# Psychological Interventions for Children with Functional Somatic Symptoms

Bonvanie, Irma J; Kallesøe, Karen H; Janssens, Karin A M; Schröder, Andreas; Rosmalen, Judith G M; Rask, Charlotte U

*Published in:*
The Journal of Pediatrics

*DOI:*
10.1016/j.jpeds.2017.03.017



*Publication date:*
2017

# Psychological Interventions for Children with Functional Somatic Symptoms: A Systematic Review and Meta-Analysis

Irma J. Bonvanie, MD[1], Karen H. Kallesøe, MD[2], Karin A. M. Janssens, PhD[1], Andreas Schröder, MD, PhD[2], Judith G. M. Rosmalen, PhD[1], and Charlotte U. Rask, MD, PhD[2,3]

**Objective** To analyze the effectiveness of psychological treatments on symptom load and associated disability in children with functional somatic symptoms, and to explore potential moderators of effects.

**Study design** Cochrane, PubMed, PsycINFO, EMBASE, and CINAHL were searched for randomized controlled trials published in peer-reviewed journals. Randomized controlled trials studying the effect of a psychological treatment on symptom load and disability in children with functional somatic symptoms were selected. Data on symptom load, disability, and school absence directly post-treatment and at follow-up were extracted by 2 assessors. Studies were appraised with the Cochrane risk of bias tool. Standardized mean differences were pooled in a random-effects model. Heterogeneity in effect-sizes was explored by use of meta-regressions. PROSPERO Registration ID: CRD42015029667.

**Results** Out of 4098 identified records, 27 studies were included in this review of which 21 were included in meta-analyses. Psychological treatments reduced symptom load (Hedges g = –0.61), disability (Hedges g = –0.42), and school absence (Hedges g = –0.51) post-treatment in children suffering from various functional somatic symptoms. Effects were maintained at follow-up. Type and duration of symptoms, age, and treatment dose did not explain heterogeneity in effect-sizes between studies. Effect-sizes should be interpreted with caution because of the variety in outcome measures, unexplained heterogeneity in found effects and potential publication bias.

**Conclusions** Psychological interventions reduce symptom load, disability, and school absence in children with functional somatic symptoms. Future research should clarify which patient and treatment characteristics modify outcomes. *(J Pediatr 2017;187:272-81).*

See editorial, p 15

Functional somatic symptoms are physical symptoms that are not fully explained by a well-defined medical psychiatric or somatic illness, such as pain and fatigue. Functional somatic symptoms are common in childhood and can become very persistent and disabling.[1-4] Unfortunately, it is mostly unclear how children with functional somatic symptoms are best treated, although growing evidence suggests that psychological interventions can be beneficial.[5-7]

It is an ongoing discussion as to whether different functional somatic symptoms represent distinct illnesses, subtypes of the same overarching syndrome,[8-10] or are purely an artifact of medical specialization.[11] Factor analyses in the general population indicate the existence of 3 or 4 main functional somatic symptoms clusters in children: gastrointestinal symptoms, pain, general or pseudoneurologic symptoms including fatigue, and cardiopulmonary symptoms.[12-16] Based on the subspecialty involved, treatments for functional somatic symptoms have so far been separately investigated for children with gastrointestinal symptoms, fatigue, headaches, and musculoskeletal pains.[5,6,17] Psychological treatments have been found to be effective for adults with various functional somatic symptom clusters, regardless of their main symptoms, indicating that these patients can be treated by comparable therapies.[18-20] Different functional somatic symptom clusters often co-occur in pediatric patients, seem to be driven by a strong general factor, and share psychological and social risk factors.[21-25] Yet, it remains unknown if children suffering from different functional somatic symptom clusters respond similarly to psychological treatments. More knowledge about this could aid in the organization of high quality and cost-effective healthcare for all pediatric patients with functional somatic symptoms.[9]

Effectiveness of psychological interventions may not only depend on the functional somatic symptoms treated but could also depend on other characteristics such as symptom severity, comorbidities, the age of the patient, and the treatment dose and content of psychological intervention.[26] These patient and treatment characteristics and their potential influence on outcomes have not yet been

CAU Care as usual

From the [1]University Medical Center of Groningen, Interdisciplinary Center Psychopathology and Emotion Regulation, University of Groningen, Groningen, The Netherlands; [2]Research Clinic for Functional Disorders and Psychosomatics; and [3]Child and Adolescent Psychiatric Center Risskov, Aarhus University Hospital, Aarhus, Denmark

The authors declare no conflicts of interest.



http://dx.doi.org10.1016/j.jpeds.2017.03.017

described or analyzed.[5,6,17] Yet, such an overview of investigated psychological treatments for children with functional somatic symptoms is essential in allocating children to the most appropriate treatment.

We aimed to investigate the effectiveness of psychological treatments on symptom load and disability in children with various functional somatic symptoms. In addition, we described the characteristics of the included participants and investigated treatments, and we analyzed the effects of these characteristics on treatment outcomes.

## Methods

A protocol of this review was registered in November 2015 (https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015029667).

Studies were considered eligible when they described a randomized controlled trial, which investigated the effect of a psychological treatment vs any other intervention or a waiting list condition on symptom load and disability in children with functional somatic symptoms, as reported by the child/parent. Only studies with ≥10 participants in both treatment arms at the end-of-treatment assessment were included. For meta-analyses, only studies, which compared psychological treatment with waiting list, care as usual (CAU), or placebo were included.

In line with recent reviews, we defined "psychological treatments" as treatments designed to alter psychological processes that may influence functional somatic symptoms,[7] such as psycho-education, cognitive behavioral therapy, acceptance and commitment therapy, relaxation, hypnosis, coping skills training, biofeedback, and narrative therapies.

Functional somatic symptoms were defined as physical symptoms not fully explained by a well-defined medical psychiatric or somatic illness. Thus, studies on participants with chronic pain complaints because of, for example, migraine or juvenile arthritis, were excluded.

When studies included mixed populations (eg, participants with tension-type headache and migraine), these studies were included if they fulfilled 1 of the following 2 criteria. The subgroup fulfilling our inclusion criteria was separately analyzed or at least 70% (with a minimum of 10 participants in both arms) of all participants fulfilled our inclusion criteria at the end-of-treatment assessment.

### Search Strategy and Information Sources

We searched Cochrane, PubMed, PsycINFO, EMBASE, and CINAHL in December 2015 for randomized controlled trials published in peer-reviewed journals between 1975 and November 2015. For the concepts "child/adolescent," "functional somatic symptoms," "psychological treatment," and "randomized controlled trial," mesh terms, synonyms, or closely related nomenclature were specified (as shown in our registered protocol for the used search string in PubMed). Searches were conducted without restrictions on language. However, only English search terms were used.

### Study Selection

The titles and abstracts of all identified records were appraised for inclusion by 2 assessors based on prespecified eligibility criteria, after removal of duplicates. Hereafter, full text articles of all potentially relevant records included in the first phase were examined for inclusion and exclusion criteria. In both selection phases any discrepancies were resolved through discussion, and the kappa estimate of initial agreement between assessors was calculated. In case of disagreement, a third assessor was consulted.

### Data Collection Process and Data Items

Data from included studies were independently extracted by 2 authors by use of a structured form, developed a priori. Disagreements were solved through discussion or when needed by consulting a third assessor. The extraction form included the aim and the design of the study, participant characteristics, details of the intervention provided based on the Tidier checklist,[27] outcome details, and effects. The authors of 11 studies were contacted to obtain missing outcome data. Seven authors were able to provide data.

### Risk of Bias in Individual Studies

Two assessors appraised the risk of bias.[28] Discrepancies were resolved through discussion. The Cochrane risk of bias assessment tool consists of 5 main domains which can be rated as "low," "high," or "unclear."[28] Because blinding of participants and therapists is usually not possible for psychological treatments, only the blinding of outcome assessors was rated. Selective outcome reporting was marked as unclear when no trial registration or study-protocol was available or when one of our main outcomes was not fully reported in the article.

The methodological quality of studies and treatments was assessed with the psychotherapy outcome study rating scale by 2 assessors.[29] This instrument consists of 21 items that can be rated poor ("0"), fair ("1"), or good ("2"). The **Appendix** (available at www.jpeds.com) provides a detailed description of the assessed items.

### Summary Measures

We were interested in the outcomes symptom load and disability. Studies measured symptom load by assessing symptom intensity or severity, frequency, and/or duration. Some studies reported school absence as a measure of disability instead of, or in addition to, physical functioning or quality of life. We therefore, decided to include school absence as a second outcome of disability. When the concepts symptom load or disability were assessed with more than 1 measure, outcomes from specific, validated, and multiple-item tools were preferred over those from nonspecific, nonvalidated, and single-item tools. When outcomes were equally valid, the one most used in other studies was chosen.

### Synthesis of Results

Almost all studies reported outcomes with continuous measures. Therefore, Hedges g was calculated for the 3 outcomes: symptom load, disability, and school absence post-treatment,

and when available at follow-up. Post-treatment was defined as every measurement between 0 and 3 months after end of treatment. Follow-up was defined as every measurement between 3 and 12 months after end of treatment, with a preference for the latest time point. The Hedges g of studies, calculated from raw means and SDs, were pooled in RevMan 5.3 in a random-effects model. Hedges g is a bias corrected standardized mean difference or Cohen d, appropriate for small sample sizes. Heterogeneity in effect sizes was assessed with the $I^2$ statistics that reflects the percentage of "true" heterogeneity because of variation in treatment effect.

Of the 7 studies that assessed school absence, 1 study did not assess this outcome post-treatment,[30] and the author of another study stated low confidence in the post-treatment data because of holidays at time of assessment.[31] Therefore, the follow-up data (9 months and 12 months post-treatment, respectively) instead of post-treatment data of these 2 studies were merged with the post-treatment data of the other 5 studies in 1 "post-treatment" meta-analyses. Only 1 other study provided follow-up data on school absence,[32] and, thus, no meta-analyses was performed on follow-up data as regards school absence.

We were not able to obtain all outcome data from 5 studies eligible for meta-analyses.[30,31,33-35] For 2 studies[30,33] we imputed the SDs reported by other studies with similar populations.[36,37] This has been shown to be a valid approach for missing SDs in meta-analysis.[38] For 1 study,[39] we imputed the SDs at follow-up from SDs reported post-treatment. From 1 study, we could only include follow-up data for the outcome symptom load.[31] Another study could not be included in any of the analyses because outcome data of our interest were assessed, but not reported in the article.[35]

### Risk of Bias Across Studies

By use of meta-regression, we investigated if a low risk vs an unclear or high risk of bias on one of the 5 domains of the Cochrane risk of bias tool influenced the outcomes. Potential publication bias was visualized in funnel plots.

### Statistical Analyses

We used inverse variance weighted random effects meta-regression in SPSS (SPSS Inc, Chicago, Illinois) estimated with restricted maximum likelihood, to explore heterogeneity.[40] The following characteristics were investigated as potential predictors of effect-sizes: symptom type, children (<13) vs adolescents (≥13), symptom duration, and treatment dose.

We first investigated if the effect of treatments on symptom load post-treatment differed for 3 functional somatic symptom clusters. We compared studies investigating abdominal symptoms (eg, abdominal pain and irritable bowel syndrome) vs fatigue vs pains (tension-type headache and musculoskeletal pain were lumped together because of the low numbers in these groups). These chosen symptom clusters derived from clinical practice and factor analyses in general populations.[5,6,12-17] Second, we investigated if effect-sizes of treatments on symptom load post-treatment differed for children (≤12) vs adolescents (≥13). These predictors were all separately entered as dummies into the model.

For calculations of the dose of treatment, we included all sessions provided by the therapist, and when reported also the hours invested in the treatment by the participant at home. When duration of the sessions was not reported, we assumed it to be around 45 minutes based on the mean duration per session across the studies we included (range of duration of a session: 15-90 minutes). Both dose of treatment and duration of symptoms were entered as a continuous variable into the model.

We originally intended to investigate the effects of symptom severity and treatment content on effect-sizes. Yet, none of the studies provided a clear indication on how severely ill their sample was in terms of baseline scores in outcome measures (ie, clinical relevance of the baseline scores) or for example existing comorbidities. The content and procedures of treatments investigated was very diverse, even when labeled as the same type (eg, CBT). Hence, we could not group studies based on these characteristics. Instead, we have provided a detailed overview of treatment characteristics in **Table I** (available at www.jpeds.com).

## Results

The selection process of studies is shown in **Figure 1**. Our search in 5 electronic databases resulted in 2520 unique records whereof 2461 were excluded after reviewing their titles and abstracts (Kappa of initial agreement = 0.92, 95% CI [0.88, 0.97]). The remaining full texts of 62 records were examined. An additional 3 full-text records were identified from reviews,[6,7,58-70] whereof 1 additional study was included.[33] In total, 32 records of 27 original studies were included in this review (Kappa of initial agreement = 0.77, 95% CI [0.62, 0.93]).[30-37,39,41-57,71-76] Screening of the references of all included studies did not reveal any additional records.

Four studies were included for descriptive purposes but not included in meta-analyses because a psychological treatment was compared with another active treatment: physiotherapy,[71] fiber supplements,[45] another format of the same psychological intervention,[43] and a multidisciplinary treatment.[57] A fifth study could not be included in any of the analyses because relevant outcome data were not reported in the article.[35]

### Study Characteristics

**Participants.** The characteristics of all 27 studies are shown in **Table II** (available at www.jpeds.com). Most studies were performed in the US (9/27), The Netherlands (5/27), or Sweden (5/27). Studies focused on functional abdominal symptoms (12/27), chronic fatigue syndrome (6/27), tension-type headache (4/27), fibromyalgia (2/27), or mixed pain complaints (3/27). Inclusion and exclusion criteria were described by all studies, but it often remained unclear how these criteria were exactly assessed. Duration of symptoms ranged from 7 to 44 months. The age of the included participants ranged from 6 to 18 years. Seven studies included predominantly children (6-12 years of age) whereas 13 studies included predominantly adolescents (13-18 years of age). Two of these studies actually reported mean ages of 13.6 and 13.9 years but were considered

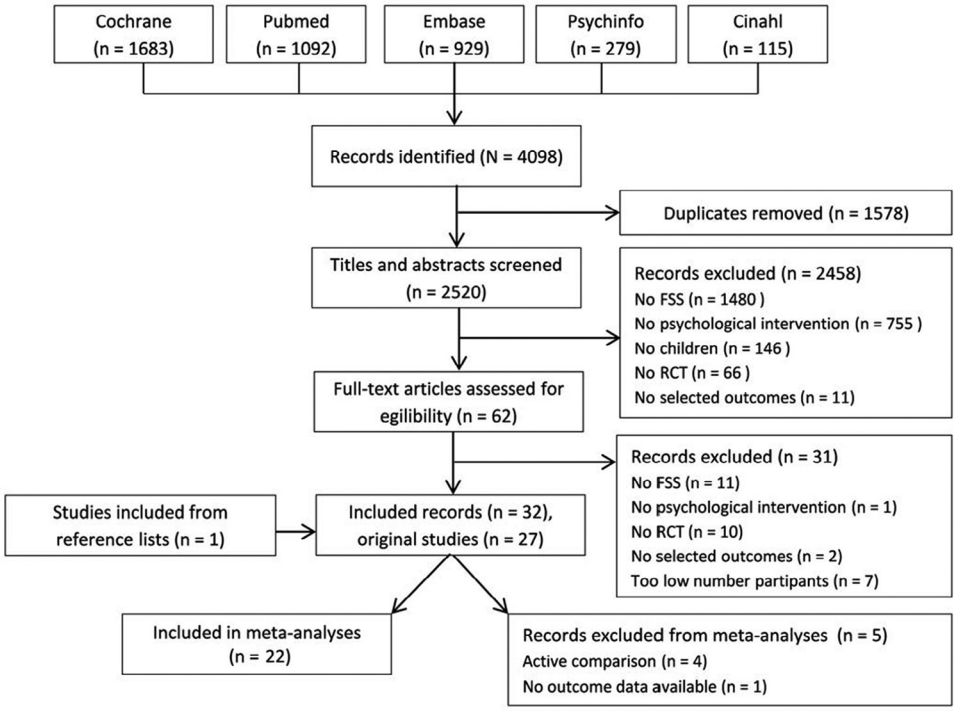


**Figure 1.** Study selection. *FSS*, functional somatic symptoms; *RCT*, randomized controlled trial.

to be studies in adolescents because of their small SDs and/or reported age ranges. We received outcome data separately for the 2 age groups from 2 studies.[37,48] The remaining 5 studies reported a mean age between 11.7 and 13.3 years and could, thus, not be labeled as either child or adolescent studies for meta-regression analysis. In general, more female than male participants were included (range: 50%-100% female). Seven studies assessed some potential psychiatric or somatic comorbidities of their included participants. When comorbidities were assessed they were often an exclusion criterion. The number of randomized participants in each study ranged from 24 to 273.

**Outcomes.** Pain was often measured by use of daily diaries assessing pain intensity (13/27). Some studies constructed indexes from several pain characteristics (eg, frequency, duration) (2/27), or used (some items of) the abdominal pain index (3/27).[77] The sample duration of the diary and ways of calculating mean scores of the diary period differed per study. Most studies in chronic fatigued adolescents used the self-reported Checklist Individual Strength-20 (4/27).[78] Studies measured disability with questionnaires assessing disease-related impairment such as the functional disability inventory (7/27),[79] or with physical functioning subscales of various quality of life questionnaires. School absence/presence was assessed by asking the child/parents, or calculated from school records over various time frames (**Table II**). Unfortunately, instruments used were not validated in a pediatric population, and also the handling of missing values in diaries generally remained unclear.

**Quality.** Summed quality ratings (range: 0-44) of included studies and their provided treatments were assessed with the psychotherapy outcome study rating scale[29] (**Appendix**). Scores ranged from 9 to 31 (possible range: 0-42). In general, studies with high quality scores used more precise and/or validated outcome measures than lower scoring studies, described their control condition more precisely, had a longer follow-up period and provided standardized or manualized treatments by experienced and trained therapists who were checked/supervised during the study.

**Treatments and Controls.** The characteristics of the treatments studied in the 27 included studies are shown in **Table I**; 15 studies investigated the effect of CBT based treatments. These treatments differed considerably in their actual delivery and duration. Some common ways of delivery were solely face-to-face sessions in a hospital clinic (14/27), and audio-, video-, or web-based treatments (9/27).

Control groups were waiting list conditions (7/27), CAU (9/27), placebo conditions (7/27), and active treatments (4/27) (the latter were not included in meta-analyses). The actual content of CAU and placebo was poorly described in most studies. Various placebo conditions were introduced which in general tried to equal for attention and time investment with an unstructured intervention missing key elements and feedback moments considered important for the main intervention to work. In general, there was no clear description on concomitant psychological treatments or medication use reported by participants in both intervention and control conditions.

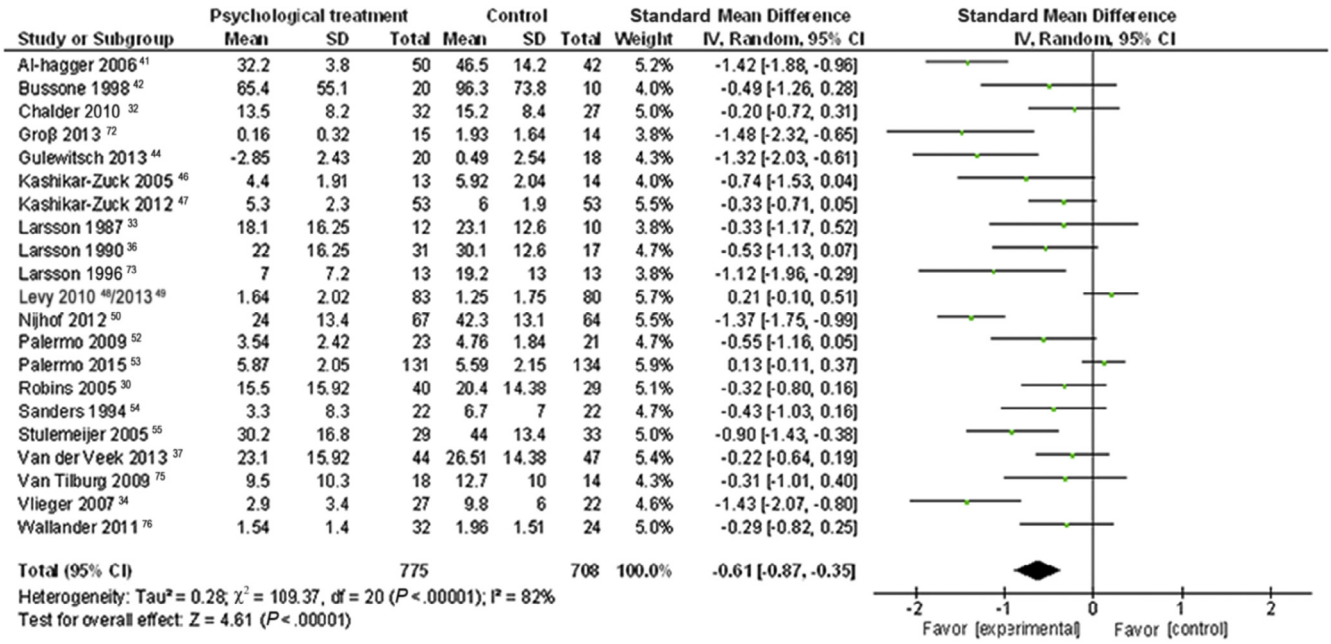


**Figure 3.** Effect of psychological treatment on symptom load post-treatment. The negative mean reported by Gulewitsch et al is a constructed value based on the centered means of diary scores on duration, frequency, and pain intensity. *IV*, inverse variance.

**Treatment Details.** Most treatments were delivered in specialized clinics (14/27), but 8/27 studies where mainly home based. The therapy was (partly) family based in 8/27 and solely group based in 3/27 studies. The duration of treatments ranged from approximately 1 hour to 18 months. The range of the (calculated) treatment dose was 1-38 hours. Most studies (19/27) concerned a manualized, protocol based, or piloted intervention. Yet, the actual rationale for treatment duration or dose, actual content of the therapy, and precise procedures were often not elaborated upon or published. Providers of the therapy were often psychologists, psychiatrists and/or psychotherapists (14/27), but also students, researchers, nurses, and pediatricians treated patients. The experience and training of the providers, and quality/adherence checks of the treatment content they delivered, were not clearly reported. Adherence of the participants to treatment was also only assessed in a minority of the studies (8/27). A detailed description of the delivered treatments is shown in **Table I**.

## Risk of Bias within Studies

The risk of bias for each study is presented in **Figure 2** (available at www.jpeds.com). Because blinding of participants with regard to psychological interventions is generally not possible and in most studies self-reported measures were used to assess the outcomes investigated in this review, most studies scored a "high risk" in the "blinding of outcome assessors" domain. In 2 studies, outcomes were assessed by blinded investigators, or participants self-reported outcomes but were unaware of their allocation (internet based treatment with placebo condition). These studies were rated as low risk. In addition, many studies scored an "unclear risk" on the selective reporting domain.

## Synthesis of Results

**Main Analyses.** All 22 studies that investigated the effect of a psychological treatment versus a waiting list condition, CAU or placebo (ie, eligible for meta-analyses) assessed symptom load. Fourteen of these studies assessed disability measured as symptom related impairments or problems with physical functioning, and 7 studies reported school absence as a measure of disability.

Twenty-one instead of 22 studies were included in our post-treatment meta-analyses because from 1 study post-treatment data were not available.[31] Psychological treatment had a significant effect on symptom load post-treatment (**Figure 3**), symptom load at follow-up (**Figure 4**: 14 studies, 1046 participants, Hedges g = –0.38 95% CI [–0.63, –0.12], $I^2$ = 73%), disability post-treatment (**Figure 5**), disability at follow-up (**Figure 6**: 8 studies, 796 participants, Hedges g = –0.31 95% CI [–0.56, –0.07], $I^2$ = 62%), and school absence "post-treatment"' (**Figure 7**), when compared with waiting list, CAU, or placebo. Please note that the data from 2 of the 7 studies included in the school absence post-treatment analyses were actually follow-up outcomes.[30,31] Post-hoc analyses revealed a slightly higher estimate when these 2 studies were left out (Hedges g = –0.66 95% CI [–1,11, –0.22], $I^2$ = 75%).

**Risk of Bias.** The funnel plots displayed in **Figures 8-12** (available at www.jpeds.com) show asymmetry and, thus, indicates publication bias; negative findings with high standard

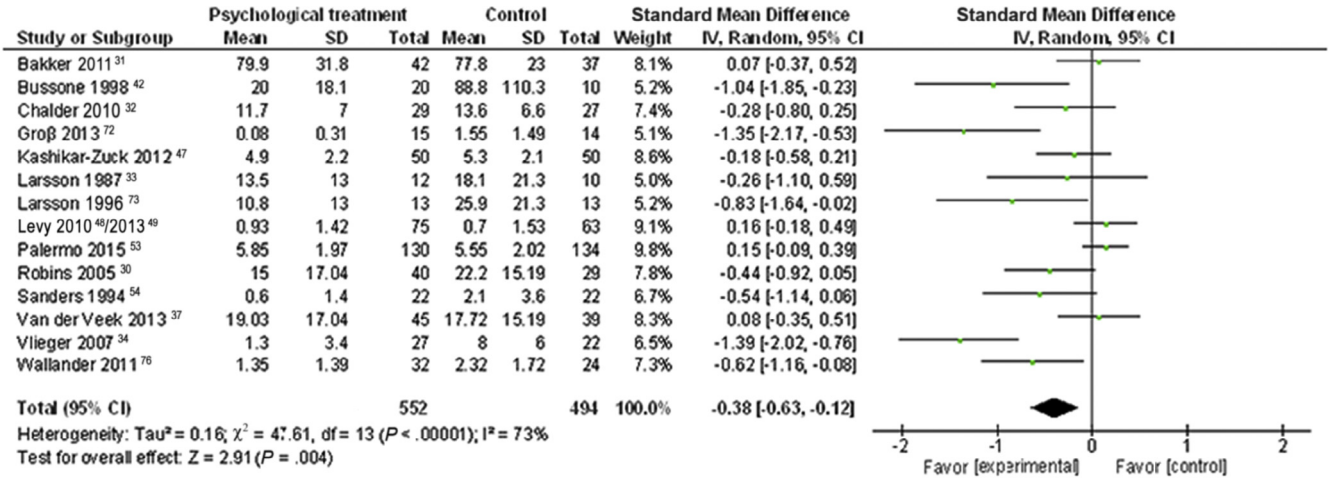


**Figure 4.** Effect of psychological treatment on symptom load at follow-up.

errors seem to be underrepresented in our review. Meta-regression based on our Cochrane risk of bias assessment revealed no influence of an unclear/high risk of bias on effectiveness of psychological therapies on symptom load post-treatment (randomization: B = –0.13, 95% CI [–0.39, 0.66], allocation concealment: B = –0.26, 95% CI [–0.71, 0.20], blinding: B = –0.003, 95% CI [–0.776, 0.770], incomplete data: B = –0.14, 95% CI [–0.39, 0.66], selective reporting: B = –0.03, 95% CI [–0.52, 0.46]).

**Explaining Heterogeneity.** The effect of psychological treatments on symptom load post-treatment stratified by symptom cluster is shown in **Figure 13** (available at www.jpeds.com). The effect-estimate of psychological treatments was the highest for fatigued children. Yet, the effect of psychological treatment on post-treatment symptom load was not significantly different for the different clusters of symptoms (abdominal symptoms vs other symptoms: n = 20, B = –0.049, 95% CI [–0.500, 0.405], chronic fatigue vs other symptoms: n = 20, B = –0.32, 95% CI [–0.896, 0.144]), pain vs other symptoms: n = 20, B = 0.32, 95% CI [–0.120, 0.775]). One study was not included in this analysis because 50% of the participants suffered from abdominal symptoms and the remainder of other symptoms.[52]

The effect-sizes of psychological treatments on symptom load stratified by age category, as shown in **Figure 14** (available at www.jpeds.com), were similar for children and adolescents. Indeed, the age category of participants did not significantly influence outcomes (adolescents vs children: n = 18, B = 0.10, 95% CI [–0.41, 0.60]). Duration of symptoms had also no effect on findings (longer symptom duration: n = 13, B = 0.01, 95% CI [–0.01, 0.04]).

The effect-sizes of psychological treatments ordered based on the treatment dose are shown in **Figure 15** (available at

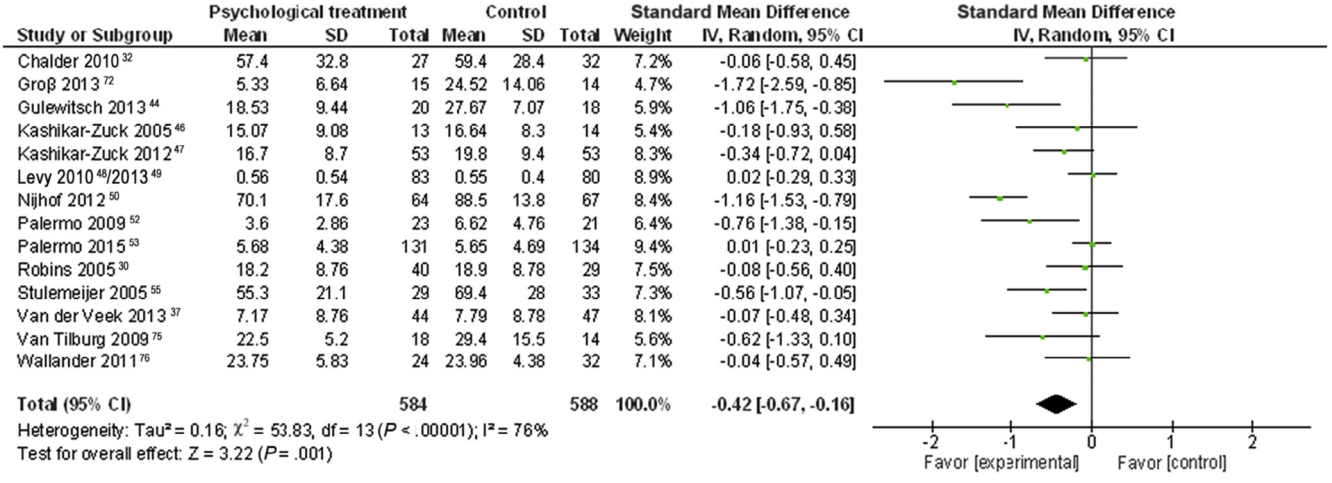


**Figure 5.** Effect of psychological treatment on disability post-treatment.

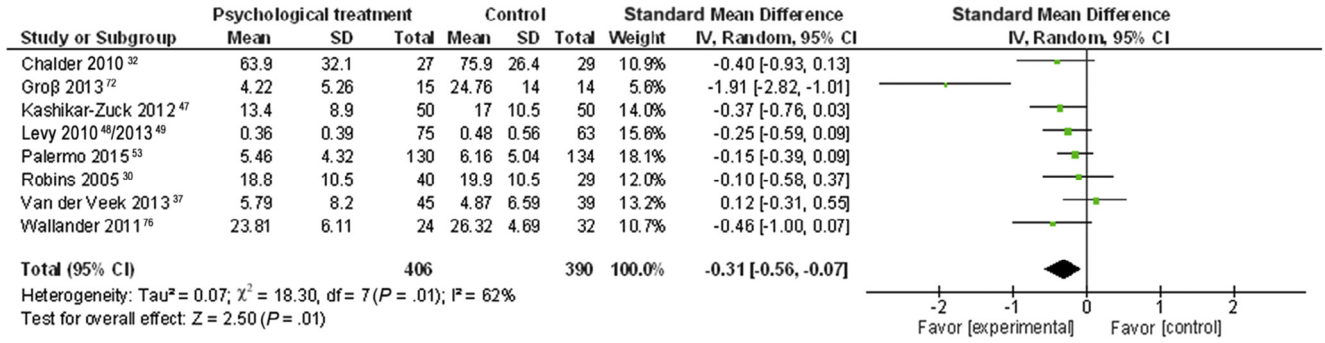


**Figure 6.** Effect of psychological treatment on disability at follow-up.

www.jpeds.com), and suggest a relation between higher treatment dose and better outcomes. Yet, the effect of treatment on the found effect-size post-treatment was not significant (higher treatment dose: n = 21, B = −0.02, 95% CI [−0.05, 0.001]). Five of the 21 studies included in this analysis did not report the exact duration of treatment sessions.[36,41,46,50,55] Please note that for these studies, we imputed a session duration of 45 minutes (the mean duration of sessions across studies). Post-hoc meta-regression without these 5 studies revealed a similar estimate.

## Discussion

Meta-analyses showed that psychological treatments improved symptom load, disability, and school attendance in children and adolescents suffering from various functional somatic symptoms including functional abdominal symptoms, fatigue, tension-type headache, and musculoskeletal pains. Heterogeneity between studies in found effect-sizes remained unexplained by the type and duration of symptoms, the age of the participants, and the treatment dose, although the latter approached significance.

Two previous reviews found that face-to-face psychological treatments improved symptom load and disabilities in children with chronic pain complaints (including pain because of medically well-defined diseases) post-treatment but, except for headaches, not at follow-up.[7,58] We found that for children with functional somatic symptom effects of psychological treatments on symptom load were maintained at follow-up. In addition, our analyses showed that psychological therapies were also beneficial for disability and school attendance post-treatment and at follow-up in children with functional somatic symptoms. This could indicate that psychological treatments are especially effective for functional somatic symptoms as opposed to chronic pain because of a medically well-defined disease such as juvenile rheumatoid arthritis. Overall, the effect-sizes we found on symptom load post-treatment were comparable to earlier findings in children with pain[7,58] but somewhat larger than estimates reported in adult populations with functional somatic symptoms.[19,80] This may indicate that children and adolescents are more susceptible to psychological treatments than adults or could be a reflection of less chronic and/or severe functional somatic symptoms in children as opposed to adults.

Unfortunately, it remains largely unclear who benefits most from psychological treatment. We were not able to explain heterogeneity in findings between studies; type of functional somatic symptoms age of participants, treatment dose, and duration of symptoms did not influence results. Two reviews showed that a higher treatment dose was more effective for headaches in children and low back pain in adults, but optimal

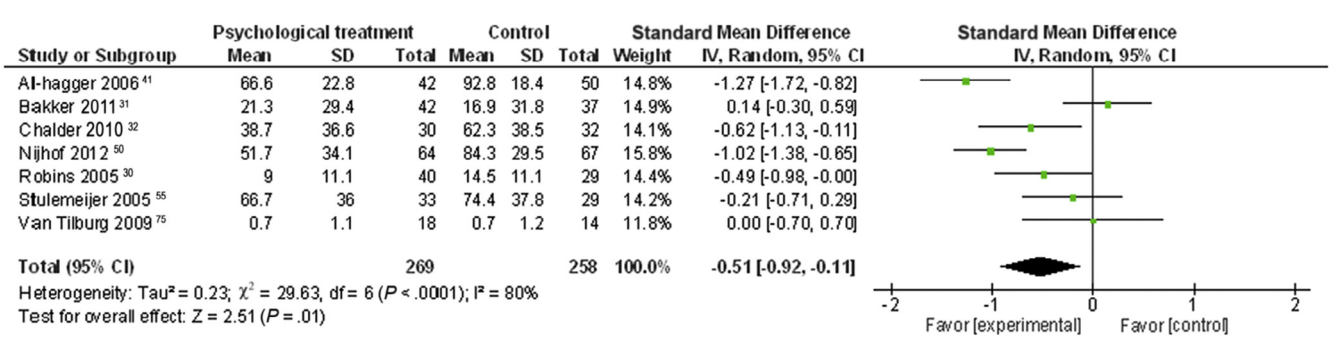


**Figure 7.** Effect of psychological treatment on school absence post-treatment.

doses could not be established.[59,81] Remotely delivered treatments have been shown to improve symptom load post-treatment but not disabilities, while face-to-face treatments improved both symptom load and disabilities.[7,58] However, only 6 studies were included in this review, and, thus, it is very likely that further trials will change these findings. One other review found that therapist skills and treatment frequency, but not symptom load, intervention duration, and study quality, had a significant effect on symptoms post-treatment in adults.[80] These nonsignificant findings seem counterintuitive; if chronicity of symptoms and treatment duration are not important, every child with functional somatic symptoms could be treated with any short intervention. However, the reason that we, and other reviews, were not able to identify specific sources of statistical heterogeneity in our meta-analyses was probably because most studies were unique in their combination of included participants and delivered treatment. For example, type of functional somatic symptoms, inclusion criteria, age of participants, duration of symptoms, type, setting, dose and procedures of treatment, and experience of therapists all differed considerably between studies. In addition, most studies did not qualify the severity of symptoms and did not report on the presence of comorbidities. This means that when we investigated one potential predictor other potential sources of heterogeneity also varied or were just unknown.

When interpreting the results some limitations should be kept in mind. As mentioned we found substantial heterogeneity in effect-sizes between studies, which could not be explained by the meta-regressions we performed. In addition, outcome measures for the constructs symptoms load, disability, and school absence varied among studies. Moreover, many instruments used were not validated for the included participants. Further, when interpreting effect sizes it should be acknowledged that our funnel plots indicated publication bias. Together with the unexplained heterogeneity and variety in outcome measures, this means that the found effect-sizes may overestimate the real effect and should thus be interpreted with caution.

Our study also has several methodological strengths. We conducted a broad search in 5 databases. Study selection, data-extraction, risk of bias, and quality assessments were independently done by 2 researchers. We included studies, which investigated psychological treatments for various types of functional somatic symptoms including abdominal symptoms and fatigue. Previous reviews did only focus on chronic pains and did not differentiate between functional somatic symptoms and medically well-defined diseases. We described the included studies and their treatments for functional somatic symptoms in children in detail and were, thus, provided a comprehensive overview of evidence based psychological treatments for children with functional somatic symptoms. The detailed data extraction also enabled us to explore potential moderators of the effectiveness of psychological treatments on functional somatic symptoms.

In future research, treatments should be clearly described and manualized. The working elements of treatments can only be identified if authors clarify why specific components are incorporated in their treatment. Ideally, treatments should be compared with placebo conditions in which those key components are missing. Collaborations between specialized centers and sharing of treatment protocols and materials would make it easier to build on to each other's work. It should also be explored how treatments can best be implemented. Some obvious treatment characteristics that might be interesting to compare in future interventional research are treatment setting and dose, involvement of family members and qualification and training of therapists. Especially more insight into the influence of treatment setting (ie, clinic-based vs remotely delivered) is relevant in terms of the accessibility and cost-effectiveness of future treatments. Further, it would be interesting to evaluate which child characteristics influence the effectiveness of treatments. We found no evidence that type of symptoms influenced the effectiveness of therapies. Chronicity and severity of symptoms, or presence of comorbidities, might actually be more important for treatment outcomes. For example, symptoms of anxiety and depression are prevalent in children with functional somatic symptoms and can predict the course of functional somatic symptoms.[24] Therefore, it seems relevant to assess and treat children with comorbidities instead of excluding those children. Another key issue is what outcome measures should be used and how outcomes should be interpreted. Some studies already chose validated instruments, verified results with parental questionnaires, and/or added more objective measures such as medication and health care use. Yet, it seemed generally unknown what the minimal clinical relevant change on instruments was, which makes it still hard to interpret outcomes.

Once specific treatment elements and child characteristics important for targeting and improving outcomes can be identified, treatments will probably become more tailored for the individual patient and thereby more effective. ■

Submitted for publication Sep 4, 2016; last revision received Jan 3, 2017; accepted Mar 7, 2017

Reprint requests: Irma J. Bonvanie, MD, Interdisciplinary Center Psychopathology and Emotion Regulation, University Medical Center Groningen, CC 72, PO Box 30001, Groningen 9700 RB, The Netherlands. E-mail: i.j.bonvanie@umcg.nl

## References

1. Janssens KA, Klis S, Kingma EM, Oldehinkel AJ, Rosmalen JG. Predictors for persistence of functional somatic symptoms in adolescents. J Pediatr 2014;164:900-5, e2.
2. Rask CU, Olsen EM, Elberling H, Christensen MF, Ornbol E, Fink P, et al. Functional somatic symptoms and associated impairment in 5-7-year-old children: the Copenhagen Child Cohort 2000. Eur J Epidemiol 2009;24:625-34.
3. Mallen C, Peat G, Thomas E, Croft P. Severely disabling chronic pain in young adults: prevalence from a population-based postal survey in North Staffordshire. BMC Musculoskelet Disord 2005;6:42.
4. Hoftun GB, Romundstad PR, Zwart JA, Rygg M. Chronic idiopathic pain in adolescence—high prevalence and disability: the young HUNT Study 2008. Pain 2011;152:2259-66.
5. Rutten JM, Korterink JJ, Venmans LM, Benninga MA, Tabbers MM. Nonpharmacologic treatment of functional abdominal pain disorders: a systematic review. Pediatrics 2015;135:522-35.

6. Knight SJ, Scheinberg A, Harvey AR. Interventions in pediatric chronic fatigue syndrome/myalgic encephalomyelitis: a systematic review. J Adolesc Health 2013;53:154-65.
7. Eccleston C, Palermo TM, Williams AC, Lewandowski HA, Morley S, Fisher E, et al. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. Cochrane Database Syst Rev 2014;5:CD003968.
8. Fink P, Toft T, Hansen MS, Ornbol E, Olesen F. Symptoms and syndromes of bodily distress: an exploratory study of 978 internal medical, neurological, and primary care patients. Psychosom Med 2007;69:30-9.
9. Schroder A, Fink P. Functional somatic syndromes and somatoform disorders in special psychosomatic units: organizational aspects and evidence-based treatment. Psychiatr Clin North Am 2011;34:673-87.
10. Fink P, Schroder A. One single diagnosis, bodily distress syndrome, succeeded to capture 10 diagnostic categories of functional somatic syndromes and somatoform disorders. J Psychosom Res 2010;68:415-26.
11. Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? Lancet 1999;354:936-9.
12. Essau CA, Olaya B, Bokszczanin A, Gilvarry C, Bray D. Somatic symptoms among children and adolescents in Poland: a confirmatory factor analytic study of the children somatization inventory. Front Public Health 2013;1:72.
13. Litcher L, Bromet E, Carlson G, Gilbert T, Panina N, Golovakha E, et al. Ukrainian application of the Children's Somatization Inventory: psychometric properties and associations with internalizing symptoms. J Abnorm Child Psychol 2001;29:165-75.
14. Vila M, Kramer T, Hickey N, Dattani M, Jefferis H, Singh M, et al. Assessment of somatic symptoms in British secondary school children using the Children's Somatization Inventory (CSI). J Pediatr Psychol 2009;34:989-98.
15. Meesters C, Muris P, Ghys A, Reumerman T, Rooijmans M. The Children's Somatization Inventory: further evidence for its reliability and validity in a pediatric and a community sample of Dutch children and adolescents. J Pediatr Psychol 2003;28:413-22.
16. Garber J, Walker LS, Zeman J. Somatization symptoms in a community sample of children and adolescents: further validation of the Children's Somatization Inventory. Psychol Assessment 1991;3:588-95.
17. Eccleston C, Palermo TM, Williams AC, Lewandowski Holley A, Morley S, Fisher E, et al. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. Cochrane Database Syst Rev 2014;5:CD003968.
18. Henningsen P, Zipfel S, Herzog W. Management of functional somatic syndromes. Lancet 2007;369:946-55.
19. van Dessel N, den Boeft M, van der Wouden JC, Kleinstauber M, Leone SS, Terluin B, et al. Non-pharmacological interventions for somatoform disorders and medically unexplained physical symptoms (MUPS) in adults. Cochrane Database Syst Rev 2014;11:CD011142.
20. Schroder A, Rehfeld E, Ornbol E, Sharpe M, Licht RW, Fink P. Cognitive-behavioural group treatment for a range of functional somatic syndromes: randomised trial. Br J Psychiatry 2012;200:499-507.
21. Walker LS, Beck JE, Garber J, Lambert W. Children's Somatization Inventory: psychometric properties of the revised form (CSI-24). J Pediatr Psychol 2009;34:430-40.
22. Perquin CW, Hazebroek-Kampschreur AA, Hunfeld JA, Bohnen AM, van Suijlekom-Smit LW, Passchier J, et al. Pain in children and adolescents: a common experience. Pain 2000;87:51-8.
23. Bonvanie IJ, van Gils A, Janssens KA, Rosmalen JG. Sexual abuse predicts functional somatic symptoms: An adolescent population study. Child Abuse Negl 2015;46:1-7.
24. Janssens KA, Rosmalen JG, Ormel J, van Oort FV, Oldehinkel AJ. Anxiety and depression are risk factors rather than consequences of functional somatic symptoms in a general population of adolescents: the TRAILS study. J Child Psychol Psychiatry 2010;51:304-12.
25. Janssens KA, Oldehinkel AJ, Dijkstra JK, Veenstra R, Rosmalen JG. School absenteeism as a perpetuating factor of functional somatic symptoms in adolescents: the TRAILS study. J Pediatr 2011;159:988-93, e1.
26. Schroder A, Sharpe M, Fink P. Medically unexplained symptom management. Lancet Psychiatry 2015;2:587-8.
27. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014;348:g1687.
28. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
29. Ost LG. Efficacy of the third wave of behavioral therapies: a systematic review and meta-analysis. Behav Res Ther 2008;46:296-321.
30. Robins PM, Smith SM, Glutting JJ, Bishop CT. A randomized controlled trial of a cognitive-behavioral family intervention for pediatric recurrent abdominal pain. J Pediatr Psychol 2005;30:397-408.
31. Bakker RJ, van de Putte EM, Kuis W, Sinnema G. Effects of an educational video film in fatigued children and adolescents: a randomised controlled trial. Arch Dis Child 2011;96:457-60.
32. Chalder T, Deary V, Husain K, Walwyn R. Family-focused cognitive behaviour therapy versus psycho-education for chronic fatigue syndrome in 11- to 18-year-olds: a randomized controlled treatment trial. Psychol Med 2010;40:1269-79.
33. Larsson B, Melin L, Lamminen M, Ullstedt F. A school-based treatment of chronic headaches in adolescents. J Pediatr Psychol 1987;12:553-66.
34. Vlieger AM, Menko-Frankenhuis C, Wolfkamp SC, Tromp E, Benninga MA. Hypnotherapy for children with functional abdominal pain or irritable bowel syndrome: a randomized controlled trial. Gastroenterology 2007;133:1430-6.
35. Duarte MA, Penna FJ, Andrade EM, Cancela CS, Neto JC, Barbosa TF. Treatment of nonorganic recurrent abdominal pain: cognitive-behavioral family intervention. J Pediatr Gastroenterol Nutr 2006;43:59-64.
36. Larsson B, Melin L, Döberl A. Recurrent tension headache in adolescents treated with self-help relaxation training and a muscle relaxant drug. Headache 1990;30:665-71.
37. Veek SM, Derkx BH, Benninga MA, Boer F, Haan E. Cognitive behavior therapy for pediatric functional abdominal pain: a randomized controlled trial. Pediatrics 2013;132:e1163-72.
38. Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. J Clin Epidemiol 2006;59:7-10.
39. Vlieger AM, Rutten JMTM, Govers AMAP, Frankenhuis C, Benninga MA. Long-term follow-up of gut-directed hypnotherapy vs. standard care in children with functional abdominal pain or irritable bowel syndrome. Am J Gastroenterol 2012;107:627-31.
40. Wilson DB. Meta-analysis macros for SAS, SPSS, and Stata. 2006. http://mason.gmu.edu/~dwilsonb/ma.html. Accessed February 19, 2016.
41. Al-Haggar MS, Al-Naggar ZA, Abdel-Salam MA. Biofeedback and cognitive behavioral therapy for Egyptian adolescents suffering from chronic fatigue syndrome. J Pediatr Neurol 2006;4:161-9.
42. Bussone G, Grazzi L, D'Amico D, Leone M, Andrasik F. Biofeedback-assisted relaxation training for young adolescents with tension-type headache: a controlled study. Cephalalgia 1998;18:463-7.
43. van Geelen SM, Fuchs CE, Sinnema G, van de Putte EM, van Geel R, Hermans HJ, et al. Self-investigation in adolescent chronic fatigue syndrome: narrative changes and health improvement. Patient Educ Couns 2011;83:227-33.
44. Gulewitsch MD, Muller J, Hautzinger M, Schlarb AA. Brief hypnotherapeutic-behavioral intervention for functional abdominal pain and irritable bowel syndrome in childhood: a randomized controlled trial. Eur J Pediatr 2013;172:1043-51.
45. Humphreys PA, Gevirtz RN. Treatment of recurrent abdominal pain: components analysis of four treatment protocols. J Pediatr Gastroenterol Nutr 2000;31:47-51.
46. Kashikar-Zuck S, Swain NF, Jones BA, Graham TB. Efficacy of cognitive-behavioral intervention for juvenile primary fibromyalgia syndrome. J Rheumatol 2005;32:1594-602.
47. Kashikar-Zuck S, Ting TV, Arnold LM, Bean J, Powers SW, Graham TB, et al. Cognitive behavioral therapy for the treatment of juvenile fibromyalgia: a multisite, single-blind, randomized, controlled clinical trial. Arthritis Rheum 2012;64:297-305.

48. Levy RL, Langer SL, Walker LS, Romano JM, Christie DL, Youssef N, et al. Cognitive-behavioral therapy for children with functional abdominal pain and their parents decreases pain and other symptoms. Am J Gastroenterol 2010;105:946-56.
49. Levy RL, Langer SL, Walker LS, Romano JM, Christie DL, Youssef N, et al. Twelve-month follow-up of cognitive behavioral therapy for children with functional abdominal pain. JAMA Pediatr 2013;167:178-84.
50. Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. Lancet 2012;379:1412-8.
51. Nijhof SL, Priesterbach LP, Uiterwaal CSPM, Bleijenberg G, Kimpen JLL, Putte EM. Internet-based therapy for adolescents with chronic fatigue syndrome: long-term follow-up. Pediatrics 2013;131:e1788-95.
52. Palermo TM, Wilson AC, Peters M, Lewandowski A, Somhegyi H. Randomized controlled trial of an Internet-delivered family cognitive-behavioral therapy intervention for children and adolescents with chronic pain. Pain 2009;146:205-13.
53. Palermo TM, Law EF, Fales J, Bromberg MH, Jessen-Fiddick T, Tai G. Internet-delivered cognitive-behavioral treatment for adolescents with chronic pain and their parents: a randomized controlled multicenter trial. Pain 2015;157:174-85.
54. Sanders MR, Shepherd RW, Cleghorn G, Woolford H. The treatment of recurrent abdominal pain in children: a controlled comparison of cognitive-behavioral family intervention and standard pediatric care. J Consult Clin Psychol 1994;62:306-14.
55. Stulemeijer M, de Jong LW, Fiselier TJ, Hoogveld SW, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. BMJ 2005;330:14.
56. Knoop H, Stulemeijer M, De JL, Fiselier TJW, Bleijenberg G. Efficacy of cognitive behavioral therapy for adolescents with chronic fatigue syndrome: long-term follow of a randomized, controlled trial. Pediatrics 2008;121:e619-25.
57. Wicksell RK, Melin L, Lekander M, Olsson GL. Evaluating the effectiveness of exposure and acceptance strategies to improve functioning and quality of life in longstanding pediatric pain–a randomized controlled trial. Pain 2009;141:248-57.
58. Fisher E, Law E, Palermo TM, Eccleston C. Psychological therapies (remotely delivered) for the management of chronic and recurrent pain in children and adolescents. Cochrane Database Syst Rev 2015;3:CD011118.
59. Fisher E, Heathcote L, Palermo TM, de C Williams AC, Lau J, Eccleston C. Systematic review and meta-analysis of psychological therapies for children with chronic pain. J Pediatr Psychol 2014;39:763-82.
60. Hechler T, Kanstrup M, Holley AL, Simons LE, Wicksell R, Hirschfeld G, et al. Systematic review on intensive interdisciplinary pain treatment of children with chronic pain. Pediatrics 2015;136:115-27.
61. Holden EW, Deichmann MM, Levy JD. Empirically supported treatments in pediatric psychology: recurrent pediatric headache. J Pediatr Psychol 1999;24:91-109.
62. Huertas-Ceballos A, Logan S, Bennett C, Macarthur C. Psychosocial interventions for recurrent abdominal pain (RAP) and irritable bowel syndrome (IBS) in childhood. Cochrane Database Syst Rev 2008;1:CD003014.
63. Janicke DM. Finnev JW. Empirically supported treatments in pediatric psychology: recurrent abdominal pain. J Pediatr Psychol 1999;24:115-27.
64. Larsson B, Carlsson J, Fichtel Å, Melin L. Relaxation treatment of adolescent headache sufferers: results from a school-based replication series. Headache 2005;45:692-704.
65. Palermo TM, Eccleston C, Lewandowski AS, Williams AC, Morley S. Randomized controlled trials of psychological therapies for management of chronic pain in children and adolescents: an updated meta-analytic review. Pain 2010;148:387-97.
66. Rutten JMTM, Korterink JJ, Venmans LMAJ, Benninga MA, Tabbers MM. Nonpharmacologic treatment of functional abdominal pain disorders: a systematic review. Pediatrics 2015;135:522-35.
67. Rutten JM, Reitsma JB, Vlieger AM, Benninga MA. Gut-directed hypnotherapy for functional abdominal pain or irritable bowel syndrome in children: a systematic review. Arch Dis Child 2013;98:252-7.
68. Trautmann E, Lackschewitz H, Kröner-Herwig B. Psychological treatment of recurrent headache in children and adolescents—a meta-analysis. Cephalalgia 2006;26:1411-26.
69. Velleman S, Stallard P, Richardson T. A review and meta-analysis of computerized cognitive behaviour therapy for the treatment of pain in children and adolescents. Child Care Health Dev 2010;36:465-72.
70. Weydert JA, Ball TM, Davis MF. Systematic review of treatments for recurrent abdominal pain. Pediatrics 2003;111:e1-11.
71. Alfvén G, Lindstrom A. A new method for the treatment of recurrent abdominal pain of prolonged negative stress origin. Acta Paediatr 2007;96:76-81.
72. Groß M, Warschburger P. Evaluation of a cognitive-behavioral pain management program for children with chronic abdominal pain: a randomized controlled study. Int J Behav Med 2013;20:434-43.
73. Larsson B, Carlsson J. A school-based, nurse-administered relaxation training for children with chronic tension-type headache. J Pediatr Psychol 1996;21:603-14.
74. Lloyd S, Chalder T, Rimes KA. Family-focused cognitive behaviour therapy versus psycho-education for adolescents with chronic fatigue syndrome: long-term follow-up of an RCT. Behav Res Ther 2012;50:719-25.
75. van Tilburg MA, Chitkara DK, Palsson OS, Turner M, Blois-Martin N, Ulshen M, et al. Audio-recorded guided imagery treatment reduces functional abdominal pain in children: a pilot study. Pediatrics 2009;124:e890-7.
76. Wallander JL, Madan-Swain A, Klapow J, Saeed S. A randomised controlled trial of written self-disclosure for functional recurrent abdominal pain in youth. Psychol Health 2011;26:433-47.
77. Walker LS, Smith CA, Garber J, Van Slyke DA. Development and validation of the Pain Response Inventory for children. Psychol Assess 1997;9:392-405.
78. Vercoulen JHMM, Swanink CMA, Fennis JFM, Galama JMD, van der Meer JWM, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994;38:383-92.
79. Claar RL, Walker LS. Functional assessment of pediatric pain patients: psychometric properties of the functional disability inventory. Pain 2006;121:77-84.
80. Gerger H, Hlavica M, Gaab J, Munder T, Barth J. Does it matter who provides psychological interventions for medically unexplained symptoms? A meta-analysis. Psychother Psychosom 2015;84:217-26.
81. Waterschoot FP, Dijkstra PU, Hollak N, de Vries HJ, Geertzen JH, Reneman MF. Dose or content? Effectiveness of pain rehabilitation programs for patients with chronic low back pain: a systematic review. Pain 2014;155:179-89.

## Appendix

The psychotherapy outcome study rating scale

1. Clarity of sample description
   - 0 Poor. Vague description of sample (eg, only mentioned whether patients were diagnosed with the disorder).
   - 1 Fair. Fair description of sample (eg, mentioned inclusion/exclusion criteria, demographics, etc).
   - 2 Good. Good description of sample (eg, mentioned inclusion/exclusion criteria, demographics, and the prevalence of comorbid disorders).
2. Severity/chronicity of the disorder
   - 0 Poor. Severity/chronicity was not reported and/or subsyndromal patients were included in the sample.
   - 1 Fair. All patients met the criteria for the disorder. Sample includes acute (<1 year) and/or low severity.
   - 2 Good. Sample consisted entirely of chronic (>1 year) patients of at least moderate severity.
3. Representativeness of the sample
   - 0 Poor. Sample is very different from patients seeking treatment for the disorder (eg, there are excessively strict exclusion criteria).
   - 1 Fair. Sample is somewhat representative of patients seeking treatment for the disorder (eg, patients were only excluded if they met criteria for other major disorders).
   - 2 Good. Sample is very representative of patients seeking treatment for the disorder (eg, authors made efforts to ensure representativeness of sample).
4. Reliability of the diagnosis in question
   - 0 Poor. The diagnostic process was not reported, or not assessed with structured interviews by a trained interviewer.
   - 1 Fair. The diagnosis was assessed with structured interview by a trained interviewer.
   - 2 Good. The diagnosis was assessed with structured interview by a trained interviewer and adequate interrater reliability was demonstrated (eg, kappa coefficient).
5. Specificity of outcome measures
   - 0 Poor. Very broad outcome measures, not specific to the disorder (eg, Symptom CheckList-90R total score).
   - 1 Fair. Moderately specific outcome measures.
   - 2 Good. Specific outcome measures, such as a measure for each symptom cluster.
6. Reliability and validity of outcome measures
   - 0 Poor. Measures have unknown psychometric properties, or properties that fail to meet current standards of acceptability.
   - 1 Fair. Some, but not all measures have known or adequate psychometric properties.
   - 2 Good. All measures have good psychometric properties. The outcome measures are the best available for the authors' purpose.
7. Use of blind evaluators
   - 0 Poor. Blind assessor was not used (eg, assessor was the therapist, assessor was not blind to treatment condition, or the authors do not specify).
   - 1 Fair. Blind assessor was used, but no checks were used to assess the blind.
   - 2 Good. Blind assessor was used in correct fashion. Checks were used to assess whether the assessor was aware of treatment condition.
8. Assessor training
   - 0 Poor. Assessor training and accuracy are not specified, or are unacceptable.
   - 1 Fair. Minimum criterion for assessor training is specified (eg, assessor has had specific training in the use of the outcome measure), but accuracy is not monitored or reported.
   - 2 Good. Minimum criterion of assessor training is specified. Inter-rater reliability was checked, and/or assessment procedures were calibrated during the study to prevent evaluator drift.
9. Assignment to treatment
   - 0 Poor. Biased assignment, eg, patients selected their own therapy or were assigned in another non-random fashion, or there is only one group.
   - 1 Fair. Random or stratified assignment. There may be some systematic bias but not enough to pose a serious threat to internal validity. There may be therapist by treatment confounds. N may be too small to protect against bias.
   - 2 Good. Random or stratified assignment, and patients are randomly assigned to therapists within condition. When theoretically different treatments are used, each treatment is provided by a large enough number of different therapists. N is large enough to protect against bias.
10. Design
    - 0 Poor. Active treatment vs waiting list condition, or briefly described treatment as usual.
    - 1 Fair. Active treatment vs treatment as usual with good description, or placebo condition.
    - 2 Good. Active treatment vs another previously empirically documented active treatment.
11. Power analysis
    - 0 Poor. No power analysis was made prior to the initiation of the study.
    - 1 Fair. A power analysis based on an estimated effect size was used.
    - 2 Good. A data-informed power analysis was made and the sample size was decided accordingly.
12. Assessment points
    - 0 Poor. Only pre- and post-treatment, or pre- and follow-up.
    - 1 Fair. Pre-, post-, and follow-up <1 year.
    - 2 Good. Pre-, post-, and follow-up ≥1 year.
13. Manualized, replicable, specific treatment programs
    - 0 Poor. Description of treatment procedure is unclear, and treatment is not based on a publicly available, detailed treatment manual. Patients may be receiving multiple

forms of treatment at once in an uncontrolled manner.
   1 Fair. Treatment is not designed for the disorder, or description of the treatment is generally clear and based on a publicly available, detailed treatment manual, but there are some ambiguities about the procedure. Patients may have received additional forms of treatment, but this is balanced between groups or otherwise controlled.
   2 Good. Treatment is designed for the disorder. A detailed treatment manual is available, and/or treatment is explained in sufficient detail for replication. No ambiguities about the treatment procedure. Patients receive only the treatment in question.
14. Number of therapists
   0 Poor. Only 1 therapist (ie, complete confounding between therapy and therapist).
   1 Fair. At least 2 therapists, but the effect of therapist on outcome is not analyzed.
   2 Good. Three, or more therapists, and the effect of therapist on outcome is analyzed.
15. Therapist training/experience
   0 Poor. Very limited clinical experience of the treatment and/or disorder (eg, students).
   1 Fair. Some clinical experience of the treatment and/or disorder.
   2 Good. Long clinical experience of the treatment and the disorder (eg, practicing therapists).
16. Checks for treatment adherence
   0 Poor. No checks were made to assure that the intervention was consistent with protocol.
   1 Fair. Some checks were made (eg, assessed a proportion of therapy tapes).
   2 Good. Frequent checks were made (eg, weekly supervision of each session using a detailed rating form).
17. Checks for therapist competence
   0 Poor. No checks were made to assure that the intervention was delivered competently.
   1 Fair. Some checks were made (eg, assessed a proportion of therapy tapes).
   2 Good. Frequent checks were made (eg, weekly supervision of each session using a detailed rating form).
18. Control of concomitant treatments (eg, medications)
   0 Poor. No attempt to control for concomitant treatments, or no information about concomitant treatments provided. Patients may have been receiving other forms of treatment in addition to the study treatment.
   1 Fair. Asked patients to keep medications stable and/or to discontinue other psychological therapies during the treatment.
   2 Good. Ensured that patients did not receive any other treatments (medical or psychological) during the study.
19. Handling of attrition
   0 Poor. Proportions of attrition are not described, or described but no dropout analysis is performed.
   1 Fair. Proportions of attrition are described, and dropout analysis or intent-to-treat analysis is performed.
   2 Good. No attrition, or proportions of attrition are described, dropout analysis is performed, and results are presented as intent-to-treat analysis.
20. Statistical analyses and presentation of results
   0 Poor. Inadequate statistical methods are used and/or data are not fully presented.
   1 Fair. Adequate statistical methods are used but data are not fully presented.
   2 Good. Adequate statistical methods are used and data are presented with M and SD.
21. Clinical significance
   0 Poor. No presentation of clinical significance was done.
   1 Fair. An arbitrary criterion for clinical significance was used and the conditions were compared regarding percent clinically improved.
   2 Good. Jacobson's criteria for clinical significance were used and presented for a selection (or all) of the outcome measures, and conditions were compared regarding percent clinically improved.
22. Equality of therapy hours (for non-waiting list condition designs only)
   0 Poor. Conditions differ markedly (≥20% difference in therapy hours).
   1 Fair. Conditions differ somewhat (10%-19% difference in therapy hours).
   2 Good. Conditions do not differ (<10% difference in therapy hours).

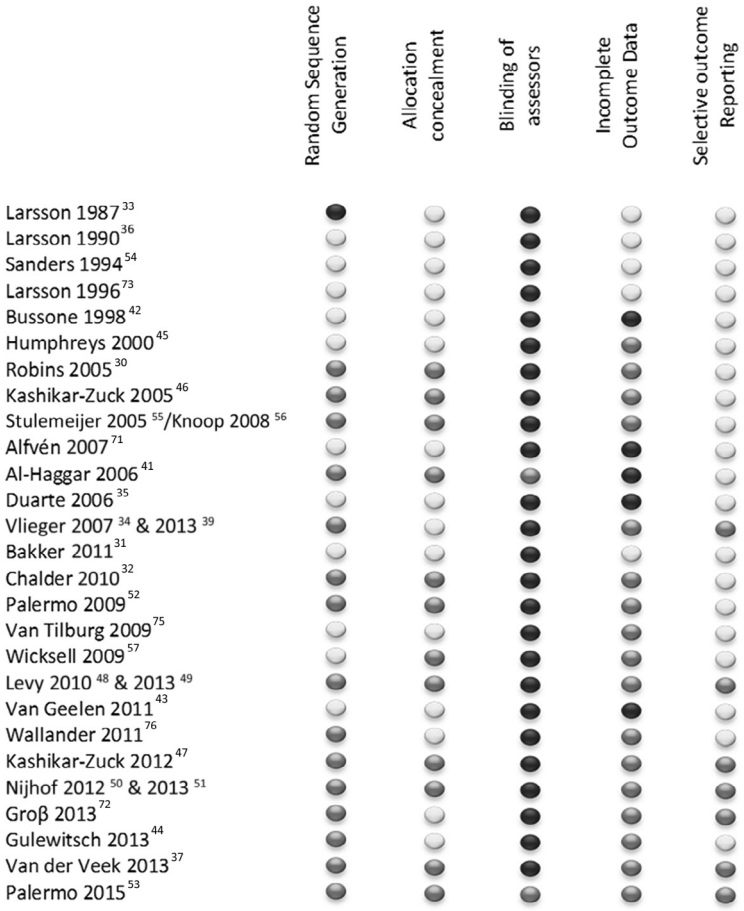


**Figure 2.** Cochrane risk of bias assessment. Only the blinding of outcome assessors was rated. Selective outcome reporting was marked as unclear when no trial registration or study-protocol was available or when one of our main outcomes was not fully reported in the article.

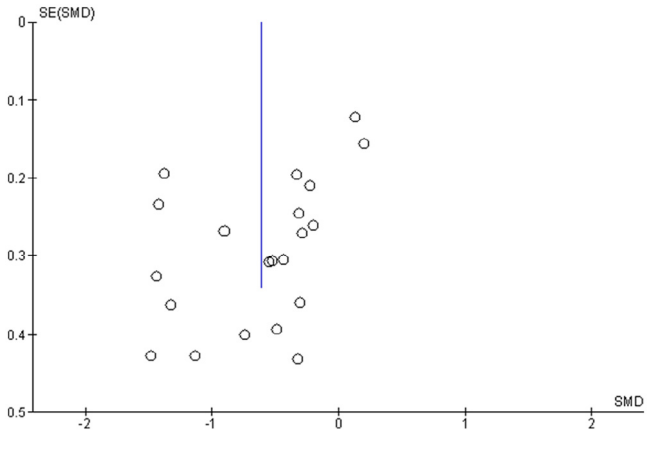


**Figure 8.** Funnel plot of effects on symptom load post-treatment. The lack of studies with a positive standardized mean difference (SMD) (effect in favor of the control group) and a wide SE (small samples or much heterogeneity) indicates publication bias.

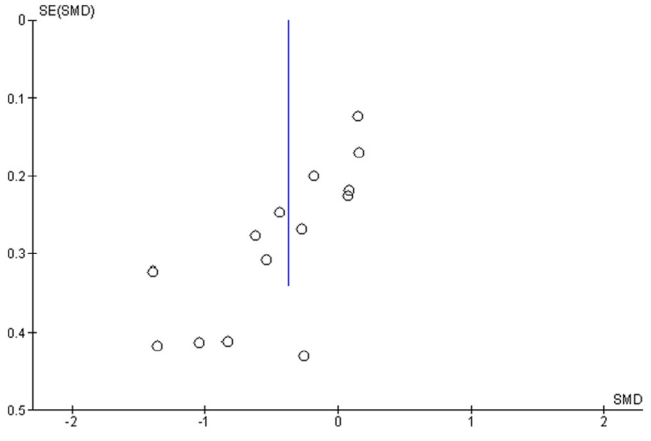


**Figure 9.** Funnel plot of effects on symptom load at follow-up.

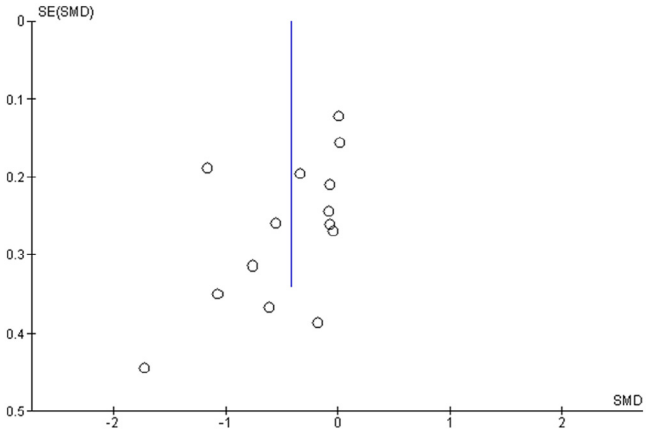


**Figure 10.** Funnel plot of effects on disability post-treatment.

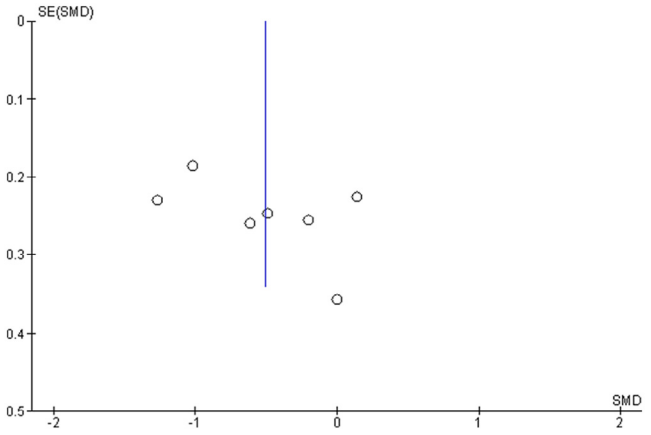


**Figure 12.** Funnel plot of effects on school absence post-treatment.

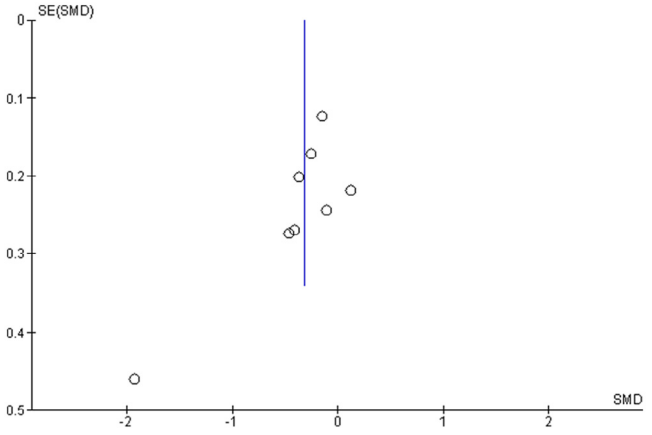


**Figure 11.** Funnel plot of effects on disability at follow-up.

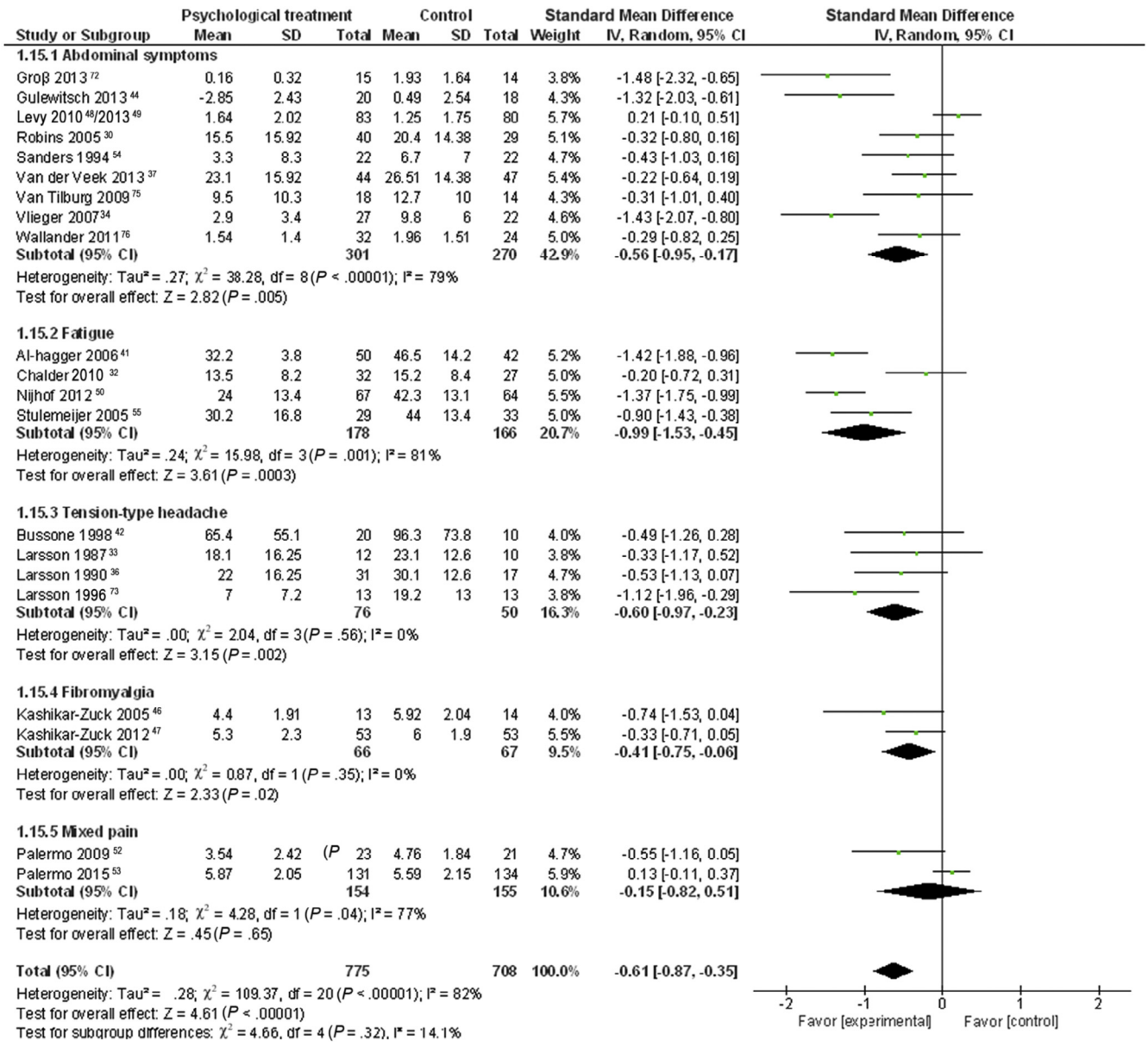


**Figure 13.** Effect of psychological treatment on symptom load post-treatment, stratified by type of symptoms. *IV*, inverse variance.

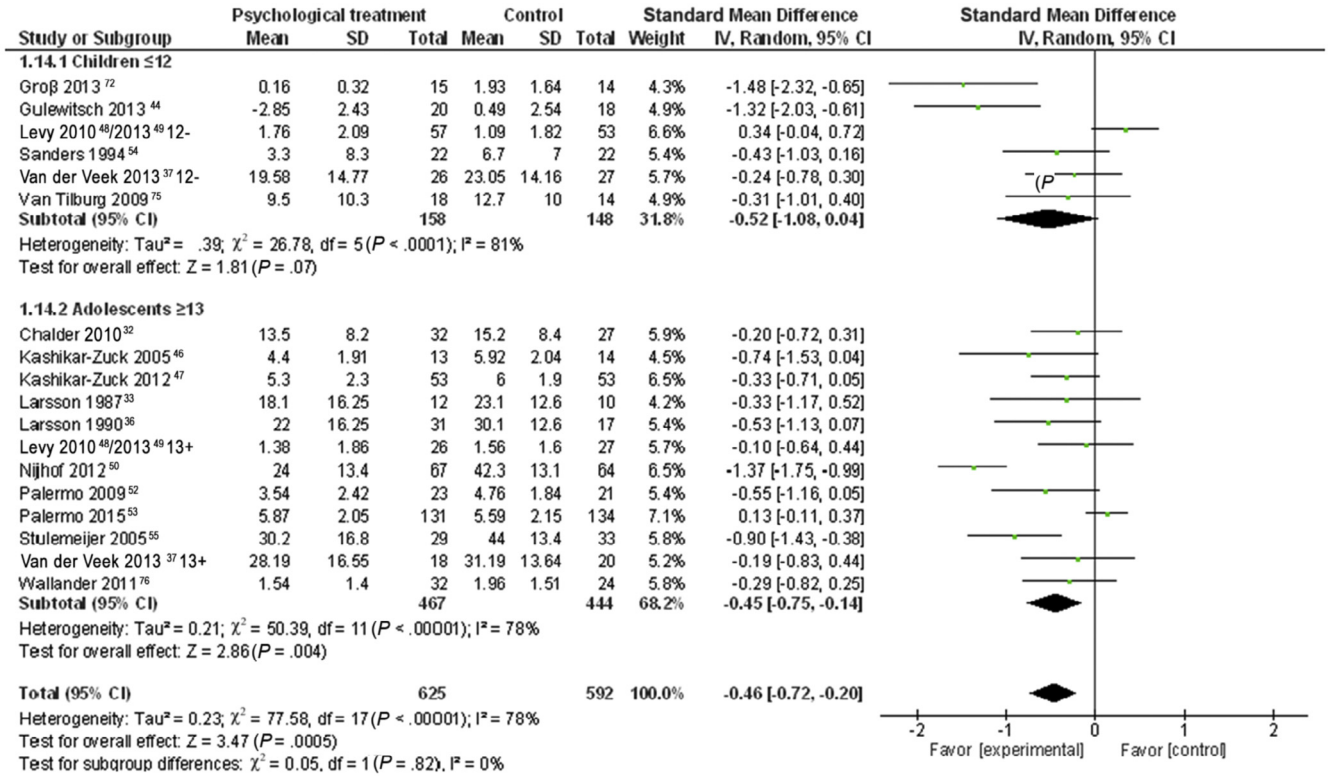


**Figure 14.** Effect of psychological treatment on symptom load post-treatment, clustered by age group.

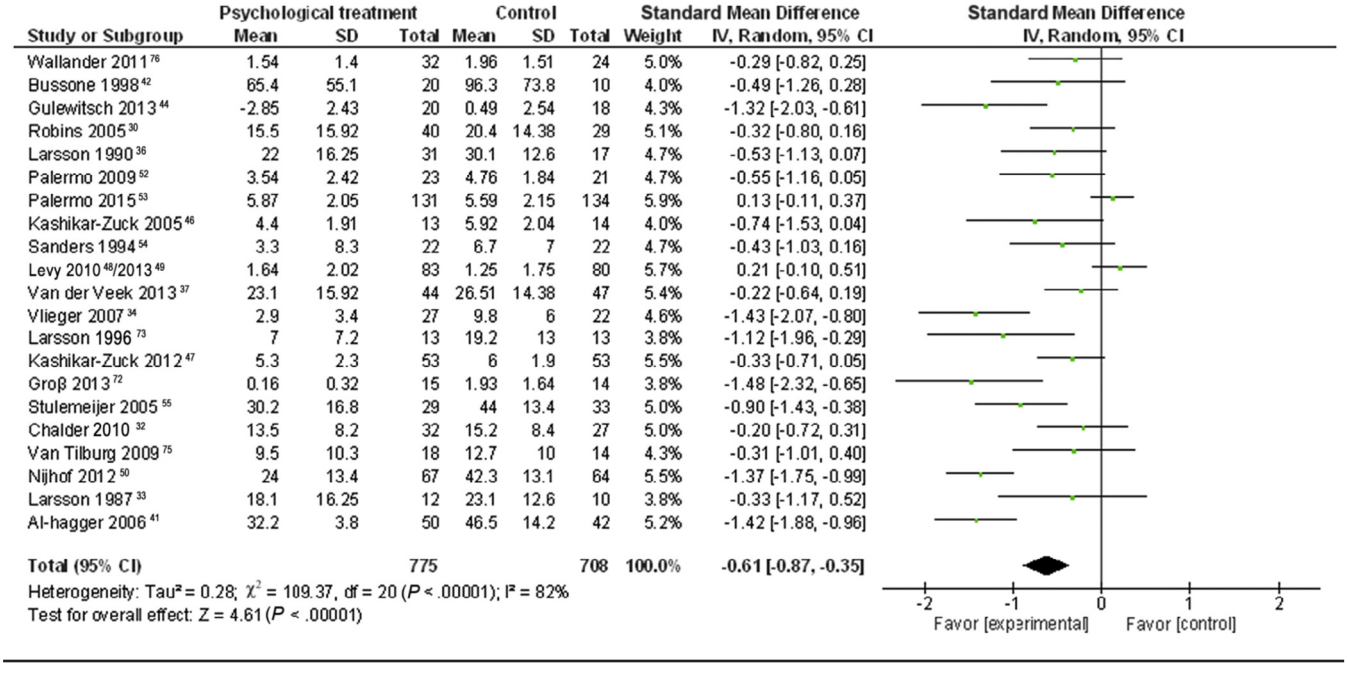


**Figure 15.** Effect of psychological treatment on symptom load post-treatment, ordered by treatment dose.

**Table I. Treatment characteristics**

| Studies | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Authors** | **Year** | **Treatment** | **Goal(s)** | **Comparison** | **Other treatments** | **Setting** | **Duration** | **Dose** | **Materials and procedures** | **Providers** | **Adherence/ fidelity** |
| Alfvén[71] | 2007 | Psychological therapy + physiotherapy | Improving the regulation of stress with problem solving techniques. | Active comparator: Physiotherapy including relaxation exercises and pain coping. | nr | Specialized clinic, not clear who is present. | Nr | At least 2 sessions Total: App. 2 h | nr | Psychologist and physiotherapist | nr |
| Al-Haggar et al[41] | 2006 | CBT + biofeedback | Change cognitions and behavior including relaxation techniques. Use biofeedback to evaluate and direct treatment. | CAU with a conservative, purely symptomatic, medical treatment. | Participants requested to not follow other treatments. | Specialized clinic, unclear if family present. | 18 mo | 40-60 sessions, 1-2/wk, duration nr Total: App. 38 h | Therapy manual, biofeedback machines. In between sessions phone and email contact. Planning of activities in diary, tailored physical activity advice. | 3 pediatric psychotherapists, trained and supervised by researchers. | nr |
| Bakker[31] | 2011 | Psycho-educative video based on CBT principles | Providing information about CFS, experienced from patients, helpful coping. Challenge own cognitions and coping. | CAU, not described. | nr | Home, not clear who is present. | Once | Once Total: App. 1 h | Video available upon request. | nr | nr |
| Bussone et al[42] | 1998 | Biofeedback-assisted relaxation | Learn to reduce muscle tension by auditory feedback. | Placebo condition with instructions to relax 'a relaxation pseudotherapy' in the same dose as treatment. | nr | Specialized clinic, participant alone. | 5 weeks | 10 sessions, 2/wk, 20 min Total: 3 h | No mentioning of manual, biofeedback machine. Encouraged to not practice at home. | Therapists, not further specified. | nr |
| Chalder[32] | 2010 | Family CBT | Change cognitions and behavior of participant and family (mother) including balance activity planning and sleep hygiene. | Placebo condition with education, less intensive than the treatment (4 sessions). | 35% on antidepressants | Specialized clinic, participants and mother attend. | 6 mo | 13 sessions, 1/ 2 wk, 60 min Total: 13 h | Treatment manual and family guide. Next to therapy close contact with schools for reintegration and home-work assignments. | 2 experienced and trained psychotherapists, supervised by researchers. | Video-based live supervision of therapists. Participants attended 12 (SD: 2.5, range: 5-13) sessions. |

(*continued*)

**Table I. Continued**

| Studies | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Authors | Year | Treatment | Goal(s) | Comparison | Other treatments | Setting | Duration | Dose | Materials and procedures | Providers | Adherence/ fidelity |
| Duarte et al[35] | 2006 | Family CBT | Change cognitions and behaviors. | Placebo condition with CAU, not described, and general medical advices in the same dose as treatment. | nr | Specialized clinic, not clear who is present. | 4 mo | 4 sessions, 1/mo, 50 min Total: 3 h | No manual mentioned, global content described. | Nr | nr |
| van Geelen[43] | 2011 | Self-investigation and confrontation method. | Explore personal narratives, their underlying motivation/ emotions, and recognize its presence in daily life situations. Change personal narrative in new situations. | Active comparator: Self-investigation which was based on the same principle as the treatment but only consisted of guided exploration (not recognizing and changing), less intensive than the treatment (6 sessions). | Participants requested to not follow other treatments. | University hospital, participants alone. | 4 mo | 12 sessions, 1/wk, 60 min Total: 12 h | No manual mentioned, global content described. | "Counselor'" not further specified. | nr |
| Groβ[72] | 2013 | CBT pain control treatment: | Change cognitions and behavior plus relaxation exercises and self-esteem improvement. | WL | nr | Clinic, groups with 3-6 children, not clear if parents also present. | 6 wk | 6 sessions, 1/wk, 90 min. One additional meeting for parents Total: 9 h | Treatment manual, CD with relaxation exercises. Recording pain and coping in diary. Home-work assignments. Parents receive nutritional advice. | Psychologist, not further specified. | nr |
| Gulewitsch et al[44] | 2013 | Brief hypnotherapeutic and behavioral therapy. | Learn relaxation and imagination techniques. Practice hypnotherapeutic trance to increase well-being, pain-managing and being brave. Parents received psycho-education. | WL | Following other treatments was an exclusion criteria. | University clinic, groups with four to seven families. | 4 wk | 2 sessions (children only), 1/2 wk, 90 min. Also 2 additional parent sessions Total: 3 h | Treatment manual, written information for participants, CD with hypnotherapy exercises, home-work assignments. | Trained psychologists, not further specified. | 97% of the participants attended both sessions. |

(*continued*)

**Table I. Continued**

| Studies | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Authors | Year | Treatment | Goal(s) | Comparison | Other treatments | Setting | Duration | Dose | Materials and procedures | Providers | Adherence/ fidelity |
| Humphreys et al[45] | 2000 | Biofeedback, CBT, parental involvement. | Change cognitions and behavior with emphasize on relaxation and self-management. Thermal biofeedback to verify ability of relaxation and self-control with low arousal. | Active comparator: Fiber treatment. | Intervention groups also received fibers. | Nr | 8 wk | 6 sessions, 1 /1-2 wk, duration nr Total: App. 5 h | Based on existing treatment protocols and previous study. | Nr | nr |
| Kashikar-Zuck et al[46] | 2005 | CBT based coping skills training | Change cognitions and behaviors aimed at coping with pain. Including relaxation, problem solving and pleasant activity planning. | Placebo condition with 'self-monitoring' which meant keeping a diary registering pain, sleep and medication. | 75% used antidepressants and 80% NSAID's. | Pediatric rheumatology clinic, parents attend 50% of the sessions. | 8 wk | 6 sessions, 1-2/wk, duration nr. In addition, 2 telephone appointments Total: App. 5 h | Treatment manual, homework assignments. | Trained pediatric psychology resident and psychology, not further specified. | Video-based checks and weekly feedback toward therapists. 90% of the participants attended all sessions. |
| Kashikar-Zuck et al[47] | 2012 | CBT | Change cognitions and behaviors including relaxation exercises, individualized problem solving, and relapse prevention. | Placebo condition with education about FM. | nr | Pediatric rheumatology clinic, parents attended 38% of the sessions. | 8 wk | 10 sessions, 1/wk, 45 min and in follow-up period 2 booster sessions Total: 8 h | Treatment manual, piloted. Homework assignments. | 5 postdoctoral pediatric psychiatrists, trained 6-8 h by PI. | Video-based checks (20% of all sessions) and supervision by independent monitors. 88% of the participants attended all sessions. |
| Larsson[33] | 1987 | Self-help relaxation training | Learn rapid relaxation techniques in daily life. | WL with only self-monitoring (assessment of outcomes) | nr | School | 5 wk | 3 sessions, 1/1-2 wk, 60 min. Total: 18 h | Treatment manual, audiotapes. Daily practicing at home (20-30 min). | 2 students clinical psychology. | nr |
| Larsson et al[36] | 1990 | Relaxation training | Relaxation training with eventually better relaxation skills for coping with tension and headaches. | WL | nr | Home | 5 wk | 5 sessions, 1/wk, duration nr Total: App. 4 h | Manual and 5 audiotapes. | Developed by a graduate student psychology. | nr |

(*continued*)

**Table I. Continued**

| Studies | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Authors** | **Year** | **Treatment** | **Goal(s)** | **Comparison** | **Other treatments** | **Setting** | **Duration** | **Dose** | **Materials and procedures** | **Providers** | **Adherence/ fidelity** |
| Larsson[73] | 1996 | Relaxation training | Relaxation training with eventually better relaxation skills for coping with tension and headaches. | WL | nr | School, groups of 3-4 participants. | 5 wk | 20 sessions, 2/wk, 20 min<br>Total: 7 h | Manual and 5 audiotapes. | 3 trained nurses supervised by physiotherapist. | nr |
| Levy et al[48,49] | 2010 and 2013 | Social learning family CBT | Change cognitions, relaxation exercises, and modify the family's responses to illness behavior. | Placebo condition with education about the GI-tract and nutrition. | Both conditions received CAU. | Pediatric clinic or home (28%), together with parent. | 3 wk | 3 sessions, 1/wk, 75 min<br>Total: 4 h | No mentioning of manual, content clearly described in paper.<br>Homework assignments were given. | 14 trained psychotherapists, experience nr. | Video-based checks (20% of all cases) on content by experienced intervention trainer: 94% elements percent. Also checked for overlap between treatment and placebo: 0%<br>88% of the participants attended all sessions, 85% completed assignments. |
| Nijhof et al[50,51] | 2012 and 2013 | Internet-based CBT: FITNET | Change cognitions and behaviors including goal setting, and scheduling activities with as main aim return to full education.<br>Parents followed a parallel program. | CAU with unstructured different regional available treatments including: CBT (66%), physical therapies (49%), alternative treatments (24%), and rehabilitation (22%). Only for control group. | Participants in treatment group requested to not follow other treatments. | Home | 6 mo | 21 modules, 1/ 1-2 wk responses to e-consult by therapist, duration nr<br>Total: App. 16 h | Website, based on existing protocols for CBT treatment by an experienced center.<br>At least 1 communication between therapist and school mentor. | 5 trained psychotherapists (2) and trainees (3), experience range from 1-10 y. | Checks for attendance of modules or content of responses by therapists nr. |

(*continued*)

**Table I. Continued**

| Studies | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Authors | Year | Treatment | Goal(s) | Comparison | Other treatments | Setting | Duration | Dose | Materials and procedures | Providers | Adherence/ fidelity |
| Palermo et al[52] | 2009 | Internet-based family CBT | Change cognitions and behavior including relaxation exercises, lifestyle, coping at school, and relapse prevention. Parents followed a parallel program. | WL with continuation of standard medical care provided by specialized clinics. | Participants requested to not follow other treatments. | Home | 8 wk | 8 modules, 1/wk assignment, 30 min Total: 4 h | Website, based on CBT protocols and piloted. Content personalized based on goal setting and answers. Weekly therapist responses standardized by manual. Participants could only proceed after assignment was finished. | 1 fellow psychology with 1 y experience. | 77% of the participants and 54% of the parents completed all modules. Mean modules completed by both 13 (SD 4) |
| Palermo et al[53] | 2015 | Internet-based family CBT | Change cognitions and behavior including relaxation exercises, lifestyle, coping at school, and relapse prevention. Parents followed a parallel program including operant strategy and communication training. | Placebo condition with internet-based education about chronic pain management and assessments of knowledge. | CAU was not altered. | Home | 8 wk | 8 modules, 1/wk, 30 min Total: 4 h | Website, based on CBT protocols, piloted and used in earlier study (2009). Content personalized based on goal setting and answers. Weekly therapist responses standardized by manual. | 5 trained and experienced study coaches (psychology fellows). | Coaches were supervised by PI in their responses, not elaborated upon. |
| Robins et al[30] | 2005 | Short CBT | Change cognitions and behaviors with emphasis on relaxation and positive thinking to manage pain. | CAU with ongoing visits, education, and medication when needed for both groups. | Following another CBT intervention was an exclusion. | Pediatric clinic, parents attended 60% of the sessions | 10 wk | 5 sessions, 1 / 2 wk, 40 min Total: 3 h | Based on intervention protocol. Homework assignments. | 2 psychology fellows/interns. | The 2providers discussed/ evaluated sessions beforehand and afterwards. |

(*continued*)

**Table I. Continued**

| Studies | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Authors** | **Year** | **Treatment** | **Goal(s)** | **Comparison** | **Other treatments** | **Setting** | **Duration** | **Dose** | **Materials and procedures** | **Providers** | **Adherence/ fidelity** |
| Sanders et al[54] | 1994 | Family CBT | Change cognitions and behaviors with emphasis on relaxation training for children and management training for parents. | CAU with 6 sessions of education and reassurance for both groups. | Any other treatment was an exclusion. | Clinic, child and mother attended sessions together. | 8 wk | 6 sessions 1/1-2 wk, 50 min Total: 5 h | Written instructions for participants, homework assignments. | 2 clinical psychologists. | nr |
| Stulemeijer et al[55] Knoop et al[56] | 2005 2008 | CBT | Change cognitions and behaviors tailored to current activity pattern with as main aim return to full education. | WL | Treatment group was not allowed to follow other treatments. | Clinic, only child attends. | 5 mo | 10 sessions 2/mo, duration nr Total: 10 h | nr | 4 experienced and trained child psychologists. | nr |
| Van Tilburg[75] | 2009 | Guided imagery therapy | Imagery training to produce relaxation and decrease discomfort. | CAU as described by own physicians. | nr | Instructions and first sessions in clinic, therapy at home. | 8 wk | 53 sessions whereof one instruction (25 min), 3/2 wk sessions (20-25 min) and at least 5/wk sessions (10-15 min). Total: 13 h | Instruction DVD with written instructions parents, CDs and portable CD player. Compliance noted on a calendar. Staff could be called for questions. | Treatment materials developed by 3 experienced investigators modeled after protocols for adults and tested. | 99% of all participants listened to the CD's at least as much as instructed. |
| Veek et al[37] | 2013 | CBT | Change cognitions and behavior including relaxation training. Cognitive therapy and behavior therapy for child and parent were tailored to needs. | Intensified CAU including education, advices and medication in the same contact almost same dose as treatment (6 × 25 min). | Allowed to visit pediatrician. | University clinic, parents 50% present if child between 7-12 years old. In one specific module presence parent 100%. | 6 wk | 6 sessions, 1/wk, 45 min. Total: 5 h | Protocol based on earlier studies, 3 optional modules could be selected depending on needs participant. Diary and homework assignment to describe performed exercises / effects of advices. | Trained masters students psychology or psychologists, biweekly supervised by experienced children's psychotherapist for treatment group. | Therapists were biweekly supervised by experienced children's psychotherapist, not elaborated upon. |

(*continued*)

**Table I. Continued**

| Studies | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Authors | Year | Treatment | Goal(s) | Comparison | Other treatments | Setting | Duration | Dose | Materials and procedures | Providers | Adherence/ fidelity |
| Vlieger et al[34,39] | 2007 and 2013 | Hypnotherapy | Hypnotherapy consisting of general relaxation, pain-control, normalization of gut-function, sleep behavior, and ego-strengthening. | CAU with education, advices and medication where symptoms were discussed and triggers explored, app. Same dose (additional 6 × 30 min supportive sessions) | Nr | Tertiary clinic, alone. | 3 mo | 6 sessions, 1/2 wk, 50 min. Total: 5 h | Manchester protocol, tailored approach. CD with standardized session, participants encouraged to practice daily at home. | 1 experienced and trained nurse. | nr |
| Wallander[76] | 2011 | Written self-disclosure | Target psychosocial stress by writing down deepest thoughts and feelings about distressing experiences. | CAU including consultations, education, advices and medication. | Nr | First session at clinic, other 2 at home | 1 wk | 3 sessions in 1 wk, 20 min Total: 1 h | Instructions were read out loud and written instructions provided. Instructions for writing at home. | Independent research associates provided instructions. | nr |
| Wicksell et al[57] | 2009 | ACT | Exposure to previously avoided situations emphasizing acceptance as an alternative coping strategy, shift toward value-based living including increasing pleasant activities. | Active comparator: Multidisciplinary treatment by a psychiatrist, child psychologist, physiotherapist and pain physician. Amitriptyline prescribed. Approximately same time dose as treatment group but during follow-up ongoing treatment h. | Pharmacological treatment continued. | Clinic | 4 mo | 10 sessions, 1/wk, 60 min 1-2 sessions with the parent, 90 min Total: 12 h | Protocol based treatment. In between sessions participants were encouraged to expose themselves, and notice and accept unpleasant experiences. | 2 experienced and trained psychologists. | Continuous discussion content and progress in research group. Average attended sessions by participants: 10 (SD: 4). |

*ACT*, activity and commitment therapy; *CBT*, cognitive behavioral therapy; *CFS*, chronic fatigue syndrome; *FITNET*, Fatigue in Teenagers via Internet; *Nr*, not reported; *NSAID*, nonsteroidal anti-inflammatory drugs; *WL*, waiting list.

## Table II. Study characteristics

| Studies | | | | | | | | | | | No. subjects randomized (drop-out) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Authors | Year | Treatment | Comparison | Diagnosis | Inclusion criteria* | Exclusion criteria | Symptom duration in mo (SD/range) | Age in y (SD/range) | Females in % | Comorbidities | IG | CG | Symptom load outcome† | Disability outcome† | Evaluations | Main results post-treatment‡ | Main results follow-up‡ | Quality rating (0-42) |
| Alfvén,[71] Sweden | 2007 | Psychological therapy + physiotherapy | Physiotherapy | RAP | Apley's + Baeyer Walker criteria Stress-related | Organic pathology | 28 (nr/3-108) | 9.4 (nr/6-15) | 75% | nr | 25 (nr) | 23 (nr) | Constructed pain score | - | After 12 mo | Pain = | Na | 10 |
| Al-haggar et al,[41] Egypt | 2006 | CBT + biofeedback | CAU | CFS | CDC criteria | Fukuda criteria Unexplained findings in medical examination | 7 (1/nr) | 12.5 (3.3/nr) | 73% | 68% headache, 50% myalgia, 41% abdominal complaints | 81 (31) | 78 (36) | Fatigue (FAS) | % school attendance | PT | Fatigue + School + | Na | 15 |
| Bakker,[31] The Netherlands | 2011 | CBT based psycho-educative video | CAU | Fatigue | Ongoing fatigue not (yet) fulfilling CDC criteria | Explained by somatic or psychiatric condition | 7 (5/nr) | 13.9 (2.0/nr) | 73% | nr | 50 (nr) (8) | 41 (nr) (4) | Fatigue (CIS-20) | % school absence past mo | At 3, 6, 9, 12 mo | nr | Fatigue = School = | 16 |
| Bussone et al,[42] Italy | 1998 | Biofeedback-assisted relaxation | Placebo | TTH | IHS criteria ≥ weekly episode | Explained by pathology in medical examination Use of preventive medication | 32 (24/nr) | 11.7 (2.4/11-15) | 50% | nr | 20 (0) (0) | 15 (5) (5) | Pain intensity (hourly ratings 4 wk diary) | - | PT FU: 1, 3, 6, 12 mo | Pain + | Pain + | 12 |
| Chalder,[32] UK Lloyd et al,[74] UK | 2010 2012 | Family CBT | Placebo | CFS | CDC or Oxford criteria | MDD, Somatization Disorder, Conversion Disorder or Self-harm Disease Organic pathology in record Anti-depressants dose not yet stabilized | 24 (nr/12-36§) | 15 (nr/14-17) | 68% | 35% psychiatric diagnosis | 32 (0) (3) At 2 y: (8) | 31 (4) (4) At 2 y: (11) | Fatigue (Chalder fatigue scale) | Physical functioning (subscale SF-36) % school attendance past 2 wk reported by parent | PT FU: 3, 6, 12, 24 mo | Fatigue = Physical functioning = School = | Fatigue = Physical functioning = School = | 29 |
| Duarte et al,[35] Brazil | 2006 | Family CBT | Placebo | RAP | Apley's criteria | Explained by organic pathology in medical examinations Positive h. Pylori or lactose-intolerance | 25 (18/nr) | 9.1 (2.2/5-13) | 69% | nr | 15 (nr) | 17 (nr) | Pain intensity (VAS) | - | Just before end of treatment | Pain = | na | 12 |
| van Geelen et al,[43] The Netherlands | 2011 | Self-confrontation therapy | Self-investigation | CFS | CDC-1994 criteria | CDC-1994 criteria | 29 (22/nr) | 16.5 (1.2/nr) | 86% | Nr | 18 (nr)¶ | 17 (nr) | Fatigue (CIS-20) | Physical functioning (CHQ-CF87) | PT FU: 10 mo | No direct comparison made. Indirect: +** | No direct comparison made. Indirect: +** | 15 |
| Groß,[72] Germany | 2013 | CBT pain control | WL | CAP | ≥3 mo, > 1/wk, impairing, additional symptoms present | Organic explanation in medical examination Psychological disorder ICD-10 Other functional GI disorder | 34 (21/nr) | 9.6 (1.5/6-12) | 86% | nr | 15 (0) (0) | 14 (0) (0) | Pain intensity (daily ratings VAS 2 wk diary) | Impairment (subscale KINDL-R) | PT FU: 3 mo | Pain + Impairment + | Pain + Impairment + | 16 |
| Gulewitsch et al,[44] Germany | 2013 | Hypnotherapy plus behavioral intervention | WL | IBS/FAP | Rome-III FAP/ IBS criteria | Ongoing other treatments Abdominal migraine or functional dyspepsia | 35 (40/nr) | 9.4 (1.7/nr) | 63% | nr | 20 (0) | 18 (0) | Constructed pain score (duration, frequency and VAS from 2 wk diary) | Disability (P-PDI) Days of school absence in 2 wk assessed by diary | PT | Pain + Disability + School nr | na | 19 |

(*continued*)

## Table II. Continued

| Studies | | | | | | | | | | | No. subjects randomized (drop-out) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Authors | Year | Treatment | Comparison | Diagnosis | Inclusion criteria* | Exclusion criteria | Symptom duration in mo (SD/range) | Age in y (SD/range) | Females in % | Comorbidities | IG | CG | Symptom load outcome† | Disability outcome† | Evaluations | Main results post-treatment‡ | Main results follow-up‡ | Quality rating (0-42) |
| Humphreys et al,[45] US | 2000 | Biofeedback + CBT + parental involvement†† | Fiber treatment | RAP | Medical diagnosis RAP | Medical diagnosis RAP | nr | 9.8 (2.5/nr) | 60% | nr | 49 (3) | 15 (0) | Pain intensity (daily ratings NRS) | School absence assessed on 10% of school records | PT | Pain + School nr | na | 9 |
| Kashikar-Zuck et al,[46] US | 2005 | CBT based coping skills training | Placebo | FM | Yunus and Masi criteria Average pain and disability at least mild | Organic pathology or severe impairments in medical chart MDD Medication dose not yet stabilized | nr (66% > 24 mo) | 15.5 (1.3/13-17) | 100% | nr | 15 (2) (2) | 15 (1) (1) | Pain intensity (VAS past 2 wk) | Functional disability (FDI) | PT, Cross-over design | Pain + Disability = | na | 23 |
| Kashikar-Zuck,[47] US | 2012 | CBT | Placebo | FM | FM criteria assessed by pediatric rheumatologist ≥ moderate pain and mild impairment | Rheumatic disease Developmental delay MDD, panic disorder, bipolar disorder, psychotic episode Opioid use Medication dose not yet stabilized | 35 (31/nr) | 15 (1.8/nr) | 92% | nr | 57 (4) (7) | 57 (4) (7) | Pain intensity (daily ratings VAS past wk) | Functional disability (FDI) | PT FU: 6 mo | Pain = Disability + | Pain = Disability + | 30 |
| Larsson et al,[33] Sweden | 1987 | Self-help relaxation | WL | TTH | Headaches ≥ 1 y, ≥ 1/ wk, troublesome | Ongoing other treatments Not completed baseline assessment | nr (66% >24 mo) | nr (nr/16-18) | 91% | 13% migraine | 12 (0) (0) | 12 (2) (2) | Pain intensity (daily ratings four wk diary) | - | PT FU: 5 mo | Pain + | Pain + | 12 |
| Larsson et al,[36] Sweden | 1990 | Self-help relaxation training | WL | TTH | AHC classification ≥ 1 y, ≥ weekly headache | Nr | nr (100% > 12 mo, 46% > 24 mo) | nr (nr/16-18) | 90% | nr | 31 (nr) | 17 (nr) | Pain intensity (daily ratings 3 wk diary) | - | PT, hereafter medication added | Pain = | na | 11 |
| Larsson,[73] Sweden | 1996 | School-based relaxation training | WL | TTH | IHS criteria ≥ 6 mo, ≥ several times a wk. | Organic pathology in medical examination | 25 (18/6-120) | nr (nr/10-15) | 96% | nr | 13 (nr) | 13 (nr) | Pain intensity (daily ratings 3 wk diary) | - | PT FU: 6 mo | Pain + | Pain + | 10 |
| Levy et al,[48,49] US | 2010 and 2013 | Social learning based family CBT | Placebo | RAP | ≥ 3 mo, ≥ 3 episodes Child and parent cohabited past 5 y | Explained by organic pathology in medical examination Chronic disease Lactose intolerance Major surgery past y Severe developmental disabilities | nr (67% > 12 mo) | 11.2 (2.6/7-17) | 73% | nr | 100 (17) (27) (22) (25) | 100 (20) (30) (24) (37) | Pain intensity (Faces-pain-scale-revised) | Functional disability (FDI) | PT FU: 3, 6, 12 mo. | Pain = Disability nr | Pain = Disability nr | 25 |
| Nijhof et al,[50,51] The Netherlands | 2012 and 2013 | Internet based CBT | CAU | CFS | CFS diagnosis by pediatrician and CDC criteria Severe fatigue and functional impairment or school absence (2 SD) | Primary psychiatric diagnosis | 18 (nr/6-108) | 15.9 (1.3, nr) | 82% | 17% and 11% scored 2 SD higher than the general population on the CDI and STAI respectively | 68 (1) | 67 (3) | Fatigue (CIS-20) | Physical functioning (CHQ-CF87) % of school attendance past 2 wk, self-reported, verified with parents | PT, cross-over design | Fatigue + Physical functioning + School + | na | 27 |

(*continued*)

## Table II. Continued

| Studies | | | | | | | | | | | No. subjects randomized (drop-out) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Authors | Year | Treatment | Comparison | Diagnosis | Inclusion criteria* | Exclusion criteria | Symptom duration in mo (SD/range) | Age in y (SD/range) | Females in % | Comorbidities | IG | CG | Symptom load outcome† | Disability outcome† | Evaluations | Main results post-treatment‡ | Main results follow-up‡ | Quality rating (0-42) |
| Palermo et al,[52] US | 2009 | Internet based family CBT | WL | Mixed pain‡‡ | Functional pain > 3 mo, ≥ 1/wk, impairing. New referral | Serious comorbid condition Already received CBT | 30 (nr/5-13) | 14.8 (2.0 / 11-17) | 73% | nr | 26 (3) | 22 (1) | Pain intensity (daily rated NRS 1 wk diary) | Impairment (daily ratings CALI 1 wk diary) | PT, cross-over design | Pain = Impairment + | na | 23 |
| Palermo et al,[53] US | 2015 | Internet based family CBT | Placebo | Mixed pain§§ | Functional pain > 3 mo, ≥ 1/wk, impairing | Serious comorbid condition Developmental disability Not living at home | nr | 14.7 (1.6/11-17) | 75% | nr | 138 (7) (8) | 135 (1) (1) | Pain intensity (daily rated NRS 1 wk diary) | Impairment (daily ratings CALI 1 wk diary) | PT FU: 6 mo and ongoing | Pain = Impairment = | Pain = Impairment + | 31 |
| Robins et al,[30] US | 2005 | CBT | CAU | RAP | Apley's criteria | Already CBT for RAP | nr | 11.3 (2.5/6-16) | 57% | nr | 46 (3) (6) | 40 (6) (11) | Constructed pain score (API) | Functional disability (FDI) Days school absence by records past 12 mo | PT FU: 3, 3-9 mo | Pain + Disability = School nr | Pain + Disability = School + | 17 |
| Sander et al,[54] Australia | 1994 | Family CBT | CAU | RAP | Apley's criteria | Past major surgery, medical illness, lactose intolerance, constipation, recent virus, loose IBS Any treatment for symptoms Psychiatric disorder | 44 (38/nr) | 9.2 (2.0/7-14) | 64% | nr | 22 (nr) | 22 (nr) | Pain intensity (daily VAS ratings 2 wk diary) | - | PT FU: 6, 12 mo | Pain = | Pain = | 17 |
| Stulemeijer et al,[55] Knoop et al,[56] The Netherlands | 2005 2008 | CBT | WL | CFS | CFS diagnosis by pediatrician and CDC criteria Severe fatigue and impairment | Psychiatric comorbidities | 17 (nr/nr) | 15.7 (2.6/nr) | 90% | nr | 36 (7) | 35 (2) | Fatigue (subscale CIS-20) | Physical functioning (SF-36) % school attendance previous wk | PT, cross-over design | Pain + Impairment + School + | na | 19 |
| Van Tilburg,[75] US | 2009 | Guided imagery therapy | CAU | FAP | FAP diagnosis by pediatric gastroenterologists ≥ 3 mo, ≥1/wk, disrupting activities and ongoing (≥1 mo) despite medication. | Experience with guided imagery Disability that may interfere with understanding Psychiatric condition with psychotic elements | nr | 10.3 (2.7/nr) | 62% | 18% abdominal migraine | 19 (1) | 15 (1) | Constructed pain score (2 items API) | Functional disability (FDI) School absence past 2 mo rated by parents | PT, cross-over design | Pain = Disability = School = | na | 19 |
| Veek et al,[37] The Netherlands | 2013 | CBT | Intensified CAU | FAP | Rome-III FAP/IBS criteria screened by pediatricians Abdominal pain is main complaint. ≥ 2 mo, ≥ 1/wk | Explained by organic pathology in medical examinations Psychiatric disorder that required treatment first | 34 (38/nr) | 11.9 (2.8, nr) | 72% | 29% anxiety disorder 4% depressive disorder or dysthymia assessed with structured interview | 52 (8) (9) (7) | 52 (5) (8) (13) | Constructed pain score (API) | Functional disability (FDI) | PT FU: 6, 12 mo | Pain = Disability = QoL = | Pain = Disability = QoL = | 25 |

(*continued*)

## Table II. Continued

| Studies | | | | | | | | | | | No. subjects randomized (drop-out) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Authors | Year | Treatment | Comparison | Diagnosis | Inclusion criteria* | Exclusion criteria | Symptom duration in mo (SD/range) | Age in y (SD/range) | Females in % | Comorbidities | IG | CG | Symptom load outcome† | Disability outcome† | Evaluations | Main results post-treatment‡ | Main results follow-up‡ | Quality rating (0-42) |
| Vlieger et al,[34,39] The Netherlands | 2007 and 2011 | Hypnotherapy | CAU | IBS/FAP | Rome-III FAP/ IBS criteria ≥ 12 mo complaints | Organic gastrointestinal disease<br>Medication influencing GI-function<br>Functional constipation<br>Already treatment for FAP/IBS<br>Mental retardation, neurologic or psychiatric problems | 41(30/nr) | 13.3 (2.7/nr) | 75% | 54% headache complaints | 28<br>(1)<br>(1) | 25<br>(0)<br>(0) | Pain intensity (daily ratings affective facial pain scale 1 wk diary) | - | During treatment PT<br>FU: 6, 12 mo, 5 y | Pain + | na | 14 |
| Wallander,[76] US | 2011 | Written self-disclosure | CAU | RAP | Apley's criteria assessed by pediatric GI specialist | Chronic illnesses | nr | 13.6 (1.9/11-18) | 70% | nr | 36<br>(2)<br>(4) | 27<br>(1)<br>(3) | Pain frequency (1 item APFR) | Physical QoL (PedsQL) | PT<br>FU: 6 mo | Pain +<br>QoL = | Pain +<br>QoL = | 15 |
| Wicksell et al,[57] Sweden | 2009 | ACT | Multidisciplinary treatment | Mixed pain¶¶ | Referrals with ≥3 mo pain | Explained by organic pathology<br>Coexisting psychosocial or psychiatric issues<br>Major cognitive dysfunctions<br>Already CBT treatment<br>Previously treated with amitriptyline | 32 (nr/6-92) | 14.8 (2.4/10-18) | 78% | nr | 16<br>(1)<br>(3) | 16<br>(2)<br>(5) | Pain intensity (VAS) by daily ratings over 2 wk. | Functional disability (FDI) | PT,<br>FU: 4, 7 mo | Pain +<br>Impairment = | Pain +<br>Impairment = | 20 |

*APFR*, abdominal pain frequency rating; *API*, abdominal pain index; *CALI*, child activities limitations interview; *CAP*, chronic abdominal pain; *CHQ-CF87*, child health questionnaire-child form 87; *CIS-20*, checklist individual strength; *FAP*, functional abdominal pain; *FAS*, fatigue assessment scale; *FDI*, functional disability inventory; *FM*, fibromyalgia; *FU*, follow-up; *GI*, gastrointestinal; *IBS*, irritable bowel syndrome; *MDD*, major depressive disorder; *Na*, not applicable; *NRS*, numeric rating scale; *PedsQL*, pediatric quality of life inventory; *P-PDI*, pediatric pain disability index; *PT*, post-treatment; *QoL*, quality of life; *RAP*, recurrent abdominal pain; *SF-36*, short form 36; *TTH*, tension-type headache; *VAS*, visual analog scale.

*General inclusion criteria like age range, language abilities and informed consent not reported here.

†Only the outcomes as included in our meta-analyses are displayed here.

‡Plus sign (+) indicates improvement on this outcome; equal sign (=) indicates no effect on this outcome.

§IQR.

¶In total 7 drop-outs, unclear how many in each group.

**Both groups were compared with healthy controls; post-treatment and at follow-up the treatment group did not longer differ from the healthy controls on fatigue and physical functioning while the comparison group did.

††Three intervention arms combined.

‡‡Abdominal pain (50%), musculoskeletal pain (25%), headache (25%), 58% multiple locations.

§§Abdominal pain (11%), musculoskeletal pain (42%), headache (7%), multiple (40%).

¶¶Abdominal pain (6%), musculoskeletal pain (47%), headache (25%), complex regional pain syndrome (22%).