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Is physical deconditioning a perpetuating factor in chronic fatigue syndrome? A controlled study on maximal exercise performance and relations with fatigue, impairment and physical activity

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ABSTRACT

Background. Chronic fatigue syndrome (CFS) patients often complain that physical exertion produces an increase of complaints, leading to a greater need for rest and more time spent in bed. It has been suggested that this is due to a bad physical fitness and that physical deconditioning is a perpetuating factor in CFS. Until now, studies on physical deconditioning in CFS have shown inconsistent results.

Methods. Twenty CFS patients and 20 matched neighbourhood controls performed a maximal exercise test with incremental load. Heart rate, blood pressure, respiratory tidal volume, O_2 saturation, O_2 consumption, CO_2 production, and blood-gas values of arterialized capillary blood were measured. Physical fitness was quantified as the difference between the actual and predicted ratios of maximal workload *versus* increase of heart rate. Fatigue, impairment and physical activity were assessed to study its relationship with physical fitness.

Results. There were no statistically significant differences in physical fitness between CFS patients and their controls. Nine CFS patients had a better fitness than their control. A negative relationship between physical fitness and fatigue was found in both groups. For CFS patients a negative correlation between fitness and impairment and a positive correlation between fitness and physical activity was found as well. Finally, it was found that more CFS patients than controls did not achieve a physiological limitation at maximal exercise.

Conclusions. Physical deconditioning does not seem a perpetuating factor in CFS.

INTRODUCTION

Chronic fatigue syndrome (CFS) is defined as a severe fatigue lasting for at least 6 months, for which no somatic explanation can be offered and which leads to severe disability in daily life. CFS patients often complain that physical exertion produces an increase in complaints, leading to a greater need for rest and more time spent in bed. In some CFS studies it has been argued that muscle deficits might cause this fatigue after activity (Schwartz *et al*. 1978; Arnold *et al*. 1984; Jamal & Hansen, 1985). More recent studies on physical exercise in CFS showed that the neuromuscular mechanism is intact (Lloyd *et al*. 1988, 1991; Rutherford & White, 1991; Gibson *et al*. 1993; Kent-Braun *et al*. 1993; Lane *et al*. 1998).

Wessely *et al*. (1989) hypothesized that physical deconditioning might play an important role in CFS. The rationale was that because CFS patients experience a worsening of complaints after activity, they learn to avoid activity in order to prevent an increase of complaints. Being inactive, however, results in a decrease of physical fitness. This means that over time

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complaints get worse at an increasingly lower level of physical activity. In this way a vicious and perpetuating circle might be established, resulting in a decreasing physical fitness. Based on this hypothesis, the role of (avoidance of) physical activity in CFS has been emphasized more and more (Wagenmakers, 1999). In cognitive behavioural therapy (Sharpe *et al.* 1996; Deale *et al.* 1997) as well as in graded exercise therapy (Fulcher & White, 1997) a gradually increasing activity programme is of main importance. One might wonder, however, whether improving physical fitness is an essential factor in CFS, or whether other factors determine treatment effects. If physical fitness is an important and perpetuating factor in CFS, one would not only expect CFS patients to have a worse physical fitness, but one would also expect a negative relationship between physical fitness and fatigue and impairment and a positive relationship between physical fitness and physical activity. Studies on aerobic or cardiocirculatory deconditioning in CFS have shown contradictory results (Montague *et al.* 1989; Riley *et al.* 1990; Cordero *et al.* 1996; Sisto *et al.* 1996; Freeman & Komaroff, 1997; De Lorenzo *et al.* 1998). These differences might be due to differences in tests, sample sizes and patient and control selection. Differences in tests used make it difficult to compare results. However, the most important reason for the inconsistencies found seems to be the use of an inappropriate control group in most studies. Physical fitness in CFS should not be compared with selected healthy and rather active controls. To deal with this problem, Sisto *et al.* (1996) used sedentary controls. In our study, well-matched neighbourhood controls are used. Although inconsistencies exist in the findings concerning physical fitness, most studies are consistent in their findings, that at least part of the CFS patient sample does not attain a physiological limitation on a maximal exercise test. The aims of the present study are to determine whether CFS patients have a worse physical fitness as compared to matched neighbourhood controls, and whether there is a negative relationship between physical fitness and fatigue and impairment and a positive relationship between physical fitness and physical activity. We also investigated whether CFS patients attain a physiological maximum on a maximal exercise test.

METHOD

Subjects

Patients diagnosed at the General Internal Medicine out-patient clinic of the University Hospital Nijmegen, who already agreed to participate in scientific studies, were asked to participate. Patients were diagnosed as having CFS if they fulfilled the Fukuda criteria (Fukuda *et al.* 1994). In addition, CFS patients were only included if they had a CIS fatigue severity score of $\geqslant 40$ and a total score on the eight SIP subscales used of > 800, to guarantee severe fatigue and disability (see instruments; Vercoulen *et al.* 1994). Patients invited for the current study were further selected on whether they lived in the surroundings of our hospital, because a heart rate monitor was brought to the patients' and controls' home a day before the exercise test and was picked up again 1 day after the test. None of the patients refused. All patients were asked to invite a neighbour of the same gender and about the same age as a control person. Twenty of 26 CFS patients fulfilled our additional criteria of the CIS and the SIP and found a neighbourhood control of about the same age and the same sex. So 20 CFS patients and 20 matched neighbourhood controls participated.

Instruments

Fatigue

Fatigue was measured by the subscale fatigue severity of the fatigue questionnaire Checklist Individual Strength (CIS) (Vercoulen *et al.* 1994). This scale consists of 8 items concerning fatigue during the last 2 weeks. Each item is scored on a 7-point Likert scale, so the range is 8–56.

Functional impairment

The Sickness Impact Profile (SIP) (Bergner *et al.* 1981; Jacobs *et al.* 1990) was used to assess functional impairment. This questionnaire measures the influence of complaints in different areas of daily functioning. Eight subscales were used (alertness behaviour, sleep, homemaking, leisure activities, work, mobility, social interactions and ambulation).

Physical activity

This was measured using the actometer

(Vercoulen *et al.* 1997). The actometer is an apparatus worn around the ankle for 2 weeks, recording the amount of movements every 5 min. The actometer consists of a piezoelectric sensor. Acceleration of the sensor results in an output signal. This information is stored to an internal memory, and can be read by use of a personal computer. The mean actometer score for the days that the actometer was worn before the exercise test was used to assess the level of physical activity.

Exercise test

A bicycle ergometer test with incremental load was used as an exercise test. The workload was increased every minute in steps of 10% of estimated maximal workload, in order to complete the maximal exercise test in approximately 10 min (Folgering *et al.* 1988). The steps varied from 10 to 30 watt/min. Subjects were instructed to go on until they could no longer continue. They were verbally encouraged to perform maximally. During this test, heart rate, blood pressure, respiratory tidal volume, O_2 saturation, O_2 consumption, CO_2 production, and blood-gas values of arterialized capillary blood (before and after exercise, at minute 3, 6, and 9 of the exercise and at maximal workload) were measured. Every 3 min and at maximal workload, the modified Borgscale was used to assess the rate of perceived exertion (Borg *et al.* 1985). On a scale from 1 to 10, patients were asked to indicate how difficult it was to perform the pedalling exercise. The intensity of anaerobic workload was measured from the difference in base excess at rest and 3 min after maximal workload, which represents the produced lactate within the cells of the leg muscles. Achieved maximal workload (W) was compared with the predicted value. The predicted maximal workload was calculated from:

$$W\text{max\_pred} = \frac{V\text{O}_2\text{max\_pred} - V\text{O}_2\text{rest\_pred}}{10{\cdot}29}$$

(Wasserman *et al.* 1994).

In this formula, predicted maximal ventilatory O_2 uptake ($V\text{O}_2$max_pred) is related to height (H/cm), age (A/year) and sex (S/m = 0, f = 1):

$$V\text{O}_2\text{max\_pred (l/min)} = 0{\cdot}046\text{H} - 0{\cdot}021\text{A} - 0{\cdot}62\text{S} - 4{\cdot}31$$

(Jones *et al.* 1985),

and

$$V\text{O}_2\text{rest\_pred} = 0{\cdot}25\ \text{l/min}$$

(Åstrand *et al.* 1986).

Maximal heart rate (HR) was compared with the predicted maximal heart rate, depending on age (A/year):

$$\text{HRmax\_pred (beats/min)} = 220 - \text{A}$$

(Wasserman *et al.* 1994).

Fitness was defined as the differences in slope of the relationships between heart rate and external workload of the individual subject *versus* a normalized slope. Fit subjects have relatively low heart rates at a certain workload and vice versa (McArdle *et al.* 1991). In formula:

$$\frac{\text{Wmax}}{\text{HRmax} - \text{HRrest}} - \frac{\text{Wmax\_pred}}{\text{HRmax\_pred} - \text{HRrest}} = \text{Watt per beat.}$$

A negative outcome indicates a fitness that is worse than would be expected; a positive outcome indicates a better fitness than expected.

Subjects were considered attaining a physiological limitation if one of the following criteria was met: (1) attainment of predicted maximal heart rate; (2) increase of base excess at 3 min after maximal workload compared with base excess at rest (lactate production) of more than 10 mmol/min; (3) increase of CO_2 pressure in blood at maximal workload compared with the value at rest.

The 24 hours heart rate

This was assessed using a Polar sport tester. The Polar sport tester consists of a belt around the chest, containing ECG electrodes, amplifier and transmitter, and a watch. The ECG signals are sent to the watch, recording the R-tops in an internal memory every 60 s, during 24 h. For the analysis in this study mean scores of every half an hour were used. The Polar sport tester was brought to the patients' and controls' home to wear during the 12 hours preceding the start of the ergometer test. After the ergometer test the Polar sport tester was worn for another 12 hours. Then the sport tester was collected from the subjects' homes.

For six controls and four CFS patients almost all data of the Polar sport testers were missing, probably because of pressing the buttons accidentally during sleep. Also, 10 subjects (one

CFS patient and nine controls) had incidental missing data. In these cases (1·7% of all sport tester data) missing values were replaced by the mean value of the half hour scores before and after the missing value of the particular subject.

Statistical analysis

Differences between groups were tested using one-way analysis of variance (ANOVA) or repeated measures ANOVA for ratio variables. The Mann–Whitney U test was used in case of skewed variables, χ^2 was used for dichotomous variables. Fisher's Exact Test was used when $> 20\%$ of the cells had an expected count < 5. Before Pearson correlation coefficients were computed, skewed variables were transformed. To test whether the correlations obtained for CFS and for controls were significantly different, both correlations were converted to Fisher's z and the difference between them was divided by the standard error of the difference to yield a normal curve deviate (z) (Howell, 1997). For all tests, the significance level was set at $P < 0{\cdot}05$.

RESULTS

Patient and control characteristics

Demographic data, height, weight, fatigue severity, functional impairment and physical activity are displayed in Table 1. There were no significant differences in gender, age, height and weight. On fatigue severity, functional impairment and physical activity differences were found as expected. Mean duration of complaints in CFS was 3·2 years ($\pm 2{\cdot}5$).

Fitness

CFS patients had a mean fitness of $-0{\cdot}32 \pm 0{\cdot}50$ watts/beat and their controls had a mean fitness of $-0{\cdot}22 \pm 0{\cdot}82$ watts/beat (non-significant: Mann–Whitney U test, $P = 0{\cdot}25$). Nine of the 20 CFS patients had a better fitness than their own control. In Fig. 1 a boxplot of fitness in CFS and controls is displayed.

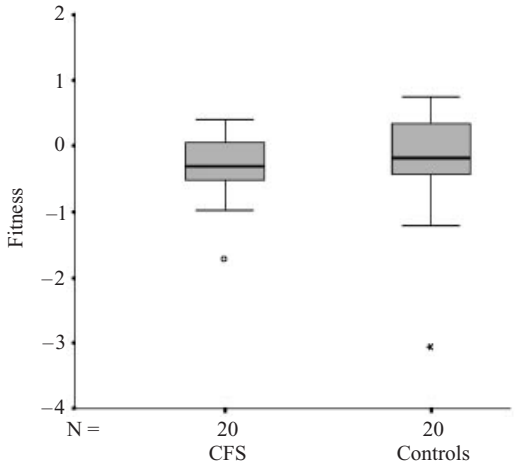

FIG. 1. Box plot of fitness for CFS and controls. (Box is 25th to 75th percentile (interquartile range, IQR), black line in box is the median, the lines above and under the box are 1·5 times above and below the 25th and under the 75th percentile respectively; °, is an outlier (between 1·5 IQR and 3 IQR from the box); *, is an extreme (> 3 IQR from the box).)

Oxygen consumption and CO_2 production

Table 2 shows the O_2 and CO_2 uptake and production. CO_2 pressure in the blood declined more for CFS than for controls ($P = 0{\cdot}03$). There were no other significant interaction effects for the respiratory exchange variables.

Heart rate

Heart rates from 12 h before the test up to 12 h after the test for CFS and their controls are displayed in Fig. 2. No significant interaction effect was found.

Table 1. *Characteristics* (*% or mean* (*S.D.*)) *of CFS patients* (N = 20) *and controls* (N = 20)

	CFS	Controls	P
Female, %	60	60	1·00
Age (years)	34·1 (8·3)	32·8 (7·2)	0·59
Height (cm)	175·7 (9·4)	174·8 (9·5)	0·78
Weight (kg)	72·0 (16·4)	71·5 (14·2)	0·91
Fatigue (CIS; range 8–56)	51·7 (5·1)	13·4 (5·1)	0·00*
Functional impairment (SIP-8)	1743 (1249–2058)	0 (0–0)	0·00*
Physical activity (actometer)†	58·2 (27·2)	99·5 (25·0)	0·00*

χ^2 for % female; Mann–Whitney U test for SIP, medians (25th and 75th percentile) presented; one-way ANOVA for other variables.
† Deviating N because of falling actometers. $N = 15$ for CFS and $N = 18$ for controls.
*$P < 0{\cdot}05$.

Table 2. *Oxygen consumption and CO_2 production* (*S.D.*) *in rest and at maximal workload for CFS* (N = 20) *and controls* (N = 20)

	Rest	Maximal workload	Within subjects *P*	Interaction effect *P*
O_2 consumption (l/min)				
CFS	0·30 (0·08)	2·01 (0·74)	0·00*	0·22
Controls	0·29 (0·08)	2·27 (0·68)	($F = 288·95$; df = 1)	($F = 1·58$; df = 1)
CO_2 production (l/min)				
CFS	0·27 (0·09)	2·37 (0·90)	0·00*	0·20
Controls	0·28 (0·09)	2·75 (0·90)	($F = 270·96$; df = 1)	($F = 1·72$; df = 1)
O_2 pressure in blood (kPa)				
CFS	9·07 (1·05)	11·29 (1·34)	0·00*	0·10
Controls	8·87 (0·92)	10·25 (1·01)	($F = 50·19$; df = 1)	($F = 2·84$; df = 1)
CO_2 pressure in blood (kPa)				
CFS	5·19 (0·51)	4·65 (0·57)	0·00*	0·03*
Controls	5·36 (0·46)	5·22 (0·59)	($F = 14·42$; df = 1)	($F = 4·89$; df = 1)

Repeated measures ANOVA.
*$P < 0·05$.

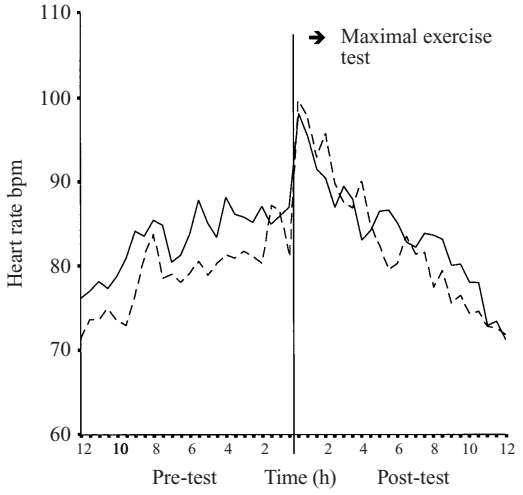

FIG. 2. Heart rate 12 h before and up to 12 h after the maximal exercise test, CFS patients (———, $N = 16$) compared with controls (– – –, $N = 14$). Repeated measures ANOVA: within subjects, $P = 0·00$ ($F = 9·66$; df = 47); interaction effect, $P = 0·75$ ($F = 0·85$; df = 47).

Fitness and relations with fatigue, impairment and physical activity

For CFS as well as for controls a significant correlation of $-0·45$ was found between fitness and fatigue ($P = 0·049$ and 0·044 respectively). In CFS significant correlations between fitness and functional impairment ($r = -0·49$, $P = 0·027$) and fitness and physical activity ($r = 0·54$, $P = 0·039$; $N = 15$ because of failing actometers) were found as well. Because 85% of the controls had a functional impairment score of zero, a correlation between functional impairment and fitness could not be computed. The correlation between fitness and physical activity in controls was non-significant ($r = 0·28$, $P = 0·260$; $N = 18$ because of failing actometers). The difference in the correlations between fitness and physical activity in CFS and in controls (0·54 and 0·28 respectively) were statistically non-significant ($P = 0·414$).

Table 3. *Exercise capacity* (*mean and* (*S.D.*)) *for CFS patients* (N = 20) *and controls* (N = 20)

	CFS	Controls	*P*
Time (min)	8·0 (2·3)	9·2 (1·9)	0·07
Workload (watt)			
Predicted value	241 (51·5)	245 (50·1)	0·81
Value reached	172 (68·3)	204 (64·1)	0·14
% of the predicted value reached†	70 (17)	83 (18)	0·02*
Heart rate			
Predicted value	186 (8·3)	187 (7·2)	0·59
Value reached	165 (16·2)	173 (13·4)	0·08
% of the predicted value reached†	89 (8)	92 (7)	0·11

One-way ANOVA.
† Value reached/predicted value $\times 100$.
*$P < 0·05$.

Exercise capacity

Neither the duration of the maximal bicycle ergometer test nor achieved workloads were significantly different for CFS and controls (Table 3). However, there was a statistically significant difference for the percentage of the predicted workload reached, being lower in

Table 4. *Percentage* (N) *of CFS patients* (N = 20) *and controls* (N = 20) *attaining a physiological limitation at maximum exercise*

	CFS	Controls	*P*
$\Delta HR > 0$†	5 (1)	15 (3)	0·61
$\Delta BE > 10$‡	35 (7)	55 (11)	0·20
$\Delta PaCO_2 > 0$§	30 (6)	40 (8)	0·51
Attaining one of these criteria	55 (11)	80 (16)	0·09

Fisher's exact test for ΔHR; χ^2 for other variables.

† ΔHR, heart rate at maximal workload − predicted heart rate.

‡ ΔBE, base excess 3 min after maximal workload − base excess at rest.

§ $\Delta PaCO_2$, CO_2 pressure in blood at maximal workload − CO_2 pressure in blood at rest.

CFS. On average, CFS patients reached 70 % of their predicted workload, whereas the controls reached 83 % of their predicted value. For heart rate scores during exercise, no statistically significant differences were found.

Attaining a physiological limitation

Of the CFS patients 55 % performed up to a physiological limitation, compared with 80 % of the controls (this difference was not significant, Table 4).

Perceived exertion

Not all subjects performed the maximal exercise test for 6 min or more. Therefore, Borgscale scores were compared 3 min after starting the test and at maximal workload only. Scores on the Borgscale 3 min after starting the test were $3{\cdot}82 \pm 0{\cdot}88$ for CFS ($N = 17$) and $2{\cdot}44 \pm 0{\cdot}86$ for controls ($N = 18$). At maximal workload Borgscale scores were $8{\cdot}76 \pm 1{\cdot}68$ for CFS and $7{\cdot}33 \pm 2{\cdot}11$ for controls. There was a significant within subjects effect ($P = 0{\cdot}00$; $F = 210{\cdot}06$; df = 1). No significant interaction effect was found ($P = 0{\cdot}94$; $F = 0{\cdot}01$; df = 1).

DISCUSSION

In the present study CFS patients did not have a worse physical fitness compared with their controls. Both groups had a lower physical fitness than would be expected according to height, age and sex. This particularly emphasizes the importance of a well-matched control group. In our study, the fitness score of one of the controls was an extreme. When this extreme is excluded from the analysis, the difference remains statistically non-significant. One might suggest that not finding a significant difference in fitness is due to a power problem, because of sample sizes. However, almost half of the CFS patients had a better fitness than their own control. This result underlines the conclusion that there is no difference in fitness between CFS patients and their controls. Our finding agrees with that of Sisto *et al.* (1996), who found that CFS patients had a low but normal fitness, comparable to sedentary controls. Another objection might be that in spite of substantial and expected differences in fatigue, functional impairment and level of activity, only a selected group of patients was included. Bedridden patients, in particular, are unlikely to participate in these scientific studies. Van der Werf *et al.* (2000) recently found that passive patients can be distinguished from the relatively active patients based on the actometer. In the present study three passive CFS patients participated. These patients resemble bedridden patients.

Concerning respiratory variables it was found that the CO_2 pressure in the blood of CFS patients decreased more than in the controls. This might indicate that CFS patients tend to hyperventilate during exercise. In other studies it was found that hyperventilation, although prevalent in a substantial part of the cases, does not seem to play an essential role in CFS (Saisch *et al.* 1994; Bazelmans *et al.* 1997). However, no other significant differences were found concerning oxygen consumption and carbon dioxide production. In addition, according to Wasserman *et al.* (1994) oxygen consumption should be $10{\cdot}29 (\pm 1)$ ml per min per watt for normal subjects. If we compute millilitre oxygen consumption per minute per watt for the subjects in our study (O_2 consumption at maximal workload minus O_2 consumption at rest multiplied by 1000 and divided by maximal workload reached) this is $9{\cdot}94 (\pm 1{\cdot}31)$ for CFS patients and $9{\cdot}71 (\pm 1{\cdot}41)$ for controls. These values are both very similar to the normal value of Wasserman *et al.* (1994). Very unfit subjects usually need more O_2 per watt. Consequently, this finding adds to the conclusion that the fitness of the CFS patients is not substantially impaired.

The maximal workload reached during an incremental bicycle ergometer test did not differ between CFS patients and controls, neither did

the heart rate at maximal workload. However, the average percentage of the predicted maximal workload reached was lower for CFS than for controls. In spite of the absence of significant differences in physical fitness, CFS patients are not performing until they are limited by physiological mechanisms. It might be supposed that achieved workload is a parallel test for physical activity. Indeed, *post hoc* analysis revealed that the average percentage of the predicted maximal workload reached is highly correlated with physical activity in CFS ($r = 0{\cdot}78$, $P = 0{\cdot}00$), but not in controls ($r = 0{\cdot}16$, $P = 0{\cdot}55$). These correlations are significantly different ($P = 0{\cdot}03$).

Because there was no significant difference in fitness between CFS and controls, it is not likely that physical fitness should be considered a perpetuating factor in CFS. The relationship between physical fitness and fatigue is of less importance now. Nevertheless, the fact that the relationship between physical fitness and fatigue is of the same strength for both groups, indicates that a worse physical fitness goes with more fatigue for all subjects, for which CFS patients are no exception. The finding that in CFS a worse fitness goes together with a lower level of physical activity (and higher level of impairment), is of interest. For controls no relationship between fitness and physical activity was found. Apparently, CFS patients with a lower physical fitness are less active, whereas controls are not. It is conceivable that CFS patients with a lower physical fitness adjust to this by being less active, while controls do not. However, although the correlations between fitness and the level of activity are different in CFS and in controls this difference is not statistically significant. Besides, the sample sizes were small. Therefore, this finding has to be interpreted with caution. Wagenmakers (1999), reviewing some of the literature on physical fitness and CFS, concludes that deconditioning might be a perpetuating factor. In this article it is supposed that CFS patients show a metabolic adaptation to a low level of physical activity. Wagenmakers suggests that the abnormal physiology found in CFS may well be a consequence of the lack of exercise in CFS patients. For this reason he suggests that exercise programmes have to be brought into practice. However, this explanation does not seem plausible: in our study the controls also had a lower physical fitness than predicted while they were not less active or fatigued. Considering the above mentioned correlations as well, it seems more likely that low levels of activity are an adaptation to a lower physical fitness of some CFS patients but not for controls, rather than that low levels of activity lead to a worse physical fitness. Besides, Fulcher & White (1997) showed that there was no relationship between improvement in CFS after an exercise treatment programme and increase of peak aerobic capacity produced by exercise after this programme. This finding adds to the hypothesis that factors other than physical fitness determine a lower level of activity, fatigue and impairment in CFS. Possibly cognitions are responsible for a lower exercise tolerance in some CFS patients. Vercoulen *et al.* (1997) found that low levels of physical activity are in part caused by attributing complaints to a physical cause. Petrie *et al.* (1995) found that CFS patients who expected that activity would have negative consequences for their complaints, were also more impaired. However, based on the results of our study, it must be concluded that a worse physical fitness does not seem to be a perpetuating factor in CFS.

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