## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | The foot in multistage ultra marathon runners: Experience in a cohort study of 22 participants of the Trans Europe Footrace project with mobile MRI |
| **AUTHORS** | Wolfgang Freund, Frank Weber, Christian Billich and Uwe H Schuetz |

## VERSION 1 - REVIEW

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| **REVIEWER** | PD Dr. med. Beat Knechtle<br>Institute of General Practice and for Health Services Research<br>University of Zurich<br>Zurich<br>Switzerland<br><br>I have no competing interests and no conflict of interest |
| **REVIEW RETURNED** | 18/03/2012 |

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| **THE STUDY** | The authors need to discuss the development of oedema from a physiological point of view |
| **GENERAL COMMENTS** | **bmjopen-2012-001118 "The foot in multistage ultra marathon runners: Experience in a cohort study of 22 participants of the Trans Europe Footrace project with mobile MRI."**<br>This study is unique and used the gold-standard in imaging of disorders of the musculoskeletal system during prolonged running. It needs publication since these results are essential for ultra-marathoners worldwide. However, the authors need to discuss the development of oedema from a physiological point of view.<br>Please insert in the 'Discussion' a section to discuss the development of oedema from a physiological point of view. Milledge *et al.* in Clin Sci (Lond). 1982 Jun;62(6):595-604 reported an increase in leg volume in multi-stage athletes. Williams *et al.* in Clin Sci (Lond). 1979 Apr;56(4):305-16 showed in their Figure 5 oedemas in multi-stage athletes. These authors were the first to report ankle oedema in multi-stage hill-walking. Both these studies assumed that an endocrine deregulation was responsible for the increase in both plasma volume and body water. However, recent findings suggest that fluid overload is the key to limb swelling in ultra-endurance athletes. In a recent case study in Journal of Human Kinetics 21:65-74, 2009, you see in the Figures 1-5 that the swelling of the feet increased after an ultra-endurance performance. It is important to know that the feet swelling increased for several days and decreased then. You can also see in that paper that fluid overload occurred and the athlete needed several days to excrete all water.<br>Generally, total body water increased in multi-stage athletes. In studies in multi-stage athletes in Br J Sports Med. 2008 Feb;42(2):121-5 and Chin J Physiol. 2011 Aug 31;54(4):255-63, total |

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| | body water increased with increasing length of the race. A good example for ultramarathoners<br>for the continuous increase in total body water is published in Journal of Sports Science and Medicine 7:357-364, 2008. Fluid overload is the most probably reason for the<br>increase in total body water and limb swelling in ultra-endurance athletes, see Res Q Exerc Sport. 2009 Sep;80(3):593-603. While the authors in Clin Sci (Lond). 1979 Apr;56(4):305-16 and Clin Sci (Lond). 1982 Jun;62(6):595-604. thought that a disorder in aldosterone secretion was the most probable reason for fluid retention and the increase in both plasma volume and total body water, an actual study in Eur J Appl Physiol. 2012 Mar;112(3):991-1003 showed that fluid overload is the most likely aetiology for limb swelling in ultra-marathoners. These authors showed that neither changes in hormones nor a change in renal function were related to limb swelling.<br>At the end of the Discussion, insert a section 'Strengths, limitations and implications for future research' and report first that this is the first study in history to follow ultramarathoners with a mobile MRI in a multi-stage ultra-marathon. Also, this is the first study to show changes in the musculoskeletal system in radiological images in multi-stage ultramarathoners.<br>As a limitation, you need also to acknowledge that subcutaneous oedema could also be due to fluid overload, see Eur J Appl Physiol. 2012 Mar;112(3):991-1003. As an<br>implication for future research, you need to cite to combine your methods with the methods reported in Eur J Appl Physiol. 2012 Mar;112(3):991-1003 to conclude that future studies need to determine fluid intake, plasma sodium concentration and changes in lower limbs using both MRI and plethysmography to determine whether the subcutaneous edema in the feet is definitely due to fluid overload or not. |

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| **REVIEWER** | Dr Robert D Pearce<br>Consultant musculoskeletal radiologist<br>Chelsea & Westminster Hospital<br>London<br>United Kingdom<br><br>Competing interests: None |
| **REVIEW RETURNED** | 12/04/2012 |

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| **THE STUDY** | The manuscript includes all the items to be included when reporting observational studies described in the supplemental document - the STROBE statement. |

## VERSION 1 – AUTHOR RESPONSE

Reviewer comments and author responses (in blue)
Reviewer: PD Dr. med. Beat Knechtle
Institute of General Practice and for Health Services Research
University of Zurich
Zurich
Switzerland

I have no competing interests and no conflict of interest

This study is unique and used the gold-standard in imaging of disorders of the musculoskeletal system during prolonged running. It needs publication since these results are essential for ultra-marathoners worldwide. However, the authors need to discuss the development of oedema from a physiological point of view.

Please insert in the 'Discussion' a section to discuss the development of oedema from a physiological point of view. Milledge et al. in Clin Sci (Lond). 1982 Jun;62(6):595-604 reported an increase in leg volume in multi-stage athletes. Williams et al. in Clin Sci (Lond). 1979 Apr;56(4):305-16 showed in their Figure 5 oedemas in multi-stage athletes. These authors were the first to report ankle oedema in multi-stage hill-walking. Both these studies assumed that an endocrine deregulation was responsible for the increase in both plasma volume and body water. However, recent findings suggest that fluid overload is the key to limb swelling in ultra-endurance athletes. In a recent case study in Journal of Human Kinetics 21:65-74, 2009, you see in the Figures 1-5 that the swelling of the feet increased after an ultra-endurance performance. It is important to know that the feet swelling increased for several days and decreased then. You can also see in that paper that fluid overload occurred and the athlete needed several days to excrete all water.
Generally, total body water increased in multi-stage athletes. In studies in multi-stage athletes in Br J Sports Med. 2008 Feb;42(2):121-5 and Chin J Physiol. 2011 Aug 31;54(4):255-63, total body water increased with increasing length of the race. A good example for ultra-marathoners for the continuous increase in total body water is published in Journal of Sports Science and Medicine 7:357-364, 2008. Fluid overload is the most probably reason for the increase in total body water and limb swelling in ultra-endurance athletes, see Res Q Exerc Sport. 2009 Sep;80(3):593-603. While the authors in Clin Sci (Lond). 1979 Apr;56(4):305-16 and Clin Sci (Lond). 1982 Jun;62(6):595-604. thought that a disorder in aldosterone secretion was the most probable reason for fluid retention and the increase in both plasma volume and total body water, an actual study in Eur J Appl Physiol. 2012 Mar;112(3):991-1003 showed that fluid overload is the most likely aetiology for limb swelling in ultra-marathoners. These authors showed that neither changes in hormones nor a change in renal function were related to limb swelling.
>>>>This section has been introduced and reads:
Increase of leg volume and ankle edema during prolonged exercise has been reported [29, 30] and has been attributed to endocrine dysregulation. However, recent studies postulate rather fluid overload as the source of the swellings [31, 32] and total body water increase has been shown [33] in long endurance athletes.

At the end of the Discussion, insert a section 'Strengths, limitations and implications for future research' and report first that this is the first study in history to follow ultra-marathoners with a mobile MRI in a multi-stage ultra-marathon. Also, this is the first study to show changes in the musculoskeletal system in radiological images in multi-stage ultra-marathoners. As a limitation, you need also to acknowledge that subcutaneous oedema could also be due to fluid overload, see Eur J Appl Physiol. 2012 Mar;112(3):991-1003. As an implication for future research, you need to cite to combine your methods with the methods reported in Eur J Appl Physiol. 2012 Mar;112(3):991-1003 to conclude that future studies need to determine fluid intake, plasma sodium concentration and changes in lower limbs using both MRI and plethysmography to determine whether the subcutaneous edema in the feet is definitely due to fluid overload or not.
>>>>>The corresponding section has been renamed and the introduced sentences read:
Strengths, limitations and implications for future research:
This is the first study in history to report results from close observation of multi stage ultra marathon athletes by mobile MRI. Therefore it is the first study to report changes in the musculoskeletal system in multi stage ultramarathoners…
The stated radiological findings like subcutaneous or intraosseous edema are important. Lacking

additional data, our study can not prove the cause for it (workload, endocrine imbalance or fluid overload, as discussed above). Therefore, additional data like fluid intake, electrolyte content of plasma and urine as well as hormonal factors should be sampled in future studies.

Reviewer: Dr Robert D Pearce
Consultant musculoskeletal radiologist
Chelsea & Westminster Hospital
London
United Kingdom

Competing interests: None

The manuscript includes all the items to be included when reporting observational studies described in the supplemental document - the STROBE statement.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Reviewer: PD Dr. med. Beat Knechtle<br>Institute of General Practice and for Health Services Research, University of Zurich, Zurich, Switzerland<br><br>I have no competing interests and no conflict of interest |
| **REVIEW RETURNED** | 18/04/2012 |

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| **THE STUDY** | The following reference needs to be inserted to the discussion of swelling of feet in ultra-marathoners due to fluid overload<br><br>Cejka C, Knechtle B, Knechtle P, Rust CA, Rosemann T. An increased fluid intake leads to feet swelling in 100-km ultra-marathoners - an observational field study. J Int Soc Sports Nutr. 2012 Apr 3;9(1):11. |
| **GENERAL COMMENTS** | The following reference needs to be inserted to the discussion of swelling of feet in ultra-marathoners due to fluid overload:<br><br>Cejka C, Knechtle B, Knechtle P, Rust CA, Rosemann T. An increased fluid intake leads to feet swelling in 100-km ultra-marathoners - an observational field study. J Int Soc Sports Nutr. 2012 Apr 3;9(1):11.<br><br>Fluid intake was positively related to the change in the volume of the feet. The authors need to insert this aspect on page 8 line 36 in their manuscript. This finding might explain their findings with the subcutaneous edema. |

**VERSION 2 – AUTHOR RESPONSE**

This reference has been introduced and the sentence now reads:
Increase of leg volume and ankle edema during prolonged exercise has been reported [29, 30] and has been attributed to endocrine dysregulation. However, recent studies postulate rather fluid overload as the source of the swellings [31, 32] and total body water increase has been shown [33] in long endurance athletes. Fluid intake had been shown to be positively correlated to the change of the volume of athletes´ feet [34], furthermore, it has been shown that the total body water has increased

over the course of multi stage runs [35, 36]. So it can be assumed that the subcutaneous edema is caused at least partially by excessive water intake.