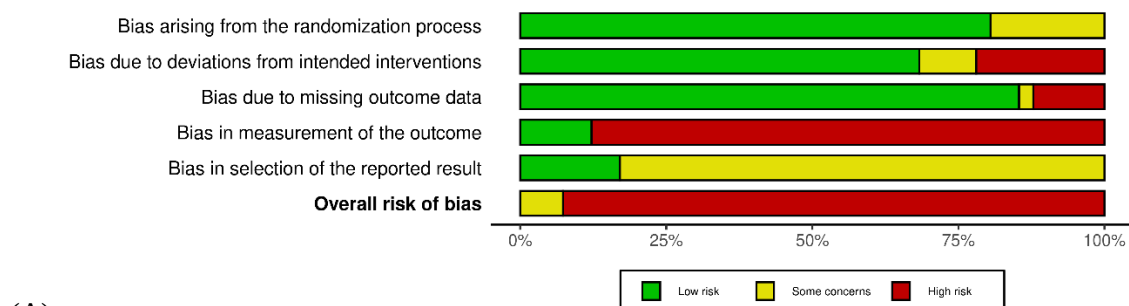
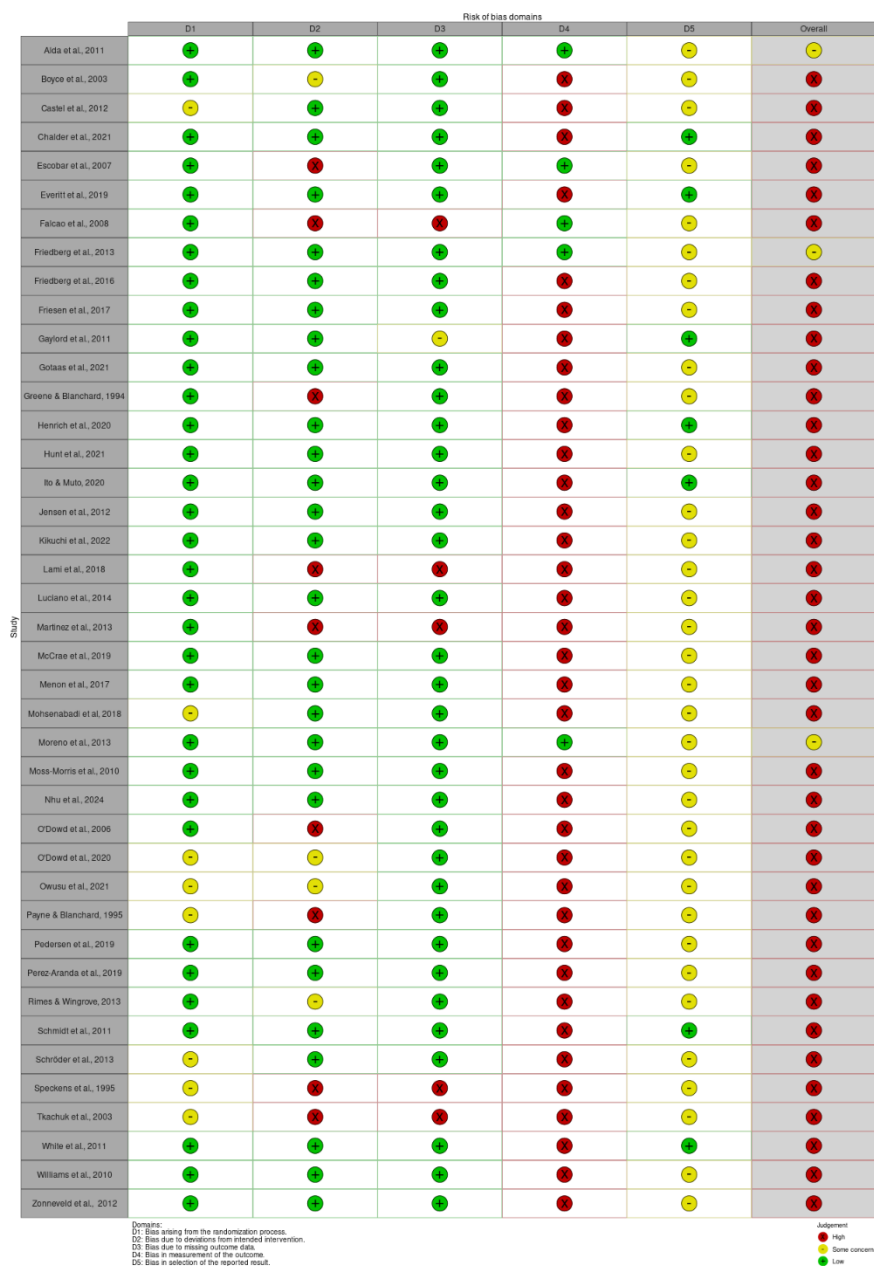
Figure S2*Risk of bias ratings for depression at post-treatment*

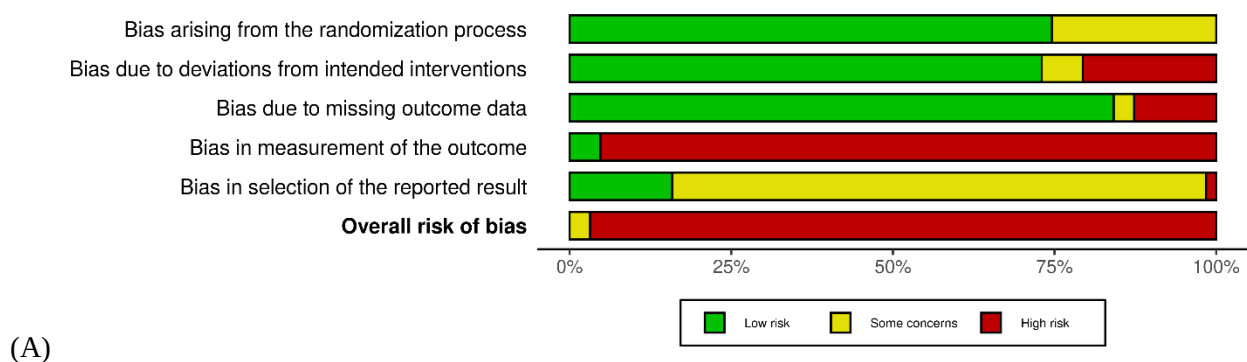
Figure S3*Risk of bias ratings for anxiety at post-treatment*

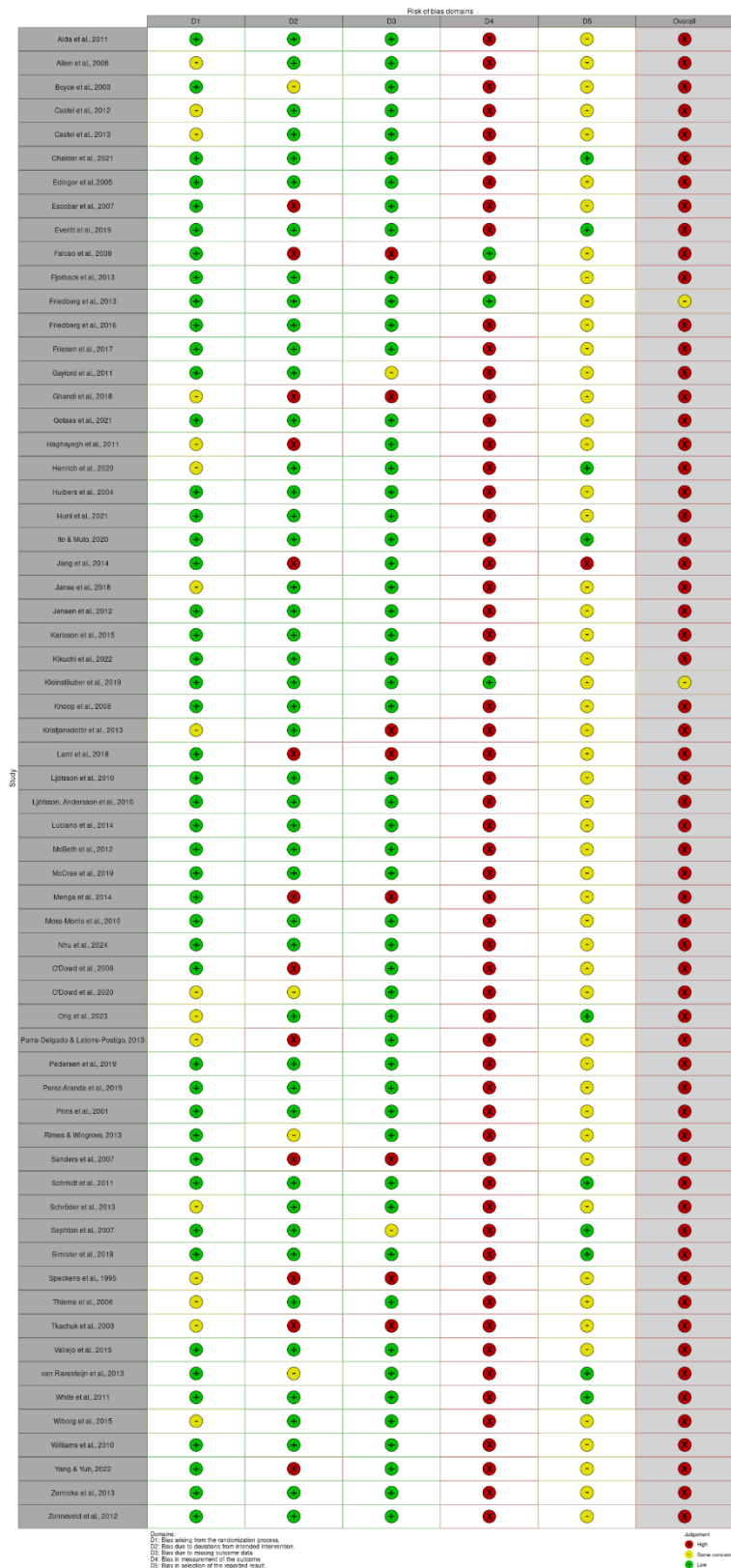
(A)



(B)

Note. A: summary plot; B: traffic light plot.

Figure S4*Risk of bias ratings for perceived health status at post-treatment*



(B)

Note. A: summary plot; B: traffic light plot.

S4 Deviations from the protocol

Several outcomes were not examined due to too little data being provided in the primary studies: *b*-criterion (DSM-5), health anxiety, health care use, consumer satisfaction, and negative effects due to the interventions. Moreover, Hedges's *g* was the preregistered effect size. However, due to possible inconsistencies in Hedges' *g* in multi-armed studies [43], Cohen's *d* was deemed preferable. For the long-term follow-up, an additional follow-up interval (> 12 months) was defined. Furthermore, the longest-available follow-up interval was examined as an exploratory sensitivity analysis.

Although planned as subgroup analyses, all moderator analyses were changed to sensitivity analyses as the networks in the respective subgroups were not comparable. The sensitivity analysis implementing the treatments being analyzed split into more detailed nodes was planned as *ACT vs MBCT vs MBSR vs CT vs CBT vs EC vs TAU vs psy plac vs att plac vs WL*. However, too little studies were found for the individual nodes, therefore cognitive therapy (CT) was included in the CBT-node, ACT was considered the sole acceptance-based therapy, while MBCT and MBSR were combined to mindfulness-based treatments (MBSR/MBCT). Similarly, the subgroup analyses for individual diagnoses (e.g., a separate network analysis only for studies focusing on IBS) as well as *guided vs self-guided* and for *computer vs web vs app-based* could not be computed due to a lack of data for the individual nodes in the respective networks. However, we computed a sensitivity analysis including all studies on somatic symptom and related disorders (bodily distress syndrome; medically unexplained symptoms; somatization disorder; abridged somatization; undifferentiated somatoform disorder) and a separate analysis for studies on functional somatic syndromes (irritable bowel syndrome; fibromyalgia, including chronic widespread pain; chronic fatigue syndrome). For the analyses on therapies implemented in individual and group setting, a different obstacle became apparent: Most AMBT were provided in a group setting; the only ones that were not were either internet-based or a single trial of a slightly different therapy program (Unified Protocol); the latter is nonetheless widely considered an AMBT. As the setting was therefore not independent from the form of treatment, the results on the according sensitivity analysis could not be properly interpreted. Nonetheless, we excluded one study [44] as the setting could not be determined. Additionally, we calculated a sensitivity analysis excluding the studies that based their inclusion diagnoses on a cut-off score on a symptom scale. Furthermore, we excluded multi-component treatments in order to capture the “pure” effect of psychological treatments.

Furthermore, we did not systematically contact other authors in the field about relevant studies additionally to our strategic literature search; however, Web of Science was additionally searched as a result from the peer-review process. The protocol initially stated that the interrater reliability would be calculated for study selection and data extraction. However, during this meta-analysis, we relied on consensus within the author group and therefore revised some decisions after collective discussion. As such, a traditional interrater reliability analysis may not reliably reflect this approach. Lastly, we limited inclusion to only English reports; this did not influence inclusion.

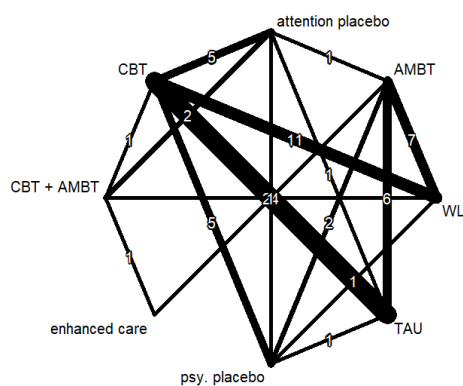
S5 R packages

In R version 4.3.4 [45] the packages `{netmeta}` [43], `{meta}` [46], `{metafor}` [47], and `{dmetar}` [48] provided functions to perform the effect size aggregation and associated analyses. The packages `{ggplot2}` [49] and `{tidyr}` [50] were used for visualization, while the package `{pcnetmeta}` [51] was used for the network plots in the overall-networks. Furthermore, to import the data sheets, we used the packages `{openxlsx}` [52]. Lastly, we used the package `{robvis}` [53] as well as the corresponding web application (<https://mcguinlu.shinyapps.io/robvis/>) to visualize the risk of bias assessment.

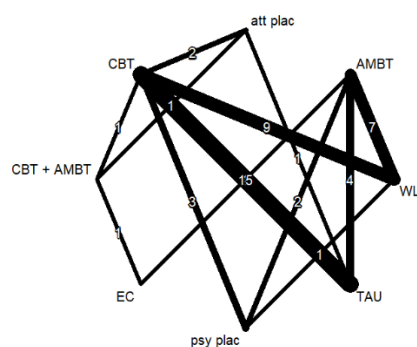
S6 Network plots

Figure S5

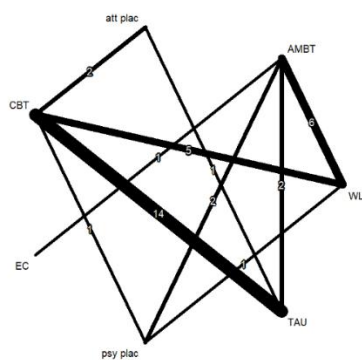
Network plots for each outcome at post-treatment



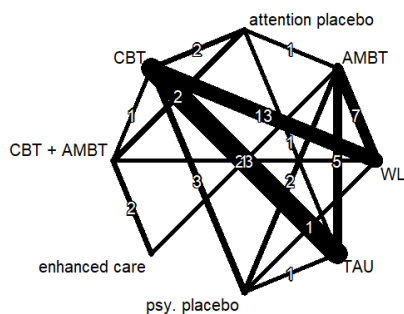
(A)



(B)



(C)



(D)

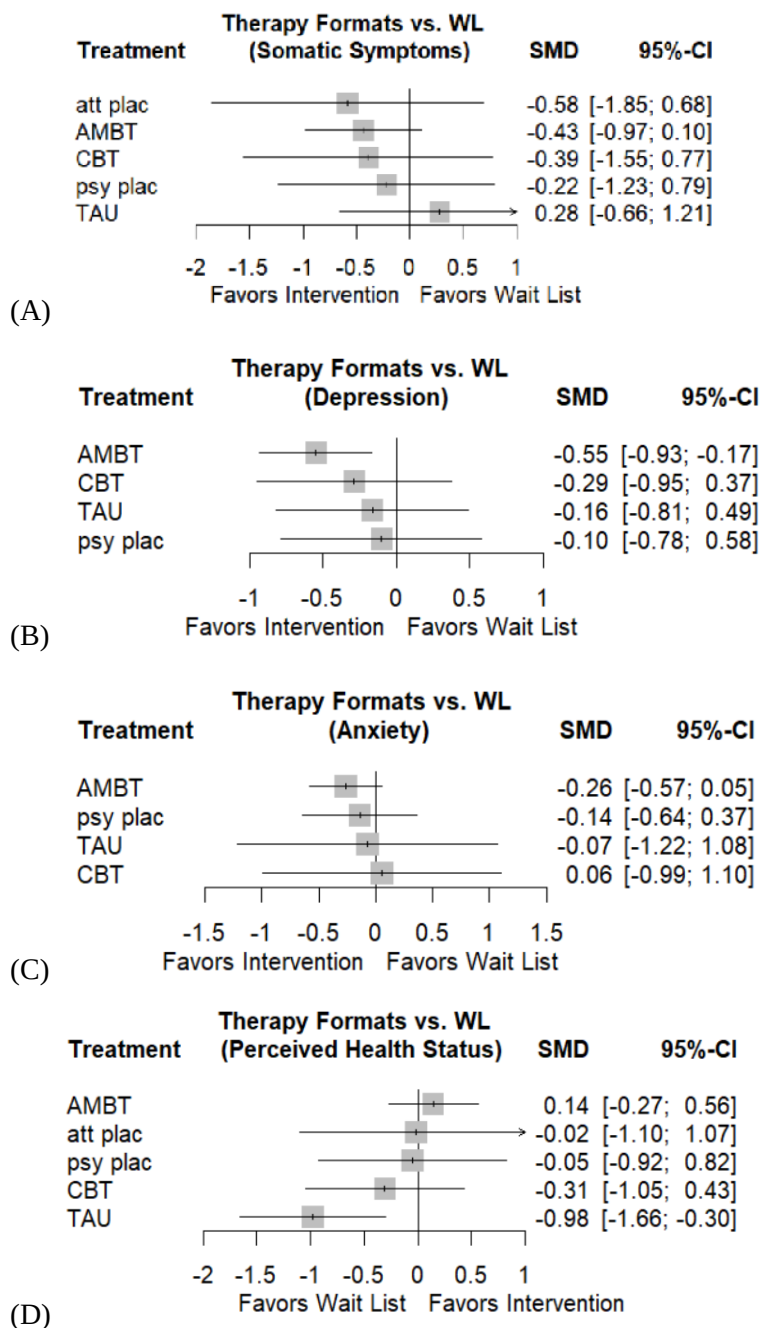
Note. A: Network plot for somatic symptom severity at post-treatment ($k = 63$, $m = 71$, $n = 6,658$); B: network plot for depression at post-treatment ($k = 44$, $m = 48$, $n = 3,893$); C: network plot for anxiety at post-treatment ($k = 31$, $m = 35$, $n = 2,795$); D: network plot for perceived health status at post-treatment ($k = 60$, $m = 66$, $n = 6,366$).

k = number of studies, m = number of pairwise comparisons, n = Number of observations.

S7 Forest plots for short-term follow-up

Figure S6

Forest plots – short-term follow-up (≤ 3 months after end of treatment)



Note. A: forest plot for somatic symptom severity; B: forest plot for depression; C: forest plot for anxiety; D: forest plot for perceived health status. Note: For perceived health status positive effects indicate efficacy of the treatments, for all other outcomes negative effects indicate efficacy of the treatments

S8 Effect size tables for long-term follow-up

Table S3

Treatment comparison estimates for somatic symptom severity at long-term follow-up (between-group effects 3-12 months after end of treatment)

AMBT	-	-	-	-0.47 (-1.11; 0.17)	-	-1.10 (-2.03; -0.18)
-0.19 (-0.79; 0.41)	CBT	-0.13 (-1.01; 0.75)	-0.43 (-1.38; 0.51)	-0.57 (-0.86; -0.29)	-0.88 (-1.53; -0.23)	0.18 (-0.74; 1.10)
-0.34 (-1.14; 0.46)	-0.15 (-0.77; 0.47)	CBT + AMBT	-0.15 (-1.06; 0.76)	-	-	-0.28 (-1.22; 0.66)
-0.55 (-1.47; 0.37)	-0.36 (-1.09; 0.37)	-0.21 (-0.93; 0.51)	EC	-	-	-
-0.73 (-1.29; -0.16)	-0.54 (-0.82; -0.26)	-0.39 (-1.06; 0.28)	-0.17 (-0.95; 0.60)	TAU	-0.05 (-0.93; 0.83)	-
-1.01 (-1.84; -0.18)	-0.82 (-1.42; -0.22)	-0.67 (-1.53; 0.19)	-0.46 (-1.40; 0.49)	-0.28 (-0.91; 0.34)	Psychological placebo	-
-0.57 (-1.26; 0.11)	-0.38 (-1.00; 0.23)	-0.23 (-0.93; 0.46)	-0.02 (-0.90; 0.85)	0.15 (-0.49; 0.79)	0.44 (-0.42; 1.29)	WL

Note. $k = 20$, $m = 22$, $n = 2627$; effect size: Cohen's d ; diagonal gives the treatments that were examined; upper triangle displays the pooled effect sizes of the direct comparisons available with 95%CIs; lower triangle contains the network meta-analysis effect sizes for each comparison with 95%Cis

Table S4

Treatment comparison estimates for depression at long-term follow-up (between-group effects 3-12 months after end of treatment)

AMBT	-	-	-	-0.31 (-0.96; 0.34)	-1.42 (-2.13; -0.72)
-0.50 (-1.07; 0.06)	CBT	-0.03 (-0.67; 0.61)	-0.18 (-0.90; 0.54)	-0.10 (-0.33; 0.13)	-0.32 (-1.01; 0.37)
-0.55 (-1.33; 0.23)	-0.05 (-0.59; 0.48)	CBT + AMBT	-0.07 (-0.75; 0.61)	-	-
-0.65 (-1.45; 0.15)	-0.15 (-0.72; 0.42)	-0.10 (-0.65; 0.46)	EC	-	-
-0.57 (-1.11; -0.02)	-0.07 (-0.30; 0.16)	-0.02 (-0.60; 0.57)	0.08 (-0.53; 0.70)	TAU	-
-1.11 (-1.69; -0.54)	-0.61 (-1.18; -0.05)	-0.56 (-1.34; 0.22)	-0.46 (-1.27; 0.34)	-0.55 (-1.13; 0.03)	WL

Note. $k = 15$, $m = 15$, $o = 1695$; effect size: Cohen's d ; diagonal gives the treatments that were examined; upper triangle displays the pooled effect sizes of the direct comparisons available with 95% CIs; lower triangle contains the network meta-analysis effect sizes for each comparison with 95% CIs

Table S5

Treatment comparison estimates for anxiety at long-term follow-up (between-group effects 3-12 months after end of treatment)

AMBT	-	-	-0.71 (-1.23; -0.18)	-1.03 (-1.61; -0.45)
-0.68 (-1.14; -0.21)	CBT	-0.10 (-0.70; 0.51)	-0.09 (-0.29; 0.11)	-0.22 (-0.79; 0.35)
-0.77 (-1.54; -0.01)	-0.10 (-0.70; 0.51)	EC	-	-
-0.76 (-1.21; -0.31)	-0.08 (-0.28; 0.11)	0.01 (-0.62; 0.65)	TAU	-
-0.96 (-1.43; -0.49)	-0.28 (-0.75; 0.18)	-0.19 (-0.95; 0.58)	-0.20 (-0.68; 0.28)	WL

Note. $k = 12$, $m = 12$, $o = 1528$; effect size: Cohen's d ; diagonal gives the treatments that were examined; upper triangle displays the pooled effect sizes of the direct comparisons available with 95%CIs; lower triangle contains the network meta-analysis effect sizes for each comparison with 95%CIs

Table S6

Treatment comparison estimates for perceived health status at long-term follow-up (between-group effects 3-12 months after end of treatment)

AMBT	-	-	-	0.39 (-0.41; 1.20)	-	2.00 (0.83; 3.18)
0.35 (-0.41; 1.10)	CBT	-0.06 (-1.18; 1.05)	0.19 (-0.97; 1.36)	0.52 (0.16; 0.88)	0.87 (0.06; 1.68)	0.16 (-0.98; 1.31)
0.58 (-0.43; 1.59)	0.23 (-0.55; 1.01)	CBT + AMBT	-0.28 (-1.42; 0.86)	-	-	0.35 (-0.81; 1.52)
0.42 (-0.72; 1.57)	0.07 (-0.83; 0.98)	-0.16 (-1.06; 0.74)	EC	-	-	-
0.80 (0.09; 1.51)	0.45 (0.10; 0.80)	0.22 (-0.62; 1.06)	0.38 (-0.58; 1.34)	TAU	0.14 (-0.98; 1.25)	-
1.17 (0.13; 2.21)	0.82 (0.07; 1.57)	0.59 (-0.49; 1.67)	0.75 (-0.43; 1.92)	0.37 (-0.42; 1.15)	Psychological placebo	-
1.14 (0.28; 2.00)	0.79 (0.02; 1.56)	0.56 (-0.31; 1.42)	0.72 (-0.37; 1.80)	0.34 (-0.47; 1.14)	-0.03 (-1.10; 1.04)	WL

Note. $k = 20$, $m = 22$, $o = 2646$; effect size: Cohen's d ; diagonal gives the treatments that were examined; upper triangle displays the pooled effect sizes of the direct comparisons available with 95% CIs; lower triangle contains the network meta-analysis effect sizes for each comparison with 95% CIs

S9 Treatment rankings

Table S7

Treatment rankings at post-treatment

Outcome	AMBT	CBT	CBT + AMBT	EC	TAU	Psy plac	Att plac	WL
Somatic symptom severity	0.80	0.72	0.87	0.71	0.15	0.32	0.23	0.20
Depression	0.94	0.63	0.64	0.71	0.29	0.54	0.13	0.13
Anxiety	0.87	0.49	n/a	0.88	0.15	0.63	0.21	0.26
Perceived Health Status	0.85	0.60	0.78	0.75	0.10	0.27	0.21	0.44

Note. The ranking of interventions, based on their corresponding P-values. Higher values indicate best fit. AMBT = acceptance- and mindfulness-based treatments; att plac = attention placebo; CBT = cognitive behavioral therapy; CBT + AMBT = combination of cognitive behavioral therapy and acceptance- and mindfulness-based treatments; EC = enhances care; psy play = psychological placebo; TAU = treatment as usual; WL = wait-list.

Table S8

Treatment rankings at long-term follow-up

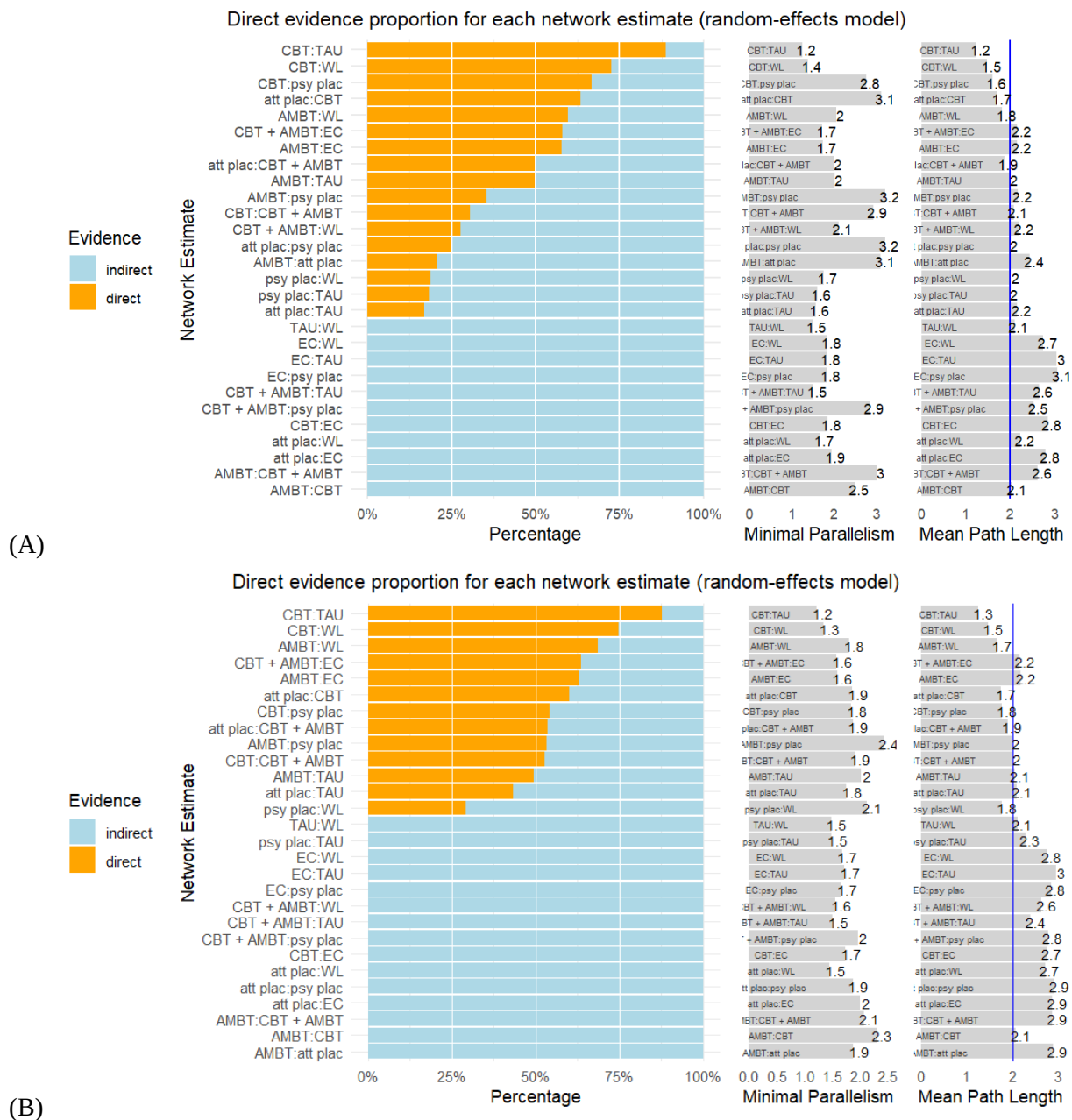
Outcome	AMBT	CBT	CBT + AMBT	EC	TAU	Psy plac	Att plac	WL
Somatic symptom severity	0.89	0.78	0.63	0.43	0.27	0.10	-	0.40
Depression	0.96	0.60	0.52	0.40	0.47	-	-	0.05
Anxiety	0.99	0.58	-	0.39	0.38	-	-	0.16
Perceived Health Status	0.91	0.73	0.53	0.63	0.37	0.15	-	0.16

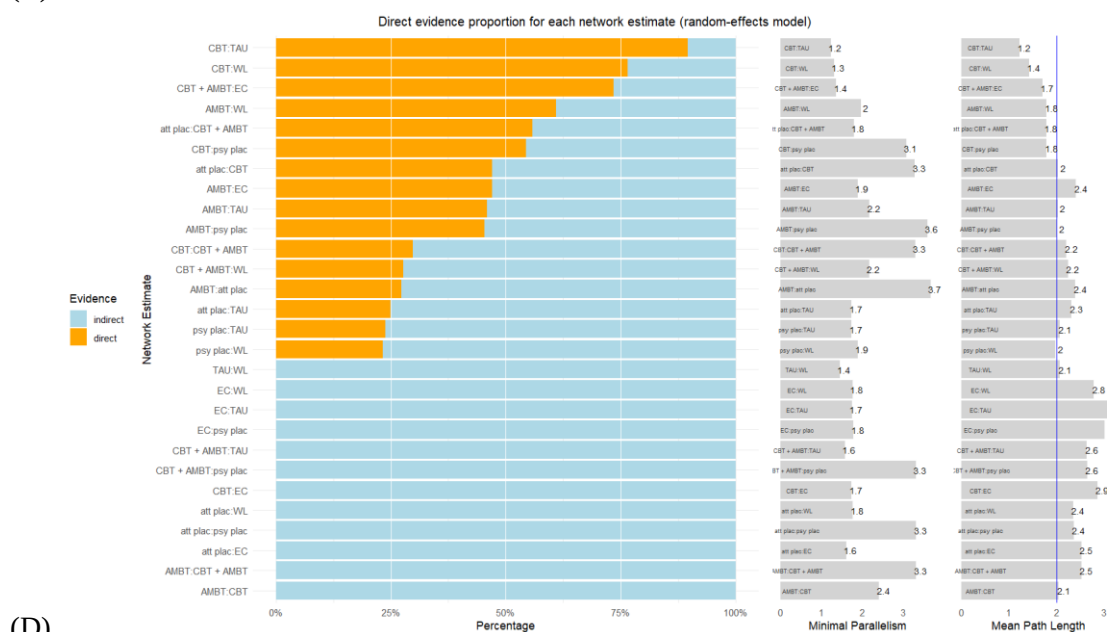
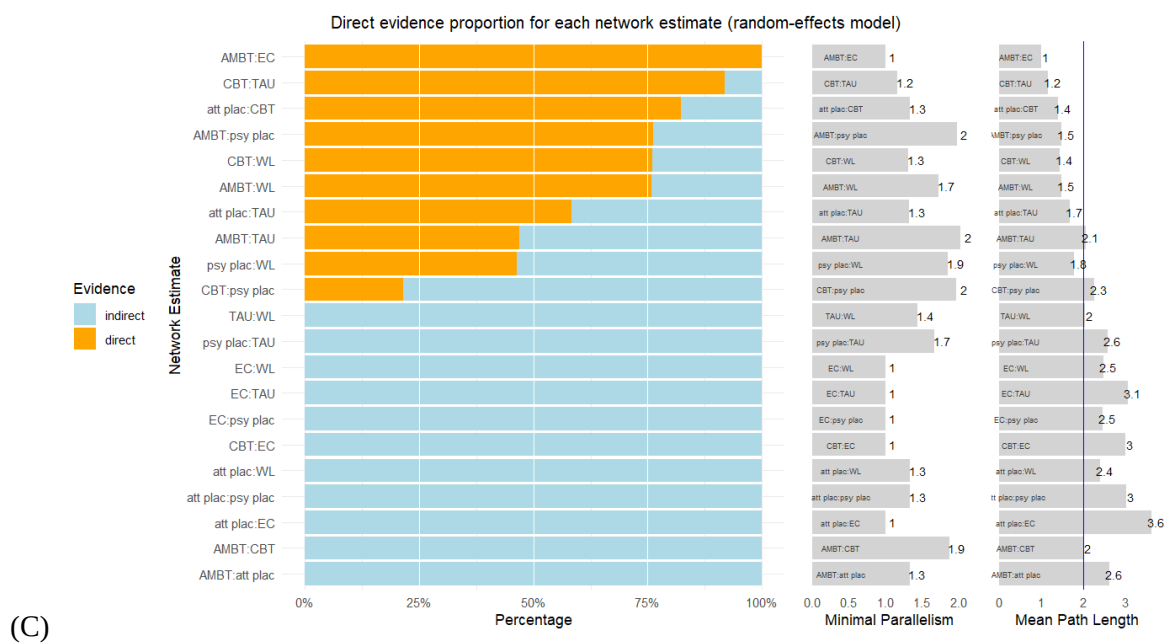
Note. The ranking of interventions, based on their corresponding P-values. Higher values indicate best fit. AMBT = acceptance- and mindfulness-based treatments; att plac = attention placebo; CBT = cognitive behavioral therapy; CBT + AMBT = combination of cognitive behavioral therapy and acceptance- and mindfulness-based treatments; EC = enhances care; psy play = psychological placebo; TAU = treatment as usual; WL = wait-list.

S10 Direct-evidence plots

Figure S7

Direct-evidence plots at post-treatment





Note. A: Direct-evidence plot for somatic symptom severity at post-treatment; B: direct-evidence plot for depression at post-treatment; C: direct-evidence plot for anxiety at post-treatment; D: direct-evidence plot for perceived health status at post-treatment.

S11 Netsplit forest plots

Figure S8

Netsplit forest plot for somatic symptom severity at post-treatment

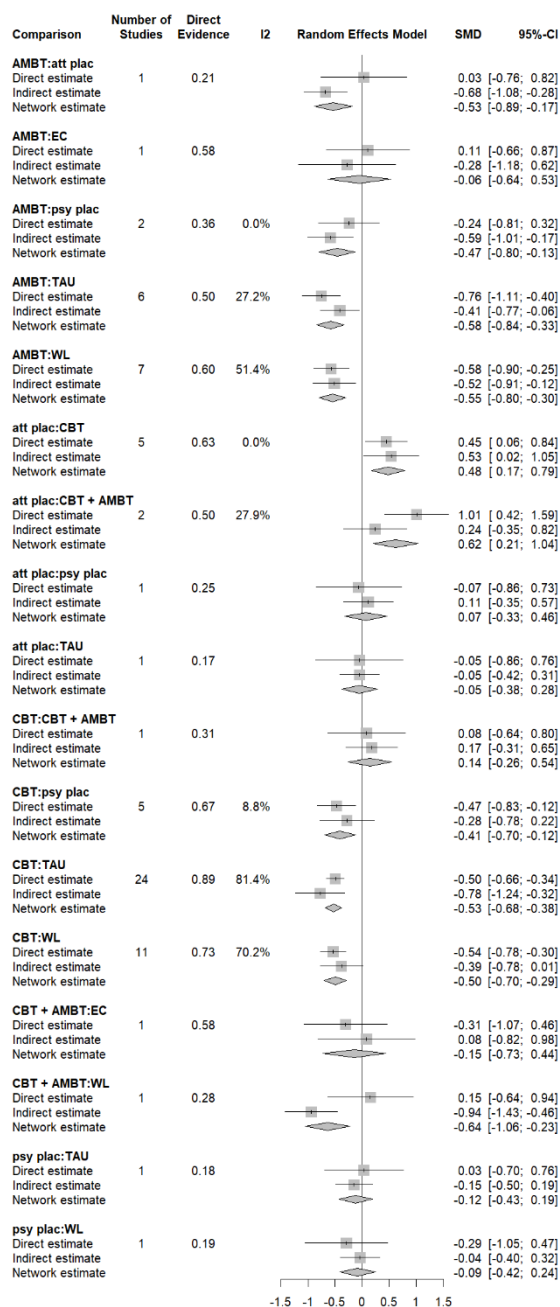


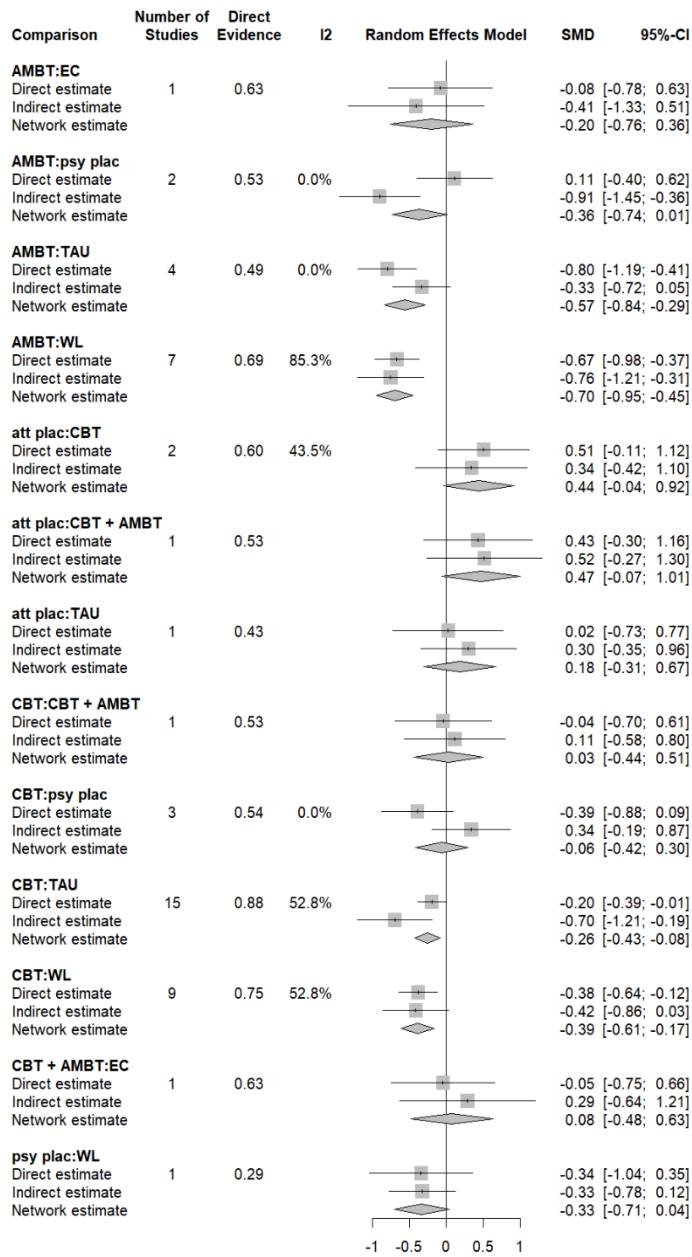
Figure S9*Netsplit forest plot for depression at post-treatment.*

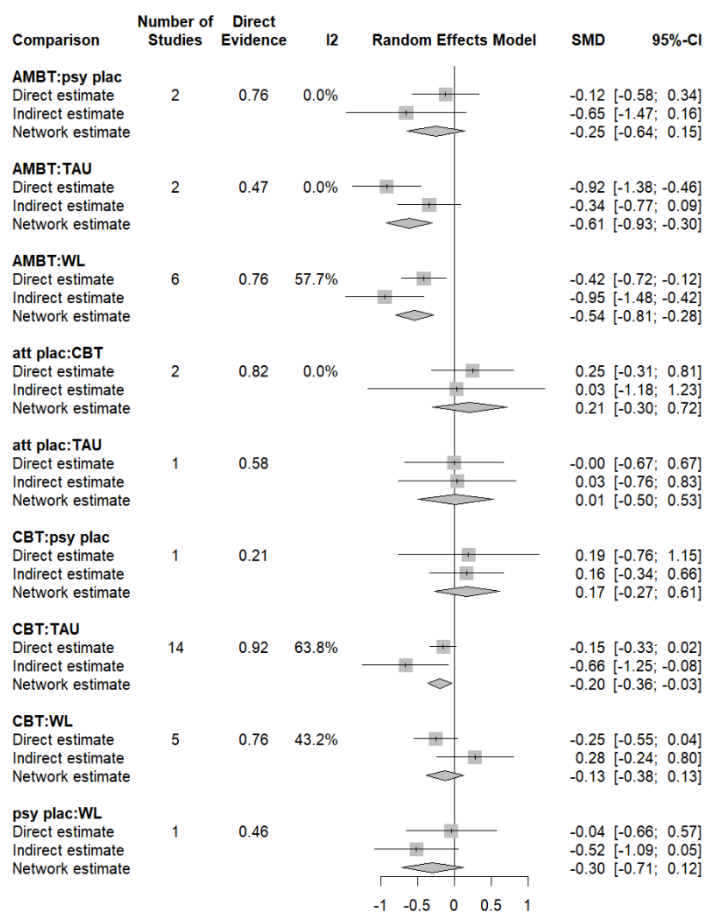
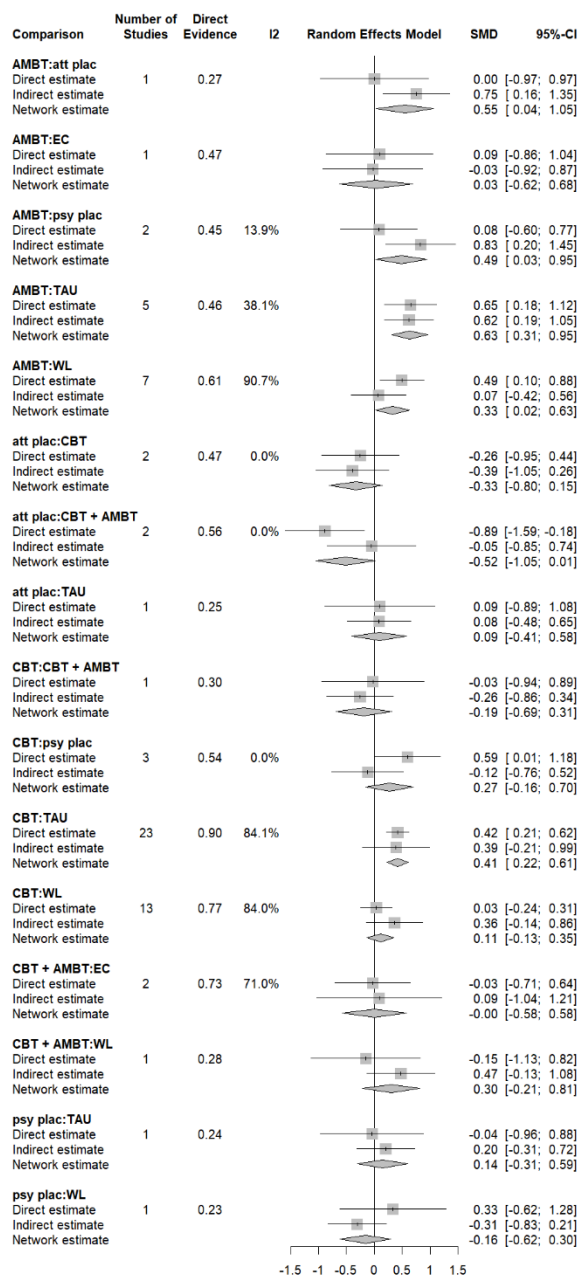
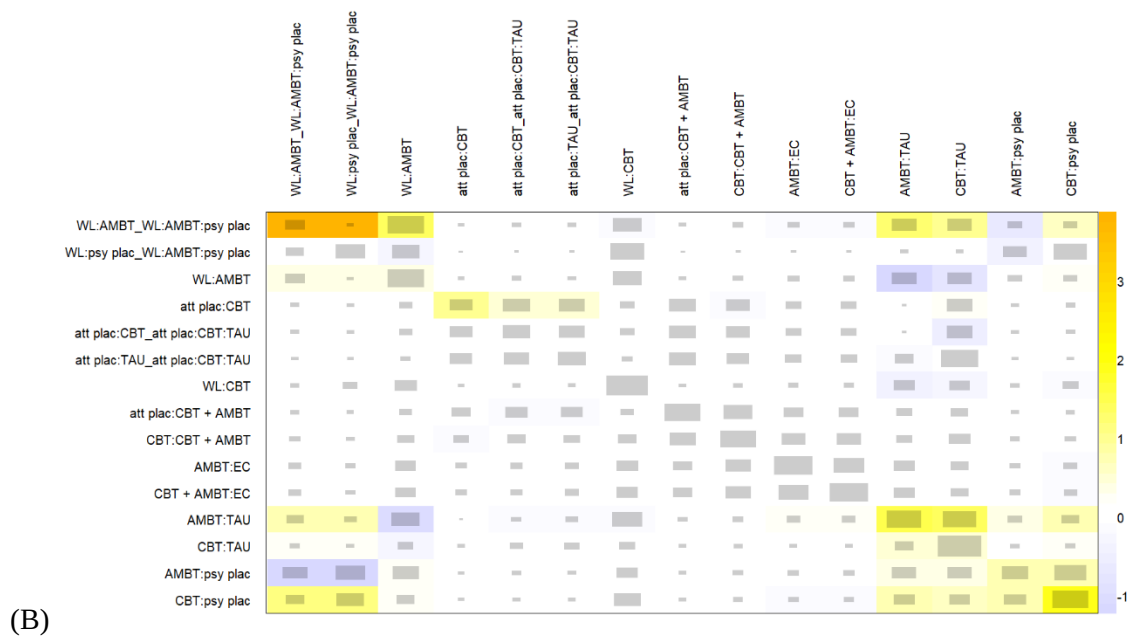
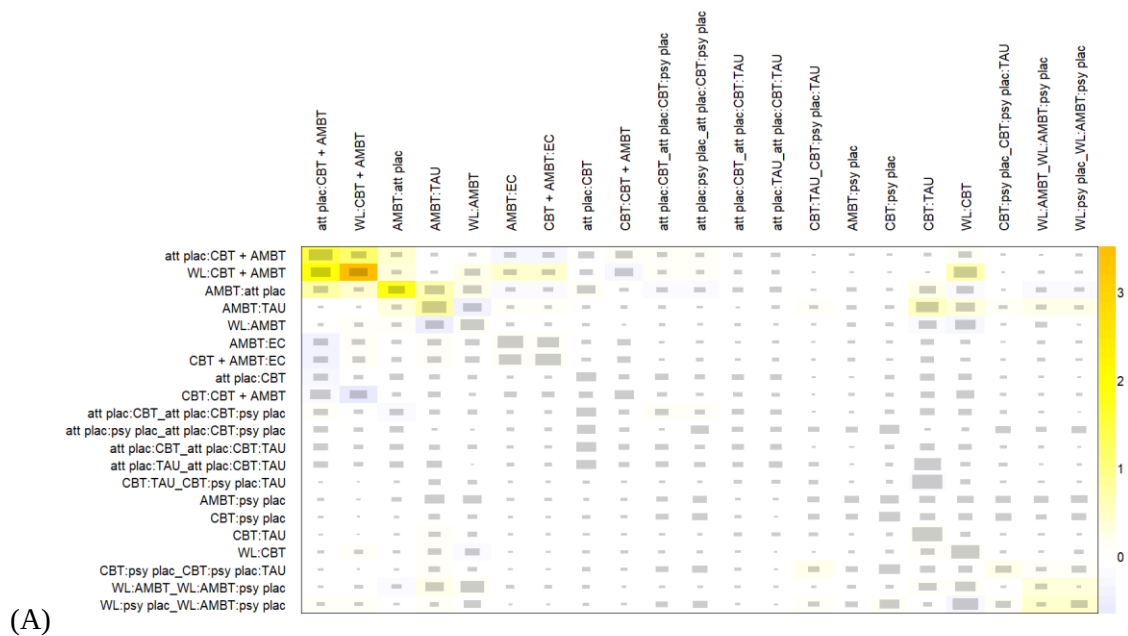
Figure S10*Netsplit forest plot for anxiety at post-treatment.*

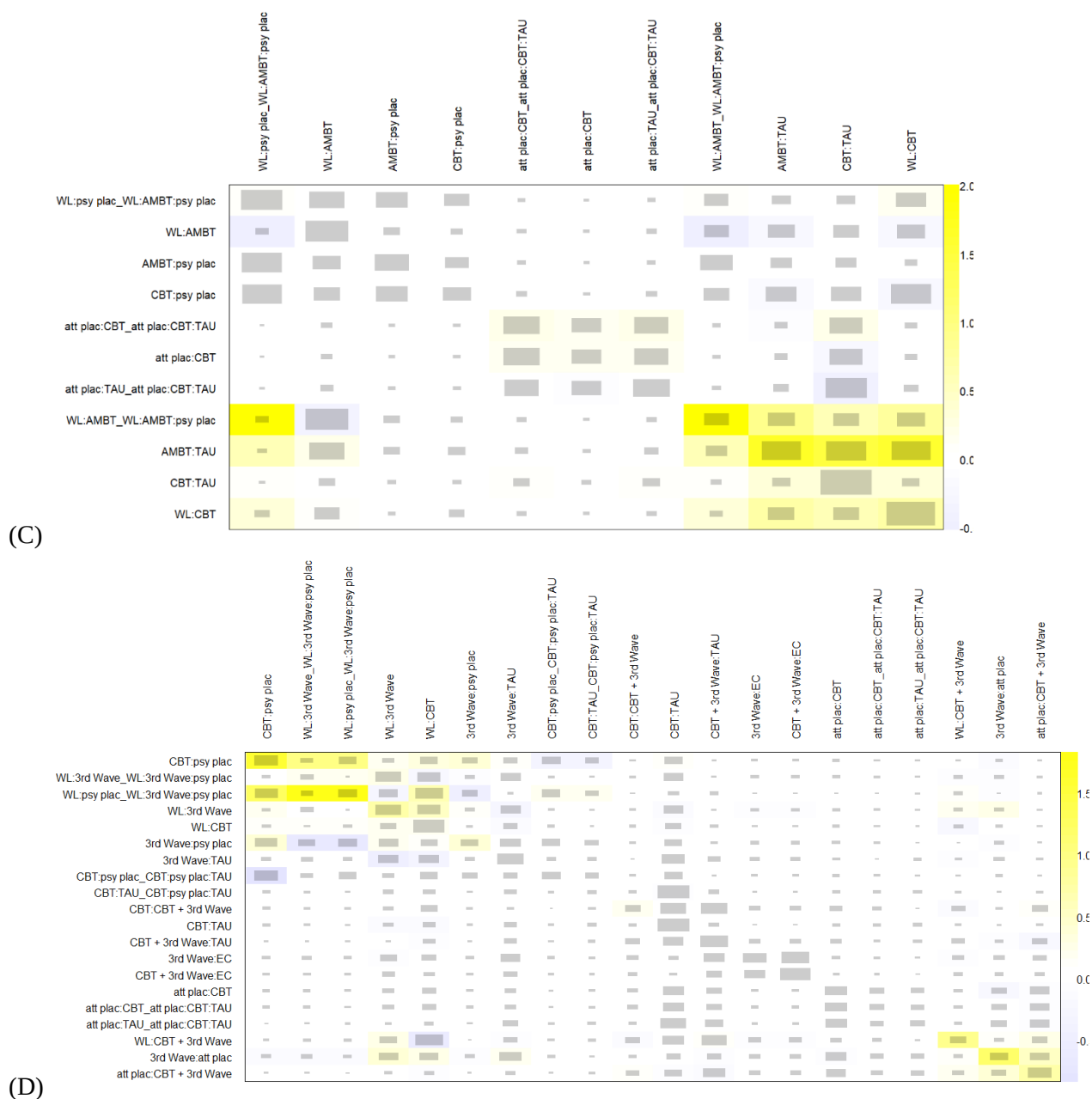
Figure S11*Netsplit forest plot for perceived health status at post-treatment*

S12 Net heat plots

Figure S12

Net heat plots at post-treatment





Note. A: Net heat plot for somatic symptom severity at post-treatment; B: net heat plot for depression at post-treatment; C: net heat plot for anxiety at post-treatment; D: net heat plot for perceived health status at post-treatment.

S13 Full design-by-treatment interaction random effects model**Table S9***Full design-by-treatment interaction random effects model for outcomes at post-treatment*

Outcome	Q^a	df^b	p^c	τ^d	τ^2
Somatic symptom severity	9.62	14	0.79	0.36	0.13
Depression	10.50	8	0.23	0.29	0.08
Anxiety	5.25	6	0.51	0.26	0.07
Perceived Health Status	6.84	12	0.87	0.49	0.24

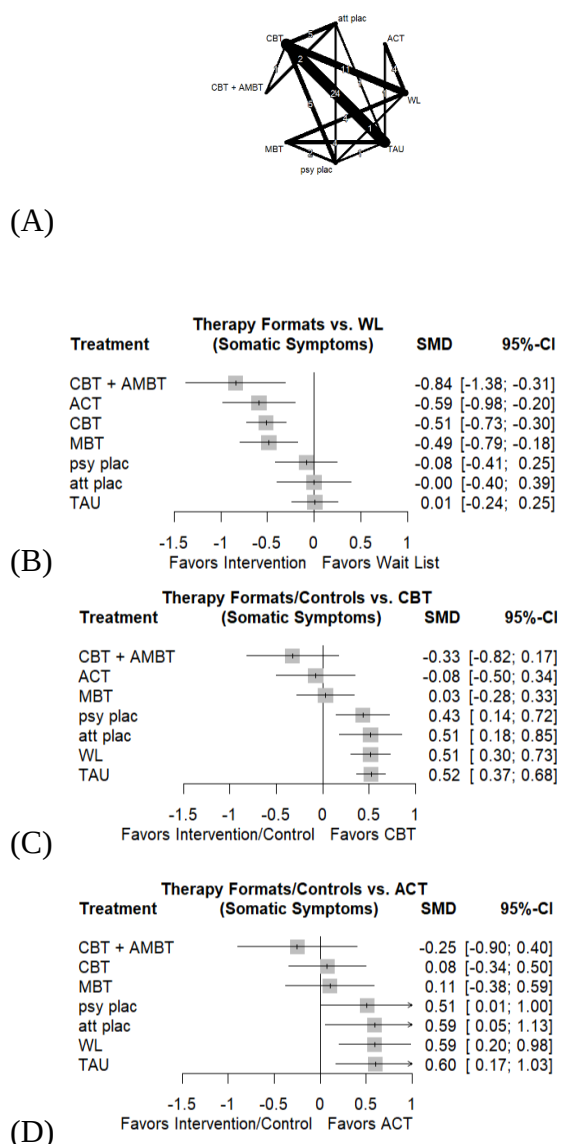
^a Q = remaining between designs inconsistency; ^b df = degrees of freedom; ^c p = p -value; ^d τ = tau within.

S14 Sensitivity analyses

S14.1 Treatment split

Figure S13

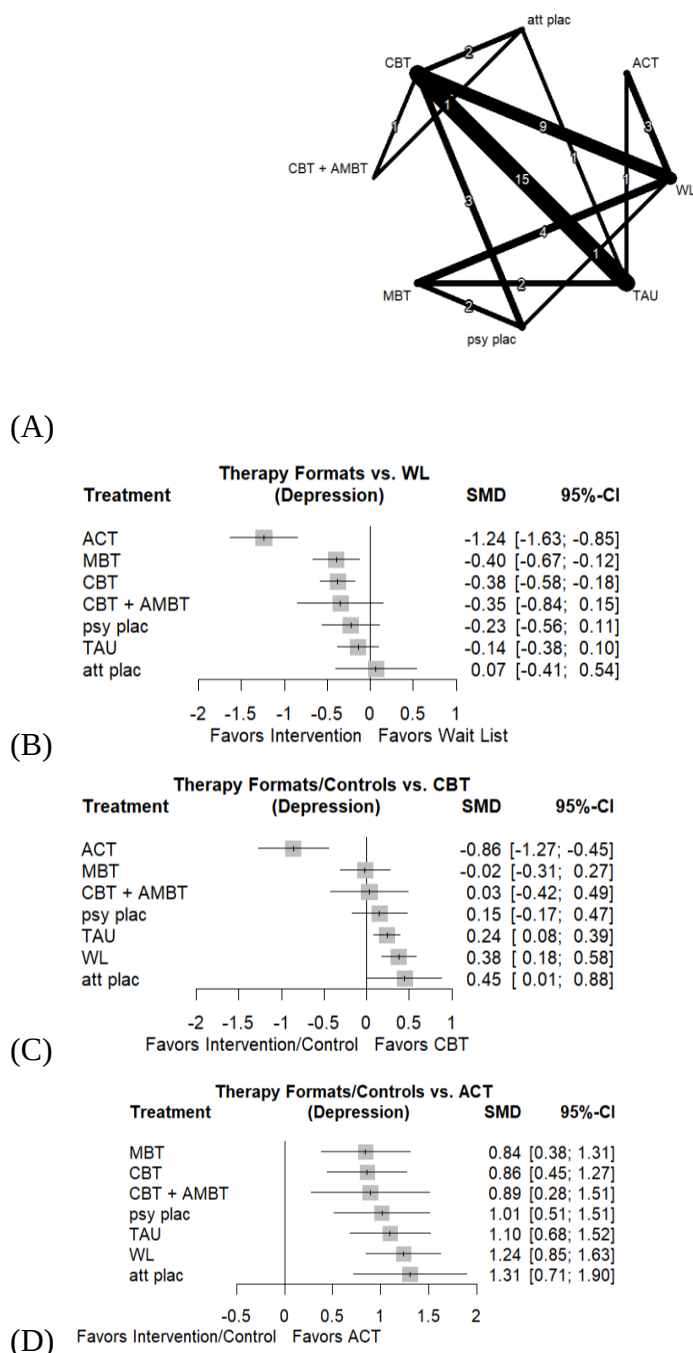
Network plot and forest plots for somatic symptom severity at post-treatment



Note. A: Network plot for somatic symptom severity at post-treatment with the acceptance- and mindfulness-based treatments split into acceptance-based (ACT) and mindfulness-based treatments ($k = 59$, $m = 67$, $n = 6,289$); B: forest plot with WL as reference group; C: forest plot with CBT as reference group; D: forest plot with ACT as reference group. Note: For perceived health status positive effects indicate efficacy of the treatments, for all other outcomes negative effects indicate efficacy of the treatments

Figure S14

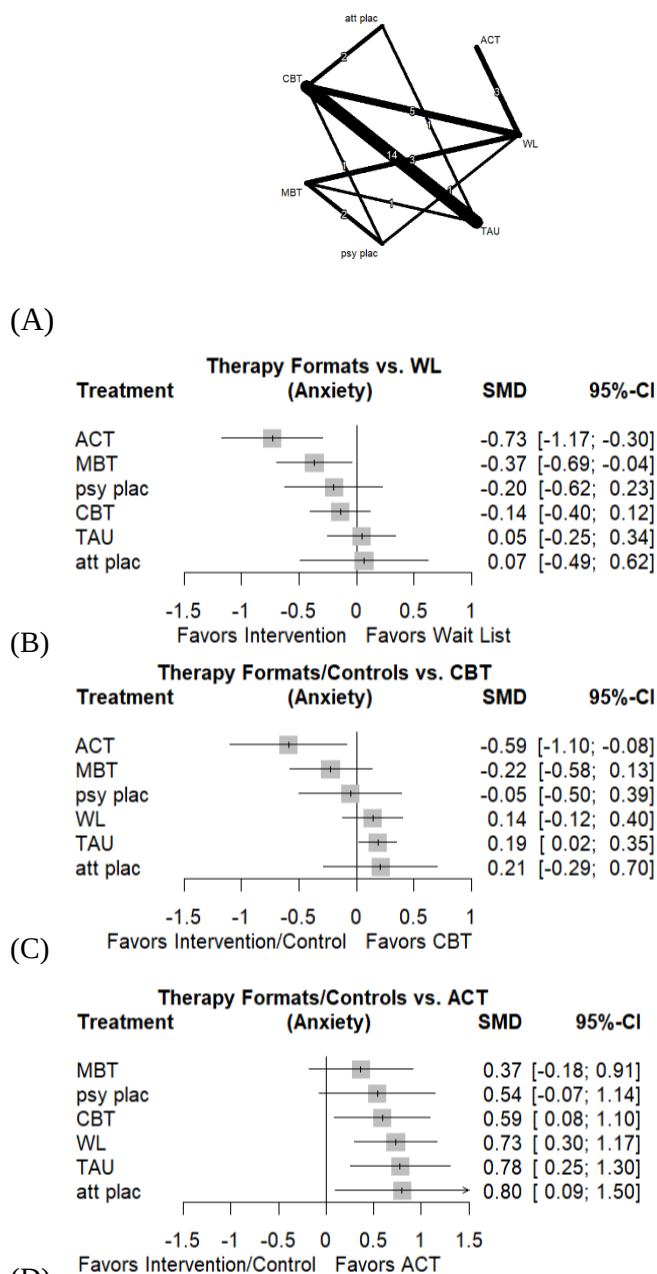
Network plot and forest plots for depression at post-treatment



Note. A: Network plot for depression at post-treatment with the acceptance- and mindfulness-based treatments split into acceptance-based (ACT) and mindfulness-based treatments ($k = 41$, $m = 45$, $n = 3,611$); B: forest plot with WL as reference group; C: forest plot with CBT as reference group; D: forest plot with ACT as reference group. Note: For perceived health status positive effects indicate efficacy of the treatments, for all other outcomes negative effects indicate efficacy of the treatments

Figure S15

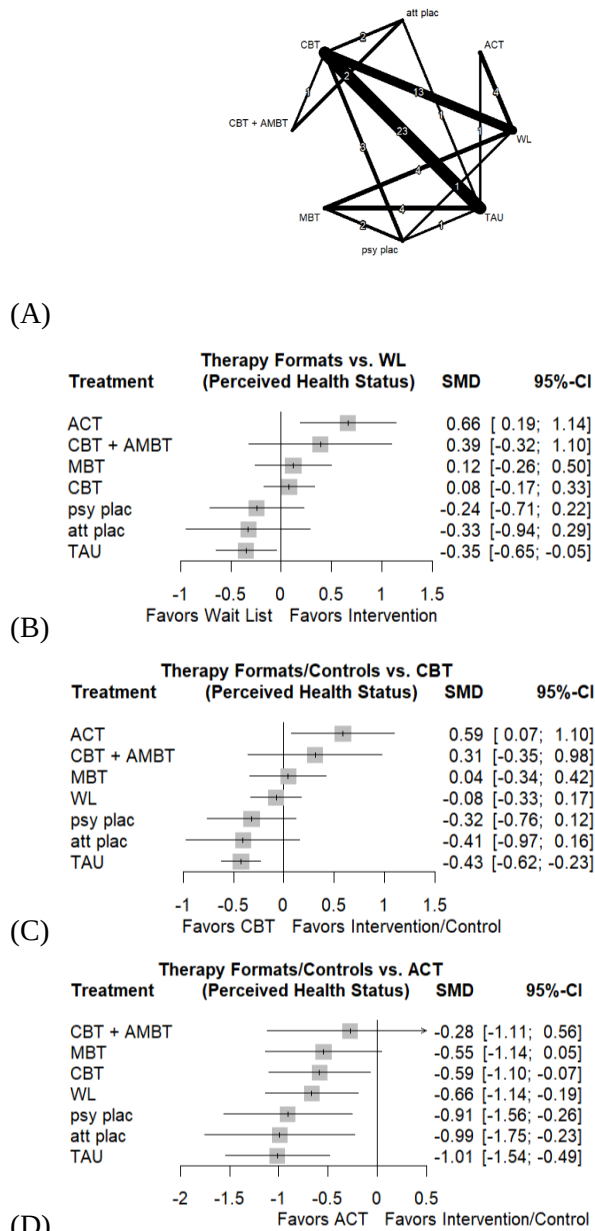
Network plot and forest plots for anxiety at post-treatment



Note. A: Network plot for anxiety at post-treatment with the acceptance- and mindfulness-based treatments split into acceptance-based (ACT) and mindfulness-based treatments ($k = 29$, $m = 33$, $n = 2,624$); B: forest plot with WL as reference group; C: forest plot with CBT as reference group; D: forest plot with ACT as reference group. Note: For perceived health status positive effects indicate efficacy of the treatments, for all other outcomes negative effects indicate efficacy of the treatments

Figure S16

Network plot and forest plots for perceived health status at post-treatment



Note. A: Network plot for perceived health status at post-treatment with the acceptance- and mindfulness-based treatments split into acceptance-based (ACT) and mindfulness-based treatments ($k = 56$, $m = 62$, $n = 5,957$); B: forest plot with WL as reference group; C: forest plot with CBT as reference group; D: forest plot with ACT as reference group. Note: For perceived health status positive effects indicate efficacy of the treatments, for all other outcomes negative effects indicate efficacy of the treatments

Table S10

Treatment comparison estimates for somatic symptom severity at post-treatment for the sensitivity analysis with treatment approaches split

ACT	-	-	-	-0.84 (-1.68; 0.00)	-	-	-0.53 (-0.96; -0.10)
-0.11 (-0.59; 0.38)	MBT	-	-	-0.62 (-1.06; -0.19)	-0.24 (-0.80; 0.31)	-	-0.42 (-0.83; -0.01)
-0.08 (-0.50; 0.34)	0.03 (-0.28; 0.33)	CBT	0.08 (-0.63; 0.79)	-0.50 (-0.66; -0.34)	-0.48 (-0.83; -0.12)	-0.45 (-0.83; -0.06)	-0.54 (-0.78; -0.30)
0.25 (-0.40; 0.90)	0.36 (-0.22; 0.93)	0.33 (-0.17; 0.82)	CBT + AMBT	-	-	-1.01 (-1.59; -0.43)	-
-0.60 (-1.03; -0.17)	-0.49 (-0.80; -0.19)	-0.52 (-0.68; -0.37)	-0.85 (-1.36; -0.34)	TAU	-0.03 (-0.75; 0.69)	0.05 (-0.75; 0.85)	-
-0.51 (-1.00; -0.01)	-0.40 (-0.77; -0.04)	-0.43 (-0.72; -0.14)	-0.76 (-1.32; -0.20)	0.09 (-0.22; 0.40)	Psychological placebo	0.07 (-0.72; 0.85)	-0.29 (-1.04; 0.46)
-0.59 (-1.13; -0.05)	-0.49 (-0.93; -0.04)	-0.51 (-0.85; -0.18)	-0.84 (-1.31; -0.37)	0.01 (-0.35; 0.37)	-0.08 (-0.50; 0.34)	Attention placebo	-
-0.59 (-0.98; -0.20)	-0.49 (-0.79; -0.18)	-0.51 (-0.73; -0.30)	-0.84 (-1.38; -0.31)	0.01 (-0.24; 0.25)	-0.08 (-0.41; 0.25)	-0.00 (-0.40; 0.39)	WL

Note. $k = 59$, $m = 69$, $n = 6289$; effect size: Cohen's d ; diagonal gives the treatments that were examined; upper triangle displays the pooled effect sizes of the direct comparisons available with 95% CIs; lower triangle contains the network meta-analysis effect sizes for each comparison with 95% CIs

Table S11

Treatment comparison estimates for depression at post-treatment for the sensitivity analysis with treatment approaches split

ACT	-	-	-	-0.87 (-1.57; -0.16)	-	-	-1.34 (-1.79; -0.88)
-0.84 (-1.31; -0.38)	MBT	-	-	-0.64 (-1.12; -0.16)	0.11 (-0.33; 0.56)	-	-0.30 (-0.63; 0.04)
-0.86 (-1.27; -0.45)	-0.02 (-0.31; 0.27)	CBT	-0.04 (-0.59; 0.50)	-0.20 (-0.36; -0.03)	-0.39 (-0.82; 0.04)	-0.48 (-1.04; 0.07)	-0.37 (-0.60; -0.15)
-0.89 (-1.51; -0.28)	-0.05 (-0.59; 0.49)	-0.03 (-0.49; 0.42)	CBT + AMBT	-	-	-0.43 (-1.07; 0.21)	-
-1.10 (-1.52; -0.68)	-0.26 (-0.56; 0.04)	-0.24 (-0.39; -0.08)	-0.21 (-0.68; 0.27)	TAU	-	-0.02 (-0.68; 0.63)	-
-1.01 (-1.51; -0.51)	-0.17 (-0.51; 0.17)	-0.15 (-0.47; 0.17)	-0.12 (-0.68; 0.44)	0.09 (-0.26; 0.43)	Psychological placebo	-	-0.34 (-0.94; 0.26)
-1.31 (-1.90; -0.71)	-0.46 (-0.98; 0.05)	-0.45 (-0.88; -0.01)	-0.41 (-0.90; 0.07)	-0.21 (-0.65; 0.24)	-0.29 (-0.83; 0.24)	Attention placebo	-
-1.24 (-1.63; -0.85)	-0.40 (-0.67; -0.12)	-0.38 (-0.58; -0.18)	-0.35 (-0.84; 0.15)	-0.14 (-0.38; 0.10)	-0.23 (-0.56; 0.11)	0.07 (-0.41; 0.54)	WL

Note. $k = 41$, $m = 45$, $n = 3611$; effect size: Cohen's d ; diagonal gives the treatments that were examined; upper triangle displays the pooled effect sizes of the direct comparisons available with 95% CIs; lower triangle contains the network meta-analysis effect sizes for each comparison with 95% CIs

Table S12

Treatment comparison estimates for anxiety at post-treatment for the sensitivity analysis with treatment approaches split

ACT	-	-	-	-	-	-0.73 (-1.17; -0.30)
-0.37 (-0.91; 0.18)	MBT	-	-0.81 (-1.38; -0.24)	-0.12 (-0.56; 0.32)	-	-0.16 (-0.55; 0.23)
-0.59 (-1.10; -0.08)	-0.22 (-0.58; 0.13)	CBT	-0.16 (-0.32; 0.01)	0.19 (-0.75; 1.14)	-0.25 (-0.80; 0.29)	-0.25 (-0.54; 0.03)
-0.78 (-1.30; -0.25)	-0.41 (-0.78; -0.05)	-0.19 (-0.35; -0.02)	TAU	-	0.00 (-0.65; 0.65)	-
-0.54 (-1.14; 0.07)	-0.17 (-0.57; 0.22)	0.05 (-0.39; 0.50)	0.24 (-0.22; 0.70)	Psychological placebo	-	-0.04 (-0.64; 0.55)
-0.80 (-1.50; -0.09)	-0.43 (-1.04; 0.17)	-0.21 (-0.70; 0.29)	-0.02 (-0.52; 0.48)	-0.26 (-0.92; 0.40)	Attention placebo	-
-0.73 (-1.17; -0.30)	-0.37 (-0.69; -0.04)	-0.14 (-0.40; 0.12)	0.05 (-0.25; 0.34)	-0.20 (-0.62; 0.23)	0.07 (-0.49; 0.62)	WL

Note. $k = 29$, $m = 33$, $n = 2624$; effect size: Cohen's d ; diagonal gives the treatments that were examined; upper triangle displays the pooled effect sizes of the direct comparisons available with 95% CIs; lower triangle contains the network meta-analysis effect sizes for each comparison with 95% CIs

Table S13

Treatment comparison estimates for perceived health status at post-treatment for the sensitivity analysis with treatment approaches split

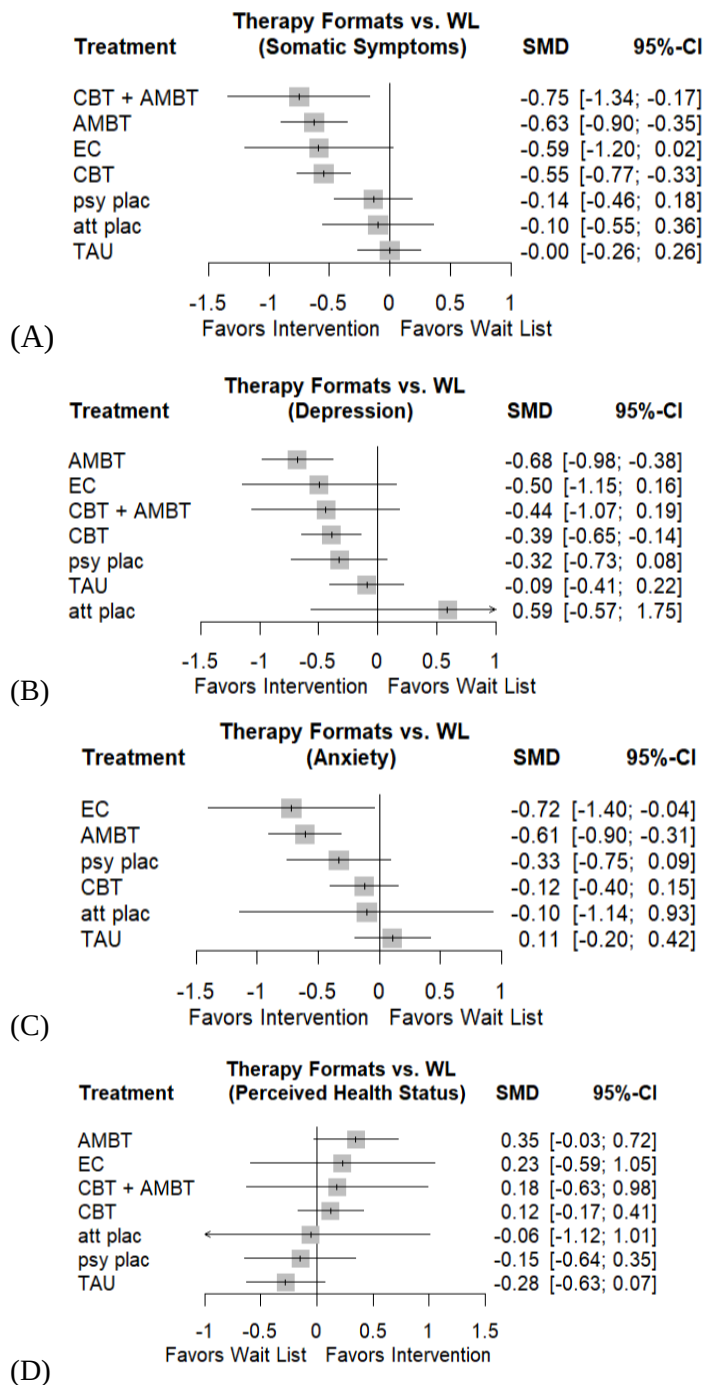
ACT	-	-	-	1.26 (0.23; 2.30)	-	-	0.60 (0.07; 1.13)
0.55 (-0.05; 1.14)	MBT	-	-	0.49 (-0.04; 1.02)	0.08 (-0.61; 0.77)	-	0.23 (-0.27; 0.73)
0.59 (0.07; 1.10)	0.04 (-0.34; 0.42)	CBT	-0.03 (-0.95; 0.89)	0.42 (0.21; 0.62)	0.59 (0.01; 1.18)	0.26 (-0.44; 0.95)	0.03 (-0.25; 0.31)
0.28 (-0.56; 1.11)	-0.27 (-1.03; 0.49)	-0.31 (-0.98; 0.35)	CBT + AMBT	-	-	0.89 (0.18; 1.60)	-
1.01 (0.49; 1.54)	0.47 (0.09; 0.84)	0.43 (0.23; 0.62)	0.74 (0.05; 1.42)	TAU	0.04 (-0.88; 0.97)	-0.09 (-1.08; 0.90)	-
0.91 (0.26; 1.56)	0.36 (-0.12; 0.85)	0.32 (-0.12; 0.76)	0.63 (-0.16; 1.43)	-0.11 (-0.56; 0.35)	Psychological placebo	-	0.33 (-0.62; 1.28)
0.99 (0.23; 1.75)	0.45 (-0.23; 1.12)	0.41 (-0.16; 0.97)	0.72 (0.12; 1.32)	-0.02 (-0.61; 0.56)	0.08 (-0.63; 0.80)	Attention placebo	-
0.66 (0.19; 1.14)	0.12 (-0.26; 0.50)	0.08 (-0.17; 0.33)	0.39 (-0.32; 1.10)	-0.35 (-0.65; -0.05)	-0.24 (-0.71; 0.22)	-0.33 (-0.94; 0.29)	WL

Note. $k = 65$, $m = 62$, $n = 5957$; effect size: Cohen's d ; diagonal gives the treatments that were examined; upper triangle displays the pooled effect sizes of the direct comparisons available with 95% CIs; lower triangle contains the network meta-analysis effect sizes for each comparison with 95% CIs

S14.2 High-intensity interventions

The following *low-intensity* treatments were excluded from the analysis:

- Edinger et al., 2005
- Friedberg et al., 2013
- Friesen et al., 2017
- Henrich et al., 2020
- Huibers et al., 2004
- Ito & Muto, 2020
- Janse et al., 2018
- Kristjánsdóttir et al., 2013
- Ljótsson et al., 2010
- Ljótsson, Andersson et al., 2011
- Martin et al., 2007
- Menga et al., 2014
- Menon et al., 2017
- Moss-Morris et al., 2010
- Nhu et al., 2024
- Ong et al., 2023
- Sanders et al., 2007
- Simister et al., 2018
- Varallo et al., 2023
- Yang & Jun, 2022

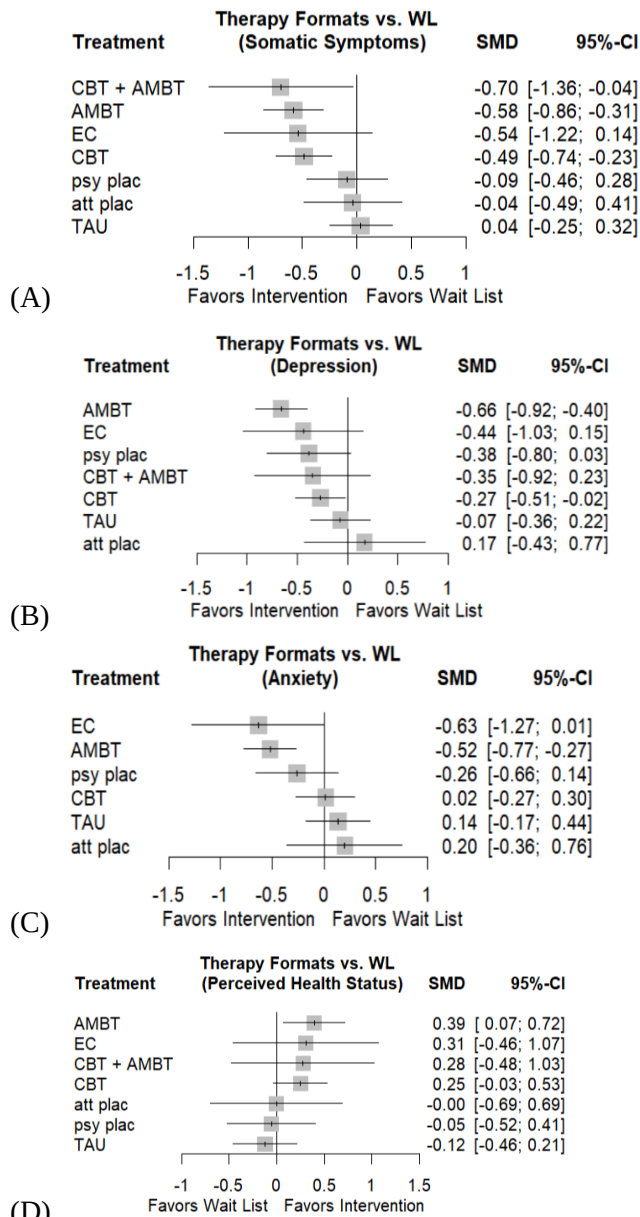
Figure S17*Forest plots (high-intensity treatments) – post-treatment*

Note. A: forest plot for somatic symptom severity for the subset of high-intensity treatments at post-treatment; B: forest plot for depression for the subset of high-intensity treatments at post-treatment; C: forest plot for anxiety for the subset of high-intensity treatments at post-treatment; D: forest plot for perceived health status for the subset of high-intensity treatments at post-treatment. Note: For perceived health status positive effects indicate efficacy of the treatments, for all other outcomes negative effects indicate efficacy of the treatments

S14.3 Face-to-face treatments

The following *self-guided/computer-/internet-/app-based treatments* were excluded from the analysis:

- Everitt et al., 2019: telephone- & web-delivered arm (combined for analysis)
- Friedberg et al., 2016: self-guided
- Friesen et al., 2017: internet-based
- Hunt et al., 2021: app
- Janse et al., 2018: internet-based
- Kikuchi et al., 2022: partly internet-based (due to COVID-19 pandemic)
- Kristjánsdóttir et al., 2013: app
- Ljótsson et al., 2010: internet-based
- Ljótsson, Andersson et al., 2011: internet-based
- Menga et al., 2014: internet-based
- Milrad et al., 2019: internet-based
- Nhu et al., 2024: internet-based
- Ong et al., 2023: internet-based
- Owusu et al., 2021: internet-based
- Sanders et al., 2007: self-guided
- Simister et al., 2018: internet-based
- Williams et al., 2010: internet-based

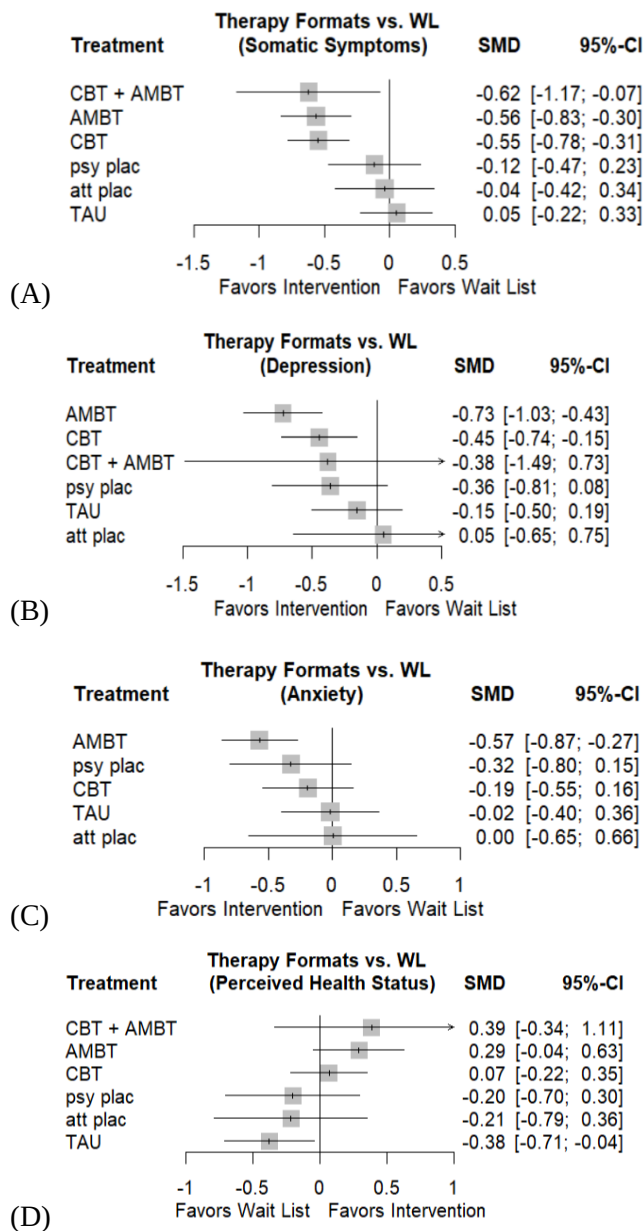
Figure S18*Forest plots (face-to-face treatments) – post-treatment*

Note. A: forest plot for somatic symptom severity for the subset of face-to-face treatments at post-treatment; B: forest plot for depression for the subset of face-to-face treatments at post-treatment; C: forest plot for anxiety for the subset of face-to-face treatments at post-treatment; D: forest plot for perceived health status for the subset of face-to-face treatments at post-treatment. Note: For perceived health status positive effects indicate efficacy of the treatments, for all other outcomes negative effects indicate efficacy of the treatments

S14.4 Functional somatic syndromes

Figure S19

Forest plots (functional somatic syndromes) – post-treatment

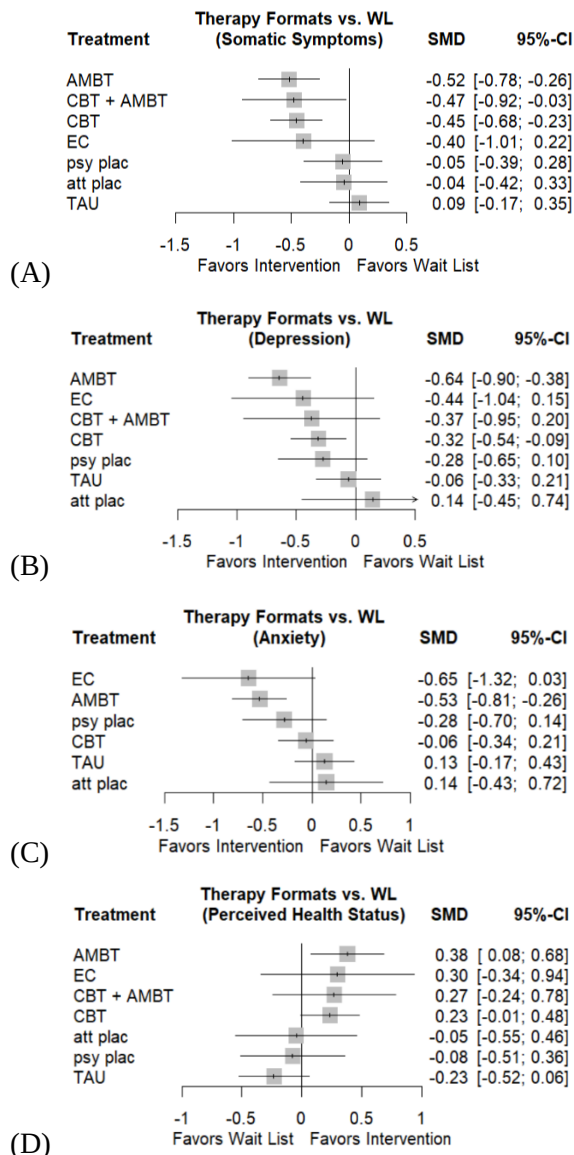


Note. A: forest plot for somatic symptom severity for the subset of functional somatic syndromes (FSS) at post-treatment; B: forest plot for depression for the subset of FSS at post-treatment; C: forest plot for anxiety for the subset of FSS at post-treatment; D: forest plot for perceived health status for the subset of FSS at post-treatment. Note: For perceived health status positive effects indicate efficacy of the treatments, for all other outcomes negative effects indicate efficacy of the treatments

S14.5 Diagnoses based on interviews or medical examinations

Figure S20

Forest plots (studies based inclusion on a clinical interview or medical examination) – post-treatment

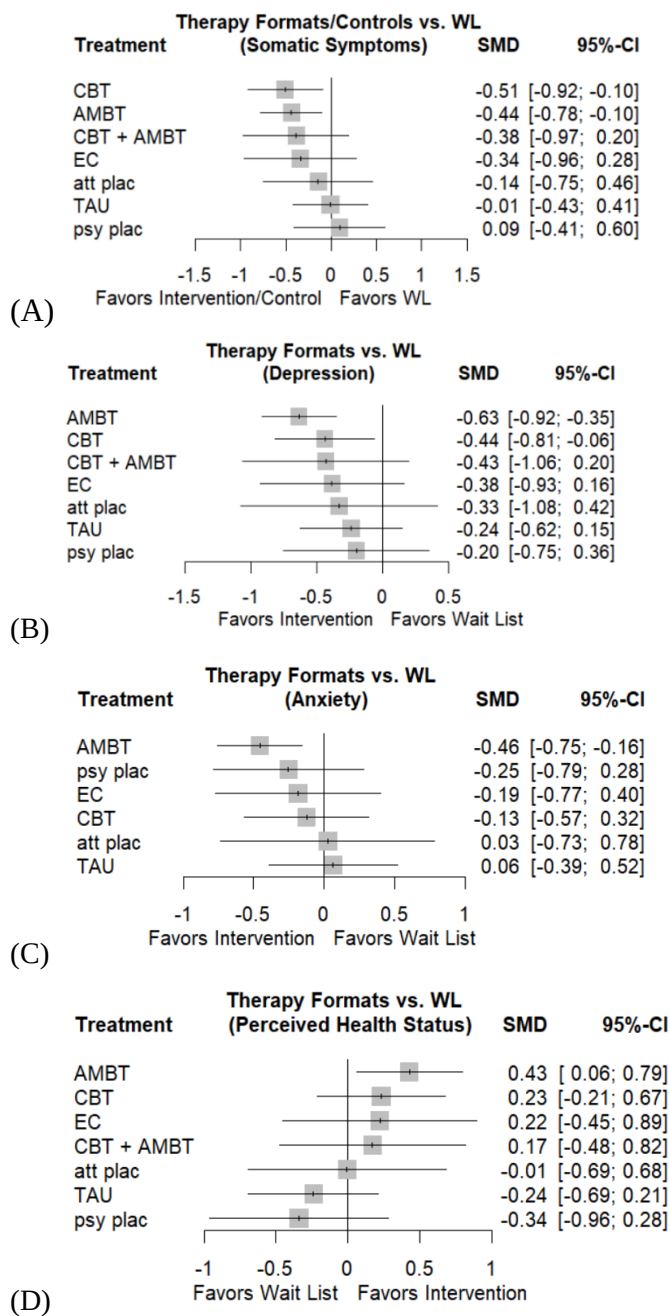


Note. A: forest plot for somatic symptom severity at post-treatment for the subset of studies using a clinical interview/medical examination for diagnosis; B: forest plot for depression at post-treatment for the subset of studies using a clinical interview/medical examination for diagnosis; C: forest plot for anxiety at post-treatment for the subset of studies using a clinical interview/medical examination for diagnosis; D: forest plot for perceived health status at post-treatment for the subset of studies using a clinical interview/medical examination for diagnosis. Note: For perceived health status positive effects indicate efficacy of the treatments, for all other outcomes negative effects indicate efficacy of the treatments

S14.6 Selection of follow-up intervals

Figure S21

Funnel plots for the longest available follow-up interval

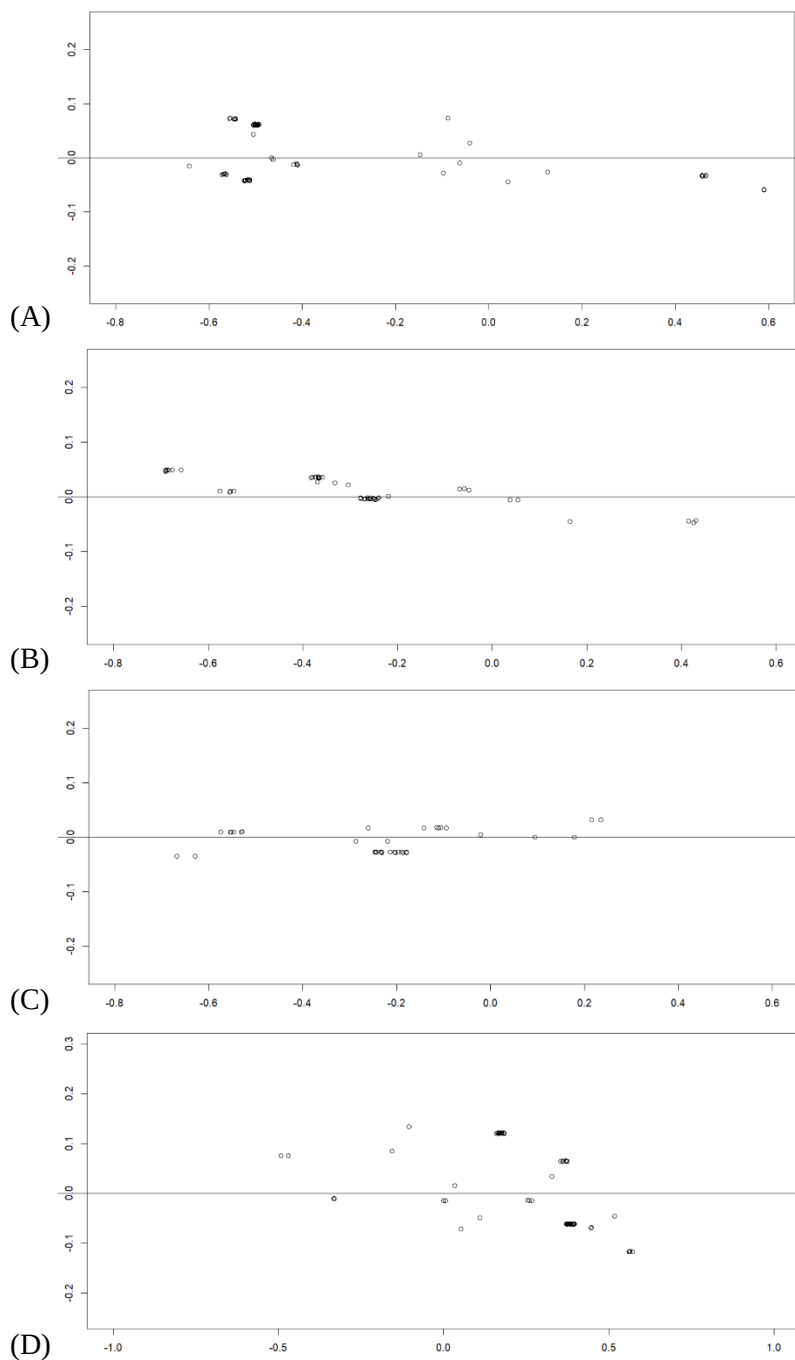


Note. A: forest plot for somatic symptom severity at the longest available follow-up interval; B: forest plot for depression at the longest available follow-up interval; C: forest plot for anxiety at the longest available follow-up interval; D: forest plot for perceived health status at the longest available follow-up interval. Note: For perceived health status positive effects indicate efficacy of the treatments, for all other outcomes negative effects indicate efficacy of the treatments

S14.7 Meta-analytic model choice

Figure S22

Bland-Altman plots – post-treatment

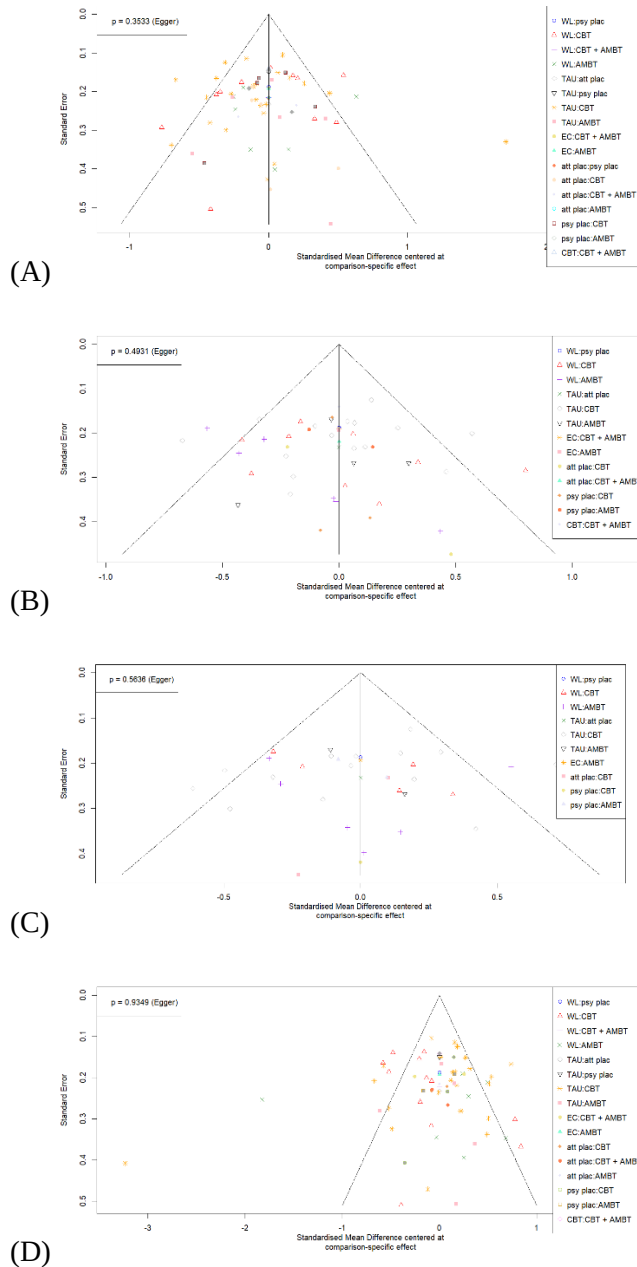


Note. A: Bland-Altman plot for somatic symptom severity; B: Bland-Altman plot for depression; C: Bland-Altman plot for anxiety; D: Bland-Altman plot for perceived health status. X-axis: mean treatment effects (in fixed effect and random effects model), y-axis: difference of treatment effect (fixed effect minus random effects model).

S15 Funnel plots

Figure S23

Comparison-adjusted funnel plots – post-treatment



Note. A: Comparison-adjusted funnel plot for somatic symptom severity at post-treatment; B: comparison-adjusted funnel plot for depression at post-treatment; C: comparison-adjusted funnel plot for anxiety at post-treatment; D: comparison-adjusted funnel plot for perceived health status at post-treatment.

S16 PRISMA 2020 Checklist

S16.1 PRISMA 2020 Main Checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	<i>Supplement S16.2</i>
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Eligibility criteria; Data analyses
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Search strategies and study selection; Supplement S1.4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplement S1.5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Search strategies and study selection; Supplement S1.3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Data extraction
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Outcome measures
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Supplement S1.6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Risk of bias assessment
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Data analyses

Topic	No.	Item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	Data analyses
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Supplement S1.6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Data analyses
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Data analyses; Supplement S5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	n/a (cf. Supplement S4)
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Methods - Sensitivity analyses
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods - Publication Bias
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results - Study selection; Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplement S4
Study characteristics	17	Cite each included study and present its characteristics.	Study characteristics
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Risk of Bias; Supplement S3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supplement S2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Treatment effects – post-treatment; Treatment effects – follow-ups; Supplement S2.3; Supplement S3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Treatment effects – post-treatment, Figure 3, Tables 1-4; Treatment effects – follow-ups; Supplement S7-13

Topic	No.	Item	Location where item is reported
Reporting biases	20c	Present results of all investigations of possible causes of heterogeneity among study results.	n/a (see above)
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Results - Sensitivity analyses
	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Results - Publication Bias
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Limitations
	23c	Discuss any limitations of the review processes used.	Limitations
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion; Future research; Conclusion
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Supplement S4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding Sources
Competing interests	26	Declare any competing interests of review authors.	Conflict of Interest Statement
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Data Availability Statement

S16.2 PRISMA Abstract Checklist

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	No
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	No
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	No
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

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