Author’s response to reviews

Title: Sub-clinical abnormalities detected by PET/MRI in household tuberculosis contacts

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Author’s response to reviews:

Dear Editors,

Many thanks for the opportunity to revise this manuscript. Please see the attached supplementary material for responses to reviewer comments. I also paste the responses below.

Kind regards

James Molton
Hanif Esmail (Reviewer 2): Many thanks for inviting me to review the manuscript again. It is well written and has been improved with revision but I still have the following concerns,

1. I do not think the term subclinical disease can reasonably be used in the title or manuscript. The term subclinical disease in tuberculosis is becoming increasingly well understood and well defined as representing a state of failure of containment of the latent infection, where evidence of disease is visible but without causing subjective symptoms (see recent review Drain et al CMR 2018). Though disease at this stage can be halted, importantly it is associated with high risk of progression to symptomatic disease. Many of the lesions described do not have strong evidence in either imaging or autopsy literature that they represent an early stage of disease and hence I do not think it reasonable to state that the abnormalities found represent subclinical disease. "Subclinical abnormalities detected by PET/MRI in household TB contacts" is a more faithful title.

Authors response: 
Title changed to “Subclinical abnormalities detected by PET/MRI in household TB contacts” as per reviewer’s request, verbatim.

Deleted “subclinical disease” from the abstract introduction

Revised the introduction to set out the spectrum of TB disease and included the reference suggested by the reviewer. We present the study in context of detecting changes of early exposure rather than seeking evidence of subclinical disease. All mention of PET changes predicting disease outcome has been removed from the introduction.

Discussion: Line 214 deleted: “It is possible that the abnormalities identified in this study may represent subclinical TB.” We have again talked, in general terms, about early changes and focused on the possibility of incipient disease, and included the review suggested by the author. We have been careful to downplay the possibility that these changes are likely to relapse.

2. The authors make the case that PET/MRI could be used for biomarker discovery, but it is critical that the imaging phenotype is understood in relation to outcome or pathological process which this study does not shed light on. Fuzzy phenotypes are not helpful for biomarker discovery.

Authors response: 
We do not conclude that PET/MRI can be used for biomarker discovery based on our current data. We stated that it “may provide a foundation for future studies to identify a simpler and cheaper biomarker” (line 257). And in the following sentence caveat that with: “However prior to this larger PET imaging studies would be necessary to confirm if the population with subclinical FDG uptake indeed represent a population at higher risk of future reactivation.” We agree with the reviewers comment here, the implication of this sentence is that if larger studies did not find this correlation to outcome then PET/MRI would not be useful in biomarker discovery.

Reviewer: 
I am still concerned by the 3 participant with PET abnormalities not identified on MRI. It is not clear at all what the significance of this is or how it might relate to TB pathology (they are also not included in the figure which they should be). Arguing that lesion may be too small to be visible but excluding lesion<6mm with minimal uptake (presumably SUVmax > 0.95) is slightly contradictory particularly...
as these lesions have fairly low uptake (SUVmax 1.3-2.8). Such lesions are not infrequently described in the literature (see Tokmak World J Nucl Med. 2013 Jan-Mar; 12(1): 38-40.) the evidence is that they usually disappear on repeat imaging (I am not sure if either of these 3 participants has had repeat imaging).

Authors response:
There is a misunderstanding of the methodology here, and we apologise for the ambiguity in the methods which we have attempted to address with changes in the text (line 126-133). Two independent image analyses were performed. One of just the MRI images (by JH) – this is what the 6mm cutoff is referring to, and one of the combined PET/MRI images (by LKK) – this is what the >0.95 SUV cutoff is referring to. We have also removed line 218 from the discussion as it seemed to give the erroneous impression that both radiologists reviewed the PET images.

We have re-reviewed the 3 images in question. While no lesions were identified on MRI when the MRI images were analysed independent of the PET by JH, the analysis of the PET/MRI combined images did identify subtle underlying MRI changes in 2 out of the 3 cases in question. This had not been reported previously as the reviewers report of the scans focussed mainly on reporting PET avidity and did not specifically report the underlying MRI changes.

Added line 178: “Subtle MRI lesions were identified underlying the regions of FDG uptake in 2 out of the 3 contacts with parenchymal lung uptake (Figure 1 F and G). In the other contact with parenchymal uptake, diffuse FDG uptake was seen in the anterior segment of the left upper lobe (SUVmax 2.2) but no underlying lung changes could be appreciated on MRI (Figure 1 D).”

The images of these 3 cases with parenchymal FDG uptake have been added to the figure as requested. In addition we have added a more thorough explanation of the MRI findings in these 3 cases to the table to allow the reader to make their own decisions regarding significance.

In the discussion we have removed the explanation that the MRI lesion may be too small to detect as this is not really consistent with the diffuse uptake seen in what is now only one case with isolated parenchymal uptake. We have added that the significance of the findings in this one case are uncertain. We include the possibility of FDG embolization (line 232) as previously requested by the reviewer. We have now added the Tokmak reference suggested by the reviewer (which refers to a single case of FDG microembolisation). From this reference, FDG embolization appears to result in a discreet high intensity lesion. It should be noted that the appearance in this reference does not fit with any of our images.

These patients did not have follow up scans.

3. The authors make the point that the PPV of IGRA is low however the NPV is extremely high (99%), TB very rarely develops in immune competent HHC with negative IGRA or TST. It is therefore of concern that >50% of those with abnormal PET/MRI had a negative IGRA, of note all 3 of the participant with FDG uptake without parenchymal lesions had negative IGRA which again makes me suspicious of the significance of this. On the whole I would be inclined to advice that these 3 lesions not be included.

Authors response:
As described above we have re-reviewed the combined PET/MRI images and now only 1 participant is considered to have parenchymal lung uptake without underlying MRI changes.
We agree with the reviewer’s statement that patients with negative IGRA are less likely to progress to TB and that the significance of FDG parenchymal uptake in this contact in the absence of MRI findings is unclear. However, rather than exclude these findings entirely and suppress this data from the manuscript, we would support presenting all the data as we found it, adding in these concerns in the discussion and let the readers make their own interpretation. We would not support excluding findings simply because we can’t definitively explain them and they don’t fit with our pre-existing concepts about disease, as this adds a degree of subjectivity and bias. Our understanding of TB has been constrained by the limitations of the traditional tests and it makes no sense to do a study exploring a new method and forcibly align the findings to fit with the old test.

To address these concerns in the discussion we have added to the statement (line 201): “One contact was identified as having diffuse FDG uptake within the lung parenchyma with no underlying structural abnormality on MRI, the significance of which is uncertain.”

To further enable readers to draw their own conclusions from the data we have added in images of these 3 into the figure as requested.