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# Best Practice & Research Clinical Rheumatology

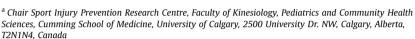
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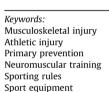
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# Current trends in sport injury prevention

Carolyn A. Emery a, \*, Kati Pasanen b



<sup>b</sup> Sport Injury Prevention Research Centre, Faculty of Kinesiology, University of Calgary, 2500 University Dr. NW, Calgary, Alberta, T2N1N4, Canada



Consequences of injury

Osteoarthritis

#### ABSTRACT

Participation in sport and recreation has important positive implications for public health across the lifespan; however, the burden of sport-related musculoskeletal injury is significant, with the greatest risk being in youth and young adults. Moving upstream to primary prevention of injury is a public health priority that will have significant implications for reducing the long-term consequences of musculoskeletal injury including early post-traumatic osteoarthritis. The primary targets for the prevention of musculoskeletal injury in sport include neuromuscular training (NMT), rule modification, and equipment recommendations. Currently, there is significant highquality evidence to support the widespread use of NMT warm up programs in team and youth sport, with an expected significant impact of reducing the risk of musculoskeletal injury by over 35%. Policy disallowing body checking in youth ice hockey has led to a >50% reduction in injuries, and rules limiting contact practice in youth American football has significant potential for injury prevention. There is evidence to support the use of bracing and taping in elite sport to reduce the risk of recurrent ankle sprain injury but not for use to prevent the primary injury, and wrist guards are protective of sprain injuries in snowboarding. Future research examining the maintenance of NMT programs across real-world sport and school settings, optimization of adherence, additional benefit of workload modification, and evaluation of rule changes in other sports is needed. © 2019 Elsevier Ltd. All rights reserved.

<sup>\*</sup> Corresponding author.

E-mail addresses: caemery@ucalgary.ca (C.A. Emery), kati.pasanen@ucalgary.ca (K. Pasanen).

### Why is sport injury prevention important?

Sport and recreation are encouraged as part of a healthy lifestyle across the lifespan and in all populations; however, the sport-related injury burden is significant, and there is a relative paucity of research evaluating injury prevention strategies in all sports and across all ages [1]. Participation and injury rates in youth and young adult sport are the highest; sport is the leading cause of injury in youth [2–5]. An estimated 20% of schoolchildren are absent from school at least one day a year due to sports injuries, and 1 in 3 youth seek medical attention for a sport-related injury annually [1–3]. It is also estimated that 1 in 3 working adults lost at least one day a year from work due to a sport-related injury [1]. Sport accounts for the greatest proportion of all injuries in youth and also has a significant impact in the adult population [1,6]. An Australian study estimates the direct cost of sport-related injury over seven years to be \$265 million Australian dollars [7]. This injury burden highlights the need for evidence-informed injury prevention interventions to reduce risk of injury in youth and across the lifespan. Lower extremity injuries account for over 60% of the overall injury burden in sport, and 60% of these are ankle and knee joint injuries [1,2].

The burden of overweight and obesity in youth has increased over the past 25 years with over 30% of children and adolescents classified as overweight or obese in Canada, and similar trends are found worldwide [8,9]. Sport injury may contribute to this burden with an estimated 8% of youth dropping out of sport annually because of injury or fear of injury [10]. A reduction in future participation in physical activity, which will adversely affect future health including obesity and post-traumatic osteoarthritis. Reducing the public health burden of sport injury in society would have a major impact on quality of life through the promotion of physical activity. There is evidence that low levels of physical activity participation are associated with multiple-cause morbidity and mortality (e.g., cancer, cardiovascular disease, diabetes, and mental illness) [11–13]. Joint injury is also a leading cause of early post-traumatic osteoarthritis (OA), with an estimated 4-fold increased risk of developing OA following knee joint injury [14]. Further, recent evidence indicates that as early as 3–10 years following a sport-related knee joint injury, youth will have more clinical symptoms, lower knee-related quality of life, higher adiposity, weaker knee muscles, poorer dynamic balance, and more structural changes (10-fold greater risk of MRI-defined osteoarthritis) consistent with future OA than uninjured controls [15–17].

Sport and recreation participation is extremely important in youth and for all age groups to maintain a healthy lifestyle, promote healthy growth and development, prevent chronic disease, and reduce stress, among other benefits. An active population is optimal; however, participation in any physical activity must be balanced with the injury risk. As such, the primary focus of this chapter will be lower extremity injury prevention. Participation in sport and recreation has important implications for public health benefits across the lifespan, and mitigating injury risk is paramount.

#### What is the optimal approach to sport injury prevention?

The four-step model for injury prevention proposed by van Mechelen has been the foundation for developing and evaluating sport injury prevention programs over the last 25 years (Fig. 1) [18]. This model indicates that the prevention of sport injuries begins with establishing the extent of injury in a given population through surveillance systems, followed by identifying risk factors for injury in that population. This leads to the development and validation of injury prevention strategies followed by their evaluation through measuring the impact of the prevention strategy on the incidence of injury using appropriate surveillance systems. Randomized controlled trials (RCT) are the optimal methods to evaluate the efficacy of a prevention strategy but not always feasible or ethical. As such, less rigorous study designs (e.g., quasi-experimental, cohort, and case—control) are also used to evaluate injury prevention intervention efficacy and effectiveness with their inherent methodological limitations that introduce study biases and limit the interpretation of study findings to some extent [19].

The "best" injury prevention program is one that can and will be adopted and sustained by athletes, coaches, and sporting bodies. Therefore, the implementation of injury prevention research into real-world settings has received a great deal of attention [20–22]. Wide-scale implementation of cost-effective intervention measures in real-life circumstances is an ongoing challenge that goes beyond evaluation through an RCT [21]. The Translating Research into the Injury Prevention Practice (TRIPP)

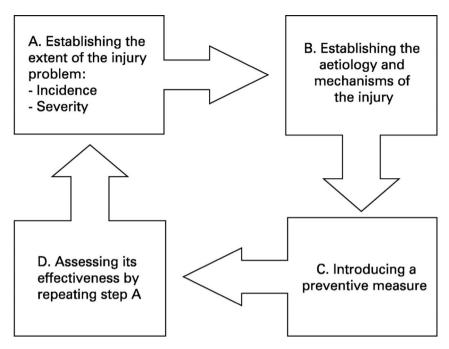


Fig. 1. The four-step model for sport injury prevention as described by van Mechelen [18] (with permission).

Framework has been widely cited to address these challenges [20]. This framework is an extension of the van Mechelen model and describes two additional steps that are required to translate effectiveness of prevention strategies into practice (Fig. 2) [23]. These additional steps involve understanding the real-world context for which an intervention is being developed and evaluating the intervention in a real-world setting. For example, if an injury prevention program is to be transferable and sustainable in the real world, it will be important to consider the sport participants' age group, level of play, sport type, and organizational structure in which the original intervention was evaluated. The RE-AIM framework (Reach Efficacy Adoption Implementation Maintenance Framework) was originally developed to evaluate the public health impact of health promotion interventions and describes five cross-cutting dimensions that identify the translatability and feasibility of a program [22]. The five steps to translate research into action described include 1) reach the target population, 2) effectiveness or efficacy, 3) adoption by target staff, settings, or institutions, 4) implementation consistency and costs and adaptions made during delivery, and 5) maintenance of intervention effects in individuals and settings over time [24]. Increasing attention has been paid to this framework in the context of sport injury prevention strategy evaluation, and this will continue to be an area of further development in the field [25-27].

The importance of the economic evaluation of injury prevention research has more recently been identified, adding relevant insights into the financial consequences and outcomes of preventive approaches. This information will inform practice and policy related to injury prevention strategies. An efficient use of limited financial resources is imperative, yet only a handful of full economic evaluations in the field of sport medicine have been published [28–31].

When developing an optimal implementation strategy that will maximize the effectiveness of a specific sport injury prevention program, it is critical to consider the multiple factors that may influence adherence to such an approach across many levels of influence (i.e., athlete/child, parent, coach/teacher/trainer, sport organization, and government) [32]. To mitigate the problems of poor adherence, it is important to ensure a balance between evidence and real-world user implementation throughout intervention development and evaluation. Owoeye et al. [33] recommend a focus on the identification

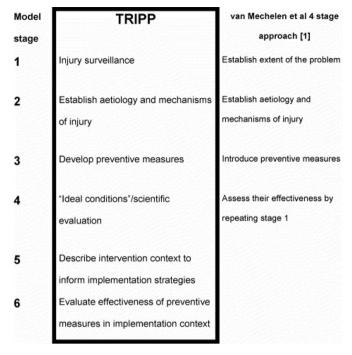


Fig. 2. Translating research into injury prevention practice (TRIPP) as described by Finch [22] (reproduced with permission).

and modification of determinants of adherence for successful implementation and maintenance using a four-step model (Fig. 3).

# What is the evidence supporting the use of sport injury prevention programs?

While injuries are arguably predictable and preventable, it is likely impossible to eliminate all injuries in sport; however, injury prevention strategies can reduce the number and severity. On the basis of relative burden, the focus of much of the evidence surrounding musculoskeletal injury prevention in sport has been on reducing the risk of lower extremity injuries. In the past decade, there have been an increasing number of epidemiological studies evaluating the efficacy of prevention strategies in youth and elite sport to prevent lower extremity musculoskeletal injuries. These evidence-informed strategies cross three themes, namely, 1) training strategies, 2) sport rule modifications and policy changes, and 3) equipment recommendations. A diversity of sport-specific (i.e., primarily, team sports) and more general sport populations (e.g., school based) have been targeted for injury prevention strategy evaluation. The greatest number of these strategies is training strategies targeting modifiable intrinsic (athlete related) risk factors (e.g. strength, endurance, and balance) through exercise interventions, primarily neuromuscular in nature. In addition, extrinsic risk (environmental) factors have been addressed through rule modification and equipment strategies in some sports (e.g., body checking in youth ice hockey, noncontact practice in American football, wrist guards for snowboarding, and ankle braces).

#### Neuromuscular training injury prevention programs

Until the past decade, there were relatively few scientifically rigorous evaluation studies examining the efficacy of injury prevention strategies in sport [34]. Epidemiological research historically focused on the evaluation of prevention strategies in elite adult amateur and professional athlete populations

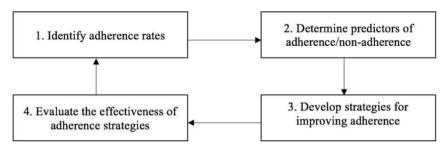


Fig. 3. The four key steps toward more rigorous approach to promote adherence to interventions as described by Owoeye et al. [33].

where injury surveillance was established with the presence of medical staff, and more recently, there has been a greater focus on youth sport [35]. The majority of prospective studies (e.g., RCT, quasi-experimental, and cohort studies) evaluate neuromuscular training (NMT) strategies in team sport, with increasing attention toward youth sport. NMT programs are typically coach or trainer led, ideally following a comprehensive coach training workshop by a physiotherapist or strength and conditioning coach with expertise in NMT workshop delivery.

Several systematic reviews, some including meta-analyses where data are combined across multiple studies, have been conducted examining studies that have evaluated the effectiveness of NMT strategies in reducing the risk of injury in sport [34–42]. Relevant meta-analyses produce combined estimates of measure of effect using incidence rate ratios (IRR) examining NMT interventions across multiple sport contexts and report consistent findings [35–37]. Examining RCTs only in youth sport (i.e., soccer, European handball, and basketball), seven studies examining overall lower extremity injury outcome were combined to estimate a 35% reduction in lower extremity injury risk [IRR = 0.65(95% CI; 0.49-0.86)] and five studies examining knee injury outcome specifically estimated a 26% reduction in knee injury risk [IRR = 0.74 (95% CI; 0.51-1.07)] that was clinically relevant but not statistically significant. In another systematic review, meta-analyses of 25 RCTs across a variety of sports (i.e., soccer, European handball, Australian rules football, floorball, and basketball) and age groups examined the protective effect of exercise interventions in reducing the risk of injury [36]. The combined estimate demonstrated a 37% reduction in overall injury risk [IRR = 0.63 (95% CI; 0.53-0.75)], 35% reduction in acute injury risk [IRR = 0.65 (95% CI; 0.5-0.84)], and 47% reduction in overuse injury risk [IRR = 0.53 (95% CI; 0.37-0.75)] [34]. Further, an even greater preventive effect was seen when NMT intervention programs focused on proprioception/balance [IRR = 0.55 (95% CI; 0.35-0.87)] and strength [IRR = 0.32 (95% CI; 0.21–0.48)] while no preventive effect was demonstrated with programs focused on stretching [IRR = 0.96 (95% CI; 0.85-1.1)]. Another study combined RCTs examining the effectiveness of NMT in reducing the risk of ankle sprains specifically and reported a 32% reduction in ankle sprain injury risk in youth basketball and soccer players [IRR = 0.68 (95% CI; 0.46-0.99)] [42]. Further, there is recent evidence that a NMT warm up is effective in reducing injury risk in pediatric soccer players under the age of 13 years by 48% [Hazard Ratio = 052 (95% CI; 0.32-0.86)] [43]. More recently, a protective effect of NMT training was found in youth rugby players when exercises were performed at least three times per week [IRR = 0.28 (95% CI; 0.14-0.51)] [44]. Further, to a sportspecific context, there is building evidence regarding the effectiveness of such NMT warm up programs in reducing the overall risk of sport and recreational injury in a school physical education context across the spectrum of age groups of children and adolescents [45–48].

NMT training programs, typically consist of exercises aimed to improve balance, strength, and agility (e.g., coordination, cutting and landing techniques) [41]. NMT programs are often introduced as part of an extended warm up routine, and as such, NMT components include aerobic, balance, strength, and agility (see Fig. 4). Ideally, levels of progression are built into each NMT exercise component such that participants can progress difficulty as they see fit. Examples of NMT components are provided in Fig. 4. To successfully reduce the burden of sport-related injury, it is critical to develop and implement feasible NMT programs that fit in a real-world sporting context (e.g., part of the warm up routine, no required equipment). Further research is required to fully understand the mechanism by which





Players stand facing each other while balancing on one leg with hip and knee slightly bent and knee aligned over the planted foot. The other knee is slightly bent. Focus on good posture and



different components of NMT reduce injury risk and optimization of adherence (i.e., utilization frequency, utilization fidelity, duration fidelity, exercise fidelity, and cumulative utilization) to NMT programs across sport contexts [33]. There is ample evidence to support a dose—response relationship of greater exposure to NMT leading to a greater reduction in injury risk across sport contexts [44,49–53]. To assess the effectiveness of differing dosages of the NMT programs, adherence needs to be measured and quantified. Assessing exercise fidelity, or the extent to which a program is followed as prescribed (i.e., correct execution of NMT warm up program), is an area that has been under-researched and not often considered when measuring adherence [54]. As such, it is not known how movement quality during the NMT warm up influences injury rates and the importance of movement quality in performing NMT components may be underestimated. As one can imagine, there are challenges in analyzing movement quality in a real-world sporting context setting where qualified personnel may observe and evaluate movement patterns, which could be influenced by observer bias and is a timeconsuming process [54]. The use of traditional biomechanical motion capture equipment to quantify movement patterns is expensive and requires trained individuals to operate the equipment, and this type of analysis is often confined to a laboratory or clinic [55]. Recent advancements in wearable technologies have provided the means to measure movement quantity and quality outside of a biomechanics laboratory [56]. The future development of wearable technologies to determine movement quality during an NMT warm up program to provide information about how exercise fidelity during an NMT warm up program influences injury rates is promising.

Further to NMT programs, Gabbett 2016 highlights the potential for load modification in reducing the risk of injuries in sport [57]. He proposes the 'Training-Injury Prevention Paradox' whereby athletes accustomed to high training loads may have a lower risk of injury than athletes training at lower workloads [57]. He argues that excessive and rapid increases in training load may increase the risk of noncontact musculoskeletal injuries (e.g., tendinopathies) and that the acute-to-chronic training workload ratio may predict training-related injuries [56]. With greater availability of wearable technologies to monitor workload (e.g., jump load in volleyball and basketball), there exists a greater opportunity to better understand the influence of workload on injury risk [58,59]. This research provides a foundation for the development and evaluation of future workload modification interventions to reduce the risk of such sport-related injuries.

Research evaluating training strategies aimed at reducing the risk of upper extremity injuries is far more limited. A Shoulder Injury Prevention Programme aimed at throwing athletes to increase gle-nohumeral internal rotation, external rotation, and scapular muscle strength and improving kinetic chain and thoracic mobility was implemented as part of a European handball warm up program in elite players and evaluated in a cluster-RCT study, reporting a 28% reduction in shoulder problems (Odds Ratio = 0.72, 95% CI; 0.52–0.98) [60]. A systematic review examining risk factors and shoulder injury prevention programs for throwing athletes summarizes the limitations in evaluating injury prevention training programs in overhead athletes due to the limited number of athletes uninjured at baseline and limited statistical power as a result of examining new injury outcomes [61].

In summary, there is evidence from adult elite, adolescent, and pediatric athletes and sport participants to inform best practice in NMT warm up program recommendations to prevent injuries across multiple team sport contexts including soccer, European handball, Australian rules football, basketball, floorball, and rugby. Translation of these findings and adaptation of sport-specific NMT programs to a more generalized population such as physical education students across child and adolescent age groups has also proven to be effective in reducing the risk of injuries in sport and recreation. It stands to reason that the development and implementation of sport-specific NMT warm up programs in sports where evaluation has not been previously done will also be effective; however, future research is necessary. Implementation and evaluation of such programs in a real-world context are necessary to gain a further understanding of adherence and maintenance of such programs across sport contexts. Research examining exercise fidelity, quality of movement, and workload also requires more attention,

**Fig. 4.** Examples of neuromuscular training warm up program components; 4a Examples of strength and balance components and 4b Neuromuscular training warm up: Examples of aerobic and agility components [acknowledgment Sport Injury Prevention Research Centre, University of Calgary, K Pasanen, with permission].

with promising opportunities using wearable technologies. Further, future research evaluating upper extremity injuries should target additional throwing sport populations.

Sporting rule modification and policy changes

Sporting rules and policy are important for the regulation of the sport, but some have been implemented specifically to reduce the risk of injury. An example of evidence-informed policy change related to the age of introduction of body checking in youth ice hockey. Body checking is a tactic used to gain competitive advantage by changing direction or leaving the established skating lane to make contact with the body of the opponent, or using hips, shoulders, or arms to push off and separate the opponent from the puck [62]. The optimal age of introduction to body checking has been a topic of debate in North America for over a decade and several studies have contributed to evidence-informed body checking policy change. In a meta-analysis, policy-allowing body checking in youth increased injury risk more than 2-fold (combined Risk Ratio = 2.45; 95% CI 1.7 to 3.6) [63]. Supporting this, evaluation of a national evidence-informed policy change in Canada disallowing body checking at all levels of play in 11- and 12-year-old leagues led to a 50% reduction in injury risk [IRR = 0.5 (95% CI; 0.33–0.75)] [64]. This evidence subsequently informed policy disallowing body checking in older age groups (ages 13–14 years) in non-elite leagues (lowest 60–70% by division of play), which also reduced the risk of injury 54% [IRR = 0.46 (95% CI; 0.27–0.77)] [65].

The lessons learned over a decade of research examining body checking policy change in youth ice hockey may have implications for other team sports such as American football, rugby, lacrosse, and soccer. Other studies evaluating rule changes in youth team sport report an association of a high school football policy restricting teams to no more than two collision practices a week with fewer head contacts in games and practices and that, combined with coach safety training, is associated with 63% lower rates of injury in practices than those with coach training alone [IRR = 0.37 (95% CI, 0.26-0.53)] [66]. Further research is required to determine whether such a strategy will have implications for the long-term reduction of injury risk in games. While there are limited studies examining the impact of rule and contact policy changes in sport, these findings have arguably exceeded the public health impact of other injury prevention approaches such as training strategies in some sports such as ice hockey.

### **Equipment recommendations**

Using protective equipment may help prevent musculoskeletal injury and/or severity in sport. Such equipment may include bracing/taping and wrist guards. In a systematic review conducted in adult and youth athletes, Dizon et al. [67] report in a systematic review a protective effect of ankle bracing and taping among previously injured adult and youth athletes in reducing the risk of ankle sprain re-injury 69% and 71%, respectively. Janssen et al. [68] demonstrate a superior effect of ankle bracing over NMT training in reducing the incidence of recurrent ankle sprain 47% compared to the NMT alone, with similar reported full compliance in the bracing (48%) and NMT (45%) groups. Interestingly, when the interventions were combined, full compliance reduced to 28%, with no significant benefit to the combined approach over NMT alone [66]. The evidence does not support the preventative effect of ankle bracing/taping or knee bracing as a primary strategy to prevent ankle and knee injuries in youth sport, except in the case of recurrent injury [69]. Further, recommendations for bracing compared to taping may be based on personal preference, comfort, availability of medical personnel for taping, and potential cost implications of each [70].

Other equipment strategies examined include wrist guard use in snowboarding [71]. A systematic review examining wrist guards in snowboarding reveals a significant protective effect in reducing the risk of wrist injury (Odds Ratio = 0.23), wrist fracture [Risk Ratio (RR) = 0.29], and wrist sprains (RR = 0.17) [71]. It is estimated that for every 50 snowboarders who wear wrist guards, one wrist injury will be prevented [71]. This research has potential implications for other sports including skate-boarding and roller blading, and further research is required to translate these findings to other contexts. Breakaway bases have been examined in baseball and softball and have consistently demonstrated a protective effect on sliding injuries in adult and youth population [72–74]. While there

is some evidence to support the use of protective equipment in youth sport, there is also evidence to support less than optimal uptake of equipment strategies (e.g., wrist guard use in snowboarding) [71]. Combining educational approaches (e.g., social media) and policy (legislation and facility/sport association requirements) may be the best way to encourage use of protective equipment.

### The role of sport injury prevention in reducing the global burden of MSK disorders

Moving upstream to primary prevention of injury in a healthy and active population may ultimately have the greatest public health impact in reducing the burden of injuries and their consequences, including early post-traumatic OA. The significant consequences of musculoskeletal injury in contributing to reduced levels of physical activity, overweight/obesity, OA, and health care costs inform the need for rigorous evaluation of primary injury prevention strategies in sport and recreation to reduce this burden. There is significant high-quality evidence to support the widespread use of NMT warm up programs in team sports and youth sport widely, with an expected significant impact in reducing the risk of musculoskeletal injury by over 35%. Future research examining the maintenance of NMT programs across real-world sport and school settings, optimization of adherence and exercise fidelity, and additional benefit of workload modification is critical. Sport-specific rule modifications and contact policy changes in youth collision sport can have significant public health impact in the reduction of injuries in youth sport. Policy disallowing body checking in some age groups and levels of play in youth ice hockey has led to a >50% reduction in injuries, and rules limiting contact practice in youth American football has significant potential for best practice in injury prevention. Future research evaluating such rule changes in other collision sports is needed. There is evidence to support the use of bracing and taping in elite sport to reduce the risk of recurrent ankle sprain injury but not for use as a primary prevention practice. Further, wrist guards are protective of wrist sprain injuries in snowboarding. Participation in sport and recreation has important implications for public health benefits across the lifespan, and mitigating injury risk is paramount.

The need for future research in the primary prevention should not, however, be underestimated, including the need for methodologically rigorous evaluation studies including RCTs in sports where research has not been undertaken. The Osteoarthritis Research Society International (OARSI) RCT recommendations were developed to inform the design, conduct, and analytical approaches to RCTs evaluating the preventative effect of primary musculoskeletal injury prevention strategies and strategies aimed at the secondary prevention of early post-traumatic OA to inform the highest level of evidence in the field [75]. Further, implementation research in the real-world context including mixed methods studies to inform barriers and facilitators to injury prevention best practice and optimization of positive behavior change in sport including implementation of NMT warm up programs broadly to have a greater public health impact in reducing the burden of musculoskeletal injuries [27]. RCTs may not always be feasible or ethical to evaluate potential training strategies, rule changes, and equipment recommendations in sport, and therefore, case—control studies (e.g., equipment), cohort studies (e.g., rule changes), quasi-experimental designs, and comparative effectiveness studies (e.g., training strategies) may be considered. Economic evaluation of injury prevention strategies is critical to inform cost-savings associated with injury prevention programs. Results from such economic evaluations will support the injury prevention community in advocating for best practice and policy with government and sporting association stakeholders who have the potential to influence a significant reduction in the burden of musculoskeletal injury in sport and recreation [28–31].

Primary prevention of injury may be the "low hanging fruit" that will have the greatest impact in reducing the burden of musculoskeletal injury in sport and recreation. Once injury has occurred, it is imperative that those individuals who are at high risk of recurrent injury and/or risk of significant consequences of injury such as early post-traumatic OA are identified, and secondary prevention strategies also considered. These recommendations are beyond the scope of this chapter and will be addressed in chapter 10. An improved evidence-base in the primary and secondary prevention of musculoskeletal injury in sport and recreation will inform health care practitioners, sport and health administrators, legislators, athletes, coaches, parents, and the public to make the best possible evidence-informed decisions regarding the prevention of injury in the broad and diverse communities in which physical activity is promoted through sport and recreation.

#### Practice points

- Neuromuscular training warm up programs including strength, balance, aerobic, and agility components can reduce the risk of musculoskeletal injuries at least 35% in team sport and other youth sport settings
- Sport rule modifications and contact policy changes in youth collision sport may have significant public health implications in reducing the risk of injury, and their potential should not be underestimated
- Ankle bracing will reduce the risk of recurrent ankle sprain injuries in elite sport but not
  considered as a strategy for primary prevention in healthy athletic populations with no
  previous history of ankle injury
- Wrist guards are protective of injury in snowboarding and hence should be promoted
- Workload modification interventions require evaluation to further inform the prevention of acute and chronic injuries in elite sport

## Research agenda

- Research examining the maintenance of NMT programs across real-world sport and school settings, optimization of adherence, and additional benefit of workload modification is needed.
- Novel outcome measurements using wearable technologies may inform research examining exercise fidelity and workload modification.
- Research evaluating rule modifications and contact policy in youth collision sports is recommended
- The effectiveness of wrist guards in sports beyond snowboarding should be evaluated.
- In the upscaling and broad-scale implementation and evaluation of injury prevention implementation strategies in real-world settings; attention to adherence, exercise fidelity, behavior change, barriers, and facilitators, and long-term maintenance is recommended

#### **Conflicts of interest**

Carolyn Emery and Kati Pasanen have no conflicts of interest to declare.

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We obtained written consent for the use of Fig. 4 in our chapter.

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