

Physical activity intensity but not sedentary activity is reduced in chronic fatigue syndrome and is associated with autonomic regulation

J.L. NEWTON¹, J. PAIRMAN¹, K. HALLSWORTH^{1,2}, S. MOORE^{1,2}, T. PLÖTZ³ and M.I. TRENELL^{1,2}

From the ¹UK National Institute for Health Research Biomedical Research Centre in Ageing & Age-related Disease, Institute for Ageing and Health, Newcastle University, Newcastle, UK, ²MRC Centre for Brain Ageing & Vitality, Newcastle University, Newcastle upon Tyne and ³School of Computing Science, Newcastle University, Newcastle upon Tyne, UK

Address correspondence to Prof. J.L. Newton, Institute for Ageing and Health, Newcastle University, Newcastle, NE2 4HH, UK. email: j.l.newton@ncl.ac.uk

Received 11 January 2011 and in revised form 4 February 2011

Summary

Background: Chronic fatigue syndrome (CFS) is a common debilitating condition associated with reduced function and impaired quality of life. The cause is unknown and treatments limited. Studies confirm that CFS is associated with impaired autonomic regulation and impaired muscle function.

Aim: Define the relationship between sedentary behaviour, physical activity and autonomic regulation in people with CFS.

Design: Cohort study.

Methods: Physical activity was assessed objectively in 107 CFS patients (Fukuda) and age, sex and body mass index (BMI)-matched sedentary controls ($n=107$). Fatigue severity was determined using the Fatigue Impact Scale in all participants and heart rate variability performed in the CFS group.

Results: The CFS group had levels and patterns of sedentary behaviour similar to non-fatigue controls ($P>0.05$). Seventy-nine percent of the CFS group

did not achieve the WHO recommended 10 000 steps per day. Active energy expenditure [time >3 METs (metabolic equivalents)] was reduced in CFS when compared with controls ($P<0.0001$). Physical activity duration was inversely associated with resting heart rate ($P=0.04$; $r^2=0.03$), with reduced activity significantly associating with reduced heart rate variability in CFS. There were no relationships between fatigue severity and any parameter of activity. Thirty-seven percent of the CFS group were overweight (BMI 25–29.9) and 20% obese (BMI ≥ 30).

Conclusion: Low levels of physical activity reported in CFS represent a significant and potentially modifiable perpetuating factor in CFS and are not attributable to high levels of sedentary activity, rather a decrease in physical activity intensity. The reduction in physical activity can in part be explained by autonomic dysfunction but not fatigue severity.

Introduction

Chronic fatigue syndrome (CFS) is a condition characterized by persistent or relapsing fatigue without underlying organic disease, which is not improved with rest. The physical symptoms reported by patients with CFS typically include: multi-joint pain,

muscle aching and weakness, swollen and tender glands, blurred vision and headaches. Also known as myalgic encephalomyelitis (ME) or immune dysfunction syndrome, CFS is a common condition affecting 0.1–1% of the population.¹

Prospective studies have shown that the duration of illness ranges from 3 to 9 years and that full

recovery is rare,² underlining both the burden to the individual and their families, and the importance of developing appropriate management strategies for this condition. Despite this, the pathogenesis of CFS remains unclear. A growing literature does, however, describe the abnormalities of the vascular system in those with CFS.^{3–8} These vascular changes are accompanied by functional abnormalities in skeletal muscle oxidative function in CFS, the severity of which associates with autonomic nervous system function.^{9,10}

Ensuring a physically active lifestyle helps maintain physical function, delays the onset of disability^{11,12} and increases the probability^{11,13}, and duration of recovery from disability with ageing.¹⁴ A physically active lifestyle also reduces mortality and extends life expectancy,^{15,16} likely through delaying the onset of cardiovascular disease,¹⁷ diabetes¹⁷ and cognitive decline.¹⁸ Habitual physical activity is reported to be reduced in CFS.^{19–21} These studies show the negative effect that CFS has upon activities of daily living and consequential impact on additional disease burden. However, despite large numbers of patients being studied, the size and quality of the matched control groups is lacking. Two recent systematic reviews have underlined the uncertainty in this area.^{22,23} None of the studies to date have matched for age, sex and BMI combined, key mediators of habitual physical activity. As such, the true impact of CFS upon physical activity remains unclear. No studies have also linked habitual physical activity with markers of physiological function that may contribute to a diminished capacity in CFS.

In light of the importance of physical activity to well-being, we therefore set out to define: (i) the levels of physical activity and physical inactivity in CFS relative to age-, sex- and BMI-matched controls and (ii) the relationship between physical activity, autonomic regulation and fatigue severity in CFS.

Subjects and methods

Subjects

One hundred and seven patients who had a diagnosis of CFS using the Fukuda Criteria²⁴ ($n = 107$) were recruited from the Northern Regional CFS Clinical Service (Newcastle upon Tyne, UK). Any patients with secondary causes for fatigue (such as hypothyroidism, diabetes, etc.) were excluded. One hundred and seven age-, gender- and BMI-matched control individuals ($n = 107$) who did not take part in regular exercise (<30 min exercise three times per week) and did not have CFS were also recruited.

Both CFS and control groups underwent objective assessment of physical activity and fatigue. The CFS group also underwent assessment of autonomic nervous system function. The study was approved by the Newcastle and North Tyneside Local Research Ethics Committee and all subjects provided written informed consent. Matching was performed by an observer blinded to the activity results.

Objective habitual physical activity assessment

Habitual physical activity was measured objectively using a validated²⁵ multi-sensor array (SenseWear Pro³, Bodymedia Inc., PA, USA) worn over 7 days. The multi-sensor array measures four key metrics: skin temperature, galvanic skin response, heat flux and motion via a 3-axis accelerometer. The sensors combined with algorithms, calculate the average daily energy expenditure relative to baseline metabolism [metabolic equivalent: MET per day (1 MET = resting metabolic rate)], total energy expenditure (calories per day), active energy expenditure (total calories expended over 3 METS per day), physical activity duration (minutes >3 METS per day) and average daily number of steps walked. Patterns of sedentary behaviour were assessed by power law analyses of the lengths of sedentary bouts fitted from raw sedentary data as described in more detail previously.²⁶ Probabilities of bout lengths were plotted against the fraction of total sedentary time. Activity patterns were also assessed by assessing transitions from active to inactive period, termed ‘zero-crossing rate’ and normalized by the length of the recording.

Fatigue Impact Scale

The Fatigue Impact Scale (FIS), a 40-item generic FIS was used to assess fatigue severity. The FIS has previously been validated for use in, and extensively utilized in CFS.²⁷

Autonomic regulation

All subjects refrained from smoking and caffeine ingestion on the day of investigation and ate a light breakfast only. All investigations were performed at the same time of day, and took place in a warm, quiet room. All cardiovascular assessments were carried out with continuous heart rate and beat-to-beat blood pressure measurement (Taskforce: CNSystems).

The integrity of the autonomic nervous system was assessed during 10 min rest using baroreflex sensitivity (calculated by the Taskforce using the ‘sequence method’)²⁸ and heart rate variability (HRV) (using spectral analysis)²⁹ to derive total power

(power spectral density), low frequency HRV (predominantly sympathetic), high frequency HRV (predominantly parasympathetic) and very low frequency HRV. The low frequency/high frequency ratio was considered as an indicator of the balance between the sympathetic and parasympathetic nervous systems.

Statistical analysis

All statistical analyses were performed using Graphpad Prism version 5 (La Jolla, USA). Control data were compared with clinical groups using an independent *t*-test. The level of significance was set at $P < 0.05$. Sedentary time was visualized by plotting probabilities of bout lengths plotted against the fraction of total sedentary time. The area under the curve served as characteristic value (normalized over session length). All values are expressed as mean \pm SD unless otherwise stated. Correlations were using a Pearson's correlation coefficient.

Results

Baseline characteristics

There were no significant differences ($P > 0.05$) in age or BMI between the CFS and control groups (general descriptions in Table 1). According to the World Health Organisation classification,³⁰ the CFS group had a high prevalence of obesity, with 37% being overweight (BMI 25–29.9) and 20% obese (BMI ≥ 30) with 3% of the CFS group underweight with BMI < 18 . Habitual physical activity was low, with 79% of the CFS group (vs. 47% of the control population; $P < 0.0001$) not achieving the 10 000 steps per day advised as the level of activity required to maintain good health.³¹

Table 1 Habitual physical activity data in CFS patients and age-, sex- and BMI-matched controls

	Controls	CFS	<i>P</i> -value
<i>n</i>	107	107	
Physical activity time (min/day)	179 (285)	72 (54)	< 0.0001
Steps (per day)	10270 (3999)	7089 (3096)	< 0.0001
Average METS (per day)	1.46 (0.2)	1.12 (0.3)	< 0.0001
Total energy expenditure (cal/day)	2973 (381)	2159 (381)	0.01
Sedentary time (min)	1213 (262)	1262 (177)	0.1
Moderate time (min)	101 (56)	71 (52)	< 0.0001
Vigorous time (min)	3.2 (4.2)	1.4 (2.9)	0.0008
Very Vigorous time (min)	0.9 (3.3)	0.2 (1.7)	0.06

General associations with physical activity

Low levels of physical activity were common with half of the group having an average daily MET energy expenditure of < 1.4 . Physical activity was inversely related to age, with older CFS participants less physically active than younger CFS participants (average METS $P = 0.03$; $r^2 = 0.05$). BMI was also associated with physical activity, with the less physically active participants having a greater BMI (steps $P = 0.003$, $r^2 = 0.1$; average METS $P = 0.005$, $r^2 = 0.1$).

Compared to the age-, sex- and BMI-matched controls; the CFS group had significantly reduced physical activity duration, steps, average METS (all $P < 0.0001$; Table 1 and Figure 1). Total energy expenditure (EE) was significantly lower in CFS compared with controls ($P < 0.0001$; Table 1); however, there was no significant difference in the time spent in sedentary activity (Table 1). A further analysis of the pattern of sedentary behaviour also shows that there are no differences in the transition from being sedentary to being active (termed zero-crossing rate) or in the duration of sedentary bout length (Figure 2). Importantly the reduction physical activity was related to significantly lower levels of moderate and vigorous activity in the CFS group compared to controls (Table 1).

Relationship between physical activity and symptoms in CFS

There were no relationships between fatigue severity assessed using the FIS and any parameter of activity in CFS.

Relationship between physical activity and autonomic function in CFS

There were significant inverse relationships between physical activity and heart rate in CFS (physical activity duration $P = 0.04$; $r^2 = 0.03$). Furthermore, there were significant relationships between total HRV and activity in CFS with reduced activity being associated with reduced HRV (Table 2). Importantly the relationship between the time taken performing vigorous activity and total HRV was also significant ($P = 0.04$; $r^2 = 0.03$). There also appeared to be a relationship between increased low frequency/high frequency (LF/HF) ratio and physical activity suggesting reduced physical activity was associated with a shift towards predominance of parasympathetic autonomic function (Table 2).

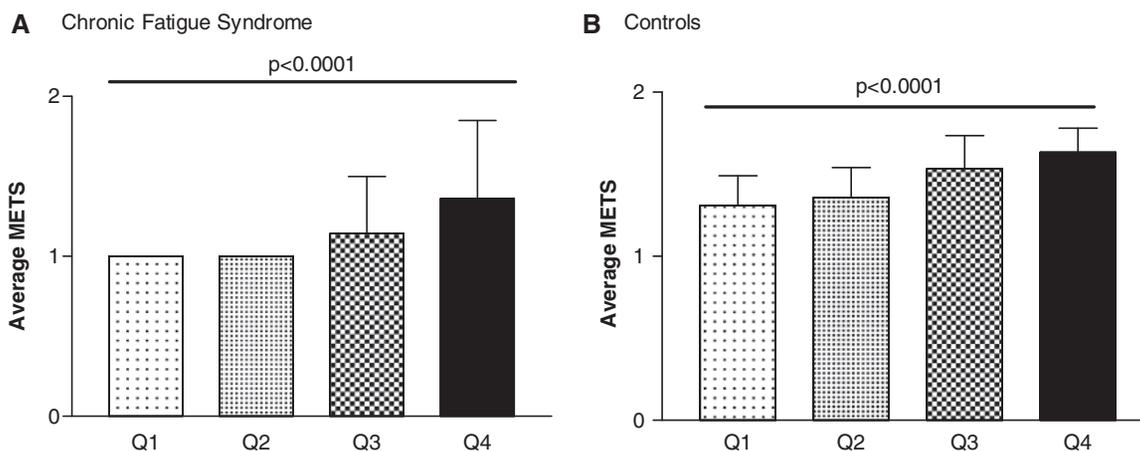


Figure 1. Objectively measured quartiles of physical activity in both (A) CFS and (B) controls were associated with lower levels of average METS in both groups but considerably lower levels in the CFS group.

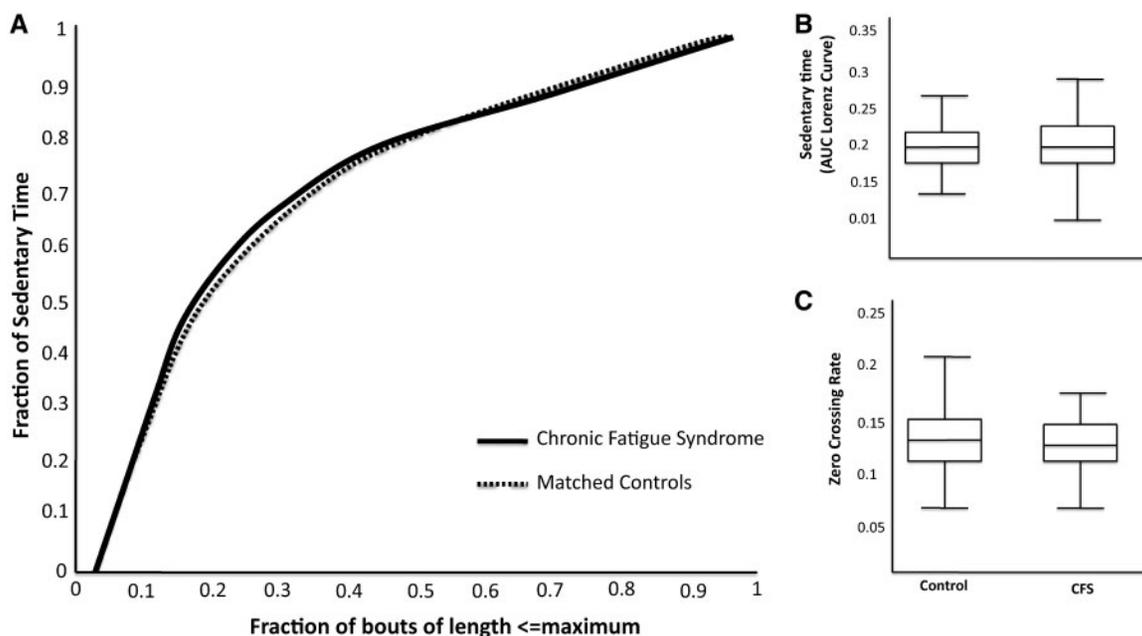


Figure 2. (A) Power law analyses of the lengths of sedentary bouts of patients with CFS (line) and controls (dashed), (B) Area under the curve of the power law analyses of the lengths of sedentary bouts of patients with CFS (line) and controls (dashed) and (C) Zero-crossing rate indicating transition from active to inactive periods in patients with CFS and controls. There are no significant differences between groups.

Discussion

CFS is a common condition that is associated with debilitating symptoms. The major findings of this study are: (i) a sedentary lifestyle is prominent in people with CFS: 79% of the participants did not achieve internationally advised levels of physical activity (10 000 steps per day),^{30,31} (ii) CFS was not associated with higher levels of sedentary behaviour but reduced levels of vigorous activity, (iii) moderate physical activity was reduced by 30% in CFS compared with age-, sex- and BMI-matched people

without CFS, (iv) physical activity was associated with objectively measured parameters of autonomic function, most notably total HRV and (v) There was no relationship between fatigue severity and physical activity.

The first key observation was the low level of physical activity in the patient cohort, with 79% of the CFS group (compared to 47% of the matched controls) not achieving 10 000 steps per day recommended for the maintenance of health. Although a reduced level of physical activity is in line with previous reports,^{19,20} the present study builds on these

Table 2 Relationship between habitual physical activity and objectively measured autonomic function assessed during 10 min rest in CFS patients

	Total HRV		LF/HF	
	P-value	r ²	P-value	r ²
Physical activity (min/day)	0.04	0.05	0.007	0.1
Steps (per day)	0.04	0.04	0.02	0.05
Ave METS (per day)	0.007	0.1	0.03	0.04
Total energy expenditure (cal/day)	0.02	0.1	0.03	0.04
Sedentary Time (min/day)	ns	0.00	ns	0.00
Moderate Activity (min/day)	ns	0.00	ns	0.00
Vigorous Activity (min/day)	0.04	0.03	0.009	0.1
Very vigorous Activity (min/day)	ns	0.00	ns	0.00

ns = not significant or $P > 0.05$.

by closely matching the patient group with age-, sex- and BMI-matched controls. Matching for BMI is important, as BMI itself is associated with reduced physical activity^{17,32} and is a potential confounding variable. Over half of the CFS group were overweight and one in five classified as obese,²⁹ further highlighting the importance of BMI matching.

Physical activity has been theoretically linked to symptom presentation,³³ with patients suggested to relate physical activity to fatigue and myalgia. This in turn produces an avoidance of physical activity as patients attempt to reduce symptoms. Despite this hypothetical link, there is very limited data to support this in CFS.²⁰ Our data on well-matched individuals shows clearly that people with CFS do not have increased periods of sedentary activity, in contrast to previous observations.²⁰ The similar level of sedentary behaviour between CFS and controls is of clinical relevance as sedentary behaviour is acknowledged to have a strong adverse influence upon healthy living, compounding metabolic diseases and reducing life expectancy.^{13,14,17,32} Recent studies report that the breaks in sedentary time provide an even stronger indicator of metabolic risk than total sedentary duration alone.³² The breaks in sedentary time, the transition from being sedentary to being active (zero-crossing rate), provides a physiological stimulus which increases peripheral blood flow maintains cellular signalling.³⁴ Our data show that the breaks in sedentary activity are similar between CFS and control, also unlike previous reports in CFS.²⁰ The difference between the present observations and the literature is likely due to the larger control sample and matching for BMI in the present study.

In contrast to the sedentary data, when comparing levels of active energy expenditure, patients with CFS show a 30% reduction in moderate energy expenditure and a 50% reduction in time spent

performing vigorous activity. Combined with the sedentary behaviour data, this observation suggests that people with CFS move the same amount as people without CFS. However, the intensity of the activity is reduced in CFS. It is possible that the reduction in physical activity intensity relates not to motivation to be physically active, rather a functional deregulation in the muscle or autonomic function. Recent observations from our group and others suggest that muscle metabolism is impaired in CFS, with a rapid accumulation of acid inside of skeletal muscle in CFS.^{9,10} Furthermore, subtle abnormalities in cardiac bioenergetic function in CFS suggest changes in autonomic function, possibly relating to altered autonomic function.³⁵ The combined effect of metabolic and autonomic deregulation observed in these studies would be a decreased exercise tolerance, a possible explanation for the decreased intensity of physical activity in the present study. Alternatively, it may be that patients with CFS avoid increased activity because of perceived negative consequences such as post-exertional malaise or increased pain.³⁶

Our finding of a relationship between activity and autonomic function assessed using HRV at rest underlines the relationship between autonomic function and muscle function in CFS^{9,10} and points towards a potential route for treatment. Our finding of reduced HRV and increased heart rate in association with reduced levels of activity are in keeping with previous findings in CFS. Further studies are needed to determine the direction of the relationship between autonomic function and activity, whether impaired autonomic function (withdrawal of sympathetic function and/or overactivity of parasympathetic function) leads to impaired physical activity, and by what route, or whether it is a consequence of inactivity.

We were surprised to find that there was no relationship between increased fatigue and reduced habitual physical activity, which is in contrast to other studies.²⁰ We would suggest that this is explained by a ceiling affect in the symptom assessment tools i.e. a relatively low symptom burden leads to significant impact upon physical activity levels. Previous studies have also reported mixed groups of patients with CFS and multiple sclerosis making comparison difficult.

It remains to be determined whether increasing physical activity or targeting autonomic function confers benefits to people with CFS. People with CFS report that physical exertion can make their symptoms worse.^{37,38} It is important to recognize that sudden and unmonitored increases in physical exertion would be expected to worsen symptoms in debilitated subjects. However, individualized

programmes targeting increases in habitual physical activity at often initially a very low level of intensity can lead to benefits for patients.³⁹ It is vital that those with CFS are encouraged to increase their habitual physical activity, as this is a significant environmental factor influencing physical fitness and well-being. Evidence suggests that physical activity helps maintain physical function, delays the onset of disability, reduces mortality and extends life expectancy in normal ageing.^{14–16} In other fatigue associated diseases (multiple sclerosis), those who participate in regular physical exercise report better fatigue, depression and quality of life scores.⁴⁰ Combined, the present study highlights the importance of targeting sedentary behaviour and exercise tolerance in CFS. Other studies suggest a benefit of increasing physical activity. The challenge ahead is to understand how these observations can be incorporated into clinical care.

This study has a number of limitations. Autonomic assessment was not performed in the control population and furthermore a number of the parameters assessed are potentially affected by the motivation of the patient.

In conclusion, the present study suggests that low levels of physical activity represent a significant and potentially modifiable risk factor in CFS. The low levels of physical activity reported in CFS are not attributable to high levels of sedentary activity, rather a decrease in physical activity intensity. The reduction in physical activity can in part be explained by autonomic dysfunction but not fatigue severity.

Acknowledgements

The study was reviewed and approved by the Newcastle and North Tyneside Local Research Ethics Committee. The authors acknowledge the funding from ME Research UK, the John Richardson Research Group, the Irish ME Trust and a fellowship from Diabetes UK and the Medical Research Council. The funders did not participate in the analysis of the study results.

Funding

The National Institute for Health Research (NIHR) Biomedical Research Centre in Ageing, UK; Myalgic Encephalomyelitis (ME) Research, UK; the John Richardson Research Group and the Irish ME Trust. Diabetes UK and the Medical Research Council (fellowship to M.T.).

Conflict of interest: None declared.

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