Author's response to reviews

**Title:** Children's and Adolescents Adjustment to Parental Multiple Sclerosis. A Systematic Review

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**Author's response to reviews:** see over
Dear Dr. Zivadinov,

We appreciate the helpful comments of the reviewers and the time they took to review our article. We were gratified to note that Reviewers 1 and 2 both commented that the study was important and interesting, and the positive remarks on writing style and methodological strength of our review made by Reviewer 1. As you know, reviewer 1 did not ask for any changes to the manuscript, so we have not directly responded. Regarding Reviewers 2 comments, we have made revisions and respond to each of his remarks below.

We feel the resulting revisions have significantly improved our manuscript. We look forward to hearing your response.

Sincerely,
Neda Razaz
Helen Tremlett
On behalf of all authors.

Reviewer 2 [Jesper Hagemeier]

Reviewer's report:

“Children’s and Adolescents Adjustment to Parental Multiple Sclerosis. A Systematic Review” is a collection of literature looking into the psychological wellbeing of children who have at least one parent diagnosed with MS. There are several methodological limitations (such as selection bias) that cannot be dismissed, however, what this review highlights is that the current literature on the subject matter is sorely lacking quality studies and that further research should be conducted into quantitative, reproducible metrics of psychosocial wellbeing of children of parents with MS.”

**Response:** We thank the reviewer for recognizing that our review was thorough in critically reviewing and highlighting the problems with the available studies. We have now emphasized these points in our manuscript even further – see response to specific comments below.

**Major:**

1. Accuracy of data abstraction was cross-checked and confirmed randomly for 10 studies using a 2nd reviewer (R.N.). Is this based on 10 out of 70 articles (as mentioned in the Literature Search section: “Seventy articles underwent full-text review”)? Or 10 out of an even larger (or smaller) group of papers? This is not clear. Out of those 10, what was the level of “agreement” between the two reviewers (on data, final score etc.).
Response: The seconded reviewer (R.N.) reviewed 10 out of the 70 articles that underwent full-text review. The level of agreement between the two reviewers was 90%, there was only one study that the two reviewers had disagreement that was solved through consensus. We have now provided clarification in the methods section of the article. (Method: lines 47-50).

2. The authors use the GATE framework as a method to evaluate the selected studies. To this reviewer’s knowledge, this is a somewhat basic method to evaluate epidemiological studies, mostly catered to students (e.g. see Baker et al. 2010). Granted, that does aid in assessing the literature quicker than other methods may allow. How confident are the authors of the GATE method, even when evaluating several works that are not purely epidemiological? Furthermore, GATE does not assign a strict “score” or “grade” to the evaluations. How confident are the authors that their (somewhat subjective) “low”, “medium” and “high” scores are reliable and reflect that actual work?

Response: We considered a number of pre-existing tools and checklists previously employed when conducting systematic reviews of epidemiologic studies – including the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines; the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort, case-control, and cross-sectional studies; and the Newcastle-Ottawa Scale for assessing the quality of non-randomised studies in meta-analyses. However, in light of the deficiencies of these tools, we chose to adapt components from the Graphic Appraisal Tool for Epidemiology (GATE) and supplement these sections with topic-specific criteria (Martin 2006). For observational and epidemiological study designs, there is currently a lack of consensus regarding the most appropriate methodology for assessing quality in the context of a systematic review (Sanderson 2007), and many published reviews fail to include any appropriate analysis (Mallen 2006). The GATE tool, which was first described by Martin and Srihari in 2006, is based on the JAMA evidence-based medicine (EBM) guidelines and includes specific questions related to the broad categories of population selection, exposure and comparison definitions, outcome assessments, follow-up time, analytic methods, and other components related to both internal and external validity. The GATE system was reviewed due to its simplicity, clarity and ability to be used to critically appraise different types of studies. As per the reviewer’s recommendation we now discuss the limitations of the GATE tool as well as the lack of consensus in this area as to the most appropriate tool to use.

Discussion (lines 278 – 283) - “For observational and epidemiological study designs, there is currently a lack of consensus regarding the most appropriate methodology for assessing quality in the context of a systematic review[42]. Although the GATE tool is an excellent tool to critically appraise different types of studies, it does not assign a grade or score to studies and therefore its use and validity might be limited [43, 44].

3. None of the 18 studies examined specified which MS diagnostic criteria were used (and only few reported disability measures). Since diagnostic criteria have changed over time, it would be of importance to know which criteria were used. Only 8 out of 18 had a control group, and 4 studies were not quantitative. Furthermore, the authors highlight that 16 studies had either “moderate” or “low” quality scores. All these factors highlight that most studies conducted so-far are of mostly low quality and more importantly drawing conclusions on a population level is difficult. To enhance the difficulty even further there does not appear to be any standard for assessing children in these households, as a wide range of measures were used to measure psychosocial wellbeing: anxiety, depression, peer relations, caregiving responsibility, family cohesion, body image, parent-child interaction, and hopefulness. Furthermore, out of 1114 studies, 1044 were excluded for not satisfying study inclusion
criteria. Then, another 52 were excluded while doing more extensive review. Only 18 studies remained in the review. Of those remaining 18, only a handful scored “high” in study quality. Originating from such a large initial sample, the fact that only 2 studies are of high quality is surprising, even more so considering the wide range of psychosocial outcomes that was included across studies. This does highlight the importance of future research in this subject matter.

However, this does also limit the possibility of drawing meaningful conclusion from this review, as more research is needed. Before more research has been carried out, the authors should refrain from drawing conclusions and need to further downplay findings of the reported studies. Please provide recommendations for future research on how studies should be standardized and improved.

Response: We thank the reviewer for recognizing the value of this review and the contribution this review makes to the field (i.e. our review outlines, as summarized above by the reviewer, how diagnostic criteria were not specified (results, lines 84-85); MS-specific clinical information on the affected parent were noted in few studies only (results, lines 86-90); lack of a control group (results, lines 101) and the quality of the included studies (results, line 97)).

We agree with the reviewer that it is difficult to make definitive conclusions based on the quality of the available evidence. As suggested, we have downplayed the findings and reviewed every concluding statement made in our review and ensured that the appropriate language is used to emphasize the lack of good evidence-based information.

Discussion (lines 180-181) - “However, overall the strength of the evidence was rather weak, with only 2 of 18 studies rated as ‘high quality’, which makes it difficult to draw evidence-based conclusions.”

Conclusion (lines 285 - 288) – “Exploring the relationship between parental MS and a child’s psychosocial adjustment is challenging. Due to the relatively few studies of high methodological quality, it is difficult to draw strong evidenced-based conclusions from the present literature and thus more comprehensive and higher quality research in this area is greatly needed.”

Specifically, we have removed the last line from the conclusion that could be construed as giving evidenced-based advice (which we recognize is lacking):

Conclusion (line 301) – Removed: “As a result, appropriate referral mechanisms for the child and family should be made available.”

Abstract/Conclusion: “Although having a parent with MS was often reported to have negative psychosocial effects on children and adolescents, there was a lack of consensus and some positive aspects were also found. However, few high quality studies were identified which makes it difficult to draw evidence-based conclusions at this point.”

Finally, as suggested by the reviewer, we have included an additional section making recommendations for future research on how studies should be standardized and improved:

Discussion (lines 259 – 270) - “To overcome many of the deficiencies raised above, we recommend a population-based approach with inclusion of a representative comparison group to avoid selection biases that may have limited many studies. In addition, rigorous, objective,
and well-validated measurement tools are needed, of which several are available, namely, the Early Child Development Instrument [39], or the Child Behaviour Checklist [40]. Along with this, measurement of appropriate confounders or explanatory variables, such as socioeconomic status, gender of the child or the marital status of the parents should be considered. Ideally these would be combined with clinical characteristics of the affected parents, such as disease duration, level of disability or presence of comorbidity, to populate a large study-specific dataset of patients and their children. Findings of these studies would help to inform policy making for healthier communities and assist us in developing and evaluating family centered interventions to improve child and family outcomes [41].

4. It is mentioned several times throughout the manuscript, including in the abstract, that “having a parent with MS was typically reported to have negative psychosocial effects…”. However, the results appear rather dispersed and unclear, for example: “8 found a negative association between exposure to parental MS and adjustment in their offspring. Five studies did not find an association and 5 studies found both positive and negative effects of caring for a parent with MS.” The authors should highlight that results vary widely and no consensus can be reached at this moment.

Response: As suggested by the reviewer, we have amended our conclusions to highlight that results vary widely and no consensus can be reached at this moment: See response to comment #3. Changes made which specifically address this point included:

Conclusion (lines 285 - 288) – “Exploring the relationship between parental MS and a child’s psychosocial adjustment is challenging. Due to the relatively few studies of high methodological quality, it is difficult to draw strong evidenced-based conclusions from the present literature and thus more comprehensive and higher quality research in this area is greatly needed.”

Conclusion (line 301) – Removed: “As a result, appropriate referral mechanisms for the child and family should be made available”.

Discussion (lines 180-181) - “However, overall the strength of the evidence was rather weak, with only 2 of 18 studies rated as ‘high quality’, which makes it difficult to draw evidence-based conclusions.”

Abstract/Conclusion: “Although having a parent with MS was often reported to have negative psychosocial effects on children and adolescents, there was a lack of consensus and some positive aspects were also found. However, few high quality studies were identified which makes it difficult to draw evidence-based conclusions at this point.”

5. Please also expand in the abstract and discussion/conclusion (not only in the limitation section) on the overall weakness of the literature investigated and that conclusion are difficult to make from the present literature.

Response: We have made substantial changes through to address this point – including:

Abstract/Conclusion: We rephrased this section to illustrate the weakness of the literature: “Although having a parent with MS was often reported to have negative psychosocial effects on children and adolescents, there was a lack of consensus and some positive aspects were also found. However, few high quality studies were identified which makes it difficult to draw evidence-based conclusions at this point.”
Discussion (line 177-181) – We added “Overall, while most studies tended to report that children of MS patients exhibited negative psychosocial behaviour compared to children of “healthy” parents, some positive aspects in caring for a parent with MS were also highlighted. However, overall the strength of the evidence was rather weak, with only 2 of 18 studies rated as ‘high quality’, which makes it difficult to draw evidence-based conclusions.”

Discussion (lines 259 – 270) – We have addressed the overall weakness of the literature in the discussion and as per reviewer’s suggestion we have made recommendations for future research on how studies should be standardized and improved.

Conclusion (lines 285 - 288) – “Exploring the relationship between parental MS and a child’s psychosocial adjustment is challenging. Due to the relatively few studies of high methodological quality, it is difficult to draw strong evidenced-based conclusions from the present literature and thus more comprehensive and higher quality research in this area is greatly needed.”

Conclusion (lines 290 - 295): We further emphasized the limitations of the included studies: “Although the few studies examining the impact of parental chronic disease on children's development and health represent important first steps, many have serious methodological limitations, particularly with respect to ascertaining individuals with definite MS, and potential sources of bias, such as failure to adjust for important demographic variables, i.e. socio-economic status, lack of a suitable comparison group and sub-optimal data collection.”

6. Finally, the authors should acknowledge the importance of investigating the psychosocial wellbeing of children with parents with MS as compared to other chronic illnesses. Especially considering that in MS disability is limited in earlier disease stages and with low EDSS scores, and lifespan may not be affected as with other chronic diseases.

Response: We have now incorporated this point regarding disability and lifespan in MS in our recommendation section.

Discussion (lines 251 – 258) - “Last, relying on cross-sectional design, fails to disentangle the interactions between normal child developmental variations and the variations produced by the progressive nature of MS, such as difficulties in the transition to adulthood. This is particularly relevant given that disability in MS can often be minimal in the early stages of the disease, and the overall lifespan may not be affected as with other chronic diseases. Furthermore, to explore if there is an MS specific characteristics that influence children’s development, it would be of interest to investigate the psychosocial wellbeing of children with MS parents as compared to other chronic diseases.”

Minor:

7. “Families are the primary source of experience for most children”. Consider rephrasing “experience” as it is ambiguous.

Response: This word was rephrased to “support and care”

Abstract/Background (Line 1) - “Families are the primary source of support and care for most children.”
8. The first sentence makes reference to “Western societies” and a range of 4 to 12% of Children with parents living in households with a parent with a chronic illness. The cited paper is part of the (north) Germany Hamburg Health Survey, and find a 4.1% prevalence rate. The authors should add additional references substantiating their claim or alter the sentence.

**Response:** We provided additional references substantiating the range of 4-10% (Background, line 3)

9. In the study description (Results section) it would be helpful to elaborate on other possible factors influencing the wellbeing of children of MS parent(s). For example, is the divorce rate or percentage of single-parent households higher among these families?

**Response:** We have incorporated this point in the discussion section of the manuscript Discussion (lines 246 – 250) - “Other factors which emerged as potentially influencing a child’s adjustment to parental illness from the included studies were: gender of the parent and the child,[24, 36, 37] children’s age and developmental stage,[10, 25] level of social support,[10] physical condition or disability caused by the disease,[25] single parenthood and family environment [10, 15, 19, 25].”

10. Results are summarized purely descriptively. It is hard to draw conclusions when no information is known about (study specific) statistical measures such as effect sizes and p-values, although this is most likely an inherent problem of the source studies.

**Response:** Initially we aimed to perform a meta-analysis to provide a statistical measure of child psychological well-being and however due to heterogeneity in outcomes and methodologies in the selected studies, a meta-analysis was not possible; therefore a narrative analysis of data was conducted, with studies broadly grouped into those finding a negative, positive or no measureable effect on the developing child living with a parent who has MS, as well as by study design (e.g. quantitative vs qualitative and use of a comparison group). This limitation of the source studies further illustrates the importance of future research in this subject matter. We have detailed this in the methods section of the review (Methods, lines 60-64)

11. Regarding line 161, 162 and 163. It should be stressed that the children who are 3x as often perceived by their parent(s) (with MS) to have psychological problems, might well be due to not the child’s actual psychological well being, but due to for example the parents’ perceived feeling of guilt.

**Response:** We have rephrased this section in the results accordingly

**Results (lines 163 – 165)** - “Yet these children were over three times more likely than a community sample to be perceived by their affected parents as having psychological problems. This might not be due to the child’s actual psychological well being, rather could relate to the parents’ perception of their own MS”

12. The limitations of the review process are adequately described. Consider also discussing the GATE method as limitation as well.

**Response:** We have added the GATE method as a limitation in our discussion
Discussion (lines 278 – 283) - “For observational and epidemiological study designs, there is currently a lack of consensus regarding the most appropriate methodology for assessing quality in the context of a systematic review[42]. Although the GATE tool is an excellent tool to critically appraise different types of studies, it does not assign a grade or score to studies and therefore its use and validity might be limited [43, 44].”

References: