PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Physical activity patterns among children and adolescents with mild-to-moderate chronic fatigue syndrome / Myalgic Encephalomyelitis
AUTHORS	Solomon-Moore, Emma; Jago, Russell; Beasant, Lucy; Brigden, Amberly; Crawley, Esther

VERSION 1 – REVIEW

REVIEWER	Reviewer name: David vickers Institution and Country: Cambridgeshire Community services NHS Trusr. Uk Competing interests: None
REVIEW RETURNED	16-Jan-2019

GENERAL COMMENTS	An useful study, with the conclusion that cfs patients vary in activity levels as helpful in guiding work with indivduals

REVIEWER	Reviewer name: Giulia Mandelli Institution and Country: Istituto Di Ricerche Farmacologiche Mario Negri, Department of Clinical Epidemiology, Italy. Competing interests: pidemiology, mortality, statistics, Intensive care
REVIEW RETURNED	24-Jan-2019

GENERAL COMMENTS	I read with interest the manuscript by Solomon-Moore at al “Physical activity patterns among children and adolescents with chronic fatigue syndrome / Myalgic Encephalomyelitis”. The aim of the study is to examine the underlying patterns of physical activity among youth with CFS/ME, and understand how these patterns are associated with health outcomes. Patients considered in the study are children and adolescents (aged 8-17 years) diagnosed with mild-to-moderate CFS/ME who wore an accelerometer for at least three valid weekdays. Three latent classes emerge from the data: ‘active’, ‘light’ and ‘inactive’. Compared to being ‘inactive’, being in the ‘light’ class is associated with greater self-reported physical function and lower fatigue, while being ‘active’ is associated with greater physical function but also greater anxiety. The authors conclude that paediatricians need to be aware that physical activity patterns vary widely before recommending treatment. I congratulate the authors for their optimal planning and management of the statistical component of the study. I find the manuscript to be generally well written and easy to follow. Here some suggestions: 1. The mean time since diagnosis of the participants is 19 months with a range between 2 and 96. It seems to me that it is a very large range, so I suggest including median and interquartile range to show where most of the population is located. 2. The t-test compare the physical activity variables of the younger children (8-11 years) with the adolescents (12-18 years).

	Since the first group consists in only 23 children, is better verify the hypothesis of the t-test. What did the authors find about it? Alternatively, I suggest performing the Wilcoxon test. 3. On page 8, the authors compare young people with CFS/ME with children from healthy populations. The Millennium Cohort Study enrolled 7-8-year-old children while B-Proact1v 8-9-year-old children. It would be better for the comparison to use only the 7-9-year-old children of the MAGENTA data. It is also motivated by the results of the descriptive statistics in which younger children seem to be less sedentary and engaged in more physical activity. It would be advisable to include the p-value of the test to support the results. 4. In the sensitivity analysis, the authors both include participants who provided 1-2 days of valid accelerometer data both select a 4-class model. I suggest doing two different analysis to better compare qualitatively the results.

REVIEWER	Reviewer name: Elise van de Putte Institution and Country: University Medical Center Utrecht Competing interests: I am working in the same area of research and we work together in a randomized controlled trial. But I am not involved in this paper, neither in the hypothesis, the data, the analysis or the discussion.
REVIEW RETURNED	31-Jan-2019

GENERAL COMMENTS	In general: This is a relevant topic to explore. But I would like to invite the authors to first reflect on relevant clinical questions regarding data derived from actigraphy in mild to moderate CFS/ME children? (in cross-sectional data pretreatment). These are my reflections: • Classifying different types of activity in children with CFS/ME is not a goal in itself. It's only a goal if it is clinical relevant. And you have to provide evidence for this. • You have to convey the relevance of the measurement of physical activity by showing in the literature the relationship between physical activity and treatment outcome (or the relationship between physical activity and adjustment of the intervention) • You have to convey the relevance of the measurement of physical activity by showing the association between physical activity and relevant clinical parameters (pain, fatigue, self-reported physical activity, anxiety??, depression???) • It is clinical relevant to zoom into the relationship between physical activity pattern and self-reported physical activity. If you find a discrepancy, this will underline the necessity to measure physical activity and not only self-reported data. • With this data you can show that reduced physical activity is a key symptom of CFS/ME and you can contribute to the discussion about the symptom complex of CFS/ME All the above questions are insufficiently addressed in the current article. But it might be possible to answer these questions with the existent data. So if the authors are able to change the focus of the article in these ways, I would suggest offering them the opportunity to resubmit. In detail: ABSTRACT:

	Please emphasize that the data are only derived from children with mild-to-moderate CFS. The aim of the study was not: understanding how the activity patterns are associated with relevant health outcomes. This would ask for a longitudinal study design with assessment of risk factors pre-treatment and assessment of health outcome after a certain amount of time (or intervention). With this cross-sectional these analyses are impossible. Analyses: be clear that physical function is self-reported (by questionnaires) (r 26) Results: I don't agree with the conclusion that participants are less active than the general child population (see analyses) Conclusions: It is not clear what the effect of classifying the physical activity pattern would be on the recommended treatment. The authors do not reflect on this in the discussion (or the introduction). INTRODUCTION Be clear that almost all literature is derived from ADULT CFS/ME patients. There is limited literature about physical activity in children with CFS/ME. One of the few articles is Takken et al 2007 (Sports Med) In the introduction you should make clear why it is relevant to measure physical activity in children with CFS/ME. See my general remarks at the beginning. And you should end with a hypothesis to make sure that data collection and data analyses are appropriate to answer your research questions and your hypothesis. It is not clear for me why it should be relevant to determine the association between physical activity patterns and anxiety and depression. Do you expect less activity in anxious children? Literature: Takken et al, 2006, Int J Sports Med, is not mentioned in the introduction. This is one of the few articles on physical activity in children with CFS/ME. Methods and recruitment Please make clear why you have only selected children with mild-to-moderate CFS/ME and what the proportion of this subcategory is in relation to the total group CFS/ME patients. Is the SF36-PFS, 10 items, validated for children and adolescents? (I thought only for adults?) I need a hypothesis for the measurement of anxiety and depression to evaluate if these instrument are necessary to answer the research question. Analysis I do see the value of creating subclasses of physical activity (if you can substantiate the clinical relevance in the Introduction) and do your analyses accordingly. But, by the way you have done the analyses now, it is hard to answer the question: how is the level of physical activity related to self-reported physical functioning in general in CFS/ME children? Because we do not know the relationship in the inactive class, only in the light and the active class in which there is a significant relation between physical activity and self-reporting PF. And this is an important question. We know that in adults the relationship of physical activity and self-reported PF is lacking.

	And that's the reason to add actigraphy to the measurements. It would be very interesting if this is different in children comparing to adults. So please, answer this question (and see my general remarks) Results Table 2. If you want to compare to the healthy population please make sure that you make proper comparions. You should split the CFS/ME group in a younger and olders group to make a proper comparison with this young healthy population (7-9 years!). As you show in this article physical activity is directly related to age with 4.2% increase in physical activity with each additional year. Either you adjust for age and gender (but then you need original data) or you stratify for age in your cohort if you compare with the healthy (younger) population. Table 6. Be careful with your conclusions. The number of patients in the active group is very small. I would wonder how the general relationship between physical activity and fatigue is. And again: why do you adjust for 'time since diagnosis'? I do not find all tables interesting. If you have reasons to do the analysis physical activity vs anxiety/depression (see general remarks), than please show all the results in one table and not in different tables. Why do you adjust the analyses for 'time since diagnosis'? Do you think that the relationship between self-reported physical functioning and physical activity is confounded by 'time since diagnosis'. If so, please reflect on this. Sensitivity analysis Please skip this paragraph. It does not really provide new insights Discussion Please emphasize that this article is limited to mild-to-moderate CFS/ME in children. Rewrite the discussion if the general questions are sufficiently addressed in hypothesis, analysis and results. P 16 r 1 t/m 17: if you have no hypothesis for the relationship between anxiety and physical activity, be very careful to draw conclusions!

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

An useful study, with the conclusion that cfs patients vary in activity levels as helpful in guiding work with individuals.

Response: We thank the reviewer for their supportive comments on the manuscript.

Reviewer: 2

I read with interest the manuscript by Solomon-Moore at al "Physical activity patterns among children and adolescents with chronic fatigue syndrome / Myalgic Encephalomyelitis".

The aim of the study is to examine the underlying patterns of physical activity among youth with CFS/ME, and understand how these patterns are associated with health outcomes. Patients considered in the study are children and adolescents (aged 8-17 years) diagnosed with mild-to-moderate CFS/ME who wore an accelerometer for at least three valid weekdays. Three latent classes emerge from the data: 'active', 'light' and 'inactive'. Compared to being 'inactive', being in the 'light' class is associated with greater self-reported physical function and lower fatigue, while being 'active' is associated with greater physical function but also greater anxiety. The authors conclude that paediatricians need to be aware that physical activity patterns vary widely before recommending treatment.

I congratulate the authors for their optimal planning and management of the statistical component of the study. I find the manuscript to be generally well written and easy to follow.

Response: Thank you for your supportive and positive comments on the manuscript. We will answer your suggestions below.

Here some suggestions:

1. The mean time since diagnosis of the participants is 19 months with a range between 2 and 96. It seems to me that it is a very large range, so I suggest including median and interquartile range to show where most of the population is located.

Response: Thank you, we have now included the median and interquartile range for the time since diagnosis (line 196), as follows:

'Median time since diagnosis was 14 months (interquartile range: 10-24).'

2. The t-test compare the physical activity variables of the younger children (8-11 years) with the adolescents (12-18 years). Since the first group consists in only 23 children, is better verify the hypothesis of the t-test. What did the authors find about it? Alternatively, I suggest performing the Wilcoxon test.

Response: Thank you for this suggestion, on reflection we agree that Wilcoxon rank-sum test is more appropriate and we have adjusted the methods (line 156-160) and Table 1 accordingly.

3. On page 8, the authors compare young people with CFS/ME with children from healthy populations. The Millennium Cohort Study enrolled 7-8-year-old children while B-Proact1v 8-9-year-old children. It would be better for the comparison to use only the 7-9-year-old children of the MAGENTA data. It is also motivated by the results of the descriptive statistics in which younger children seem to be less sedentary and engaged in more physical activity. It would be advisable to include the p-value of the test to support the results.

Response: Thank you for the suggestion, but we are unable to compare with only the 8-9-year-old children in the study due to the small sample of 8-9 year-olds (N=8). Therefore, we have made it clearer in the results that this is purely a descriptive comparison (line 207), as follows:

'To compare physical activity levels of young people with CFS/ME from the present study with children from healthy populations, we descriptively examined physical activity variables from other UK studies that used the same accelerometer cut points.'

We have also made it clearer in the discussion that it is difficult to make comparisons in the data, due to the association between physical activity and age (line 286-293), as follows:

‘Compared to a nationally-representative sample of younger children aged 7-8 years,[39] paediatric CFS/ME patients were sedentary for an additional 2.7 hours per day, and participated in less than half the amount of MVPA. However, it is difficult to make comparisons, as a multi-nation longitudinal study of children and adolescents (aged 2-18 years) from the general population, demonstrated that from the age of five years there is an average cross-sectional decrease of 4.2% in physical activity with each additional year.[41] This is consistent with the findings from the present study, whereby younger children aged 8-11 years were more active and less sedentary than adolescents.’

4. In the sensitivity analysis, the authors both include participants who provided 1-2 days of valid accelerometer data both select a 4-class model. I suggest doing two different analysis to better compare qualitatively the results.

Response: Thank you for this suggestion, however, due to conflicting advice between reviewers, and the small number of cases in the sensitivity analysis (N=22 with 1-2 days of valid data), separating the sensitivity analysis for participants who provided 1 or 2 days of valid data would not add to the understanding, and as such this has not been done.

Reviewer: 3

In general:

This is a relevant topic to explore. But I would like to invite the authors to first reflect on relevant clinical questions regarding data derived from actigraphy in mild to moderate CFS/ME children? (in cross-sectional data pretreatment).

Response: Thank you for your support and suggestions for improvement of the manuscript. Please see more detailed responses to your reflections below.

These are my reflections:

• Classifying different types of activity in children with CFS/ME is not a goal in itself. It’s only a goal if it is clinical relevant. And you have to provide evidence for this.

Response: Thank you, we have now provided detail in the introduction about how physical activity patterns of adolescent CFS/ME patients have previously been used to adapt treatment protocols with promising results (line 88-95). This study’s findings provide support for why classifying patterns of physical activity in children and adolescent CFS/ME is clinically relevant.

‘Another study investigated the efficacy of cognitive behavioural therapy for adolescent CFS/ME patients (N=29, mean age 15.6±1.3 years), with treatment protocols adapted to patients’ accelerometer-assessed physical activity patterns (“passive” versus “active”).[23] Passive and active patients showed equal improvements for fatigue, functional impairment, and school attendance,[23] and rates of improvement were larger than seen in previous studies where one protocol was used to treat all patients.[24] These results suggest that adapting treatment to different physical activity patterns may improve treatment outcome.[23]’

• You have to convey the relevance of the measurement of physical activity by showing in the literature the relationship between physical activity and treatment outcome (or the relationship between physical activity and adjustment of the intervention)

Response: As above, we have now provided detail in the introduction about how physical activity patterns of adolescent CFS/ME patients have previously been used to adapt treatment protocols with promising results (line 88-95).

This study's findings provide support for how classifying patterns of physical activity in children and adolescent CFS/ME could be used to adapt treatment and potentially influence treatment outcomes. We have also added a section to the discussion to reflect on this (lines 302-311), as follows:

'These results highlight the diversity of physical activity behaviour among young people with CFS/ME, suggesting treatment protocols should be adapted based on physical activity assessment. In a study by Stulemeijer and colleagues,[23] 'active' patients were encouraged to reduce their activity, recognise their limitations and accept their condition before building up activity levels, while 'passive' patients were encouraged to address and challenge beliefs that activity would aggravate symptoms and build up activity as soon as possible. Despite receiving different treatments, both groups reported decreases in fatigue severity and improvements in school attendance,[23] and improvement rates were greater than studies where only a single protocol was used.[24]'

- You have to convey the relevance of the measurement of physical activity by showing the association between physical activity and relevant clinical parameters (pain, fatigue, self-reported physical activity, anxiety??, depression???)

Response: We have added a paragraph discussing the association between these factors to the introduction (line 97-102), as follows:

'Children and adolescents with CFS/ME experience higher rates of mood disorders than healthy populations,[25-27] with around 30% of adolescent CFS/ME patients experiencing anxiety and/or depression.[26, 27] For most children, anxiety and depression appear to develop because of their condition.[28, 29] Whilst co-morbid mood disorders are associated with increased disability, fatigue and pain, there is no evidence on the relationship between co-morbid mood disorders in CFS/ME and objectively-measured physical activity.'

- It is clinical relevant to zoom into the relationship between physical activity pattern and self-reported physical activity. If you find a discrepancy, this will underline the necessity to measure physical activity and not only self-reported data.

Response: We have now added detail in the introduction (lines 76-79) to explain that the majority of studies to date have used self-report measures of physical activity, but that self-report measures have low reliability and correlation with objective measures (e.g., accelerometry). Therefore, demonstrating that more studies with objective measures of physical activity are warranted.

'However, the majority of studies used self-reported questionnaires to assess physical activity levels, which have low reliability and correlation with objective physical activity measurements (e.g., accelerometry) in patient and healthy populations.[16, 20, 21]'

- With this data you can show that reduced physical activity is a key symptom of CFS/ME and you can contribute to the discussion about the symptom complex of CFS/ME

Response: We disagree that reduced physical activity is a symptom of CFS/ME. Post exertional malaise (or an increase in symptoms in response to exercise) is a symptom. The classic pattern of physical activity as described in treatment protocols is a fluctuating level of physical activity. However, this is based on assumptions which have not been proven previously (or indeed in this paper).

All the above questions are insufficiently addressed in the current article. But it might be possible to answer these questions with the existent data. So if the authors are able to change the focus of the article in these ways, I would suggest offering them the opportunity to resubmit.

In detail:

ABSTRACT:

Please emphasize that the data are only derived from children with mild-to-moderate CFS.

Response: We have now made this clearer in the abstract in the 'Objective' section (line 34).

The aim of the study was not: understanding how the activity patterns are associated with relevant health outcomes. This would ask for a longitudinal study design with assessment of risk factors pre-treatment and assessment of health outcome after a certain amount of time (or intervention). With this cross-sectional these analyses are impossible.

Response: Thank you, we have now made it clearer in the abstract that we just examined cross-sectional associations between factors (lines 34-36), as follows:

'Cross-sectional associations between physical activity patterns with self-reported physical function, pain, fatigue, anxiety and depression, were also examined.'

Analyses: be clear that physical function is self-reported (by questionnaires) (r 26)

Response: We have now made it clearer that physical function is self-reported (lines 41-42).

Results: I don't agree with the conclusion that participants are less active than the general child population (see analyses)

Response: We have now changed this sentence to focus on how active participants were compared to Government recommendations for physical activity (lines 44-45), as follows:

'Overall, participants did less than half the Government recommended level of physical activity for children and adolescents, …'.

Conclusions: It is not clear what the effect of classifying the physical activity pattern would be on the recommended treatment. The authors do not reflect on this in the discussion (or the introduction).

Response: As above, we have now added detail in the introduction about how physical activity patterns of adolescent CFS/ME patients have previously been used to adapt treatment protocols with promising results (lines 88-95). This study's findings provide support for why classifying patterns of physical activity in children and adolescent CFS/ME is clinically relevant. We have also added a section to the discussion to reflect on this (lines 302-311).

INTRODUCTION

Be clear that almost all literature is derived from ADULT CFS/ME patients. There is limited literature about physical activity in children with CFS/ME. One of the few articles is Takken et al 2007 (Sports Med)

Response: Thank you, we have now made this clearer in the introduction that most of the literature is derived from adults CFS/ME patients (lines 73-74), as follows: 'The majority of studies that have examined physical activity among CFS/ME patients have focused on adult populations.[9-19]'

In the introduction you should make clear why it is relevant to measure physical activity in children with CFS/ME. See my general remarks at the beginning.

Response: We have answered this above, a previous study demonstrated how adolescent physical activity levels have been used to adapt CFS/ME treatment protocols with promising results. We have included detail of this in the introduction, providing rationale for why measuring physical activity in children and adolescents is clinically relevant (lines 88-95).

And you should end with a hypothesis to make sure that data collection and data analyses are appropriate to answer your research questions and your hypothesis. It is not clear for me why it should be relevant to determine the association between physical activity patterns and anxiety and depression. Do you expect less activity in anxious children?

Response: Thank you. Depression and/or anxiety could be associated either way with physical activity or with patterns of physical activity. Increasing physical activity could be associated with an improvement in mood, particularly if associate with an increase in fun activities (we have published on the views of children in this regard). However, if an increase of activity is associated with an increase in symptoms, this could increase anxiety or low mood. As this is a cross sectional study, our view is that we can draw little in this particularly paper, but this descriptive analyses is important for our future work. In the trial (from which this data is derived) we have longitudinal data and we will be able to answer many of these questions.

For now, to avoid adding many more text to the introduction, which we feel would reduce the readability, we have added the following (lines 97-102):

'Children and adolescents with CFS/ME experience higher rates of mood disorders than healthy populations,[25-27] with around 30% of adolescent CFS/ME patients experiencing anxiety and/or depression.[26, 27] For most children, anxiety and depression appear to develop because of their condition.[28, 29] Whilst co-morbid mood disorders are associated with increased disability, fatigue and pain, there is no evidence on the relationship between co-morbid mood disorders in CFS/ME and objectively measured physical activity.'

We have also added the following to the conclusion (lines 361-362): 'Future research is needed to investigate the relationship between physical activity patterns and treatment outcome.'

Literature: Takken et al, 2006, Int J Sports Med, is not mentioned in the introduction. This is one of the few articles on physical activity in children with CFS/ME.

Response: Thank you, we have now mentioned this study in the introduction (lines 85-88).

'One study investigated exercise capacity in children and adolescents with CFS/ME (N=20, mean age 14.9±3.7 years), finding that maximal exercise capacity was only reduced in a minority of patients, and was related to current physical activity levels.[22]

Methods and recruitment

Please make clear why you have only selected children with mild-to-moderate CFS/ME and what the proportion of this subcategory is in relation to the total group CFS/ME patients.

Response: Only children with mild-to-moderate CFS/ME were recruited to this study, because only patients with mild-to-moderate CFS/ME turn up to clinical assessments.

Is the SF36-PFS, 10 items, validated for children and adolescents? (I thought only for adults?)

Response: The SF36-PFS has been shown to be valid for adolescents (aged 14+) and adults (Gee et al., 2002; Journal of Cystic Fibrosis), and has been shown to differentiate psychiatric patients, patients with minor conditions and chronic diseases (McHorney et al., 1993; Med Care). To our knowledge, the SF36-PFS has not been validated with children or younger adolescents. Therefore, we have added a sentence to the limitations section to explain this (lines 343-347). However, the SF36-PFS has been used in many trials with children and adolescents with CFS/ME, therefore, we feel it is an appropriate measure.

I need a hypothesis for the measurement of anxiety and depression to evaluate if these instrument are necessary to answer the research question.

Response: As above, we have added sections to the text in the introduction and conclusion.

Analysis

I do see the value of creating subclasses of physical activity (if you can substantiate the clinical relevance in the Introduction) and do your analyses accordingly.

But, by the way you have done the analyses now, it is hard to answer the question: how is the level of physical activity related to self-reported physical functioning in general in CFS/ME children? Because we do not know the relationship in the inactive class, only in the light and the active class in which there is a significant relation between physical activity and self-reporting PF. And this is an important question. We know that in adults the relationship of physical activity and self-reported PF is lacking. And that's the reason to add actigraphy to the measurements. It would be very interesting if this is different in children comparing to adults. So please, answer this question (and see my general remarks)

Response: Based on your recommendation to demonstrate the clinical relevance of classifying patterns of physical activity for children with CFS/ME, we have added more support to this in the introduction. The introduction provides evidence from a study with adolescent CFS/ME patients that have classified physical activity patterns in order to adapt treatment protocols (lines 88-95). Therefore, we feel it is beneficial to examine the cross-sectional associations between physical activity and health variables, such as physical function.

Results

Table 2.

If you want to compare to the healthy population please make sure that you make proper comparions. You should split the CFS/ME group in a younger and olders group to make a proper comparison with this young healthy population (7-9 years!). As you show in this article physical activity is directly related to age with 4.2% increase in physical activity with each additional year. Either you adjust for age and gender (but then you need original data) or you stratify for age in your cohort if you compare with the healthy (younger) population.

Response: Thank you for the suggestion, but we are unable to compare with only the 8-9-year-old children in the study due to the small sample of 8-9 year-olds (N=8). Equally, we do have the original data for the comparison studies, so we cannot adjust them for age and gender. Therefore, we have made it clearer in the results that this is purely a descriptive comparison (line 207), as follows:

'To compare physical activity levels of young people with CFS/ME from the present study with children from healthy populations, we descriptively examined physical activity variables from other UK studies that used the same accelerometer cut points.'

We have also made it clearer in the discussion that it is difficult to make comparisons in the data, due to the association between physical activity and age (line 286-293), as follows:

'Compared to a nationally-representative sample of younger children aged 7-8 years,[39] paediatric CFS/ME patients were sedentary for an additional 2.7 hours per day, and participated in less than half the amount of MVPA. However, it is difficult to make comparisons, as a multi-nation longitudinal study of children and adolescents (aged 2-18 years) from the general population, demonstrated that from the age of five years there is an average cross-sectional decrease of 4.2% in physical activity with each additional year.[41] This is consistent with the findings from the present study, whereby younger children aged 8-11 years were more active and less sedentary than adolescents.'

Table 6.

Be careful with your conclusions. The number of patients in the active group is very small. I would wonder how the general relationship between physical activity and fatigue is.

Response: Thank you, we have edited the discussion (lines 318, 328-329, 332, 341-342, 357) to ensure we are more cautious and /make readers aware that the null-finding for physical activity and fatigue in the 'active' class may be due to the small sample size.

And again: why do you adjust for 'time since diagnosis'?

Response: We have added detail about why we have adjusted for time since diagnosis to the methods section (lines 185-187), as follows:

'We adjusted for time since diagnosis because we hypothesised that children who had been ill for longer would be less fit and engage in lower levels of physical activity.'

I do not find all tables interesting. If you have reasons to do the analysis physical activity vs anxiety/depression (see general remarks), than please show all the results in one table and not in different tables.

Response: Based on comments from the editor we have now moved these tables to the supplementary material.

Why do you adjust the analyses for 'time since diagnosis'? Do you think that the relationship between self-reported physical functioning and physical activity is confounded by 'time since diagnosis'. If so, please reflect on this.

Response: As above, we hypothesised that children who had been ill for longer would be less fit and engage in lower levels of physical activity. We have added detail about this to the methods section (lines 185-187).

Sensitivity analysis

Please skip this paragraph. It does not really provide new insights

Response: Thank you for this suggestion, however, due to conflicting advice between reviewers, with the other reviewer suggesting we extend our sensitivity analyses, we have decided to keep this paragraph in.

Discussion

Please emphasize that this article is limited to mild-to-moderate CFS/ME in children.

Response: We have now emphasized throughout the discussion, including the limitations section, that the data is limited to children with mild-to-moderate CFS/ME (lines 280, 349-350, 354, 360).

Rewrite the discussion if the general questions are sufficiently addressed in hypothesis, analysis and results.

Response: We feel this would reduce the readability of the paper but will re-write the paper on the advice of the editor.

P 16 r 1 t/m 17: if you have no hypothesis for the relationship between anxiety and physical activity, be very careful to draw conclusions!

Response: As above, we have added a section to the text in the introduction about the association between anxiety and CFS/ME. We have also ensured we are more careful with the conclusions drawn in the discussion, as follows (lines 329-332):

'Being 'active' was associated with greater anxiety compared to being in the 'inactive' class. It may be that young people are anxious because they are physically active or that anxiety is driving them to be active. However, the cross-sectional nature of the study and the very small sample size of the 'active' class, limits any inferences that can be made.'