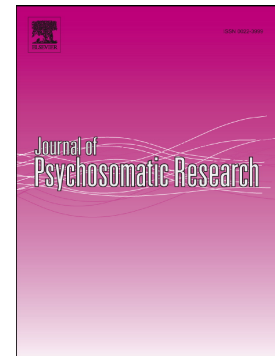


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**Long-term economic evaluation of cognitive-behavioural group treatment versus
enhanced usual care for functional somatic syndromes**

Running title: Long-term economic evaluation of group CBT for FSS

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ABSTRACT

Objective

Patients with functional somatic syndromes (FSS) such as fibromyalgia and chronic fatigue syndrome have a poor outcome and can incur high healthcare and societal costs. We aimed to compare the medium-term (16 months) cost-effectiveness and the long-term (40 months) economic outcomes of a bespoke cognitive-behavioural group treatment (STreSS) with that of enhanced usual care (EUC).

Methods

We obtained complete data on healthcare and indirect costs (i.e. labour-marked-related and health-related benefits) from public registries for 120 participants from a randomised controlled trial. Costs were calculated as per capita public expenses in 2010 €. QALYs gained were estimated from the SF-6D. We conducted a medium-term cost-effectiveness analysis and a long-term cost-minimization analysis from both a healthcare (i.e. direct cost) and a societal (i.e. total cost) perspective.

Results

In the medium term, the probability that STreSS was cost-effective at thresholds of 25,000 to 35,000 € per QALY was 93 - 95 % from a healthcare perspective, but only 50 - 55 % from a societal perspective. In the long term, however, STreSS was associated with increasing savings in indirect costs, mainly due to a greater number of patients self-supporting. When combined with stable long-term reductions in healthcare expenditures, there were total cost savings of 7,184 € (95 % CI 2,271 to 12,096, $p=0.004$) during the third year after treatment.

Conclusion

STreSS treatment costs an average of 1545 €. This cost was more than offset by subsequent savings in direct and indirect costs. Implementation could both improve patient outcomes and reduce costs.

Keywords

economic evaluation; cost-effectiveness; cognitive-behavioural therapy; functional somatic syndromes; bodily distress syndrome; fibromyalgia; chronic fatigue syndrome

Author contribution

AS, MS and PF are co-investigators of the STreSS-1 trial. AS, EØ and PF conceived and designed the study. AS and EØ obtained and combined data from public registries and calculated individual direct and indirect costs. EØ and JSJ conducted statistical analysis. AS drafted the paper. All authors participated in the interpretation of the findings, were involved in critically revising the paper and approved the final manuscript.

Conflict of interest

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf. The authors have no competing interests to report.

Word count

4070

BACKGROUND

Functional somatic syndromes (FSS) such as fibromyalgia, irritable bowel and chronic fatigue syndrome are a major public health issue. FSS are prevalent worldwide in all medical settings, and when severe pose a major burden on sufferers, health services, and on society. They incur considerable direct and even greater indirect costs.¹⁻⁷ The direct costs mainly reflect repeated referrals to secondary medical care in order to exclude physical disease.^{5;8} Indirect costs are consequences of reduced productivity at work, sick leave, dependence on social benefits and, in the most severe cases, a permanent loss of the ability to support oneself.^{6;8-11} Whilst psychological treatments such as cognitive-behavioural therapy (CBT) may reduce symptom severity and improve health-related quality of life in patients with various FSS,¹²⁻¹⁶ knowledge about their long-term effects on direct and indirect costs in these patients is limited.^{8;17}

Potentially effective psychological treatments for FSS are currently not routinely delivered, even in severe cases, because of organisational and other barriers.^{18;19} We have addressed these barriers with a group CBT programme (Specialised Treatment for Severe Bodily Distress Syndromes, STreSS) designed as a common treatment for patients with a range of severe and impairing FSS, and suitable for delivery in a general University hospital setting.²⁰ In a recent trial we found STreSS to be superior to enhanced usual care (EUC) both on the primary outcome (self-rated physical health) and also on most secondary outcomes, including somatic symptoms, illness worrying and social functioning.²¹ The specific FSS diagnosis had no differential effect on treatment response.¹⁹

In our trial patients were sampled using the severe multi-organ subtype of the newly proposed diagnosis bodily distress syndrome (BDS), the criteria for which have been included in the current draft of the World Health Organization's International Classification of Diseases, 11th Revision, with some adaptations.²² Recent studies have confirmed the high

healthcare costs and unfavourable prognosis of untreated multi-organ BDS, especially as regards a high risk of new disability pension awards.^{23;24} Although the trial results show the effectiveness of STreSS, the long-term economic consequence of the treatment is not known.

We therefore conducted a long-term economic evaluation. We did this within the context of the Danish healthcare and welfare system, which is tax-financed, and where access to both direct (i.e. healthcare expenditures) and indirect (i.e. public expenditures associated with occupational status and social benefits) cost data is possible through public registries.²⁵⁻²⁹ This allowed us to do analyses from both a healthcare (direct costs) and a societal (total costs, i.e. direct plus indirect) perspective.

The aims of this study were to: (1) compare healthcare and total costs during and following STreSS and EUC up to 40 months after randomisation, and (2) compare the cost-effectiveness of STreSS and EUC in terms of QALYs gained and percentage of patients achieving clinically significant improvement for the trial period of 16 months.

METHODS

Study design and participants

The STreSS-1 trial (clinicaltrial.gov NCT00132197) was a two-arm, single-site, non-blinded, randomised controlled trial comparing a group CBT programme (STreSS) with usual care enhanced by a thorough clinical assessment (EUC).^{20;21} The trial was conducted at Aarhus University Hospital, Denmark from 2005 to 2008 within a general hospital setting. Most patients were referred by their primary care physician. Referred patients were included in the trial if they fulfilled criteria for the severe multi-organ subtype of bodily distress syndrome.³⁰ This unifying definition captures both patients with severe FSS diagnoses, and also most patients with somatoform disorders.³¹ Other inclusion criteria were: age 20-45 years and multiple symptoms for at least 2 years. Exclusion criteria have been reported previously.²¹

A total of 54 patients were randomly assigned to STreSS and 66 to EUC since unequal patient attrition had been expected (but not observed). Self-report data were obtained immediately prior to randomisation and 4, 10 and 16 months after randomisation. Direct and indirect cost data were obtained from Danish registers for 12 months before and up to 40 months after randomisation.

Interventions

Enhanced usual care

Usual care was delivered by patients' primary care physicians and various specialists. There was no restriction on the psychological or pharmacological interventions that could be given to these patients, or on new referrals to secondary care services. Usual care was 'enhanced' by a thorough clinical assessment prior to randomisation that aimed to achieve a shift from

diagnostic procedures to the management of somatic symptoms and comorbid mental illness. Details of the assessment are reported elsewhere.^{32;33}

STreSS

Patients allocated to STreSS received the same assessment as patients in the EUC group. Additionally, they received nine modules of manualised group CBT, each of 3.5 h duration and delivered to groups of nine patients by two psychiatrists over a 4-months period. Details about the STreSS treatment modules have been reported previously.^{18;20;21} The STreSS treatment contained no module or specific interventions regarding patients' occupational situation, but individual goals to enhance one's work ability or solve specific problems at the working place could be set by participants. The STreSS treatment manual is freely available at www.functionaldisorders.dk.

As previously reported, 83 % of allocated patients completed STreSS, while 11 % did not receive any treatment module. Only 3 patients (6 %) discontinued treatment. We did not find any differences regarding other psychological or psychiatric treatment between the EUC and the STreSS group.²¹

Outcomes

QALYs and clinical improvement

Quality-adjusted life years (QALYs) were generated on the basis of eleven items of the 36-item Short Form Health Survey (SF-36)³⁴ converted into SF-6D utility scores based on weights of the general UK population according the method of Brazier.³⁵ The accrual of QALYs during the 16 months after randomisation was calculated using the area under the curve, assuming a linear change between each available time point (0, 4, 10 and 16 months after randomisation).

In order to add a condition-specific evaluation of cost-effectiveness, we calculated costs per patient achieving clinically significant improvement from baseline to 16 months on two different measures: 1) Self-rated physical health (primary trial outcome), assessed with an aggregate score of the SF-36 scales physical functioning, bodily pain and vitality,³⁶ and 2) distressing somatic symptoms (secondary outcome) measured with the SCL-90 R somatisation subscale.²¹ Clinically significant improvement was defined conventionally as a 0.5 SD change,³⁷ equalling 4 points increase on the SF-36 aggregate score and 0.35 points reduction on the SCL-90 R somatisation subscale.

Questionnaire data (SF-6D utilities, physical health and somatic symptoms) were available for all 120 patients at baseline and for 105, 96 and 94 patients at 4, 10 and 16 months, respectively.²¹

Healthcare (i.e. direct) costs

Denmark runs a nationwide centralized register of personal information, the Civil Registration System, for which purpose every citizen is given a unique personal identification number. All public registries in Denmark use this unique number, which allows linkage of registers and of trial data to register data. Data on healthcare costs for each trial participant were obtained from four national health registers.²⁵⁻²⁸ The cost data in these registries are based on DRG codes (i.e. average costs for specific procedures or hospital stays) for in-patient and out-patient treatment in Danish hospitals, on actual reimbursement for primary care and medical specialists, and on public expenses for prescription medication. In a first step, all healthcare costs were calculated separately for each patient and each calendar month within each registry, and inflated to 2010 prices. In a second step, these costs were allocated to study months (i.e. months before or after a patient's randomisation date),

summed up across the four registers, and collapsed into the following sectors and domains:

(1) primary care, covering family physicians including primary care based physiotherapists and chiropractors, (2) inpatient and outpatient general hospital care, covering both hospital based care and medical specialists, (3) inpatient and outpatient mental healthcare, covering both hospital based care and psychiatrists and psychologists, and (4) medication. The specific costs for assessment and treatment within the trial for both EUC and STreSS were obtained from the same registries, and added under the domain outpatient mental healthcare costs. In a third step, costs within each domain and sector were summed to create annual costs with exception of the trial's 4-months treatment period for which costs were calculated separately. For the third year after treatment, only costs for medication and primary care were available when we obtained data, and estimated annual healthcare costs for the third year are therefore not comparable with the preceding years. For each domain the percentage of patients with costs within this domain (i.e. the number of patients contributing to the mean costs with values other than zero) was calculated. Finally, costs were summed across sectors to calculate total annual healthcare costs.

Public expenses associated with occupational status and social benefits (i.e. indirect costs)

Indirect costs, i.e. per capita public expenses associated with occupational status and social benefits, were calculated in 2010 € on the basis of information registered in The Danish Register-based Evaluation of Marginalization (DREAM) database.²⁹ DREAM is administered by the Danish Labour Market Authority and contains weekly information on transfer payments for all citizens in Denmark since 1991.²⁹ Transfer payments include sickness benefits, disability pensions, unemployment benefits, and reimbursement to the employer for jobs created for persons with limited working capacity ('flexible work'), amongst others. In case of sick leave, the first two weeks are paid by the employer, which

means that short-term sick leave is not registered in DREAM. DREAM uses specific codes for each type of transfer payment. We assigned these codes weekly standard costs in accordance with statutory social payments, or average calculations where standard payments were not available, according to procedures developed by the governmental agency KORA.³⁸ In weeks where no social benefits were registered or where patients were registered with transfer payments not related to reduced work ability or unemployment, such as maternity pay or state education grants, patients were regarded as self-supporting. They were assigned negative costs to reflect estimated public tax income, again according to advise from KORA.³⁸ Cost tariffs for indirect costs used in this study are provided in table A.1.

We summed weekly indirect costs to create annual indirect costs before and after randomisation for each patient, except for the trial's 4-months treatment period where costs were calculated for this period separately. We further divided the annual indirect costs into the following three main categories: (1) health-related benefits, either temporary (i.e. sickness benefit and vocational rehabilitation) or permanent (disability pension and flexible work), (2) labour-marked related benefits (i.e. unemployed benefits and social assistance), and (3) self-support (i.e. estimated tax income). Moreover, for each category the percentage of patients with costs within this category (i.e. the number of patients contributing to the mean costs with values other than zero) was calculated.

Statistical Analysis

We addressed our aims in two separate economic analyses. First, we performed a cost-minimisation analysis (CMA) as regards both healthcare (direct costs) and total costs (sum of direct and indirect costs) for the three years after the 4-months treatment period. Second,

we performed a cost-effectiveness analysis (CEA) for the trial period of 16 months where we had access to self-report outcome data.

Long-term cost-minimization analysis (CMA)

We compared healthcare and total costs before, during and after treatment between STreSS and EUC by means of test for equality of means using non-parametric bootstrap with 1000 repetitions. Total costs were presented both with and without estimated tax income.

Furthermore, we compared healthcare and total costs for the first, second and third year after treatment between both groups using regression models controlling for baseline costs (i.e. costs during the year before randomisation). Between-group differences were calculated using non-parametric bootstrap and presented with 95 % norm based confidence intervals with the bootstrapped standard error (BCI). Since costs in the domain of inpatient mental healthcare were limited to very few participants (no more than 3 % for all periods), but very high when they occurred, inpatient mental healthcare costs were excluded in CMA.

Medium –term cost-effectiveness analysis (CEA)

CEA compared STreSS and EUC from both a healthcare (direct costs) and a societal perspective (total costs) combining data on incremental costs and incremental effects; adjusted for differences in mean utility score and mean costs at baseline.³⁹ Incremental costs were calculated by means of a linear regression with costs from the 16 months after randomisation as dependent variable, and intervention and cost from the previous year before randomisation as covariates. The coefficient for intervention was the mean difference in costs adjusted for baseline value. Likewise, the incremental effect was estimated with linear regression for QALYs gained, and with generalised linear regression with binomial family and identity link to obtain the difference in proportions of patients achieving

clinically important improvements. Complete cost data were used in the calculation of incremental costs in all analyses. However, due to missing data in the estimation on the incremental effects (outcome data), multiple imputation (MI) was invoked in accordance with the procedure applied during sensitivity analysis of the primary trial report.^{21;40} MI used the mvn data augmentation procedure in Stata 13 applying 50 imputations using the following complete variables in the imputation procedure: gender, age, work status, lifetime psychiatric comorbidity, and clinician-rated impairment.

We calculated incremental cost-effectiveness ratios (ICERs) by dividing extra cost by extra effect. The ICERs hence indicate the costs per QALY gained or costs per additional patient achieving clinically important change after STreSS as compared with EUC. To evaluate the impact of the uncertainty inherited in the estimates of incremental cost and incremental effect, cost-effectiveness acceptability curves (CEAC) were made.⁴¹ We used non-parametric bootstrap with 1000 replications of the dataset. To further illustrate missing data influence 50 acceptability curves were produced in a similar fashion one for each MI dataset and the mean curve of these was constructed.⁴² The threshold range used to assess the QALY ICERs was 25,000 to 35,000 €, which is in accordance with similar studies from other European countries^{17,43} and current UK NICE cost-effectiveness thresholds. The threshold used to assess the clinical improvement ICERs was 5,000 €, based on an estimation of actual treatment costs and number needed to treat.

Ethical approval

The local research ethics committee approved the trial protocol, and all patients provided written informed consent. Both the original trial and this subsequent economic analysis were further approved by the Danish Data Protection Agency.

RESULTS

Sample characteristics

In the trial 120 patients were randomised, 54 to STreSS and 66 to EUC. Table 1 presents demographic and clinical characteristics at baseline, as well as use of healthcare and social welfare through the last year before randomisation. Groups were comparable on all measures including social benefits.

Long-term cost-minimization analysis (CMA)

Healthcare costs

Average annual healthcare costs are presented in Table 2a. Costs were comparable between both groups in the year before randomisation (ASL=0.209). During the 4-months treatment period, STreSS incurred as expected significantly higher total healthcare costs than did EUC (2369 € vs 976 €, ASL<0.001), which was explained by additional treatment costs for STreSS of 1545 € (95% BCI 1358 to 1731, range 0 to 2970 €, median 1697 €) and accordingly higher costs in the domain outpatient mental healthcare (Table 2a).

In the three years after treatment, participants who had received STreSS had significantly lower healthcare costs than those given EUC (all ASL below 0.05): the baseline-adjusted differences for healthcare costs were –1569 € (95% BCI –2904 to –234, p=0.021) and –1133 € (95% BCI –2591 to 326, p=0.128) in the first and second year, respectively. In the third year after treatment the difference was –361 € (95% BCI –688 to –34, p=0.031) for primary care and medication.

Total costs

Annual indirect costs and total costs with and without savings due to taxes are presented in Table 2b. Total costs were comparable between the treatment groups in the last year before and the first year after treatment, while STreSS in the sensitivity analysis without tax income was associated with higher total costs during the treatment period (ASL=0.013). This may be explained by higher costs associated with temporary health related benefits during STreSS than during EUC (2421 € vs. 1406 €, ASL= 0.040). In the second and third year after treatment, STreSS patients incurred significantly lower total costs than did EUC (ASL=0.029 and 0.004, respectively). Baseline-adjusted differences were –938 € (95% BCI –5186 to 3308, p=0.665), –4314 € (95% BCI –9102 to 474, p=0.077) and –7184 € (95% BCI –12096 to –2271, p=0.004) for the first, second and third year after treatment, respectively. The sensitivity analysis without tax income showed a similar pattern of increasing total cost savings. This pattern of increasing total costs savings after STreSS was explained by slightly increasing rates of self-support in the STreSS group on the one hand, and strongly increasing rates of permanent benefits in the EUC group on the other (Table 2b).

Medium-term cost-effectiveness analysis (CEA)

Table 3 presents utility scores and QALYs accrued during the 16 months trial period, and percentages of patients reaching clinically significant improvement at 16 months.

Table 4 presents the incremental effects, incremental costs and ICERs for the three outcomes, adjusted for baseline scores and baseline costs. Controlling for baseline utility scores, STreSS patients accrued 0.035 more QALYs than did EUC patients, this difference just reached statistical significance (95 % CI 0.00006 to 0.070). Significantly more patients improved after STreSS than after EUC (20 to 28 % depending on the criterion defining

improvement). STreSS was 'dominant' (i.e. better effect at lower costs) as regards healthcare costs for all outcomes, while total costs were higher for STreSS, leading to ICERs of 24,640 € per QALY and 3035 € to 4398 € per patient improved.

Figure 1 shows cost-acceptability curves for QALYs (Figure 1A) and for the two condition-specific outcomes (Figure 1B) from both a healthcare and a societal perspective. Using thresholds of 25,000 to 35,000 € per QALY, the likelihood that STreSS was cost-effective compared to EUC was very high (93 - 95 %) from a healthcare perspective, but less certain (50 - 55 %) from a societal perspective. Condition-specific cost-effectiveness analysis based on clinical improvement reached very similar results. Cost-effectiveness planes are provided in Figure 2.

DISCUSSION

This study compared the medium-term cost-effectiveness and long-term economic consequences of a group CBT programme (STreSS) for patients with a range of severe FSS with that of enhanced usual care (EUC). Our main findings were that STreSS had a high likelihood of being cost-effective from a medium-term healthcare perspective, and was associated with increasing savings in public expenses during long-term follow-up. To our knowledge, no previous studies have shown such clear, long-lasting economic effects of behavioural interventions for FSS.

We found the medium-term cost-effectiveness from a societal perspective to be uncertain because of the short-term higher indirect costs associated with the STreSS treatment period, illustrating that intensive treatment may be associated with temporarily increased sick-leave. However, in the longer term, STreSS was associated with markedly reduced indirect costs, and with stable reductions in healthcare expenditures as compared with EUC.

Our medium-term results are consistent with other studies that have explored the cost-effectiveness of group or individual CBT for FSS patients in terms of gains in quality-adjusted life years (QALYs).^{8;17} In the PACE trial, which compared four treatments for chronic fatigue syndrome, CBT was most likely to be cost-effective from both a healthcare and societal perspective.^{16;17} However, data were available for 12 months only, and estimation of indirect costs was less conservative since unpaid informal care from relatives was included. Our study estimated indirect costs on the background of actual public transfer payments, an approach that may underestimate rather than overestimate the real economic savings for society, as it does not account for reduced productivity at work in employed patients.⁶ Moreover, the PACE trial used the EQ-5D as measure of preference-based utility,

while our study used the SF-6D. Studies indicate that the minimally important difference for the SF-6D is about half the range of the EQ-5D, which may explain the rather small gain of QALYs accrued in this study.⁴⁴ Moreover, studies of patients with pain syndromes have demonstrated that the SF-6D may be less responsive to change.⁴⁵ Taken together, the gain of QALYs found in this study is comparable with that found in similar studies.

A recent study of individual psychodynamic interpersonal treatment for patients with multisomatoform disorder reported low likelihood for the psychological treatment to be cost-effective.⁴³ However, the economic analysis in that study was conducted from the payer's perspective and included only direct intervention costs. The economic analyses are hence not comparable.

STreSS had no systematic focus on employment-related topics and did not use strategies for individual placement.^{46;47} It is unclear whether the addition of such strategies would further increase the intervention's ability to reduce indirect costs, which has been found in patients with depression and anxiety.⁴⁸ However, another recent study in patients with depression found long-lasting effects of traditional CBT on employment rates compared with antidepressant medication.⁴⁹ A systematic focus on employment during therapy may therefore not be necessary to achieve long-term improvements in employment status, since patients may generalize required skills from symptom management to the vocational sphere.

Strengths and limitations

Our study has a number of strengths. First, we explored the economic consequences of the STreSS intervention by means of two different analytic approaches using all available data for each type of analysis. Moreover, we calculated indirect costs both with and without tax savings. As the results point towards beneficial economic consequences of the STreSS intervention in all analytic approaches, our conclusions are robust. Second, we relied on

high-quality register data, which not only provided us with a complete dataset, but also avoided any recall- or response-bias. This is especially important as patients could not be blinded to treatment allocation, leading to a possibility of bias in self-reported outcomes. Third, we were able to follow patients up to three years post-treatment and found not only stable, but also increasing economic effects, thereby reducing the likelihood that the observed cost-reduction following STreSS was only temporary. Finally, we included patients with a range of FSS from both primary and secondary care, still using a precise diagnostic algorithm, which strengthens the generalisability and clinical relevance of our findings.¹⁹

Our study also has potential limitations. First, we had some attrition of self-report data in CEA, making this part of the study slightly more prone to potential bias. However, we were able to address this by means of multiple imputations. Second, our trial had a moderate sample size, and as cost data were highly skewed, we had limited power to carry out CMA. However, we were able to address this by a number of statistical methods such as bootstrapping. Third, we calculated the intervention costs from register data, which does not account for additional costs associated with the development and implementation of a new treatment and training of health professionals to deliver it. However, by using the same independent data source as for all other cost, intervention costs mirror actual reimbursement in routine clinical care. In addition, applying higher intervention costs would not change the observed pattern of increasing savings following STreSS. Fourth, our estimate for total cost savings of 7,184 € during the third year after treatment may be influenced both by the unavailability of cost data for general hospital care for this period, and our use of transfer payments to calculate indirect costs. Since costs for the domain general hospital care were lower after STreSS than after EUC in both the first and second year after treatment, the lack of this domain during the third year after treatment may result in an underestimation of direct

cost savings after STreSS. Moreover, as transfer payments used to calculate public expenses do not take loss of productivity into account, they may underestimate real indirect cost savings after STreSS. Taken together, potential inaccuracies in our estimation of cost savings may underestimate rather than overvalue the long-term economic consequences of STreSS. Finally, we cannot assume that our finding generalise to countries with different healthcare and welfare systems.⁵⁰ However, while direct and indirect costs associated with FSS may differ between countries, the beneficial long-term effect of STreSS on healthcare use and employment status found in our study would very likely be associated with cost savings in other economic and healthcare systems.

Implications

A bespoke cognitive-behavioural group treatment for people with a range of FSS had a very high likelihood to be cost-effective from a healthcare perspective and was associated with lasting, long-term reductions of both direct and indirect costs. The wider implementation of STreSS may therefore not only lead to better functioning and increased quality of life for many patients, but also to substantial savings in public expenditures.

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ACCEPTED MANUSCRIPT

REFERENCES

- 1 Simon G, Gater R, Kisely S, Piccinelli M. Somatic symptoms of distress: an international primary care study. *Psychosomatic Med* 1996; 58: 481-8.
- 2 Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? *Lancet* 1999; 354: 936-9.
- 3 Whitehead LC. Quest, chaos and restitution: Living with chronic fatigue syndrome/myalgic encephalomyelitis. *Soc Sci Med* 2005; 62: 2236-45.
- 4 Barsky AJ, Orav EJ, Bates DW. Somatization increases medical utilization and costs independent of psychiatric and medical comorbidity. *Arch Gen Psychiatry* 2005; 62: 903-10.
- 5 Burton C, McGorm K, Richardson G, Weller D, Sharpe M. Healthcare costs incurred by patients repeatedly referred to secondary medical care with medically unexplained symptoms: a cost of illness study. *J Psychosom Res* 2012; 72: 242-7.
- 6 Konnopka A, Kaufmann C, König HH, Heider D, Wild B, Szecsenyi J et al. Association of costs with somatic symptom severity in patients with medically unexplained symptoms. *J Psychosom Res* 2013; 75: 370-5.
- 7 Creed F, Henningsen P, Fink P. Medically unexplained symptoms, somatisation and bodily distress. Developing better clinical services. In: Creed F, Henningsen P, Fink P, editors. Cambridge University Press; 2011.
- 8 Konnopka A, Schaefer R, Heinrich S, Kaufmann C, Lupp M, Herzog W et al. Economics of medically unexplained symptoms: a systematic review of the literature. *Psychother Psychosom* 2012; 81: 265-75.
- 9 Chandran A, Schaefer C, Ryan K, Baik R, McNett M, Zlateva G. The comparative economic burden of mild, moderate, and severe fibromyalgia: results from a retrospective chart review and cross-sectional survey of working-age U.S. adults. *J Manag Care Pharm* 2012; 18: 415-26.
- 10 Fjorback LO, Carstensen T, Arendt M, Ornbol E, Walach H, Rehfeld E et al. Mindfulness therapy for somatization disorder and functional somatic syndromes: analysis of economic consequences alongside a randomized trial. *J Psychosom Res* 2013; 74: 41-8.
- 11 Rask MT, Rosendal M, Fenger-Gron M, Bro F, Ornbol E, Fink P. Sick leave and work disability in primary care patients with recent-onset multiple medically unexplained symptoms and persistent somatoform disorders: a 10-year follow-up of the FIP study. *Gen Hosp Psychiatry* 2015; 37: 53-9.
- 12 Zijdenbos IL, de Wit NJ, van der Heijden GJ, Rubin G, Quartero AO. Psychological treatments for the management of irritable bowel syndrome. *Cochrane Database Syst Rev* 2009;1: CD006442.
- 13 Henningsen P, Zipfel S, Herzog W. Management of functional somatic syndromes. *Lancet* 2007; 369: 946-55.

- 14 Glombiewski JA, Sawyer AT, Gutermann J, Koenig K, Rief W, Hofmann SG. Psychological treatments for fibromyalgia: A meta-analysis. *Pain* 2010; 151: 280-95.
- 15 Kleinstaub M, Witthoft M, Hiller W. Efficacy of short-term psychotherapy for multiple medically unexplained physical symptoms: a meta-analysis. *Clin Psychol Rev* 2011; 31: 146-60.
- 16 White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet* 2011; 377: 823-36.
- 17 McCrone P, Sharpe M, Chalder T, Knapp M, Johnson AL, Goldsmith KA et al. Adaptive pacing, cognitive behaviour therapy, graded exercise, and specialist medical care for chronic fatigue syndrome: a cost-effectiveness analysis. *PLoS ONE* 2012; 7: e40808.
- 18 Schröder 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.
- 19 Schröder A, Sharpe M, Fink P. Medically unexplained symptom management. *The Lancet Psychiatry* 2015; 2: 588.
- 20 Schröder A. Cognitive-behavioural group therapy for severe functional somatic syndromes: treatment model and empirical evidence. *Verhaltenstherapie und Verhaltensmedizin* 2014; 35: 3-23.
- 21 Schröder A, Rehfeld E, Ornbøl 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.
- 22 Lam TP, Goldberg DP, Dowell AC, Fortes S, Mbatia JK, Minhas FA et al. Proposed new diagnoses of anxious depression and bodily stress syndrome in ICD-11-PHC: an international focus group study. *Fam Pract* 2013; 30: 76-87.
- 23 Rask MT, Ørnbøl E., Rosendal M, Fink P. Long-term outcome of bodily distress syndrome in primary care: a follow-up study on healthcare costs, work disability, and self-rated health. *Psychosom Med* 2016; DOI: 10.1097/PSY.0000000000000405.
- 24 Budtz-Lilly A, Vestergaard M, Fink P, Carlsen AH, Rosendal M. The prognosis of bodily distress syndrome: a cohort study in primary care. *Gen Hosp Psychiatry* 2015; 37: 560-6.
- 25 Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011; 39 (Suppl): 38-41.
- 26 Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011; 39 (Suppl): 30-3.
- 27 Andersen JS, Olivarius NF, Krasnik A. The Danish National Health Service Register. *Scand J Public Health* 2011; 39 (Suppl): 34-7.

- 28 Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health* 2011; 39 (Suppl): 54-7.
- 29 Hjollund NH, Larsen FB, Andersen JH. Register-based follow-up of social benefits and other transfer payments: accuracy and degree of completeness in a Danish interdepartmental administrative database compared with a population-based survey. *Scand J Public Health* 2007; 35: 497-502.
- 30 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.
- 31 Fink P, Schröder A. One single diagnosis, Bodily distress syndrome, succeeded to capture ten diagnostic categories of functional somatic syndromes and somatoform disorders. *J Psychosom Res* 2010; 68: 415-26.
- 32 Creed F, van der Feltz-Cornelis C, Guthrie E, Henningsen P, Rief W, Schröder A et al. Identification, assessment and treatment of individual patients. In: Creed F, Henningsen P, Fink P, editors. *Medically unexplained symptoms, somatisation and bodily distress*. New York: Cambridge University Press; 2011.
- 33 Skovenborg EL, Schröder A. Is physical disease missed in patients with medically unexplained symptoms? A long-term follow-up of 120 patients diagnosed with bodily distress syndrome. *General Hospital Psychiatry* 2014; 36: 38-45.
- 34 Ware J, Kosinski M, Gandek B. *SF-36 Health Survey: Manual & Interpretation Guide*. Lincoln, RI: Quality Metric Incorporated; 2005.
- 35 Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002; 21: 271-92.
- 36 Schröder A, Ørnbøl E, Licht RW, Sharpe M, Fink P. Outcome measurement in functional somatic syndromes: SF-36 summary scores and some scales were not valid. *Journal of Clinical Epidemiology* 2012; 65: 30-41.
- 37 Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003; 41: 582-92.
- 38 Houlberg K, Kolodziejczyk C, Christensen N. Evaluering af Det Store TTA-projekt. Delrapport om økonomisk evaluering. 2012. Copenhagen, KORA, Det Nationale Institut for Kommuner og Regioners Analyse og Forskning.
- 39 Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005; 14: 487-96.
- 40 Manca A, Palmer S. Handling missing data in patient-level cost-effectiveness analysis alongside randomised clinical trials. *Appl Health Econ Health Policy* 2005; 4: 65-75.

- 41 Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves--facts, fallacies and frequently asked questions. *Health Econ* 2004; 13 :405-15.
- 42 Burton A, Billingham LJ, Bryan S. Cost-effectiveness in clinical trials: using multiple imputation to deal with incomplete cost data. *Clin Trials* 2007; 4: 154-61.
- 43 Chernyak N, Sattel H, Scheer M, Baechle C, Kruse J, Henningsen P et al. Economic evaluation of brief psychodynamic interpersonal therapy in patients with multisomatoform disorder. *PLoS ONE* 2014; 9: e83894.
- 44 Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res* 2005; 14 :1523-32.
- 45 Sogaard R, Christensen FB, Videbaek TS, Bunger C, Christiansen T. Interchangeability of the EQ-5D and the SF-6D in long-lasting low back pain. *Value Health* 2009; 12: 606-12.
- 46 Reme SE, Grasdal AL, Lovvik C, Lie SA, Overland S. Work-focused cognitive-behavioural therapy and individual job support to increase work participation in common mental disorders: a randomised controlled multicentre trial. *Occup Environ Med* 2015; 72: 745-52.
- 47 Burns T, Yeeles K, Langford O, Montes MV, Burgess J, Anderson C. A randomised controlled trial of time-limited individual placement and support: IPS-LITE trial. *Br J Psychiatry* 2015; 207: 351-6.
- 48 Lagerveld SE, Blonk RW, Brenninkmeijer V, Wijngaards-de ML, Schaufeli WB. Work-focused treatment of common mental disorders and return to work: a comparative outcome study. *J Occup Health Psychol* 2012; 17: 220-234.
- 49 Fournier JC, DeRubeis RJ, Amsterdam J, Shelton RC, Hollon SD. Gains in employment status following antidepressant medication or cognitive therapy for depression. *Br J Psychiatry* 2015; 206: 332-338.
- 50 Eilenberg T, Frostholm L, Schroder A, Jensen JS, Fink P. Long-term consequences of severe health anxiety on sick leave in treated and untreated patients: Analysis alongside a randomised controlled trial. *J Anxiety Disord* 2015; 32: 95-102.

Table 1
Demographic and clinical characteristics and service use at baseline

	STreSS group (N=54)	Enhanced Usual Care group (N=66)
<i>Demographic characteristics</i>		
Age (years): mean (s.d.)	35.4 (6.3)	36.2 (6.5)
Gender: female, n (%)	40 (74 %)	55 (83 %)
Education, n (%)		
Basic school (7 th — 10 th)	31 (57 %)	36 (55 %)
Further education	23 (43 %)	30 (45 %)
<i>Clinical characteristics</i>		
Number of functional somatic symptoms: mean (s.d.)	32.3 (7.5)	32.6 (10.0)
Illness duration, years: median (IQR)	6.7 (3-14)	9.5 (4-15)
Functional somatic syndromes, ^{a,b} n (%)		
Chronic fatigue syndrome	30 (56 %)	41 (62 %)
Fibromyalgia	38 (70 %)	40 (61 %)
Irritable bowel syndrome	19 (35 %)	24 (36 %)
Non-cardiac chest pain	28 (52 %)	34 (52 %)
Hyperventilation syndrome	10 (19 %)	12 (18 %)
Tension-type headache	41 (76 %)	48 (73 %)
At least one of the above diagnoses	53 (98 %)	60 (91 %)
Lifetime psychiatric comorbidity, n (%)	31 (57 %)	40 (61 %)
Somatoform disorders (DSM-IV codes), ^b n (%)		
Somatisation disorder (300.81)	21 (39 %)	33 (50 %)
Undifferentiated somatoform disorder (300.82)	33 (61 %)	33 (50 %)
Pain disorder (307.80)	22 (41 %)	19 (29 %)
Hypochondriasis (300.7)	6 (11 %)	1 (2 %)
At least one of the above diagnoses	54 (100 %)	66 (100 %)
<i>Social benefits and healthcare use</i>		
Received benefits within past 12 months, ^c n (%)		
Health related benefits		
Temporary	22 (41 %)	23 (35 %)
Permanent	11 (20 %)	17 (26 %)
Labour-market related benefits	12 (22 %)	20 (30 %)
At least one of these benefits	40 (74 %)	51 (77 %)
Service used within past 12 months, n (%)		
Family physician	54 (100 %)	66 (100 %)
Physiotherapy / Chiropractor	16 (30 %)	30 (45 %)
General hospital care		
Outpatient	52 (96 %)	64 (97 %)
Inpatient	15 (28 %)	14 (21 %)
Mental health care		
Outpatient ^d	10 (19 %)	17 (26 %)
Inpatient	0 (0 %)	1 (2 %)
Prescription medication	41 (76 %)	45 (68 %)

IQR, interquartile range

^a Diagnoses based on functional somatic symptoms in the past 2 years, according to SCAN-diagnostic interview and review of clinical records.

^b Allowing more than one diagnosis per patient.

^c Allowing more than one type of benefit per patient.

^d Without project-related procedures (clinical assessment).

Table 2a: Healthcare (i.e. direct) costs before and after randomisation

% of patients using the service, and mean service costs in 2010 Euro		1 year before	Treatment period 4 months ^a	1. year after	2. year after	3. year after
primary care						
Family physician	EUC	100%, 482	98%, 130	98%, 373	98%, 356	98%, 319
	STreSS	100%, 382	89%, 99	98%, 245	96%, 266	96%, 252
Physiotherapy/Chiropractor	EUC	45%, 143	24%, 36	32%, 158	35%, 148	41%, 63
	STreSS	30%, 48	19%, 11	36%, 27	30%, 25	28%, 22
general hospital care						
outpatient	EUC	97%, 1092	61%, 327	91%, 1217	91%, 1204	n.a.
	STreSS	96%, 1383	65%, 286	91%, 886	89%, 985	n.a.
inpatient	EUC	21%, 1253	3%, 78	23%, 1438	18%, 1187	n.a.
	STreSS	28%, 802	13%, 228	15%, 614	20%, 854	n.a.
mental health care						
outpatient	EUC	98%, 671	18%, 221	32%, 347	24%, 297	n.a.
	STreSS	100%, 655	94%, 1631	22%, 131	17%, 159	n.a.
inpatient	EUC	2%, 141	2%, 133	3%, 797	3%, 472	n.a.
	STreSS	0%, -	2%, 16	0%, -	2%, 1109	n.a.
medication						
	EUC	68%, 465	59%, 183	65%, 668	62%, 744	62%, 751
	STreSS	76%, 273	56%, 112	74%, 346	69%, 271	59%, 248
Total annual healthcare costs^d						
	EUC	4106	976 ^a	4200	3937	1132 ^c
	STreSS	3544	2369 ^a	2250	2560	523 ^c
Difference in means? (ASL)^b		no (0.209)	yes (0.000)	yes (0.002)	yes (0.034)	yes (0.001)

n.a. = not available; ASL = achieved significance level

a. Actual costs for the 4-months treatment period, numbers are not directly comparable with annual cost data.

b. Test for equality of means, non-parametric bootstrap with 1000 replications

c. Without general hospital and mental health care (data not available); numbers are not comparable with the preceding years

d. Without inpatient mental health care costs, cf. Methods

Table 2b. Indirect and total costs (all public expenses, both direct and indirect) before and after randomisation

% of patients receiving transfer payments, and mean indirect costs in 2010 Euro		1 year before	Treatment period 4 months ^a	1. year after	2. year after	3. year after
health-related benefits						
temporary	EUC	35%, 6460	23%, 1406	24%, 2615	18%, 1955	17%, 2015
	STreSS	41%, 7805	39%, 2421	39%, 4226	22%, 2094	13%, 1415
permanent	EUC	26%, 5909	32%, 2269	45%, 9420	58%, 11879	62%, 13015
	STreSS	20%, 4683	22%, 1602	33%, 6856	39%, 8507	44%, 9415
labour-marked related benefits						
	EUC	30%, 4868	26%, 1413	26%, 4377	26%, 3411	20%, 2015
	STreSS	22%, 3429	22%, 1258	31%, 4504	31%, 3772	19%, 2015
self-support (tax income)	EUC	42%, -5438	39%, -2175	41%, -5814	33%, -5073	30%, -3015
	STreSS	44%, -6971	41%, -2164	46%, -6717	50%, -7580	50%, -7515
Total annual costs (direct plus indirect)						
including tax income	EUC	15904	3888 ^a	14799	16109	15704
	STreSS	12489	5487 ^a	11118	9353	6334
Difference in means? (ASL)^b		no (0.105)	no (0.108)	no (0.153)	yes (0.029)	yes (0.001)
without tax income	EUC	21342	6063 ^a	20613	21182	19664
	STreSS	19460	7650 ^a	17835	16933	14274
Difference in means? (ASL)^b		no (0.208)	yes (0.013)	no (0.099)	yes (0.023)	yes (0.001)

ASL = achieved significance level

a. Actual costs for the 4-months treatment period, numbers are not directly comparable with annual cost data.

b. Test for equality of means, non-parametric bootstrap with 1000 replications

c. Without general hospital and mental health care (data not available); numbers are not comparable with the preceding years

Table 3
QALYs and treatment response

SF-6D utilities (mean, 95% CI) and QALYs accrued during 16 months

	EUC	STreSS
Time point	(n=66)	(n=54)
Baseline	0.56 (0.54 – 0.58)	0.58 (0.55 – 0.60)
4 months*	0.56 (0.54 – 0.58)	0.60 (0.57 – 0.62)
10 months*	0.56 (0.54 – 0.59)	0.61 (0.58 – 0.64)
16 months**	0.56 (0.53 – 0.58)	0.62 (0.58 – 0.65)
QALYS accrued*	0.75 (0.72 – 0.78)	0.80 (0.77 – 0.84)

Percentage (95% CI) achieving clinically significant improvement during 16 months

Outcome: Physical health ^{*,a}	27% (15 – 39)	46% (32 – 61)
Outcome: Somatic symptoms ^{**,b}	17% (7 – 27)	45% (30 – 60)

* statistically significant difference between groups, $p < 0.05$; ** $p < 0.01$

^a Primary trial outcome, measured with aggregate score of SF-36 scales physical functioning, bodily pain and vitality

^b Secondary trial outcome, measured with SCL-90-R somatisation subscale

EUC = Enhanced Usual Care, STreSS = Specialised Treatment for Severe Bodily Distress Syndromes (group CBT programme)

CI = Confidence interval

Table 4

Cost-effectiveness results from healthcare and societal perspectives, 0-16 months

	STreSS vs. EUC [95 % CI]
Outcome: QALYs	
Incremental effect	0.035 [0.00 ; 0.07]*
Incremental healthcare cost	-917 € [-3769 € ; 1936 €] ^{NS}
ICER (healthcare)	dominant (-26,311 €) ^d
Incremental total (i.e. direct plus indirect) cost	858 € [-5068 € ; 6785 €] ^{NS}
ICER (societal)	24,640 €
Outcome: Physical health	
Incremental effect ^a	20% [0.4% ; 39%]*
ICER (healthcare) ^{b,c}	dominant (-4696 €) ^d
ICER (societal) ^{b,c}	4398 €
Outcome: Somatic symptoms	
Incremental effect ^a	28% [10% ; 46%]*
ICER (healthcare) ^{b,c}	dominant (-3241 €) ^d
ICER (societal) ^{b,c}	3035 €

* p<0.05 NS=non significant

a. Percentage point difference between groups.

b. Per person improved (as compared to EUC).

c. Incremental healthcare and total (direct plus indirect) costs are the same for all three outcomes.

d. A treatment is regarded 'dominant' if its costs are lower and its outcomes better than another treatment. In this case, incremental cost-effectiveness ratio (ICER) is negative and usually not calculated, as it is difficult to interpret.

EUC = Enhanced Usual Care, STreSS = Specialised Treatment for Severe Bodily Distress Syndromes (group CBT programme)

CI = Confidence interval

Figure captions

Figure 1 A, B Cost-effectiveness acceptability curves

Cost-effectiveness acceptability curves for quality-adjusted life years (QALYs, A) and additional patient improvement (B) from both a healthcare and a societal (i.e. total cost) perspective. This medium-term analysis covers the trial-period of 16 months. Dotted vertical lines indicate levels at which society may value health effects, i.e. the threshold willingness to pay for one additional QALY (35,000 €) or one additional patient achieving clinically significant improvement (5,000 €) as compared with enhanced usual care.

STreSS = Specialised Treatment for Severe Bodily Distress Syndromes (cognitive-behavioural group treatment)

Figure 2 Cost-effectiveness planes

Cost-effectiveness planes of 1000 bootstrap replicated incremental cost-effectiveness ratios comparing STreSS and enhanced usual care. Data are presented from both a healthcare (left column) and a societal (i.e. total cost, right column) perspective. Effects represent quality-adjusted life years (QALYs, top row) and additional proportion of patients reporting clinically significant symptom reduction (middle row) or physical health improvement (bottom row). Scatter plots in the southeast quadrant indicate that STreSS produces more QALYs or a higher proportion of improved patients at a lower cost than enhanced usual care.

STreSS = Specialised Treatment for Severe Bodily Distress Syndromes (cognitive-behavioural group treatment)

Appendix

Table A.1

Cost tariffs for indirect costs^a

Category	Costs / week (2010 €) ^b
health-related benefits	
<i>temporary</i>	477 - 500
<i>permanent</i>	442 - 446
labour-marked related benefits	400 - 500
self-support (tax income)^c	-382

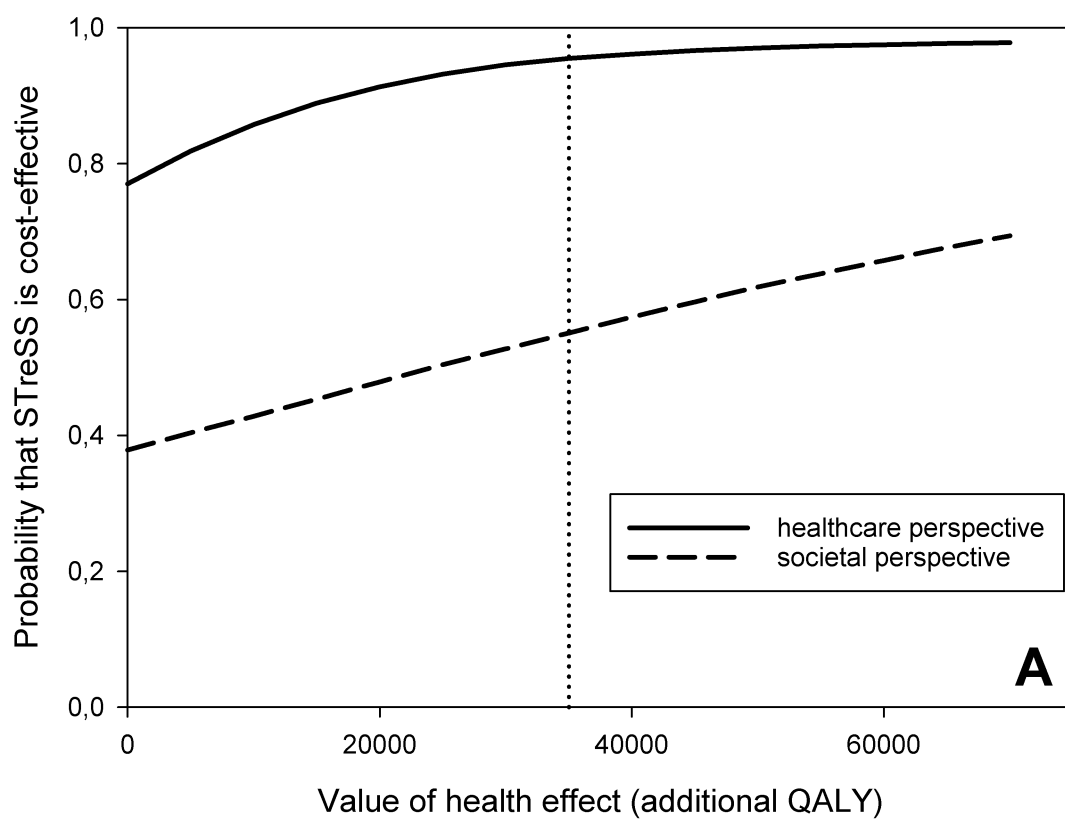
DREAM = Danish Register-based Evaluation of Marginalization database⁵

a. Indirect costs were calculated as public expenses associated with occupational status and social benefits

b. Weekly standard costs within the category (min - max); assigned costs were based on specific DREAM codes^{29,38}

c. Weeks without transfer payments were assigned negative costs due to estimated public tax income; or zero in sensitivity analyses without tax income

A list linking standard costs to specific DREAM codes is available from the authors on request



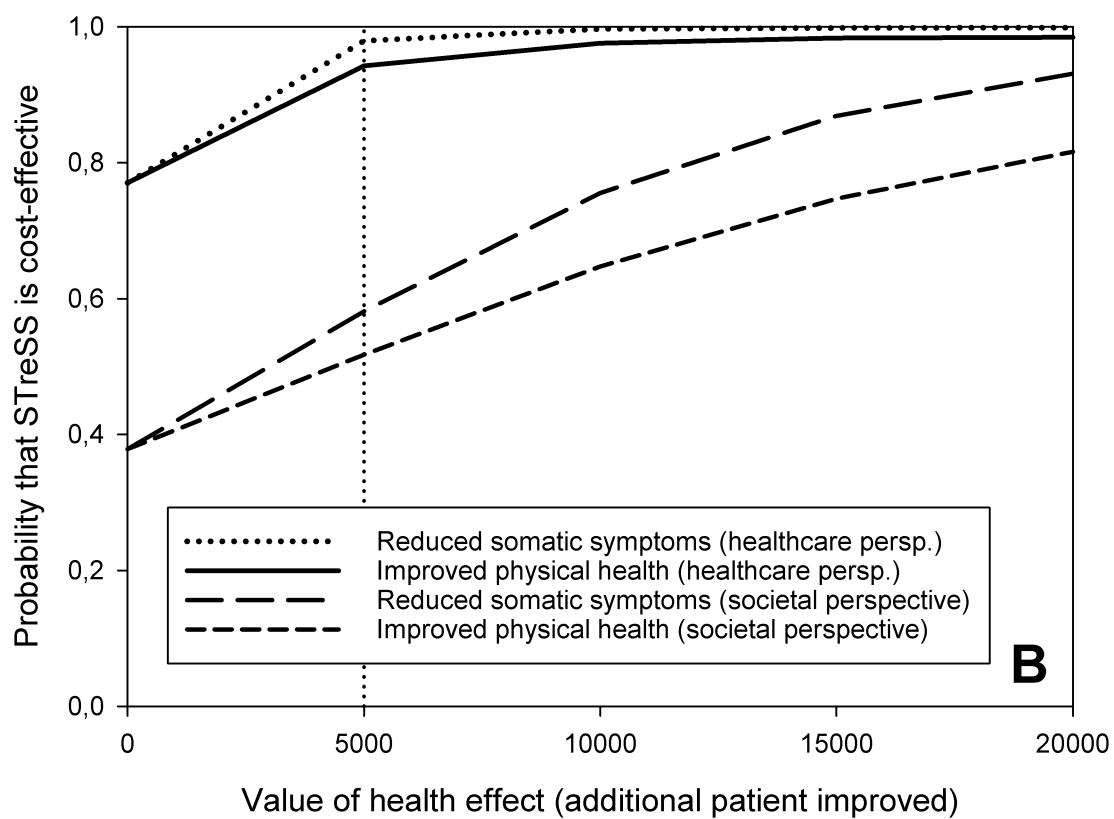
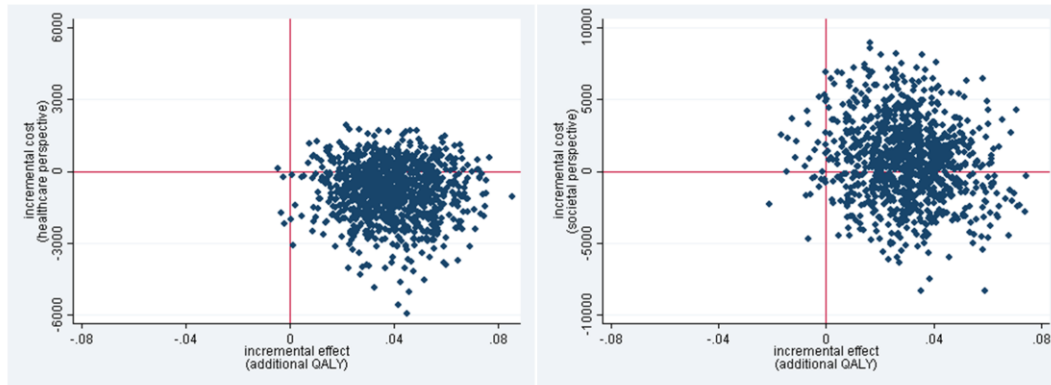


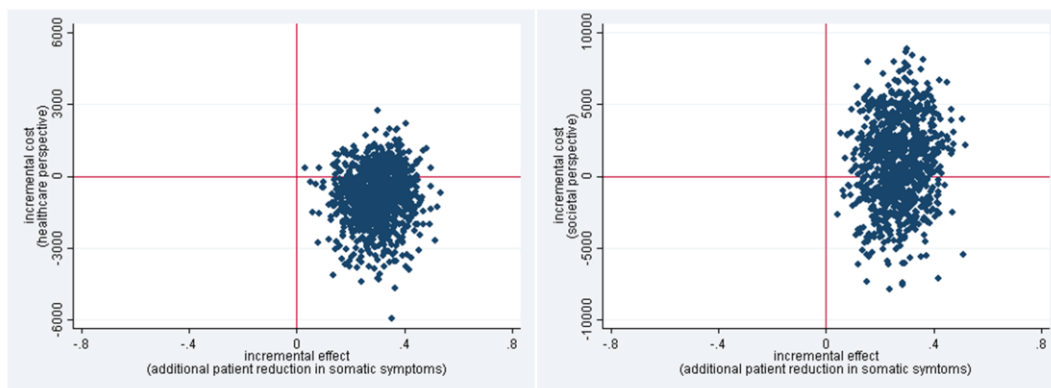
Fig. 1

**Cost-effectiveness planes from healthcare (left column)
and societal (right column) perspectives, 0-16 months**

1. QALYs



2. Reduction in somatic symptoms



3. Improvement in physical health (primary outcome)

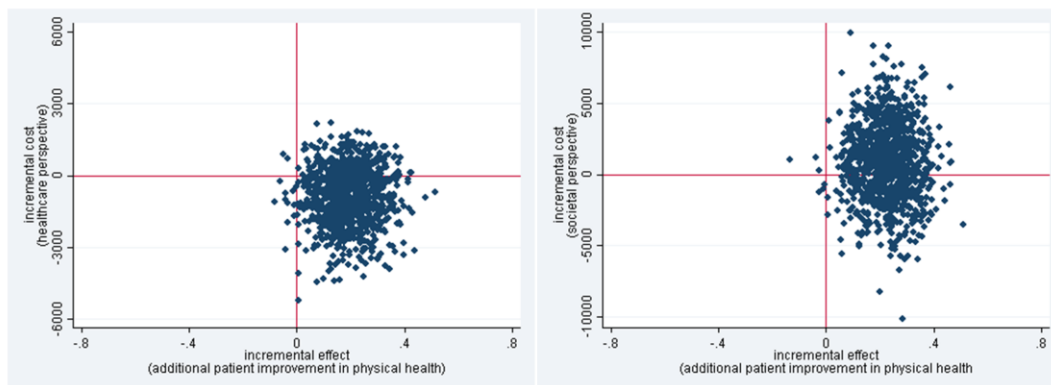


Fig. 2

Highlights

- STreSS had a very high likelihood to be cost-effective from a healthcare perspective
- Medium-term cost-effectiveness from a societal perspective was uncertain
- This may be due to higher indirect costs (i.e. sickness benefits) during treatment
- In the long-term, STreSS was associated with increasing cost savings
- Implementation may lead to substantial savings in public expenditures