Reviewer's report

Title: Chronic fatigue syndrome after Giardia enteritis: clinical characteristics, disability and long-term sickness absence.

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Reviewer: Simon Wessely

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I have had a careful read of the manuscript

The real problem is the disconnect between the original survey, published in a tropical medicine journal, and the current paper. One would like to see the connections between the two examined, but as far as I can see this has not happened, and there has been no attempt at record linkage which might make this a far more valuable study.

For example, the outbreak was 2004. The initial study was 2006, already two years had passed. But what were the fatigue scores in 2006 in the cases that were recruited for the current study? It doesn’t say, and indeed there is no overlap in the authorship between the original survey, which seemed to cover all of those in the outbreak, and got a reasonable response rate, and the current paper. One would expect then an analysis of the current cases (sick) against a random sample of exposed but not sick, in other words a classic nested case control study, but this hasn’t been done, and it’s hard to know why it hasn’t been done because it would be a much more powerful analysis.

I agree with reviewer two that including “delayed onset” cases is a mistake, and I note that the authors have now conceded this. As I don’t have access to the original manuscript hard to know what changes that made to the prevalence. Review two states that a “significant proportion” had delayed onset. Am assuming then that the authors have made those changes and reduced the prevalence – one wonders by how much.

Overall, I take the points made by reviewer 2, Peter White, who is the doyenne of these kind of studies. This current study is not a proper epidemiological study, for the reasons he mentions. Retrospective assessment of pre exposure fatigue and/or life events is basically worthless. When we did our post infectious fatigue study (Wessely et al, Lancet 1995) we obtained real data on fatigue/psychological morbidity before exposure, and then could show that this was in fact the most powerful predictor of post exposure fatigue/CFS. However, that design would not be possible in the current study, because they had no prior knowledge of exposure. They could however use Norway’s excellent primary care records to look for previous psych disorder, but chose not to. They could also record link with the HUNT study, which provides amazing population based data on Bergen, but again chose not to – I don’t know why, but either would have
substantially added to the value of the study. Finally, they could have investigated a random sample of those who had not presented in a classic two stage design, which would then have enabled them to get the true prevalence of CFS in the population, but again they don’t. All of these are missed opportunities.

However, I still think the report is of interest, for one reason only. They do have a true inception cohort, since am assuming that the background rate of giardiasis in Bergen is close to zero, so they can be sure that all their inception cohort are exposed, and none of the rest of the population, assuming that registration was complete (I don’t have the Original report of the epidemic to confirm that, its sadly not a journal i can access from home, but am making that assumption). So they can set a lower, but an upper, limit on the number of CFS cases arising after giardiasis, again, assuming that they have excluded anyone with delayed onset, in whom causality is very disputed and dodgy. And that lower limit does seem high. I take Peter White comments that comparing to other population data bases/studies is unsafe, i agree, but nevertheless, the prevalence they report is sufficiently high to suggest that there might be a link between exposure and CFS. Frankly, given the rest of the post infectious fatigue literature, this would not surprise me.

The authors finally could suggest that giardiasis might be another trigger for CFS, and i think that is likely, but given the PIFS literature they should also point out that this is unlikely to be specific trigger. We know that EBV for example for sure does this, we know that some odd Australian viruses can, we know that influenza doesn’t (Our study) but viral meningitis does (our earlier study) and so on and so forth.

So overall, am not as negative as Peter. I think that it would be a pity to waste the opportunity from the Bergen epidemic, even if the investigation was not as epidemiological rigorous as it could be (and i urge the authors now to consider doing the record linkage studies that would definitely increase knowledge of risk factors etc), and i think they have provided evidence that is suggestive, no more, that giardia is one more of the infective agents that can trigger CFS, adn that the mechanism is likely to be non specific, given the range of agents that already are known to do this.