Web-based cognitive behavioural therapy blended with face-to-face sessions for chronic fatigue in type 1 diabetes

Web-based cognitive behavioural therapy blended with face-to-face sessions for chronic fatigue in type 1 diabetes: a multicentre randomised controlled trial

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Summary

Background Fatigue in type 1 diabetes is prevalent and persistent, but so far, no evidence-based treatments are available. We aimed to investigate the efficacy of cognitive behavioural therapy (CBT) in reducing fatigue severity in patients with type 1 diabetes.

Methods We did a multicentre randomised controlled trial at one university medical centre and four large teaching hospitals in the Netherlands. Eligible patients were aged 18–70 years and had type 1 diabetes for at least 1 year and chronic fatigue for at least 6 months. We randomly assigned patients (1:1) to CBT or waiting list using computer-generated blocked randomisation, stratified by type of enrolment. The CBT intervention (Dia-Fit) was given for 5 months in blended form, consisting of face-to-face and web-based sessions. The primary outcome was fatigue severity assessed 5 months after randomisation, directly after the intervention or waiting list period, with the Checklist Individual Strength fatigue severity subscale. Secondary outcomes were functional impairment (assessed with the total score of the Sickness Impact Profile-8), glycaemic control (HbA_{1c}), and glucose variability. Analyses were done by intention to treat. This trial is registered with the Nederlands Trial Register, number NTR4312.

Findings Between Feb 6, 2014, and March 24, 2016, we randomly assigned 120 eligible patients to either CBT (n=60) or waiting list (n=60), all of whom were included in the intention-to-treat analyses. Compared with patients in the waiting list group, those in the CBT group had significantly lower fatigue severity scores (mean difference 13·8, 95% CI 10·0–17·5; p<0·0001) and significantly lower scores for functional impairment (mean difference 513, 95% CI 340–686; p<0·0001) after 5 months. HbA_{1c} and glucose variability did not change after treatment and there was no difference between groups. Five patients in the CBT group and seven in the waiting list group reported adverse events; none were deemed to be related to the study intervention.

Interpretation Although our findings need to be confirmed in larger and longer-term studies, they suggest that CBT can effectively reduce fatigue severity and functional impairment in type 1 diabetes.

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Introduction

Chronic fatigue, defined as severe fatigue that is present for at least 6 months and has a substantial effect on daily functioning, is a prevalent and burdensome complaint of patients with type 1 diabetes, according to findings from the few studies done so far.[1] In these studies, up to 40% of patients with type 1 diabetes are reported to have chronic fatigue and have significantly higher scores on fatigue scales than people from the general population.[2,3] Patients have reported that fatigue is one of the most burdensome symptoms of their disease,[2] and fatigue is persistent in three of four severely fatigued patients with type 1 diabetes.[4] Although an association between fatigue in type 1 diabetes and glycaemic control seems plausible, several studies[2,4,5] could not clearly confirm an association.

To our knowledge, no intervention studies to investigate the management of fatigue in patients with type 1 diabetes have been reported before now. Randomised controlled trials in other chronic diseases and conditions characterised by severe and disabling fatigue have shown that cognitive behavioural therapy (CBT) can significantly reduce fatigue.[6–8] CBT is based on a cognitive-behavioural model of fatigue, assuming that disease-specific elements trigger the fatigue, whereas the fatigue is maintained by cognitive-behavioural factors.[9] Applied to type 1 diabetes, the primary disease—specifically hyperglycaemia, diabetes-related complications, or somatic comorbidities—seems likely to trigger fatigue,[10] whereas several cognitive-behavioural factors such as self-efficacy concerning fatigue, pain, sleep disturbances, and physical inactivity perpetuate fatigue.[2,4] On the basis of this construct, we developed a CBT intervention for chronic fatigue in type 1 diabetes, which is delivered in blended form as a combination of face-to-face sessions and web-based modules.[10]

In the present study, we investigated the efficacy of this CBT approach in reducing severe fatigue after 5 months of treatment. Additionally, we studied the effects of CBT on functional impairment, glycaemic control (HbA_{1c}), and glucose variability, because we speculated that reduced

Research in context

Evidence before this study

Fatigue in patients with type 1 diabetes is prevalent, associated with functional impairment, and reported as one of the most disabling symptoms of type 1 diabetes by patients. Additionally, it has been reported that fatigue in patients with type 1 diabetes is persistent and perpetuated by cognitive behavioural variables. We systematically searched Cochrane databases, PubMed, and PsycINFO for research articles (and protocols) of randomised controlled trials testing the efficacy of cognitive behavioural interventions for fatigue in patients with type 1 diabetes from the databases' inception until Jan 11, 2017. We used the search terms "type 1 diabetes mellitus" or "insulin-dependent diabetes mellitus" or "juvenile-onset diabetes mellitus"; and "fatigue" in MesH heading and free text words, and "cognitive behavioural therapy" or "cognitive therapy" or "psychotherapy". We used no language restrictions in our search. Aside from the published protocol for the present trial, we did not identify any reports or protocols of randomised controlled trials on cognitive behavioural interventions that address fatigue in patients with type 1 diabetes.

Added value of this study

To our knowledge, the present randomised controlled trial is the first to provide evidence of a cognitive behavioural intervention on fatigue in patients with type 1 diabetes. Our results show that cognitive behavioural therapy (CBT) leads to a significant reduction of fatigue severity and functional impairment in chronically fatigued patients compared with a waiting list control group. HbA_{1c} and glucose variability were not affected by the CBT intervention.

Implications of all the available evidence

Despite its high prevalence and associated disability, fatigue in type 1 diabetes remains an understudied symptom. The findings from the present study show that fatigue in type 1 diabetes is significantly reduced after CBT compared with a waiting list control group. Although these findings need to be replicated, they suggest that fatigue in type 1 diabetes can be effectively treated and CBT can reduce the burden of fatigue for patients with type 1 diabetes.

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fatigue might enable patients to improve diabetes self-management. Furthermore, in an explorative uncontrolled analysis, we investigated whether the expected positive effects of treatment were sustained at follow-up, 6 months after the post-treatment assessment.

Methods

Study design and participants

For this multicentre randomised controlled trial, we recruited patients from one university medical centre and four large teaching hospitals in the southeast of the Netherlands, and by placing advertisements on social media and sending flyers to other hospitals in the area. Eligible patients were aged 18–70 years; had been diagnosed with type 1 diabetes for at least 1 year; were able to speak, read, and write Dutch; had a score of 35 or higher on the fatigue severity subscale of the Checklist Individual Strength, reflecting a score higher than the mean and at least two SDs above the score of a healthy population;[11] and had a duration of fatigue of 6 months or longer, as indicated by the patient. Exclusion criteria were moderate-to-severe renal failure (estimated glomerular filtration rate ≤45 mL/min per 1·73 m²), blindness or severe visual impairment, medical history of congestive heart failure, medical history of a stroke in the past 5 years, BMI of 40 kg/m² or higher, wheelchair-dependence, and other concurrent psychiatric or medical comorbidity that could account for the fatigue.

Patients were screened by their treating consultant for the first three inclusion criteria (age, type of diabetes and time since diabetes diagnosis, and ability to speak, read, and write Dutch) and all exclusion criteria. Eligible patients received an invitation letter for the study with a screening questionnaire for chronic fatigue attached to it (fatigue severity and duration were assessed with the Checklist Individual Strength fatigue severity subscale and a question regarding the duration of fatigue). A consultant from the Radboud University Medical Centre, Nijmegen, Netherlands, screened patients who enrolled for the study via self-referral for eligibility before inclusion.

The local medical ethical committees of all hospitals reviewed and approved the study (registration number 2013/165, NL43178.091.13). All participants received written and verbal information about the study, and provided written informed consent. A detailed description of the study protocol has been published.[10]

Randomisation and masking

Patients were randomly assigned (1:1) to either the intervention group (CBT) or a waiting list control group. The waiting list control is representative of usual care because no evidence-based fatigue treatment for patients with type 1 diabetes is available.

The randomisation was computer-generated with blocks of six, stratified by type of enrolment (referred from hospitals *vs* self-referred via social media or flyers). A test assistant who was not involved in the trial did the randomisation in the presence of the patient and the researcher (JM). Patients were unmasked because of the nature of the study and the researcher was unmasked for practical reasons. The researcher who obtained the data (JM) was unmasked to the patients' assignment condition. An independent researcher who was not involved in the study and was masked to treatment allocation did the statistical analyses.

Procedures

The intervention was CBT for chronic fatigue in type 1 diabetes (named Dia-Fit), designed to address fatigue-perpetuating factors.[10] Dia-Fit was given in blended form consisting of five to eight face-to-face sessions of 50 min with a therapist and web-based modules offered through an internet portal. Dia-Fit had a duration of 5 months and consisted of up to eight modules: goal setting, regulation of the sleep-wake pattern, formulation of helpful fatigue-related beliefs, activity regulation and graded activity, coping with pain, optimisation of social support and interactions, reduction of diabetes-related distress, and step-by-step realisation of goals. The intervention was tailored to the individual pattern of perpetuating factors of patients. The criteria for the indication of the modules and their content is described in the appendix and in the trial protocol.[10]

Three clinical psychologists (licensed cognitive behavioural therapists from the Radboud University Medical Centre, Nijmegen, Netherlands) delivered the treatment. All therapists were experienced in the treatment of chronic fatigue and were trained in delivering the Dia-Fit intervention. During the trial, therapists received supervision every 2 weeks from a clinical psychologist (HK). The supervision was given in between the face-to-face sessions to discuss the treatment's progress. Face-to-face sessions were audiotaped, and emails sent in the web-based portal were stored. Two independent evaluators rated a random sample of 5% of both face-to-face sessions and emails to determine treatment integrity. We calculated the proportion of intervention elements that was delivered in accordance with the treatment protocol, and the inter-rater agreement. We determined treatment adherence with two measures: a scale of 0 (not adherent at all) to 10 (fully adherent), filled in by the therapist at the end of treatment; and a scale of 1 (not adherent at all) to 5 (fully adherent), filled in by the patient for each module. The two measures were correlated with the change score of fatigue severity (pre-post score). We distinguished between non-starters (ie, patients who completed not more than one face-to-face session), and study withdrawals (ie, patients who completed at least two face-to-face sessions but stopped the treatment prematurely).

Patients assigned to the waiting list control group also received the intervention after a 5 month waiting period, and were informed about this at randomisation. Patients in the waiting list group were free to mention their complaints to health-care providers and could undergo additional tests for fatigue.

Outcomes

All outcome measures were assessed before randomisation (baseline assessment), and 5 months after randomisation (at the end of the intervention or waiting period; second assessment). Additionally, outcome measures were assessed 6 months after treatment was finished (follow-up assessment) in the CBT group only. For ethical reasons, we decided to offer patients from the control group CBT after their participation in the waiting list study group. Therefore, the planned follow-up analysis to determine if the effect of CBT was sustained was uncontrolled.

The primary outcome was fatigue severity assessed at the end of the intervention or waiting list period (second assessment; 5 months after randomisation) with the Checklist Individual Strength fatigue severity subscale.[11] The eight questions of the fatigue severity subscale are scored with a Likert Scale ranging from 1 to 7. Total scores range from 8 to 56, with a score of 35 or higher indicating severe fatigue.[11] The Checklist Individual Strength has good psychometric properties.[12] Cronbach's α (a measure of internal consistency) in a sample of 214 patients with type 1 diabetes was high (α=0·952).[2]

Secondary outcomes were functional impairment assessed with the Sickness Impact Profile-8 total score (SIP-8),[13] HbA_{1c}, and glucose variability, assessed by standardised laboratory methods. The SIP-8 measures functional impairment in eight categories: sleep and rest, homemaking, mobility, social interactions, ambulation, leisure activities, alertness behaviour, and work, with higher scores indicating more severe impairment. Validity and reliability of the SIP-8 are high.[13] HbA_{1c} measurements were retrieved from medical records when possible (for baseline, when the measurement was made within 8 weeks before randomisation and, for second and follow-up data, when the measurement was made within 4 weeks after the second and follow-up assessment). When these data were not available, HbA_{1c} was measured for the study at the baseline, second assessment, and follow-up visits. In most patients, HbA_{1c} was measured pairwise within the same hospital. The participating hospitals share similar reference ranges for HbA_{1c} determination. Glucose variability was measured by the total SD of 14 glucose measures (ie, seven measures throughout the day during 2 consecutive days [before and after breakfast, before and after lunch, before and after dinner, and bedtime]).[14] Participants were asked to measure blood glucose values for the study immediately before randomisation for baseline, after the 5 month intervention or waiting period for second assessment, and 6 months after the end of the intervention for follow-up assessment.

Questionnaires assessing fatigue severity and functional impairment were filled in online whenever possible. When this was not possible, patients received a paper and pencil version of the questionnaires at home.

Statistical analysis

With an assumed clinically meaningful difference of 6 points between the intervention and waiting list group on the Checklist Individual Strength fatigue severity

subscale, and an SD of 8·6, we calculated that 120 participants (60 in each group) would be needed, assuming a power of 90%, a two-sided α of 0·05, a design factor of 0·96, and a 25% loss to second assessment.[10,15] The assumed clinically meaningful difference of 6 points was based on findings from a study that determined the efficacy of CBT in patients with chronic fatigue syndrome.[16]

We used the independent sample *t* test and χ^2 tests to assess differences between patients who enrolled via self-referral and via hospitals. Analyses of outcomes were done according to intention to treat. We hypothesised that the CBT intervention would reduce fatigue severity and functional impairment, improve HbA_{1c}, and reduce glucose variability, compared with the waiting list. For all outcomes, we used ANCOVA, with the second assessment score as dependent variable, the baseline score as covariate, and the study group (CBT *vs* waiting list group) as fixed factor. We repeated the analysis with an extra covariate (type of enrolment) to control for the possible effect of this variable on the effect of the intervention. Missing values were replaced with multiple imputation of 20 iterations under the assumption that data were missing at random.[17] We did two sensitivity analyses to test the robustness of the results. In the first approach, we replaced missing values with the last observation of that variable (last observation carried forward). In the second approach, we used a modified worst case scenario, in which missing values in the CBT group were replaced by the highest score of the CBT group at baseline and missing values in the waiting list group were replaced by the lowest score of the waiting list group at baseline. Finally, we did a post-hoc, per-protocol analysis excluding all participants who did not adhere to the treatment protocol.

We calculated the effect size (Cohen's *d*) for all significant outcome measures (ie, by subtracting the mean scores of the CBT group and the waiting list group at second assessment divided by the pooled SD of both groups); this analysis was post hoc. An effect size was classified as small (d=0·2–0·49), medium (d=0·5–0·79), or large (d≥0·8).[18]

We did a post-hoc analysis to assess whether more patients in the CBT group than in the control reported a clinically significant improvement on the primary outcome measure. We defined clinically significant improvement as a statistically reliable change,[19] plus a Checklist Individual Strength fatigue severity score of 34 or less. The statistically reliable change was calculated by a reliable change index with a normative group (n=110) of non-severely fatigued patients with type 1 diabetes.[2] We analysed the differences in the proportions of patients with clinically significant improvement between the CBT group and the waiting list group with χ^2 tests. Clinically significant improvement was visually displayed in a scatter plot.[20] Because depressive symptoms and diabetes distress are prevalent in patients with type 1 diabetes, we also did a post-hoc analysis with depressive symptoms (assessed with the Beck Depression Inventory for Primary Care)[21] and diabetes distress (assessed with the Problem Areas in Diabetes questionnaire[22] at baseline) as covariates in the ANCOVA to control for the possible effects of these variables on the effect of the intervention.

We investigated the follow-up effects of the CBT group with paired *t* tests, comparing the scores at follow-up

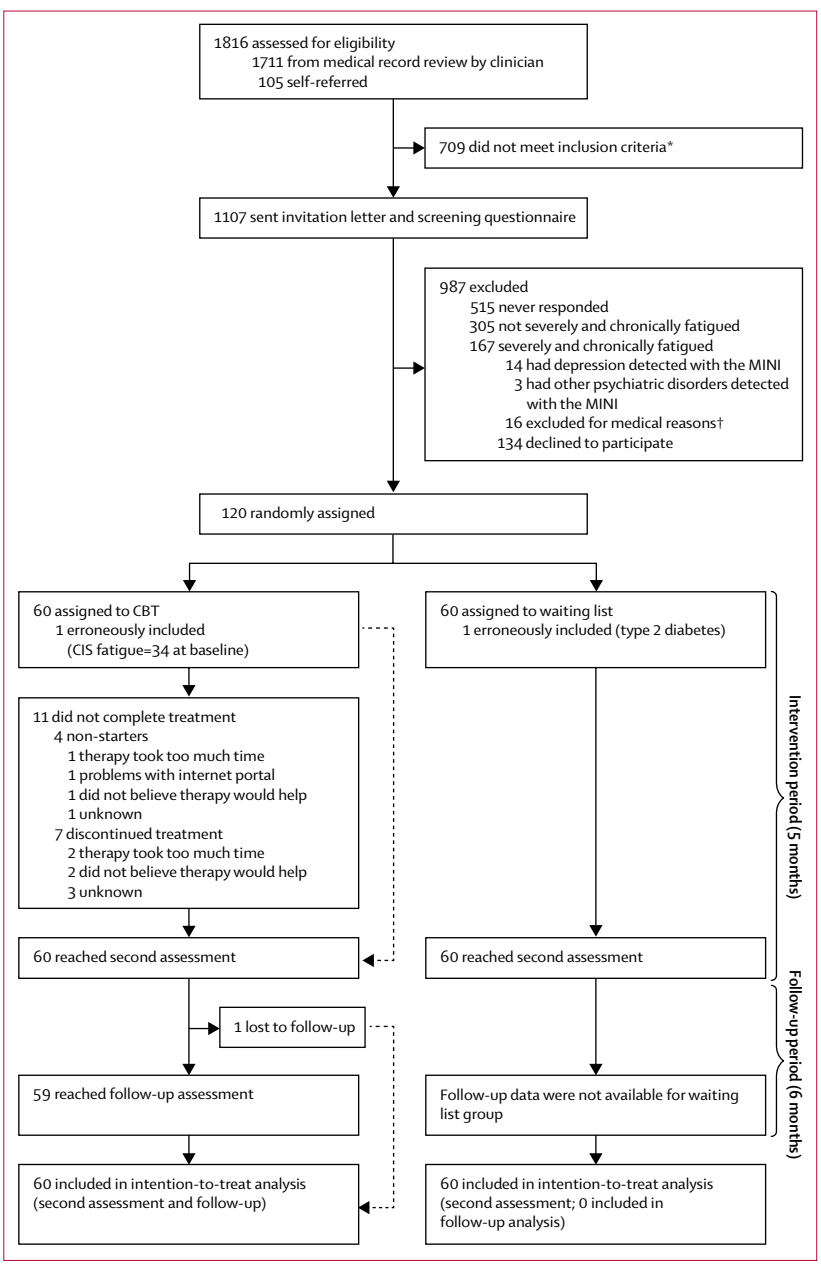

Figure 1: **Trial profile**
MINI=Mini International Neuropsychiatric Interview. CBT=cognitive behavioural therapy. CIS fatigue=Checklist Individual Strength, subscale fatigue severity. *Inclusion criteria assessed by the treating medical consultant. †Medical reasons were prespecified exclusion criteria that were not detected by the consultant at the first step of screening (sleep apnoea [n=2], fibromyalgia [n=3], rheumatoid arthritis [n=3], sarcoidosis [n=1], uncontrolled severe Graves' disease [n=1], congestive heart failure [n=2], estimated glomerular filtration rate ≤45 mL/min per 1·73 m^2 [n=1], BMI ≥40 kg/m^2 [n=1], and no type 1 diabetes [n=2]).

with the scores at second assessment for all outcome measures. When these scores differed significantly, we repeated *t* tests by comparing the scores at follow-up with the scores at baseline. The analysis was done by intention-to-treat. We also calculated the proportion of patients with clinically significant improvement at follow-up by post-hoc analysis.

The presence of adverse events during the trial was assessed by recording any spontaneously adverse events reported by patients or noted by the researcher, and at second assessment by patients' self-report. Adverse events were not assessed at follow-up assessment. Additionally, the investigator recorded serious adverse events during the study. There was no data monitoring committee, but the data entry was checked by an independent data manager.

All statistical analyses were done with IBM SPSS Statistics, version 22.0.[23]

This study is registered with the Nederlands Trial Register, number NTR4312.

	CBT (n=60)	Waiting list (n=60)
Age (years)	44·4 (12·1)	42·9 (12·5)
Women	37 (62%)	37 (62%)
Education level*		
Low	11 (18%)	7 (12%)
Medium	30 (50%)	31 (52%)
High	19 (32%)	22 (37%)
Diabetes duration (years)	24·2 (13·3)	24·1 (13·9)
HbA_{1c} (mmol/mol)	65 (11)	64 (11)
HbA_{1c} (%)	8·1 (1·0)	8·0 (1·0)
Glucose variability (mmol/L)	3·5 (1·1)	3·6 (1·1)
Mean number of diabetes complications	0·6 (1·1)	0·6 (1·1)
Diabetes complications		
Retinopathy	13 (22%)	14 (23%)
Nephropathy	3 (5%)	3 (5%)
Neuropathy	12 (20%)	11 (18%)
Numbness in the feet	5 (8%)	5 (8%)
Cardiovascular disease	3 (5%)	3 (5%)
Myocardial infarction	1 (2%)	0 (0%)
Stroke	0 (0%)	1 (2%)
Insulin therapy		
Multiple daily injections	22 (37%)	15 (25%)
CSII	38 (63%)	45 (75%)
CGM	7 (12%)	12 (20%)
Drugs		
Antihypertensives	15 (25%)	18 (30%)
Cholesterol-lowering therapy	17 (28%)	16 (27%)
Anticoagulants	3 (5%)	2 (3%)
Psychopharmacological drugs	5 (8%)	5 (8%)
Analgesics	7 (12%)	6 (10%)
BMI (kg/m^2)	26·2 (4·8)	26·0 (4·0)
Fatigue severity (CIS fatigue)	45·9 (5·9)	46·0 (5·8)
Functional impairment (SIP-8)	929 (635)	855 (543)
Depressive symptoms (BDI-PC)	3·5 (2·7)	3·3 (2·1)
Diabetes distress (PAID)	26·1 (18·3)	26·9 (17·0)

Data are mean (SD) or n (%), unless otherwise stated. CBT=cognitive behavioural therapy. CSII=continuous subcutaneous insulin infusion. CGM=continuous glucose monitoring. CIS fatigue=Checklist Individual Strength, subscale fatigue severity. SIP-8=sickness impact profile-8. BDI-PC=Beck Depression Inventory for Primary Care. PAID=Problem Areas in Diabetes questionnaire. *Education level classified as low (4 years of secondary education), medium (5 years of secondary education), or high (6 or more years of secondary education).

Table 1: **Baseline characteristics**

See Online for appendix

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 6, 2014, and March 24, 2016, we screened 1816 patients with type 1 diabetes. 1107 (61%) patients met the medical inclusion criteria and received an invitation letter with the screening questionnaire for chronic fatigue. Of these, 515 did not respond, 305 were not chronically and severely fatigued, and 33 were excluded because of medical reasons. Of the 254 remaining patients, 134 declined to participate, and 120 were randomly assigned (60 to CBT and 60 to waiting list; figure 1). The main reasons for non-participation were time investment and travel distance to the treatment centre (data not shown). At baseline, we noted no major differences between the study groups with respect to demographic and outcome variables (table 1). Of the 120 participants, 36 (30%) enrolled via social media (self-referral) and 84 (70%) via hospitals. Patients who enrolled via self-referral were significantly more often female, had lower numbers of diabetes complications (especially retinopathy), used less antihypertensive drugs, and reported more functional impairments than patients who enrolled via hospitals (appendix).

Among the 120 participants, the numbers with missing values at second assessment were 0 for fatigue severity, two (2%) for functional impairment, four (3%) for HbA_{1c}, and eight (7%) for glucose variability. Two patients at baseline and five patients at second assessment refused a new HbA_{1c} test for the study, and, for these patients, HbA_{1c} values from medical records that were closest to the assessments were used. In 116 participants, HbA_{1c} was assessed pairwise at the same hospital (at baseline and second assessment). In four participants, HbA_{1c} was not assessed pairwise. These patients were self-referrals who were seen at the Radboud University Medical Center at baseline, but HbA_{1c} determination at second assessment was done in their own hospitals. Four patients filled in a paper and pencil version of the questionnaires due to internet problems. Four (7%) of 60 patients who received CBT did not start treatment (ie, had no more than one session). Seven (12%) patients who received CBT

withdrew from CBT intervention: four after the second face-to-face session and three after the third session. Mean time between randomisation and second assessment was 153 days (SD 18) in the CBT group, and 154 days (SD 10) in the waiting list group. No patients reported any adverse events spontaneously during the study, and the investigator did not record any serious adverse events during the trial. 12 patients reported adverse events at second assessment (five in the CBT group and seven in the waiting list group); these adverse events were deemed to be unrelated to the CBT and waiting list group (appendix). Data for adverse events at second assessment were missing for nine patients, all in the waiting list group.

Compared with patients in the waiting list group, patients in the CBT group reported significantly lower fatigue severity scores (mean difference 13·8, 95% CI 10·0–17·5; p<0·0001) after 5 months. The decrease in fatigue severity and functional impairment was significantly greater in the CBT group than in the waiting list group, with a large effect size for both fatigue severity (d=1·3, 95% CI 0·9–1·7) and functional impairment (d=0·8, 0·4–1·1; table 2). We identified no significant differences in HbA_{1c} and glucose variability between the groups (table 2). Sensitivity analyses showed similar results (appendix). Type of enrolment had no significant effect on fatigue severity (data not shown). The proportion of participants with clinically significant improvement in fatigue severity in the CBT group (46 [77%] of 60; 95% CI 66–87) was significantly higher than in the waiting list group (15 [25%] of 60; 14–36; χ^2=32; p<0·0001; figure 2).

For the per-protocol analysis, we excluded 11 patients: four who did not start CBT treatment and seven who withdrew from the CBT treatment prematurely. The per-protocol analysis showed similar results to the intention-to-treat analysis (appendix). Two patients were included erroneously (one had type 2 diabetes and one had a Checklist Individual Strength fatigue severity score of 34;

	CBT (n=60)	Waiting list (n=60)	Treatment effect (95% CI)	p value	Effect size (Cohen's *d* [95% CI])*
Fatigue severity (CIS fatigue)	26·5 (11·6)	40·4 (10·4)	13·8 (10·0 to 17·5)	<0·0001	1·3 (0·9 to 1·7)
Functional impairment (SIP-8)	326 (417)	792 (744)	513 (340 to 686)	<0·0001	0·8 (0·4 to 1·1)
HbA_{1c} (mmol/mol)	64 (11)	63 (11)	0·2 (–2·2 to 2·6)	0·8890	NA
Glucose variability (mmol/L)	3·1 (1·1)	3·3 (1·2)	0·1 (–0·5 to 0·3)	0·5369	NA

Scores are means (SD) at second assessment unless otherwise stated. Two HbA_{1c} values at baseline could not be retrieved within 8 weeks before randomisation, so we used values from the medical records that were the closest to randomisation; one was determined 1 month too early (waiting list [n=1]), and one was determined 4 months too early (CBT [n=1]). These patients refused a new HbA_{1c} test at the study's baseline assessment. Five HbA_{1c} values at second assessment could not be retrieved within 4 weeks after the second assessment measurement; three were determined 1 month too late (waiting list [n=2], CBT [n=1]), and two were determined 1 month too early (CBT [n=2]). These patients refused a new HbA_{1c} test at the study's second assessment. CBT=Cognitive behavioural therapy. CIS fatigue=Checklist Individual Strength, subscale fatigue severity. SIP-8=Sickness Impact Profile-8. NA=not applicable. *Effect sizes could be classified as small (d=0·2–0·49), medium (d=0·5–0·79), or large (d≥0·8).[18]

Table 2: **Effect of treatment on primary and secondary outcome measures**

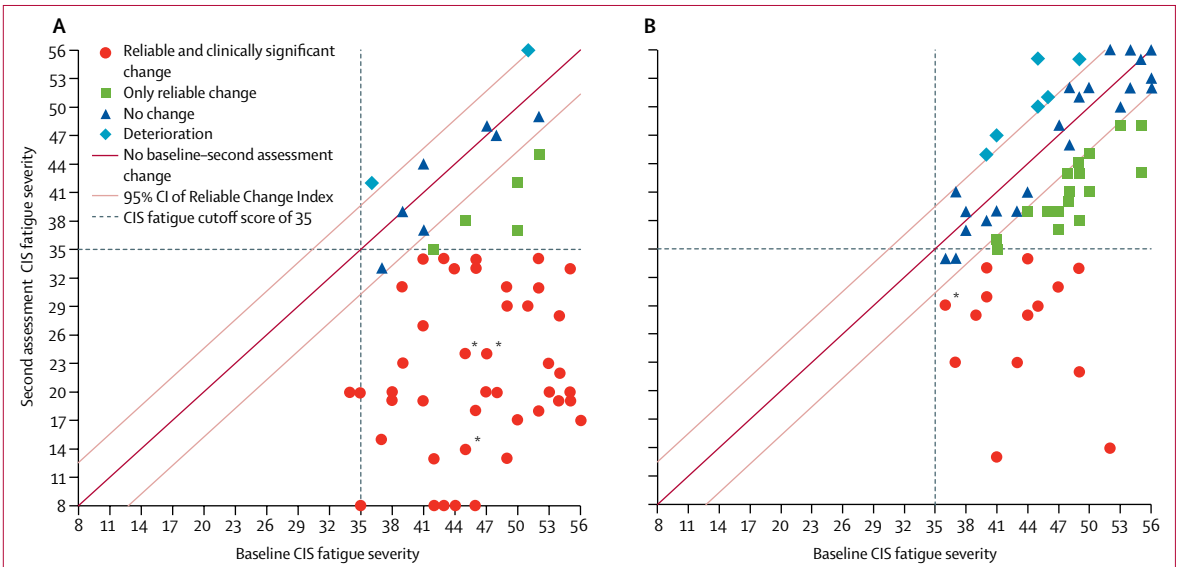

Figure 2: **Change in fatigue severity scores between baseline and second assessment for the CBT (A) and waiting list (B) groups**
Clinically significant improvement is defined as a second assessment score of less than 35 in combination with the criterion for reliable change. CBT=cognitive behavioural therapy. CIS fatigue=Checklist Individual Strength, subscale fatigue severity. *These points are double as two participants had the same scores.

figure 1); we repeated the analysis without these patients, but this did not affect the results (data not shown).

At follow-up (6 months after intervention period; CBT group only), one (2%) of 60 participants had missing values for fatigue severity, three (5%) of 60 had missing values for functional impairment, three (5%) had missing values for HbA_{1c}, and nine (15%) had missing values for glucose variability. The intention-to-treat analysis of the follow-up effects showed that the fatigue severity score at follow-up increased compared with the fatigue severity score at second assessment (30·2 [SD 11·4] *vs* 26·5 [SD 11·6]; mean difference 3·7; p=0·0067). However, fatigue severity was still significantly lower at follow-up than at baseline (30·2 [SD 11·4] *vs* 45·9 [SD 5·9]; mean difference 15·7; p<0·0001). 36 (61%) of 59 patients reported a clinically significant improvement at follow-up. The analysis of the scores on functional impairment showed that the positive effects at second assessment were sustained at follow-up (326 [SD 417] *vs* 353 [SD 433]; mean difference 27·2; p=0·5541; appendix). HbA_{1c} and glucose variability scores at follow-up did not differ significantly from scores at second assessment. Post-hoc analysis with depressive symptoms (p=0·6458) and diabetes distress (p=0·1562) as covariates and fatigue severity as a dependent variable showed that both were not significant covariates.

In the CBT group, the mean number of face-to-face sessions given during treatment was 5·4 (SD 1·5) and the mean number of emails sent by the therapists was 3·6 (SD 2·3). Mean time of website usage was 5 h 33 min, with a range of 21 min to 22 h 48 min. Treatment integrity was high for both face-to-face sessions (92%) and emails (93%). Inter-rater agreement was 96% for face-to-face sessions and 95% for emails. Therapists rated the participants' level of adherence with a mean score of 7·4 (SD 1·4; range 0–10). The mean adherence of all modules rated by patients was 3·4 (SD 0·8; range 1–5). The change score of fatigue severity was significantly correlated with the mean adherence score rated by patients (r=0·329, p=0·0272), but not with the adherence score rated by therapists (r=0·213, p=0·1424).

Discussion

The CBT-based Dia-Fit intervention significantly decreased fatigue severity in patients with type 1 diabetes compared with the waiting list control. CBT also significantly decreased functional impairment and showed large effect sizes for both fatigue severity and functional impairment. The proportion of patients who improved to a clinically significant extent with respect to fatigue was significantly higher in the CBT group (77%) than in the waiting list group (25%). HbA_{1c} and glucose variability did not seem to be affected by the CBT intervention.

Our findings in patients with type 1 diabetes and fatigue confirm that CBT is a safe treatment, as has been previously shown in other populations.[24] Adverse events reported in the study were not related to the intervention and were not more prevalent in the CBT group than in the waiting list group. The treatment integrity in our study was high and it seems reasonable that CBT in patients with type 1 diabetes can be easily done by therapists, if they receive adequate training. Our treatment was delivered by web-based modules in combination with face-to-face sessions. Nonetheless, the most frequently mentioned reasons for non-participation in our study were time investment and travel time to the treatment centre. These barriers could be overcome by a fully web-based treatment, since this form is probably more time-efficient both for patients and therapists, and is easily accessible for most patients.[25]

Patients who enrolled via self-referral were more often female, were more functionally impaired, and had fewer diabetes-related complications than patients who were referred via hospitals. Previous evidence suggests that women are more likely to gather online information about health problems than men,[26] which could account for the first of these findings. The significantly higher scores on functional impairment could suggest that self-referral patients have more problems in daily functioning as a consequence of fatigue than patients referred via the hospitals, which could have been the reason that they enrolled in the study. This discrepancy between enrolment types and the high level of motivation for treatment could have led to a selection bias. However, we did not identify differences between these two groups with respect to treatment effects, but the skewed distribution of self-referrals (30%) and hospital-referrals (70%) might have limited statistical power to detect a possible difference. In most cases, the study participation was offered through the treating physicians who screened patients for eligibility. In clinical practice, the treatment would probably be offered to patients in the same way, so any selection bias would be unlikely to affect the generalisability of our findings to clinical practice. The treatment adherence measured by patient self-report was correlated with the fatigue severity change score. Therefore, further optimisation of adherence in future treatments is likely to be important to ensure positive outcomes for patients.

We identified a substantial improvement on fatigue in the CBT group, but patients in the waiting list group also improved with respect to fatigue (albeit only one in four patients). This improvement seems in line with natural fluctuations in severe fatigue as shown by a recent study in which 19 (24%) of 78 patients with type 1 diabetes and severe fatigue improved over time without treatment.

We did not identify an effect of CBT on glycaemic control (HbA_{1c}) or glucose variability. In a recent meta-analysis[27] investigating the effects of CBT for patients with diabetes on psychological outcomes and glycaemic control, Uchendu and Blake reported that CBT has beneficial effects on short-term and medium-term glycaemic control, but not on long-term glycaemic control. However, none of the studies included in the meta-analysis investigated CBT

for chronic fatigue, which makes it impossible to generalise these findings to our study population. Our findings regarding glycaemic control are in line with existing evidence that fatigue in type 1 diabetes is not related to HbA_{1c} or glucose variability.[2,5] However, these findings should be interpreted with caution because we did not base our power calculation on these secondary outcomes, although based on our results we believe that a larger study sample would be unlikely to produce different findings.

We have not scored the number of hypoglycaemic events or the occurrence of severe hypoglycaemia. As far as we know, none of the participants had severe hypoglycaemia during the trial. Nevertheless, several patients who participated in the trial were very well controlled (often treated by pump and sensor) and some of these patients had hypoglycaemic events, impaired awareness of hypoglycaemia, or a history of severe hypoglycaemia. In an earlier study,[2] we did not find an association between glucose variability, as measured by continuous glucose monitoring, and fatigue, and found no association with time spent in the hypoglycaemic range; in fact, this time was a little less in the fatigued group. The underlying mechanism between diabetes control and chronic fatigue might be attributable to a U-shaped association: patients who do not pay much attention to their diabetes will have poor control with high glucose variability, which might contribute to fatigue, as might concerns about potential complications. Patients who put a lot of effort into their diabetes control will have better, less variable glycaemic control, but at the same time will have a substantially increased burden associated with treatment, which in turn will also drain energy.

Depression and diabetes-related distress are common psychosocial problems in diabetes.[28] We excluded patients with a depressive disorder from our study. A post-hoc analysis with depressive symptoms and diabetes distress as covariates showed that CBT significantly reduced fatigue independent of the level of depressive symptoms or diabetes distress at baseline. Depressive symptoms or diabetes distress might be reduced after CBT; as such, future studies (eg, using mediation analysis) should investigate the relation between these possible effects and the decrease in fatigue. We think that changes in the perpetuating factors of fatigue addressed in the CBT modules (eg, sleep disturbances or self-efficacy concerning fatigue) probably mediate the positive effects of CBT on fatigue. Research in other chronic disorders has shown that changes in these perpetuating factors can mediate the effects of CBT on fatigue.[29] Researchers should investigate the mechanisms of change of CBT in type 1 diabetes because this knowledge could help to improve the effectiveness and efficiency of this intervention.

Chronic fatigue is an understudied symptom in patients with type 1 diabetes;[1] what contributes to fatigue in type 1 diabetes is not fully understood. A recently published systematic review[1] showed that most studies on fatigue in patients with type 1 diabetes are of low quality, suggesting that additional high-quality research on fatigue in type 1 diabetes is needed.

Our study might have clinical implications. As reported, severe fatigue in type 1 diabetes is persistent in three of four severely fatigued patients, meaning an effective treatment intervention would be welcome. The results of our trial show that CBT is indeed effective in reducing fatigue and improving functional impairment. The explorative analysis of the follow-up assessment in the CBT group showed that the mean fatigue severity at follow-up was increased compared with the fatigue severity directly after treatment, but the scores were still significantly lower than at baseline. At follow-up, most patients in the CBT group still had a clinically significant improvement in fatigue (61%; compared with 77% directly after treatment), which suggests that the treatment effects are maintained over time. However, these findings should be interpreted with caution because the follow-up assessment was uncontrolled.[10] Additional future research investigating the long-term effectiveness of CBT for fatigue in type 1 diabetes is needed.

The present study has limitations. First, we used a waiting list control group as a comparator, rather than an active control intervention. The design of an active control group in psychosocial intervention studies is challenging,[30] and this is the first study to test the efficacy of an intervention for fatigue in type 1 diabetes so it is difficult to determine what would be an appropriate active control without a specific effect on fatigue. The use of a waiting list group could have provoked nocebo effects (ie, patients' negative expectations about the effects on fatigue of having to wait). However, the course of fatigue in our waiting list group was similar to the natural course of fatigue without any intervention,[4] which suggests that a nocebo effect is unlikely to have occurred in the study. Second, because of the type of intervention and for practical reasons, we were unable to mask participants or the researcher to the treatment allocation. To reduce potential bias, an independent researcher, masked to the treatment allocation, did the analyses and almost all participants filled in questionnaires online at home to keep contact with the unmasked researcher (JM) to a minimum. Third, the sample size was fairly small and we recruited a selected sample of patients without severe complications or comorbidities. Whether patients with severe complications or comorbidities would also benefit from CBT for fatigue is unclear. Finally, an objective measurement of adherence and of the time patients spent on each treatments' web-based module (rather than just total time logged in to the portal) would have improved validity; however, this approach was not possible because of the technical limitations of the web portal software.

In summary, this study shows beneficial effects of CBT on fatigue severity and functional impairment, with large effect sizes and a large proportion of patients with clinically significant improvement in the CBT group compared with the waiting list control group. Glycaemic control and glucose variability did not improve after CBT.

Contributors
CJT and HK were responsible for the study conception and design. JM, CJT, and HK analysed and interpreted the data. JM, CJT, and HK drafted the Article. JM, CJT, ACvB, HJJ, JPvdB, MJTMM, MMG, RD, and HK critically revised the Article for important intellectual content. JM, CJT, ACvB, HJJ, JPvdB, MJTMM, MMG, RD, and HK gave final approval of the Article. JM, RD, and HK provided statistical expertise. JM collected and assembled the data.

Declaration of interests
We declare no competing interests.

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