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Review

Tired of ACL Injures: A Review of Methods and Outcomes of Neuromuscular Fatigue as a Risk Factor for ACL Injuries

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Abstract: Background/Objectives: One potential risk factor that remains especially contentious in the anterior cruciate ligament (ACL) injury literature is the role of neuromuscular fatigue in ACL injury risk. Therefore, the purposes of this review are (i) to present the research and practical concepts of lower extremity neuromuscular fatigue; and (ii) to review the literature relating to neuromuscular fatigue as an ACL injury risk factor and mechanism. **Methods:** A structured review was performed in the Medline database using a search strategy that included terms such as "anterior cruciate ligament injury" and "knee injuries" combined with terms such as "injury" and "fatigue". Articles were included if they included young healthy participants (18–35) and made a comparison between non-fatigued and fatigued states that were assessed with at least one lower extremity biomechanical variable associated with ACL injury risk. **Results:** Overall, there were 67 studies included, accounting for 1440 participants (627 male and 813 female) across a variety of sports and activities. Of these, 53 (79%) reported a post-fatigue change in the kinematics, kinetics, neuromuscular, and/or other (e.g., proprioceptive) outcomes that indicate that the participants would be at an increased risk of an ACL injury. The most common argument against fatigue as a risk factor is that ACL injuries do not tend to occur later in a game or season, when it is assumed that athletes would be most fatigued. **Conclusions:** The evidence presented in this review suggests that localized neuromuscular fatigue is a risk factor, among multiple factors, for ACL injuries, providing another modifiable risk factor that should be considered when developing ACL injury risk reduction interventions.

Keywords: kinematics; kinetics; injury risk; lower extremity; knee; peripheral fatigue; muscle mechanics

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1. Introduction

The anterior cruciate ligament (ACL) is the most injured ligament in the knee, frequently occurring in young, active individuals [1], with incidence rates ranging from 0.03 to 0.42 per 1000 exposures, depending on sex [2], competition level, and environment [3]. Injuries to the ACL have been identified as a multi-factorial injury, and numerous non-modifiable and modifiable ACL injury risk factors have been recognized [4]. Sex [4] and lower extremity anthropometry [5] are two examples of commonly cited non-modifiable risk factors. For example, a systematic review with a meta-analysis indicated that the incidence rate of ACL injuries is statistically different between sexes and is approximately three times higher in females compared to males [6]. With respect to lower extremity morphology and anthropometry, a recent systematic review concluded that more than five different anatomical deviations (small intercondylar notch, offset femoral condyles, and a steep posterior tibial slope) were all significantly associated with an increased risk of ACL injury [7].

While it is important to understand the underlying mechanisms associated with the non-modifiable risk factors, arguably more important is comprehending the modifiable risk factors that would allow clinicians, rehabilitation specialists, and researchers to develop and apply effective injury risk reducing interventions. Although there still remains debate around the association of biomechanical factors and the risk of ACL injury [8], of the most cited and investigated modifiable biomechanical risk factors are those related to an individual's lower extremity kinematics and kinetics. Boden et al. (2007) [9] analyzed videos of professional basketball players performing decelerations and landing maneuvers to quantify knee joint kinematics and compared them between individuals who suffered an ACL injury and healthy controls. They found that initiating decelerations and landings with the heel increased the risk of ACL injury as the impact could not be adequately absorbed throughout the kinetic chain. Prospective research, such as that conducted by Hewett et al. (2005) [10], showed that an increased knee valgus angle and abduction moment during jump landings at baseline testing increased an athlete's risk of ACL injury throughout their competitive season. Krosshaug et al. (2016) [11] also identified medial knee displacement as a risk factor in individuals who had previously experienced an ACL injury. Although Leppanen et al. (2017) [12] did not identify knee valgus as a risk factor for ACL injury, they did identify that increases in vertical ground forces increased injury risk.

Further to this, strain on the ACL caused by anterior translation has been shown to be greater than the strain caused by isolated knee valgus forces or internal rotation moments. For example, 100 N of anterior translation resulted in 3.7% ACL strain, while 200 N of valgus and 10 Nm of internal rotation produced only 2.5% and 2.0% ACL strain, respectively [13]. However, combinations of anterior translation, valgus, internal rotation, and near end-range extension have also been implicated as a common ACL injury mechanism [14].

There appears to be a relative consensus that some patterns of lower extremity joint kinematics and kinetics have a role in inducing ACL injuries. A potential modulator of this is neuromuscular fatigue that occurs to the musculature of the lower extremity. Neuromuscular fatigue, defined as a change in the force generating capacity of the muscle along with alterations in the firing patterns at the neuromuscular junction [15], may result in altered motor unit recruitment (i.e., fatigue affects both the magnitude and timing of muscle force production), which in turn may lead to changes in the kinematics at the affected joint(s). It is the altered kinematics that are suggested to be responsible for an increase in ACL injury risk.

In the most general sense, neuromuscular fatigue can be referred to as a change in the force-generating capacity of the muscle along with alterations in the firing patterns at the neuromuscular junction and incorporates both central and peripheral processes [15]. However, it has been argued that this definition alone does not fully encapsulate the range of fatiguing processes and the effect these have on all types of performance [16]. Alternatively, Enoka and Duchateau (2016) [16] proposed a taxonomy of fatigue that addresses the two main attributes of fatigue: (i) performance fatigability and (ii) perceived fatigability. In the simplest form, however, performance fatigability includes those processes and outcomes that result in a decline in objective measures of fatigue such as contractile function and muscle activation. Perceived fatigability, however, relates to the sensations of fatigue that affect performance and includes both homeostasis and the psychological state of the individual. While it is important to understand this process, these taxonomies [16,17] are still governed by central and peripheral processes of fatigue.

While the Enoka and Duchateau provides a mechanism to categorize different types of fatigue, this framework was further updated by Behrens et al. (2023) [17] to parse out the differences between motor and cognitive performance and the perception of fatigue in acute fatigue settings. Here, they suggest that while motor performance fatigue is defined by the traditional neuromuscular markers of fatigue, the onset and measurement of cognitive motor fatigue (e.g., decreased reaction time) is less well agreed upon but likely depends on the performance of the central nervous system. Finally, a major strength of the updated framework is the acknowledgment that the measurement of state fatigue should include objective measures and that the onset and measurement of motor and cognitive fatigue can be affected by perceived fatigue.

1.1. Central Fatigue

Central fatigue refers to fatigue-related processes proximal to and at the neuromuscular junction (NMJ). In their review, Taylor et al. (2016) [18] categorized central fatigue primarily as the decreased stimulatory output of motor neurons caused by either a decrease in their excitatory output or an increase in their inhibitory output. This is similar to Potvin and Fuglvand's [15] description of firing-rate adaptation, where over time and with a constant excitatory drive, the neural inhibition of muscle activity rises exponentially to limit force production before the signal reaches the muscle. These aspects of central fatigue could be categorized as performance fatigability [16] or perceived motor and cognitive fatigue [17].

Cognitive or mental fatigue is another type of centralized fatigue and was defined by Marcora et al. (2009) [19] as "a psychobiological state caused by prolonged exposure to a cognitively demanding task where individuals may report feelings of tiredness or lack of energy"; or, according to the previously defined taxonomy, aspects of perceived fatigability. To induce this type of fatigue, researchers have typically asked participants to complete a difficult cognitive task; however, this type of fatigue is difficult to measure and quantify. Cutsem et al. (2017) [20] performed a systematic review that included 11 studies describing and attempting to quantify the effect of mental and/or cognitive fatigue on aerobic performance. Overall, they reported that cognitive fatigue led to a consistent decrease in endurance performance, accompanied by an increase in the athletes' rate of perceived exertion. However, this was not accompanied by any physiological markers of endurance fatigue (e.g., increased heart rate, increased lactate concentration) or changes in strength and power. This suggests that psychological or cognitive fatigue may be different, and elicit different responses, compared to neuromuscular fatigue.

1.2. Peripheral Fatigue

Peripheral [16], or motor performance [17], fatigue primarily refers to fatigue at and distal to the NMJ [15]. This often involves the force-generating capabilities and intrinsic fatiguability of motor units (MUs) within a muscle and can be categorized as performance fatigability [16,17]. Burke et al. (1973) [21] described this as a decrease in force capacity within a muscle after repetitive stimulation. Potvin and Fuglevand (2017) [15] also examined this principle in their muscle fatigue model. This model simulates peripheral fatigue following sustained contractions with marked decreases in contractile speed where decreases were greatest in the stronger, most fatigable MUs. It is this type of localized fatigue that we hypothesize primarily contributes to ACL injuries.

Despite the current understanding of the types and process of fatigue, fatigue as an injury risk factor or fatigue as an injury mechanism has remained contentious in the literature for a variety of reasons. Therefore, the purposes of this review are (i) to present the research and practical concepts of lower extremity neuromuscular fatigue; and (ii) to review the literature related to neuromuscular fatigue as an ACL injury risk factor and mechanism.

2. A Review: Fatigue and ACL Injuries

Search and Analysis Methods

A structured approach to the literature search was taken to ensure that a thorough, broad, and representative sample of literature was collected and reviewed. The Medline database was searched on 23 June 2023, using a structured search strategy that included terms such as "anterior cruciate ligament injury" and "knee injuries" combined with terms such as "injury" and "fatigue". Details of the full search strategy can be found in the Supplemental Materials. Initially, 577 articles were included (567 from the initial search and 10 after searching reference lists) with 30 duplicates removed (Figure 1). Articles were included if (1) they involved young healthy participants (18–35); (2) made a comparison between non-fatigued and fatigued states; (3) measured at least one lower extremity biomechanical variable associated with ACL injury risk; and ((4) was published within the last 30 years (after 1993). Articles were excluded if they (1) included pediatric participants; (2) studied participants post-ACLR; and/or (3) specifically studied runners with a focus on running biomechanics. Systematic reviews were also excluded. After screening, a total of 60 articles were included for data extraction.

Sample demographics, including the number of participants, age, and sex, were extracted, in addition to the activity level and/or the sport participation of the participants (Table 1). Methodological information was then extracted and summarized, which included the fatiguing protocol, the way in which fatigue was identified/assessed, and the tasks that were used to test the effect of fatigue on lower extremity biomechanics (Table 1).

Table 1. Summary of the included studies detailing the demographics of the participants included, the methods used to induce and assess the inset of fatigue, and the tasks used to compare between pre-fatigue and fatigued conditions.

Author	Year	N	Mean (SD) Age	Male/ Female	Sport/ Activity	Fatigue Method	Fatigue Assessment	Testing Task
Abergel [22]	2021	21	24.8 (5.5)	0 M/ 21 F	Dancers	• Repeated 1 min dance sequence performed at 100 bpm	Borg RPE > 17	• 12 Sauté jumps
Allison [23]	2016	20	23.35 (2.70)	10 M/ 10 F	Healthy physically active	• 3 sets of isokinetic knee extension/flexion with 40 s rest between reps1st and 2nd set consisted of 40 maximal-effort repetitions • During the 3rd set, participants performed repetitions until the torque value of 3 consecutive repetitions fell below 25% of the initial knee-extensor or -flexor peak torque value • If participants did not reach fatigue in this manner, the 3rd set was truncated at 90 repetitions	Torque decreased by 25% of initial value or 90 reps Confirmed post hoc with MPF analysis	• Force sense protocol: match the sensation of 15% MVIC
Bedo [24]	2022	20	21 (3.4)	0 M/ 20 F	Handball	• Circuit consisting of sprint, jump, lateral shifting, back shifting • The number if set was increased by 1 each round	Reduction in force during countermove-ment jump or inability to complete protocol	• Single-leg landing sidestep maneuver • Drop vertical jump
Behrens [25]	2015	26	26 (3)	13 M/ 13 F	Healthy physically active	• Sets of 5 maximal counter movement jumps and 30 m sprint	Inability to reach 50% of maximum jump height over 3 consecutive jumps	• Anterior tibial translation (AT) in response to AT perturbation

Table 1. *Cont.*

Author	Year	N	Mean (SD) Age	Male/ Female	Sport/ Activity	Fatigue Method	Fatigue Assessment	Testing Task
Benjaminse [26]	2008	30	M22.7 (1.6)/ F22.1 (1.7)	15 M/ 15 F	Healthy physically active	• Modified Astrand Protocol (treadmill running)	Unable to run at maximum effort	• Single-leg standing jump followed by a maximal effort vertical jump
Borotikar [27]	2008	24	21.2 (2.5)	0 M /24 F	D1 Basketball Soccer, Volleyball	• Continuous sets of 5 double-leg squats at 1 Hz	Could no longer complete 3 consecutive squats	• Land on left foot jump to right • Land on right foot and jump left • Land on both feet jump vertically
Bossuyt [28]	2016	15	22 (3)	0 M/ 15 F	Healthy physically active	• Short-term high-intensity exercise protocol (SAFT-5)	Completion of the protocol	• Concentric quad and hamstring contractions • Drop vertical jump • Single-leg hop
Brazen [29]	2010	24	M21.3 (2.8) F19.5 (1.7)	12 M/ 12 F	Healthy physically active	• A circuit consisting of ladder agility drills, side-to-side bounds, trampoline jumps, mini hurdle hops, and vertical jumps	Unable to complete a circuit, up to 6 circuits	• Single-leg drop landing
Chappel [30]	2005	20	M23.7 (0.8) F21.7 (2.1)	10 M/ 10 F	Healthy physically active	• Cycle of 5 vertical jumps (115% vertical reach) and 30 m sprint	Volitional exhaustion	• Foreword stop jump • Vertical stop jump • Backward stop jump
Coratella [31]	2015	22	20.1 (2.4)	20 M/ 0 F	Soccer	• 2 × 20 m shuttle runs separated by 10 s recovery THEN • 5 sets of run, walk, sprint at 55% and 95% of maximal aerobic speed (MAS) on a 20 m shuttle track THEN • 20 m shuttle run at 55% MAS until exhaustion	First and third tests ended when participants could not complete 2 consecutive shuttles	• Hamstring and quadriceps isometric dynamometer at 1.05, 3.14, and 5.24 rad/s
Cortes [32]	2014	18	19 (0.9)	0 M/ 18 F	Soccer	• 3 counter movement jumps at 90% max jump • 3 parallel squats • 5-10-5 agility drill • 30 cm step ups at 200 BPM	Failure to meet jump standard- and/orheart rate plateau within 90% max HR	• 45° crossover step
Cortes [33]	2013	18	19.2 (0.9)	0 M/ 18 F	Soccer	• Sets of 3 counter movement jumps at 90% max jump, 3 parallel squats, 5-10-5 agility drill, 30 cm step ups at 200 BPM	Failure to meet jump standard- and/orheart rate plateau within 90% max HR	• 45° crossover step measured at 50% and 100% fatigue
Cortes [34]	2012	15	19.2 (0.8)	0 M/ 15 F	Soccer	• Sets of 30 cm step ups at 200 BPM for 20 s • 5 sets of 4.5-yard L drill (front cone, back cone, front cone, cut to side cone), 18–22% of max jump, agility ladder at 220 BPM	4 sets and 85% of estimated max HR	• 45° crossover step, • Stop jump soccer header
Dickin [35]	2015	11	22.58 (3.09)	0 M/ 11 F	Healthy physically active	• 30 s squats and 30 s jumping lunges both to 90° with weighted vest (6.5 kg)	Unable to hit 80% max jump height	• Drop jumps at 30, 40, 50 cm
El-Ashker [36]	2019	100	M28.7 (4.5) F27.0 (5.8)	50 M/ 50 F	Healthy physically active	• Intermittent submaximal (60%IMVC) isometric contractions (6 s contraction 4 s relaxation)	Unable to obtain 60% IMVC for three consecutive contractions	• Hamstring and quadriceps isometric dynamometer at 60, 180, and 300 deg/s
Gehring [37]	2009	13	25 (2.4)	13 M/ 0 F	Healthy physically active	• Repetitive knee flex/ext in a leg press machine at 50% 1 RM	No longer able to perform the task	• Bi-lateral landing from 52 cm box

Table 1. *Cont.*

Author	Year	N	Mean (SD) Age	Male/ Female	Sport/ Activity	Fatigue Method	Fatigue Assessment	Testing Task
Geiser [38]	2010	20	20 (1.7)	0 M/ 20 F	Healthy physically active	• Repetitive hip abduction (60 deg/s) and adduction (300 deg/s)	No longer able to adduct within 1 s	• Drop side-step • Drop jump
Gillot [39]	2019	19	20.9 (2.4)	0 M/ 19 F	Handball	• 25 maximal repetitions of concentric flexion/extension at 180 deg/s	Completion of protocol	• Anterior translation at 200 N anterior force
Greco [40]	2013	22	23.1 (3.4)	22 M/ 0 F	Soccer	• Soccer specific interment protocol: walking at 6 km/g 6 × 35.3 s; jogging at 12 km/h 6 × 50.3 s; cruising at 15 km/h 3 × 51.4 s; sprinting 21 km/h 8 × 10.5 s	Completion of protocol	• 5 max con knee ext and flex contractions (60 and 180 deg/s) • 5 maximal ecc knee flex contractions at 180 deg/s • 5 s max iso contract at 70 deg knee flex
Greig [41]	2019	10	24.7 (4.4)	10 M/ 0 F	Soccer	• Soccer specific intermittent protocol (see Greco for details)	Completion of protocol	• 3 repetitions of max hamstring eccentric contractions at 160 deg/s • Single-leg hops: inversion hop, eversion hop, and neutral hop
Harato [42]	2021	25	20.5 (1.5)	0 M/ 20 F	15 Basketball10 Recreational	• Double-leg squats to 90 deg knee flex	Unable to complete fatigue protocol RPE >17	• Double-leg drop landing from 30 cm box
Hassanlouei [43]	2012	9	27 (3)	9 M/ 0 F	Healthy physically active	• Bicycle ergometer at 80–90% of max HR	Volitional exhaustion	• Postural perturbations: 8 cm forward 8 cm backward at 300 and 120 cm/s
Hunt [44]	2017	18	25.2 (3.5)	9 M/ 9 F	Healthy physically active	• Sets of 60 maximal concentric ankle plantar flexion contractions at 180 deg/s	Ankle plantar flex MVIC <60% of pre-fatigue or self-reported fatigue	• Self-selected gait
Iguchi [45]	2014	23	M22.9 (1.0) F21.9 (1.2)	11 M/ 12 F	Healthy physically active	• Successive CMJs	<70% of the max CMJ height on 2 consecutive jumps	• 60 deg side-step cutting • 30 deg crossover cutting
Kellis [46]	2009	20	M24.3 (1.25) F23.5 (1.43)	10 M/ 10 F	Healthy physically active	• 2 sets of con efforts of the knee ext or flex at 120 deg/s	Unable to produce 30% of the maximum moment	• Single-leg drop landing from 30 cm
Kernozek [47]	2008	30	M23.8 (0.4) F23.0 (0.9)	16 M/ 14 F	Healthy physically active	• At least 4 sets of maximal reps of 60% 1 RM smith machine barbell squat	Completed at least 4 sets and could no longer lift the weight	• Single-leg drop landings from overhead bar
Khalid [48]	2015	12	M201.7 (1.83) F19.33 (1.97)	6 M /6 F	Soccer	• Yo-Yo intermittent recovery:shuttle between two cones spaced 20 m apart with increasing speed	Failed to return to start position 2 consecutive times	• Pre-planned side-stepping • Unplanned side-stepping • Pre-planned Crossover • Unplanned crossover
Kim [49]	2021	10	26.6 (1.35)	5 M/ 5 F	Healthy physically active	• 3 sets of side lying hip abduction at 60 BPM to 35 degrees	Unable to reach 35 deg target; confirmed with glute med MnPF	• Single-leg landings on dominant leg from 45 cm

Table 1. *Cont.*

Author	Year	N	Mean (SD) Age	Male/ Female	Sport/ Activity	Fatigue Method	Fatigue Assessment	Testing Task
Kim [50]	2017	24	M 21.3 (2.2) F20.8 (1.0)	11 M/ 13 F	Healthy physically active	• Isokinetic flex/ext at 60 deg/s for 0 to 90 repetitions	Knee flex/ext torque less than 50%/30% on 3 consecutive reps	• Jump landing from 30 cm box with side cut
Lattanzio [51]	1997	16	M23.9 (2.85) F22.1 (2.3)	8 M/ 8 F	Healthy physically active	• Ramped cycle ergometer test to exhaustion • Continuous test on cycle ergometer at 80% of VO2max • Interval test on cycle ergometer at alternating workloads of between 120% and 40% VO2max	Unable to maintain 60 rpm	• Joint position sense quantified as the absolute angular error (AAE)
Lessi [52]	2017	40	M22.8 (2.9) F23.6 (3.0)	20 M/ 20 F	Healthy physically active	• Sets of 10 bilateral squats to 90 deg, 2 bilateral max effort vertical jumps, and 20 steps to a 311 cm box	Inability to hop 20% of maximal single leg hop distance	• Single-leg drop vertical jump from 31 cm box
Liederbach [53]	2014	80	25	40 M/ 40 F	40 Dancers40 athletes	• Sets of 50 step ups onto 30 cm box and 15 max vertical jumps	10% decrease in max vertical jump	• Drop landings
Longpre [54]	2015	25	18–30	0 M/ 25 F	Healthy physically active	• Sets of 50 isotonic knee ext and flex at 50% MVIC	25% decrease in either isometric flex or ext	• Squats and lunges
Longpre [55]	2013	20	18–30	0 M/ 20 F	Healthy physically active	• Sets of 50 dynamic isotonic knee ext and flex at 50% MVC	25% decrease in torque	• Gait
McEldowney [56]	2013	7	23.7 (6.1)	0 M/ 7 F	Dancers	• High-Intensity Dance Performance Fitness Test	Completion of protocol	• Single-leg drop-landings from 30 cm
McLean [57]	2007	20	M20.7 (1.3) F20.8 (0.8)	10 M/ 10 F	D1 athletes	• 4 min of 20 step ups and downs andplyometric bounding over 12 m with change in direction	Completion of protocol	• Jump landing from 50 cm
McLean [58]	2009	20	19.2 (1.7)	0 M/ 20 F	D1 athletes	• Sets of 3 single-leg squats	Unable to complete 3 sequential squats	• Single-leg landings with cuts • Double-leg landings with a vertical jump
Mejane [59]	2019	19	25 (2.4)	0 M/ 19 F	Healthy physically active	• Sets of 15 one-legged squats alternating legs between each set	Unable to complete 15 sequential squats	• Double-leg forward leap • Single-leg landing • Lateral cutting
Miura [60]	2004	27	22.2 (19–31)	27 M/ 0 F	Healthy physically active	• Local Fatigue—60 consecutive maximum concentric knee ext/flex • General Fatigue—5 min treadmill running at 10 km/h at 10% grade	Local—changes in peak torque General—change in HR	• Joint position sense (AAE)
Moran [61]	2009	15	20.9 (1.1)	0 M/ 15 F	Soccer	• Incremental running—start at 6 mph at 3% grade increasing 1.5% every minute	RPE of 17	• Drop jump from 15, 30, 45 cm
Moran [62]	2006	15	21.4 (1.5)	15 M/ 0 F	Healthy physically active	• Incremental running program—start at 6 mph at 3% grade increasing 1.5% every minute	RPE of 18	• Drop jump from 30 and 50 cm
Murdock [63]	2012	20	19–35	10 M/ 10 F	Healthy physically active	• 50 max effort knee ext at 90 deg/s	completion of protocolpost hoc analysis of torque and median PF	• Gait

Table 1. *Cont.*

Author	Year	N	Mean (SD) Age	Male/ Female	Sport/ Activity	Fatigue Method	Fatigue Assessment	Testing Task
Nyland [64]	1994	19	20.8 (1.8)	0 M/ 19 F	D1Volleyball Basketball	• Incremental running program—start at 1.35 m/s at 10% grade increasing 2% every minute	Volitional exhaustion	• Run with rapid stop
O'Connor [65]	2015	11	21.3 (1.2)	0 M/ 11 F	Healthy physically active	• 3 sets of maximum effort knee flexor concentric and isokinetic contractions	3 consecutive repetitions during the 3rd set below 25% peak flexor torque	• CMJ • Vertical stride landing • Lateral stride landing
Orishimo [66]	2006	13	33.9 (7.2)	13 M/ 0 F	Healthy physically active	• 2 sets of 50 step-ups (30 cm) separated by a 1 min rest.	Hop distance reduced to 80% of max	• Single-leg hop
Ortiz [67]	2010	15	24.6 (2.6)	0 M/ 15 F	Healthy physically active	• 30 s Wingate anaerobic test	Fatigue index (change in power output)	• 40 cm single-leg drop • 20 cm up-down hop
Patrek [68]	2011	20	21.0 (1.3)	0 M/ 20 F	Healthy physically active	• Repeated con hip abduction to 30 deg at 60 BPM	RPE >19Confirmed (post hoc) by a decrease MnPF	• 40 cm drop landings
Quammen [69]	2012	15	19.2 (0.8)	0 M/ 15 F	Elite Soccer	• Functional Agility Short-Term Fatigue Protocol (FAST-FP) • Slow Linear Oxidative Fatigue Protocol	4 sets of the FAST-FPVolitional exhaustion for the oxidative fatigue protocol	• Running stop jump
Qu [70]	2018	32	22.6 (2.2)	32 M/ 0 F	Healthy physically active	• Body weight squat at 30 Hz	RPE of >17	• Landing from 40 cm box with cross-over
Radzak [71]	2020	38	21.6 (4.02)	38 M/ 0 F	ROTC	• Exhaustive run at a speed to elicit 80% VO2 max at a 1% grade	RPE > 17 or an FAS score > 7, whichever came second	• Running at 4 m/s
Rahnama [72]	2003	13	23.3 (3.9)	13 M/ 0 F	Soccer	• Soccer specific interment protocol	Completion of protocol	• Isokinetic strength
Ribeiro [73]	2011	40	22.1 (3.0)	40 M/ 0 F	Healthy physically active	• 30 max con/ecc knee ext/flex contractions	Completion of protocol	• Joint position sense
Salgado [74]	2015	14	25.9 (4.6)	14 M/ 0 F	Semi-proSoccer	• Soccer match		• Joint position sense
Sanna [65]	2008	12	20.1 (1.2)	0 M/ 12 F	D1 Soccer	• Intermittent shuttle run (ISR) protocol; 60 min 3-phase protocol	Completion of protocol	• CMJ • Run and Cut
Savage [75]	2018	8	19.4 (1.6)	8 M/ 0 F	Australian Football	• 4, 20 min simulated quarters consisting of standing, walking, jogging, fast run, max sprint	Completion of protocolPost hoc RPE and HR	• Sidestepping • Cross-over cutting
Schmitz [76]	2015	10	25.3 (4.0)	5 M/ 5 F	Healthy physically active	• Cycles of 15 leg presses and 10 s rest at 60% BW between 10 and 40 deg	Unable to complete a full round of 15 presses	• Anterior tibial translation (Vermont Knee Laxity Device)
Smeets [77]	2019	18	21.3 (1.5)	10 M /8 F	Healthy physically active	• 5 min match play simulation protocol (SAFT)	Completion of protocol	• Single-leg hop • Medial hop • Vertical hop with 90 deg medial rotation
Thomas [78]	2010	42	M20.3 (0.85) F20.3 (1.3)	13 M/ 12 F	Healthy physically active	• Alternating quad/ham MVCC until the torque measured in both muscle groups dropped below 50% of the subject's baseline peak torque value for three consecutive repetitions followed by 20 s rest	Until the first 5 reps fell below 50% MVCC	• Single-leg hops

Table 1. *Cont.*

Author	Year	N	Mean (SD) Age	Male/ Female	Sport/ Activity	Fatigue Method	Fatigue Assessment	Testing Task
Thomas [79]	2011	16	18–22	0 M/ 16 F	Healthy physically active	• Alternating hip rotator or triceps surae MVCC fatigue until the torque measured in both muscle groups dropped below 80% of the subject's baseline peak torque value for three consecutive repetitions followed by 20 s rest	Until the first 5 reps fell below 80% MVCC	• Forward jump over a 17 cm high box
Tsai [80]	2009	15	25.6 (3.7)	0 M/ 15 F	Healthy physically active	• Sequence of 5 vertical jumps followed by a 30 m sprint	Inability to reach a jump height of 50% max vertical jump	• Side-step cutting
Weeks [81]	2015	60	25.3 (4.3)	30 M/ 30 F	Healthy physically active	• Sets of 20 lunges for the first 3 sets followed by sets of 10 for the remaining sets	Vertical jump diminished by 20% or were unable to complete a set of lunges	• Single-leg squat
Weinhandl [82]	2011	12	M 22 (2) F 22 (1)	6 M/ 6 F	Healthy physically active	• 1 drop jump from a 20 cm box every 20 s	Unable to jump to 80% of their max jump height	• Drop vertical jumps
Wojtys [83]	1996	10	21.3	6 M/4 F	Healthy physically active	• Isokinetic flex/ext at 240 deg/s for 85 to 135 reps	50% decrease in work	• Anterior tibial translation in response 134 N force
Wong [84]	2020	12	21.3 (1.49)	0 M/ 12 F	College athletes	• Sets of 50 step ups onto 30 cm box and 15 single-leg max jumps	10% decreases in max vertical jump and RPE >17	• 30 cm drop vertical jump
Xia [85]	2017	15	20.9 (0.8)	15 M/ 0 F	Jumping athletes	• Constant speed running at 4 m/s • Sets of 5 vertical jumps and 6 × 10 m shuttle	Constant speed running—volitional failureShuttle—vertical jump less than 7% max	• 60 cm bilateral drop landing
Zago [86]	2021	20	24.3 (3.6)	0 M/ 20 F	Elite Soccer	• Repeated 5 m shuttle run at 70% max aerobic speed	Missed two beats in a row	• Change in direction during shuttle run
Zebis [87]	2011	14	25 (5)	0 M/ 14 F	Handball	• Simulated handball match consisting of 50 min of side-steps, cross-overs, jumps, and high- and low-intensity running	Completion of protocol	• Side cutting

Following the extraction of the data, the results of each included study were summarized as kinematic, kinetic, neuromuscular, or other (Table 2 and Supplementary Table S1). We qualitatively assessed the results and further classified as to whether they indicated an increased or decreased risk of ACL injury post-fatigue (Table 2 and Supplementary Table S1). The kinematic risk factors identified with increasing the risk of ACL injury were decreased knee flexion [88,89], increased knee abduction [10,88], internal rotation [89], and anterior translation [90]. Increases in trunk lateral position following fatigue were also considered as an increased risk of ACL injury [91]. With respect to the kinetic factors, an increased risk of ACL injury was assessed as an increase in the knee abduction moment [10] and anterior tibial shear [91] and increases in vertical ground reaction force [10]. We assessed quadriceps and hamstring strength and activation variables as increasing the risk of ACL injury post-fatigue if the quadriceps to hamstring ratios decreased (i.e., indicating a larger contribution of the quadriceps post-fatigue) [92–94]. Finally, the primary variable that was included in the "other category" was related to measures of proprioception. In these instances, an increased risk of ACL injury post-fatigue was assessed as an increase in the absolute or relative angle or force sense errors.

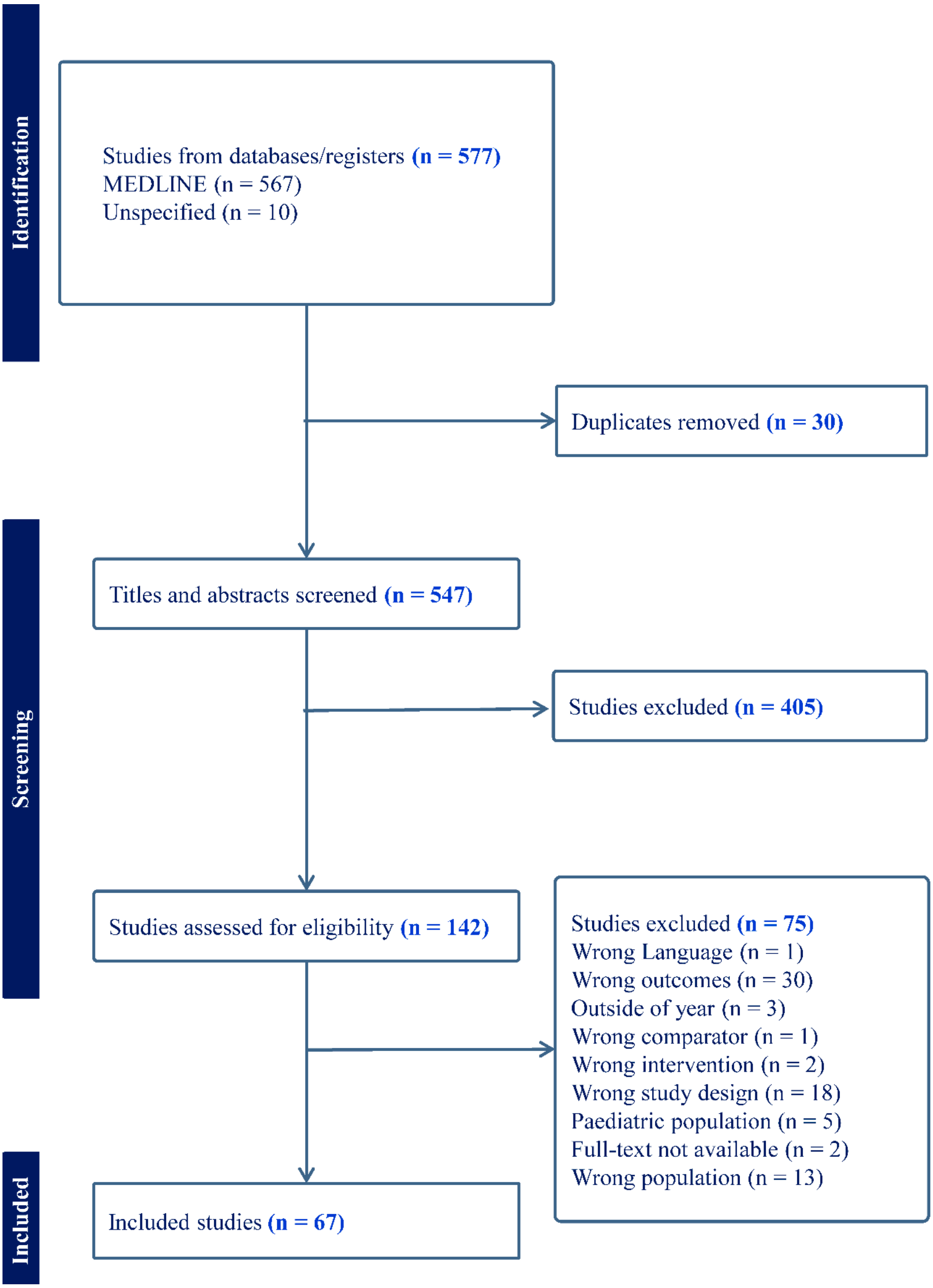

Figure 1. PRISMA flowchart showing the review process.

Table 2. Summary of the outcomes of each included study.

Author	Kinematics	Kinetics	Neuromuscular	Other
Abergel [22]				
Allison [23]				
Bedo [24]				
Behrens [25]				
Benjaminse [26]				
Borotikar [27]				
Bossuyt [28]				
Brazen [29]				
Chappel [30]				
Coratella [31]				
Cortes [32]				
Cortes [33]				
Cortes [34]				
Dickin [35]				
El-Ashker [36]				
Gehring [37]				
Geiser [38]				
Gillot [39]				
Greco [40]				
Greig [41]				
Harato [42]				
Hassanlouei [43]				
Hunt [44]				
Iguchi [45]				
Kellis [46]				
Kernozek [47]				
Khalid [48]				
Kim [49]				
Kim [50]				
Lattanzio [51]				
Lessi [52]				
Liederbach [53]				
Longpre [54]				
Longpre [55]				
McEldowney [56]				
McLean [57]				
McLean [58]				
Mejane [59]				
Miura [60]				
Moran [61]				
Moran [62]				

Table 2. *Cont.*

Author	Kinematics	Kinetics	Neuromuscular	Other
Murdock [63]	Green			
Nyland [64]	Green	Green	Red	
O'Connor [65]	Red	Red		
Orishimo [66]	Green	Green	Yellow	
Ortiz [67]	Red	Green	Green	
Patrek [68]	Green	Green	Yellow	
Quammen [69]	Red			
Qu [70]	Red	Red		
Radzak [71]	Green	Red		
Rahnama [72]			Red	
Ribeiro [73]				Red
Salgado [74]				Red
Sanna [65]	Red			
Savage [75]	Green	Red		
Schmitz [76]	Red	Red		
Smeets [77]	Green	Green		
Thomas [78]	Red	Red		
Thomas [79]	Red	Green		
Tsai [80]	Red	Red		
Weeks [81]	Green			
Weinhandl [82]	Red	Green		
Wojtys [83]	Red		Yellow	
Wong [84]	Red	Red		
Xia [85]	Green	Green		
Zago [86]	Red			
Zebis [87]	Red	Green	Red	

Red = an increased risk of ACL injury following fatigue; green = a reduction in the risk of ACL injury following fatigue; yellow = variables that would likely increase the risk of ACL injury but for which there is limited information to support.

3. Results

Overall, there were 1440 participants across the 67 included articles with 627 male and 813 female participants with a mean (SD) age of 27.2 (2.2) years. The studies included participants from a variety of sports and activities including soccer (*n* = 14), dance (*n* = 3), handball (*n* = 3), basketball (*n* = 3) volleyball (*n* = 2), Australian football (*n* = 1), and jumping athletes (*n* = 1) (Table 1). In addition, forty studies included healthy physically active participants, one recruited reserve officer's training corps (ROTC) participants, and four included division one college athletes (the sport was not specified). There was generally no consistency in the specific fatigue-inducing protocols, but these did include aerobic, anaerobic, and isometric or cyclical concentric methods (Table 1). While the specific parameters associated with the different tasks differed between studies, these could be generally categorized as landing (*n* = 36), jumping (*n* = 23), cutting (*n* = 14), proprioception (*n* = 5), muscle strength (*n* = 7), and clinical anterior translation testing (*n* = 4) (Table 1). Finally, the specific methods used to indicate fatigue onset were highly heterogenous across the included studies. The majority of the studies utilized a volitional failure method (*n* = 53) that could be described as either an RPE criteria ($n = 7$) or methods that used a measured decrease in effort ($n = 39$); seven of the studies did not include any additional measures of fatigue. A second group of studies ($n = 14$) stopped the fatigue testing when the participants had completed the fatigue protocol of a pre-determined time or number of cycles (Table 1). Only one of the included studies [50] objectively measured neuromuscular fatigue during the fatigue protocol via the EMG mean power frequency.

Of the 67 included studies, 53 (79%) reported a post-fatigue change in the kinematics, kinetics, neuromuscular, and/or other (e.g., proprioceptive) outcomes that would indicate that the participants would be at an increased risk of an ACL injury (Table 2).

4. Discussion

The aim of this review was to determine the effect of neuromuscular fatigue on the biomechanical risk factors for ACL injury. The main finding of this study was that, although the methods used to induce and measure fatigue are highly variable across studies, the majority of those included in this review found that fatigue increased at least one biomechanical risk factor for ACL injury.

Evidence was provided in this review that supports the notion that neuromuscular fatigue may increase the risk of ACL injury. For example, in 20 professional and elite female soccer players, Zago et al. (2021) [86] demonstrated post-fatigue kinematic and kinetic changes in 100% and 85% of their sample, respectively, in response to a change in direction task. The specific changes that were quantified are consistent with an increased risk of ACL injury including decreases in knee flexion angles and increases in knee valgus moments. Tsai et al. (2009) [80] reported significant increases in both knee internal rotation (4.9º) and knee valgus (2.4º) angles in a cutting task after a fatiguing protocol. Benjaminse et al. (2008) [26] reported significantly less knee flexion (2.1º) when landing from a single-leg drop jump–vertical jump after a fatiguing protocol, and Moran and Marshall (2006) [62] noted significant increases from the baseline measures in tibial impact acceleration (24%) during a drop jump after inducing fatigue. McLean and Samorezov (2009) [58] found significant decreases in knee flexion upon initial contact and significant increases in knee abduction and the knee abduction moment during the descent landing phase of a single-leg jump landing when fatigued. Cortes et al. (2012) [34] found significant increases in knee abduction angles (3º) and decreases in knee flexion angles (10º) at initial contact during a crossover task compared to pre-fatigue values. Bedo et al. (2022) [24], using statistical parametric mapping, reported significant increases in knee abduction angles at initial ground contact from a single-leg jump landing and significant decreases in knee flexion angles in the first third of a cutting task and the first 75% of a drop vertical jump task after a fatigue protocol. Wojtys et al. (1996) [83] found a significant 32.5% post-fatigue increase in anterior tibial translation during a tibial translation stress test when compared to the non-fatigued state. This body of evidence that includes a range of tasks and biomechanical outcome measures suggests that fatigue is a contributor to ACL injuries.

While the majority of evidence suggests that fatigue is likely a contributor to ACL injuries, there were still 21% of the included studies that did not find a difference in the biomechanical outcomes following a fatigue protocol. Bourne et al. (2019) [95] and Doyle et al. (2019) [96] provide the strongest arguments against fatigue as a risk factor for ACL injuries. They argue that neuromuscular fatigue results in athletes moving slower, which leads to less force production, thus decreasing the risk of injury. This argument counters previous research, which has demonstrated that fatigued athletes may land from jumps with stiffer legs (less knee flexion upon landing), which requires more eccentric force from the quadriceps muscles and requires more non-contractile tissues to bear significant load, resulting in a higher risk of injury [26]. Kim et al. (2021) [49] found that when the gluteus medius was fatigued, there was no significant increase in ACL load but a significant decrease in the knee abduction moment in response to a single-leg landing task. This is relevant, as it has often been assumed that control of hip ab/adduction reduces the likelihood of valgus collapse, which has been cited as an indicator of increased ACL injury risk [97]; although recently, the role of valgus collapse as an injury risk factor and mechanism has been debated [98]. Even so, there were significant increases in trunk lateral flexion and excursion, which have been identified as increasing the risk of ACL injury. Furthermore, in their clinical commentary, Bourne et al. (2019) [95] include several studies [26] that demonstrate small to no effect of fatigue on frontal plane lower extremity kinematics. However, these studies still demonstrate sagittal plane kinematic changes (e.g., decreases in knee flexion upon ground contact) that are consistent with ACL injury mechanisms.

Another major argument against fatigue as a risk factor of ACL injury is that ACL injuries do not appear to occur more frequently at the end of a game or season compared to earlier time-points. For example, Bourne et al. (2019) [95] and Doyle et al. (2019) [96] argued that since the odds ratios of ACL injuries were not different between the first and second halves of individual competitions (odds ratio = 0.43) or full seasons (odds ratio = 1.27), fatigue cannot be associated with these injuries. This theory has also been supported by other research groups who found that more ACL injuries occurred earlier in the season [99] or that the distribution of ACL injuries was not different across timepoints [100,101]. However, a limitation of this approach is that none of these studies included a physiological measure of fatigue. While it would be a difficult task, experimentally, to collect in-game physiological and/or biomechanical data, recent advances in wearable technologies suggest that this may be feasible and should be explored in future research of this kind. Additionally, lower extremity neuromuscular fatigue can occur at any point within a shift, series, game, or other unit of playing time and is not exclusive to end-of-game scenarios or later in the season. The studies that have used time of season or game as a surrogate of fatigue have not adequately considered the specific physical circumstances that occurred prior to the injury. For example, although the injury may have occurred in the first half of a game, the injured athlete could have performed a maximal effort task, leading to localized neuromuscular fatigue, just prior to the injury. Furthermore, medial collateral ligament (MCL) injury research in professional soccer players has demonstrated a significant increase in the proportion of MCL injuries in the last 15 min of each half compared to other 15 min intervals throughout a soccer match [102]. Although Berns et al. (1992) [13] demonstrated that knee valgus alone (the primary mechanism for MCL injury) is not enough to cause an ACL rupture and that a combination of loading patterns and/or anterior tibial translation is required. Many of the studies presented above arguing in favor of fatigue as a risk factor for ACL injury do demonstrate multiple kinematic changes.

A consistent criticism of the literature surrounding the effects of fatigue on lower extremity kinematics is that protocols to induce and quantify fatigue are highly variable, making it difficult to reach a consensus or conduct an impactful meta-analysis [103]. Three primary methods of inducing lower extremity fatigue have been presented in the literature: aerobic, aerobic-anaerobic, and isometric or cyclical concentric methods. These methods all induce different underlying physiological processes and may fatigue different musculature depending on the selection of fatiguing tasks. Therefore, the following paragraphs will describe these fatigue methods in detail, with the goal of moving toward more standardized approaches for future research.

Aerobic fatiguing methods have commonly required a participant to perform a treadmill or bike test until volitional failure, at which point neuromuscular fatigue is assumed to have occurred [62]. The tests commence with the participant running or cycling at a baseline intensity that increases linearly every 1–3 min until the test is terminated [104]. To quantify fatigue with this method, researchers typically rely on the rate of perceived exertion (RPE), a subjective measure reported by the participant based on their effort level. Participants may also be instructed to stop the test when they have reached volitional failure (i.e., when they feel fatigued). There are several limitations associated with the aerobic approach that may influence the desired outcomes. First, this approach includes the lack of objective quantification, as RPE, by definition, is a subjective rating. As such, these subjective measures do not indicate if fatigue has occurred at the neuromuscular level or if participants have simply lost motivation to continue. Evidence suggests that an individual's tolerance to suffering may affect their overall performance and therefore their volitional indication of being fatigued [105]. Another limitation associated with aerobic fatigue methods is the type of fatigue that is being induced. Given that this is aerobic fatigue with sustained, low-intensity muscular efforts, it is likely that the cardiovascular system is the limiting factor and that maximal changes at the neuromuscular level have not or will not occur. Finally, there is limited external validity associated with utilizing aerobic fatigue to induce changes consistent with ACL injury risk. There are few sport scenarios that require one long and sustained aerobic effort, and different protocols can result in a different time to failure for the same individual [104].

Aerobic-anaerobic methods rely on participants performing a combination of exercises in a cyclic manner. For example, some studies have used a whole-body sawing task [106], while others have incorporated sport-specific and/or agility-based tasks in circuits [24,32,34,86,107–109]. There are also protocols that implement a combination of sprints, squats, and/or (sub)maximal vertical jumps to induce fatigue [30,84,110]. Regardless of the specific tasks, these methods all attempt to emulate sport settings, where participants are fatigued with a combination of short-duration high-intensity bouts over longer durations. Fatigue is often defined/measured using a more quantitative approach to volitional failure, often defined as a decrease in the force produced or performance (e.g., a 10% decrease in maximal jump height). A limitation with these protocols, however, is the arbitrary selection of criteria that defines when fatigue has occurred. For example, Lessi et al. (2018) [111] defined fatigue as when participants' maximal single-leg vertical jump height decreased by 20% relative to baseline measures, while Chappell et al. (2005) [30] defined fatigue as volitional failure (terminating task) in a circuit involving sprints and submaximal (115% reach height) double-leg vertical jumps. While this does add a quantitative element to measuring fatigue, it still relies on the assumption that the participant is truly fatigued and has not simply lost motivation to continue performing at a near-maximal level.

Finally, isometric or cyclical concentric fatigue protocols include either repeated or a single sustained contraction where movement at the designated joint is mechanically blocked or controlled such that it is purely uniplanar (e.g., isolated knee flexion and extension). Within this method, fatigue is often defined as a decrease in force and/or torque production as measured with a load cell [54,83]. This method also requires an arbitrarily defined cut-off point. For example, Wojtys et al. (1996) [83] defined fatigue as a 50% decrease in work, but Longpre et al. (2013) [55] used either a decrease in peak knee extension or flexion torque of at least 25%. These methods also have less external validity than the other methods as neuromuscular fatigue in sport and exercise settings is reached dynamically, with multiple joints and movements being involved in inducing fatigue [30]. More specifically, there are very few instances in sport where athletes are tasked with a maximal isometric or controlled cyclical concentric effort to fatigue. However, this method is useful in computer models of fatigue as it is easiest to simulate and can provide valuable insights into neuromuscular fatigue [15].

Within the neuromuscular fatigue research, there are methods available to objectively quantify fatigue, such as an analysis of the EMG signal by quantifying the mean power frequency (MnPF) and assessment of evoked potentials. However, the subsequent sections will focus on the MnPF, as it offers the most feasible method of objectively quantifying fatigue in real-time in response to dynamic ecologically valid tasks. Calculating the MnPF involves computing the mean power by converting the electromyography (EMG) signal from the time domain to the frequency domain and analyzing the power spectrum [112,113]. As EMG records the electrical activity at the neuromuscular junction, this method quantifies localized or peripheral fatigue [15]. This requires performing a fast Fourier transformation on the EMG signal and calculating the mean power (amplitude squared) over predetermined time intervals of data [113,114]. A decrease in the MnPF of 10–20% has been associated with the onset of neuromuscular fatigue. This reduction occurs because of a progressive reduction in muscle motor unit spike amplitude and firing frequency, both of which are physiological indicators of neuromuscular fatigue [115,116]. Fatigue-induced changes in MnPF are greater for higher intensity muscle contractions (>30% maximum voluntary isometric contraction [MVIC]) compared to lower intensities (<20% MVIC) (Arendt-Nielsen et al., 1989). Additionally, Hummel et al. (2005) [117] demonstrated that decreases in MnPF were correlated with increases in participants' RPE, suggesting that the metric closely aligns with participants' subjective rating of their fatigue. As such, the use of MnPF is warranted for the objective quantification of neuromuscular fatigue.

5. Conclusions

ACL injury is a well-researched phenomenon that is complex and multi-factorial. The research related to the potential effect that fatigue has on ACL injuries remains a controversial topic, given the difficulties in defining, measuring, and inducing fatigue in a repeatable and standardized manner. While the research remains a controversial topic, localized neuromuscular fatigue is likely a risk factor, among multiple factors, for ACL injuries. This is another modifiable risk factor that should be considered when developing ACL injury risk reduction interventions. Although further work is needed to best identify how fatigue can be integrated into risk reduction and rehabilitation programs, introducing assessments of individuals in the fatigued state is a possible first step. Implementing controlled training while fatigued may also allow individuals to develop movement strategies in the fatigued state. Finally, including a focus on neuromuscular endurance training may improve an individual's resiliency to the factors that induce fatigue (e.g., greater force-generating capacity prior to reaching the point of fatigue). Future work should also aim to develop standardized methods of defining, measuring, and inducing neuromuscular fatigue to address current limitations and move toward a consensus.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/biomechanics5010011/s1, Table S1: Search terms and strategy used in the Medline database; Table S2: Detailed summary of the outcome of each of the included studies.

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