Author's response to reviews

Title: SMART: Physical activity and cerebral metabolism in the elderly: study protocol for a randomized controlled trial.

Authors:

Johannes Fleckenstein (Johannes.fleckenstein@ikom.unibe.ch)
Silke Matura (Matura@allgemeinmedizin.uni-frankfurt.de)
Tobias Engeroff (engeroff@sport.uni-frankfurt.de)
Eszter Füzeki (fuezeki@sport.uni-frankfurt.de)
Valentina Tesky (Tesky@allgemeinmedizin.uni-frankfurt.de)
Ulrich Pilatus (u.pilatus@em.uni-frankfurt.de)
Elke Hattingen (Elke.Hattingen@kgu.de)
Ralf Deichmann (deichmann@med.uni-frankfurt.de)
Lutz Vogt (l.vogt@sport.uni-frankfurt.de)
Winfried Banzer (banzer@sport.uni-frankfurt.de)
Johannes Pantel (Pantel@allgemeinmedizin.uni-frankfurt.de)

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Author's response to reviews: see over
Dear Professor Harridge,
Dear Madam or Sir,
Dear Reviewer,

Thank you for giving us the opportunity to revise our manuscript. We are grateful to the referee who has made valuable suggestions for improving the manuscript. On the basis of the reviewers’ comments please find attached a revised version of our manuscript (MS: 212686937157448) entitled: “SMART: Physical activity and cerebral metabolism in the elderly: study protocol for a randomized controlled trial.”.

We have revised the manuscript and made adjustments according to the suggestions of the reviewer. In the following we provide a point-by-point description of our changes with regard to the concerns of the reviewer. Changes in the manuscript are highlighted in yellow.
To referee #1

**Question:** Abstract. I am not entirely clear I understand the method of randomisation as described in the abstract.

**Answer:** In accordance with the reviewer we revised this section (p. 3 l.54ff) to: “Participants are allocated to either the intervention or control group using a computer-generated randomisation sequence. The exercise physiologist in charge of training opens sealed and opaque envelopes and informs participants about group allocation. For organisational reasons, he schedules the participants for upcoming assessments and exercise in groups of 5. All assessors and study personal other than exercise physiologists are blinded.”

**Question:** Methods. It is clear that residents in the assisted living facilities are invited to participate. It is unclear how widely distributed the newspaper adverts are and whether the participants will differ between the two sources of recruitment.

**Answer:** In order to clarify the recruitment process we added the following sentence to the manuscript (p.6 l.128): “In addition, the press agency of the university released information to local print media, once.”

Still we agree, that at present we cannot anticipate if participants from the living facilities will differ from other participants. As our inclusion criteria are held very strict, and residents are in a general condition more likely reflecting the age-matched non-residents than traditional nursing home inhabitants, we assume to collect data from a homogenous group.

**Question:** I am unclear whether the group of 5 undergoing pre randomisation measures are individually randomised or randomised as a cluster to one or other intervention – this needs to be clearer. From the description the five patients seem to be allocated to the same treatment group – this in effect a cluster randomisation which has a significant impact on any power calculation. There are only 12 clusters! This does not seem to be acknowledged in the power calculation.

**Answer:** We agree with the reviewer that this part was confusing by trying to explain different procedures at the same time. All subjects were randomized on a 1:1 basis. However, for organizational reasons, the exercise physiologists -i.e. the person in charge of the training- scheduled the participants by groups of 5 to facilitate comparable time frames between baseline and re-assessments and exercise. We revised the abstract (see above) and the description within the manuscript accordingly (p.7f l.180ff): “The
randomisation is performed on a 1:1 basis. If participants comply with inclusion criteria, the exercise physiologist opens a sealed and opaque envelope (compiled by an independent third party), allocating participants to either INT or CON. The randomisation sequence is generated using a computer-based algorithm (Research Randomizer, Version 4.0). For organisational reasons, the exercise physiologist schedules participants into groups of 5. Participants within these blocks belong to the same treatment modality (i.e. intervention or control). Grouping is only allowed in the order of recruitment to the study. All assessors and study personal other than exercise physiologists are blinded. (…) Organisational reasons for building groups of 5 include a) facilitation of comparable time frames between assessments (e.g. sports medicine and brain imaging), visits (e.g. Visit 1a and exercise (e.g. from last assessment (MRSI) to the first exercise session or from the last exercise session to the beginning of the next assessment) and b) to conduct the exercise intervention in familiar groups of 5 participants.”

**Question:** Of course if the investigators are simply exploring the effects of exercise on a wide range of physiological parameters then a power calculation is of limited value.

**Answer:** We agree with the reviewer, that a simple data sampling requires different power calculations. However, our main outcome relies on the change in cerebral metabolism as addressed in other comparable studies, too. Sample size estimations have been made in this regard. Thus we assume our power to be of adequate value.

**Question:** It is unclear how soon after the last exercise session patients will have their outcomes measured. Does this matter?

**Answer:** We agree with the reviewer and apologise our manuscript was not clear enough in this regard. We added the following section (p. 8 l. 218): “At all time points, outcome parameters will be assessed within a timeframe of 1 week. At baseline it is the week immediately prior to inclusion into the study, at 12 and 24 weeks it is the week immediately following thereafter.”

**Question:** Might exercise simply have a very short term effect lasting hours, or does its effect last days or longer. This point may be worth discussing.

**Answer:** To address this point we chose to implement the 12 week follow-up period (from week 12 to week 24). As participants in the intervention group are supposed to return towards their daily levels of activity once finishing the exercise intervention, the analysis
of the upcoming 12 weeks will give hint on the sustainability of the effects evoked after
the first 12 weeks.

**Question:** The protocol includes measurement of all the parameters at baseline, after the INT
group has completed 12 weeks exercise, and then again after the CON group has
completed 12 weeks of exercise. It is unclear what analyses will be performed on the
outcomes collected at 3a.

**Answer:** At visit 3a (psychometric testing), we collect for the third time data reflecting
different cognitive outcomes with the aim to determine on the one hand if exercise-
related effects on cognitive performance could also be observed in the CON group, and
on the other hand as a clinical measure of cognition to determine the sustainability of
effects in the INT group. For details of tests please refer to p. 10 l. 282ff psychometric
testing.

**Question:** If inter group comparisons are made at that point then this would be better
described as a cluster randomised crossover study. The issue is then how long any
changes resulting from exercise persist. There is no wash out period to account for a
persistence of any effect.

**Answer:** We agree with the reviewer about the importance of the longtime effects of
exercise. Regardless the chosen randomisation process, the periods between outcome
measurements are equal for all participants, i.e. 12 weeks between Visit 1 and 2 and 12
weeks between Visit 2 and 3. The time between week 12 and week 24 in the INT group
can be considered a wash out period. Participants in this group will be strictly controlled
for additional voluntary exercise (chip card, exercise diary). Thus, we expect to be able to
identify a subgroup large enough to define the effects of persistence. Still, it is to state,
that this is not the primary outcome of our study, and results have to be interpreted
cautiously.

**Question:** I think the investigators need to be clearer about what comparisons they will
make. They are collecting a huge amount of data on each patient. They will be making a
huge number of statistical comparisons and are therefore inevitably going to identify a
lot of statistically significant differences at the 95% level. Whilst the investigators
acknowledge that this study is exploring the effects of exercise on multiple measures, I
think this limitation needs to be discussed.
Answer: We agree with the reviewer that multiple testing is a limitation in the interpretation of a study and added a comment to the discussion, accordingly (p.15 l.456f): "Still, multiple measures can be concerned a limitation when interpreting the results of a study. In the present study, we accentuate on the primary outcome (changes in cerebral metabolism) and will strictly adhere to statistical conventions with the analysis of secondary outcomes."

Nevertheless, we defined the change in cerebral metabolism assessed by MRSI as main outcome (confer to Methods). Analysis of this parameter follows current recommendations and protocols. Interpretation of results will be primarily based on these outcomes.

The design of this study allows us to address other confounding factors, too. In a first step, baseline differences regarding such parameters will be accounted for by covariate analysis (see p.13 l.395f), applying the established statistical methods for the correction of the alpha error. In a second step we will focus on possible correlations of hitherto contemplated variables. In both cases we will take into account the limitation of multiple measures.

Questions: There are several phrases which don’t make sense to me:

- **What is “pain catastrophizing”**
  
Pain catastrophizing is a standard term used in pain therapy and is conceptualized as a negative cognitive-affective response to anticipated or actual pain and has been associated with a number of important pain-related outcomes (e.g. Quartana et al. Expert Rev Neurother. 2009).

- **What does “This has been shown to extendedly impair objective neuropsychological functions” mean?**
  
This sentence was meant to describe the important influence of the cofactors mentioned. We changed it to “This has been shown to remarkably impair cognitive performance” (p.4 l.103).

- **What is meant by “every-life” confounders?**
  
The term refers to the activities and experiences that constitute a person’s normal existence. We suppose nutrition, lifetime physical activity or pain experience being factors, that influence daily-life in the respective age group of our study (see Ito et al. Geriatrics & gerontology international 2013).

- **Voluntariness is not a word I recognise**
According to the Oxford Dictionary, voluntariness can be used as a noun in the context of voluntarily acting participants.

- **What is “regular mental capacity”?**
  This term reflects to the ability to think and behave in a normal and rational manner. We think that the term “capacity to consent” already includes this meaning, therefore we removed the term.

- **Instable should be unstable**
  We replaced this, accordingly.

- **Aortal should be aortic**
  We replaced this, accordingly.

- **Not sure what cardiac malformations refers to**
  Cardiac malformations especially refer to untreated and circulatory relevant malformations of the heart such as septal defects, patent ductus arteriosus or valvular stenosis. We added this information to the manuscript (p.7 l.173). The list of exclusion criteria was strictly reviewed and amended by the Ethics Committee.

- **What does “poseyed” mean?**
  This term was supposed to mean, that participants were held fixed with a belt to the seat. We changed the term accordingly (p.12 l. 352).

We appreciate the constructive criticism and are of the opinion that the resulting changes have raised the quality of the paper.

Thank you for considering our resubmission for publication in *Trials*.

Sincerely yours,

Dr. Johannes Fleckenstein