Author's response to reviews

Title: Characteristics, changes and influence of body composition during a 4486km transcontinental ultramarathon. Results from the TransEurope FootRace mobile whole body MRI-Project.

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Author's response to reviews: see over
Dear editors and reviewers,

major revision on the article is done. We tried to consider all remarks and proposed correction of reviewers 1, 2 and 3. Sometimes they were contradictory and we tried to find the best solution for both reviewers. During revision process we found one relevant error in our statistics regarding the difference of percentage volumes of specific tissue compartment between finisher and non-finisher group. Due to relevant changes after correction of this error figure 16 was totally changed and chapter ‘Results’, ‘Discussion’, ‘Conclusion’ and in the ‘Abstract’ corresponding and resulting adaptations were done. Additionally the following changes and corrections were done according to the reviewers:

- Title specification was done
- Lacking definitions are added now (according to reviewer 1 and 2)
- Specific hypotheses of the study were implemented in ‘Introduction’ (according to reviewer 2)
- Absolute data of all subjects regarding body compartments are shown: new table 2 (according to reviewer 3)
- The parameters body weight (new table 3), body height (and BM) were added to this chapter and to the chapter ‘results’ with a new figure 4 indicating the coherence of MRI data (TV) and anthropometric data. Analysis on relationship between BM and TV was done in addition. (according to reviewer 3)
- Test on difference between prerace performances and finisher/non-finisher is added
- Test on relationship between prerace performances, body composition and race performance is added: new tables 7,8,9, new figures 16,17,18,19
- Test on relationship between segmental tissue changes (legs, arms, trunk) and race performance was done: new figure 14 was added.
- Complete revision of section ‘Discussion’ is done. Most important results are emphasized. Elusive information is abandoned. Discussion of literature not specific to ultramarathon is abandoned. (according to reviewer 2)
- Dropout rate was added: new figure 15 (according to reviewer 2)
- Reasons for non-finishing the race and possible explanations are discussed (‘Discussion’) in regard to our results on body composition (changes) and pre-race conditions of the athletes (according to reviewer 2)
- Total number of references is reduced, new references on running mechanics and economy are added. (according to reviewer 2)
- Initial figures 4,5, 11 were deleted (according to reviewer 2 and 3)
All figures got revision and n is provided for all (sub-)groups now (according to reviewer 2)

Revised manuscript is presented in 2 versions:
1. _revision-with corr: This version of the new revised manuscript shows all corrections in red labels.
2. _revision-without corr: This version of the manuscript shows new revised manuscript without enhancement of corrections done.

The research has been conducted after approval of the Ethics Committee of our University. All authors have agreed to publication in your journal and have read the final version of the paper; the manuscript or parts of it are not submitted elsewhere. There are no financing or non-financing competing interests of other people or organizations influencing our interpretation of data or presentation of information.

Sincerely,

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Answers to Reviewer: Beat Knechtle, reviewer 1

Minor Essential Revisions

Abstract
- Please define the abbreviations MRI, MR, T1w and TSE
  Lacking definitions are added now.
- In the Conclusion, you mention ‘unpreventable chronic negative energy balance’. However, you have not measured energy intake or energy expenditure, so you have not energy balance.
  The sentence was changed in:
  “Participants lost more than the half of their adipose soft tissue and even lean tissue volume decreased (mainly skeletal muscle tissue) and without any exception, every subject showed a significant loss of body volume. This indicates, that running an MSUM of nearly 4.500km without any day rest is linked with an unpreventable chronic negative energy balance due to the massive running burden.”
  The lack of energy balance intake measurement was mentioned in the last section “Limitations.” in the discussion.

Introduction
- Page 3, first paragraph, line 5: the sentence should start with ‘However’ not with ‘But’
  Corrected

Materials and Methods
- In the section ‘Body composition analysis’ in the first line, change ‘fa’ to ‘fat’.
  Corrected

Discussion
- In the section ‘ultra endurance related changes in body composition’ or ‘mass loss’ I suggest inserting the reference Knechtle B, Duff B, Schulze I, Kohler G, A multi-stage ultra-endurance run over 1,200 km leads to a continuous accumulation of total body water, Journal of Sports Science and Medicine 7:357-364, 2008, where the authors showed a decrease in both fat mass and skeletal muscle mass in a multi-stage ultra-marathon.
  This reference was included in the sections ‘ultra endurance related changes in body composition’ and ‘mass loss’. As reviewer 2 mentioned to reduce the amount of reference, this addition contradicts the request reviewer 2.

  To follow the request of reviewer 2 in limiting the number of references, we decided not to add these 2 references because they are case reports and/or investigate other ultra endurance sports with a limited length and number of stages, compared to our collective.
Answers to Reviewer: Gregoire Millet, reviewer 2

- Major Compulsory Revisions
Provide data on the relative error and reproducibility for the quantification of the different volumes and tissues. (Jürgen Machann)

Data on reliability according to literature are implemented in ‘Material and Methods’

Provide clear hypotheses regarding your study that appears as exclusively descriptive.

Specific hypotheses are implemented in ‘Introduction’ now.

Modify the discussion to discuss the most important results. The current discussion is very elusive. Beyond the exceptional setup of your data record, the novelty of your results remains unclear.

Complete revision of section ‘Discussion’ is done. Most important results are emphasized. Elusive information is abandoned. Discussion of literature not specific to ultramarathon is abandoned.

- Minor Essential Revisions
P2 – Methods:
MR – not defined, MRI – not defined, T1, TSE – not defined

Lacking definitions are added now.

P2 – Results:
All abbreviations not defined (TV, …)

We do not understand this comment, there must be a misunderstanding: All abbreviations had been defined in the section ‘Materials and methods’ initially.

P2 – Conclusions:
Energy balance was not measured
The sentence “the relative amount…” is not supported by data reported in the abstract.

In the abstract the significance of difference between finisher and non-finisher at start of TEFR09 is mentioned initially in section ‘Results’. But for more precise reporting, we changed the sentence and added the absolute values of percentage visceral fat volume of the two groups.

“Before start the non-finisher group had significantly more percentage volume of total visceral tissue compared to the finishers, due to more visceral fat (3.6vol% vs. 2.3vol%).”

In ‘conclusions’ the sentence was specified:
“The ratio of adipose tissue contribution between the visceral and somatic compartments had an influence on giving up during the first stages.”

P3 – Introduction:
Ref 1,2 – too many self-citations with many in low-quality journals. I would recommend you choose more wisely your references.

We reduced the references regarding Knechtle B, because some of them were not specific enough and reported results from studies on (ultra-)triathlon. References on multistage ultra-marathons are rare in literature. For discussion on this specific field of endurance sports, every reference is valuable. Quality of results is discussed critically in section ‘Discussion’. Though the reader should be able to decide about quality of our results compared to other data. Additional references on this topic from the last two years were implemented.
Knechtle B. is no author or Co-author and had no participation in any field of investigation regarding this manuscript/article about the results of whole-body MRI-measurements at TEFR09. Therefore, self-citation is not given from our point of view.

Mean age.. please provide SD.
SD were added.

P3 – Material and Methods:
Due to various reasons: please provide details.
Body fa = body fat
Corrected

P4- Image post-processing
Please detail the error due to the absence of INF. How did you guarantee that this absence of INF?
The following data are provided now in section ‘image post-processing’: “At start of TEFR09, ABM and INF together account for 13.2% of total adipose tissue. Due to continuous loss of adipose body tissue, this ratio rises up to 28.2% till the end of race. For visceral adipose tissue, the account for INF rises from 3% at start up to 65.4% at the end of TEFR09.”

Report the CV in % for all volumes, tissues and compartments.
To all investigated body compartments the absolute data are provide now in the new ‘Table 2’ for all measurement intervals. The table was placed at the beginning of chapter ‘results’ after the ‘casuistry’:
“The absolute volume data of all investigated body tissue compartments and segments are shown in table 2.” (correction of table numbering was done).
New figure 14 was added showing results of segmental data analysis.

P5
Why is the mean difference in TAT so important 8.13% when compared to other tissues ?
The difference between manual and automatic procedure rises with the amount of volume measured, therefore our manual corrections are appropriate regarding the data of Würslin et al..
For clarification of this the sentence in section ‘image post-processing’ was corrected:
… “procedure (2.07% for TV, 8.13% for TAT, 3.21% for VAT), the described additional manual corrections regarding the small volumes of ABM and INF are appropriate.”

P6 – Performance
P-value is mentioned twice.
Deleted.

P6 – Results – Casuistry
We don’t understand how the Figure 4 (a case report) shows that non-standardized position of the subject did not affect the validity and accuracy of your methods.
This statement focused of figure 3 (mistake by us). As figure 3 shows, that small differences in subject positioning results in only little discrepancies of topography regarding table position (slices 1-100). We deleted this sentence to prevent confusion of the reader. Figure 4 and 5 were deleted.

P8 – Finisher vs non-Finisher
Please provide a clear view of the respective number of F vs NF at the different
measurements (also in Figure 16 and 17).

The respective numbers of F vs. NF are provided in all figures and the manuscript text now.

P8 – discussion
I would suggest you reorganize your discussion for highlighting first your main results. The discussion on the validity of the methods should come later.

Complete revision of section ‘Discussion’ is done. Most important results are emphasized. Elusive information is abandoned. Discussion of literature not specific to ultramarathon is abandoned. Results on tests on difference and relationship between body composition changes and race and pre-race performance are added and discussed with literature.

P9 – Ultra-endurance related to changes in body composition
Since you compare with other UM events, please provide explanations. It remains purely comparative

Which mechanisms might explain that “with defined breaks, body mass remains stable…”

Explanation is done (‘If there are not sufficiently long breaks in ultra-endurance races, some participants might not find enough time for regeneration and restoration of their energy depots before the next stage. With progression of the race this is leading to implementation of muscle tissue for energy provision’).

P9 – Mass loss.
Similarly the comparison between UM running vs cycling or triathlon event is of interest only if you suggest some mechanisms for the differences.

The differentiation between running, swimming and cycling is not in the scope of this article and the main topics of TEFR-MRI-project, because the important factor of caloric intake throughout such events was not possible during the 10 weeks of TEFR09. References and discussion on other ultra-endurance sports like ultra-triathlon and -swimming, -cycling are eliminated.

P9 – Adipose tissue vs age/gender
This chapter is not relevant since 1. You don’t have the sample for such comparison ; 2. The discussion is vague and sometimes inappropriate (“obese patients” ?)

Emphasis in the text is reduced.

P10 – VAT
Again the discussion on the redistribution of adipose tissue for health-related problem is very vague and your data not appropriate for summarizing that “a very good and effective way… is endurance running”. Where is the novelty of such statement? how did your results improve running-exercise prescription in such patients ?

The novelty is, that we showed, that VAT decreases more rapid and more severe than somatic adipose tissue, when doing endurance running. This is new and emphasized. Another importance of VAT regarding performance and risk of failure is added due to new data.

P10 – Metabolic changes
Again a lack of documentation of the energy intake would reduce your results to pure description.

That’s what we stated in this section and in the section ‘limitations’. But the parabolic flattening of the fat tissue loss is obvious and, as we mentioned, not related to any additive energy intake, because these athletes eat as much as they can from the beginning of the race. It was not possible to document the caloric uptake, because they always eat, at every pause during the stages and
afterwards. Documenting this would have led to an immense loss of compliance, which was very high. Not one subject left the project during the whole 9 weeks!

We detailed our explanation for reduction of fat volume loss per km with progression of TEFR09 by additional data on relationship between running mechanism and long-distance run.

P11 - F vs NF
Most of the discussion here is on data either reported in your previous study or not reported at all. The influence of the bone tissue on the stress fracture or shin splints would be of high interest but your present data don’t enable such analysis.

During revision process we found one relevant error in our statistics regarding the difference of percentage volumes of specific tissue compartment between finisher and non-finisher group. Due to relevant changes after correction of this error figure 16 was totally changed and chapter ‘Results’, ‘Discussion’, ‘Conclusion’ and in the ‘Abstract’ corresponding and resulting adaptations were done.

Dropout rate was added: new figure 15. Reasons for non-finishing the race and possible explanations are discussed (‘Discussion’) in regard to our results on body composition (changes) and pre-race conditions of the athletes. Specifications on reasons for dropping out of race were added.

P11 – Body composition and performance.
Here again, purely comparative with (self-cited) other UM events.

On this topic, there is no citation of references, where authors of this manuscript have had any participation.

References
You should reduce the number by at least one third and reduce the self-citations.

Total number of references is reduced, new references on running mechanics and economy are added.

Self-citations on these manuscript are:


It’s necessary to inform the reader about the total multidisciplinary TEFR-project and cannot be excluded.


To provide more technical details for the interested reader on the used MRI protocols and image post processing with their relative errors and reproducibility. As reviewer 2 himself wants more information about these data, there is no necessity to exclude these references.

New reference which is emphasizing the massive negative energy burden of a transcontinental footrace and shows similar volume losses of grey matter of the subjects is added.

Figures
The number should be reduced. For example, Fig 3, 4, 5 are not so interesting.
Provide the n in all figures for all sub-groups (e.g. F vs NF)
The respective numbers of F vs. NF are provided in all Figures and the manuscript text now. Figure 4 and 5 were deleted. Figure 3 is maintained to show the reader, how whole body MRI and segmentation of tissues occurs. When using nearly 100 slices.
Figure 11 was also deleted, because it contained mainly same information than Figure 10.

1. Is the question posed by the authors new and well defined?
No, the study is mainly (too) descriptive and there isn’t any sound and relevant Hypothesis.
We cannot share this assessment. This is the nearly first time, as a cohort of 22 subjects, performing a 4500 km race, where measured in details of body tissue composition with a MRI, as a field study during the total race (not only at the beginning and after the end)! This data are unique and of interest for everybody doing research on endurance sports. So the results are new and extensive and differentiated as never before, and the tissue segmentation was well defined! Field studies in their major parts are descriptive.
We hope with that with this revised manuscript the now added data and test give also enough conclusions from this field study to the readers.

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
The methods (mobile whole body MRI) are of high quality. However, it seems that other relevant data to this topic (e.g. IMCL) are not included in the present study.
This shows a wish to segment the data in a detrimental manner while crossing the various fields would strength the overall analysis.
This was an interdisciplinary project over several fields of medicine. 2 years ago, we tried to give more data in one manuscript for publication in BMC medical. The reviewers insisted in shortening the manuscript and split the data on different topics like musculoskeletal system, whole body tissue composition, influences on the heart, the vessels and the brain. The revision of this first manuscript led in our first publication on BMC medicine and in a second on the brain now. BMC chief editors had asked us to do several manuscripts on their BMC-series on sports medicine in summer of 2012. We accepted the publication of the already accepted manuscript about 2 months later than possible, due to these series. We cannot understand, why we should now comprise the data again from several parts of the projects in one paper, this is contradictory to further revision statements by BMC chief editors.
We have not the wish to detriment our data and initially did not separate the topics. In contrary, our wish is to bring all our results in differentiated form to the readers. With further analysis of data, we realized, that BMC editors were right to ask for such differentiation and separation of project data pool. Crossing the various field of these project in one manuscript is not possible, because other topics may be no further publishable in a differentiated way, if some subtopics of them are published earlier. New data should only be published once.
‘Whole body mobile MRI protocols did not measure ectopic fat such as intracellular fat of organs (e.g. liver) and muscles (IMCL). For IMCL measurement specific mobile $^1$H-MR-spectroscopy of muscles of the lower legs were implemented in TEFR-project [Error! Bookmark not defined.], but due to the dependence of this MR-method on a stable external magnetic field around the magnetom, the analysis of mobile$^1$H-MR-spectroscopy during TEFR09 did not lead to valid data and needed further development and implementation of post-imaging proof algorithms.’ (added in ‘Limitations’)

3. Are the data sound and well controlled?
The field setup led to some approximation in the quantification of the different volumes and the relative error is not provided. **There is no approximation in quantification. These are defined measurements with MRI methods, being the gold standard in this field. Bioelectrical impedance analysis and other methods are approximations, but not MRI. Relative errors are measured by Würslin and Machann et al. and can be read in their literatures as mentioned in the chapter ‘materials and method’. We do not understand this comment here. Till now, only indirect measurements were done in this field studies on endurance athletes. MRI is a direct measurement!**

The weakest point is that there isn’t any quantification of the energy intake and nutritional plan. Therefore, the estimation of the energy balance is not possible and the reported changes in the different compartments cannot be explained. **Explanation is done above.**

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
There are too many figures reporting single case data. Some other figures are not well explained. **Figure 4 and 5 were deleted. Figure 3 is maintained to show the reader, how whole body MRI and segmentation of tissues occurs. When using nearly 100 slices.**

5. Are the discussion and conclusions well balanced and adequately supported by the data?
This is another weak point. The discussion is elusive, purely comparative with previous studies (most of them from the same research group) but the comparison with other ultra-endurance events (as cycling or triathlon) is not always appropriate. There aren’t any mechanisms suggested (due to the impossibility to report energy balance). Some topics as gender differences or effects on injuries that are not supported by the present results are (poorly) discussed. **Total revision of section ‘Discussion’ is done as mentioned above.**

6. Do the title and abstract accurately convey what has been found?
Yes, but since there aren’t any hypothesis, the title shows the descriptive nature of this study. **Hypotheses are added in the chapter ‘Introduction’**

7. Is the writing acceptable?
The discussion is elusive and doesn’t show an overall coherence. The manuscript needs a proof reading. **Another proof reading was done.**
Answers to Reviewer: Satoshi Muraki, reviewer 3

Minor Essential Revisions

Introduction
The originality of this study is obscure. The originality of this study is that the use of a mobile MRI gives new findings of changes in body composition during transcontinental ultra marathon over several weeks. So, paragraph 2 in the methods section should be moved to the introduction section.

*The usage of a mobile MRI scanner is the main method of this project, and therefore description belongs to the chapter ‘material and methods’, in our opinion. It was initially mentioned in the chapter ‘introduction’. Methods are not presented in the ‘introduction’. The originality of this project is not only the mobile MRI unit. It is also the first time, that multistage ultramarathon was investigated with such a long distance to run (64 stages), with such a high amount of subjects, and in field study like this. This is all mentioned in the chapter ‘introduction’.* We do not feel to put a wrong focus in this chapter or the title of the manuscript.

Material and methods
1) Please indicate information about the participant’s height, body weight in both finishers and non-finishers and race performance in finishers. *The parameters body weight (new table 3), body height (and BM) were added to this chapter and to the chapter ‘results’ with a new figure 4 indicating the coherence of MRI data (TV) and anthropometric data. Analysis on relationship between BM and TV was done in addition.* (according to reviewer 3)

2) Page 3 Line 5 from the bottom: “fa” should read as “fat”

Results
1) Because there too many graphs, it will be difficult for readers to catch important findings. So, I recommend reducing the number of graphs. For example, *Figure 4 and 5 are not really necessary*, because other graphs with percentile also show similar information. *Figure 10 shows same information as Figure 11. Figure 4 and 5 and Figure 11 were deleted. Figure 3 is maintained to show the reader, how whole body MRI and segmentation of tissues occurs. When using nearly 100 slices.*

2) On the other hand, this paper does not indicate absolute values at start for any indexes. If this paper indicates them, the left graph of *Figure 7, Figure 12, and the upper graph of Figure 14 can be left out.* *To all investigated body compartments the absolute data are provide now in the new ‘Table 2’ for all measurement intervals. The table was placed at the beginning of chapter ‘results’ after the ‘casuistry’.*

Discussion
The paragraph of VAT (Page 10) addresses relationships between the results and public health promotion. Although the findings might be indirectly useful to develop the strategy of health promotion, the main purpose of this study is not to do it. If this study was conducted to investigate health promotion, it should be
addressed and included in the Introduction section.

*The novelty is, that we showed, that VAT decreases more rapid and more severe than somatic adipose tissue, when doing endurance running. This is new and emphasized. Therefore this topic has important information: Endurance running leads to rapid VAT loss, which is the fat that includes high risk on cardiovascular diseases. And this is the first field study measuring this directly with the gold-standard MRI, and not with approximation methods like BIA or others, which can not separated between visceral and somatic tissue changes. So this topic should be discussed here, in our opinion. We reduced the length of discussion of this topic and modified discussion due to this remarks of reviewer 3.*

*Another importance of VAT regarding performance and risk of failure is added due to new data.*