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The foot in multistage ultra marathon runners: Experience in a cohort study of 22 participants of the Trans Europe Footrace project with mobile MRI.

Short title: MRI based observation for foot lesions during a multistage ultra marathon.

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ABSTRACT

Objectives
67 runners participated in the Trans Europe FootRace 2009 (TEFR09), a 4487 km (2789 mi) multi stage ultra marathon covering the south of Europe (Bari, Italy) to the North Cape. Reports on ultra marathons are lacking, but the literature reports overuse injuries in athletes, especially to the Achilles tendon (AT), ankle or hind foot. Bone edema may be related to exposure and is present in fatigue fractures.
The aim of the study therefore was to determine prospectively if sustained maximal load during an ultra marathon leads to damage to the foot.

Design and Participants
In a cohort study, repeated scanning of the 22 athletes participating in the study was performed before and during (approximately every 1000 km) the race. Using the obtained fat saturated inversion recovery sequence, two experienced readers blinded to the clinical data rated the images regarding foot lesions. Statistical analysis included regression analysis and computation of the interrater reliability.

Setting
The TEFR09 course. MRI scanning was performed according to prearranged schedules for every participant, using a mobile 1.5 Tesla MRI unit on a trailer following the race.

Primary outcome measures
MRI data such as AT diameter, bone or tendon lesions, subcutaneous, plantar fascia or intraosseous edema.

Results
The 22 study participants did not differ significantly from the total of the 68 TEFR09 runners regarding height, weight and age.
The AT diameter increased significantly from 6.8 to 7.8 mm as did intraosseous signal, bone lesions and subcutaneous edema. However, finishers differed only regarding plantar aponeurosis and subcutaneous edema from participants aborting the TEFR09. Interrater reliability was 0.88-0.98.

Conclusions
Under the extreme stress of the TEFR09, an increase of the AT diameter as well as bone signal are thought to be adaptive, since only subcutaneous edema and plantar fascia edema were related to abortion of the race.

ARTICLE SUMMARY

Article focus:

- A study on effects of ultra marathon running, in this case the multi stage TransEurope FootRace covering 4487 km from Bari (Italy) to the North Cape.
- Observational cohort study using MRI to look for possible lesions to the foot.

Key messages:

- During sustained maximal load, Achilles tendon diameter and bone MRI STIR signal (hinting at subtle edema) increases. This is thought to be adaptive.
- Subcutaneous edema and plantar fascia signal were related to abortion of the race. These measurements seem to be related to relevant changes leading to discontinuation of the run.
- No relevant new foot joint or tendon lesions were detected during the race over 4487 km.

Strengths and limitations of this study:

- Repeated measurement prospectively during the run was possible only because of the mobile MRI unit used for this research project.
- The number of included runners (22) is high compared to other MRI based studies but may have been too small to detect less frequent lesions.

INTRODUCTION

In 2009 (April 19th to June 21th) the TransEurope FootRace 2009 (TEFR09) took place. It was the second European transcontinental multistage ultra marathon race and covered the distance from the south of Italy (Bari) to the North Cape. A collective of 67 endurance runners with a mean age 50.5 years (range 26 to 74) and consisting of 11 women and 56 men from 12 nations met the challenge. Their goal was to run the 4,487 km in 64 days without any day rest. Thus they expected to complete an average distance of 70.1 km resp. 1.7 marathon distances (min 44 km, max 95.1 km) on every stage for 64 consecutive days.[1]

The permanent overuse during such an ultra marathon especially endangers ankle and foot. While reliable reports on ultra marathon effects are lacking, the present literature describes overuse injuries [2, 3] in endurance sport and shows the Achilles tendon (AT) to be a structure of high risk because it is regularly injured in sports.[4, 5] Also, ankle and hind foot injuries are frequent among athletes,[6, 7] with visible bone edema even in asymptomatic individuals increasing their exposure.[8] Other reports show high rates of fatigue fractures in army recruits after exerting marches.[9, 10] To diagnose these sport related injuries, MRI is the diagnostic procedure of choice.[11-13] In most reports, MRI was performed with sagitally oriented fat saturated T2 weighted sequences.[14]

The present study with serial MRI before and during the run was performed under the hypothesis that long distance endurance runners are able to endure the race associated injuries and the accompanying pain but will nevertheless show changes in Achilles tendon and bones of the foot. We expected the changes to accumulate during the run. Also we expected that bone marrow edema will increase during the run but decrease during pauses. Furthermore we expected that participants aborting the race will have more severe lesions on MRI. Finally we were looking for predictive parameters (risk factors) indicating failure to complete the run.

PARTICIPANTS AND METHODS

Study participants

After approval of the local ethics committee and in accordance to the Declaration of Helsinki, the participants of the TEFR ultra marathon were recruited for the MRI based cohort study. The inclusion criterion for the ultra marathon group obviously was participation in the event, exclusion criteria were contraindications against MRI. Since MRI scanning time and the athletes' time was limited, only a part of the examinations concerned the foot region. Of the 44 athletes consenting to participate in the MRI project, 22 were randomized into the foot study. Their data will be presented here.

MRI acquisition

For each measurement, both feet were scanned consecutively with a dedicated foot coil that was table fixed with a boot-like design and 8-channel coils. MRI data were acquired with a mobile 1.5T MR scanner (Magnetom Avanto™ mobile MRI 02.05, software version: Syngo™ MR B15, Siemens Ltd., Erlangen, Germany) on a MRI-trailer travelling with the runners on the TEFR09 from stage to stage, day by day.

The MRI measurements were planned in a schedule for each participant, assuring equal distribution of measurements at all timepoints.
Every participant was scanned at a baseline time point 1 prior to the run and roughly every 1000 km or directly after abortion of the run. Schedules were made for time point 2 (day 17-22 at km 1131-1487), time point 3 (day 29-35 at km 1985- 2362), time point 4 (day 43-46 at km 2964-3161) and time point 5 (day 50 to 58 at km 3430-4037).

MRI sequences
The imaging sequence used in the reported study was a fat saturated short tau inversion recovery (STIR) sagittal sequence, resulting in a T2-weighted fat suppressed image with edema or effusion showing as increased signal. Sequence parameters were:
Slice thickness of 2 mm, repetition time was 8490 ms, echo time 60 ms, inversion time120 ms. Flip angle was 140°, echo train length 13, bandwidth130 Hz/voxel, the matrix was 512x512 (interpolated from 358x358), field of view 300x300 mm and time of acquisition was 3min 50s for each side.

MRI data measurements
Two researchers (experienced radiologists WF and US) without access to clinical data independently assessed the datasets at PACS workstations. All signal intensities were measured in a region of interest covering a volume of 25mm^2.
The measurements closely resemble the technique published earlier.[15]

The following measurements (see also table 1) were made on the sagittal MRI images:
The greatest anteroposterior diameter of the Achilles tendon (AT) and AT signal intensity at insertion. Also, signal intensity at mid tendon or at site of lesion, if a lesion is visible, and lesion distance from AT insertion were taken. The number of new lesions in comparison to the preceding examination was counted.
The signal intensity of the calcaneus at AT insertion and at a normally innocuous area in the middle between most cranial point of the posterior talocalcanear articular surface and the most caudal point of the lateral process of the calcaneus (see figure 1) was measured.
The highest intraosseous signal intensity in any bone of the foot was taken.
The number of bone bruises / subchondral or osseous lesions was noted.
The signal intensity of fascia plantaris was rated, taking note if there was edema or effusion (yes/no).
Also a possible bursa retrocalcanearis greater than 2 mm sagitally was noted (yes/no).
Any soft tissue signal intensity indicative of fasciitis, peritendonitis, subcutaneous edema (see figure 2) was noted (yes/no).

Finisher status
To allow discrimination between runners finishing the race and others aborting, their status F (finisher) or NF (non finisher) was recorded, also the stated cause (Table 2).

Time from finish of stage to MRI
Since it was hypothesized that bone marrow edema will increase during the run and decrease during rest (presumably lying down), the time from finish of the daily run to MRI scanning was recorded. For non finishers the time point has not been recorded

because they stayed at some checkpoint until transportation. Therefore, their last resting period was guessed to start at noon.

Interrater reliability

Interrater reliability was calculated on two measurements where previous data [15] had demonstrated good reliability: AT diameter and intraosseous signal intensity of the calcaneus (this time at the clearly defined "innocuous" location described above).

Statistical analysis

Data were analyzed using R. version 2.11.1, R Foundation for Statistical Computing, 2010.[16] Given the longitudinal nature of the test data, specialised regression models (linear mixed effect models) were applied. The package "nlme" [17] was used.

Univariate and multivariate regression analyses were performed.

Results were significant when p was < 0.05.

Taking into account the critique of Bland and Altman [18] concerning the correlation coefficient to calculate the interrater reliability, we decided to use lambda as proposed by Jepsen et. al.[19] Lambda can be calculated as follows: $\lambda = \frac{2 \cdot VAR_X - VAR_D}{2 \cdot VAR_X}$.

VAR denotes the variance of the measurements X and D the difference of the measurments of the two raters. The interrater-reliability is rated as low for λ < 0.25. Values up to .5 are rated as fair, .5-.75 as moderate to good and λ > 0,75 demonstrates good to excellent reliability.[20]

RESULTS

Study participants

The TEFR09 participants comprised 57 men and 11 women, aged 26 to 74 years with a mean of 50.5 and a standard deviation (SD) of 10.5 years. They had a body height of 1.75 m (SD .08) and weight of 70.6 kg (SD 9.5).

Out of the total, 22 participated in this experiment. 2 were female and 20 male with a mean age of 49.1 years (11.5) at the time of the first MRI scan. They were 1.74 m (.09) tall and weighed 70.9 kg (11.3). The differences of the biometric markers of our sample to the whole group were not significant (t-test p= 0.6 - 0.9).

Exemplary measurements are shown in figure 1. The evolution of soft tissue and osseous edema is depicted in figure 2 and foot swelling as well as resulting shoe modifications are shown in figure 3.

MRI measurements

The predefined parameters were taken on the MRI examinations. The resulting measurements are detailed in table 1. The evolution of intraosseous signal intensities is depicted in figure 4.

Table 1: Measurements of MRI parameters and correlation with distance run

Time from stage finish to MRI examination

There was no significant effect of the time elapsed between stage finish and scanning (i.e. the length of the resting period before the scan, spent lying down and

thus decreasing potential edema) on the measured MRI parameters to be found in univariate and multivariate regression analyses.

Side differences
Looking for significant side differences in the observed measures, the following were found to be larger on the right side: Signal intensity of the AT at insertion (p=0.04), the number of bone lesions (0.002), the signal intensity of the plantar aponeurosis (0.03). The distance to an AT lesion from the point of calcanear insertion (p=0.04) was larger on the left side.

Differences between finishers and non finishers
21 athletes out of 67 participants had to exit the race. Out of the 22 participants in our study, 13 (59.1%) completed our study, while 12 finished the TEFR09, and 10 aborted the run. The athlete who finished our study (participation in the MRI at time point 5) but had to abort the race afterwards because of a hand phlegmonia has been counted as not aborting for our study, since the cause for abortion was not related to a problem of the feet and the measurements are thought to be independent from the later evolution of a hand phlegmonia.
The rate of abortion didn't differ significantly between the total and our study participants. The stated causes are listed in table 2. Most of the problems occurred in the lower legs (shin splint and perimyositis).
F and NF showed significant differences at the beginning of the TEFR09 only in the signal intensity of the plantar aponeurosis (p=0.03).
During the run, there were significant differences in the evolution of edema of the right plantar aponeurosis (p=0.02) and subcutaneous edema of the right (0.05) and left side (0.04), with NF showing higher rates of edema.

Interrater reliability
The interrater reliability was calculated for the diameter of the AT as well as the Signal intensity of an innocuous region of the calcaneus. The lambda values were for AT diameter of the right /left side 0.95 / 0.88 and for the signal intensity of the normally inoccuous region of the calcaneus on the right/ left side 0.97 / 0.98 respectively.

DISCUSSION

The TEFR09 participants had to endure an immense physical exposure, leading to stress fractures, swollen feet, sometimes necessitating cutting away part of the running shoe in order to continue running,[1] but 46 out of 67 (68.7%) were able to finish. Our study participants showed changes during the run with an increase of the AT diameter and intraosseous signal intensity as well as subcutaneous edema. Non finishers displayed higher rates of soft tissue edema.

We had hypothesized that runners will show increasing pathology of hindfoot and ankle as well as AT during the run even if they are able to finish the TEFR09.
The literature up to date had been inconclusive as to the consequences of marathon training, including our own data[15] that had shown little changes in MRI appearance of the hindfoot and AT during training and participation of a (half) marathon.
However, the TEFR09 with extended running load over 64 stages without any day rest is not comparable to other sporting events or normal leisure activities.
The results show a gradual increase of the diameter of the AT from a mean of 6.8 to a mean of 7.8mm over the course of the run. This stands in contrast to reports linking

AT diameter to disease[21] or showing decrease of AT diameter with training.[22] However, the results match with previous data on runners[23] and healthy marathoners[15] or reports stressing the relevance of AT signal intensity SI[24] or calcaneus edema at tendon insertion[25] for pathology. No significant correlation could be shown to tendon signal intensity or lesions or calcaneus bone edema at tendon insertion, further strengthening the point that the observed AT changes seem to be adaptive.

Furthermore, gradual increases over the run in osseous signal of the calcaneus as well as the maximal intraosseous signal in any foot bone and the number of bone lesions could be shown (see figure 4).
The increased signal intensity draws attention to reports on stress fractures,[9, 10] but the appearance of the recorded alterations in our study occurred early and didn't coincide with stress fractures. Thus the signal increase is thought to result from stress response[12] as reported in asymptomatic runners.[8, 26-28] Sometimes diffuse bone edema in nearly all end phalanges pointed to contusions because of tight shoes. However, bone edema and lesions were not linked to abortion of the run (NF status).

Also, increases in subcutaneous edema occurred over the course of the run (see figure 2). Here, subcutaneous edema at the time of the start of TEFR09 was rare with around 5% (see table 1), while it rose sharply at time point 2 (after a mean of 1068km) to ca. 65% and increased only moderately to ca. 70% at time point 5 (after a mean of 3669km). This corresponds to the sometimes grotesque swelling of runners' feet, necessitating cutting of running shoes to resemble crude sandals (see figure 3).

We had hypothesized that bone edema and the corresponding SI would decrease during rest (lying down). However, our data showed no correlation of the resting time to the SI. So the observed bone edema seems to reflect true load effects and not simple hydrostatic changes.

We had expected to see more severe lesions in NF than in F and had hoped to find risk factors or predictive parameters for NF. Here, significant differences could be shown only for soft tissue parameters: At the beginning of the TEFR09 only the SI of the left plantar aponeurosis was significantly higher in NF, pointing to possible overload even before the start. During the run, NF showed significantly more subcutaneous edema and edema of the (right) plantar aponeurosis. This may indicate that soft tissue edema is more relevant to the possible abortion of the run than the intraosseous changes described above or tendon problems. Especially the signal alterations in the plantar aponeurosis point to plantar fasciitis, a problem thought to be the main cause of inferior heel pain in runners and is detected easily by MRI.[29]
Considering clinical data on abortion of the run (see table 2), the stated soft-tissue related causes refer mainly to the legs (mostly shin splint and perimyositis). These regions were not included in the current investigation. However, it is probable that edema related to shin splint or perimyositis had spread along the lower legs to the foot, so that the visible subcutaneous edema was not directly related to a pathology in the foot.

With lambda values between 0.88 and 0.98, the interrater reliability can be rated as excellent.[20]

Limitations:
The chance to observe an event like the TEFR09 with a mobile MRI scanner had been great, but the difficulties of tight schedules of the athletes prohibited greater numbers.
Poor infrastructure and difficult local situations at the stage destinations sometimes made a nearby commissioning of the mobile MRI impossible. However, the strongest influence forcing the staff to change and adapt their research work daily, was the athlete himself, with his individual personality and more or less daily changing mental and physical condition and necessities: pain, injuries, fatigue, fears, doubts, illness, regeneration program and nutrition plan.

The inclusion of 22 runners permitted detailed examinations but the number may have been too small to detect factors distinguishing NF. However, the study sample of 22 athletes had been randomized out of all participants, their biometric data shows that they are representative of the whole group of TEFR09 participants. So their results may be generalized.

Concluding:
During the TEFR09 and under extreme stress, adaptive changes like the increase of the AT diameter could be detected with MRI as well as signs of soft tissue overload with swelling and edema. The meaning of the SI increase of the foot bones is thought to resemble a stress response, but is not correlated to abortion of the race or development of stress fractures during the observed transcontinental multistage ultramarathon.

Competing interests
None.

Trial registration
University of Ulm, Germany Ethics Committee Nr. 78/08-UBB/se.

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Data sharing statement
No additional data available.

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Contributorship

WF designed the study, read the images and planned the statistical analysis. He wrote the manuscript and approved the final manuscript.
US designed the study, acquired the MRI data, read the images and critically revised the manuscript and approved the final manuscript.
FW designed and performed the statistical analysis. He wrote parts of the manuscript and approved the final manuscript.
CB designed the study, acquired the MRI data and critically revised the manuscript and approved the final manuscript.
Also, MRI scanning was performed by Heike Wiedelbach.

Tables

Table 1: Measurements of MRI parameters and correlation with distance run.
For quantitative data the mean (with standard error SE) is given, for qualitative data the percentage of positive measurements (mean over both readers).
Correlation with distance run: P is calculated by a univariate regression model with the parameter in question as the dependent variable and total distance as the independent variable. Statistically significant correlations are in bold script.

time point / Parameter	side	1	2	3	4	5	correlation with distance run
mean days run		0.1	15.5	29.1	42.8	52.5	
mean distance run, in km (in miles)		5 (3.2)	1068 (664)	2062 (1282)	2964 (1842)	3669 (2280)	
AT diameter (SE)	right	6.8 (0.37)	7.2 (0.44)	7.6 (0.54)	7.8 (0.53)	7.8 (0.55)	**<0.001**
	left	6.8 (0.39)	7.3 (0.49)	7.6 (0.53)	7.7 (0.60)	7.8 (0.66)	**<0.001**
SI at insertion of AT	right	32.4 (3.96)	38.5 (5.39)	40.0 (6.49)	42.1 (7.08)	39.2 (7.43)	0.6
	left	30.4 (1.80)	31.8 (2.72)	28.5 (1.50)	32.2 (2.37)	29.5 (1.77)	0.5
SI in the middle of the AT	right	35.9 (2.72)	42.9 (6.03)	45.5 (4.94)	42.2 (6.52)	47.9 (8.97)	0.05
	left	38.3 (3.92)	41.1 (5.28)	36.4 (3.06)	36.7 (3.80)	34.1 (5.42)	0.7
New lesions in the AT	right	NA	0.06	0.15	0	0	0.33
	left	NA	0.03	0	0.09	0	0.7
Distance of the lesion to the insertion of the AT	right	12.7 (4.02)	15.6 (5.19)	16.5 (3.52)	15.8 (4.23)	11.9 (6.03)	
	left	21.8 (4.57)	21.5 (2.50)	26.2 (6.19)	24 (6.03)	19	
SI in the calcaneus at the AT insertion	right	112.8 (7.30)	153.3 (13.80)	170.6 (15.66)	176.8 (19.66)	180.1 (18.97)	**<0.001**
	left	107.2 (5.38)	144.7 (9.90)	160.2 (11.70)	160.5 (11.54)	167.0 (12.65)	**<0.001**
SI in an inoccuous area of the calcaneus	right	158.2 (6.78)	210.8 (18.25)	243.9 (22.59)	246.1 (27.49)	250.2 (26.43)	**<0.001**
	left	164.0 (7.20)	216.4 (14.38)	248.8 (21.45)	251.5 (25.1)	268.6 (25.33)	**<0.001**
Maximal SI in any bone	right	312.5 (26.58)	411.7 (30.17)	423.3 (32.14)	386.2 (22.29)	399.9 (26.10)	**0.003**
	left	283.4 (24.29)	357.7 (24.59)	385.8 (35.06)	410.7 (35.43)	417.3 (39.79)	**<0.001**
Number of bone lesions	right	2.1 (0.6)	3.2 (0.62)	3.5 (0.58)	3.2 (0.59)	3.6 (0.61)	**0.016**
	left	2.3 (0.44)	2.4 (0.43)	2.3 (0.45)	3.1 (0.54)	3.2 (0.55)	**0.002**
SI in the plantar aponeurosis	right	25.4	28	27.9	33.7	34.8	0.4

		(4.95)	(5.79)	(6.59)	(8.86)	(9.54)	
	left	21.4 (1.31)	22.4 (1.29)	22.3 (1.31)	22.1 (2.14)	20.9 (1.37)	0.2
Edema in the plantar aponeurosis (y/n)	right	0.07	0.06	0.09	0.11	0.12	0.9
	left	0	0	0	0.04	0	n.a.
Retrocalcanear Bursa (y/n)	right	0.07	0.19	0.18	0.14	0.15	0.8
	left	0.03	0.21	0.24	0.18	0.12	0.3
Subcutaneous edema (y/n)	right	0.05	0.64	0.65	0.79	0.81	**<0.001**
	left	0.07	0.68	0.61	0.64	0.65	**<0.001**

Table 2: Stated causes for abortion of the run in participating Athletes.

Athlete	Pathology
1	Perimyositis of the thigh
2	Stress fracture of the tibia
3	Hallux valgus / bunion
4	Phlegmonia of the hand
5	Shin splint
6	Perimyositis of the lower leg
7	Perimyositis of the thigh
8	Shin splint
9	Perimyositis, gluteal and shin splint bilateral
10	Shin splint

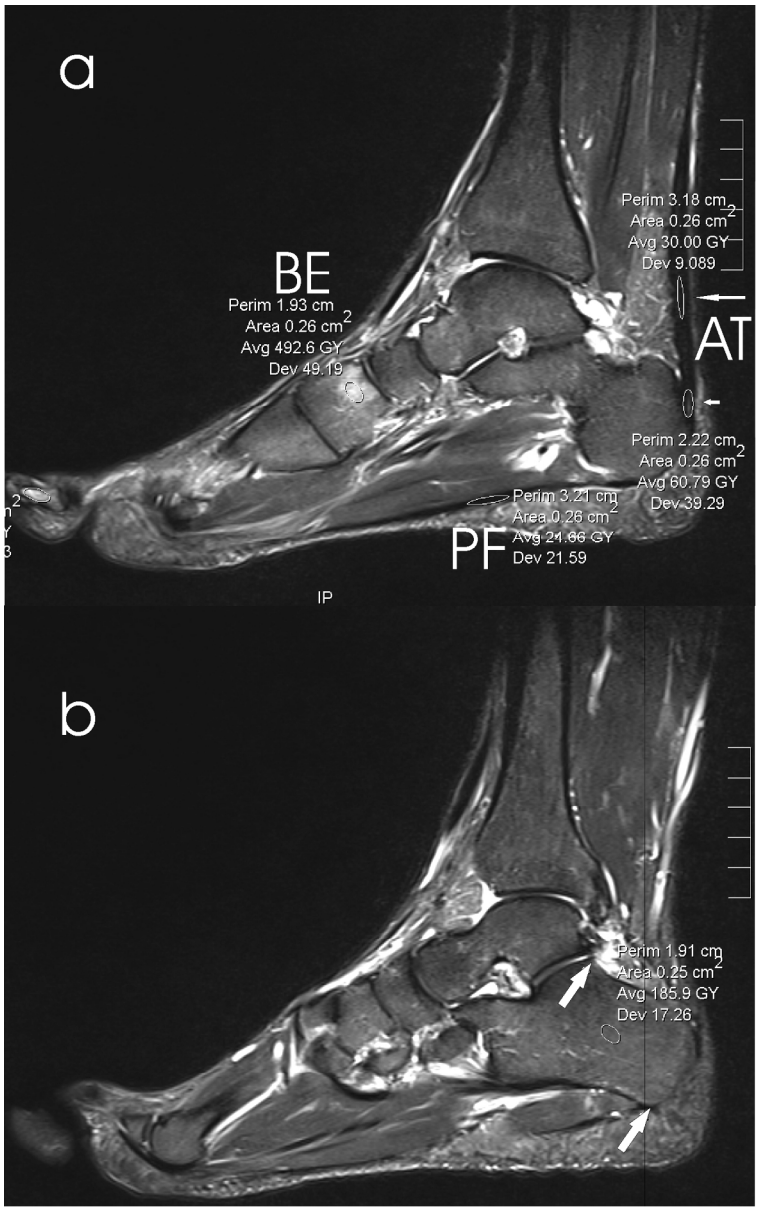
Legends

Figure 1: Measurements of MRI parameters on a sagittal STIR weighted MRI scan.
a)
PF: The measurement in the plantar fascia.
BE: Bone edema (in the medial cuneiform bone)
Short and long arrows pointing to measurements in the Achilles tendon (AT). The short arrow points to a intratendinous lesion near the insertion, the long arrow points to a inoccuous area situated cranially.
b)
The measurement of the normally inoccuous region of the calcaneus is placed between the most cranial portion of the posterior talocalcanear facet and the most caudal point of the lateral process of the calcaneus (see arrows and round measurement site).

Figure 2: Subcutaneous edema on a sagittal STIR weighted MRI scan.
The six dates represent different MRI measurements of the same foot of one TEFR09 participant, each with identical window settings.
The long diagonal arrow points to tubular high intensity structures, probably corresponding to peritendinous fluid.
The short arrow points to subcutaneous edema and edema in Kager´s fat pad of the AT.
The translucent arrow points to intraosseous signal near the AT insertion evolving later than the subcutaneous edema.

Figure 3: Makeshift sandals.
Subcutaneous edema resulting in ankle (black arrow) and foot swelling (white arrows) necessitated cutting away parts of the shoes, creating makeshift sandals to accommodate the athletes' feet.

Figure 4: Figure 4: Intraosseous signal intensity in the time course of the TEFR09.
Signal intensity measurements in the calcaneus at AT insertion (black triangles), in a normally inoccuous area of the calcaneus (gray squares) and at the individual´s area of the highest intraosseous signal (black dots) are shown together with the standard error values. The measurements were performed at several time points during the TEFR09. The cumulative distance run is shown below the graph.



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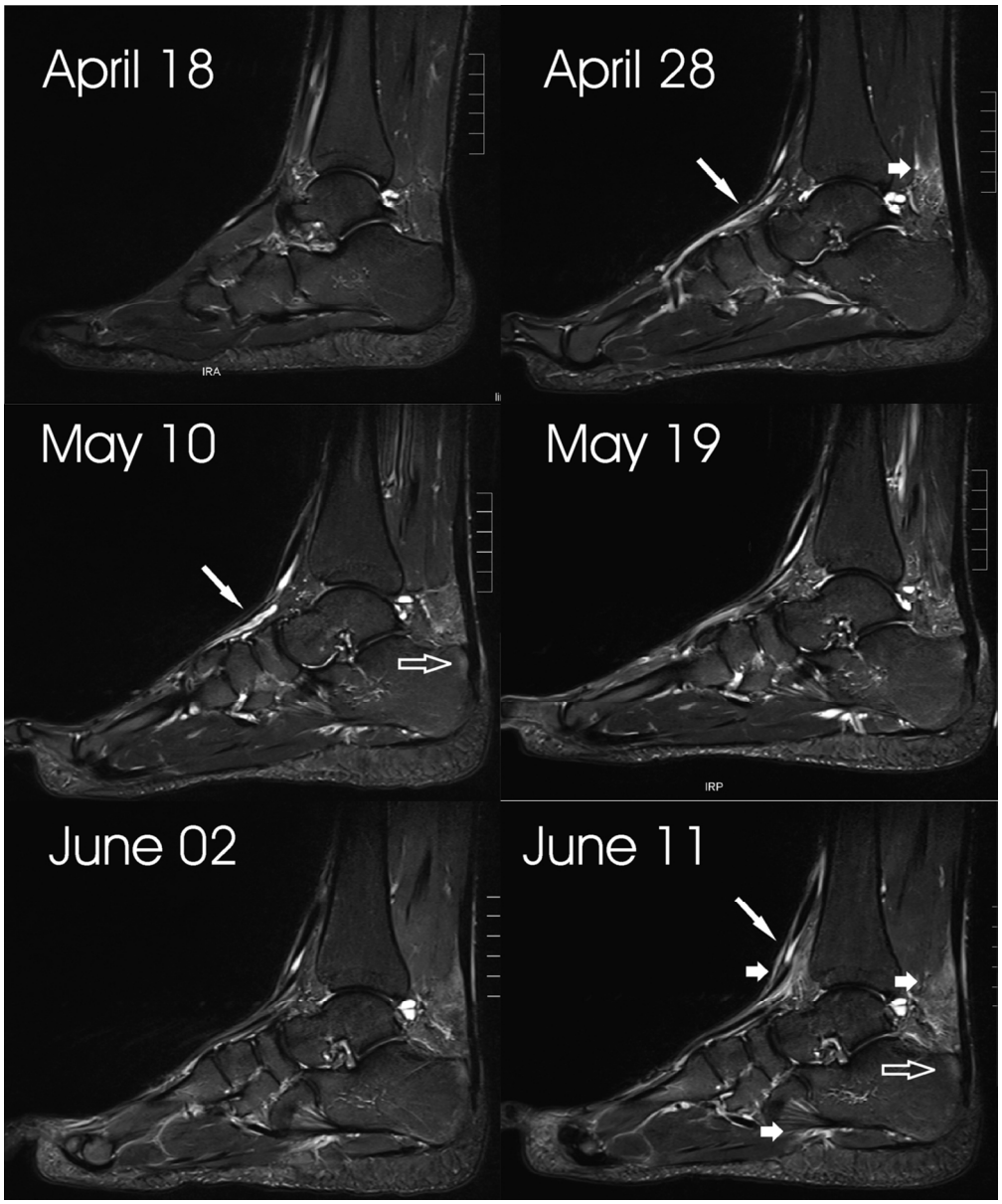

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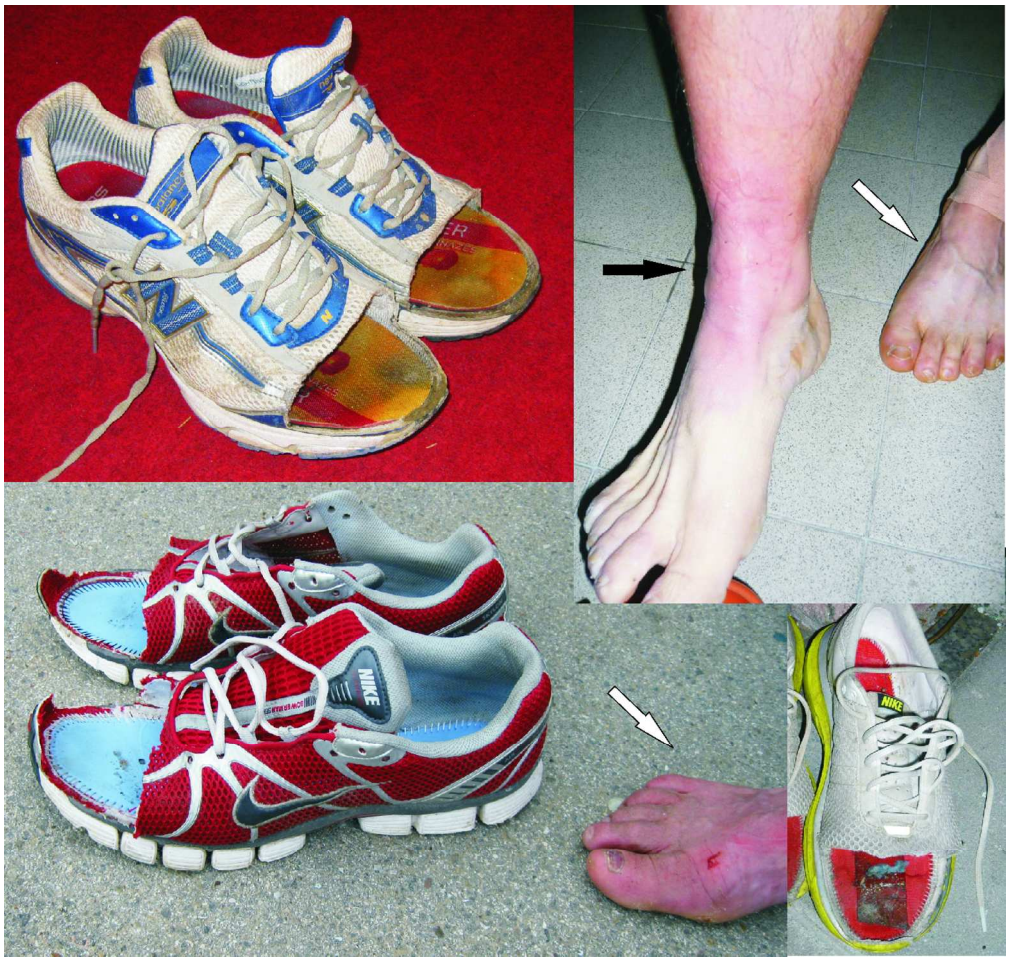
The translucent arrow points to intraosseous signal near the AT insertion evolving later than the subcutaneous edema.
114x137mm (300 x 300 DPI)



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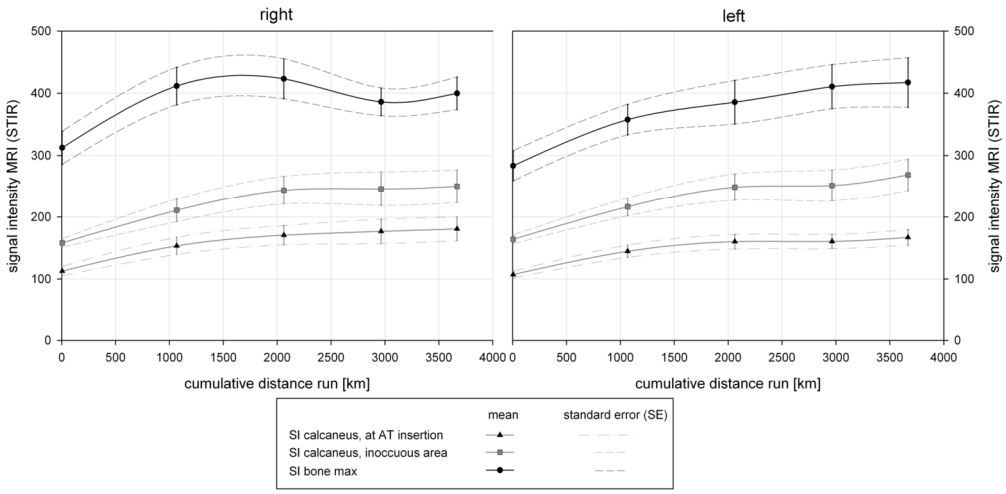

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141x68mm (300 x 300 DPI)

STROBE Statement
Strengthening the reporting of observational studies in epidemiology

STROBE Statement—Items to be included when reporting observational studies in a conference abstract

Item	Recommendation
Title	Indicate the study's design with a commonly used term in the title (e.g cohort, case-control, cross sectional)
Authors	Contact details for the corresponding author
Study design	Description of the study design (e.g cohort, case-control, cross sectional)
Objective	Specific objectives or hypothesis
Methods	
Setting	Description of setting, follow-up dates or dates at which the outcome events occurred or at which the outcomes were present, as well as any points or ranges on other time scales for the outcomes (e.g., prevalence at age 18, 1998-2007).
Participants	*Cohort study*—Give the most important eligibility criteria, and the most important sources and methods of selection of participants. Describe briefly the methods of follow-up *Case-control study*—Give the major eligibility criteria, and the major sources and methods of case ascertainment and control selection *Cross-sectional study*—Give the eligibility criteria, and the major sources and methods of selection of participants
	Cohort study—For matched studies, give matching and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	Clearly define primary outcome for this report.
Statistical methods	Describe statistical methods, including those used to control for confounding
Results	
Participants	Report Number of participants at the beginning and end of the study
Main results	Report estimates of associations. If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Report appropriate measures of variability and uncertainty (e.g., odds ratios with confidence intervals
Conclusions	General interpretation of study results

BMJ open

The foot in multistage ultra marathon runners: Experience in a cohort study of 22 participants of the Trans Europe Footrace project with mobile MRI.

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The foot in multistage ultra marathon runners: Experience in a cohort study of 22 participants of the Trans Europe Footrace project with mobile MRI.

Short title: MRI based observation for foot lesions during a multistage ultra marathon.

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Keywords:
MRI, Achilles tendon, foot, ultra marathon, stress reaction.

Word count: 2703

ABSTRACT

Objectives
67 runners participated in the Trans Europe FootRace 2009 (TEFR09), a 4487 km (2789 mi) multi stage ultra marathon covering the south of Europe (Bari, Italy) to the North Cape. Reports on ultra marathons are lacking, but the literature reports overuse injuries in athletes, especially to the Achilles tendon (AT), ankle or hind foot. Bone edema may be related to exposure and is present in fatigue fractures.
The aim of the study therefore was to determine prospectively if sustained maximal load during an ultra marathon leads to damage to the foot.

Design and Participants
In a cohort study, repeated scanning of the 22 athletes participating in the study was performed before and during (approximately every 1000 km) the race. Using the obtained fat saturated inversion recovery sequence, two experienced readers blinded to the clinical data rated the images regarding foot lesions. Statistical analysis included regression analysis and computation of the interrater reliability.

Setting
The TEFR09 course. MRI scanning was performed according to prearranged schedules for every participant, using a mobile 1.5 Tesla MRI unit on a trailer following the race.

Primary outcome measures
MRI data such as AT diameter, bone or tendon lesions, subcutaneous, plantar fascia or intraosseous edema.

Results
The 22 study participants did not differ significantly from the total of the 68 TEFR09 runners regarding height, weight and age.
The AT diameter increased significantly from 6.8 to 7.8 mm as did intraosseous signal, bone lesions and subcutaneous edema. However, finishers differed only regarding plantar aponeurosis and subcutaneous edema from participants aborting the TEFR09. Interrater reliability was 0.88-0.98.

Conclusions
Under the extreme stress of the TEFR09, an increase of the AT diameter as well as bone signal are thought to be adaptive, since only subcutaneous edema and plantar fascia edema were related to abortion of the race.

ARTICLE SUMMARY

Article focus:

- A study on effects of ultra marathon running, in this case the multi stage TransEurope FootRace covering 4487 km from Bari (Italy) to the North Cape.
- Observational cohort study using MRI to look for possible lesions to the foot.

Key messages:

- During sustained maximal load, Achilles tendon diameter and bone MRI STIR signal (hinting at subtle edema) increases. This is thought to be adaptive.
- Subcutaneous edema and plantar fascia signal were related to abortion of the race. These measurements seem to be related to relevant changes leading to discontinuation of the run.
- No relevant new foot joint or tendon lesions were detected during the race over 4487 km.

Strengths and limitations of this study:

- Repeated measurement prospectively during the run was possible only because of the mobile MRI unit used for this research project.
- The number of included runners (22) is high compared to other MRI based studies but may have been too small to detect less frequent lesions.

INTRODUCTION

In 2009 (April 19th to June 21th) the TransEurope FootRace 2009 (TEFR09) took place. It was the second European transcontinental multistage ultra marathon race and covered the distance from the south of Italy (Bari) to the North Cape. A collective of 67 endurance runners with a mean age 50.5 years (range 26 to 74) and consisting of 11 women and 56 men from 12 nations met the challenge. Their goal was to run the 4,487 km in 64 days without any day rest. Thus they expected to complete an average distance of 70.1 km resp. 1.7 marathon distances (min 44 km, max 95.1 km) on every stage for 64 consecutive days.[1]

The permanent overuse during such an ultra marathon especially endangers ankle and foot. While reliable reports on ultra marathon effects are lacking, the present literature describes overuse injuries [2, 3] in endurance sport and shows the Achilles tendon (AT) to be a structure of high risk because it is regularly injured in sports.[4, 5] Also, ankle and hind foot injuries are frequent among athletes,[6, 7] with visible bone edema even in asymptomatic individuals increasing their exposure.[8] Other reports show high rates of fatigue fractures in army recruits after exerting marches.[9, 10] To diagnose these sport related injuries, MRI is the diagnostic procedure of choice.[11-13] In most reports, MRI was performed with sagitally oriented fat saturated T2 weighted sequences.[14]

The present study with serial MRI before and during the run was performed under the hypothesis that long distance endurance runners are able to endure the race associated injuries and the accompanying pain but will nevertheless show changes in Achilles tendon and bones of the foot. We expected the changes to accumulate during the run. Also we expected that bone marrow edema will increase during the run but decrease during pauses. Furthermore we expected that participants aborting the race will have more severe lesions on MRI. Finally we were looking for predictive parameters (risk factors) indicating failure to complete the run.

PARTICIPANTS AND METHODS

Study participants

After approval of the local ethics committee and in accordance to the Declaration of Helsinki, the participants of the TEFR ultra marathon were recruited for the MRI based cohort study. The inclusion criterion for the ultra marathon group obviously was participation in the event, exclusion criteria were contraindications against MRI. Since MRI scanning time and the athletes' time was limited, only a part of the examinations concerned the foot region. Of the 44 athletes consenting to participate in the MRI project, 22 were randomized into the foot study. Their data will be presented here.

MRI acquisition

For each measurement, both feet were scanned consecutively with a dedicated foot coil that was table fixed with a boot-like design and 8-channel coils. MRI data were acquired with a mobile 1.5T MR scanner (Magnetom Avanto^{TM} mobile MRI 02.05, software version: Syngo^{TM} MR B15, Siemens Ltd., Erlangen, Germany) on a MRI-trailer travelling with the runners on the TEFR09 from stage to stage, day by day.

The MRI measurements were planned in a schedule for each participant, assuring equal distribution of measurements at all timepoints.
Every participant was scanned at a baseline time point 1 prior to the run and roughly every 1000 km or directly after abortion of the run. Schedules were made for time point 2 (day 17-22 at km 1131-1487), time point 3 (day 29-35 at km 1985- 2362), time point 4 (day 43-46 at km 2964-3161) and time point 5 (day 50 to 58 at km 3430-4037).

MRI sequences
The imaging sequence used in the reported study was a fat saturated short tau inversion recovery (STIR) sagittal sequence, resulting in a T2-weighted fat suppressed image with edema or effusion showing as increased signal. Sequence parameters were:
Slice thickness of 2 mm, repetition time was 8490 ms, echo time 60 ms, inversion time120 ms. Flip angle was 140°, echo train length 13, bandwidth130 Hz/voxel, the matrix was 512x512 (interpolated from 358x358), field of view 300x300 mm and time of acquisition was 3min 50s for each side.

MRI data measurements
Two researchers (experienced radiologists WF and US) without access to clinical data independently assessed the datasets at PACS workstations. All signal intensities were measured in a region of interest covering a volume of 25mm^2.
The measurements closely resemble the technique published earlier.[15]

The following measurements (see also table 1) were made on the sagittal MRI images:
The greatest anteroposterior diameter of the Achilles tendon (AT) and AT signal intensity at insertion. Also, signal intensity at mid tendon or at site of lesion, if a lesion is visible, and lesion distance from AT insertion were taken. The number of new lesions in comparison to the preceding examination was counted.
The signal intensity of the calcaneus at AT insertion and at a normally innocuous area in the middle between most cranial point of the posterior talocalcanear articular surface and the most caudal point of the lateral process of the calcaneus (see figure 1) was measured.
The highest intraosseous signal intensity in any bone of the foot was taken.
The number of bone bruises / subchondral or osseous lesions was noted.
The signal intensity of fascia plantaris was rated, taking note if there was edema or effusion (yes/no).
Also a possible bursa retrocalcanearis greater than 2 mm sagitally was noted (yes/no).
Any soft tissue signal intensity indicative of fasciitis, peritendonitis, subcutaneous edema (see figure 2) was noted (yes/no).

Finisher status
To allow discrimination between runners finishing the race and others aborting, their status F (finisher) or NF (non finisher) was recorded, also the stated cause (Table 2).

Time from finish of stage to MRI
Since it was hypothesized that bone marrow edema will increase during the run and decrease during rest (presumably lying down), the time from finish of the daily run to MRI scanning was recorded. For non finishers the time point has not been recorded

because they stayed at some checkpoint until transportation. Therefore, their last resting period was guessed to start at noon.

Interrater reliability

Interrater reliability was calculated on two measurements where previous data [15] had demonstrated good reliability: AT diameter and intraosseous signal intensity of the calcaneus (this time at the clearly defined "innocuous" location described above).

Statistical analysis

Data were analyzed using R. version 2.11.1, R Foundation for Statistical Computing, 2010.[16] Given the longitudinal nature of the test data, specialised regression models (linear mixed effect models) were applied. The package "nlme" [17] was used.

Univariate and multivariate regression analyses were performed.

Results were significant when p was < 0.05.

Taking into account the critique of Bland and Altman [18] concerning the correlation coefficient to calculate the interrater reliability, we decided to use lambda as proposed by Jepsen et. al.[19] Lambda can be calculated as follows: $\lambda = \frac{2 \cdot VAR_X - VAR_D}{2 \cdot VAR_X}$.

VAR denotes the variance of the measurements X and D the difference of the measurments of the two raters. The interrater-reliability is rated as low for λ < 0.25. Values up to .5 are rated as fair, .5-.75 as moderate to good and λ > 0,75 demonstrates good to excellent reliability.[20]

RESULTS

Study participants

The TEFR09 participants comprised 57 men and 11 women, aged 26 to 74 years with a mean of 50.5 and a standard deviation (SD) of 10.5 years. They had a body height of 1.75 m (SD .08) and weight of 70.6 kg (SD 9.5).

Out of the total, 22 participated in this experiment. 2 were female and 20 male with a mean age of 49.1 years (11.5) at the time of the first MRI scan. They were 1.74 m (.09) tall and weighed 70.9 kg (11.3). The differences of the biometric markers of our sample to the whole group were not significant (t-test p= 0.6 - 0.9).

Exemplary measurements are shown in figure 1. The evolution of soft tissue and osseous edema is depicted in figure 2 and foot swelling as well as resulting shoe modifications are shown in figure 3.

MRI measurements

The predefined parameters were taken on the MRI examinations. The resulting measurements are detailed in table 1. The evolution of intraosseous signal intensities is depicted in figure 4.

Table 1: Measurements of MRI parameters and correlation with distance run

Time from stage finish to MRI examination

There was no significant effect of the time elapsed between stage finish and scanning (i.e. the length of the resting period before the scan, spent lying down and

thus decreasing potential edema) on the measured MRI parameters to be found in univariate and multivariate regression analyses.

Side differences
Looking for significant side differences in the observed measures, the following were found to be larger on the right side: Signal intensity of the AT at insertion (p=0.04), the number of bone lesions (0.002), the signal intensity of the plantar aponeurosis (0.03). The distance to an AT lesion from the point of calcanear insertion (p=0.04) was larger on the left side.

Differences between finishers and non finishers
21 athletes out of 67 participants had to exit the race. Out of the 22 participants in our study, 13 (59.1%) completed our study, while 12 finished the TEFR09, and 10 aborted the run. The athlete who finished our study (participation in the MRI at time point 5) but had to abort the race afterwards because of a hand phlegmonia has been counted as not aborting for our study, since the cause for abortion was not related to a problem of the feet and the measurements are thought to be independent from the later evolution of a hand phlegmonia.
The rate of abortion didn't differ significantly between the total and our study participants. The stated causes are listed in table 2. Most of the problems occurred in the lower legs (shin splint and perimyositis).
F and NF showed significant differences at the beginning of the TEFR09 only in the signal intensity of the plantar aponeurosis (p=0.03).
During the run, there were significant differences in the evolution of edema of the right plantar aponeurosis (p=0.02) and subcutaneous edema of the right (0.05) and left side (0.04), with NF showing higher rates of edema.

Interrater reliability
The interrater reliability was calculated for the diameter of the AT as well as the Signal intensity of an innocuous region of the calcaneus. The lambda values were for AT diameter of the right /left side 0.95 / 0.88 and for the signal intensity of the normally inoccuous region of the calcaneus on the right/ left side 0.97 / 0.98 respectively.

DISCUSSION
The TEFR09 participants had to endure an immense physical exposure, leading to stress fractures, swollen feet, sometimes necessitating cutting away part of the running shoe in order to continue running,[1] but 46 out of 67 (68.7%) were able to finish. Our study participants showed changes during the run with an increase of the AT diameter and intraosseous signal intensity as well as subcutaneous edema. Non finishers displayed higher rates of soft tissue edema.

We had hypothesized that runners will show increasing pathology of hindfoot and ankle as well as AT during the run even if they are able to finish the TEFR09.
The literature up to date had been inconclusive as to the consequences of marathon training, including our own data[15] that had shown little changes in MRI appearance of the hindfoot and AT during training and participation of a (half) marathon.
However, the TEFR09 with extended running load over 64 stages without any day rest is not comparable to other sporting events or normal leisure activities.
The results show a gradual increase of the diameter of the AT from a mean of 6.8 to a mean of 7.8mm over the course of the run. This stands in contrast to reports linking

AT diameter to disease[21] or showing decrease of AT diameter with training.[22] However, the results match with previous data on runners[23] and healthy marathoners[15] or reports stressing the relevance of AT signal intensity SI[24] or calcaneus edema at tendon insertion[25] for pathology. No significant correlation could be shown to tendon signal intensity or lesions or calcaneus bone edema at tendon insertion, further strengthening the point that the observed AT changes seem to be adaptive.

Furthermore, gradual increases over the run in osseous signal of the calcaneus as well as the maximal intraosseous signal in any foot bone and the number of bone lesions could be shown (see figure 4).
The increased signal intensity draws attention to reports on stress fractures,[9, 10] but the appearance of the recorded alterations in our study occurred early and didn't coincide with stress fractures. Thus the signal increase is thought to result from stress response[12] as reported in asymptomatic runners.[8, 26-28] Sometimes diffuse bone edema in nearly all end phalanges pointed to contusions because of tight shoes. However, bone edema and lesions were not linked to abortion of the run (NF status).

Also, increases in subcutaneous edema occurred over the course of the run (see figure 2). Here, subcutaneous edema at the time of the start of TEFR09 was rare with around 5% (see table 1), while it rose sharply at time point 2 (after a mean of 1068km) to ca. 65% and increased only moderately to ca. 70% at time point 5 (after a mean of 3669km). This corresponds to the sometimes grotesque swelling of runners' feet, necessitating cutting of running shoes to resemble crude sandals (see figure 3).

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.

We had hypothesized that bone edema and the corresponding SI would decrease during rest (lying down). However, our data showed no correlation of the resting time to the SI. So the observed bone edema seems to reflect true load effects and not simple hydrostatic changes.

We had expected to see more severe lesions in NF than in F and had hoped to find risk factors or predictive parameters for NF. Here, significant differences could be shown only for soft tissue parameters: At the beginning of the TEFR09 only the SI of the left plantar aponeurosis was significantly higher in NF, pointing to possible overload even before the start. During the run, NF showed significantly more subcutaneous edema and edema of the (right) plantar aponeurosis. This may indicate that soft tissue edema is more relevant to the possible abortion of the run than the intraosseous changes described above or tendon problems. Especially the signal alterations in the plantar aponeurosis point to plantar fasciitis, a problem thought to be the main cause of inferior heel pain in runners and is detected easily by MRI.[34]
Considering clinical data on abortion of the run (see table 2), the stated soft-tissue related causes refer mainly to the legs (mostly shin splint and perimyositis). These regions were not included in the current investigation. However, it is probable that edema related to shin splint or perimyositis had spread along the lower legs to the

foot, so that the visible subcutaneous edema was not directly related to a pathology in the foot.

With lambda values between 0.88 and 0.98, the interrater reliability can be rated as excellent.[20]

~~Limitations~~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 chance to observe an event like the TEFR09 with a mobile MRI scanner had been great, but the difficulties of tight schedules of the athletes prohibited greater numbers.
Poor infrastructure and difficult local situations at the stage destinations sometimes made a nearby commissioning of the mobile MRI impossible. However, the strongest influence forcing the staff to change and adapt their research work daily, was the athlete himself, with his individual personality and more or less daily changing mental and physical condition and necessities: pain, injuries, fatigue, fears, doubts, illness, regeneration program and nutrition plan.
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.
The inclusion of 22 runners permitted detailed examinations but the number may have been too small to detect factors distinguishing NF. However, the study sample of 22 athletes had been randomized out of all participants, their biometric data shows that they are representative of the whole group of TEFR09 participants. So their results may be generalized.

Concluding:
During the TEFR09 and under extreme stress, adaptive changes like the increase of the AT diameter could be detected with MRI as well as signs of soft tissue overload with swelling and edema. The meaning of the SI increase of the foot bones is thought to resemble a stress response, but is not correlated to abortion of the race or development of stress fractures during the observed transcontinental multistage ultramarathon.

Competing interests
None.

Trial registration
University of Ulm, Germany Ethics Committee Nr. 78/08-UBB/se.

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Data sharing statement
No additional data available.

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Contributorship
WF designed the study, read the images and planned the statistical analysis. He wrote the manuscript and approved the final manuscript.
US designed the study, acquired the MRI data, read the images and critically revised the manuscript and approved the final manuscript.
FW designed and performed the statistical analysis. He wrote parts of the manuscript and approved the final manuscript.
CB designed the study, acquired the MRI data and critically revised the manuscript and approved the final manuscript.
Also, MRI scanning was performed by Heike Wiedelbach.

Tables

Table 1: Measurements of MRI parameters and correlation with distance run.
For quantitative data the mean (with standard error SE) is given, for qualitative data the percentage of positive measurements (mean over both readers).
Correlation with distance run: P is calculated by a univariate regression model with the parameter in question as the dependent variable and total distance as the independent variable. Statistically significant correlations are in bold script.

time point / Parameter	side	1	2	3	4	5	correlation with distance run
mean days run		0.1	15.5	29.1	42.8	52.5	
mean distance run, in km (in miles)		5 (3.2)	1068 (664)	2062 (1282)	2964 (1842)	3669 (2280)	
AT diameter (SE)	right	6.8 (0.37)	7.2 (0.44)	7.6 (0.54)	7.8 (0.53)	7.8 (0.55)	**<0.001**
	left	6.8 (0.39)	7.3 (0.49)	7.6 (0.53)	7.7 (0.60)	7.8 (0.66)	**<0.001**
SI at insertion of AT	right	32.4 (3.96)	38.5 (5.39)	40.0 (6.49)	42.1 (7.08)	39.2 (7.43)	0.6
	left	30.4 (1.80)	31.8 (2.72)	28.5 (1.50)	32.2 (2.37)	29.5 (1.77)	0.5
SI in the middle of the AT	right	35.9 (2.72)	42.9 (6.03)	45.5 (4.94)	42.2 (6.52)	47.9 (8.97)	0.05
	left	38.3 (3.92)	41.1 (5.28)	36.4 (3.06)	36.7 (3.80)	34.1 (5.42)	0.7
New lesions in the AT	right	NA	0.06	0.15	0	0	0.33
	left	NA	0.03	0	0.09	0	0.7
Distance of the lesion to the insertion of the AT	right	12.7 (4.02)	15.6 (5.19)	16.5 (3.52)	15.8 (4.23)	11.9 (6.03)	
	left	21.8 (4.57)	21.5 (2.50)	26.2 (6.19)	24 (6.03)	19	
SI in the calcaneus at the AT insertion	right	112.8 (7.30)	153.3 (13.80)	170.6 (15.66)	176.8 (19.66)	180.1 (18.97)	**<0.001**
	left	107.2 (5.38)	144.7 (9.90)	160.2 (11.70)	160.5 (11.54)	167.0 (12.65)	**<0.001**
SI in an inoccuous area of the calcaneus	right	158.2 (6.78)	210.8 (18.25)	243.9 (22.59)	246.1 (27.49)	250.2 (26.43)	**<0.001**
	left	164.0 (7.20)	216.4 (14.38)	248.8 (21.45)	251.5 (25.1)	268.6 (25.33)	**<0.001**
Maximal SI in any bone	right	312.5 (26.58)	411.7 (30.17)	423.3 (32.14)	386.2 (22.29)	399.9 (26.10)	**0.003**
	left	283.4 (24.29)	357.7 (24.59)	385.8 (35.06)	410.7 (35.43)	417.3 (39.79)	**<0.001**
Number of bone lesions	right	2.1 (0.6)	3.2 (0.62)	3.5 (0.58)	3.2 (0.59)	3.6 (0.61)	**0.016**
	left	2.3 (0.44)	2.4 (0.43)	2.3 (0.45)	3.1 (0.54)	3.2 (0.55)	**0.002**
SI in the plantar aponeurosis	right	25.4	28	27.9	33.7	34.8	0.4

		(4.95)	(5.79)	(6.59)	(8.86)	(9.54)	
	left	21.4 (1.31)	22.4 (1.29)	22.3 (1.31)	22.1 (2.14)	20.9 (1.37)	0.2
Edema in the plantar aponeurosis (y/n)	right	0.07	0.06	0.09	0.11	0.12	0.9
	left	0	0	0	0.04	0	n.a.
Retrocalcanear Bursa (y/n)	right	0.07	0.19	0.18	0.14	0.15	0.8
	left	0.03	0.21	0.24	0.18	0.12	0.3
Subcutaneous edema (y/n)	right	0.05	0.64	0.65	0.79	0.81	**<0.001**
	left	0.07	0.68	0.61	0.64	0.65	**<0.001**

Table 2: Stated causes for abortion of the run in participating Athletes.

Athlete	Pathology
1	Perimyositis of the thigh
2	Stress fracture of the tibia
3	Hallux valgus / bunion
4	Phlegmonia of the hand
5	Shin splint
6	Perimyositis of the lower leg
7	Perimyositis of the thigh
8	Shin splint
9	Perimyositis, gluteal and shin splint bilateral
10	Shin splint

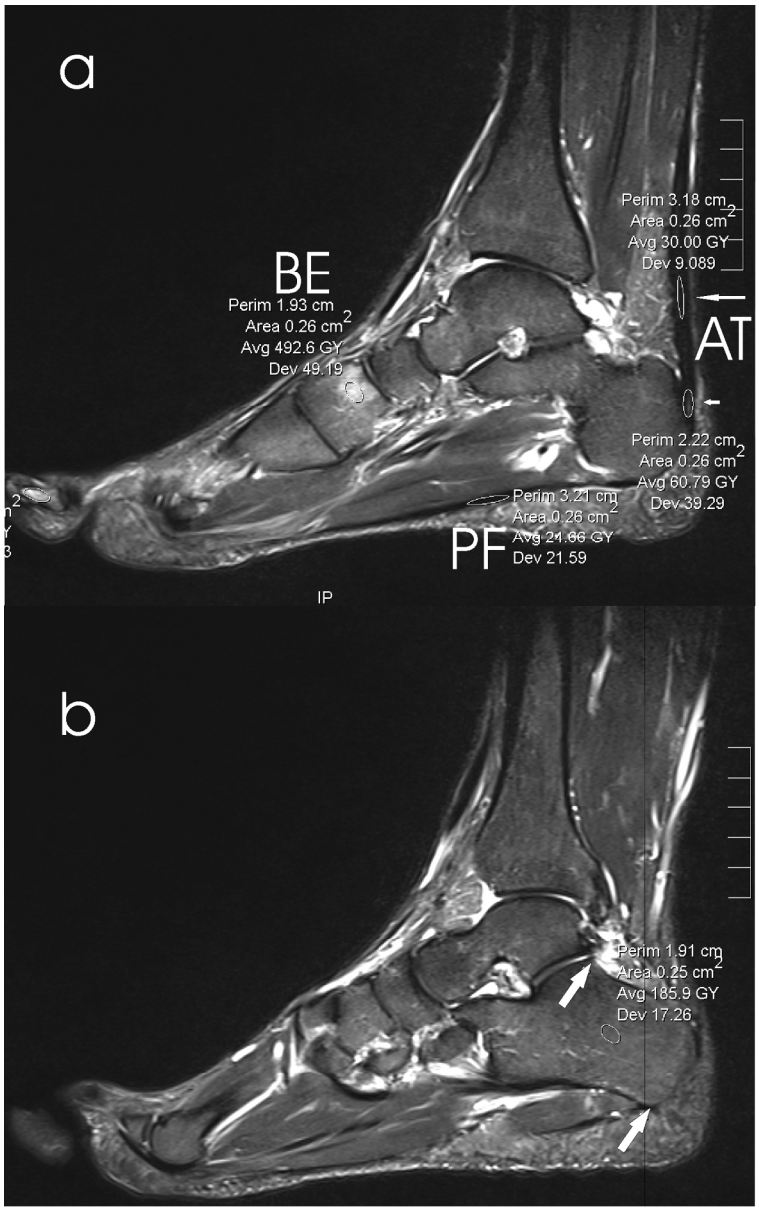
Legends

Figure 1: Measurements of MRI parameters on a sagittal STIR weighted MRI scan.
a)
PF: The measurement in the plantar fascia.
BE: Bone edema (in the medial cuneiform bone)
Short and long arrows pointing to measurements in the Achilles tendon (AT). The short arrow points to a intratendinous lesion near the insertion, the long arrow points to a inoccuous area situated cranially.
b)
The measurement of the normally inoccuous region of the calcaneus is placed between the most cranial portion of the posterior talocalcanear facet and the most caudal point of the lateral process of the calcaneus (see arrows and round measurement site).

Figure 2: Subcutaneous edema on a sagittal STIR weighted MRI scan.
The six dates represent different MRI measurements of the same foot of one TEFR09 participant, each with identical window settings.
The long diagonal arrow points to tubular high intensity structures, probably corresponding to peritendinous fluid.
The short arrow points to subcutaneous edema and edema in Kager´s fat pad of the AT.
The translucent arrow points to intraosseous signal near the AT insertion evolving later than the subcutaneous edema.

Figure 3: Makeshift sandals.
Subcutaneous edema resulting in ankle (black arrow) and foot swelling (white arrows) necessitated cutting away parts of the shoes, creating makeshift sandals to accommodate the athletes' feet.

Figure 4: Figure 4: Intraosseous signal intensity in the time course of the TEFR09.
Signal intensity measurements in the calcaneus at AT insertion (black triangles), in a normally inoccuous area of the calcaneus (gray squares) and at the individual´s area of the highest intraosseous signal (black dots) are shown together with the standard error values. The measurements were performed at several time points during the TEFR09. The cumulative distance run is shown below the graph.



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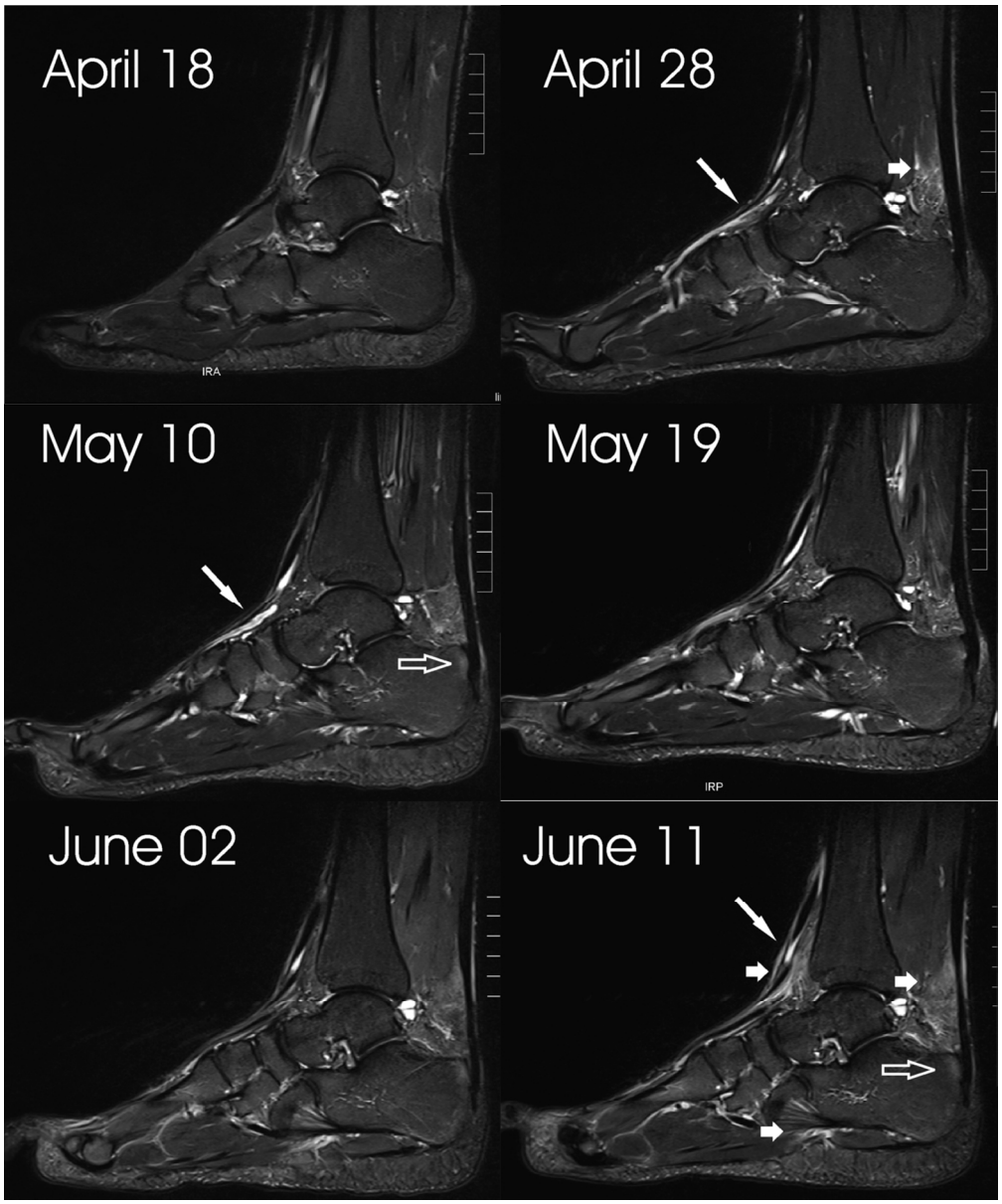

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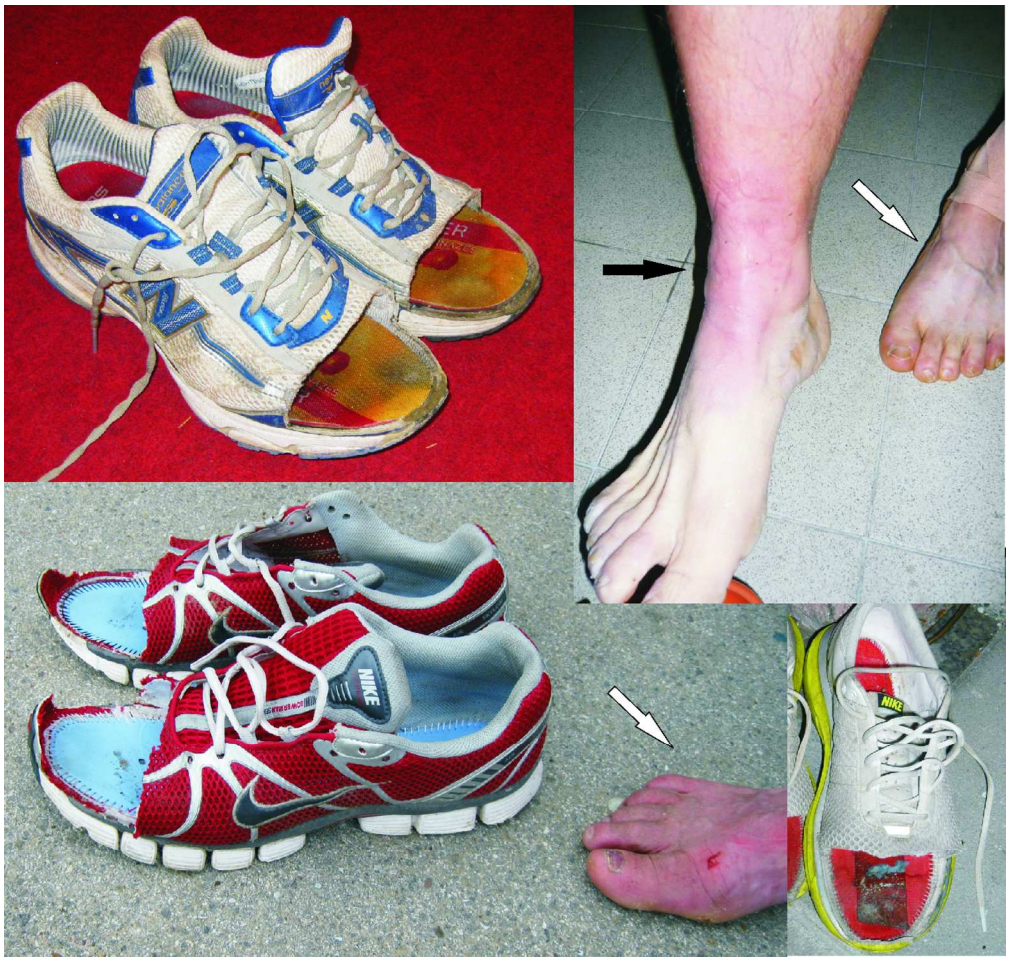
114x137mm (300 x 300 DPI)



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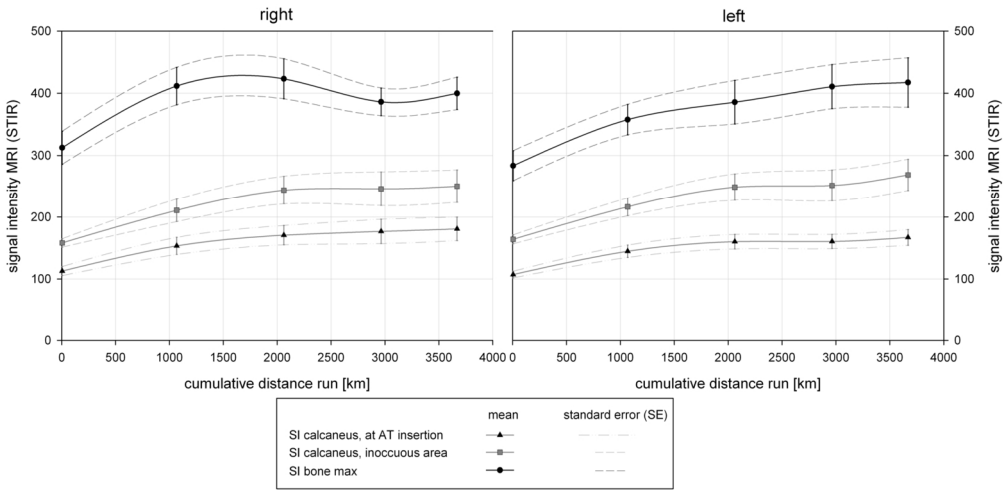

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141x68mm (300 x 300 DPI)

STROBE Statement—Items to be included when reporting observational studies in a conference abstract

Item	Recommendation
Title	Indicate the study's design with a commonly used term in the title (e.g cohort, case-control, cross sectional)
Authors	Contact details for the corresponding author
Study design	Description of the study design (e.g cohort, case-control, cross sectional)
Objective	Specific objectives or hypothesis
Methods	
Setting	Description of setting, follow-up dates or dates at which the outcome events occurred or at which the outcomes were present, as well as any points or ranges on other time scales for the outcomes (e.g., prevalence at age 18, 1998-2007).
Participants	*Cohort study*—Give the most important eligibility criteria, and the most important sources and methods of selection of participants. Describe briefly the methods of follow-up *Case-control study*—Give the major eligibility criteria, and the major sources and methods of case ascertainment and control selection *Cross-sectional study*—Give the eligibility criteria, and the major sources and methods of selection of participants
	Cohort study—For matched studies, give matching and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	Clearly define primary outcome for this report.
Statistical methods	Describe statistical methods, including those used to control for confounding
Results	
Participants	Report Number of participants at the beginning and end of the study
Main results	Report estimates of associations. If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Report appropriate measures of variability and uncertainty (e.g., odds ratios with confidence intervals
Conclusions	General interpretation of study results

BMJ open

The foot in multistage ultra marathon runners: Experience in a cohort study of 22 participants of the Trans Europe Footrace project with mobile MRI.

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The foot in multistage ultra marathon runners: Experience in a cohort study of 22 participants of the Trans Europe Footrace project with mobile MRI.

Short title: MRI based observation for foot lesions during a multistage ultra marathon.

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ABSTRACT

Objectives
67 runners participated in the Trans Europe FootRace 2009 (TEFR09), a 4487 km (2789 mi) multi stage ultra marathon covering the south of Europe (Bari, Italy) to the North Cape. Reports on ultra marathons are lacking, but the literature reports overuse injuries in athletes, especially to the Achilles tendon (AT), ankle or hind foot. Bone edema may be related to exposure and is present in fatigue fractures.
The aim of the study therefore was to determine prospectively if sustained maximal load during an ultra marathon leads to damage to the foot.

Design and Participants
In a cohort study, repeated scanning of the 22 athletes participating in the study was performed before and during (approximately every 1000 km) the race. Using the obtained fat saturated inversion recovery sequence, two experienced readers blinded to the clinical data rated the images regarding foot lesions. Statistical analysis included regression analysis and computation of the interrater reliability.

Setting
The TEFR09 course. MRI scanning was performed according to prearranged schedules for every participant, using a mobile 1.5 Tesla MRI unit on a trailer following the race.

Primary outcome measures
MRI data such as AT diameter, bone or tendon lesions, subcutaneous, plantar fascia or intraosseous edema.

Results
The 22 study participants did not differ significantly from the total of the 68 TEFR09 runners regarding height, weight and age.
The AT diameter increased significantly from 6.8 to 7.8 mm as did intraosseous signal, bone lesions and subcutaneous edema. However, finishers differed only regarding plantar aponeurosis and subcutaneous edema from participants aborting the TEFR09. Interrater reliability was 0.88-0.98.

Conclusions
Under the extreme stress of the TEFR09, an increase of the AT diameter as well as bone signal are thought to be adaptive, since only subcutaneous edema and plantar fascia edema were related to abortion of the race.

ARTICLE SUMMARY

Article focus:

- A study on effects of ultra marathon running, in this case the multi stage TransEurope FootRace covering 4487 km from Bari (Italy) to the North Cape.
- Observational cohort study using MRI to look for possible lesions to the foot.

Key messages:

- During sustained maximal load, Achilles tendon diameter and bone MRI STIR signal (hinting at subtle edema) increases. This is thought to be adaptive.
- Subcutaneous edema and plantar fascia signal were related to abortion of the race. These measurements seem to be related to relevant changes leading to discontinuation of the run.
- No relevant new foot joint or tendon lesions were detected during the race over 4487 km.

Strengths and limitations of this study:

- Repeated measurement prospectively during the run was possible only because of the mobile MRI unit used for this research project.
- The number of included runners (22) is high compared to other MRI based studies but may have been too small to detect less frequent lesions.

INTRODUCTION

In 2009 (April 19th to June 21th) the TransEurope FootRace 2009 (TEFR09) took place. It was the second European transcontinental multistage ultra marathon race and covered the distance from the south of Italy (Bari) to the North Cape. A collective of 67 endurance runners with a mean age 50.5 years (range 26 to 74) and consisting of 11 women and 56 men from 12 nations met the challenge. Their goal was to run the 4,487 km in 64 days without any day rest. Thus they expected to complete an average distance of 70.1 km resp. 1.7 marathon distances (min 44 km, max 95.1 km) on every stage for 64 consecutive days.[1]

The permanent overuse during such an ultra marathon especially endangers ankle and foot. While reliable reports on ultra marathon effects are lacking, the present literature describes overuse injuries [2, 3] in endurance sport and shows the Achilles tendon (AT) to be a structure of high risk because it is regularly injured in sports.[4, 5] Also, ankle and hind foot injuries are frequent among athletes,[6, 7] with visible bone edema even in asymptomatic individuals increasing their exposure.[8] Other reports show high rates of fatigue fractures in army recruits after exerting marches.[9, 10] To diagnose these sport related injuries, MRI is the diagnostic procedure of choice.[11-13] In most reports, MRI was performed with sagitally oriented fat saturated T2 weighted sequences.[14]

The present study with serial MRI before and during the run was performed under the hypothesis that long distance endurance runners are able to endure the race associated injuries and the accompanying pain but will nevertheless show changes in Achilles tendon and bones of the foot. We expected the changes to accumulate during the run. Also we expected that bone marrow edema will increase during the run but decrease during pauses. Furthermore we expected that participants aborting the race will have more severe lesions on MRI. Finally we were looking for predictive parameters (risk factors) indicating failure to complete the run.

PARTICIPANTS AND METHODS

Study participants

After approval of the local ethics committee and in accordance to the Declaration of Helsinki, the participants of the TEFR ultra marathon were recruited for the MRI based cohort study. The inclusion criterion for the ultra marathon group obviously was participation in the event, exclusion criteria were contraindications against MRI. Since MRI scanning time and the athletes' time was limited, only a part of the examinations concerned the foot region. Of the 44 athletes consenting to participate in the MRI project, 22 were randomized into the foot study. Their data will be presented here.

MRI acquisition

For each measurement, both feet were scanned consecutively with a dedicated foot coil that was table fixed with a boot-like design and 8-channel coils. MRI data were acquired with a mobile 1.5T MR scanner (Magnetom Avanto^{TM} mobile MRI 02.05, software version: Syngo^{TM} MR B15, Siemens Ltd., Erlangen, Germany) on a MRI-trailer travelling with the runners on the TEFR09 from stage to stage, day by day.

The MRI measurements were planned in a schedule for each participant, assuring equal distribution of measurements at all timepoints.
Every participant was scanned at a baseline time point 1 prior to the run and roughly every 1000 km or directly after abortion of the run. Schedules were made for time point 2 (day 17-22 at km 1131-1487), time point 3 (day 29-35 at km 1985- 2362), time point 4 (day 43-46 at km 2964-3161) and time point 5 (day 50 to 58 at km 3430-4037).

MRI sequences
The imaging sequence used in the reported study was a fat saturated short tau inversion recovery (STIR) sagittal sequence, resulting in a T2-weighted fat suppressed image with edema or effusion showing as increased signal. Sequence parameters were:
Slice thickness of 2 mm, repetition time was 8490 ms, echo time 60 ms, inversion time120 ms. Flip angle was 140°, echo train length 13, bandwidth130 Hz/voxel, the matrix was 512x512 (interpolated from 358x358), field of view 300x300 mm and time of acquisition was 3min 50s for each side.

MRI data measurements
Two researchers (experienced radiologists WF and US) without access to clinical data independently assessed the datasets at PACS workstations. All signal intensities were measured in a region of interest covering a volume of 25mm^2.
The measurements closely resemble the technique published earlier.[15]

The following measurements (see also table 1) were made on the sagittal MRI images:
The greatest anteroposterior diameter of the Achilles tendon (AT) and AT signal intensity at insertion. Also, signal intensity at mid tendon or at site of lesion, if a lesion is visible, and lesion distance from AT insertion were taken. The number of new lesions in comparison to the preceding examination was counted.
The signal intensity of the calcaneus at AT insertion and at a normally innocuous area in the middle between most cranial point of the posterior talocalcanear articular surface and the most caudal point of the lateral process of the calcaneus (see figure 1) was measured.
The highest intraosseous signal intensity in any bone of the foot was taken.
The number of bone bruises / subchondral or osseous lesions was noted.
The signal intensity of fascia plantaris was rated, taking note if there was edema or effusion (yes/no).
Also a possible bursa retrocalcanearis greater than 2 mm sagitally was noted (yes/no).
Any soft tissue signal intensity indicative of fasciitis, peritendonitis, subcutaneous edema (see figure 2) was noted (yes/no).

Finisher status
To allow discrimination between runners finishing the race and others aborting, their status F (finisher) or NF (non finisher) was recorded, also the stated cause (Table 2).

Time from finish of stage to MRI
Since it was hypothesized that bone marrow edema will increase during the run and decrease during rest (presumably lying down), the time from finish of the daily run to MRI scanning was recorded. For non finishers the time point has not been recorded

because they stayed at some checkpoint until transportation. Therefore, their last resting period was guessed to start at noon.

Interrater reliability

Interrater reliability was calculated on two measurements where previous data [15] had demonstrated good reliability: AT diameter and intraosseous signal intensity of the calcaneus (this time at the clearly defined "innocuous" location described above).

Statistical analysis

Data were analyzed using R. version 2.11.1, R Foundation for Statistical Computing, 2010.[16] Given the longitudinal nature of the test data, specialised regression models (linear mixed effect models) were applied. The package "nlme" [17] was used.

Univariate and multivariate regression analyses were performed.

Results were significant when p was < 0.05.

Taking into account the critique of Bland and Altman [18] concerning the correlation coefficient to calculate the interrater reliability, we decided to use lambda as proposed by Jepsen et. al.[19] Lambda can be calculated as follows: $\lambda = \frac{2 \cdot VAR_X - VAR_D}{2 \cdot VAR_X}$.

VAR denotes the variance of the measurements X and D the difference of the measurments of the two raters. The interrater-reliability is rated as low for λ < 0.25. Values up to .5 are rated as fair, .5-.75 as moderate to good and λ > 0,75 demonstrates good to excellent reliability.[20]

RESULTS

Study participants

The TEFR09 participants comprised 57 men and 11 women, aged 26 to 74 years with a mean of 50.5 and a standard deviation (SD) of 10.5 years. They had a body height of 1.75 m (SD .08) and weight of 70.6 kg (SD 9.5).

Out of the total, 22 participated in this experiment. 2 were female and 20 male with a mean age of 49.1 years (11.5) at the time of the first MRI scan. They were 1.74 m (.09) tall and weighed 70.9 kg (11.3). The differences of the biometric markers of our sample to the whole group were not significant (t-test p= 0.6 - 0.9).

Exemplary measurements are shown in figure 1. The evolution of soft tissue and osseous edema is depicted in figure 2 and foot swelling as well as resulting shoe modifications are shown in figure 3.

MRI measurements

The predefined parameters were taken on the MRI examinations. The resulting measurements are detailed in table 1. The evolution of intraosseous signal intensities is depicted in figure 4.

Table 1: Measurements of MRI parameters and correlation with distance run

Time from stage finish to MRI examination

There was no significant effect of the time elapsed between stage finish and scanning (i.e. the length of the resting period before the scan, spent lying down and

thus decreasing potential edema) on the measured MRI parameters to be found in univariate and multivariate regression analyses.

Side differences
Looking for significant side differences in the observed measures, the following were found to be larger on the right side: Signal intensity of the AT at insertion (p=0.04), the number of bone lesions (0.002), the signal intensity of the plantar aponeurosis (0.03). The distance to an AT lesion from the point of calcanear insertion (p=0.04) was larger on the left side.

Differences between finishers and non finishers
21 athletes out of 67 participants had to exit the race. Out of the 22 participants in our study, 13 (59.1%) completed our study, while 12 finished the TEFR09, and 10 aborted the run. The athlete who finished our study (participation in the MRI at time point 5) but had to abort the race afterwards because of a hand phlegmonia has been counted as not aborting for our study, since the cause for abortion was not related to a problem of the feet and the measurements are thought to be independent from the later evolution of a hand phlegmonia.
The rate of abortion didn't differ significantly between the total and our study participants. The stated causes are listed in table 2. Most of the problems occurred in the lower legs (shin splint and perimyositis).
F and NF showed significant differences at the beginning of the TEFR09 only in the signal intensity of the plantar aponeurosis (p=0.03).
During the run, there were significant differences in the evolution of edema of the right plantar aponeurosis (p=0.02) and subcutaneous edema of the right (0.05) and left side (0.04), with NF showing higher rates of edema.

Interrater reliability
The interrater reliability was calculated for the diameter of the AT as well as the Signal intensity of an innocuous region of the calcaneus. The lambda values were for AT diameter of the right /left side 0.95 / 0.88 and for the signal intensity of the normally inoccuous region of the calcaneus on the right/ left side 0.97 / 0.98 respectively.

DISCUSSION
The TEFR09 participants had to endure an immense physical exposure, leading to stress fractures, swollen feet, sometimes necessitating cutting away part of the running shoe in order to continue running,[1] but 46 out of 67 (68.7%) were able to finish. Our study participants showed changes during the run with an increase of the AT diameter and intraosseous signal intensity as well as subcutaneous edema. Non finishers displayed higher rates of soft tissue edema.

We had hypothesized that runners will show increasing pathology of hindfoot and ankle as well as AT during the run even if they are able to finish the TEFR09.
The literature up to date had been inconclusive as to the consequences of marathon training, including our own data[15] that had shown little changes in MRI appearance of the hindfoot and AT during training and participation of a (half) marathon.
However, the TEFR09 with extended running load over 64 stages without any day rest is not comparable to other sporting events or normal leisure activities.
The results show a gradual increase of the diameter of the AT from a mean of 6.8 to a mean of 7.8mm over the course of the run. This stands in contrast to reports linking

AT diameter to disease[21] or showing decrease of AT diameter with training.[22] However, the results match with previous data on runners[23] and healthy marathoners[15] or reports stressing the relevance of AT signal intensity SI[24] or calcaneus edema at tendon insertion[25] for pathology. No significant correlation could be shown to tendon signal intensity or lesions or calcaneus bone edema at tendon insertion, further strengthening the point that the observed AT changes seem to be adaptive.

Furthermore, gradual increases over the run in osseous signal of the calcaneus as well as the maximal intraosseous signal in any foot bone and the number of bone lesions could be shown (see figure 4).
The increased signal intensity draws attention to reports on stress fractures,[9, 10] but the appearance of the recorded alterations in our study occurred early and didn't coincide with stress fractures. Thus the signal increase is thought to result from stress response[12] as reported in asymptomatic runners.[8, 26-28] Sometimes diffuse bone edema in nearly all end phalanges pointed to contusions because of tight shoes. However, bone edema and lesions were not linked to abortion of the run (NF status).

Also, increases in subcutaneous edema occurred over the course of the run (see figure 2). Here, subcutaneous edema at the time of the start of TEFR09 was rare with around 5% (see table 1), while it rose sharply at time point 2 (after a mean of 1068km) to ca. 65% and increased only moderately to ca. 70% at time point 5 (after a mean of 3669km). This corresponds to the sometimes grotesque swelling of runners' feet, necessitating cutting of running shoes to resemble crude sandals (see figure 3).

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.

We had hypothesized that bone edema and the corresponding SI would decrease during rest (lying down). However, our data showed no correlation of the resting time to the SI. So the observed bone edema seems to reflect true load effects and not simple hydrostatic changes.

We had expected to see more severe lesions in NF than in F and had hoped to find risk factors or predictive parameters for NF. Here, significant differences could be shown only for soft tissue parameters: At the beginning of the TEFR09 only the SI of the left plantar aponeurosis was significantly higher in NF, pointing to possible overload even before the start. During the run, NF showed significantly more subcutaneous edema and edema of the (right) plantar aponeurosis. This may indicate that soft tissue edema is more relevant to the possible abortion of the run than the intraosseous changes described above or tendon problems. Especially the signal alterations in the plantar aponeurosis point to plantar fasciitis, a problem thought to be the main cause of inferior heel pain in runners and is detected easily by MRI.[37]

Considering clinical data on abortion of the run (see table 2), the stated soft-tissue related causes refer mainly to the legs (mostly shin splint and perimyositis). These regions were not included in the current investigation. However, it is probable that edema related to shin splint or perimyositis had spread along the lower legs to the foot, so that the visible subcutaneous edema was not directly related to a pathology in the foot.

With lambda values between 0.88 and 0.98, the interrater reliability can be rated as excellent.[20]

~~Limitations~~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 chance to observe an event like the TEFR09 with a mobile MRI scanner had been great, but the difficulties of tight schedules of the athletes prohibited greater numbers.
Poor infrastructure and difficult local situations at the stage destinations sometimes made a nearby commissioning of the mobile MRI impossible. However, the strongest influence forcing the staff to change and adapt their research work daily, was the athlete himself, with his individual personality and more or less daily changing mental and physical condition and necessities: pain, injuries, fatigue, fears, doubts, illness, regeneration program and nutrition plan.
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.
The inclusion of 22 runners permitted detailed examinations but the number may have been too small to detect factors distinguishing NF. However, the study sample of 22 athletes had been randomized out of all participants, their biometric data shows that they are representative of the whole group of TEFR09 participants. So their results may be generalized.

Concluding:
During the TEFR09 and under extreme stress, adaptive changes like the increase of the AT diameter could be detected with MRI as well as signs of soft tissue overload with swelling and edema. The meaning of the SI increase of the foot bones is thought to resemble a stress response, but is not correlated to abortion of the race or development of stress fractures during the observed transcontinental multistage ultramarathon.

Competing interests
None.

Trial registration
University of Ulm, Germany Ethics Committee Nr. 78/08-UBB/se.

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Data sharing statement
No additional data available.

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Contributorship
WF designed the study, read the images and planned the statistical analysis. He wrote the manuscript and approved the final manuscript.
US designed the study, acquired the MRI data, read the images and critically revised the manuscript and approved the final manuscript.
FW designed and performed the statistical analysis. He wrote parts of the manuscript and approved the final manuscript.
CB designed the study, acquired the MRI data and critically revised the manuscript and approved the final manuscript.
Also, MRI scanning was performed by Heike Wiedelbach.

Tables

Table 1: Measurements of MRI parameters and correlation with distance run.
For quantitative data the mean (with standard error SE) is given, for qualitative data the percentage of positive measurements (mean over both readers).
Correlation with distance run: P is calculated by a univariate regression model with the parameter in question as the dependent variable and total distance as the independent variable. Statistically significant correlations are in bold script.

time point / Parameter	side	1	2	3	4	5	correlation with distance run
mean days run		0.1	15.5	29.1	42.8	52.5	
mean distance run, in km (in miles)		5 (3.2)	1068 (664)	2062 (1282)	2964 (1842)	3669 (2280)	
AT diameter (SE)	right	6.8 (0.37)	7.2 (0.44)	7.6 (0.54)	7.8 (0.53)	7.8 (0.55)	**<0.001**
	left	6.8 (0.39)	7.3 (0.49)	7.6 (0.53)	7.7 (0.60)	7.8 (0.66)	**<0.001**
SI at insertion of AT	right	32.4 (3.96)	38.5 (5.39)	40.0 (6.49)	42.1 (7.08)	39.2 (7.43)	0.6
	left	30.4 (1.80)	31.8 (2.72)	28.5 (1.50)	32.2 (2.37)	29.5 (1.77)	0.5
SI in the middle of the AT	right	35.9 (2.72)	42.9 (6.03)	45.5 (4.94)	42.2 (6.52)	47.9 (8.97)	0.05
	left	38.3 (3.92)	41.1 (5.28)	36.4 (3.06)	36.7 (3.80)	34.1 (5.42)	0.7
New lesions in the AT	right	NA	0.06	0.15	0	0	0.33
	left	NA	0.03	0	0.09	0	0.7
Distance of the lesion to the insertion of the AT	right	12.7 (4.02)	15.6 (5.19)	16.5 (3.52)	15.8 (4.23)	11.9 (6.03)	
	left	21.8 (4.57)	21.5 (2.50)	26.2 (6.19)	24 (6.03)	19	
SI in the calcaneus at the AT insertion	right	112.8 (7.30)	153.3 (13.80)	170.6 (15.66)	176.8 (19.66)	180.1 (18.97)	**<0.001**
	left	107.2 (5.38)	144.7 (9.90)	160.2 (11.70)	160.5 (11.54)	167.0 (12.65)	**<0.001**
SI in an inoccuous area of the calcaneus	right	158.2 (6.78)	210.8 (18.25)	243.9 (22.59)	246.1 (27.49)	250.2 (26.43)	**<0.001**
	left	164.0 (7.20)	216.4 (14.38)	248.8 (21.45)	251.5 (25.1)	268.6 (25.33)	**<0.001**
Maximal SI in any bone	right	312.5 (26.58)	411.7 (30.17)	423.3 (32.14)	386.2 (22.29)	399.9 (26.10)	**0.003**
	left	283.4 (24.29)	357.7 (24.59)	385.8 (35.06)	410.7 (35.43)	417.3 (39.79)	**<0.001**
Number of bone lesions	right	2.1 (0.6)	3.2 (0.62)	3.5 (0.58)	3.2 (0.59)	3.6 (0.61)	**0.016**
	left	2.3 (0.44)	2.4 (0.43)	2.3 (0.45)	3.1 (0.54)	3.2 (0.55)	**0.002**
SI in the plantar aponeurosis	right	25.4	28	27.9	33.7	34.8	0.4

		(4.95)	(5.79)	(6.59)	(8.86)	(9.54)	
	left	21.4 (1.31)	22.4 (1.29)	22.3 (1.31)	22.1 (2.14)	20.9 (1.37)	0.2
Edema in the plantar aponeurosis (y/n)	right	0.07	0.06	0.09	0.11	0.12	0.9
	left	0	0	0	0.04	0	n.a.
Retrocalcanear Bursa (y/n)	right	0.07	0.19	0.18	0.14	0.15	0.8
	left	0.03	0.21	0.24	0.18	0.12	0.3
Subcutaneous edema (y/n)	right	0.05	0.64	0.65	0.79	0.81	**<0.001**
	left	0.07	0.68	0.61	0.64	0.65	**<0.001**

Table 2: Stated causes for abortion of the run in participating Athletes.

Athlete	Pathology
1	Perimyositis of the thigh
2	Stress fracture of the tibia
3	Hallux valgus / bunion
4	Phlegmonia of the hand
5	Shin splint
6	Perimyositis of the lower leg
7	Perimyositis of the thigh
8	Shin splint
9	Perimyositis, gluteal and shin splint bilateral
10	Shin splint

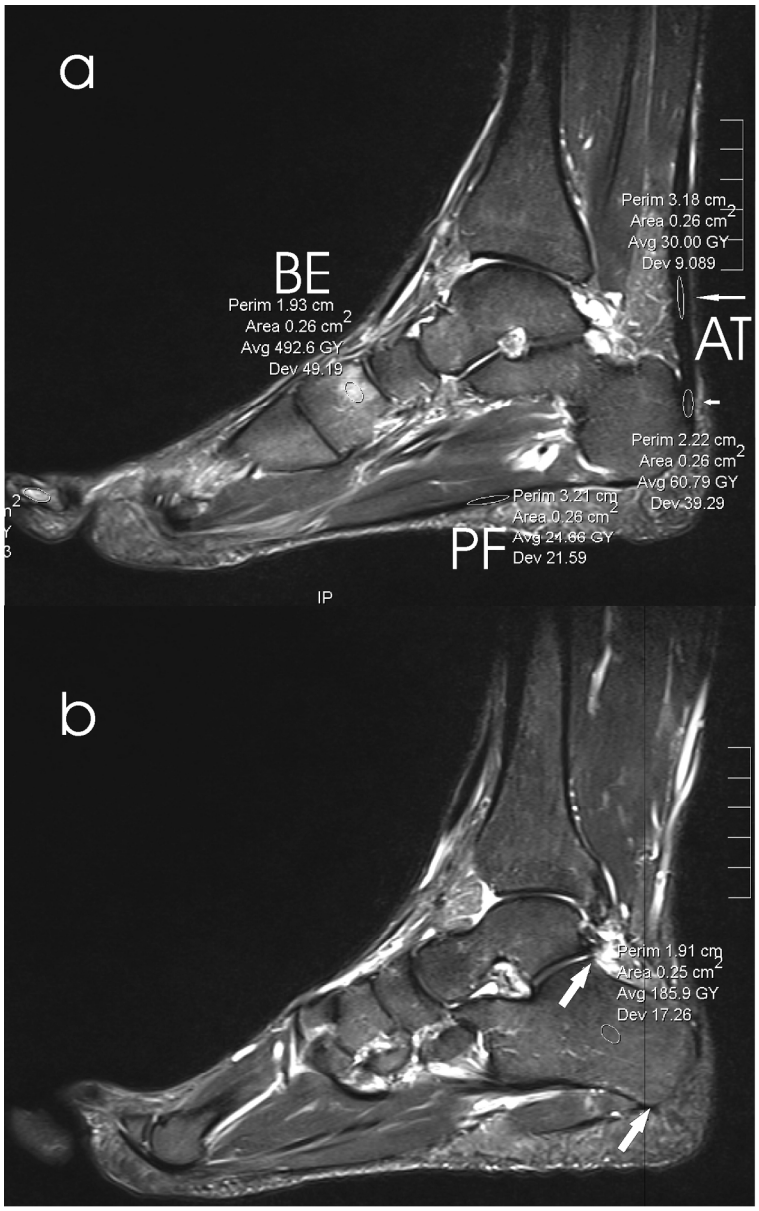
Legends

Figure 1: Measurements of MRI parameters on a sagittal STIR weighted MRI scan.
a)
PF: The measurement in the plantar fascia.
BE: Bone edema (in the medial cuneiform bone)
Short and long arrows pointing to measurements in the Achilles tendon (AT). The short arrow points to a intratendinous lesion near the insertion, the long arrow points to a inoccuous area situated cranially.
b)
The measurement of the normally inoccuous region of the calcaneus is placed between the most cranial portion of the posterior talocalcanear facet and the most caudal point of the lateral process of the calcaneus (see arrows and round measurement site).

Figure 2: Subcutaneous edema on a sagittal STIR weighted MRI scan.
The six dates represent different MRI measurements of the same foot of one TEFR09 participant, each with identical window settings.
The long diagonal arrow points to tubular high intensity structures, probably corresponding to peritendinous fluid.
The short arrow points to subcutaneous edema and edema in Kager´s fat pad of the AT.
The translucent arrow points to intraosseous signal near the AT insertion evolving later than the subcutaneous edema.

Figure 3: Makeshift sandals.
Subcutaneous edema resulting in ankle (black arrow) and foot swelling (white arrows) necessitated cutting away parts of the shoes, creating makeshift sandals to accommodate the athletes' feet.

Figure 4: Figure 4: Intraosseous signal intensity in the time course of the TEFR09.
Signal intensity measurements in the calcaneus at AT insertion (black triangles), in a normally inoccuous area of the calcaneus (gray squares) and at the individual´s area of the highest intraosseous signal (black dots) are shown together with the standard error values. The measurements were performed at several time points during the TEFR09. The cumulative distance run is shown below the graph.



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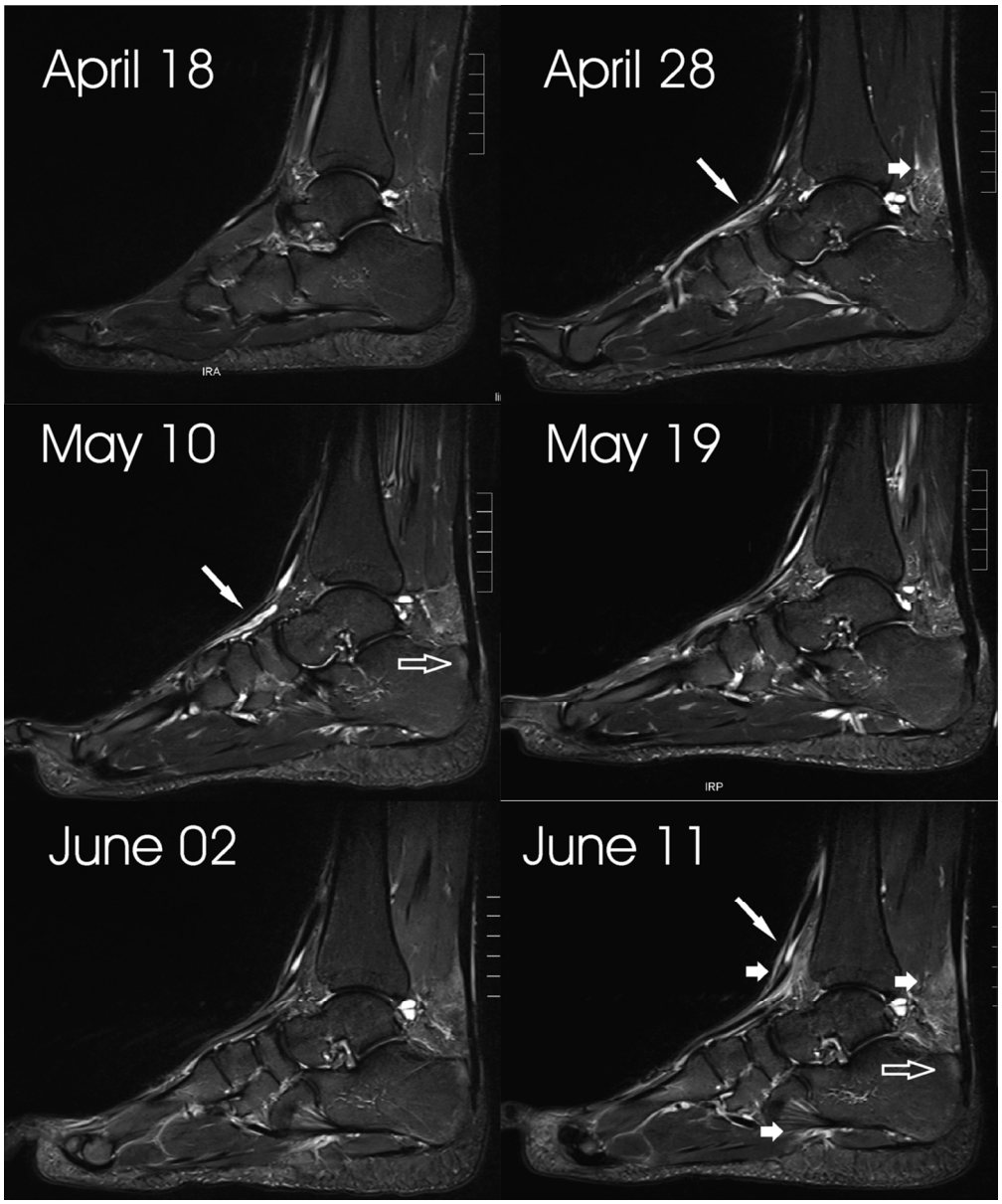

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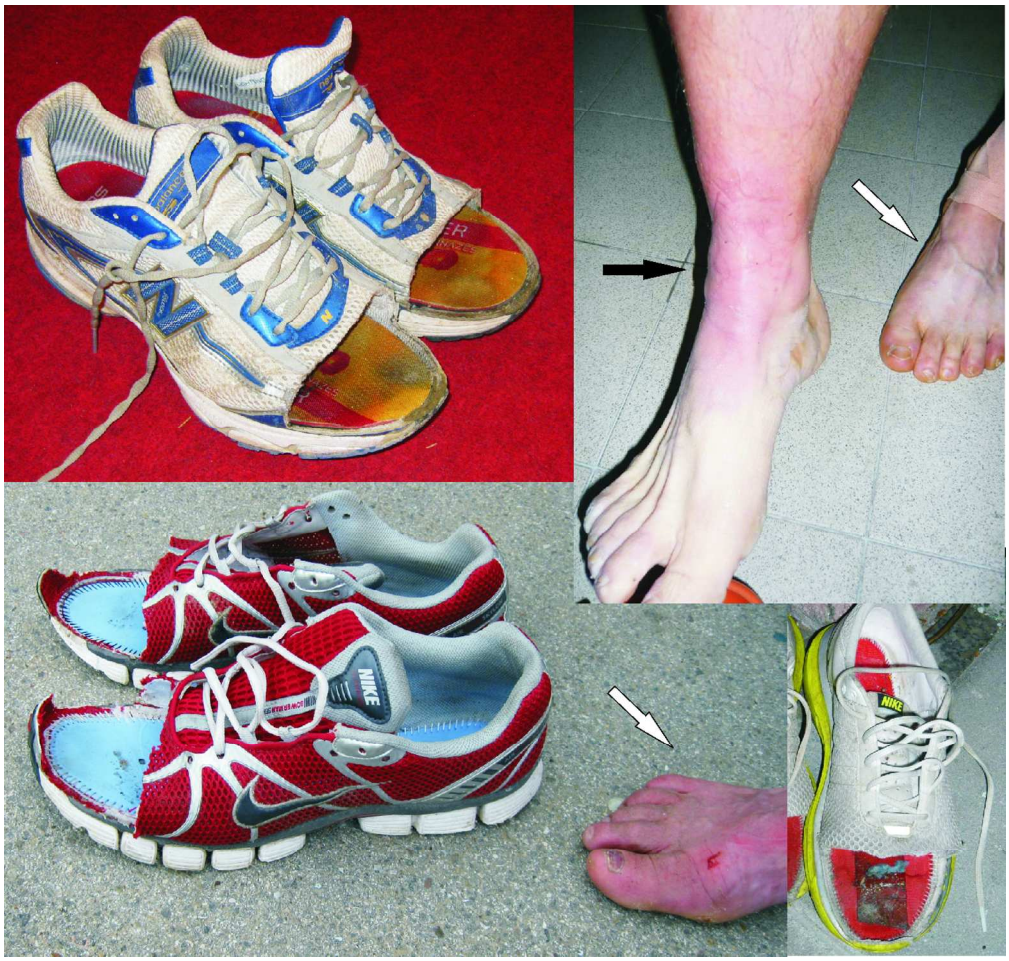
The translucent arrow points to intraosseous signal near the AT insertion evolving later than the subcutaneous edema.
114x137mm (300 x 300 DPI)



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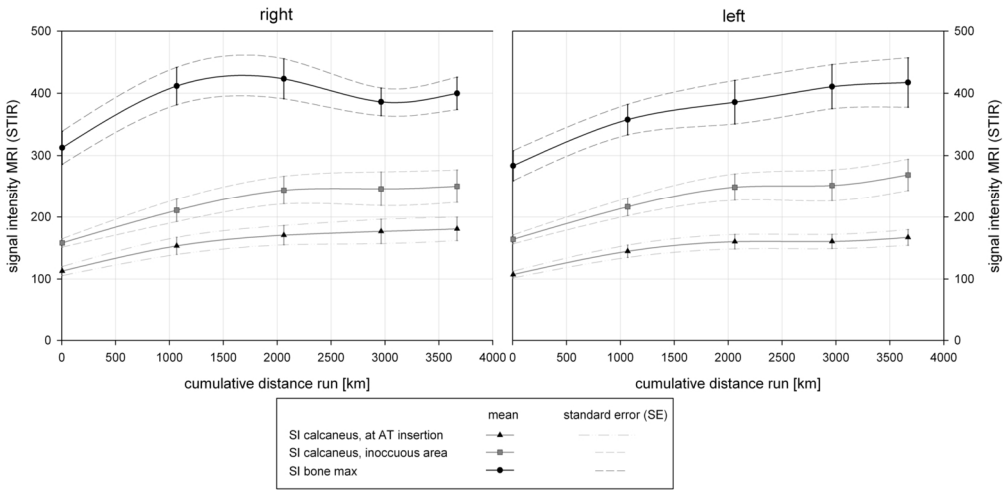

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141x68mm (300 x 300 DPI)

STROBE Statement—Items to be included when reporting observational studies in a conference abstract

Item	Recommendation
Title	Indicate the study's design with a commonly used term in the title (e.g cohort, case-control, cross sectional)
Authors	Contact details for the corresponding author
Study design	Description of the study design (e.g cohort, case-control, cross sectional)
Objective	Specific objectives or hypothesis
Methods	
Setting	Description of setting, follow-up dates or dates at which the outcome events occurred or at which the outcomes were present, as well as any points or ranges on other time scales for the outcomes (e.g., prevalence at age 18, 1998-2007).
Participants	*Cohort study*—Give the most important eligibility criteria, and the most important sources and methods of selection of participants. Describe briefly the methods of follow-up *Case-control study*—Give the major eligibility criteria, and the major sources and methods of case ascertainment and control selection *Cross-sectional study*—Give the eligibility criteria, and the major sources and methods of selection of participants
	Cohort study—For matched studies, give matching and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	Clearly define primary outcome for this report.
Statistical methods	Describe statistical methods, including those used to control for confounding
Results	
Participants	Report Number of participants at the beginning and end of the study
Main results	Report estimates of associations. If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Report appropriate measures of variability and uncertainty (e.g., odds ratios with confidence intervals
Conclusions	General interpretation of study results