



**Rebuttal to Ickmans et al. Association between cognitive performance, physical fitness, and physical activity level in women with chronic fatigue syndrome. *J Rehabil Res Dev.* 2013;50(6):795-810.**

[www.rehab.research.va.gov/jour/2013/506/pdf/ickmans506.pdf](http://www.rehab.research.va.gov/jour/2013/506/pdf/ickmans506.pdf)

Dear Editor:

In a study recently published in *Journal of Rehabilitation Research and Development*, Ickmans et al. [1] found a substantially deteriorated physical exercise capacity in myalgic encephalopathy/chronic fatigue syndrome (ME/CFS), as established by a cardiopulmonary exercise test (peak oxygen uptake [ $VO_{2max}$ ]:  $19.1 \pm 4.6$  mL/min/kg, peak heart rate:  $145.1 \pm 22.4$  beats per minute [bpm], peak workload:  $114.2 \pm 31.3$  W, compared with  $27.2 \pm 5.6$  mL/min/kg,  $170.0 \pm 36.2$  bpm, and  $114.2 \pm 31.3$  W, respectively, in sedentary controls). Ickmans et al. also observed various cognitive deficits in ME/CFS, e.g., prolonged choice and simple reaction times in various Stroop subtests and the psychomotor vigilance task test (PVT), more errors of omission in the PVT, and worse letter recall scores on the operation span task test, indicative for working memory impairment and reduced psychomotor speed. They also found correlations between lower  $VO_{2max}$  and peak heart rate at the exercise test and the reduced psychomotor speed and maximal hand-grip strength and working memory performance ( $p < 0.05$ ). However, this

study did not establish an association between the physical activity levels (PALs) and cognitive performance as was expected a priori. A posteriori analysis showed a correlation between physical exercise capacity and PALs. The authors hypothesized that physical activity (PAL) is a potential mediator of the relationship between the exercise capacity ( $VO_{2max}$ ) and cognitive function.

Van Oosterwijck et al. observed that postexertional malaise, defined as “symptom exacerbation as a result of excessive exercise,” is triggered by submaximal and self-paced, low-level exercise [2]. The authors suggested that the reduced exercise capacity is a consequence of an underlying fear of postexertional malaise, which could be reversed by graded exercise therapy.

As argued before [2], cognitive deficits in ME/CFS can plausibly be explained by neurological abnormalities, e.g., hypoperfusion of and hypometabolism in specific brain regions, impaired cerebral oxygenation during exercise and orthostatic stress, SPECT-scan abnormalities in the cerebral cortex, and a reduction in white and gray matter. A correlation between neurological abnormalities and neurocognitive functioning has been observed repeatedly.

As substantiated by Meeus et al. [3], elevated oxidative and nitrosative stress, frequently observed in ME/CFS, can account for mitochondrial dysfunction, a decrease of the aerobic exercise capacity, and increased pain sensitivity.

Various studies, including the study of Ickmans et al. [1], have observed a (strongly) reduced exercise capacity when compared with sedentary controls. As indicated by the peak respiratory exchange ratio in the study of Ickmans et al. [1] and others [4], this low exercise capacity reflects maximal effort. More importantly, various studies have found that a single exercise test can have a long-lasting effect on symptoms (postexertional malaise) [4,6] and (pre-existing) abnormalities, e.g., (low-grade) inflammation and increased oxidative and nitrosative stress [5]. Snell et al. found that ME/CFS patients achieved significantly lower values for the oxygen uptake and workload at peak exercise and at the anaerobic threshold at a second exercise test 24 h later and that the results of the second exercise test could classify patients and sedentary controls with great accuracy (95.1%.) [4].

This would imply that many subjects with ME/CFS are physically incapable of improving their activity levels gradually. This is illustrated by the observation that even moderate exercise induces postexertional malaise, an increase in pain, “fatigue,” etc., and various (durable) abnormalities, e.g., an increase in metabolite detecting pain receptors [6], the fact that ME/CFS patients are unable to sustain a graded walking program starting at low levels and exhibit exercise intolerance, as implicated by reduced total activity after 4 to 10 days [6], and the observation that the increase in distance walked in 6 min after cognitive behavioral therapy

and Graded Exercise Therapy is very minimal and insufficient to qualify as clinical improvement [7].

The reduced oxygen uptake and cognitive deficits in ME/CFS seems to be the consequence of organic abnormalities, e.g., mitochondrial dysfunction due to elevated oxidative and nitrosative stress, partly due to chronic inflammation, reduced blood flow to the brain and the muscles, diminished prefrontal cortex oxygenation during incremental exercise, neurologic aberrations, etc. [2].

Looking at the evidence at present, the hypothesis of Ickmans et al. [1] that activity level is a mediator of the relationship between the exercise capacity (e.g.,  $VO_{2max}$ ) and cognitive functioning does not seem very likely. It seems more plausible that the low exercise capacity reflects the clinical status of a patient and that the negative effect of (moderate) exercise on the oxygen uptake and the anaerobic threshold puts the patient in a “catch-22” position, including characteristic low exercise capacity and cognitive deficits.

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## RESPONSE

We would like to thank the Editor for giving us the opportunity to

respond to the Letter to the Editor by Frank Twisk. We do value the correspondence through this Letter to the Editor to facilitate the international debate, but at the same time we have concerns about the scientific credibility of the Letter.

First, in his Letter Twisk refers two times to reference number 2. The first time he refers to an article of Van Oosterwijck et al. [1], while the reference of this article is not included in the reference list. The second time he refers to his own Letter to the Editor [2], which was a comment on a meta-analysis by Cockshell and Mathias [3]. Thus, rather than citing original research data, Twisk prefers citing his own Letter. This makes it difficult for the readership to assess whether the arguments are evidence-based or represent hypotheses.

A similar reasoning applies to another argument postulated by Twisk, when he states that an article written by our group substantiates that elevated oxidative and nitrosative stress can account for mitochondrial dysfunction, a decrease of the aerobic exercise capacity, and increased pain sensitivity in ME/CFS. In opposition to what has been stated by Twisk, the referenced article [4] formulates no more than hypotheses on this. Again, citing original research data is required for scientific argumentation.

Another important remark to the Letter of Twisk is his supposition that many patients with CFS are physically incapable of improving their activity levels gradually. He bases this statement on evidence that was found in a study performed by Snell et al. [5] in which people with CFS achieved significantly lower values for oxygen uptake and workload at peak exercise and at the anaerobic

threshold at a second exercise test. However, a key point here is that these results were found after the performance of a double maximal exercise tests (separated by 24 h). Extrapolation of findings after the performance of a double maximal exercise test to exercise therapy for CFS is not appropriate, not to mention incorrect. It is important to make a distinction between the effects from therapeutic interventions using exercise therapy in CFS (e.g., de Lang et al. [6] and Wallman et al. [7]) and findings from studies examining the effects of acute exercise and exercise physiology in people with CFS (e.g., Van Oosterwijck et al. [1], Nijs et al. [8], Sorensen et al. [9]). The latter often use one bout of exercise to examine the acute response to (often very strenuous) exercise. Such exercise physiology studies provide us with valuable information on the biology of postexertional malaise in CFS but cannot interfere with evidence from studies examining the long-term effects of low-intensity exercise programs. These are two distinct issues. Making this distinction is likely to result in a broader view on this severe and underestimated illness. We and others have invested considerable research time and funding in studying the exercise (patho)physiology of ME/CFS. It is frightening to see that findings from exercise physiology studies, addressing the acute effects of exercise, are extrapolated to effects of long-term exercise or physical activity interventions.

Finally, Twisk suggests that cognitive deficits in ME/CFS can be explained by neurological abnormalities and changes in brain structure and function [2], including orthostatic intolerance and a reduction in gray matter volume, among others.

We support this view and acknowledge the existing evidence regarding involvement of the (central and/or autonomic) nervous system in cognitive impairment in CFS [6,10–12]. However, we disagree with his firm beliefs that exercise therapy would be detrimental to people with CFS. In fact, we feel that Twisk has made conclusions based on selective and incomplete knowledge of the scientific literature in the field. Research on the effects of acute exercise on cognitive functioning in CFS shows either no difference in cognitive performance [13–14] or significantly worse cognitive performance after exercise [15]. However, de Lange et al. showed a significant relationship between gray matter volume and the amount of physical activity in people with CFS [11]. In a subsequent study, de Lange et al. found a significant improvement in CFS patients' cognitive performance following cognitive behavioral therapy [6]. Furthermore, as already stated in the discussion of our article [16], Wallman et al. [7] showed a positive effect on cognitive functioning after a 12 wk graded exercise intervention in people with CFS. Thus, contrary to what Twisk is advocating, science has taught us that conservative interventions may have positive, rather than negative, effects on cognitive functioning in patients with CFS. It would be unfair to CFS patients to keep such important findings from them.

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