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REVIEW

Risk factors associated with medial tibial stress syndrome in runners: a systematic review and meta-analysis

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Background: Medial tibial stress syndrome (MTSS) affects 5%–35% of runners. Research over the last 40 years investigating a range of interventions has not established any clearly effective management for MTSS that is better than prolonged rest. At the present time, understanding of the risk factors and potential causative factors for MTSS is inconclusive. The purpose of this review is to evaluate studies that have investigated various risk factors and their association with the development of MTSS in runners.

Methods: Medical research databases were searched for relevant literature, using the terms "MTSS AND prevention OR risk OR prediction OR incidence".

Results: A systematic review of the literature identified ten papers suitable for inclusion in a meta-analysis. Measures with sufficient data for meta-analysis included dichotomous and continuous variables of body mass index (BMI), ankle dorsiflexion range of motion, navicular drop, orthotic use, foot type, previous history of MTSS, female gender, hip range of motion, and years of running experience. The following factors were found to have a statistically significant association with MTSS: increased hip external rotation in males (standard mean difference [SMD] 0.67, 95% confidence interval [CI] 0.29–1.04, $P<0.001$); prior use of orthotics (risk ratio [RR] 2.31, 95% CI 1.56–3.43, $P<0.001$); fewer years of running experience (SMD −0.74, 95% CI −1.26 to −0.23, $P=0.005$); female gender (RR 1.71, 95% CI 1.15–2.54, $P=0.008$); previous history of MTSS (RR 3.74, 95% CI 1.17–11.91, $P=0.03$); increased body mass index (SMD 0.24, 95% CI 0.08–0.41, $P=0.003$); navicular drop (SMD 0.26, 95% CI 0.02–0.50, $P=0.03$); and navicular drop >10 mm (RR 1.99, 95% CI 1.00–3.96, $P=0.05$).

Conclusion: Female gender, previous history of MTSS, fewer years of running experience, orthotic use, increased body mass index, increased navicular drop, and increased external rotation hip range of motion in males are all significantly associated with an increased risk of developing MTSS. Future studies should analyze males and females separately because risk factors vary by gender. A continuum model of the development of MTSS that links the identified risk factors and known processes is proposed. These data can inform both screening and countermeasures for the prevention of MTSS in runners.

Keywords: medial tibial stress syndrome, injury prevention, risk factors, running injuries

Background

Medial tibial stress syndrome (MTSS) is usually brought on by running or impact loading of the lower limb, and the resulting pain will typically limit running activity. MTSS is generally considered to be a discrete clinical entity that is differentiated from chronic exertional compartment syndrome, stress fracture, popliteal artery entrapment syndrome, and the various neuropathies. Coexistence and interrelationships of these entities is acknowledged but not clearly understood.[1] Inconsistent use of terminology,

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such as "shin splint syndrome" and "soleus enthesopathy", is evident in the historic and current literature, and it is likely that such variation in nomenclature has contributed to the current lack of understanding of the condition.[2,3]

A range of hypotheses has been proposed in regard to the anatomic structures most likely to be the source of pain in MTSS, with myofascial strain, enthesopathy, periosteal inflammation, and bone stress reaction theories most prevalent. Histologic studies have been small, and very few have identified inflammatory markers within the periosteal margins with any consistency to support the periostitis hypothesis.[4–7]

Cadaveric studies of the myofascial anatomy are inconsistent as to which myofascial element is involved.[8–11] There is large variation in the site of attachment of the deep crural fascia, soleus, flexor digitorum longus, and tibialis posterior, and there is contention about how well these attachments relate to the site of pain in MTSS. One larger study (50 legs) found a predominant absence of myofascial attachment at the medial tibial border where MTSS pain occurs.[11] However, posteromedial muscular tenderness is a consistent clinical feature of the syndrome. It may be that this tenderness is a consequence of muscular overuse and chronic fatigue. Whether this is a primary cause or an effect of the condition remains unclear.[12,13]

Recent interpretation arising from imaging and related studies suggests bone stress reaction to be the most likely cause of symptoms in MTSS.[14–20] Advances in computed tomography, dual energy X-ray absorptiometry, and magnetic resonance imaging techniques have enabled researchers to identify marrow edema consistently, periosteal lifting due to underlying bone exudate, and bony resorption of the posteromedial tibial border in MTSS. The accuracy of the different techniques varies greatly and may be dependent on the timing of imaging in relation to injury onset.[21,22] Only a limited number of histologic studies have included bone biopsy, but these positively confirm bone stress markers.[6,7] Some imaging studies demonstrate bony lesions associated with a clinical diagnosis of MTSS in sites such as the proximal tibia and the anterolateral tibial cortex, that are inconsistent with clinically significant sites of pain,[3,19] and this raises questions about the differential diagnosis of MTSS as well as about the nature of the pathology itself.

It is probable that a combination of structures are involved in MTSS, and some authors have suggested grading systems based on this premise (Figure 1).[1] A clear understanding of the pathology is needed for future studies, and particularly in regard to the development of targeted intervention strategies.

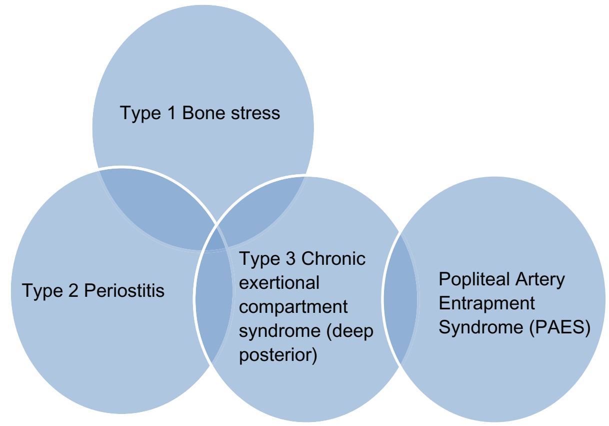

Figure 1 Traditional differential diagnosis and classification of medial tibial stress syndrome.
Note: Concept from Detmer.[1]

Recovery times in MTSS tend to be long. A recent randomized controlled trial found that subjects from a nonmilitary sample of runners, in 3 treatment groups, took an average of 102–118 (SD 52–64) days to recover sufficiently to complete an 18-minute run.[23] Times between 250 and 300 days were taken for 90% of these participants to recover sufficiently to complete an 18-minute run. This timeframe should influence most clinicians' prognostic planning and education of patients. Trials investigating a range of interventions for MTSS have not as yet established any clearly effective management that is better than prolonged reduction and management of load.[2,23–25]

Several authors have sought to investigate the risk factors associated with the condition with a view to developing screening and preventive countermeasures for MTSS. The variables investigated in these studies fall into categories of range of motion (ROM) and muscle length measures, including joints from hip to hallux, static posture of lower limb segments, kinematic analyses of the lower limb, muscle strength and endurance, running volumes, anthropometric measures, dietary, hormonal, and smoking status, past history of injury, and orthotic and shoe use (Table 1). The majority of the papers that have reported investigations of these associations have been case-control or retrospective in design, thus raising questions about the attribution of cause and effect.

To the present time, no meta-analysis has been performed to investigate the associations of various risk factors and the prospective development of MTSS. Therefore, the aim of this review was to identify quality prospective studies that have investigated risk factors for MTSS in runners and to combine their results through meta-analysis.

Table 1 Risk factors investigated for association with MTSS in runners in the literature

Risk factor	References
Hip ROM	31,38,70–73
Ankle ROM	12,31,34,38,70–74
Knee ROM	38,71–73
Rear/forefoot ROM	34,38,70–73
Hallux ROM	72–74
Hamstring length, gastrocnemius length, soleus length	38,73–75
Leg length	70,74,76
Q angle	31
Tibial varus/valgus	34,38,75
Static genu varus/valgus	31,38,71,76
Static calcaneal varus/valgus, standing foot angle qualitative and instrumented	38,71,73,75,76
Static arch height/Foot Posture Index[32]/foot typing	12,70,71,76,77
Navicular drop test/navicular drop test difference/navicular drop test >x	31,34,37,38,73,75,78
Dynamic genu varus/valgus	37,38,72
Dynamic calcaneal varus/valgus	33,35,37,38,72
Dynamic plantar pressure plate data: pronated versus supinated at various phases of gait, time to peak heel rotation	33,35,37,38,72,74
Plantar flexor endurance	78,79
Strength PF/DF/inversion/eversion	34,38
Strength hip abduction	31,38,73
Lean calf girth	70,73
Mileage per unit time (weeks, months)	34,77
Running experience years	34,75,77,80
Run times per unit distance/fitness	33,70
Time per week running	12
Previous history of MTSS	12,34,78,80
Previous history of stress fracture	34,78
Previous history of lower leg injury	34,77,78
Orthotic use	34,70,78,80
Menstrual regularity	34
BMI	31,33,70,77,78,80
Gender	13,31,75,78,80
Height	31,33,70,80
Shin pain on palpation in asymptomatic MTSS	13
Shin edema on palpation in asymptomatic MTSS	13
Claw toe	53
Neuromuscular control deficit of intrinsic foot muscles	46,47,53
Straight leg raise	31
Smoking	33

Abbreviations: BMI, body mass index; PF, plantar flexion; DF, dorsiflexion; MTSS, medial tibial stress syndrome; ROM, range of motion.

Methods

Criteria for considering studies for this review

Types of studies

We selected papers that were of prospective design and investigated a range of biometric variables and their associations with MTSS. Explicit criteria for diagnosis of MTSS had to be described in each paper with sufficient detail to exclude stress fracture and ischemic causes. All participants in all papers were runners or played sports that were running-based. All participants had to be asymptomatic at the time of baseline testing.

To enable calculation of combined results, the papers included had to report MTSS group and non-MTSS group scores, standard deviations, and sample sizes, or sufficient alternative data for these to be calculated. Categorical data had to include the sample sizes in each matrix cell.

Quality of the papers was assessed using a combination of the Quality Index[26] and Revman5 (Cochrane) criteria (see Figure 2). Each criterion was applied to each paper, and a classification of "low-risk" was assigned where the paper had clearly met the criterion. "Unclear risk" was assigned where there was insufficient detail to determine if the criterion was met or not, and "high-risk" where the criterion was unlikely to be met or bias was highly likely.

Types of participants

The 1,924 participants in the final selection of studies included runners from military and recreational groups, and tennis, volleyball, track and field, and soccer players.

Electronic searches

The CINAHL, SPORTDiscus, Pedro, PubMed Central, and Cochrane databases were searched using keyword search terms (keyword contains "medial tibial stress syndrome"

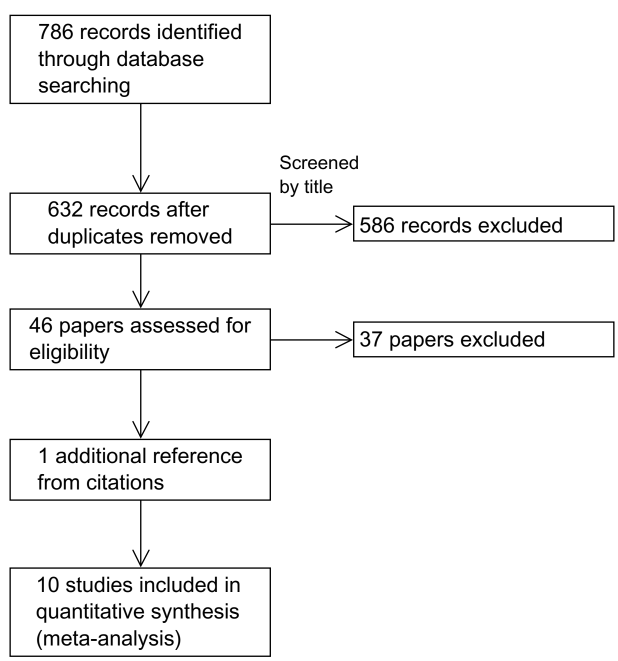

Figure 2 Papers selected from initial search to final inclusion.

AND keyword contains "prevention" OR "risk" OR "prediction" OR "incidence"). No date limits were applied and the search was completed in March 2013. The resulting references from each database search were combined.

Papers were filtered in accordance with the sequence in Figure 2.

Data extraction and management

Each included paper was searched for raw scores and group numbers for a range of measured risk factors. Where two or more papers reported the same type of risk factor or measure, the results were combined and analyzed using Review Manager (RevMan version 5.2; Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Standard mean differences (SMDs) or pooled risk ratios (RRs) were generated to determine the pooled effect size of each risk factor. The random effects model was applied when I^2 tests for heterogeneity were moderate to high (>25%).[27] When heterogeneity was low (≤25%), fixed effects modeling was applied. Effect sizes for each continuous variable were defined as trivial (0–0.2), small (0.2–0.6), moderate (0.6–1.2), large (1.2–2.0), or very large (>2.0).[28] Effect sizes for each RR were likewise defined as trivial (1–1.2), small (1.2–1.9), moderate (1.9–3.0), large (3.0–5.7), or very large (>5.7).[28]

The *P*-value for significance of the pooled effects analyses was set at ≤0.05. Funnel plots were constructed where four or more studies were included in the meta-analysis to assess the influence of publication bias when the *P*-value was ≥0.05. The study authors were emailed to request original data when raw scores or group data were not recorded in the paper; however, no additional data were made available to be included in meta-analyses.

Results

Description of studies

The initial database search found 768 articles that matched the search terms. After predefined exclusion criteria were applied, ten papers were identified for meta-analysis (Figure 2). Studies excluded at the abstract review or full text review stage were either retrospective or case-control designs that would be unable to differentiate cause or effect relationships. The risk of bias in these papers was high due to failure to blind assessors. Some papers were excluded due to nonspecific differentiation of lower leg pain and MTSS. Some variables within the final ten papers were collected only at diagnosis, so these variables were not analyzed. The quality of the final ten papers was high against the criteria applied (Figure 3). A total of 13 variables were able to be pooled for analysis (Table 2).

Risk factors and associations with MTSS

Navicular drop

Four papers reported results of the navicular drop test measured in millimeters. This is a test that measures the difference in height of the navicular tuberosity in the subtalar neutral stance position and the height of the navicular tuberosity in relaxed stance.[29,30] Three of the four papers measured navicular drop with feet shoulder width apart, and one paper performed the measurement in tandem stance position.[31] This test was found to be significantly associated with MTSS injury (SMD 0.26, 95% confidence interval [CI] 0.02–0.50, *P*=0.03, Figure 4). The meta-analysis indicates that a larger navicular drop is associated with increased risk of MTSS.

Navicular drop >10 mm

Two papers evaluated a dichotomous variable of navicular drop greater than 10 mm. This test was found to be significantly associated with MTSS injury (Figure 5). Those with a navicular drop >10 mm are 1.99 times more likely to develop MTSS than not (RR 1.99, 95% CI 1.00–3.96, *P*=0.05). The meta-analysis also indicates that a larger navicular drop is associated with increased risk of MTSS.

Pronated foot type

Three studies reported classification by foot type in their papers. In two studies, this was done using either all or part of the Foot Posture Index.[32] The Foot Posture Index aggregates categorical scores from six domains of foot classification, ie, talar head palpation, malleolar curve, calcaneal position, prominence of talonavicular joint, congruence of medial longitudinal arch, and abduction/adduction of the forefoot on rearfoot. Aggregated scores are then used to classify the foot into pronated, normal, or supinated categories. In a study reported by Sharma et al,[33] foot type was classified according to pressure plate data that determined proportion of medial to lateral foot pressure during a barefoot walking task. For the purposes of this analysis, the results were pooled and compared on a derived dichotomous variable of "pronated" or "not pronated". This measure was not found to be a significant predictor of MTSS (RR 1.61, 95% CI 0.37–6.98, *P*=0.52)

Orthotic use

Three of the papers included in this review surveyed participants on their prior orthotic insole use. A total of 403 participants were surveyed. Those who had used

	Diagnostic criteria for MTSS explicit	Hypothesis clear	Population described	Population distribution described	Main findings clearly described	Random variability estimated	Actual probabilities reported	Valid sample invited subjects	Valid sample willing subjects	No retrospective data dredging	Statistics appropriate	Main measures valid and reliable	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)
Bennett et al[75]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bennett et al[78]	?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Burne et al[70]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hubbard et al[34]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Newman et al[13]	+	+	+	+	+	+	+	+	+	+	+	?	+	+	+	+	+
Plisky et al[80]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Reinking et al[77]	−	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	?
Sharma et al[33]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Yagi et al[31]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Yates and White[12]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Figure 3 Risk of bias summary: reviews authors' judgments about each risk of bias item for each included study.
Note: Green = low risk; yellow = unclear risk; red = high risk.
Abbreviation: MTSS, Medial tibial stress syndrome.

orthotics had a higher relative risk of developing MTSS (RR 2.31, 95% CI 1.56–3.43, $P<0.0001$, Figure 6).

Body mass index

Five papers provided body mass index (BMI) data. In a total of 753 participants, higher BMI was significantly associated with development of MTSS (SMD 0.24, 95% CI 0.08–0.41, $P=0.003$, Figure 7).

Ankle dorsiflexion (soleus)

Four papers investigated the relationship of dorsiflexion ROM at the ankle measured with the knee bent to diminish any effect of gastrocnemius muscle tightness. A total of 886 individuals were tested. There was no significant pooled effect relating this variable to the development of MTSS (SMD –0.06, 95% CI –0.21 to 0.10, $P=0.48$).

Ankle dorsiflexion (gastrocnemius)

Five papers investigated the relationship of dorsiflexion ROM at the ankle measured with the knee straight. A total of 785 individuals were tested. Similarly, there was no significant pooled effect relating this variable to the development of MTSS (SMD 0.05, 95% CI –0.018 to 0.28, $P=0.66$).

Running experience

Four papers surveyed participants to establish their years of running experience. Two papers reported only dichotomized data that could not be equated for consistent analysis, leaving two papers that could be pooled for analysis. In a total group of 182 participants, there was a significant effect relating decreased running experience to the development of MTSS (SMD –0.74, 95% CI –1.26 to –0.23, $P=0.005$, Figure 8).

Previous MTSS history

Five of ten papers surveyed participants to establish if they had suffered with any previous occurrence of MTSS. In a total group of 515 participants, we found a large and significant effect relating a previous history of MTSS to repeat occurrence of MTSS (RR 3.74, 95% CI 1.17–11.91, $P=0.03$, Figure 9).

Table 2 Risk factors and associations with MTSS

Outcome or subgroup	Studies	n	Statistical method	Effect estimate
Navicular drop	4	565	SMD (IV, random, 95% CI)	0.26 (0.02–0.50)
Navicular drop >10 mm	2	164	Risk ratio (M-H, fixed, 95% CI)	1.99 (1.00–3.96)
Foot type	3	448	Risk ratio (M-H, random, 95% CI)	1.61 (0.37–6.98)
Orthotic use	3	403	Risk ratio (M-H, fixed, 95% CI)	2.31 (1.56–3.43)
BMI	5	753	SMD (IV, fixed, 95% CI)	0.24 (0.08–0.41)
BMI <18.5	3	257	Risk ratio (M-H, fixed, 95% CI)	1.16 (0.79–1.73)
Ankle DF ROM (soleus)	4	886	SMD (IV, fixed, 95% CI)	–0.06 (–0.21–0.10)
Ankle DF ROM (gastrocnemius)	5	785	SMD (IV, random, 95% CI)	0.05 (–0.18 to 0.28)
More years of running	2	182	SMD (IV, fixed, 95% CI)	–0.79 (–1.15, –0.44)
Previous history MTSS	5	515	Risk ratio (M-H, random, 95% CI)	3.74 (1.17–11.91)
Female gender	8	1226	Risk ratio (M-H, random, 95% CI)	1.91 (1.11–3.28)
Male hip IR ROM	2	268	SMD (IV, random, 95% CI)	0.36 (–0.31 to 1.03)
Male hip ER ROM	2	268	SMD (IV, random, 95% CI)	0.67 (0.29–1.04)

Abbreviations: BMI, body mass index; CI, confidence interval; DF, dorsiflexion; M-H, Mantel Haenszel test; IR, internal rotation; ER, external rotation; ROM, range of motion; SMD, standard mean difference; MTSS, medial tibial stress syndrome; IV, inverse variance.

Female gender

Nine of ten papers involved both male and female participants. In total, 187 cases of MTSS developed in 513 females and 210 cases of MTSS developed in 957 males. Females were found to be at significantly higher risk of developing MTSS than males, at a ratio of 1.71:1 (RR 1.71, 95% CI 1.15–2.54, *P*=0.008, Figure 10).

Male hip external rotation

Two papers reported male and female hip rotation ranges (internal and external) measured via goniometry. Both reported male and female data separately. Increased external rotation ROM of the hip was found to be significant only for males (n=268) in this meta-analysis (SMD 0.67, 95% CI 0.29–1.04, *P*<0.001, Figure 11).

Discussion

In clinical practice, multiple risk factors are seen as being linked to MTSS as a result of various research findings, or as a result of practitioners' beliefs, experiences, biases, and paradigms. Examples of the array of risk factors discussed in the literature review for this paper are provided in Table 1. The present paper provides clear evidence as to which risk factors can be most reliably linked to MTSS in runners. We propose and discuss a continuum model of pathogenesis of MTSS within the context of current evidence, clinical sequelae, related conditions, and the risk factors we have identified (Figure 12).

Structural/anatomic risk factors

Greater navicular drop is associated with an increased risk of developing MTSS. The effect size for the continuous variable is small, suggesting that the MTSS group had only a slightly increased navicular drop when compared with the uninjured group. The mean difference in navicular drop between MTSS and non-MTSS groups was 0.85 mm, which is a difference that is almost clinically impossible to detect given that the standard error of the measure is between 1.1 mm and 3.0 mm

Study of subgroup	MTSS Mean	MTSS SD	MTSS Total	No MTSS Mean	No MTSS SD	No MTSS Total	Weight	SMD IV, random, 95% CI
Bennett et al[78]	11.6	4.4	11	8	4.1	59	11.7%	0.86 [0.20, 1.52]
Hubbard et al[34]	8.6	3.2	29	7.8	3	117	25.5%	0.26 [−0.15, 0.67]
Plisky et al[80]	11.2	4.5	16	11	3.6	89	16.9%	0.05 [−0.48, 0.59]
Yagi et al[31]	4.9	3	102	4.35	2.9	142	45.9%	0.19 [−0.07, 0.44]
Total (95% CI)			**158**			**407**	**100.0%**	**0.26 [0.02, 0.50]**

Heterogeneity: τ^2=0.02; χ^2=4.03, *df*=3 (*P*=0.29); I^2=26%

Test for overall effect: *Z*=2.13 (*P*=0.03)

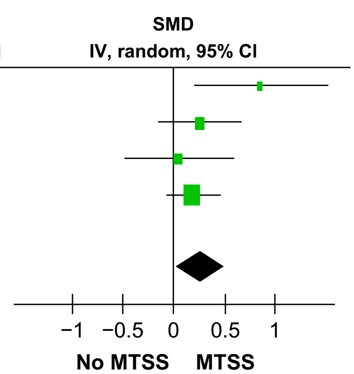

Figure 4 Forest plot of comparison: risk factors and associations with MTSS and navicular drop.

Notes: Green squares = SMD for each study, the size of the squares represent relative *n*. Black diamond = pooled effect of variable.

Abbreviations: CI, confidence interval; MTSS, medial tibial stress syndrome; SD, standard deviation; SMD, standard mean difference; IV, inverse variance.

Study of subgroup	Nav drop >10 mm Events	Nav drop >10 mm Total	Nav drop ≤10 mm Events	Nav drop ≤10 mm Total	Weight	Risk ratio M-H, fixed, 95% CI
Bennett et al[78]	8	26	3	33	25.7%	3.38 [1.00, 11.50]
Plisky et al[80]	16	67	6	38	74.3%	1.51 [0.65, 3.54]
Total (95% CI)		**93**		**71**	**100.0%**	**1.99 [1.00, 3.96]**
Total events	24		9			
Heterogeneity: χ^2=1.13, *df*=1 (*P*=0.29); I^2=11%						
Test for overall effect: *Z*=1.97 (*P*=0.05)						

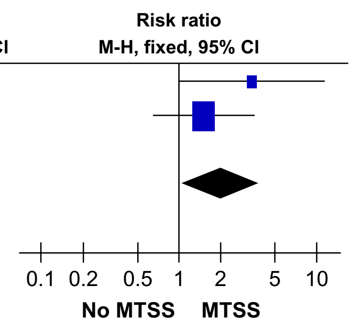

Figure 5 Forest plot of comparison: risk factors and associations with MTSS and navicular drop >10 mm.
Notes: Blue squares = RR for each study, the size of the squares represent relative *n*. Black diamond = pooled effect of variable.
Abbreviations: CI, confidence interval; MTSS, medial tibial stress syndrome; M-H, Mantel Haenszel test; Nav, navicular; RR, risk ratio.

Study of subgroup	Orthotics yes Events	Orthotics yes Total	Orthotics no Events	Orthotics no Total	Weight	Risk ratio M-H, fixed, 95% CI
Burne et al[70]	4	17	19	164	19.5%	2.03 [0.78, 5.28]
Hubbard et al[34]	15	29	25	117	54.1%	2.42 [1.48, 3.97]
Plisky et al[80]	8	23	8	53	26.4%	2.30 [0.99, 5.39]
Total (95% CI)		**69**		**334**	**100.0%**	**2.31 [1.56, 3.43]**
Total events	27		52			
Heterogeneity: χ^2=0.10, *df*=2 (*P*=0.95); I^2=0%						
Test for overall effect: *Z*=4.17 (*P*<0.0001)						

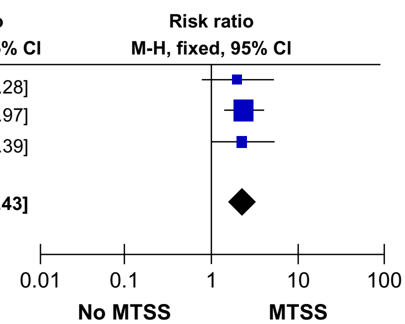

Figure 6 Forest plot of comparison: risk factors and associations with MTSS and orthotic use.
Notes: Blue squares = RR for each study, the size of the squares represent relative *n*. Black diamond = pooled effect of variable.
Abbreviations: CI, confidence interval; MTSS, medial tibial stress syndrome; M-H, Mantel Haenszel test; RR, risk ratio.

Study of subgroup	MTSS Mean	MTSS SD	MTSS Total	No MTSS Mean	No MTSS SD	No MTSS Total	Weight	SMD IV, fixed, 95% CI
Burne et al[70]	22.4	2.6	23	21.35	2.5	135	13.0%	0.42 [−0.03, 0.86]
Hubbard et al[34]	21.47	2.2	29	21.3	1.5	117	15.5%	0.10 [−0.30, 0.51]
Reinking et al[77]	19.8	2.1	45	19.6	2	48	15.5%	0.10 [−0.31, 0.50]
Yagi et al[31]	19.9	3.45	102	18.9	1.4	142	38.9%	0.40 [0.15, 0.66]
Yates and White[12]	23.95	2.5	40	23.9	2.5	72	17.2%	0.02 [−0.37, 0.41]
Total (95% CI)			**239**			**514**	**100.0%**	**0.24 [0.08, 0.41]**
Heterogeneity: χ^2=4.31, *df*=4 (*P*=0.37); I^2=7%								
Test for overall effect: *Z*=3.00 (*P*=0.003)								

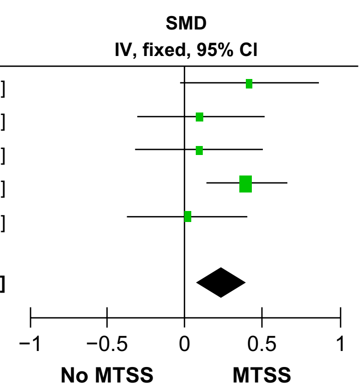

Figure 7 Forest plot of comparison: risk factors and associations with MTSS and BMI.
Notes: Green squares = SMD for each study, the size of the squares represent relative *n*. Black diamond = pooled effect of variable.
Abbreviations: BMI, body mass index; CI, confidence interval; MTSS, medial tibial stress syndrome; SD, standard deviation; IV, inverse variance; SMD, standard mean difference.

Study of subgroup	MTSS Mean	MTSS SD	MTSS Total	No MTSS Mean	No MTSS SD	No MTSS Total	Weight	SMD IV, random, 95% CI
Bennett et al[75]	1.7	1.2	15	2.2	1.2	21	37.9%	−0.41 [−1.08, 0.26]
Hubbard et al[34]	5.3	1.8	29	8.8	4	117	62.1%	−0.95 [−1.37, −0.53]
Total (95% CI)			**44**			**138**	**100.0%**	**−0.74 [−1.26, −0.23]**
Heterogeneity: τ^2=0.06; χ^2=1.79, *df*=1 (*P*=0.18); I^2=44%								
Test for overall effect: *Z*=2.84 (*P*=0.005)								

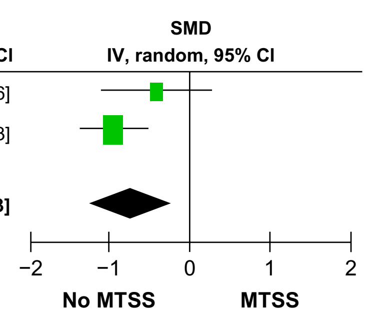

Figure 8 Forest plot of comparison: risk factors and associations with MTSS and years of running experience.
Notes: Green squares = SMD for each study, the size of the squares represent relative *n*. Black diamond = pooled effect of variable.
Abbreviations: CI, confidence interval; MTSS, medial tibial stress syndrome; SD, standard deviation; SMD, standard mean difference; IV, inverse variance.

Study of subgroup	Yes Hx Events	Yes Hx Total	No Hx Events	No Hx Total	Weight	Risk ratio M-H, random, 95% CI
Bennett et al[75]	10	44	1	15	15.0%	3.41 [0.48, 24.45]
Hubbard et al[34]	25	44	4	102	22.1%	14.49 [5.36, 39.17]
Newman et al[13]	0	0	0	0		Not estimable
Plisky et al[80]	9	42	7	63	22.7%	1.93 [0.78, 4.78]
Reinking et al[77]	44	77	1	16	15.4%	9.14 [1.36, 61.59]
Yates and White[12]	11	26	29	86	24.9%	1.25 [0.73, 2.15]
Total (95% CI)		**233**		**282**	**100.0%**	**3.74 [1.17, 11.91]**
Total events	99		42			

Heterogeneity: τ^2=1.33; χ^2=23.70, *df*=4 (*P*<0.0001); I^2=83%
Test for overall effect: *Z*=2.23 (*P*=0.03)

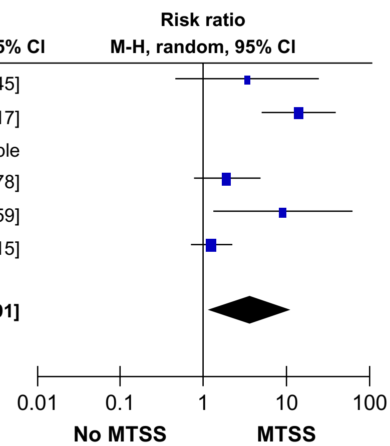

Figure 9 Forest plot of comparison: risk factors and associations with MTSS and previous history of MTSS.
Notes: Blue squares = RR for each study, the size of the squares represent relative *n*. Black diamond = pooled effect of variable.
Abbreviations: CI, confidence interval; MTSS, medial tibial stress syndrome; M-H, Mantel Haenszel test; Hx, previous history of MTSS; RR, risk ratio.

(intraclass correlation coefficient 0.84).[31,34] The standard error of the measure is the standard deviation of the measure-remeasure difference distribution, and therefore reflects the kinds of differences that might arise from measurement error alone. There were some differences in how the reviewed papers measured navicular drop. Whilst these differences in methodology introduce variance,[35] the fact that the meta-analysis still returns a significant finding emphasizes the importance of the measurement.

It is likely that differences in measurement technique are important, particularly when determining clinically relevant cutoff values. Notably, the tandem stance technique appears to yield much smaller differences in navicular height. When the dichotomous variable, navicular drop greater than 10 mm, was analyzed, the effect size improved to within the moderate range. Classification of individuals who are at risk of developing MTSS using this cutoff point is a much more useful clinical tool, and one that can be used with confidence.

Pronated foot type and dynamic overpronation have long been thought to contribute to higher loads in the kinetic chain and therefore to higher rates of injury.[36] Various kinematic analyses have investigated lower limb loads, in association with pronation rate and amplitudes with various results that are beyond the scope of this paper.[35,37–39] Irrespective of the consensus or otherwise of these papers, pronated foot type was not found to be associated with MTSS in this meta-analysis. Whilst the navicular drop test and the Foot Posture Index have demonstrated good intertest reliability independently of each other,[40,41] the correlation between these two methods has not been established. Both are measures of pronation, but only navicular drop appears to be a useful predictor in MTSS. It may be important that the medial

Study of subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk ratio M-H, random, 95% CI
Bennett et al[75]	13	68	2	57	5.1%	5.45 [1.28, 23.15]
Bennett et al[78]	7	28	4	31	7.1%	1.94 [0.63, 5.92]
Burne et al[70]	11	36	12	122	10.6%	3.11 [1.50, 6.44]
Hubbard et al[34]	9	39	20	107	10.9%	1.23 [0.62, 2.48]
Newman et al[13]	26	96	32	288	13.5%	2.44 [1.53, 3.87]
Plisky et al[80]	10	46	6	59	8.6%	2.14 [0.84, 5.45]
Reinking et al[77]	49	62	54	63	16.1%	0.92 [0.78, 1.09]
Yagi et al[31]	44	98	58	146	15.1%	1.13 [0.84, 1.52]
Yates and White[12]	18	40	22	84	13.1%	1.72 [1.05, 2.82]
Total (95% CI)		**513**		**957**	**100.0%**	**1.71 [1.15, 2.54]**
Total events	187		210			

Heterogeneity: τ^2=0.24; χ^2=44.88, *df*=8 (*P*<0.00001); I^2=82%
Test for overall effect: *Z*=2.67 (*P*=0.008)

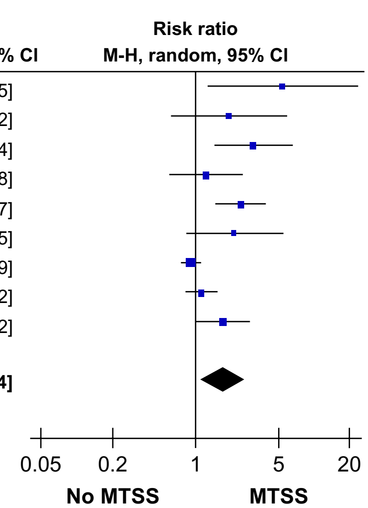

Figure 10 Forest plot of comparison: risk factors and associations with MTSS and female gender.
Notes: Blue squares = RR for each study, the size of the squares represent relative *n*. Black diamond = pooled effect of variable.
Abbreviations: CI, confidence interval; MTSS, medial tibial stress syndrome; M-H, Mantel Haenszel test; RR, risk ratio.

Study of subgroup	MTSS Mean	MTSS SD	MTSS Total	No MTSS Mean	No MTSS SD	No MTSS Total	Weight	SMD IV, random, 95% CI
Burne et al[70]	61.5	7	12	53	9	110	30.7%	0.96 [0.35, 1.56]
Yagi et al[31]	44.5	8.9	58	39.7	8.8	88	69.3%	0.54 [0.20, 0.88]
Total (95% CI)			**70**			**198**	**100.0%**	**0.67 [0.29, 1.04]**

Heterogeneity: τ^2=0.02; χ^2=1.37, *df*=1 (*P*=0.24); I^2=27%

Test for overall effect: *Z*=3.48 (*P*=0.0005)

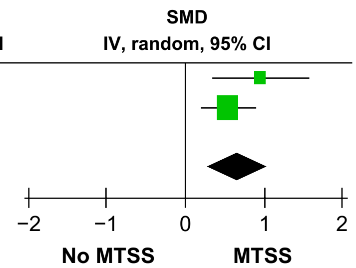

Figure 11 Forest plot of comparison: risk factors and associations with MTSS and male hip external rotation ROM.
Notes: Green squares = SMD for each study, the size of the squares represent relative *n*. Black diamond = pooled effect of variable.
Abbreviations: CI, confidence interval; MTSS, medial tibial stress syndrome; SD, standard deviation; ROM, range of motion; IV, inverse variance; SMD, standard mean difference.

longitudinal arch control systems, both passive and active, need to be isolated from calcaneal and subtalar systems to enable further understanding of these relationships.[35,42–45]

Increased BMI was significantly associated with development of MTSS. However, the effect size was small. This finding could mean that the heavier impact loads that are likely to be associated with increased BMI are a factor, or that deconditioning plays a part. Fitness data for these participants were not included in the papers, but would be a useful addition to further studies in this area. The mean BMI values in these papers and the ranges, where reported, do not suggest that these participants were anything but within the normal range. Further investigation of fitness, bone/fat/muscle ratios, and MTSS prevalence is needed. Low BMI of $<$18.5 was not found to be a significant risk factor for MTSS in this meta-analysis.

Increased or decreased range of motion of dorsiflexion can be confidently ruled out as a risk factor for the development of MTSS. While tightness of plantar flexors is often a feature of MTSS sufferers, it is likely an effect of the condition and not a cause. Stretching of gastrocnemius and soleus is commonly advised for runners to avoid injury, because improvements in range of motion at the ankle are thought to assist the absorption of impact loads. Whether stretching is useful in either the treatment or prevention of MTSS is beyond the scope of this paper.

Historical risk factors

Fewer years of running experience was significantly related to the development of MTSS. Conditioning of neuromuscular and bone adaptation systems is clearly important within current understanding about the pathology of MTSS.[42,46–49] Previous studies have shown that the recovery time from MTSS is generally long. This is best illustrated in a randomized controlled trial by Moen et al, which revealed that recovery to the level of presymptomatic running volumes took 6–10 months for the majority of sufferers.[23] Determination of cutoff values for running experience and MTSS risk are needed for further clarification. The effect of preconditioning programs for reducing injury in runners has not yet been

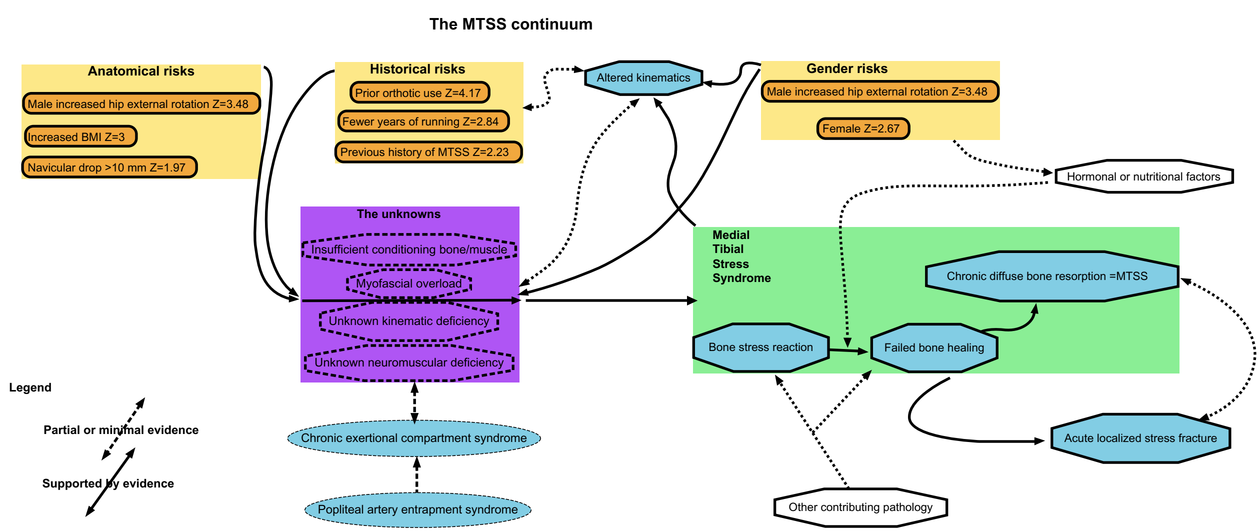

Figure 12 Proposed continuum model of pathogenesis of MTSS.
Abbreviations: BMI, body mass index; MTSS, medial tibial stress syndrome.

established; however, a randomized controlled trial has shown that a 4-week program is insufficient.[50] Data on the volume and intensity of training, and the nature of training surface, also need to be gathered as qualifiers to help understand what constitutes an optimal time for positive adaptation. This risk factor is probably the most modifiable and therefore the most important to investigate and understand in more detail. Standardization of data is important here and should include frequency, distance, and speed as a minimum for future comparisons.[51]

Prior use of orthotics was found to be a highly significant risk factor for developing MTSS. The effect size was large. Examining the relationship between orthotic use and subsequent development of MTSS necessitates consideration of what orthotics do. Kinematic effects,[52] neuromuscular pattern effects,[46,53,54] and shock attenuation effects[44,55] of orthotics are not well understood. Orthotics are commonly prescribed to correct or support a foot that has been deemed to be in less than optimal alignment, but their role in prevention and intervention is unclear according to a recent systematic review.[56] Our analysis suggests their use is a causative risk factor and therefore they are not useful for prevention. The mechanism of this effect is unclear. It could be a result of deconditioning of the lower limb or foot musculature, but no study has detected weakness or lack of muscular endurance to be a risk. If orthotics have a shock attenuation effect, it may be that the tibial bone is not loaded sufficiently for adequate adaptation to occur. At least 25% of the participants included in this meta-analysis had been prescribed orthotics prior to developing MTSS. The orthotic materials, designs, and nature of corrections are not specified in the papers used for the current analysis. A recent systematic review with meta-analysis[54] highlights the complexity and variability of orthotic effects in the domains of shock attenuation, kinematics, and neuromuscular control. Design and material properties, as well as history of injury, will influence the effect of orthotics. For example, Mills et al found that in uninjured subjects, only a posted-molded orthotic had a positive shock attenuation effect.[54] Peak rearfoot eversion was reduced by orthotics, but only if the orthotics were nonmolded and only in uninjured subjects. Further, orthotic use was associated with increases in electromyographic activity of tibialis anterior and peroneus longus by between 19% and 37% of maximal voluntary contraction with no increase in soleus or tibialis posterior activity, but these effects were different depending on injury status. Without knowledge of orthotic types involved in each of the meta-analysis papers, application of these findings to the present study is not possible.

There was a large and significant effect linking a previous history of MTSS to the development of repeat occurrence of MTSS. Either the causes of MTSS are persistent because they are intrinsic, or the effects of MTSS are resistant to change. Magnusson et al found residual evidence of bony demineralization in MTSS sufferers for up to 8 years after an episode.[15] Myofascial structures tend to heal more rapidly than bone or entheses[57,58] and this lends weight to the theory of failed bone healing in MTSS. This is a nonmodifiable risk factor that endorses the need to focus on strategies to prevent MTSS from developing.

Gender-related risk factors

The risk factors for developing MTSS have previously been shown to differ between genders.[59] In this paper, increased external rotation ROM of the hip was found to be a significant predictor of MTSS, but only in males. Both of the relevant papers in this analysis used passive hip ROM measures with the hip in 90 degrees of hip flexion. It is currently unclear how motion measured in this way is related to running postures. There are known and significant differences between both active and passive external rotation ROM measures taken at 90 degrees of hip flexion versus those taken at 0 degrees flexion.[60–63] There is no reported consistent difference in hip external rotation ROM between males and females; however, earlier lumbopelvic movement in men when performed actively has been identified.[64] It is possible that the passive ROM of hip external rotation may lead to an altered movement pattern in running that is specific to males. Hip muscle activation patterns have been found to influence impact loads distally.[65]

Females are at significantly greater risk of developing MTSS than males. A number of studies have investigated gender-related differences in running kinematics.[63,66] These studies have shown female runners to have greater knee abduction at heel contact, decreased knee flexion, increased peak internal rotation of the hip, and increased femoral adduction. These variables appear to fit a pattern associated with MTSS sufferers as well as anterior cruciate ligament injury and patellofemoral pain syndrome, but none of these variables were able to be included in this meta-analysis.[37] Kinematics may also be influenced by hormonal status and phase.[67] Further studies need to investigate female kinematics prospectively for an association with MTSS and to incorporate gender as a covariate in the study design.

Female athletes typically have later onset of menarche, and female runners suffer more commonly from menstrual disturbance than the general population. The latter feature has been associated with lower bone mineral density[68] but not consistently in the tibia. It is possible that female runners are at risk of MTSS if they are starting from a lower base amount of bone density. Bennell et al, in a prospective study of 53 female athletes, found age of menarche, menstrual disturbance, lower bone mineral density, leg length discrepancy, less lean mass of the shank, and a lower fat diet were significant risk factors for stress fracture in females. None of these risk factors were predictive in males.[69] Further prospective analysis of these risk factors in females who develop MTSS is warranted.

Continuum theory of pathogenesis of MTSS

The factors addressed in this review can be linked in a model that combines the factors with processes that represent a continuum of increasing risk of developing MTSS (Figure 12). Many of these processes ("the unknowns") are yet to be supported by prospective evidence. The mechanism by which these risk factors influence the development of MTSS remains unclear.

Cohort studies have identified altered kinematics in MTSS sufferers, which may partly explain the link between previous history of MTSS and future MTSS, but to date no prospective trial has identified a specific kinematic risk factor.

The contributions and interrelationships between popliteal artery entrapment syndrome, chronic exertional compartment syndrome, stress fracture, and MTSS are also unclear, yet clinically they can coexist. This model may provide a visual representation of where further research may focus.

Conclusion

Female gender, a previous history of MTSS, fewer years of running experience, orthotic use, increased BMI, an increased navicular drop, and increased external rotation hip ROM in males are all significantly associated with an increased risk of developing MTSS in runners. The mechanism by which these risk factors influence the development of MTSS remains unclear.

Implications for practice

Runners who have combinations of risk factors identified in this paper should be advised to minimize their total impact loads whilst attempting to modify their risk. For example, a runner with a history of MTSS and who has navicular drop >10 mm should be closely monitored in building their running, until they have survived long enough to have a "low-risk" volume of running established. This precaution is enhanced if they are female or have high hip external rotation range as a male.

Implications for research

The suite of variables identified in this review needs to be tested in a prospective trial to see if the calculated risks are confirmed. A large field study of these variables is needed to build a predictive model and algorithm, and to establish cutoff values for the various factors. Future studies should analyze males and females separately, given that risk factors vary by gender.

Author contributions

Phil Newman performed the review and undertook the main write up, Jeremy Witchalls assisted with design and analysis, and Gordon Waddington and Roger Adams assisted with design. All authors were involved in drafting the article or revising it critically for important intellectual content.

Disclosure

The authors report no conflicts of interest in this work.

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