

LETTER TO THE EDITOR

Chronic fatigue syndrome: a clinical and laboratory study with a well-matched control group

DEAR SIR,

It is an ongoing debate whether concurrent occurrence of particular additional symptoms should be part of the definition of chronic fatigue syndrome (CFS) [1–5] or not. Studies on the similarities and differences between patients satisfying the various definitions are indispensable to solve this dispute.

Swanink *et al.* [6] studied CFS patients satisfying the criteria described by Sharpe *et al.* [3], i.e. additional symptoms may be present but are not required. Part of the group also satisfied the more stringent CFS criteria by the Centers for Disease Control (CDC) [1], which require the additional presence of at least eight specific symptoms. When the number of complaints was included as the covariate, no significant differences on fatigue severity, depression and functional impairment were found between CFS patients who fulfilled the CDC criteria and who did not. Furthermore, the authors remarked that the sole effect of applying the CDC symptom criteria to their study group is separating patients with few symptoms from patients with many symptoms.

These results are very misleading and have often been misinterpreted. The authors' analysis of variance (ANOVA) yielded a lot of significant differences between CDC–CFS and non-CDC–CFS patients. That these were lost in their subsequent analysis of covariance (ANCOVA) is because the level of the covariate and the treatment (fulfilment of the CDC criteria) are highly dependent, as fulfilment of the CDC criteria requires the presence of at least nine symptoms (fatigue included). Because the ANCOVA assumption that the covariate is statistically independent of the treatment is not met, the ANCOVA

*It is for now assumed that the other ANCOVA assumptions are met.

results are artificial and have little practical meaning [7, 8].

What happened* is illustrated in Fig. 1. ANOVA checks whether CDC–CFS and non-CDC–CFS patients have equal test score means \bar{Y}_{CDC} and $\bar{Y}_{\text{non-CDC}}$. ANCOVA, however, checks the equality of *adjusted* test score means $\bar{Y}_{\text{CDC,adj}}$ and $\bar{Y}_{\text{non-CDC,adj}}$. These are obtained by transporting \bar{Y}_{CDC} and $\bar{Y}_{\text{non-CDC}}$ from the treatment covariate means \bar{X}_{CDC} and $\bar{X}_{\text{non-CDC}}$ along parallel regression lines to the grand covariate mean \bar{X} . Thus ANCOVA predicts if test score means of CDC–CFS and non-CDC–CFS patients would have been equal if both groups had exactly the same mean number of complaints. It provides an answer to a question that has no relevance – the mean number of complaints is inherently different for these two groups. In particular, Table 1 of the article learns that the grand covariate mean as reported with the standardized questionnaire equals $\bar{X} = 674/88 = 7.66$: the adjusted mean $\bar{Y}_{\text{CDC,adj}}$ corresponds to a group of CDC–CFS patients that does not even exist in reality!

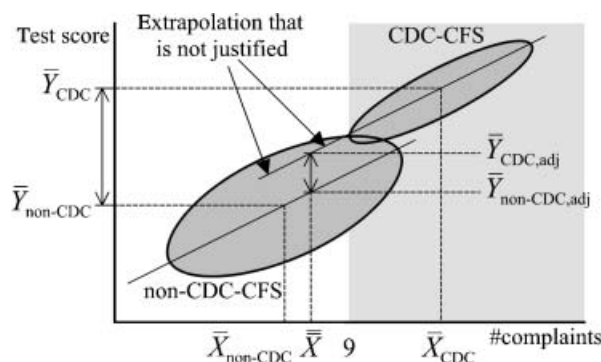


Fig. 1 Difference between analysis of variance (ANOVA) and analysis of covariance (ANCOVA). ANOVA compares the treatment means \bar{Y}_{CDC} and $\bar{Y}_{\text{non-CDC}}$, whereas ANCOVA compares the adjusted treatment means $\bar{Y}_{\text{CDC,adj}}$ and $\bar{Y}_{\text{non-CDC,adj}}$ corresponding to the same level of the covariate for both groups. Note that the grand covariate mean \bar{X} corresponds to a group of CDC–CFS patients that does not exist in reality.

Although their ANCOVA was inappropriate, the authors' ANOVA did result in valuable information. ANOVA of CDC-CFS versus non-CDC-CFS yielded significant differences (at least $P < 0.05$) in concentration, activity, sleep and rest, ambulation, alertness behaviour, and recreation and pastimes, which according to the authors means that CDC-CFS patients are significantly more impaired in daily functioning. As the subjective fatigue subscale of the checklist individual strength (CIS-fatigue) easily reaches the extreme end of its scale in CFS samples (see e.g. [9, 10]), it is obvious that no significant differences in fatigue severity as measured by CIS-fatigue could be found. Generally speaking, assessing fatigue severity using a scale without this flaw may well result in different outcomes (see e.g. [10]).

Because the inadequate ANCOVA made it appear that there are no clinical differences between CDC-CFS and non-CDC-CFS patients, this study has often been cited to permit leaving out additional symptom criteria when considering CDC-CFS. This has had major consequences for scientific research as well as for clinical practice. In scientific literature, non-CDC-CFS patients are labelled as having 'a diagnosis of CFS according to the CDC criteria' [10] or fulfilling 'the CDC criteria for CFS' [11], although other sources by the same authors explicitly state that they do not [12, 13]. In a large randomized study on cognitive behaviour therapy for CFS [14], one of the two reasons that patients without the required number of additional symptoms were included is that 'patients who fulfilled the CDC-criteria did not differ concerning the severity of the complaints from patients who did not satisfy the CDC criteria' [13]. The CFS definition used for clinical practice in large parts of the Netherlands [15] is based on CDC criteria, but patients without the required additional symptoms are also diagnosed CFS because 'clinically this distinction has no meaning, as it has turned out from Dutch research' [16]. This means that if the mistakes above would have been noted at an earlier stage, literally thousands of chronically fatigued patients might have had a different diagnosis in the Netherlands.

Apparently [13] the incorrect results of the article have also been presented during a recent meeting held for revising the latest CDC-CFS definition (presentation Bleijenberg, CDC consensus meeting, Atlanta 2000). To prevent more scientific research on CDC-CFS that disregards additional symptoms

and more CFS definitions that are based on statistical errors rather than on data, it is important that the mistakes in the article are corrected as soon as possible.

Conflict of interest statement

No conflict of interest was declared.

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