Investigating the relationship between changes in physical activity levels and injury risk among children and adolescents

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Abstract

Physical activity is a key component of maintaining a healthy lifestyle, and is particularly important for the healthy development of children and adolescents. However, physical activity also has an inherent risk of injury. There exists limited research and few guidelines on the impact of increasing physical activity levels on injury risk among children and adolescents. While the evidence base is larger for adults, existing studies are limited by sample size and methodological issues. Further, few studies have explicitly aimed to estimate the causal effect of changes in activity on injury risk. The objectives of this manuscript-based thesis are (1) to assess the relationship between changes in physical activity levels and injury risk among children and adolescents, and (2) to inform the methodology for future research in this area. Manuscript 1 is a narrative review of the pathophysiological and epidemiologic principles underlying musculoskeletal sport injuries. It is targeted towards epidemiologists without formal training in this substantive area. Manuscript 2 explores how past physical activity levels are associated with incident injury risk in schoolchildren using flexible weighted cumulative exposure methods. It shows that activity performed ten or more weeks ago has a protective association with current injury risk, while activity performed in two to nine weeks ago has a detrimental association. Manuscript 3 is a methodological commentary on immortal time bias in observational studies of changes in activity and injury risk. It shows how conventional approaches for measuring activity result in bias, and provides recommendations for avoiding these biases. Manuscript 4 is a methodological commentary that discusses how observational data can be used to estimate the causal effect of changes in activity on injury risk through the application of the target trial framework. Manuscript 5 applies the target trial framework to adolescent ice hockey players and assesses the intention-to-treat effect of increasing participation duration by varying amounts on injury risk. It employs flexible non-linear modelling approaches to show that injury risk increases consistently with increases in planned participation duration among adolescents. Together, these manuscripts advance the methodology used for assessing the relationship between changes in physical activity levels and injury risk, with the ultimate goal of generating valid recommendations to promote physical activity among children and adolescents while minimizing risk of injury.

Resumé

L’activité physique constitue un élément clé du maintien d’un mode de vie sain et est particulièrement importante pour le développement sain des enfants et des adolescents. Cependant, l’activité physique comporte également un risque inhérent de blessure. Les recherches sur l’impact de l’augmentation des niveaux d’activité physique sur le risque de blessure chez les enfants et les adolescents sont restreintes, et peu de lignes directrices existent à ce sujet. Même si la base de données probantes est plus vaste pour les adultes, les études existantes sont limitées par la taille des l’échantillons et des problèmes méthodologiques. De plus, peu d’études ont visé explicitement à estimer l’effet causal des changements d’activité sur le risque de blessure. Les objectifs de cette thèse sont (1) d'évaluer la relation entre les changements dans les niveaux d'activité physique et le risque de blessure chez les enfants et adolescents, et (2) d'éclairer la méthodologie des recherches futures dans ce secteur. Le manuscrit 1 est une revue narrative des principes physiopathologiques et épidémiologiques qui sous-tendent les blessures sportives musculo-squelettiques. Il s'adresse aux épidémiologistes sans formation formelle dans ce domaine particulier. Le manuscrit 2 explore la manière dont l'activité physique antérieure est associée au risque de blessure accidentelle chez les écoliers à l'aide de méthodes flexibles d'exposition cumulative pondérée. Cela montre qu'une activité antérieure effectuée il y a dix semaines ou plus a une association protectrice par rapport au risque de blessure actuel, tandis qu'une activité menée au cours des deux à neuf semaines précédentes a une association préjudiciable. Le manuscrit 3 est un commentaire méthodologique sur le biais de temps immortel dans les études observationnelles sur les changements d'activité et le risque de blessure. Il montre comment les approches conventionnelles de mesure de l'activité entraînent des biais et fournit des recommandations pour éviter ces biais. Le manuscrit 4 est un commentaire méthodologique qui explique comment les données d'observation peuvent être utilisées pour estimer les associations causales entre les changements d'activité et le risque de blessure grâce à l'application du cadre d'essai cible. Le manuscrit 5 applique le cadre d'essai cible à des joueurs de hockey sur glace qui sont adolescents et évalue l'effet de l’intention de traiter en augmentant la durée de participation prévue sur le risque de blessure. Il utilise des approches de modélisation non linéaires flexibles pour montrer que le risque de blessure augmente de manière cohérente par suite d’une augmentation de la durée de participation prévue chez les adolescents.

Ensemble, ces manuscrits font progresser la méthodologie utilisée pour évaluer la relation entre les changements dans les niveaux d’activité physique et le risque de blessure, dans le but ultime de générer des recommandations valides pour promouvoir l'activité physique chez les enfants et les adolescents tout en minimisant le risque de blessure.

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Contribution to Original Knowledge

The contents of this thesis constitute an original contribution to the field of sport injury epidemiology, providing novel insights into (1) the relationship between changes in physical activity and injury among children and adolescents, and (2) the methodology that can be applied for causal inference in this area.

Manuscript 1 is a narrative review on the definitions, mechanisms, and healing of sport injuries from an epidemiological and biological perspective. It was written with the goal of providing a concise introductory overview for epidemiologists interested in advancing this field of research. To our knowledge, there are no other reviews with this purpose in the literature.

Manuscript 2 is the first study to apply flexible weighted cumulative exposure methods in the field of sport injury epidemiology, and is one of only two studies to apply flexible non-linear methods to describe patterns of sport or physical activity. It is also the first study to specifically assess how patterns of previous physical activity are associated with injury risk in children.

Manuscript 3 is the first manuscript to explicitly define an issue where individuals with small observed changes in activity levels appear to have an increased risk of injury as a type of immortal time bias. It is also the first to provide concrete strategies to prevent or mitigate this bias within this field of research.

Manuscript 4 is a methodological commentary that describes the application of the target trial framework to questions of activity and injury. It is the first manuscript to propose the use of the target trial framework in this area of research, and the first to describe the application of any such framework to estimate the causal effect of changes in activity on injury risk.

Manuscript 5 is one of few studies to examine the relationship between increases in activity and injury risk in adolescent ice hockey. It is also the first study to apply the target trial framework to a research question concerning the relationship between changes in activity and injury risk.

Contribution of Authors

Manuscript 1: Chinchin Wang, Steven D. Stovitz, Jay S. Kaufman, Russell Steele, Ian Shrier

C.W. and I.S. conceptualized the review. C.W. drafted the initial manuscript. As clinicians working in the field of sport injury epidemiology, S.D.S. and I.S. provided important clinical knowledge relating to the concepts covered in the manuscript. As epidemiologists without substantive expertise in the field, J.S.K. and R.S. provided important feedback regarding clarity for non-experts. All authors were involved in critically reviewing and revising the manuscript. All authors approved the final manuscript for submission.

Manuscript 2: Chinchin Wang, Michal Abrahamowicz, Marie-Eve Beauchamp, Jay S. Kaufman, Russell Steele, Eva Jespersen, Niels Wedderkopp, Ian Shrier

C.W., M.A., M-E.B., J.S.K., R.S., and I.S. conceptualized the use of flexible weighted cumulative exposure methods to summarize physical activity patterns. M.A. is the original developer of these methods, and M-E.B. has contributed greatly to the development of statistical packages and code to utilize these methods. C.W. conceptualized the study. C.W., M.A., M-E.B., J.S.K., R.S., and I.S. designed the study. C.W. conducted analyses, with guidance from M.A. and M-E.B. C.W. drafted the initial manuscript, and M.A. and M-E.B. contributed to drafting text related to statistical methodology. N.W. is the principal investigator for the parent study that generated the data for this study. E.J. and N.W. were involved in data collection for the parent study. All authors were involved in critically reviewing and revising the manuscript. All authors approved the final manuscript for submission.

Manuscript 3: Chinchin Wang, Jay S. Kaufman, Ian Shrier

C.W. conceptualized this commentary based on discussions with I.S. C.W. drafted the initial manuscript. All authors were involved in critically reviewing and revising the manuscript. All authors approved the final manuscript for submission.

Manuscript 4: Chinchin Wang, Jay S. Kaufman, Russell Steele, Ian Shrier

C.W. conceptualized the application of the target trial framework to studies on activity and injury, based on discussions with R.S. and I.S. C.W. conceptualized and drafted the initial manuscript. All authors were involved in critically reviewing and revising the manuscript. All authors approved the final manuscript for submission.

Manuscript 5: Chinchin Wang, Paul Eliason, Jean-Michael Galarneau, Carolyn A. Emery, Sabrina Yusuf, Russell J. Steele, Jay S. Kaufman, Ian Shrier

C.W. conceptualized this study. C.W. designed the study and conducted analyses. R.J.S. and I.S. contributed to study design, and R.J.S. provided important guidance regarding analyses. C.A.E. is the principal investigator for the parent study that generated the data for this study. P.E., and J-M.G. are part of the research team that collected and validated data for the parent study. C.W., S.Y., and I.S. also contributed to data validation. C.W. drafted the initial manuscript. All authors were involved in critically reviewing and revising the manuscript. All authors approved the final manuscript for submission.

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List of Abbreviations and Acronyms

ACWR	Acute:chronic workload ratio
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
CI	Confidence interval
df	Degrees of freedom
DLNM	Distributed lag non-linear model
DOMS	Delayed onset muscle soreness
EWMA	Exponentially weighted moving average
GAM	Generalized additive model
GAMM	Generalized additive mixed model
GEE	Generalized estimating equations
GLM	Generalized linear model
GLMM	Generalized linear mixed model
HR	Hazard ratio
IOC	International Olympic Committee
IRF	Injury report form
ITT	Intention to treat
LRT	Likelihood ratio test
PH	Proportional hazards
PP	Per protocol
RCT	Randomized controlled trial
RPE	Rating of perceived exertion
RR	Risk ratio
sRPE	Session RPE
WCE	Weighted cumulative exposure
WES	Weekly exposure sheet

Chapter 1: Introduction

Physical activity plays a crucial role in maintaining healthy lifestyles.[1] Among children and adolescents, physical activity promotes healthy bone growth and development, improves cardiovascular health, and prevents obesity and its related morbidities.[2] Organized sport participation is a common avenue for children and adolescents to obtain regular physical activity, and provides additional psychosocial benefits including improved socialization and mental health.[3]

Despite its benefits, physical activity and sport participation have an inherent risk of injury.[4] Consequences of injury are wide-ranging, and may include time lost from participation in sport or physical activity due to recovery needs or reduced enthusiasm, impaired development, and the need for surgical intervention.[5,6] Sport-related injuries are also an economic burden,[7,8] with physical activity and sport participation accounting for over 50,000 emergency room visits in Canada between 2007 and 2010.[9] As such, reducing injuries while maintaining or increasing physical activity is an important goal for children and adolescents, parents, coaches, and clinicians.

Current guidelines recommend that children and adolescents obtain a minimum threshold of physical activity for health, with further activity resulting in greater health benefits.[10] There are limited research and no guidelines on the risks of injury associated with increasing physical activity levels among children and adolescents. Among adults, the International Olympic Committee (IOC) currently recommends that athletes increase their activity by less than 30% in a given week to minimize injury risk.[11] However, these recommendations are based off studies with small sample sizes and methodological issues, and are unlikely to be valid.[12,13] There remains an evidence gap in the relationship between changes in physical activity levels and injury risk, particularly among children.

The objectives of this thesis are (1) to assess the relationship between changes in physical activity levels and injury risk among children and adolescents, and (2) to inform the methodology for future research in this area. Our overarching goal is to inform recommendations

for promoting increased physical activity while minimizing injury risk among children and adolescents.

Organization of Thesis

Chapter 2 reviews the relationship between physical activity and injury, including current evidence in the literature and their limitations. Chapter 3 reviews statistical methods relevant to this thesis. Chapter 4 contains Manuscript 1, a narrative review on the biological and epidemiologic principles underlying musculoskeletal sport- and physical activity-related injuries. Chapter 5 contains Manuscript 2, a research study that employs flexible non-linear methods to determine the association between previous physical activity patterns and current injury risk in schoolchildren. Chapter 6 contains Manuscript 3, a methodological commentary on immortal time bias in observational studies of changes in activity and injury risk. Chapter 7 contains Manuscript 4, a methodological commentary on the potential application of the target trial framework to estimate causal associations between change in activity and injury risk using observational data. Chapter 8 contains Manuscript 5, a research study that applies the target trial framework to adolescent ice hockey players to determine the effect of increasing planned participation on injury risk. Chapter 9 discusses the overall findings of the thesis, limitations, and future directions.

Chapter 2: Literature Review

Preface

In this chapter, I provide a summary overview of the relationship between physical activity and injury. A more in-depth review of musculoskeletal sport injuries, their mechanisms, and various definitions and categorizations used in epidemiologic research is provided in Chapter 4 (Manuscript 1).

Mechanism of physical activity-related and sport injuries

Physical activity and sport exposes individuals to various forces. The sum of these forces acting on a tissue is referred to as load (or tissue load).[14] Although tissues within the human body have a certain tolerance for load, loads beyond a tissue's load capacity will result in tissue damage.[14,15] Significant tissue damage that can be visualized without a microscope or that results in physical symptoms are generally considered injuries.[14,15]

The musculoskeletal system is primarily responsible for human movement and the ability to be physically active.[16] Musculoskeletal tissues, which include bones, muscles, ligaments, and tendons, typically adapt and strengthen in response to loads that are close to or minimally above their load capacities, given sufficient recovery time.[17,18] However, without sufficient recovery, microdamage will accumulate and load capacity will decrease, resulting in injury even at normal loads (known as "overuse" injuries).[14,15,19] Further, sudden large loads will cause immediate tissue damage and injury (known as "acute" injuries).[14,15]

Injuries can also occur to other organ systems during physical activity. Most notable among children and adolescents are neurological injuries, including concussions.[20] The biological mechanism for neurological injuries are similar to musculoskeletal injuries, where excessive loads will lead to tissue damage.[21] Neurological injuries generally occur due to trauma or stretching,[20] and as such are considered acute injuries.[22]

Fatigue and injury

Fatigue is a complex phenomenon that within this review, is defined as the decreased capacity of an individual to perform maximal physical activity due to prolonged physical exertion.[23] Fatigue can occur with unaccustomed or strenuous physical activity, and has both physical and mental aspects.[23,24] On a physiological level, fatigue is often associated with changes in cellular states that decrease the capacity of tissues and organs to sustain the original level of physical activity using typical resources.[23] Muscle fatigue in particular refers to a reduction in the maximal force a muscle can exert.[23,25] Mental fatigue is a psychological state caused by prolonged cognitive activity.[23,24] Mental fatigue reduces an individual's cognitive and physical capacities, and is often associated with feelings of tiredness.[23,24] Muscle and mental fatigue are reversible with sufficient rest and recovery,[23] and are not considered injuries.

Both muscle and mental fatigue are causal risk factors for injury through various mechanisms. Muscle fatigue is caused by the accumulation of tissue microdamage, resulting in a decreased load capacity and increased susceptibility to overuse injuries.[14,17] Both muscle and mental fatigue can impair balance, proprioception, spatial awareness, and reaction time,[23,26–30] increasing susceptibility to acute injuries (musculoskeletal or neurological) through falls or collisions.

Measurement of load and physical activity

Although it is the load on tissues that affects physical adaptations and injury, in practice, tissue loads are rarely measured.[31] Direct measurements of tissue load require invasive and expensive methods,[31] and are thus infeasible for epidemiologic studies. Tissue load can be approximated using external force, which refers to the forces applied to the surface of the human body.[14,31] However, the measurement of external force requires specialized sensors that are generally infeasible on a population level.[14,31] Instead, load is typically quantified using indirect measures.

A note on terminology

I defined "load" earlier as the sum of the forces that an individual is exposed to during physical activity and sport. However, sport medicine researchers often use "load" as a short-form for "workload" or "training load".[32] Training load has been described as the input variable that is

manipulated to elicit a desired training response.[33–35] Workload is another common term that is often used interchangeably with training load.[32] In practice, "load", "workload", and "training load" are generic terms used to cover a broad range of exposure variables related to sport and physical activity that may act as indirect measures of tissue load.[32,35] While I generally use the terms "physical activity" or "activity" to represent my exposures of interest, depending on the context and target audience for a particular manuscript, I may use "load" in the same sense. For the remainder of this thesis, the term "load" is used to refer to a general exposure variable related to sport or physical activity rather than tissue load itself, unless otherwise stated.

Internal and external load

Load measures can be described as "external" or "internal.[33] External loads generally encompass measures that individuals are physically exposed to, while internal loads encompass psychophysiological measures relating to how individuals respond to activity.[33,35] Individuals exposed to the same external load may have different internal loads.[33]

Measures of load in epidemiology

Measures of load usually relate to one or several components of physical activity: frequency, intensity (rate of energy expenditure), time (duration), and type.[36] These components can be combined into a single measure of energy expenditure.[36] The gold standard for measuring energy expenditure is the doubly labeled water method;[37] however, it has a high cost and cannot separate out the individual components of physical activity.[36,38] As such, it is rarely applied in epidemiologic research.[38]

In epidemiologic studies, load is often defined simply by the frequency or duration of activity. These are measures of external load, and can be general (e.g. number of activity sessions per week, total duration of activity per week), or specific to the sporting context (e.g. distance covered, weight lifted).[33] Frequency, duration, and type of physical activity are relatively straightforward to assess through self-report or direct observation, although self-reported measures can be limited by measurement error and recall or response biases.[39,40]

The intensity of activity also impacts tissue load.[14,40] Intensity can be assessed using devices or through self-report. The rate of oxygen consumption is an internal physiological measure of the intensity of activity that is sometimes used to assess endurance activities.[31] While oxygen consumption can be measured directly, it is normally approximated by heart rate.[41,42] Heart rate monitors are relatively low cost, portable, and non-invasive devices that can often measure duration of activity as well as heart rate.[41,42]

Accelerometers are another low cost and portable device used to assess physical activity. Accelerometers measure the human body's acceleration in multiple planes, which can be used to predict intensity and energy expenditure.[41] They are also able to measure frequency and duration, and can differentiate between some types of activity (e.g. running vs. cycling).[41,43] However, accelerometers are not necessarily reliable,[44] and are not able to accurately detect all types of movements.[45] Accelerometers have been employed in several large-scale population studies, including national surveys in Canada and the US.[43]

Despite the benefits of device-based measures of physical activity, their associated costs can be prohibitive, particularly for large-scale longitudinal studies.[46] Further, device reliability can be affected by human error (e.g. forgetting to wear the device or accidentally altering the device position).[44,46] Intensity can be measured subjectively using ratings of perceived exertion (RPE). RPE is self-reported, typically using a numerical scale, and is a measure of internal load.[47,48] RPE has been found to be correlated with physiological measures like heart rate and oxygen consumption.[48] Session RPE (sRPE) is a modified measure calculated by multiplying RPE by duration of activity.[49] Perceived exertion can vary greatly between individuals,[48,50] and is affected by age, sex, and expertise as well as psychological factors like anxiety and stress.[50] Further, activity duration can influence RPE,[51] as individuals typically perceive greater exertion during prolonged activities due to fatigue.[48] This complicates the interpretation of sRPE, as duration is accounted for twice in its calculation.[51]

Quantifying the relationship between physical activity and injury

Absolute activity and injury risk

It is generally accepted that large absolute amounts of physical activity result in increased injury risk, regardless of the measure.[52,53] As injuries occur when tissue load exceeds the load capacity,[14,15] it follows that larger loads result in higher injury risks.

Increased frequency and/or duration of activity can result in increased risk of injury not only through increased loading on tissues, but through increased exposure time at risk and fatigue.[4,54] With increased exposure time, there is greater opportunity for inciting events that result in tissue loads exceeding load capacity, such as a fall or rapid movement.[55] Further, increased activity frequency and duration increases the risk of fatigue and resultant injuries.[23]

To minimize injury risk, individuals must minimize fatigue and exposure to tissue loads near or above their load capacity. Because fatigue and load capacity are functions of tissue strength and preparedness from previous activity,[14,23] studying current activity relative to previous activity can provide more insight into the relationship between physical activity and injury.

The fitness-fatigue model

In the 1970's, Banister et al. proposed a "fitness-fatigue" model to relate training patterns to athletic performance.[56] In this model, performance is determined by a combination of fitness, or beneficial physiological effects of long-term training, and fatigue, or negative physiological effects of short-term training.[56–58] As tissue adaptations take time, activity performed in the past is regarded to improve fitness whereas activity performed in the present or very recently is regarded to cause fatigue.[56] Performance is optimal when fitness is high and fatigue is low.[56–58]

The acute:chronic workload ratio

In 2014, Gabbett et al. proposed a model called the "acute:chronic workload ratio (ACWR)" to relate training patterns to injury risk.[59,60] Similar to the "fitness-fatigue" model, past activity ("chronic load") represents a proxy for fitness, or the activity to which an individual is accustomed to, whereas current or recent activity ("acute load") represents a proxy for

fatigue.[59,60] The ACWR is calculated by dividing the acute load by the chronic load.[59,60] Injury risk was proposed to increase as the acute load outweighs the chronic load (ACWR > 1).[59]

Gabbett et al. defined the acute load as the load in the present week (1-week period), and the chronic load as the unweighted weekly average of load in the present and previous 3 weeks (4-week period).[59] The ACWR was originally applied to cricket fast bowlers, with load quantified as (1) the number of balls bowled per week, and (2) sRPE.[59] The authors found that bowlers with ACWRs greater than 2 had a 3.3-times greater injury risk in the subsequent week than bowlers with ACWRs between 0.5 and 0.99, but no association between the ACWR and injury in the current week.[59]

Subsequently, Gabbett et al. also applied the ACWR in studies of rugby and Australian football, quantifying load as distance covered while running. They developed a general model for the relationship between the ACWR and injury risk using data from these three studies. This model identified ACWRs between 0.8 and 1.3 as being associated with the lowest risk of injury in the subsequent week, and ACWRs below 0.8 or above 1.3 as being associated with increased risk of injury.[60] It had several methodological limitations, including arbitrary discretization of the ACWR prior to modelling, sparse data, and not accounting for repeated measures.[12] Further, it combined different measures of load, with results unlikely to be applicable to a wide range of sporting contexts. Even so, this model was used to generate training recommendations for athletes across all team sports in the 2016 "International Olympic Committee (IOC) consensus statement on load in sport and risk of injury".[11]

Variations of the ACWR

Coupled versus uncoupled measure

In the original formulation of the ACWR, the acute load was defined as the load over the current week, whereas the chronic load was the average weekly load over the current week and previous 3 weeks.[59] This creates a "coupled" measure, where the acute load is included in the numerator and denominator, and is a proportion rather than a true measure of change.[12] The coupled measure with an acute window of 1 week and chronic window of 4 weeks is capped at ACWR=4 as the acute load increases towards infinity and the chronic load decreases towards zero,[12,61] and

is thus limited in its ability to differentiate injury risks at high acute loads.[12,62] An alternative "uncoupled" measure[12] defines the chronic load as the average weekly load over the 3 weeks prior to the acute load week, so that the acute load is not included in the chronic load calculation. The use of uncoupled acute and chronic loads allows for simpler calculations and interpretations of changes in load.[12]

Acute and chronic time windows

Although the original time windows of 1 week (acute) and 4 weeks (chronic) were chosen arbitrarily,[59] they have since been used in the majority of studies employing the ACWR.[63–65] Some studies have explored chronic time windows between 2 and 8 weeks, and found differences in model fit.[62,66–71] Other studies have explored acute time windows of 2 weeks,[69] or have calculated ACWRs using daily data (e.g., 3 day acute load and 21 day chronic load).[71,72] Although multiple authors have recommended that the choice of time windows be decided based on the sporting context and schedule,[63,64,71] there remains no clear guidance on identifying the relevant time windows.

Unweighted versus weighted averages

The chronic load is defined as an unweighted weekly average in the original formulation of the ACWR.[11,60] The use of an unweighted average obscures daily variations in activity, and assumes that activity performed in each week is equally associated with injury risk.[73] This is unlikely to be the case, as the physiological effects of activity on tissues and performance decay over time.[74,75] In 2017, Williams et al. proposed the use of an exponentially weighted moving average (EWMA) to calculate acute and chronic loads.[76] The EWMA assigns exponentially decreasing weights for activity performed in each previous day, such that activity performed furthest in the past should have the lowest weight.[76] In actuality, while weights decrease exponentially, activity performed on the day furthest in the past takes on a much higher weight than more recent activity due to the EWMA's mathematical formulation.[12]

Although we previously explored a modified EWMA that assigned decreasing weights to data summarized weekly,[62] the EWMA is normally applied only when daily data are available. Several studies have found that ACWRs measured with the EWMA had greater associations with

injury than ACWRs measured with a daily rolling average,[64,70,77] while others found no difference between the two methods.[78]

A proposed alternative weighting approach is to use non-linear functions based on daily or weekly data to represent weighted cumulative acute and chronic loads.[79] In simulations, a distributed lag non-linear model was found to better fit the relationship between relative changes in load and injury risk than the coupled unweighted ACWR (7 day acute window and 28 day chronic window).[80] In Manuscript 2, we explore applying flexible weighted cumulative exposure methods to summarize activity.

Current or lagged injury risk

Studies have assessed associations between the ACWR and injury in the acute time window (e.g. current day or week), as well as those occurring in a subsequent time period (most often the subsequent week).[63] The assessment of injury during the acute time window ignores temporality between activity and injury.[81] Individuals who get injured early in the acute time window are likely to have systematically lower loads than those who remain uninjured. This systematic difference can lead to an observed increase in current injury risk at low ACWRs as reported by the IOC consensus statement,[11] even if low ACWRs are causally protective against injury.[12,52] This bias is covered in more detail in Chapter 7 (Manuscript 3).

Employing a lag period for injury avoids this bias. Some authors have suggested that the use of a lag period is also important because spikes in activity can predispose individuals to higher injury risks for up to 4 weeks.[63,69] However, the use of a lag period ignores the principle that a current tissue load beyond the load capacity is the impetus for injury. It also ignores variations in current activity that may influence injury risk.[12] This is of particular concern when acute and chronic loads are measured using weekly blocks.[12] For instance, an athlete with a low ACWR in the current week might become injured upon increasing their load in the subsequent week (i.e. have a high ACWR in the subsequent week). This would result in an apparent increased injury risk in the subsequent week at low ACWRs in the current week, even if low ACWRs are causally protective against injury.

Current state of evidence

Since its introduction, the ACWR has been employed in numerous studies assessing injury risk in both team[63,64] and individual sports.[82–85] In fact, the number of PubMed-listed publications employing the ACWR has been increasing exponentially year-to-year as of 2020.[86] Study populations have ranged in performance levels (i.e. recreational, amateur, elite, professional) and age groups.[63,64,87] Further, the ACWR model presented in the IOC consensus statement has been employed to monitor training and generate recommendations across a variety of sporting contexts.[88–90]

Multiple authors have raised criticisms of the ACWR. These relate mainly to the methodological approaches applied to ACWR studies, including those that led to the IOC consensus model (e.g. discretization, small sample sizes, not accounting for repeated measures, no control for confounding, p-hacking).[12,91,92] Despite being used to make training recommendations, requiring causal interpretations of findings, the majority of studies have been associational, without consideration of causal assumptions.[12,92,93] To our knowledge, there are no studies that have employed causal frameworks to study the effect of the ACWR (or load more generally) on injury risk.[93] The varying results obtained under different ACWR variations (i.e. load definition, time window, coupled vs. uncoupled measure, unweighted vs. weighted average, injury lag period) has also been cited as a reason against its use.[13,94] Some authors have also suggested that the use of a ratio to express changes in activity in itself is inappropriate because the ACWR does not scale consistently across its range of values (i.e. inaccurate normalization).[95–97] Despite recommendations to develop new conceptual models for the relationship between physical activity and injury,[94] the ACWR remains one of the only such models and is by far the most commonly used by both researchers and the general public.[79]

Chapter 3: Overview of Methods

Preface

In this chapter, I provide a brief overview of the statistical methods used in this thesis, as well as other relevant methods.

Measures of injury incidence

Injury incidence is normally expressed as a risk or a rate. Injury risk is defined as the number of injured individuals divided by the number of individuals at risk over a specified period of time.[98] Injury rate is defined as the number of injuries divided by the total person-time at risk.[98] Rates might be expressed as the number of injuries per game, activity session, or minutes active.[99]

One could also express injury incidence as a time-to-event or hazard (instantaneous event rate).[100] This requires analyzing data using survival analyses, and requires extensions to account for recurrent or subsequent injuries.[100,101] While these measures can provide important insights for reducing injury incidence, they are often less interpretable[100] and prone to selection bias.[102]

Finally, injury incidence can be expressed as an odds. Injury odds is defined as the probability of injury occurring (injury risk) divided by the probability of injury not occurring (1 - injury risk).[103] Injury odds are a less intuitive measure than injury risks or rates for the general public, but are the basis for common statistical procedures (i.e. logistic regression).[103] As such, they are often employed in the literature.

Injury rates may be the preferred measure for comparing injury incidence between different mechanisms (e.g. sports), as they account for differences in exposure time.[98,104] However, injury risks are generally more intuitive for individual decision-making.[98] For example, suppose that soccer has an injury rate of 0.10 injuries per hour of participation, while hockey has an injury rate of 0.12 injuries per hour of participation. Suppose that a typical practice session in children's soccer lasts 60 minutes while a practice session in children's hockey lasts 45 minutes. While we might conclude that hockey is a more dangerous sport given its higher injury rate, parents might conclude that soccer is a more dangerous sport given that the risk of their child getting injured

within a practice session is greater in soccer (10% injury risk per session in soccer compared to 9% in hockey).

The overarching goal for athletes, coaches, clinicians, and parents is to increase activity while minimizing risk of injury. Increases in activity generally involve an increase in the exposure time at risk. Unlike injury risks, comparisons of injury rates do not directly contrast injury likelihood under different activity patterns. The exception is when only the intensity of activity is increased. If we consider the effects of increases in intensity that occur without changing activity frequency or duration, the injury risk will be equivalent to the injury rate over the same period of time.

Most load metrics involve a time component (e.g., duration of activity, number of activity sessions, sRPE). This must be taken into consideration when comparing injury risks under different loads. For instance, an individual might be interested in the risk of increasing their activity from 1 hour to 2 hours. Absent a causal effect of changing activity on injury, the injury risk for 2 hours of activity would be expected to be double the risk for 1 hour of activity simply because the exposure time is doubled. However, the injury rate under these two situations would be expected to be equal. If the injury risk for 2 hours of activity was 3-fold that of the risk for 1 hour of activity, the risk of injury associated with increasing activity duration would be greater than expected. Therefore, we would conclude a causal effect of increasing activity duration on injury if the necessary assumptions for causal inference are met.[99]

Injury effect measures

Ratios are often used to compare injury incidences between groups.[98] Although risk ratios, rate ratios, odds ratios, and hazard ratios all represent different measures of association, they will approximate each other if the risk of the outcome is rare or when measured over a short period of time.[105–107] Injury incidences can also be compared between groups using differences,[98] which take into account the absolute magnitude of injury incidence.[108]

Risk ratios are collapsible, meaning that in the absence of confounding, the weighted average of stratified risk ratios will equal the marginal risk ratio. Similarly, adjustment for a variable that is not a confounder will not change the value of the risk ratio.[109,110] Odds ratios, rate ratios, and

hazard ratios are non-collapsible, and as such are more difficult to interpret causally than risk ratios.[102,109–111]

Modelling injury data

Injury probability distributions

Normally, the injury outcome is assumed to follow a binomial distribution for inferences on injury risks or odds, and a Poisson or negative binomial distribution for inferences on injury rates or counts.[103,112] These assumptions should be checked before conducting analyses, as they may not always hold. Injury hazards are most commonly modelled using the Cox proportional hazards (PH) model, which does not make assumptions about the distribution of survival times (time-to-injury).[113]

Generalized linear models

Generalized linear models (GLMs) are a class of models where the outcome variable is assumed to follow an exponential family distribution which is related by a linear or non-linear link function to a linear combination of the explanatory variables.[114] GLMs include logistic models, which use a logit link function, Poisson models, which use a log link function, and log-binomial models, which also use a log link function.[114] GLMs impose a single functional form for the relationship between the explanatory variables and link-transformed outcome variable across their entire range.[115] GLMs encompass the most commonly used models in epidemiology, and are simple to interpret and computationally efficient.[116] However, they may result in erroneous inferences if the assumptions regarding functional form are not met.[116]

Generalized additive models

Generalized additive models (GAMs) are an extension of GLMs which employ locally smooth functions rather than imposing a single functional form for the relationship between the explanatory and outcome variables.[115] These smooth functions can be estimated non-parametrically, and do not have to be specified.[114] GAMs can be used with any of the link functions employed under GLMs.[115] As such, they are a flexible, non-linear alternative to

GLMs.[115] GAMs are not necessarily uniformly better than GLMs. They are more computationally intensive than GLMs, more difficult to interpret, and may result in overfitting.[117]

We employ GAMs to model the relationship between changes in hockey participation and injury risk in Manuscript 5.

Cox proportional hazards model

The Cox PH model is the most commonly used model for survival analyses.[113] It is a semi-parametric model, in that it does not make distributional assumptions about survival times.[115] This makes it popular over parametric models such as the exponential or Weibull model.[118] However, the Cox PH model does specify the form in which the explanatory variables affect the hazard rate (a multiplicative or "proportional" relationship so that the relative hazards are constant over time, known as the proportional hazards assumption).[113,115] Violations of this assumption can be handled by including time-varying covariates within the Cox PH model,[119] or stratification by variables that do not satisfy the assumption.[120] While explanatory variables are generally assumed to be linearly related to the log hazard in a Cox PH model,[113] the form of the explanatory variables can be expressed flexibly with non-linear functions.[115]

Cox PH models are limited in that while the magnitude of hazard ratios tends to vary over time, simply fitting a Cox PH model will provide an average hazard ratio over time (ignoring period-specific changes in hazard ratios).[102] Further, they have a built-in selection bias where the calculation of hazard ratios at a particular time point is limited to those who have survived up to that time.[102] This is of particular concern for research questions involving physical activity and injury risk, because those who remain uninjured will accumulate more observed physical activity than those who become injured earlier on. An alternative survival method that may be more amenable for causal inference is the Aalen additive hazards model; however, it is much less utilized in the literature.[121,122]

We employ the Cox PH model to assess the association between previous activity and time-to-first injury in Manuscript 2.

Estimating injury risks and risk ratios using regression

Binary data are often analyzed using logistic regression.[123] Logistic regression involves modelling the log odds of an outcome, and is used to estimate odds ratios.[123] However, injury odds and odds ratios are rarely the incidence measure of interest.[103] Further, injury is not necessarily a rare outcome, and as such, injury odds and odds ratios may not be good approximators of injury risks and risk ratios.[103]

Log-binomial regression yields estimates of risk ratios.[124] However, there are frequent issues with fitting log-binomial models due to failed convergence.[124] A modified Poisson regression can also be used to estimate risk ratios; however, expected probabilities may not be constrained between 0 and 1.[124,125]

Logistic regression can be used to derive risks and risk ratios through marginal standardization.[125,126] Briefly, one could fit a logistic model to the data, and calculate predicted odds of the injury outcome for the study population under different treatment conditions. Covariate values are set to their observed values, so that only the treatment variable changes. The odds can be converted to risks, and risk ratios calculated by dividing the risks under the different treatment conditions.[126] Bootstrapping can be used to calculate standard errors and confidence intervals for the risks and risk ratios.[125,126] Marginal standardization is implemented to calculate risks and risk ratios in Chapter 8 (Manuscript 5).

Accounting for repeated measures

Injury is a recurrent event, in that it can occur multiple times in the same individual.[101] Most longitudinal studies relating to sport injuries collect repeated measurements of activity and injury within the same participants over time.[127,128] Standard modelling approaches assume that each observation (i.e. occurrence of injury) is independent.[127] However, observations within an individual are often correlated more strongly than observations between individuals. Not accounting for this correlation will result in overly precise and potentially biased estimates.[101,128] Further, individuals may have different risk factors that make them more or less susceptible to injury, and therefore different baseline injury risks.[101] The influence of different covariates on injury risk may also differ between individuals.[101] Standard modelling approaches assume the

same baseline injury risk given a set of covariates for all individuals, and the same influence of covariates on injury risk.[101] Below, I briefly discuss several analytical techniques that can be used to account for repeated measures.

Mixed effect models

Repeated measures can be accounted for by including a random effect (intercept and/or slope) within a GLM or GAM. Random effects are able to vary across clusters (in this case individuals), as opposed to fixed effects which are set to a particular value for all individuals.[129] Models that allow for random effects are generally referred to as mixed effect models, and include generalized linear mixed models (GLMMs) and generalized additive mixed models (GAMMs).[129,130] These models account for correlation within clusters in their standard errors.[129]

When the probability of injury is modelled using a standard fixed effect model (GLM or GAM), individuals are assumed to have the same baseline injury risk, reflected in a fixed intercept.[101] The influence of covariates on injury risk are also assumed to be the same across all individuals and injuries, reflected in fixed slopes.[101] Random intercepts on the individual-level allow the baseline injury risk to vary between individuals, whereas random slopes allow the influence of covariates to vary.[101] Mixed effect models make distributional assumptions about their random effects, and may generate biased estimates if the model is misspecified.[131] Several packages exist to implement GLMMs and GAMMs in standard statistical software.[132,133] Issues with convergence tend to occur as more random effects are included in a model.[134]

Generalized estimating equations

Generalized estimating equations (GEE) account for repeated measures by estimating the correlation within individuals through an iterative process.[135] Unlike mixed effect models, GEE employs robust estimation of standard errors, and as such, does not require a correctly specified error distribution.[131] Whereas mixed effect models provide estimates conditional on the individual, GEE is used to fit marginal or population average models.[131] While a mixed effect model might be used to estimate the average change in injury risk associated with a change in activity level (high vs. low) within an individual, a population average model would estimate the change in the average injury risk for high versus low activity levels for the population.[131]

Conditional estimates may of greater interest to individuals or clinicians looking to decrease their own or their patient's risk of injury, whereas marginal estimates may be of more interest to policymakers looking to decrease injuries within a population. Parameter estimates for mixed effect models versus GEE typically differ when using logistic regression, with population average estimates closer to the null value of 1.[131] While GEE can be easily implemented with GLMs using standard statistical software,[136] extensions to GAMs are limited.

Cluster bootstrapping

Cluster bootstrapping is an alternative approach to account for repeated measures, particularly when the number of clusters is low.[137] Cluster bootstrapping is based off of standard bootstrapping. Whereas standard bootstrapping involves drawing a random sample of observations (i.e. rows of data) equal to the size of the dataset repeatedly with replacement, cluster bootstrapping involves drawing a random sample of clusters (e.g. individuals) equal to the number of clusters with replacement.[137] All observations within the sampled clusters are included when computing the statistics of interest, and confidence intervals are derived using standard procedures (e.g. by taking the 2.5% and 95% percentiles of the distribution of the sample statistic).[137,138]A major limitation of cluster bootstrapping compared to mixed effect models and GEE is its computational intensity.[137]

We employ cluster bootstrapping to account for repeated measures on the individual level in Manuscripts 2 and 5.

Summarizing physical activity data

As discussed in Chapter 2, researchers often employ unweighted or weighted averages to represent cumulative physical activity or load data, particularly those that occurred in the past (i.e. chronic load). We explore using flexible weighted cumulative exposure (WCE) methods to represent cumulative physical activity in Manuscript 2.

Flexible weighted cumulative exposure methods

WCE methods were originally proposed as a way to summarize past exposures (specifically doses) in pharmacoepidemiology.[139] Cumulative doses at any given time were calculated as a weighted mean of past doses, with higher weights assigned to more recent doses, using a pre-specified weight function.[140] The cumulative dose could then be included as a time-varying exposure in a Cox PH model.[140] Flexible WCE methods are an extension to this approach, where the weight functions are estimated flexibly using cubic regression B-splines rather than imposing a specific functional form.[141] The weight function is then included as the exposure of interest in a Cox PH model, which allows for the adjustment of additional covariates.[139,141]

Flexible WCE methods offer a data-driven approach to (1) weighting past exposures, and (2) determining the relevant time window over which a cumulative exposure is associated with an outcome.[139,142] These methods may be particularly beneficial for assessing the effect of cumulative loads on injury, as both the relative importance of loads at different time points and the time window over which previous loads may affect current risk of injury are unknown.

Flexible WCE methods are easily implemented using the *WCE* package in R.[143] Briefly, the user specifies the time-varying exposure, outcome, and covariates, the time window of interest, and the number of knots used for the cubic B-spline regression. A higher number of knots offers increased flexibility of the weight function.[139] The Akaike Information Criterion (AIC) or Bayesian Information Criterion (BIC) can be used to compare the fit of models with different knots and time windows.[142] Below, I outline some technical details on how the weight functions are estimated.

Weighted cumulative exposure

The weighted cumulative exposure at time *u*, for individual *i*, is defined as:

$$WCE_i(u) = \sum_t^u w(u-t)X_i(t),$$

where $X_i(t)$ is the exposure for individual *i* at time *t*, *u-t* is the time elapsed since the exposure $X_i(t)$, and $w(u-t)$ is an estimated weight assigned to exposure at time *t*, based on time elapsed since exposure *u-t*. The estimated weights quantify the relative importance of exposures that occurred *u-t* weeks prior for the hazard of outcome at time *u*, with positive weights indicating

increased hazard and negative weights indicating decreased hazard.[140,144] Weighted past exposures are summed for each past time *t*, from the start of a user-selected time window of relevant past exposure up to time *u*. The resulting $WCE_i(u)$ is a time-varying exposure metric, calculated at each time *u* during follow-up, until the time of event or censoring.[141]

The weight function is estimated flexibly using cubic regression B-splines, avoiding having to specify *a priori* the form of the function. The weight function is defined as:

$$w(u-t) = \sum_{j=1}^{m+4(-2)} \theta_j B_j(u-t)\,,$$

where *m* is the number of interior knots within the estimated spline function which determines its flexibility and degrees of freedom, B_j are the m+4(-2) functions in the B-spline basis, and θ_j are coefficients that are estimated from the data.[141]

The time window over which the WCE function is modelled, [u - a, u], must also be specified. Exposures occurring before this interval ($t < u - a$) are thought to be too far in the past to be etiologically relevant to the risk of outcome at time *u*. The function can be constrained so that weights smoothly decrease to zero at either end of the time window.[141]

Chapter 4: Manuscript 1

Preface

Sport injury epidemiology is a growing research area concerned with the prevention, diagnosis, and management of injuries sustained during sport and physical activity. It plays an important role in reducing injury incidence among individuals of all ages and backgrounds. While some researchers in this field are medical professionals or otherwise have an extensive understanding of the biological and clinical basis of sport injuries, this is not a given. In fact, sport injury epidemiology is a field that can benefit from skilled methodologists with other substantive backgrounds.

The most common type of sport injuries, particularly among children, are those affecting the musculoskeletal system. This manuscript is a narrative review on musculoskeletal sport injuries targeted toward epidemiologists without a substantive background in this field. It was written with the goal of providing a concise introductory overview for future researchers and methodologists interested in advancing this field of research.

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Principles of musculoskeletal sport injuries for epidemiologists: a review

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Abstract

Background: Musculoskeletal injuries are a common occurrence in sport. The goal of sport injury epidemiology is to study these injuries at a population level to inform their prevention and treatment.

Main Body: This review provides an overview of musculoskeletal sport injuries and the musculoskeletal system from a biological and epidemiologic perspective, including injury mechanism, categorizations and types of sport injuries, healing, and subsequent injuries. It is meant to provide a concise introductory substantive background of musculoskeletal sport injuries for epidemiologists who may not have formal training in the underlying anatomy and pathophysiology.

Conclusion: An understanding of sport injuries is important for researchers in sport injury epidemiology when determining how to best define and assess their research questions and measures.

Keywords: sport injuries, musculoskeletal system, epidemiology, strains and sprains

Background

Sport and physical activity are crucial to maintaining a healthy lifestyle for people of all ages. Their wide-ranging benefits include prevention of chronic diseases, reduced morbidity and mortality, and improved mental health.[1] However, participation in sports and physical activity can also result in injury. Referred to as "sport injuries", they occur most commonly to the musculoskeletal system that allows the human body to move. Sport injuries can result in morbidity, predispose to further injuries, and decrease subsequent activity due to time lost during recovery or reduced desire to be active.[2] By studying the epidemiology of sport injuries, we can inform their prevention and management at a population level.

Epidemiologists conducting research in the sport injury field may not have formal training in the anatomy and pathophysiology of sport injuries and the musculoskeletal system. This review aims to provide a concise introductory overview of musculoskeletal sport injuries for epidemiologists, covering 1) definition of a sport injury from biological and epidemiological perspectives; 2) common categorizations of sport injuries and subsequent injuries; 3) a summary of the musculoskeletal systems and the injuries occurring to specific tissues and organs; 4) principles of healing and rehabilitation of sport injuries.

Main text

What is a sport injury?

An injury is generally considered a sport injury when it occurs in relation to participation in sport or physical activity. Sport injuries occur most commonly to the musculoskeletal system[3] and as such, we focus on musculoskeletal sport injuries in this review. However, sport participation can also result in injuries to other organ systems such as the neurological system (e.g. concussions, spinal cord injuries and peripheral nerve injuries), cardiovascular system (e.g. arrhythmias), and other systems.[4,5] In this section, we provide definitions of injury from both the biological and epidemiological perspectives.

Biological perspective

Biologically, injuries are broadly defined as tissue damage.[6] When an individual performs activity, their body is exposed to various forces. For simplicity, we will refer to the sum of these forces as load.[6] Load causes tissues to undergo deformation. Upon deformation, tissue cells try to keep or restore themselves to their original state, causing an internal resistance known as stress.[6–8] Loads beyond a tissue's load capacity (or load tolerance) will cause excessive stress leading to tissue damage (Figure 1A).[6,8]

Tissue damage can occur to varying extents. Large loads beyond a tissue's load capacity will cause immediate tissue damage. The amount of damage can usually be visualized without a microscope, and may result in physical symptoms (e.g. pain) and limitations of tissue function.[6,8] Healing involves structural changes, where damaged tissue may be repaired or replaced with scar tissue.[9] Smaller loads that are close to or minimally above a tissue's load capacity can cause microdamage or microtrauma, referring to microscopic tears or cracks within a cellular membrane that can be viewed using traditional light microscopy.[6,8,10–12] While generally considered an injury in a biological sense, when microdamage is isolated, tissues are usually able to restore tissue integrity without scar tissue, and without most of the physical symptoms of injury.[8] Given sufficient recovery time, structural adaptations in response to microdamage lead to increased tissue strength and load capacity (Figure 1B).[13,14] However, repeated microdamage without sufficient recovery can result in injury, limiting tissue function and resulting in physical symptoms and scar tissue formation (Figure 1C).[6,8,9]

Damage can also be restricted to the internal structure of a tissue cell, which might be only visible using electron microscopy.[12] This includes damage at the cell cytoskeleton level.[15,16] The cytoskeleton is responsible for cellular structure and stability, and plays crucial roles in cell movement, division, and intracellular transport.[16] Damage to the cytoskeleton might impair transport of important molecules, leading to decreased cell function.[16] This damage may or may not be considered an injury. For instance, concussion injuries usually involve a decrease in neuronal brain function without visible microscopic damage.[17] While the underlying mechanisms for the decreased function are not fully understood, this is consistent with the hypothesis of cell cytoskeleton damage.[18]

Finally, fatigue is the loss of tissue strength upon repeated loading and associated microdamage. While not considered an injury in itself, it results in decreased load capacity,

which can make a tissue more susceptible to injury.[6] Muscle fatigue specifically refers to a reduction in the maximal force or ability to maintain maximal force of the muscles due to repeated use, and is reversible with rest.[19] It occurs due to impairments in the contractile proteins and structures that allow muscles to generate force, which can be considered as damage at the cell cytoskeleton level.[20,21]

Epidemiologic perspective

The International Olympic Committee consensus definition of injury for surveillance and epidemiologic studies is "tissue damage or other derangement of normal physical function due to participation in sports, resulting from rapid or repetitive transfer of kinetic energy".[22] This is distinct from their definition of illness, which is a complaint or disorder where the primary mode does not involve the transfer of kinetic energy.[22] Illnesses include disorders resulting from the loss of vital elements (e.g. dehydration),[22] or from the external environment (e.g. heat stroke) during sport, among others.

Injuries often present as pain or other physical symptoms such as aches, soreness, stiffness, or deformities that affect normal physical function.[23–25] As such, injuries are sometimes recorded as any patient-reported symptom or complaint of the musculoskeletal system due to physical activity.[22,26] However, the perception of pain can differ between individuals based on age, sex, and level of activity. [23,27,28] Further, injuries can occur without pain (e.g., microdamage), and pain can be present independent of tissue damage.[23] Therefore, the same underlying biological damage in different individuals may not be similarly defined as an injury.

Some athletes and researchers use a more restricted definition of injury compared to the consensus definition. Many athletes (particularly elite) consider pain and other physical symptoms as a normal part of sport participation.[25,29,30] They perceive an injury as a condition that must preclude them from performing at their normal or optimal level, beyond the experience of pain, which results in altered or missed participation from sport.[25,29]

Common definitions of injury in epidemiologic studies are "any complaint", encompassing all injuries whether the complaint is symptom- or performance-based; "medical attention injuries", or injuries where medical attention was sought; and "time-loss injuries", or injuries causing the

athlete to be unable to complete a current or future activity session. [22] Medical attention injuries may or may not limit an athlete's ability to participate in sport, and not all time-loss injuries may be reported, nor require or result in medical attention.[22] The optimal definition for a sport injury depends on the research question of interest. For example, researchers may be interested in tissue damage as evidenced by microscopy, a medical diagnosis, a patient-reported complaint, or time lost from sport participation.

Although diagnosing injuries is beyond the scope of this article, a positive diagnostic test for an injury could occur due to 1) an actual injury; 2) a false positive test (i.e. test illustrates abnormal morphology when it is normal); or 3) a misunderstanding of what is "abnormal" (i.e. test accurately illustrates abnormal morphology which is not an actual injury). For example, over 30% of individuals over 50 years who have not had back pain (i.e. uninjured) will have disc herniation on a magnetic resonance image.[31] Epidemiologists must avoid conflating abnormal tests with clinical diagnoses, especially in small, individual clinic-based studies.

Categorizations of musculoskeletal sport injuries

Musculoskeletal sport injuries are often categorized by characteristics such as their mode of onset, severity, and anatomical and tissue location in research and surveillance. These categorizations can be used to study the prevention or occurrence of specific groups of injuries. Common categorizations are summarized in Table 1 and discussed further below, and in "The musculoskeletal system" section.

Table 1. Common categorizations of sport injuries in sport injury epidemiology.

Category	Categorization	Definition
Mode of onset	• Acute vs. overuse	• Acute: Sudden onset related to a specific inciting event • Overuse: Gradual onset, may or may not be related to a specific inciting event
	• Traumatic vs. atraumatic	• Traumatic: Related to a specific traumatic inciting event • Atraumatic: Not related to a specific traumatic inciting event
Severity	• Duration of time-loss	• Time from which sport participation is ceased until full return to participation
	• Duration of symptoms	• Time from onset of symptoms (e.g., pain) until symptoms cease
	• Acute vs. chronic	• Acute: symptoms present for a short period of time • Chronic: symptoms present for a long period of time • The period of time distinguishing acute vs chronic often varies according to tissue type and anatomical location
	• Severity of symptoms	• Self-reported severity of symptoms, assessed using a scale or scoring system
	• Functional consequences	• Self-reported or clinician assessed functional consequences of injury, assessed using a scale or scoring system
	• Amount of tissue damage	• Higher degree injuries represent greater severity, although specific definitions may differ depending on the injury type and location • 1st degree: Least severe (e.g. minimal damage or tearing with minimal symptoms) • 2nd degree: Moderately severe (e.g. visible damage or partial tearing with symptoms) • 3rd degree: Most severe (e.g. complete tearing or rupture of tissue)
Anatomical location	• Body part or region of injury	• Upper extremity: Shoulder, upper arm, elbow, forearm, wrist, hand • Lower extremity: Hip, groin, thigh, knee, lower leg, ankle, foot, • Trunk: Chest, abdomen, thoracic spine, lumbar spine • Head and neck: Head, neck
Tissue type	• Injuries by tissue type	• Bone: fracture • Muscle: strain • Ligaments: sprain • Tendon: tendinopathy, tendinosis, tendinitis, partial or complete rupture

Different categorizations may use the same terms with different meanings. We refer readers to the text for discussion of the limitations of these categorizations.

Mode of onset

A common categorization of sport injuries is by their mode of onset or mechanism of injury. Injuries are often categorized as acute versus overuse, although these definitions are not always consistent. Acute injuries have a sudden onset related to a specific event.[22] Biologically, this occurs when an undamaged tissue is subjected to a sudden load beyond its load capacity.[32] One such injury is a broken bone (i.e. fracture) occurring upon a fall. Overuse injuries, on the other hand, occur gradually due to repetitive loading and associated microdamage to a tissue, without a specific inciting event.[22] For example, an athlete might develop considerable pain in the calf muscle (i.e. strain) occurring gradually with repeated physical activity that impedes further activity. The term "overuse" implies that these injuries occur due to excessive activity beyond what the tissues are prepared for from previous activity and loading. Instead, we could consider that these injuries occur from previous "underuse" of the tissues, whereby the individual has not been sufficiently active previously and has not developed the load capacity within their tissues to handle this level of activity.[33]

Despite these distinctions, there are grey zones and limitations to this categorization. Some injuries with specific inciting events may have been due to underlying "overuse" (i.e. repeated loading and microdamage without sufficient recovery) rather than a sudden load. An injury may occur if the damaged tissue is subjected to a load that would normally be tolerated if not for the microdamage and reduced load capacity (Figure 1C).[22] While these injuries occur acutely, their underlying mechanism is consistent with that of overuse.

Another closely-related categorization that is sometimes used in the literature is traumatic (similar to and often used as a synonym for acute) or atraumatic (a.k.a. non-traumatic, similar to overuse).[34] Like acute injuries, traumatic injuries have a sudden onset related to a specific event. Atraumatic injuries occur without a specific inciting event. Injuries occurring alongside a specific event but that are due to underlying microdamage are considered traumatic under this categorization. For instance, a bone can be weakened due to repetitive activity and associated microdamage without any symptoms. The bone might fracture due to a sudden force, such as pushing off during a sprint race. This might be considered an acute injury

because it occurred alongside a specific inciting event, but atraumatic because there was no direct trauma.

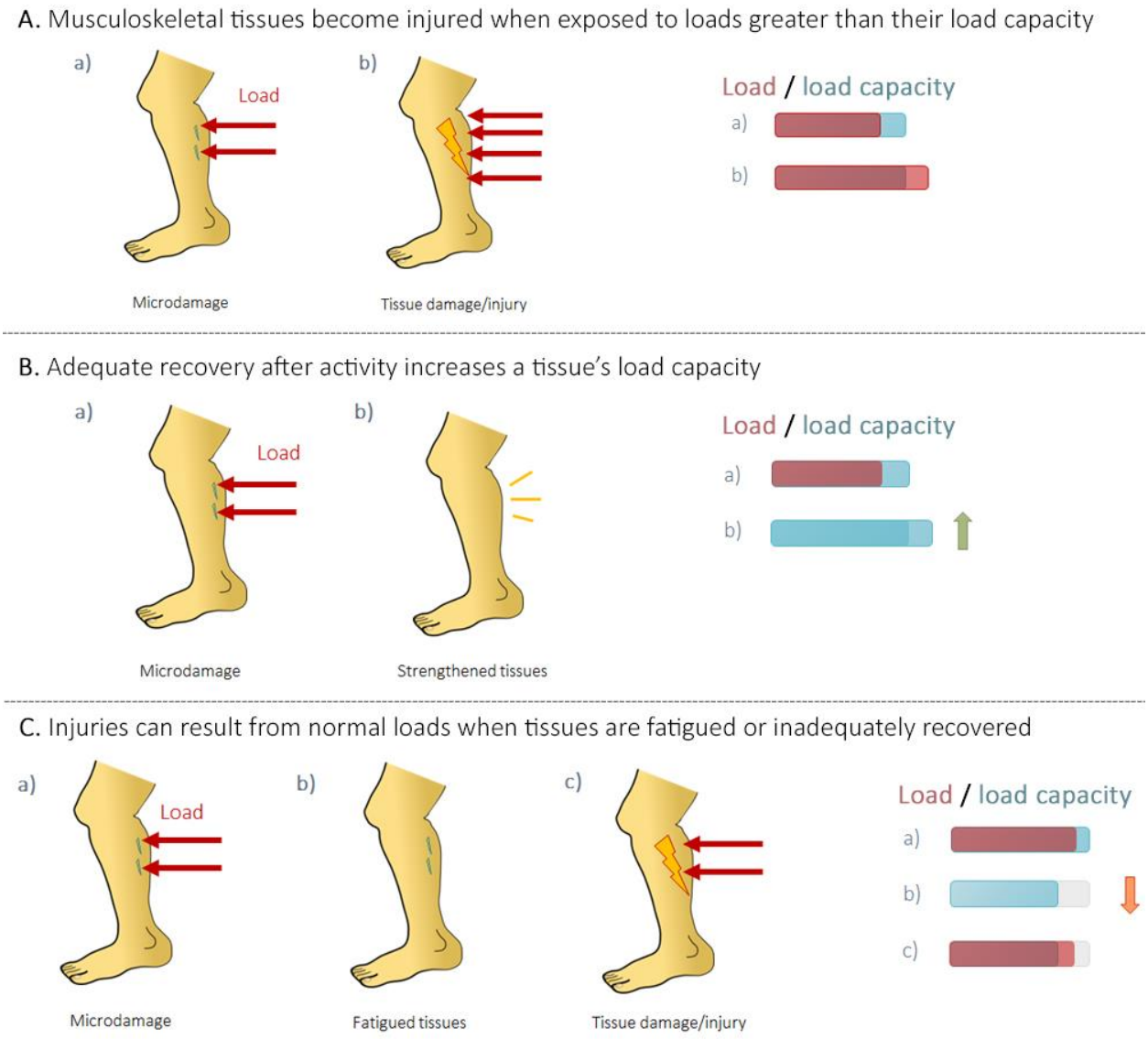

Figure 1. Relationship between a musculoskeletal tissue's load capacity, load, and injury. The red coloured bars represent load on a tissue, while the blue coloured bars represent the tissue's load capacity. **A.** Tissues exposed to loads lower than their load capacity experience microdamage (panel a), while tissues exposed to loads greater than their load capacity experience immediate tissue damage and injury (panel b). **B**. Given sufficient recovery, microdamage from loads below a tissue's capacity (panel a) will result in strengthening and increased load capacity (panel b). **C.** Tissues without sufficient recovery (panel a) have a decreased load capacity (panel b) which can lead to immediate tissue damage and injury even with normal loads (panel c).

Injury severity

Injuries can also be described by their severity. Severity may have different meanings for different athletes (e.g., the need for medication or surgery),[35] but is often defined as the duration of injury, particularly duration of time lost from participation.[22] Time loss is assessed from the date that an athlete begins to have altered or missed participation from sport (which may not be the date of injury onset from a biological standpoint), until the date that they are fully able to participate.[22] Time loss can underestimate severity if an athlete returns to sport before the injury is resolved, or overestimate severity if an athlete does not resume their normal participation upon healing (e.g., because their fitness and performance is not at a competitive level).[22]

A similar measure to injury duration is the duration of symptoms. While defined as the amount of time that symptoms are present, it is sometimes dichotomized as acute versus chronic. Under this categorization, acute injuries refer to recent injuries, while chronic injuries refer to injuries where symptoms have been present for an extended period of time. For example, some categorize back pain as chronic when symptoms have been present longer than 12 weeks, and as acute when symptoms have been present for less than 12 weeks.[36,37] Some authors use chronic as a synonym for overuse when describing mode of onset;[38] however, these are separate concepts. [22] Symptom duration may be longer than time loss duration if an athlete returns to full participation with lingering symptoms, or shorter if an athlete does not resume their normal participation at the time their symptoms cease.

Injury severity can also be described by the severity of symptoms, functional consequences, or a composite score (i.e. patient-reported outcome measure), as self-reported by athletes[20,24,37] or assessed by a clinician. Severity can also be assessed through functional tests. These measures are often assessed using scales or scoring systems.[22,26,39]

Finally, strain (muscle) and sprain (ligament) injuries are often graded as 1st, 2nd, or 3rd degree based on amount of tissue damage and/or clinical symptoms, with 1st degree being the least severe and 3rd degree being the most severe.[6,40,41] However, we note that certain injuries are graded based on factors other than severity of symptoms or tissue damage. These categorizations are reviewed in “The musculoskeletal system” section.

Injury anatomical location

Injuries are often grouped by their anatomical location for summary purposes. These groups may be broad (e.g., upper extremity, lower extremity, trunk) or specific (e.g., knee, lower leg, ankle) depending on the context.[42] While reporting specific anatomical locations is recommended for injury surveillance programs,[22] different injuries to the same location can have very different clinical presentations and outcomes. Although specific locations are important for clinicians who are recommending treatment, epidemiologists often focus on broader categories. These broader categories result in larger sample sizes with potentially greater generalizability, although they have limitations when considering specific injuries.[22,35]

The musculoskeletal system and its injuries by tissue type

The musculoskeletal system is made up of distinct tissues that function together to provide shape, stability, and movement to the human body. It plays a central role in the ability for humans to do sport and physical activity.[43]

The major connective tissues of the musculoskeletal system are bone, cartilage, skeletal muscle, tendons, and ligaments. Bones are the structural basis for the human skeleton.[44] The attachment points of adjacent bones are known as joints. Joints allow for movement of bones with respect to each other.[44] Joints contain cartilage, and are surrounded by ligaments, which are tissue bands that physically attach bones to other bones.[45] Muscles pass over joints, and are attached to two different bones by tissue bands called tendons.[44] Muscles can be thought of as elastics that shorten (i.e., when contracting) and lengthen (i.e., when relaxing). When a muscle shortens, their attachment sites to each bone come closer together. In general, this leads to movement at the joint.[44]

The following section expands on each location and tissue, and summarizes the injuries that can occur to them.

Bones

Bones make up the human skeleton, which provides structure and support for the body.[44] They provide a rigid attachment point for muscles, which allow bones to move.[44] Bones also protect the internal organs, produce blood cells, and store and release minerals and fats.[44,46]

Bone composition

Bones are comprised of two types of bone tissue: cortical, and cancellous. Cortical bone is dense and forms a protective outer layer around cancellous bone, which is spongey and responsible for absorbing the load transmitted to bones.[6,10,44] The thickness of cortical bone and the relative distribution of cortical and cancellous bone tissue differs between different locations within a bone and between bones.[10] Bones are surrounded by an outer fibrous sheath called the periosteum. The periosteum contains nerves and blood vessels, and plays a role in bone remodelling both regularly and after injury.[44,47]

In the long bone of the limbs, the end of a bone is termed the epiphysis, and primarily consists of cancellous bone.[44] The main shaft of a bone is the diaphysis, and consists primarily of cortical bone.[44] The metaphysis lies between the diaphysis and epiphyses, and consists primarily of cancellous bone.[44] Between the metaphysis and the epiphyses is the epiphyseal plate (growth plate) in children, which is a region of bone growth in long bones such as the tibia (shin bone) or femur (thigh bone).[48] While the epiphyseal plate is composed of cartilage during childhood and adolescence, it calcifies into bone tissue after growth has completed.[10,44] Damage to the epiphyseal plate can result in the slowing or stopping of growth for the affected bone, which can lead to angular deformities or asymmetry in lengths of the lower limbs.[49,50]

Bone injuries

Bones respond to load by thickening in mass and strengthening.[44] However, forces beyond the load capacity may result in injury to the bone, called a fracture.[10] Among athletes, fractures generally occur after a sudden traumatic event such as a fall, contact with another athlete, or contact with an object (e.g. ball travelling with speed).[51]

Stress fractures are distinct from regular fractures in that they do not arise from a single traumatic event, but rather repeated exposure to load (i.e., overuse injury).[8,52] Bones are normally

in a state of remodelling, where bone tissue breaks down (resorption) and is replaced by new tissue.[52,53] Remodelling increases in response to load and associated microdamage.[52,53] Without adequate recovery time, more bone tissue is resorbed than deposited, creating stress fractures that appear as small cracks.[52,53] While most stress fractures will heal with adequate rest and rehabilitation,[54] some may require surgery.[55] Continued loading onto a stress fracture without adequate recovery may result in a complete fracture.[55]

Two special types of fractures that occur in children are greenstick and buckle fractures. Greenstick fractures only affect one side of the bone, creating a crack that does not extend through the entire bone and causing bending of the bone rather than a full break.[56] This may be due to increased cartilage content and compliance of young bones compared to adult bones, or because the periosteum sheath surrounding a bone is more elastic in children than in adults, decreasing the likelihood of complete fractures.[47] Greenstick fractures occur most commonly after a fall.[56] Buckle fractures, also referred to as torus fractures, occur due to compression of cortical bone that creates a bulge on one side of the bone, without a full break.[57] These fractures are common among children and are generally simple to treat through immobilization.[57]

Muscles

Muscles are the core component of the human muscular system, which is responsible for generating force and movement.[58] While there are three types of muscle (smooth, cardiac, and skeletal), only skeletal muscles are responsible for movement of the human body.[58]

Muscle composition

Skeletal muscle tissue is comprised of individual muscle fibres.[44] The patterns in which the muscle fibres are organized help determine the strength and velocity of the muscular contraction.[8,44] Muscle is the tissue that is the most capable of strengthening in response to load.[8] This occurs primarily through hypertrophy, in which muscle fibres increase their cross-sectional area.[8] Skeletal muscle tissue also contains structures that convey information about muscle tension and position.[59]

Muscle injuries

There are several types of muscle injuries. Muscle tissue will become damaged when the applied load exceeds its load capacity, either through a single event or repetitive microdamage. These injuries are referred to as strains (or pulled muscles by the general public) when caused by stretching or contraction forces.[8] Strains are the most common sport injury.[8,40] The amount of damage can range from tearing of a few muscle fibres with minimal loss of strength (1st degree) to visible partial tearing of the muscle tissue (2nd degree) to a complete tear/rupture of the muscle (3rd degree).[40,41] Damage to muscle tissue may also damage the structures within the tissue responsible for sensing tension and position through the same mechanisms. For instance, a stretching of the muscle will also stretch these structures. As such, balance and position sense are often disrupted in muscle strains.[60]

Muscles can also be injured by compressive forces that exceed the load capacity, typically through a direct blow to the muscle. These injuries are referred to as contusions.[8,61] Contusions are often associated with rupture of blood vessels, causing internal bleeding that results in a bruise.[8,61] Internal bleeding can lead to various clinical consequences, including some conditions that result in permanent disability.[8,61]

One particular consequence of unaccustomed activity is delayed onset muscle soreness (DOMS), which is sometimes used as a proxy for injury.[62] DOMS presents as soreness, stiffness, or pain that follows 1 to 3 days after unaccustomed activity.[8,63] Although frequently studied in animal models, its mechanism is not entirely understood. It is unclear whether findings from studies on DOMS are generalizable to muscle injuries.[12]

Tendons

Tendons represent connective tissue that physically connects muscles to bones.[44] They enable the transmission of force from muscle to bone, and help stabilize joints.[8,64]

Tendon composition

Tendons are composed of dense collagen fibres aligned in the same direction as the muscle fibres.[8,64] Tendons contain few elastic fibres,[8] which causes them to experience only a small

change in length for a large amount of force compared to muscle.[64] The muscle-tendon interface contains receptors that sense and transmit information about forces within the tendon.[65]

Tendon injuries

Tendons will stiffen when lengthened in response to increasing load but become damaged under excessive load.[64] Sudden injuries to the tendons are known as tears or ruptures. These can range in severity from partial tearing/rupture of the tissue to complete tearing/rupture.[8,64]

Tendons can also experience overuse injuries.[8] Repetitive loading and microdamage to tendons result in chronic pain, known as tendinopathy.[8] Tendinopathies include tendinosis in cases with tissue degeneration, and tendinitis in cases with tendon inflammation.[6,8,66]

Most musculoskeletal injuries occur at the junction where the muscle joins the tendon.[67] Although the tendon may be involved, these are generally considered muscle injuries. In general, tendon injuries that are not close to the muscle-tendon junction often have poor blood supply, resulting in longer recovery times for tendon-specific injuries compared to muscle injuries.[68,69]

Joints

A joint is the point where two or more bones connect. Joints may provide stability or support movement depending on their type and composition.[44]

Joint composition

There are three types of joints that differ in composition and function: fibrous, cartilaginous, and synovial joints.

Fibrous joints are fixed, generally immobile joints comprised of dense collagen rather than cartilage, and are found in the skull among other locations.[70] Cartilaginous joints are joined by fibrocartilage or hyaline cartilage (see “Cartilage” section) and are slightly mobile or immobile.[71] The epiphyseal plate in long bones, which connects the diaphysis and epiphyses in childhood and adolescence, is considered a cartilaginous joint.[71] They are found where the right pelvis joins the left pelvis, among other locations.[72]

Synovial joints are the most common joints in the human body and include the major joints of the limbs (e.g. knee, elbow, shoulder).[44] They are mobile and are comprised of a joint cavity, consisting of the ends of the bones that are covered by articular cartilage.[73,74] The joint cavity is surrounded by fibrous tissue known as a joint capsule, and lined with a synovial membrane that secretes fluid to keep the joint lubricated.[44,74,75] The joint capsule seals the joint cavity, keeping synovial fluid inside, and provides stability by limiting joint movements and preventing bones from separating.[75] As synovial joints allow for movement, they are the most commonly implicated in sport injuries.[6]

Joints can be categorized by the types of movement they allow. Joints can move in three planes: sagittal (longitudinal), frontal (coronal), and transverse (axial).[54] Movement in the sagittal plane is seen from the side of the body (e.g. knee flexion and extension), movement in the frontal plane is seen from the front of the body (e.g. hip abduction and adduction), and movement in the transverse plane is seen from above (e.g. hip rotation).[54] Hinge (uniaxial) joints are a type of synovial joint where most movement occurs in a single plane, and are found in the elbow and knee.[76,77] Biaxial joints often experience movement in two planes, and include the metacarpophalangeal (finger knuckle) joints.[78] Multiaxial joints often experience movement in three planes, and include the hip and shoulder joints.[79,80]

Joint injuries

Joint dislocations are a common injury that occur when the bones that connect at the joint are displaced, resulting in immediate pain and limited range of motion.[81,82] Dislocations typically occur through a sudden traumatic force such as a collision or fall, and occur commonly in the shoulder and elbow among athletes.[81,82] Dislocations can cause damage to the ligaments, cartilage, and bones.[81] Dislocations are treated by physical manipulation of the joint back into its normal location, followed by a recovery period often involving immobilization to heal tissue damage.[81,82] Recurrent dislocations in some joints (e.g. shoulder) are common among athletes.[81]

Subluxations are partial joint dislocations where the connecting bones do not completely separate. Unlike full dislocations, subluxations sometimes spontaneously “relocate” to their original position without physical manipulation.[83] Joint injuries also include specific injuries to cartilage and ligaments. These injuries are covered in their respective sections.

Cartilage

Cartilage is an important connective tissue mainly present in joints.[44] Cartilage is weaker and more flexible than bone. However, it is still weight-bearing and resilient.[44] There are three types of cartilage: hyaline, fibrocartilage, and elastic.[44] Elastic cartilage, which is present in the ear and larynx, is not considered a component of the musculoskeletal system.[84]

Hyaline cartilage composition

Hyaline cartilage is the most common cartilage in the human body.[85] It does not contain any nerves or blood vessels, and is limited in its ability to repair itself following damage.[86] It is found inside joints covering the ends of adjacent bones, where it is referred to as articular cartilage.[85]

Articular cartilage is a highly specialized tissue that reduces friction and provides a smooth surface for movement at the joints.[86] It redistributes pressure across bones to minimize high pressure point loads that could cause bone swelling and injury.[86] Its nutrition comes from molecules dissolved in the normal joint fluid (synovial fluid). As the joint moves, synovial fluid circulates and distributes nutrients.[86] When joint movement is restricted, for instance due to injury or casting, cartilage nutrition is impaired.[86,87] Immobilizing a joint is one method of creating osteoarthritis in animals.[88]

Hyaline cartilage injury

Similar to bone, hyaline cartilage can be injured through a single traumatic event.[89] Furthermore, extensive damage to articular cartilage with insufficient repair leads to unequal redistribution of forces within the joint. One possible consequence of articular damage is post-traumatic osteoarthritis, a condition characterized by joint pain, dysfunction, and malalignment.[89] Although articular cartilage itself is not visible on x-rays, insufficient repair may lead to a decreased cartilage thickness, causing the two bones of a joint to appear much closer together than normal on an x-ray. This is called joint space narrowing, and is an important sign for clinically meaningful osteoarthritis.[90]

Fibrocartilage composition

Fibrocartilage is a stronger and denser type of cartilage than hyaline cartilage.[44] Unlike hyaline cartilage, it contains nerves and blood vessels, but only at its periphery.[8] It is typically found in larger joints, and functions to absorb and distribute forces more evenly across bones.[8] Fibrocartilage tissue is present in the meniscus of the knee, and the labrum in the hip and shoulder.[8,44] It also forms part of the intervertebral discs that lie between the bones of the lumbar spine.[44]

Fibrocartilage Injury

Damage to fibrocartilage occurs in meniscal and labral injuries (tears). Acute meniscal tears occur due to trauma to the knee, and can occur in isolation, or alongside injury to ligaments.[91] Degenerative meniscal tears are more common with increasing age and increased loading (e.g. weight-bearing activities).[92,93] As we age, the meniscus becomes weaker and more susceptible to tears with low loads. Labral tears in the hip and shoulder can also occur from trauma or degeneration from repetitive loading.[94–96] Hip labral tears are associated with certain types of abnormal hip morphologies.[96]

Ligaments

Ligaments represent connective tissue that physically connects bones, spanning a joint.[45] They are often just local prominent thickenings of the joint capsule tissue that run from one bone to the other, with a different tissue composition.[75] However, some ligaments exist inside or outside of the joint capsule.[75] Their primary function is to stabilize joints and prevent excessive movement at the joint.[45,54] However, ligaments also play an important role in proprioception as they contain nerve endings that convey information about joint position and movement that are necessary to coordinate contractions by different muscles during movement.[8] Ligaments stretch out in response to low amounts of load, but will resist movement when pulled tight in response to further load, thus preventing further movement of the joint.[45,54] However, ligaments will tear if stretched too far, causing injury.[45,64]

Ligament composition

Ligaments are primarily composed of dense collagen fibres, with only small amounts of elastic fibres.[45,54] They are generally strong and stiff, with limited elasticity.[54] The degree of stiffness differs by the relative composition of collagen versus elastic fibres and other components.[97] The stiffness of a ligament also increases as the ligament is stretched.[45]

Ligament injuries

While ligaments have a relatively high load tolerance, excessive load will cause damage and injury to the ligaments and other joint structures.[45,64] Injuries to ligaments are referred to as sprains.[6] These can range in severity from some tissue damage with minimal symptoms (1st degree), partial tear of the ligament (2nd degree), to complete tearing/rupture and separation of the damaged ends of the ligament (3rd degree). Grade definitions and terminology can differ by injury type. For instance, there are three ligaments that are implicated in a lateral ankle sprain. Some categorizations use 3rd degree ankle sprain to refer to the complete tearing of each ligament, while some consider a 3rd degree ankle sprain to mean all three ligaments are damaged.[98,99] Surgery may be recommended for some complete ligament tears but not others.[100–102] Because damage to a ligament may damage local nerves, proprioception, balance and position sense are often disrupted in sprains.[8]

Nearly all ligament injuries occur due to a single event.[6] However, ligaments and other joint structures may also experience microdamage when subjected to repetitive loading.[45,97] This microdamage is usually asymptomatic, but may affect joint stability and predispose individuals to other injuries.[8]

Healing and rehabilitation of injury

Biological and clinical perspective

Injury healing occurs in three overlapping phases: 1) inflammation; 2) repair or regeneration; and 3) remodelling.[103] Briefly, inflammation causes damaged cells and tissues to degenerate.[103,104] Tissue repair or regeneration replaces damaged cells with new cells. Finally, the repaired or regenerated tissue is remodelled to regain optimal strength and function in a process that can take months to years.[103,104] The specific healing process of an injury depends on the type of tissue that

is damaged and the degree of damage. Bone heals by a regenerative process, whereby the healed tissue is the same as the original bone tissue.[8] Other musculoskeletal tissues heal by a regenerative process when there is less severe tissue damage or microdamage. However, severe tissue damage heals by a repair process, where the healed tissue is a scar tissue rather than the original tissue.[8,105,106] While scar tissue is initially weak, its strength increases during the repair and remodelling process until it is close to that of the original uninjured tissue.[40] Extensive scar tissue formation due to tissue bleeding and inflammation may result in decreased tissue strength and increased risk of recurrent injuries (discussed below).[8]

Tissue strength can be increased during the repair and remodelling process by applying progressive loads that cause microdamage and subsequent adaptation, but remain below the load capacity for injury.[14,107–112] Overloading may lead to further tissue damage and disrupt the healing process. For instance, low loads during a recovery period may still be large enough to cause further tissue damage because of the reduced load capacity.[14] Just as overloading may cause tissue damage, underloading or extensive immobilization may prevent tissues from strengthening and cause tissue atrophy.[107,110,111,113]

Clinicians usually prescribe rehabilitation therapy for injuries. Rehabilitation refers to restoring the tissue to its preinjury state, and involves many components that are not always well described in studies.[114] Most injury rehabilitation programs start with reducing pain and preventing excess bleeding and inflammation, reducing scar tissue formation. Additionally, injuries often result in decreased range of motion, strength and proprioception. Therefore, exercises including those for balance, strengthening, and stretching are often prescribed to specifically address these limitations.[113] Other components of rehabilitation may include electronic modalities (e.g. ultrasound), manual therapy (e.g. massage, mobilizations, manipulations), and prevention education. Finally, patients are recommended to gradually return to participation in sport once they are largely symptom-free and have regained adequate strength to minimize injury recurrence.[113]

Epidemiological perspective

Injury healing can be assessed under different definitions, which will affect calculated injury durations. Ideally, an injury is considered healed when the athlete is able to return to their previous amount of activity without pain. When detailed data are available, healing date can be determined from clinical records or self-report of symptoms. Alternatively, researchers might use the date of last treatment for injury, under the assumption that treatment is only provided while an injury remains unhealed.[115] However, the decision to stop treatment has subjectivity.[115] As such, clinical data may not always minimize error or bias in the measurement of healing.

Unfortunately, detailed data are often unavailable and researchers often operationalize the healing date of an injury as the date of full return to participation or play in sport.[22,115] However, many athletes return to activity while they are still symptomatic, which could result in measurement error if utilizing return to play or even medical clearance date as the healing date. Epidemiologists should recognize that return to participation decisions can vary between athletes, coaches, and clinicians, and may not necessarily reflect biological healing.[22,115]

Subsequent and recurrent injuries

Initial injuries may predispose to subsequent injuries due to muscle imbalances, deficits in strength and proprioception, or changes in biomechanics.[116] Subsequent injuries to the same location account for a considerable proportion (10-25%) of all injuries.[115]

Researchers must consider how to define and account for subsequent injuries, particularly in the longitudinal follow-up of athletes. Subsequent injuries generally refer to injuries that occur after an initial index injury. Subsequent injuries to a different body part are considered "subsequent new injuries".[115] Subsequent injuries to the same body part but a different tissue type are called "local injuries". Finally, subsequent injuries to the same body part and tissue type are called "recurrent injuries".

Recurrent injuries can be exacerbations or re-injuries. An "exacerbation" is a worsening of an index injury that was not fully healed or recovered.[22,115] A "re-injury" is a recurrent injury that occurs to the same location and tissue as an index injury that was fully healed or recovered.[22] Recurrences are sometimes further categorized by the time that they occurred following healing

of the index injury (early: within 2 months; late: within 2 to 12 months; or delayed: more than 12 months).[115]

These categorizations have limitations. For instance, it can be unclear whether a subsequent injury is related or not related to the initial injury.[117] Further, the definition of healing within an epidemiologic study will affect whether an injury is considered a re-injury or an exacerbation. This will in turn affect the overall injury count, risk, rate, and length of time loss. Consider an individual who suffers an index injury on January 1st and returns to participation on January 10th but continues to experience symptoms and receive medical treatment. They then experience a worsening of symptoms on January 30th. If healing is defined as return to participation, the individual will be considered as having had two injuries (an index injury and a subsequent/recurrent injury), each with a separate length of time loss with the sum being the total time lost. If healing is defined as date of last treatment or by cessation of symptoms, the individual will be considered as having one injury (an index injury and an exacerbation), with a longer time loss (equal to the total time lost). While there is no consensus for the optimal definition of healing, researchers would benefit from clearly defining their outcomes. Further, when synthesizing and interpreting findings from multiple studies, researchers should ensure that aggregated results use similar definitions.

Conclusion

Sport injuries are a concern for anyone participating in physical activity. Applying epidemiologic methods can greatly contribute to determining how to best prevent and treat sport injuries and their related morbidities. Understanding what constitutes a sport injury from a biological and epidemiologic perspective is important for researchers in these fields, who must determine how to best define and assess their research questions and measures.

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CW and IS conceived the manuscript. CW drafted the initial manuscript. IS, JK, RS, and SS critically reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Chapter 5: Manuscript 2

Preface

In Chapter 2, I discussed strategies for summarizing previous and current levels of physical activity using the acute:chronic workload ratio framework. The vast majority of studies investigating the relationship between changes in physical activity and injury have summarized activity occurring over particular time windows using either unweighted or exponentially weighted moving averages. Both these approaches make assumptions about the associations between physical activity performed at different timepoints and current injury risk.

In this manuscript, we explore the use of flexible weighted cumulative exposure methods to summarize previous levels of physical activity and determine their cumulative association with current injury risk.

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Time-varying associations between physical activity and injury risk among children

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Running head: Physical activity and injury risk in children

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Abstract

Background: Physical activity has time-varying associations with injury risk among children. While previous activity may predispose to injury through tissue damage, fatigue, and insufficient recovery, it may protect against injury by strengthening tissues and improving fitness and skills. It is unclear what the relevant time window and relative importance of past activity are with regard to current injury risk in children. The objectives of this study were to assess how previous activity patterns are associated with injury risk among children.

Methods: Our data source was a prospective cohort study of Danish school children conducted between 2008 and 2014. We applied flexible weighted cumulative exposure methods within a Cox proportional hazards model to estimate the time-varying association between number of weekly activity sessions and time-to-first injury in each school year. We estimated several models with varying time windows and compared goodness-of-fit.

Results: The best-fitting model included 20 weeks of past physical activity. Higher levels of activity performed 10 to 20 weeks ago were associated with decreased injury risk, while higher levels of activity performed 2 to 9 weeks ago were associated with increased injury risk. The estimated injury hazard ratio was 1.63 (95% CI: 1.18, 2.23) for children who were highly active in the past 10 weeks after being minimally active 11 to 20 weeks ago, relative to those who were minimally active for the past 20 weeks.

Conclusions: Flexible weighted cumulative exposure methods provide insight into the time-specific associations between physical activity history and injury in children.

Keywords: child, adolescent, exercise, wounds and injuries, fatigue

Introduction

Physical activity plays an important role in the health and development of children and adolescents.[1,2] However, physical activity also increases likelihood of injury and related morbidities.[2] Understanding how different activity patterns are associated with injury risk is an important step in injury prevention.

The association between physical activity and injury is time-varying,[3,4] but not necessarily linear.[14] When an individual performs activity, their tissues are exposed to physical stresses known as load.[5] Loads below a tissue's load capacity cause microscopic damage, while loads above the load capacity cause significant damage defined as injury.[5,6] Although tissues strengthen and increase their load capacity given sufficient recovery time, repeated microscopic damage decreases load capacity, increasing susceptibility to overuse injury.[5,6] Large amounts of physical activity without sufficient recovery also cause fatigue.[7] Fatigue results in decreased load capacity,[5] and affects physical capacities including balance and proprioception.[8–11] As such, fatigue increases susceptibility to overuse and acute injuries. Previous physical activity can protect against injury by strengthening tissues and improving fitness and skill,[12,13] or predispose to injury through fatigue.

It is unclear what the relevant time window and relative importance of past activity at different time points are regarding injury risk. Research on the association between loads and injury risk has largely been based on the acute:chronic workload ratio (ACWR), defined as the ratio of current (acute) load to previous (chronic) load.[15,16] Chronic load is most commonly measured over 4 weeks, although windows of up to 8 weeks have been explored.[15,17] ACWR-based studies have summarized chronic loads as an unweighted average, or an exponentially weighted moving average (EWMA).[15] The unweighted average assumes that activity performed in each previous week is equally associated with current injury risk, while EWMA weights assume that recent activity has a greater association with current injury risk.

Flexible weighted cumulative exposure (WCE) methods are an alternative for estimating the cumulative effect of a time-varying exposure without imposing a pre-specified (e.g. exponential) function.[18] The WCE metric is a weighted sum of past exposures, combining information about duration, intensity, and timing into a summary metric.[18] The objective of this study is to

determine the relative importance of activity in past weeks on current injury risk using flexible WCE methods. Specifically, we aim to determine how previous activity patterns are associated with injury risk in a cohort of Danish schoolchildren.

Methods

Data Source

Our data source was the Childhood Health, Activity, and Motor Performance School Study Denmark (CHAMPS), a prospective cohort study conducted between 2008 and 2014. Schoolchildren aged 6 to 15 were followed during each school year.[25] Each week, parents reported the number of recreational activity sessions their child participated in over the past week using a short message service text. Parents also reported whether their child experienced any musculoskeletal pain, and whether pain was new or continuing from a previous injury (see Supplementary Material for specific questions). Children with new pains were offered to be examined by a clinician, who would establish a diagnosis if warranted.[25]

All children in the 10 primary schools that agreed to participate were eligible for the parent study. Participants could enter or leave the study at any time. Missing activity data were imputed by random hot deck imputation with 5 datasets.[26] In total, 1,667 children were eligible for the current study, contributing 7,296 schoolyears.

Ethics committee approval was obtained for the CHAMPS study (ID S20080047). The study was registered with the Danish Data Protection Agency, as stipulated by the law J.nr. 2008-41-2240. Parents provided written informed consent for study participation.

Exposure definition

The time-varying exposure was the number of activity sessions a child participated in within a given week, including parent-reported recreational activity and physical education classes.

Outcome definition

The outcome was the first clinician-diagnosed injury (acute or overuse) within a schoolyear.

Weighted cumulative exposure

The weighted cumulative exposure at week *u,* for participant *i,* is defined as:

$$WCE_i(u) = \sum_t^u w(u-t)X_i(t),$$

where $X_i(t)$ is the number of activity sessions for participant *i* at week *t*, *u-t* is the time elapsed since the exposure $X_i(t)$, and $w(u-t)$ is an estimated weight assigned to exposure at week *t*, based on time elapsed since exposure *u-t*. The estimated weights quantify the relative importance of exposures that occurred *u-t* weeks prior for the hazard of injury at week *u*, with positive weights indicating increased hazard and negative weights decreased hazard.[23,24] Weighted past exposures are summed for each past week *t,* from the start of a user-selected time window of relevant past exposure up to week *u*. The resulting $WCE_i(u)$ is a time-varying exposure metric, calculated at each week *u* during follow-up, until the end of the participant's follow-up, at the time of event or censoring.[18]

The weight function $w(u-t)$ is estimated using flexible cubic regression B-splines.[18] A higher number of interior knots increases the number of spline functions, and therefore flexibility of the weight function.[18]

Statistical Analysis

We fit multivariable Cox proportional hazards models for time to first injury, defined as the number of weeks elapsed until the first reporting of musculoskeletal pain leading to clinician-diagnosed injury. Time zero was the start of each schoolyear. The time-varying exposure was the WCE metric for previous activity (up to 1 week ago), with activity in the current week (last 7 days), sex, and school-grade included as covariates. Children who did not get injured were censored at the end of each school year.

We estimated alternative WCE models using various combinations of (a) the number of interior knots *m* to be between 1 and 3, and (b) time windows of 5, 10, 15, 20, 25, and 30 past weeks of activity. Weight functions were constrained to smoothly decrease to zero at the week furthest in the past.[18] We used the Bayesian Information Criterion (BIC)[30] to identify the best-fitting WCE

model.[18] We employed likelihood ratio tests (LRT) and the Akaike Information Criterion (AIC) to compare the fit of the best-fitting WCE model with (a) the conventional cumulative exposure model that relied on the unweighted sum of exposures over the same time window, and (b) the Cox model that included covariates but excluded the time-varying exposure.[18] The former comparison assessed the usefulness of differential weighting of past exposures, while the latter provided evidence that the estimated association was unlikely to only reflect sampling error. Using the best-fitting model, we estimated hazard ratios (HRs) for injury comparing different physical activity patterns. The 95% confidence bands for the weight function and the 95% confidence intervals (CI) for the hazard ratios were estimated by cluster bootstrap (accounting for clustering within children who contributed several schoolyears) with 300 replicates.[29]

We conducted a sensitivity analysis where we included musculoskeletal pain reported in the previous 4 weeks (not resulting in a clinician-diagnosed injury) as a binary time-varying covariate. We also conducted subgroup analyses stratified by sex. We pre-specified a time window of 20 weeks and 1 interior knot for sex-stratified analyses, based on the best-fitting WCE model for the main analyses.

We tested for effect modification by sex by conducting separate analyses where time windows and numbers of knots were allowed to vary by sex. We identified the best-fitting models for each sex, and assessed to what extent these sex-specific weight functions improved fit compared to the overall weight function by comparing deviances using LRTs and AIC (further details provided in Supplementary Material).[31]

All results were averaged over the 5 imputed datasets. Analyses were conducted in R,[32] specifically the *WCE* package.[33]

Results

Table 1 describes characteristics of the study population. Injuries occurred in 986 participants (59%) at least once. A total of 1,752 first injuries in a given schoolyear were included in analyses, with an incidence rate of 16.6 (95% CI: 15.8-17.4) per 1,000 person-weeks (16.8, 95% CI: 15.8-17.9 among girls; 15.8, 95% CI: 16.8-17.9 among males). The average time-to-first injury from the beginning of the schoolyear among injured participants was 18 weeks, with a

median of 15 weeks. The median number of activity sessions per week was 4 (interquartile range: 3-5).

In WCE analyses, the best-fitting weight function for the association between physical activity and time-to-first injury had a time window of 20 weeks and 1 interior knot (Table S1 displays BICs for all models). The final WCE model improved the fit over the Cox model that excluded the time-varying exposure (LRT $p < 0.005$ and smaller AICs across imputed datasets) and the unweighted cumulative exposure model (LRT $p < 0.01$ and smaller AICs across imputed datasets), confirming the importance of differential weighting of past exposures. The best-fitting weight function (Figure 1) suggested that higher levels of activity performed more than 10 weeks ago were associated with decreased injury risk, while higher levels of activity 2 to 9 weeks ago were associated with increased injury risk (peaking at 5 weeks ago). Activity performed one week ago was associated with a slight reduction in injury risk, with large uncertainty. The weight function was qualitatively similar when recent musculoskeletal pain was included as a covariate (Figure S1).

Table 2 displays HRs comparing different activity patterns. Consistently higher activity levels were associated with higher hazard of injury than consistently lower activity levels. Injury hazard was 60% greater for those who were highly active recently after only being minimally active 11 to 20 weeks ago relative to those who were consistently minimally active, and 30% greater for those who were moderately active recently. Injury hazard was 20% lower for those who were minimally active recently after being moderately active relative to those who were consistently moderately active.

Figure 2 displays sex-stratified weight functions. For both sexes, increased activity 3 to 9 weeks ago was associated with increased injury risk, peaking at 5 weeks. However, positive weights were somewhat greater but less spread over previous weeks for females. While activity performed over 9 weeks ago was associated with a lower injury risk among females, no decrease was observed for males.

The optimal sex-stratified weight functions both had 1 interior knot, and time windows of 15 weeks for females and 10 weeks for males (data not shown). While the optimal sex-stratified WCE models yielded slightly lower deviance, differences were not large enough to indicate a

systematic improvement in goodness-of-fit over the common model for both sexes (LRT p-values between 0.10 and 0.17, with higher AICs).

Discussion

In this study, we applied a data-driven method to examine how activity patterns in previous weeks are associated with current injury risk in children. We found that higher levels of activity performed more than 10 weeks ago had a protective association with the risk of first injury in a schoolyear, whereas higher levels of activity performed between 2 and 10 weeks ago had an adverse association.

Unlike the ACWR framework,[16] these results imply that previous activity does not necessarily protect against injury. Indeed, recent loads may increase injury risk by causing microscopic damage and fatigue without adequate recovery.[5,6] Biologically, activity performed more than 10 weeks ago might result in a decreased risk of injury by increasing tissue strength and load capacity,[5] as well as improving fitness, skill, and coordination.[12,13] Given that an individual has been active and uninjured for over 10 weeks, they have likely had sufficient recovery time and are at lower risk of injury due to the long-term beneficial effects of activity. In contrast, an individual who has only begun being active in the previous 10 weeks may not have developed the load capacity and fitness to handle the same amount of activity, putting them at higher risk of fatigue and injury. The protective association of activity performed more than 10 weeks ago may also be attributed to a "survivor effect",[34] where only those who were uninjured for a 20-week interval are observed (i.e. uncensored) for the entire 20-week time window. Those who are more susceptible to injury may have been censored prior to achieving 20 weeks of activity, and would not contribute to the protective associations observed in the 10-to-20 week time window.

We also found limited evidence for a protective association of activity performed one week previous, with high uncertainty. This may be because those who were able to do more activity one week ago are unlikely to have experienced early symptoms of injury (e.g., soreness, pain) or fatigue. These individuals may be less likely to be injured in the current week than those who were unable to do as much activity due to early symptoms of injury experienced prior to clinician diagnosis. Although we did not observe qualitative differences with our weight functions when

the presence of recent musculoskeletal pain was included as a covariate in sensitivity analyses, other factors such as fatigue may also result in decreased activity and increased risk of injury.[35]

Our analyses stratified by sex did not meaningfully differ from our overall analyses; however, we may not have had sufficient power to detect meaningful differences. These analyses suggested that patterns of physical activity may be more strongly associated with injury risk among females than males. We similarly found in a previous study with the same data source that large increases in activity in the current week were more strongly associated with injury risk for females than for males.[36] This is consistent with other studies that found higher rates of musculoskeletal pains and overuse injuries among females than males,[37–39] which some have hypothesized might be partially attributed to biological differences in hormones or anatomy.[40] It may also be that males are self-regulating their activity more than females to avoid injury, resulting in smaller associations between previous activity and injury risk.

Based on the best-fitting WCE model, we found that physical activity done up to 20 weeks ago is associated with injury risk in the current week. This contrasts with the most common formulations of the ACWR used to assess injury risk based on increases in load, which assume equal weight for each previous week of activity. The conventional ACWR is defined as the ratio of load in the current week (acute load) to the average load over the current and previous 3 weeks (chronic load).[4]

Instead, some researchers have employed an exponentially weighted moving average (EWMA) function to summarize loads before calculating the ACWR.[28,41] The EWMA gives exponentially decreasing weights for activity done further in the past.[14,28] Typically, the EWMA function is employed for both the acute load and the chronic load, and assumes that all activity performed in the current week is adverse and that all activity performed in previous weeks is protective against injury. As such, when considering previous activity, activity done one week ago would have the greatest protective association with current injury risk, whereas activity done 20 weeks ago would have only a slight protective association (Supplementary Material, Figure S1). The assumption that all previous activity has a protective association is inconsistent with the biological principle that recent activity can result in reduced load capacity and fatigue if there is

insufficient recovery.[5] In contrast, our results suggested that activity performed in the previous 3 to 4 weeks is associated with increased risk of injury in our study population.

The cumulative effect of load on injury risk among elite youth handball players has previously been explored using distributed lag non-linear models (DLNMs).[42] Like WCE models, DLNMs use flexible weight functions used to represent the cumulative effect of a time-varying exposure on an outcome.[43,44] They were originally developed for use in time series analysis, but have been extended to other contexts.[44] Unlike the current study, the handball study used daily session ratings of perceived exertion as a proxy for load, with a previous time window of 28 days. Their outcome of interest was health problems, which includes injuries, illnesses, and pains or soreness that may not result in clinician-diagnosed injuries.[45] The authors did not condition on activity done on the current day; rather, it was included in their lag function. They found, with high uncertainty, an increased risk of health problems on the current day with increasing activity, and protective associations for activity performed further than 6 days ago.[42] Their shorter period of adverse associations compared to our period of 10 weeks may be attributed to differences in exposure and outcome definitions, time window of analysis (limited to 28 days), as well as the study population. The handball study focused on elite athletes, who may be accustomed to increases in activity and have shorter tissue recovery periods relative to our population of schoolchildren.

Strengths and Limitations

This study employed a large dataset to assess how previous activity patterns are associated with injury risk in children and adolescents. It is one of few studies to explore the use of non-linear methods to express the cumulative effect of physical activity on injury, and the first to use flexible WCE methods specifically in this area.

This study had several limitations. We only had data available on activity frequency, not intensity or duration. Our exposure definition of the number of activity sessions a child participated in within a given week was parent-reported and very broad, and there was likely large heterogeneity in the intensity, duration, and type of activity. As such, our findings are an average across many different contexts. Limiting the target population to specific sports and

employing an exposure definition that accounts for intensity and duration would provide more precise inferences, at the cost of decreased generalizability.

We assumed that all children have the same weight function regardless of their sex, age, and other characteristics. Although we explored effect modification by sex, future studies may also wish to explore other effect modifiers in the relationship between activity and injury. We also grouped together all types of injuries for our outcome, and different patterns may exist for acute versus overuse injuries. Our study sample included children from a single county within Denmark, and findings may not be generalizable to all populations.

We only assessed time to first injury within each schoolyear in our analyses, as subsequent injuries within a short timeframe may be influenced by the initial injury, and the resulting changes in activity patterns. Finally, we employed an approach that did not account for confounding in the relationship between physical activity patterns and injury risk. As such, our results should not be interpreted as causal. Fatigue and soreness are two unmeasured factors that may confound or mediate the relationship between physical activity patterns and injury. WCE methods have been adapted to marginal structural model Cox analyses to handle time-varying confounders or mediators, which could be applied in future research given sufficient data.[46]

Conclusion

WCE methods provide insight into the time-specific associations between past physical activity history and injury in children. High levels of activity performed in the recent past is associated with increased injury risk, potentially due to acute tissue damage or fatigue. Activity performed further in the past is associated with decreased injury risk, which may be attributed to improved fitness and strengthened tissues.

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Tables

Table 1. Characteristics of study participants from a Danish cohort of schoolchildren, 2008-2014 (N=1,667).

Characteristic	**Number of participants (%)**
Sex	
Male	789 (47%)
Female	878 (53%)
Danish school grade (age group) at baseline, 2008	
0-1 (6-9 years)	648 (39%)
2-3 (8-11 years)	711 (43%)
4 (10-12 years)	308 (19%)

Table 2. Injury hazard ratios for different patterns of activity over the previous 20 weeks. Activity levels are defined by number of activity sessions per week: minimally active = 1 session/week, moderately active = 4 sessions/week, highly active = 7 sessions/week.

<table>
<tr><th colspan="2">Activity pattern</th><th>Reference</th><th>HR (95% CI)</th></tr>
<tr><td colspan="2">Moderately active in previous 20 weeks</td><td rowspan="2">Minimally active in previous 20 weeks</td><td>1.15 (0.99, 1.36)</td></tr>
<tr><td colspan="2">Highly active in previous 20 weeks</td><td>1.32 (0.98, 1.86)</td></tr>
<tr><td rowspan="2">Minimally active 11-20 weeks ago</td><td>Moderately active 1-10 weeks ago</td><td rowspan="2">Minimally active in previous 20 weeks</td><td>1.27 (1.49, 1.09)</td></tr>
<tr><td>Highly active 1-10 weeks ago</td><td>1.63 (1.18, 2.23)</td></tr>
<tr><td>Moderately active 11-20 weeks ago</td><td rowspan="2">Minimally active 1-10 weeks ago</td><td rowspan="2">Minimally active in previous 20 weeks</td><td>0.90 (0.78, 1.00)</td></tr>
<tr><td>Highly active 11-20 weeks ago</td><td>0.81 (0.62, 1.00)</td></tr>
<tr><td>Moderately active 11-20 weeks ago</td><td>Minimally active 1-10 weeks ago</td><td>Moderately active in previous 20 weeks</td><td>0.78 (0.67, 0.92)</td></tr>
</table>

Abbreviations: HR, hazard ratio; CI, confidence interval.

Figures

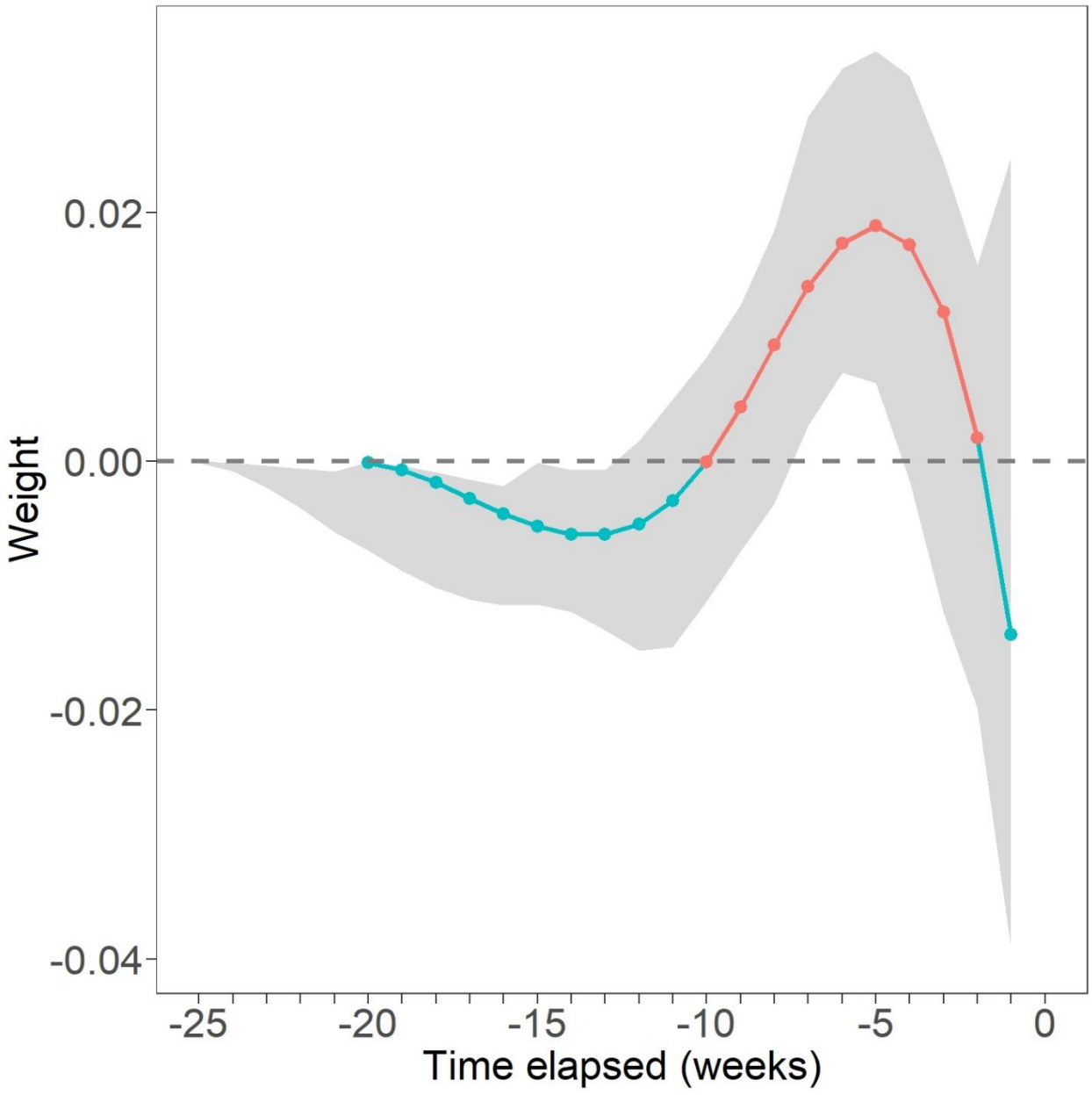

Figure 1. Weight function for the association between past physical activity and the current hazard of first injury in children. The curve represents the best fitting weight function, averaged over 5 imputed datasets. The shaded area represents the 95% bootstrapped confidence bands. Time elapsed = 0 represents the current week (last 7 days). The values of the points represent relative importance weights estimated for activity performed in specific weeks. Positive weights (red) imply a harmful association while negative weights (blue) imply a protective association.

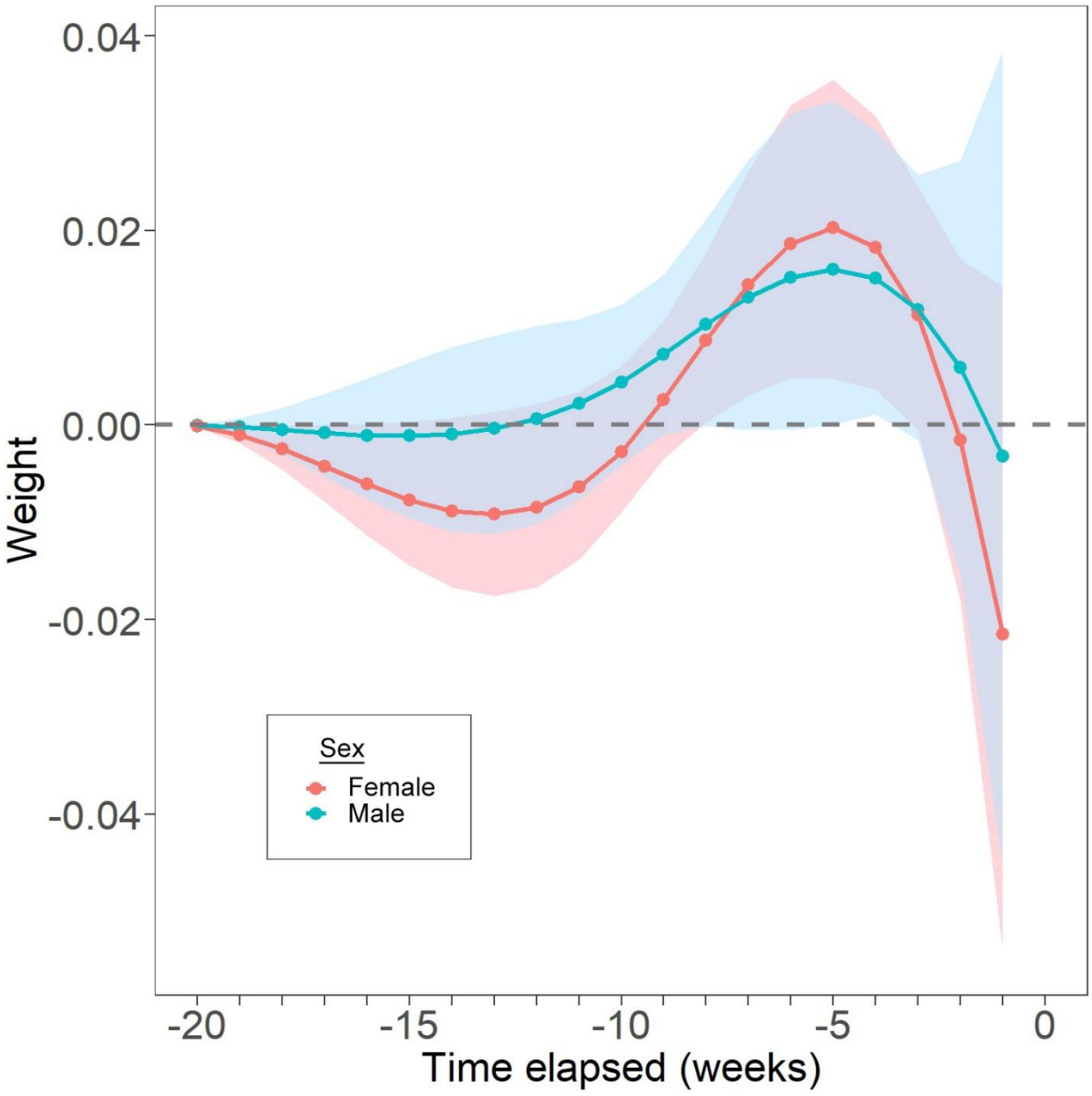

Figure 2. Weight functions for the separate associations between past physical activity and the current hazard of first injury in children, stratified by sex. The curves represent the best fitting weight functions averaged over 5 imputed datasets. The shaded areas represent the 95% bootstrapped confidence bands. Time elapsed = 0 represents the current week (last 7 days). The values of the points represent relative importance weights estimated for activity performed in specific weeks.

Supplementary Material

Collection of physical activity and pain data in the Childhood Health, Activity, and Motor Performance School Study Denmark

Musculoskeletal pains and physical activity participation were measured weekly by the "Short Messaging Service-Track-Questionnaire" (SMS-Track) version 2.1 (New Agenda Solutions, SMSTrack ApS, Esbjerg). SMS-Track is a web based IT-system developed as a tool for frequent surveillance, complying with Shiffman´s principle of Ecological Momentary Assessment.

The questionnaire was automatically sent to the parent's mobile phone once a week asking:

A. "Has [NAME OF CHILD] during the last week had any pain in

1. Neck, back or low back
2. Shoulder, arm or hand
3. Hip, leg or foot
4. No my child has not had any pain."

Parents were instructed to type the number in front of the correct answer.

B. "How many times did [NAME OF CHILD] engage in sports during the last week"? Parents were instructed to answer with a relevant number between 0 and 8. The answers 0 to 7 represent the unique number of times engaging in sports, whereas 8 stood for 'more than 7 times'.

The returned answers were automatically recorded and inserted into a database. To improve compliance rate, the responders were contacted by telephone if the answer did not meet the instructions. Furthermore, a reminder was automatically sent, if participants had not responded 72 hours later and, if necessary, 120 hours after receiving the message.

Assessing effect modification by sex

We tested for possible effect modification by sex by conducting separate analyses where the time windows and numbers of knots were allowed to vary by sex. We identified the models with the lowest BIC for each sex, and assessed to what extent these separate sex-specific weight functions improved fit in order to test for possible effect modification by sex. In particular, using a test proposed in an earlier WCE study,[1] we compared the total deviances for the entire dataset, obtained using two different sex-stratified WCE analysis approaches, in which the previously estimated weight functions were used to define pre-specified time-varying WCE exposures. (i) The first 'common model' approach used the same weight function, based on the best fitting main model for all children, for each sex. (ii) In contrast, the 'sex-specific models' approach employed separate weight functions, corresponding to the BIC-optimal WCE model for each sex. For each approach, the total deviance was calculated as the sum of the deviances yielded by the models fit to females and males. Finally, the difference between the total deviances of the (i) common *versus* (ii) sex-specific models was used as a likelihood ratio test (LRT) statistic for a chi-square test with 3 degrees of freedom (df).[1] Three df's correspond to the three additional spline coefficients used to fit *two* constrained cubic spline weight functions with one interior knot for the sex-stratified models, compared to the common model with only a single weight function.[1,2] We also used the aforementioned total deviances to calculate and compare the Akaike Information Criterion (AIC) for each of the two models.

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Table S1. Bayesian Information Criterion for weighted cumulative exposure models with different user-specified time windows and interior knots. WCE models modelled the association between cumulative past activity sessions and current injury risk. BICs were averaged across 5 imputed datasets.

Time window	Number of interior knots	BIC
5	1	41,453.21
	2	41,458.86
	3	41,466.62
10	1	41,371.56
	2	41,372.76
	3	41,374.54
15	1	41,448.67
	2	41,454.06
	3	41,461.61
20	1	41,447.86
	2	41,456.17
	3	41,462.21
25	1	41,449.67
	2	41,455.62
	3	41,463.88

Abbreviations: BIC, Bayesian Information Criterion; WCE, weighted cumulative exposure

Comparison between WCE and EWMA

We compared injury risks using flexible weight function versus using an exponentially weighted moving average (EWMA) function over 20 weeks.[28] The EWMA function for a given week *t* is estimated as:

$$EWMA(t) = X_i(t) * \left(\frac{2}{N+1}\right) + \left(\left(1 - \left(\frac{2}{N+1}\right)\right) * EWMA_{t-1}\right),$$

where $X_i(t)$ is the number of activity sessions for participant *i* at week *t*, and N is the time window of interest (20 weeks).[28]

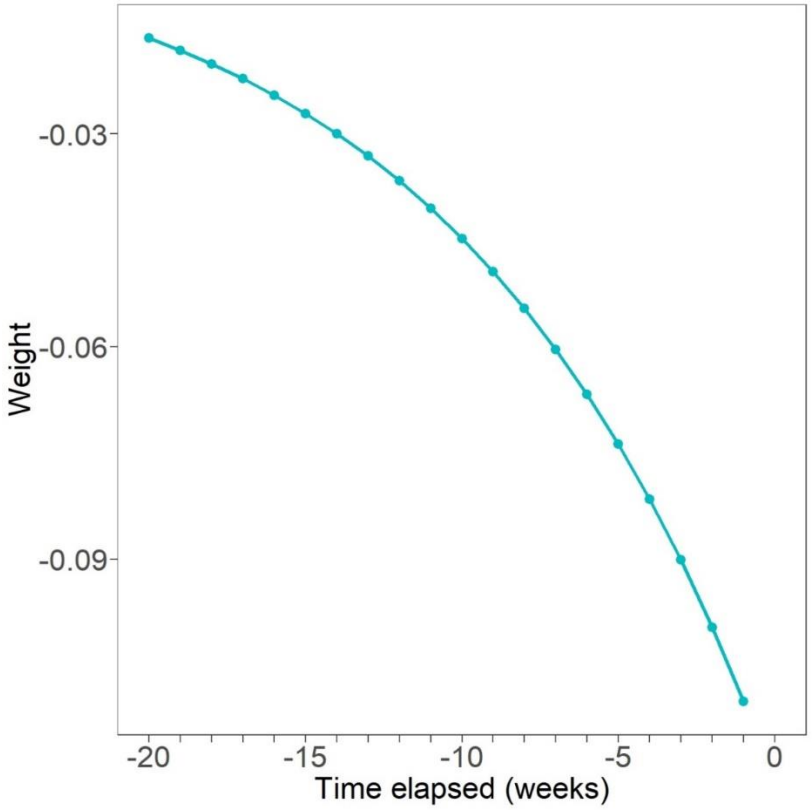

Figure S1. Exponentially weighted moving average (EWMA) function for the association between previous physical activity and injury. The line represents the EWMA function for activity performed in the previous 20 weeks, conditional on activity in the current week. Time elapsed = 0 represents the current week. The points represent weights for activity performed in specific weeks. Negative weights (blue) imply a protective association.

Chapter 6: Manuscript 3

Preface

In Chapter 2, I discussed limitations with the current state of evidence regarding the relationship between changes in physical activity and injury risk. Specifically, I noted that the IOC consensus statement on load in sport and injury risk indicates an increased injury risk at low ACWRs, which is expected due to bias. Our research group had noted this problem in a previous critical review published in *Sports Medicine* in 2020 (written as part of the requirements for my MSc);[12] however, we did not have concrete strategies to resolve it at the time. In this manuscript, I identify the apparent increase in injury risk at low ACWRs as occurring due to "immortal time bias", a commonly acknowledged issue in other fields of epidemiology. I also discuss strategies for mitigating immortal time bias in the context of load and injury.

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Immortal time bias: a common problem in observational studies of training load and injury

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Abbreviations: ACWR, acute:chronic workload ratio

Abstract

Several observational studies of the relationship between training load and injury have found increased risks of injury at low loads. These associations are expected because load is often assessed at the end of the injury follow-up period. As such, athletes who get injured earlier in the follow-up period will have systematically lower loads than athletes who get injured later in the follow-up period. In this commentary, we identify this problem as a type of "immortal time bias", a methodological issue that has been recognized in other areas of epidemiology. We also discuss how immortal time bias can be prevented by aligning the measurement of load with the start of follow-up for injury.

Keywords: training load, injury, acute:chronic workload ratio, immortal time bias

What is new

- Immortal time bias is common in observational studies of training load and injury risk
- Bias occurs because the measurement of load occurs after the start of follow-up for injuries
- Immortal time bias can be prevented by using planned rather than observed loads as the exposure of interest, following up for injuries after load measurement, or advanced methods such as inverse probability weighting

Introduction

The relationship between training load (referred to as "load" for simplicity) and injury has become a popular topic in sports injury epidemiology in recent years. Much research in this area have been observational in nature, taking advantage of existing training surveillance systems or cohort studies. While observational studies have the advantages of larger sample sizes, feasibility, and lower cost compared to randomized trials, they are also more easily prone to biases in their analyses. In this commentary, we introduce the concept of immortal time bias as applied to the relationship between load and injury, and discuss strategies for prevention.

Source of immortal time bias

The "acute:chronic workload ratio" (ACWR) is a common metric used to summarize relative changes in load, including by the International Olympic Committee in a consensus statement on load and injury in sport.[1] We previously identified flaws in the relationship presented in this statement, including that increased injury risks are expected at low ACWRs due to bias.[2] Briefly, consider Athlete A who planned 2 hours of activity each day for the next week, and Athlete B who planned 1 hour of activity each day. Athlete A gets injured on Day 2, with an observed weekly load of 4 hours. Athlete B gets injured on Day 6, with an observed weekly load of 6 hours. Athlete A will have a lower load and ACWR than Athlete B, despite having planned more activity and having performed more activity in Days 1 and 2 (Figure 1).

This is a type of "immortal time bias", a methodological issue that has been recognized in other areas of epidemiology.[3] "Immortal time" refers to a period of time during which the outcome cannot occur conditional on the exposure. Generally, immortal time bias will occur when treatment assignment (load measurement) is not aligned with the start of follow-up [time zero (*t0*)].[4,5] Studies of load and injury commonly follow-up for injury over a particular period (e.g. one week), and measure load in that same week. Since load is not determined until the end of that week, treatment assignment occurs after the start of follow-up. This problem occurs in both studies looking at changes in load, and absolute load.

In our example, load measurement only occurs at the end of follow-up (*t1* in Figure 1). Given Athlete B's planned load of 1 hour per day and their observed load of 6 hours over the week, Athlete B must not have been injured between Days 1 and 6. As such, they were "immortal" for

this time. Similarly, Athlete A is "immortal" for Days 1 and 2 given their planned load of 2 hours per day and their observed load of 4 hours over the week. In other words, the timing of their injuries are fixed given the available information on their planned and observed loads.

The extent of the immortal time bias depends on the degree to which load and injury data are summarized. Load is often defined using daily moving averages, with injury incidence measured over a day rather than a week.[6] While this reduces bias, as the use of smaller time intervals means less possible immortal time, load measurement still occurs after the start of follow-up. Athletes who get injured earlier in the day will have necessarily smaller loads than athletes who complete the day uninjured.[2] If acute load is defined as the load on the current day, the relative bias may remain considerable.

Preventing immortal time bias in studies of load and injury

To prevent immortal time bias, we must align treatment assignment with time zero. In other words, we must determine load using only information we have at time zero.[4,5] One way to do this is to use planned load rather than observed load as the exposure and estimate the intention-to-treat effect of load on injury. In our example, we know that Athlete A planned 14 hours of activity while Athlete B planned 7 hours. By comparing their injury risk using planned loads, we would infer that Athlete A's larger planned load resulted in a greater risk of injury.

Alternatively, we can align treatment assignment with time zero by measuring injury risk over a follow-up period that begins at the time that load is measured.[2] In our example, we might compare injury risks for Athletes A and B in the subsequent week. While this avoids immortal time bias, it does not account for variations in load in the subsequent week that affect injury, and may still result in biased inferences.[2] For instance, an athlete with a low ACWR in the current week may be exposed to a large increase in load in the subsequent week that they were not sufficiently prepared for, resulting in injury. This would result in an apparent increased injury risk at low ACWRs, as observed in the International Olympic Committee consensus statement.[1] Alternatively, load can be measured using daily moving averages, with injury incidence measured in the subsequent day to minimize (but not avoid) unaccounted variations in load leading up to the time of injury.

Another option is to assign each individual to multiple treatments at time zero, and censor them when their treatment is no longer consistent with their assignment.[4,5] Censoring must be accounted for with inverse probability weighting to avoid selection bias.[4,5] For instance, suppose we wanted to investigate whether a weekly load of 4 hours was associated with the same injury risk as a weekly load greater than 4 hours, as was seen in our naïve analysis of Athletes A and B. We could clone each individual and assign each clone to a different treatment at time zero (≤ 4 hours versus > 4 hours of activity). We would then follow-up each clone for injury, and censor the clone at the point that their observed load is no longer consistent with their treatment assignment. The Athlete B clone assigned to ≤ 4 hours of activity would therefore be censored after doing 4 hours of activity, and any injuries occurring after that point would not be included in the analysis (Figure 2). As such, we would conclude that the risk of injury at a load > 4 hours is greater than ≤ 4 hours. We note that such an analysis is only feasible when treatments are categorical, as assessing injury risk for specific load or ACWR values would result in an infinite number of clones.

Conclusion

Immortal time bias is a common problem in observational studies of load and injury risk. To prevent this bias and estimate causal effects, we must design our analyses so that treatment assignment or load measurement occurs at time zero, or the start of follow-up. This can be done by using planned loads rather than observed loads as the exposure, or through cloning and censoring individual observations in the case of categorical exposures.

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CW conceptualized the manuscript, drafted the initial manuscript, and critically reviewed and revised the manuscript.

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IS critically reviewed and revised the manuscript.

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Figures

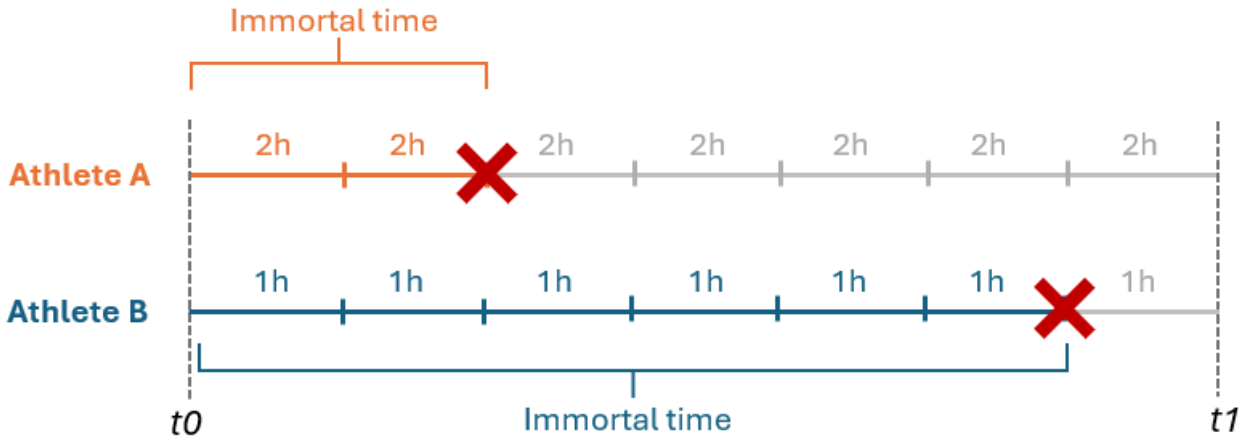

Figure 1. Immortal time bias in the measurement of load. Loads (measured using activity duration) are indicated for each Day 1-7 during the calendar week. Observed loads are indicated in orange for Athlete A, and blue for Athlete B. Planned loads that were not observed due to injury are indicated in grey. Injuries are represented by red X's. Follow-up for injury starts at time zero (*t0*, beginning of the calendar week) and ends at *t1* (end of the calendar week). Load is assessed at *t1*. Despite having planned a larger load and having been exposed to a larger load up to the point of injury, a smaller load is observed for Athlete A than Athlete B.

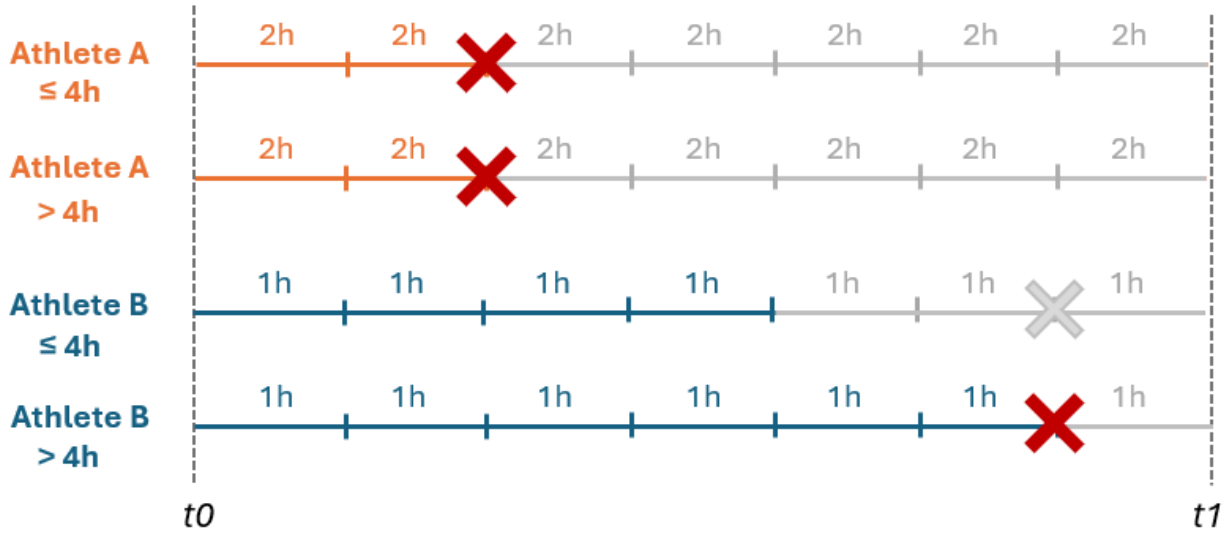

Figure 2. Cloning and censoring method to prevent immortal time bias in studies of load and injury. Loads (measured using activity duration) are indicated for each Day 1-7 during the calendar week. Observed loads are indicated for Athlete A, and blue for Athlete B. Injuries are represented by red X's. At time zero (*t0*), each Athlete is cloned and assigned to a different treatment (≤4 hours or >4 hours). Clones are censored (indicated in grey) when either (a) they become injured, or (b) their observed exposure is no longer consistent with their assigned treatment. Calculated injury risks are 50% for athletes assigned ≤4 hours of load, and 100% for athletes assigned >4 hours of load, correctly indicating an increased rather than equal risk for the >4 hour treatment group.

Chapter 7: Manuscript 4

Preface

In Chapter 2, I discussed how the vast majority of studies regarding the relationship between changes in physical activity or load and injury risk are associational; yet their findings have been used to generate recommendations for athletes and the general public. Various authors have emphasized the need to employ causal frameworks to determine the relationship between changes in load and injury risk.[12,35,93,145,146] However, to our knowledge, no studies have done so up to this point in time. Further, limited guidance exists for researchers looking to conduct causal inference in the area of sport injury epidemiology.

Studies in other fields of epidemiology have employed a "target trial framework" to estimate causal effects in observational data. This framework has been shown to provide results consistent with those from randomized controlled trials. Its application helps to avoid biases in observational analyses, including the immortal time bias described in Manuscript 3. In this manuscript, I discuss the potential application of the target trial framework to studies on changes in physical activity or load on injury risk, and provide guidance to researchers looking to employ this framework for various causal questions.

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The target trial framework for determining the effect of changes in training load on injury risk using observational data: a methodological commentary

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Abstract

In recent years, a large focus has been placed on managing training load for injury prevention. To minimize injuries, training recommendations should be based on research that examines causal relationships between load and injury risk. While observational studies can be used to estimate causal effects, conventional methods to study the relationship between load and injury are prone to bias. The target trial framework is a valuable tool that requires researchers to emulate a hypothetical randomized trial using observational data. This framework helps to explicitly define research questions and design studies in a way that estimates causal effects. This article provides an overview of the components of the target trial framework as applied to studies on load and injury, and describes various considerations that should be made in study design and analyses to minimize bias.

Keywords: load monitoring, training load, sport injury, injury prevention, target trial

Summary Box

What is already known on this topic:

- There is large interest among athletes, coaches, and clinicians in managing changes in training load for injury prevention
- Longitudinal data from observational studies or load monitoring programs can provide valuable insights into the causal effect of changing load on injury risk, but data must be analyzed appropriately
- The target trial framework is a tool for designing and analyzing observational studies in a way that emulates a randomized controlled trial and minimizes bias

What this study adds:

- This review discusses considerations for applying the target trial framework to studies examining the causal effects of changes in load on injury risk
- We provide guidance for defining the research question, eligibility criteria, treatment strategies, and outcomes, and for conducting appropriate analyses

How this study might affect research, practice or policy

- The application of the target trial framework in research can be used to generate valid recommendations to minimize injuries
- The insights outlined in this review can aid researchers in designing rigorous observational studies that estimate the causal effects of changing load on injury risk

Introduction

Avoiding injury is an important goal for athletes of all sports and levels. Training load (also referred to as 'load' or 'workload') is considered an important risk factor for injury.[1,2] Training load refers generally to a broad range of exposure variables related to sport or physical activity that can be manipulated to elicit a physiological response.[3–5] For simplicity, the term 'load' will be used to refer to this concept henceforth. It is generally accepted that larger absolute loads are associated with higher injury risks.[1,2] Mechanistically, this may occur through increased mechanical stress on tissues, increased fatigue affecting decision-making, coordination, and/or neuromuscular control,[6] and increased exposure time at risk.[7]

In recent years, a large focus has been placed on the relationship between changes in load and injury. Gabbett et al. proposed an "acute-chronic workload ratio" (ACWR) model to relate changes in load to injury based on Banister et al.'s fitness and fatigue performance model.[6,8,9] In this model, athletes with similar acute loads (causing fatigue) and chronic loads (proxy for fitness) are thought to be performing activity at a level that they are well-prepared for, minimizing injury risk, whereas athletes with high acute loads and low chronic loads are generally exceeding what they are prepared for, increasing injury risk.[6,9] Athletes with low acute loads and high chronic loads are also thought to be at increased injury risk.[6,10] Although no biological explanations were initially provided, it was later suggested that one's past (chronic) load may promote physical adaptations (e.g. tissue strengthening) that protect against injury.[6,10] However, one's recent (acute) load may cause fatigue and decrease tissue strength and mechanical stress capacity, increasing risk of injury.[6] No biological explanations have been provided for the increased injury risk associated with low acute loads and high chronic loads (excluding a decrease in technical skill following rest periods for sports requiring high precision such as gymnastics)[11], and this finding is likely due to methodological flaws.[12,13]

The monitoring of load to inform training decisions with the goal of reducing injury is now done across a variety of sport types and levels.[14] Training recommendations largely depend on existing models resulting from observational studies.[6,14] While randomized controlled trials (RCTs) are considered the gold standard for identifying causal relationships and evidence-based decision making, they are not often feasible. RCTs generally require a large sample size and long follow-

up, which is often impractical, especially in elite settings.[15] As such, researchers often rely on observational data. However, none of the observational studies reported in existing systematic reviews have explicitly estimated a causal effect of changes in load on injury risk.[1,2,16–18] Further, conventional methods used to study this relationship are prone to bias, and are unlikely to correspond to true causal effects.[12]

Observational data can be used to estimate causal effects only if certain assumptions hold. Meaningful differences have been observed between results from observational studies with traditional study designs and those from RCTs, leading to concerns about their validity. However, some authors have shown that if the observational study design and analysis emulates a hypothetical randomized trial (called a "target trial"),[19] the results are generally consistent with those from RCTs,[20–24] although this is not always the case.[25,26] We propose that this framework be applied to studies of load and injury risk to generate higher quality evidence regarding their relationship.

The objective of this review is to describe the components of the target trial framework as applied to studies of load and injury risk, including potential biases and other challenges as well as strategies to address them.

Target trial framework components

The target trial framework requires researchers to define their research question and study protocol in a way that mimics a hypothetical RCT, and conduct their study analyses using observational data in a way that emulates that protocol.[19] This process minimizes errors and resulting biases that are common in observational analyses.

The major components of a target trial protocol are: 1) eligibility criteria (population); 2) treatment strategies (intervention and comparison); 3) assignment procedures; 4) outcome; 5) follow-up period; 6) causal contrasts of interest; and 7) analysis plan. These components have been described in further detail elsewhere.[20,27] In this section, we outline these components and discuss specific considerations for studies of changes in load and injury risk.

Eligibility criteria

In an RCT, we would start by identifying our population of interest, and specifying inclusion and exclusion criteria to determine eligible individuals. The same criteria should be used for an observational study. Eligibility should be determined at "time zero", or the start of follow-up, and only using baseline information prior to the follow-up period.[28] If there are missing data on important baseline variables, results may not be meaningful given the potential for bias.

Defining the population of interest

In both RCTs and target trial emulations, the population should be defined by who we are interested in intervening on. This may be a specific athletic population (e.g. elite soccer players) or a general population (e.g. youth). When studying general populations, we note that an intervention of a "change in load" is likely to have different effects in different participants (effect heterogeneity). For instance, the same increase in load is expected to affect inactive individuals and regularly active individuals differently. This can promote generalizability; however, if we are interested in a specific subset of the population (e.g. regularly active individuals) it may be appropriate to restrict our study population to those with certain baseline levels of activity measured over a run-in period, with participants only eligible for analyses following this period. Otherwise, we may explore heterogeneity using stratification or an interaction term between baseline activity and the intervention. Any subgroup analyses of primary interest (i.e. not exploratory or hypothesis generating) should be considered in the sample size calculation.

We must also consider how our outcome of injury informs our population of interest. Previous injury is considered an important risk factor for new injuries.[29] In an RCT, we might restrict to healthy individuals (e.g. those who are not currently injured or recovering from injury). We would include the same restrictions in an observational study. Data from a participant who is eligible at baseline is included until injury. Once recovered, data from the same participant would only be included once they are again eligible for the study, after several (e.g. four or five) weeks without injury.

Selection bias affecting internal validity

Individuals should not be included or excluded from analyses based on information gathered during follow-up. The selection of individuals based on factors that result from their intervention and outcome may cause bias through several mechanisms, affecting the internal validity of findings.[30] One example might be analyses that are restricted to those who attended a certain number of training sessions over the follow-up period. Participants who experience health problems (e.g. illness, pain, mental health conditions) are less likely to participate in training,[31] and health problems may be a consequence of changes in load and injury. Excluding participants based on training participation during follow-up may therefore create bias in both RCTs and observational studies. Rather, alternative methods exist that address adherence/non-adherence to planned activity within RCTs (see discussion of per-protocol effects below).[32] The same principles should be applied to observational studies.

Dropouts and censoring

Dropouts affect both RCTs and observational studies. Individuals who drop out or are lost to follow up are considered censored, as their outcome (and potentially their intervention) is not observed.[33] Excluding censored individuals from analyses will result in selection bias when the reason for drop out/loss to follow up are associated with the intervention and outcome.[33] For instance, individuals who are less accustomed to activity and experience higher levels of discomfort or soreness from small increases in activity may be less motivated to remain in a study. Instead, censoring can be accounted for by imputing missing data,[34] or using inverse probability weighting, assuming that data are available on the covariates associated with drop out.[33]

Treatment strategies

Most analyses of RCTs and observational studies compare two treatment strategies: an intervention, and a comparison or control. In our context, the intervention is a change in load. Load has been operationalized in numerous ways,[3] and over various time frames.[16] The optimal measure of load depends on the research context and available data. However, the same principles apply for defining treatment strategies regardless of the load metric.

Defining changes in load

The target trial framework prompts researchers to define treatment strategies that are relevant to stakeholders (e.g., athletes, coaches, policymakers) within the specific sporting context. When defining a "change in load", we must consider the baseline load, whether change is expressed as an absolute vs. relative amount, and whether change is measured at a single time point or as a continuous intervention.

Measurements of change require a baseline or reference value. A simple measure of change in load might be a weekly change, or the change in load during the follow-up week (beginning at time zero) relative to the previous week. In this case, the baseline load would be the absolute load in the previous week. Other options might be an unweighted average load over multiple weeks (akin to chronic load within the ACWR framework), a weighted average, or a cumulative measure. When deciding on a baseline load, researchers should consider any theories underlying the relevance of previous loads in affecting current injury risk, as well as utility for athletes, clinicians, and other stakeholders. For instance, whereas large increases in load may increase susceptibility to injury, these increases are common after recovery or taper weeks which are thought to reduce injury risk.[35]

We must also consider whether to express change as an absolute amount (e.g. an hour more of training this week) or a relative amount (e.g. 10% increase in running distance this week). We will distinguish between individual and policy-level interventions to illustrate this decision. Individuals are typically interested in how their injury risk may differ under different behaviours or patterns to inform their training decisions. For instance, a runner might ask questions like "What is my injury risk if I increase my total distance covered by 5km this week?" (absolute change) or "What is my injury risk if I increase my total distance covered by 10% this week?" (relative change). The impact of changes in load on injury risk on an individual is expected to differ by their baseline fitness.[36] For instance, a 5km increase in running distance is likely to result in a much greater injury risk for someone who regularly runs 5km per week versus 50km per week. Similarly, a 10% increase in distance may also result in differing injury risks for these two individuals, but perhaps not to the same extent as the absolute change. Policymakers are interested in improving the health of an entire population. Policies are generally on an absolute

scale, such as one where children within a school are mandated to take at least one physical education class,[37] or where youth community rugby players are allowed a maximum of 90 minutes of playing time per day.[38]

Furthermore, we must decide whether we are interested in change at a single time point or as a continuous intervention. While a soccer team might be interested in increasing their practices by one hour in a single week (single time point), individuals training for a marathon might be interested in gradually increasing their running distance relative to their previous distance over several weeks (continuous intervention). Within continuous interventions, changes in load are not limited to an increase or a decrease. An intervention to decrease injury risk might incorporate maintenance weeks and recovery weeks (e.g. taper) where load is unchanged or decreased. These weeks are not easily studied under single time point interventions, particularly when baseline load is measured as an average over several weeks such as in the ACWR framework.[12] Under a continuous framework, we might compare: (1) a tapering program with a 10% increase in activity for 3 weeks followed by a 20km decrease in activity for 1 week prior to competition, versus (2) a 10% increase in activity for 4 weeks prior to competition. Note that a continuous intervention can incorporate both absolute and relative changes in load.

Defining the comparison strategy

The comparison of two treatment strategies should reflect meaningful real-world decisions, such as a reasonable alternative behaviour/pattern/policy, or one that is currently in place. For instance, a suitable comparison for a runner interested in increasing their total distance by 20% each week might be an increase in total distance by 10% each week, until a maximal distance is reached, while a suitable comparison for a soccer team wanting to include an extra hour of training moving forwards might be maintaining their current training schedule. A comparison for a policy mandating at least one physical education class per week might be to not have this mandate in place, allowing the population to participate in physical education as they choose.

To determine causal effects, ideally all aspects of training would be maintained between the treatment strategy and comparator except for the aspect that is being intervened on. For instance, if we were interested in increasing training volume (e.g. distance run), we would want to keep

intensity (e.g. pace) constant. This may not be feasible using observational data, and we may instead be limited to assessing the impact of increasing training volume on injury risk regardless of intensity. This is a limitation of using observational data compared to RCTs. At the same time, it is a strength of the target trial emulation approach because it makes these challenges more transparent compared to traditional observational approaches.

Thus far, we have only considered comparisons between 2 treatment strategies, with specific yet arbitrary values for changes in load. In practice, researchers may choose to dichotomize or categorize changes in load when defining their treatment strategies (e.g. increase distance by 5-10km versus increase distance by 0-4 km). These categorizations should be done in a way that reflects realistic training practices, rather than arbitrarily. Determining the effect of a continuous range of changes in load on injury risk is analogous to determining a dose-response curve. The development of a dose-response curve requires a single RCT with many arms, or multiple RCTs. This remains true with the target trial emulation approach, and therefore requires defining multiple comparison strategies and a more complex analytical strategy (covered in more detail in "Analysis plan").

Consistency and positivity

Positivity and consistency are two conditions necessary for causal inference (along with exchangeability, covered in the following section).[39] Under positivity, each individual should theoretically have a positive probability of receiving each level of exposure for every combination of covariates.[39,40] As such, each individual should be theoretically capable of changing their load by a specified amount, which may not be the case for large relative increases in load (e.g. tripling training time in a day when someone is currently training for eight hours per day). The treatment strategies should be realistic given the eligibility criteria for a study.

Briefly, consistency requires that treatments be defined unambiguously so that there cannot be two versions of a single treatment that would result in the same individual having different outcomes.[39–41] In our context, this involves specifically defining what a change in load represents, including the type of activity, frequency, intensity, and/or duration. Further, there cannot be interference, where an individual's outcome depends on another individual's

treatment. In our context, one individual's load should not affect another individual's injury risk. Consistency is likely to be violated when there is a broad intervention, such as an increase in activity duration that does not account for intensity over a variety of sports. While this can be avoided by having more specific research questions, in reality, stakeholders may be interested in general recommendations. Researchers should aim to strike a balance between defining clear treatment strategies and generalizability.

Assignment procedures

Controlling for baseline confounders

In an RCT, treatments are assigned at random at baseline. This achieves exchangeability, one of the necessary conditions for causal inference, given a large enough sample size and perfect adherence to the assigned treatment strategy.[39] Simply, exchangeability means that there is no inherent difference in the risk of injury between treatment and control groups, and that any observed differences are due to the treatment itself. Under full exchangeability, the outcomes for the intervention group are the same as the outcomes for the control group had the control group received the intervention, and the outcomes for the control group are the same as the outcomes for the intervention group had the intervention group not received intervention, all else being equal.[42]

Training decisions are rarely random in observational data. An individual's magnitude of change in load may be influenced by factors such as sex, age, experience, baseline activity levels, planned strength and conditioning training, recent recovery or taper weeks, or previous injuries. These factors may also influence injury risk, and therefore act as confounders. As full exchangeability requires that there be no unmeasured confounding,[42] confounders must be adjusted for in observational analyses through methods such as inverse probability of treatment weighting,[43] multivariable regression, or both (doubly robust estimation).[44]

For a treatment strategy that occurs at a single time point (e.g. increase in load in a single week), adjustment must only be done for factors measured at baseline. Adjustment for factors measured during follow-up affected by the treatment or outcome (e.g. illness) may result in bias[30,45] and decrease precision.[45] For treatment strategies that occur over a period of time (e.g. consistently

increasing load by 10% each week), there may be time-varying confounders that affect injury risk and subsequent changes in loads. One example is fatigue or soreness causing one to decrease their load. Time-varying confounding must be handled using specialized methods developed by Robins and colleagues.[39]

Timing of treatment assignment and immortal time bias

Treatment assignment, or the observational analogue of defining an individual's exposure, must be done at baseline to properly emulate a target trial. However, observational studies of changes in load and injury often only measure acute load at the end of the follow-up period. As such, any injury occurring during follow-up can affect one's measured load and cause a bias akin to immortal time bias in other fields of epidemiology.[28,46] For instance, load may be measured as one's activity performed over a week. Athletes who get injured earlier in the calendar week will not be able to perform their planned activity for the rest of the week, and will have systematically lower loads than athletes who complete the week without injury.[12] The same principles apply when daily averages are used to calculate loads, but with reduced bias.[12]

Researchers sometimes impose an injury lag period, in which only injuries occurring in a specified time window (e.g. one week) subsequent to the load window will be attributed to that load.[16] In this setting, treatment assignment would occur at the beginning of the follow-up period, defined as the week following the load window. This eliminates the bias explained above, but ignores the principle that current load is the inciting factor for injury and assumes that the load between the end of the load window and the time of injury is not relevant.[12] Alternatively, researchers may use planned loads rather than observed loads to calculate changes in load, and estimate an intention-to-treat (ITT) effect of changes in load on activity. ITT effects are discussed further under "Causal contrasts of interest".

Outcome

A well-designed study requires a clear definition of the outcome. Injury can be defined in many ways. Common categorizations include any athlete-reported complaint, medical attention injuries, and/or time-loss injuries.[47] The onset of injury might be defined at the time of first complaint, initiation of time lost from sport, or at the time of medical diagnosis.

Multiple injuries

Injuries can and often do occur more than once in the same individual, and one's risk of subsequent injury may be affected by previous injuries.[29] Furthermore, injuries often influence one's subsequent activity patterns. As such, previous or current injuries are a confounder for the relationship between changes in load and injury, and must be accounted for in study design or analyses.

Previous or current injuries at the start of follow-up can be adjusted for as baseline confounders in observational studies. These might be included as dichotomous variables (e.g. yes/no injury in the previous X months), or continuous variables (e.g. number of injuries in the previous X months). However, most RCTs would only include healthy individuals as part of their eligibility criteria, excluding those who have returned to training but are not fully healed. We might emulate this criterion by only including individuals in our study up to their initial injury, after which they are no longer eligible. However, this would greatly reduce our effective sample size. Alternatively, we may believe that one's injury risk is unaffected by previous injuries after a certain time period (e.g. one month). Similar to an RCT that might restrict to individuals who have not been injured in the past month, we can restrict our observational analyses to those who have been uninjured for one month prior to the start of follow-up. This is equivalent to a "washout" period commonly employed in pharmacoepidemiology studies, where participants are observed for a period of time prior to follow-up to ensure that outcomes are not due to exposures that occurred prior to the study.[48,49] However, if we are interested in a sustained intervention such as an increase in load over several time points, we must treat injuries occurring during follow-up as time-varying confounders, and account for them using the appropriate methods.[12]

Finally, we may explore effect heterogeneity between initial and subsequent injuries through stratified analyses or by assessing interactions if relevant to our research question.

Causal contrasts of interest

Data from RCTs can be used to obtain an intention-to-treat (ITT) or per-protocol (PP) effect estimate.[50] Analogs of these effects can be estimated using observational data.[20]

ITT versus PP effects

The ITT estimate addresses the question "What is the effect of assigning a policy or intervention on injury?". Participants are analyzed in the group that they were assigned during randomization, irrespective of the treatment they actually received, non-adherence, or drop-out. This maintains exchangeability between groups assuming no drop-outs, but will generally result in conservative effect estimates for the treatment actually received due to noncompliance.[50,51] The ITT estimate may be of interest on a policy level because not everyone is expected to comply to policies or recommendations in real life.[32] For instance, coaches or clinicians may be interested in ITT estimates because they prescribe training plans rather than follow them.

The PP estimate addresses the question "What is the effect of a policy or intervention on injury if everyone adhered to the policy or intervention?".[39] Traditional methods to estimate the PP effect include "as-treated" analyses which compare participants based on the treatment they actually took, or "naïve per protocol"/"on-treatment" analyses that are restricted to participants who followed their assigned treatment.[52] These analyses are essentially observational, as individuals are able to choose their intervention. To properly estimate the PP effect, more sophisticated analyses with additional assumptions are required to adjust for confounding and non-adherence to avoid bias, even in an RCT setting.[39,52] For example, although the objective of a recent RCT was to estimate the ITT effect of providing a load management software program on injury risk, the conclusion referred to "managing training loads" (a PP effect).[53] Such a conclusion would require more assumptions, different analyses, and higher quality data. The PP estimate is generally of greater interest to individuals for informing decisions (e.g. athletes trying to minimize injury risk).[39]

The ITT and PP estimates will differ when there is non-adherence to treatment assignment. Non-adherence to a training plan or pattern may occur due to reasons such as injuries at baseline, fatigue, soreness, illness, or motivation. Importantly, individuals who get injured during follow-up and stop training should be considered as having adhered to their treatment assignment so long as they were following their strategy up to the point of injury, as we would not expect injured participants to continue their regular training.

Estimating ITT effects using observational data

To estimate ITT effects using observational data, we must determine an individual's treatment assignment using their planned loads at baseline, and adjust for baseline confounders related to their planned training. This is only feasible if planned loads such as a weekly training program are available. We recommend that planned training schedules be collected in observational studies to allow ITT analyses to be conducted, and to avoid immortal time bias as discussed above. Within team sports, participants generally have the same training schedule and planned loads. However, their baseline loads may differ due to absences, non-adherence, etc. The planned "changes in load" should be based on each individual's observed baseline load. Further, because participants on the same team may have similar training schedules and propensities for injury, clustering by team should be accounted for in analyses.

Estimating PP effects in observational data

To estimate PP effects using observational data, we must compare individuals based on their actual activity patterns, as opposed to their planned training.

Above, we discussed how immortal time bias can occur if acute load is measured at the end of the follow-up period. This creates difficulties in estimating PP effects, as we are unable to obtain an unbiased measure of an individual's observed exposure or training. To estimate PP effects for a specific change in load at a single timepoint, we must impose an injury lag period and follow-up for injuries *after* the acute load is measured. For instance, we could define the outcome as injuries occurring within a day after the current week, and assign treatments based on an individual's change in load for that week compared to the previous week. In a nested target trial approach, the follow-up period for injury would be on the following Monday for the trial where load was measured from Monday to Sunday, the following Tuesday for the trial where load was measured from Tuesday to Monday, and so forth. However, this approach would ignore variations in load in the current day that might affect injury risk. Despite the advantages of target trial emulation, it does not solve the challenge in estimating PP effects for specific single timepoint interventions which may be of interest for athletes, coaches, and clinicians.

PP effects can be estimated using a cloning and censoring approach when the treatment is categorical.[20] For instance, we might be interested in whether an increase in distance by 5-10km increases injury risk compared to an increase in distance by 0-4 km. Under this approach, we would clone each individual in our analyses, assigning each clone to a different treatment at time zero (5-10km vs. 0-4km). We would follow-up each clone for injury, and censor the clone at the point that their observed load is no longer consistent with their treatment assignment. Such an analysis is only feasible for dichotomous treatments or treatments with few categories, as assessing injury risk for a continuous range of changes in load would result in an infinite number of clones.

For sustained interventions such as a consistent increase in load over several weeks, we must adjust for time-varying confounders related to non-adherence and injury using methods such as inverse probability weighting or g-estimation.[52] Important confounders include fatigue and soreness, and this information should be collected in load and injury surveillance or studies to determine causal effects. Alternatively, if training schedules are available, planned training can be used as an instrumental variable to estimate the effect of changing load on injury in the presence of unmeasured confounding, providing the underlying assumptions are likely to hold true.[12,52]

Analysis plan

Generally, the study analysis requires creating a statistical model that reflects the relationship between the exposure and outcome, and estimating the effect of interest.[45]

Pooling multiple trials

In RCTs, eligible participants are typically identified and randomized into one of two treatment groups at baseline or “time zero”. In observational data, an individual may meet eligibility criteria at multiple time points. To increase the number of observations and effective sample size, we might allow individuals to contribute multiple trials or follow-up periods, given they meet eligibility requirements.[25] This is analogous to a repeated measures design in an RCT, where individuals participate in a trial multiple times.[39,55] In both a repeated measures RCT and

observational study, we would have to account for repeated measures in the analyses (e.g. through cluster bootstrapping,[56] mixed models,[57,58] or generalized estimating equations[59]).

Estimating effects using observed versus predicted data

The majority of studies employing the target trial framework assign individuals to a treatment group consistent with their observed data. For instance, if we were interested in the per-protocol effect on injury risk for an increase in load by 2-fold or more versus less than 2-fold, we would categorize each individual into a group based on their observed increase in load assessed at time zero. If an individual's observed exposure was compatible with multiple treatments at time zero, we could employ a cloning and censoring approach to minimize bias.[20]

Treatment assignment using observed data becomes inefficient for treatments that are continuous variables. For instance, we may be interested in comparing injury risk for an increase in load by 2-fold compared to 1-fold. Any individual with an increase in load by a value other than 2-fold or 1-fold would be excluded from analyses, drastically reducing the sample size. Instead, we can employ marginal standardization.[60,61] Briefly, we create a model reflecting the relationship between continuous increases in load and injury risk (appropriately accounting for confounding, loss to follow-up, etc.), and predict each individual's outcomes under different hypothetical treatments. In this scenario, we could include all eligible individuals in our predictive model, and predict whether or not they would become injured under either treatment (2-fold increase vs. 1-fold increase). We can then use these results to estimate the average treatment effect across the different treatments, with bootstrapping to calculate standard errors and confidence intervals.[60,61]

Conclusion

To inform training recommendations and prevent injuries among athletes, we require evidence on the relationships between changes in load and injury. While observational data is often used in studying the relationship between changes in load and injury risk, conventional analytic approaches are prone to bias. The target trial framework is a valuable and simple tool to explicitly define causal questions and design studies to estimate causal effects using observational data. By applying this framework, we can strengthen the validity of future research in the sport medicine field. Although the target trial framework solves some of the challenges

compared to current approaches, other challenges remain including isolating the effects of a single aspect of load, implementing intention-to-treat or instrumental variable analyses when planned loads are not available, and limitations in estimating per-protocol effects.

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Figures

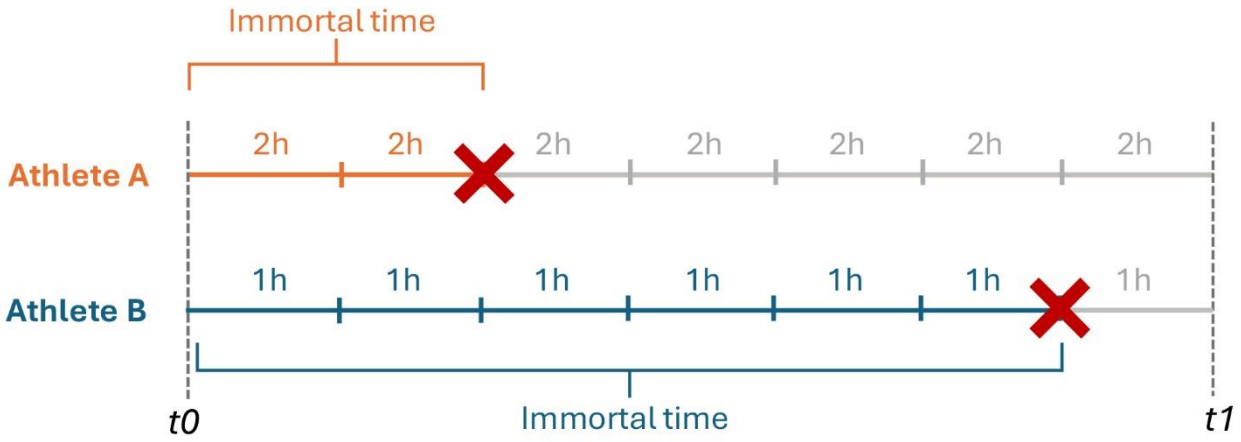

Figure 1. Immortal time bias in the measurement of load. Loads (measured as duration) are indicated for each Day 1-7 during the calendar week. Observed loads are indicated in orange for Athlete A, and blue for Athlete B. Planned loads that were not observed due to injury are indicated in grey. Injury is represented by a red X. Follow-up for injury starts at time zero (*t0*, beginning of the calendar week) and ends at *t1* (end of the calendar week). Load is assessed at *t1*. Despite having planned a larger load and having been exposed to a larger load up to the point of injury, a smaller load is observed for Athlete A than Athlete B who completed the week without injury. This creates a bias known as "immortal time bias" in epidemiology.[28,46]

Chapter 8: Manuscript 5

Preface

In Manuscript 3, I noted that immortal time bias can be avoided in studies of changes in load and injury risk by measuring the "intention-to-treat effect", or the effect of a planned (rather than observed) change in load on injury risk. In Manuscript 4, I discussed the application of the target trial framework to observational studies of changes in physical activity or load and injury risk. In this manuscript, I employ this framework to determine the intention-to-treat effect of changes in participation in practice and games on injury risk among adolescent ice hockey players. It is the first study to our knowledge to employ the target trial framework in sport injury epidemiology.

This manuscript has undergone one round of revisions in *Journal of Science and Medicine in Sports*. Conference abstracts based on contents of this manuscript were accepted as an oral presentation at the Canadian Academy of Sports and Exercise Medicine Annual Symposium (Niagara Falls, May 2024), and as a poster presentation at the Society for Epidemiology Annual Meeting (Austin, June 2024).

The effect of changes in planned participation on injury risk in adolescent ice hockey players: a target trial emulation

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Abstract

Objective: Few studies have estimated causal relationships between training load and injury risk. Target trial emulation is a framework for conducting causal inference using observational data. We employ this framework to estimate the effect of changing planned participation duration, measured using the acute:chronic workload ratio (ACWR), on injury risk among adolescent ice hockey players without recent injuries.

Design: Prospective cohort study designed to emulate a hypothetical randomized trial.

Methods: We used data from a 5-year cohort study (2013-2018) of ice hockey players aged 13 to 17 years in Alberta and British Columbia. We estimated injury risks associated with different planned changes in hockey participation duration (e.g. half [ACWR=0.5], no change [ACWR=1], two-fold [ACWR=2], three-fold [ACWR=3], and five-fold [ACWR=5]) relative to participation in the previous 4 weeks. Outcomes were modelled using generalized additive models. We conducted secondary analyses restricted to concussions, and stratified by league bodychecking status.

Results: There were 2,633 eligible participants, contributing 115,821 player-trials. Injury risk was 1.9% (95%CI: 1.7%-2.3%) for no change in participation (ACWR=1). Injury risk ratios (RRs) were 0.43 at ACWR=0.5 (95%CI: 0.31-0.54), 1.62 (95% CI: 1.33-1.98) at ACWR=2, 1.91 at ACWR=3 (95%CI: 1.52-2.48) and 2.35 at ACWR=5 (95%CI: 1.68-3.26). Patterns were similar by league bodychecking status. Concussion RRs were stable between ACWR=1 to 1.5, but RRs were greater than for any injury past ACWR=2.

Conclusion: Within the assumptions of this target trial emulation, injury risk increases consistently (no sweet spots) for increases in planned changes in participation duration relative to the previous 4 weeks among adolescent ice hockey players without recent injuries. Increases in injury risk are less than expected for the increased exposure time at risk, suggesting beneficial effects of increasing participation that partially counteract the increased exposure time.

Keywords: injury, concussion, adolescent, male, female, humans, hockey, workload, cohort studies, intention-to-treat analysis

Introduction

Ice hockey is a popular sport among adolescents in Canada.[1] However, it is also a high-risk sport for injuries, particularly concussions.[1,2] It is important to minimize injury risk while promoting the benefits of ice hockey participation.

Participation in sports such as ice hockey exposes individuals to forces, known collectively as "load".[3] Injuries occur when tissues are exposed to greater loads than their load capacity.[3,4] Injuries may occur due to sudden large loads, such as falls or collisions.[2,5] These are acute injuries,[6] and include concussions, sprains/strains, dislocations, bruises, cuts, and fractures.[2] Injuries may also occur due to repeated exposure to loads without sufficient recovery, resulting in decreased load capacity and eventual significant damage.[7,8] These are gradual onset injuries,[6] and include tendinopathies, apophyseal injuries, and stress fractures, among others.[9–11]

Increases in sport participation may increase injury risk through multiple pathways: 1) increased exposure time at risk,[12] 2) increased physical and/or mental fatigue from increased loads affecting balance, proprioception, spatial awareness, and reaction time in the case of acute injuries,[13–18] and 3) increased loads without sufficient recovery time affecting load capacity in the case of overuse injuries.[3]

The acute:chronic workload ratio (ACWR) is a popular metric for quantifying relative changes in load.[19–21] The ACWR is calculated as the acute (i.e. current) load divided by the chronic (i.e. previous) load. As tissue loads are infeasible to measure, particularly on a population-level, various proxy measures are used to quantify load that may differ depending on the sport and research context.[20–22] Some previous studies have found higher injury risks at high ACWR values,[20,21,23] consistent with the principle that loads beyond what an individual is prepared for cause injury, whether through increased time at risk, fatigue, or insufficient recovery. However, other studies have found lower injury risks at high ACWRs.[24,25] Despite being used to make recommendations about sport participation,[26] most ACWR-based studies have been associational, with methodological limitations that are likely to create biases which could explain these contradictory findings.[27,28] Further, some studies have suggested that the associations between week-to-week changes (an absolute measure) and injury risk are similar to those

between the ACWR and injury risk.[29] Despite these limitations, we use the ACWR in this study as a measure of relative changes in load based on its popularity in current literature.

Target trial emulation is a framework for conducting causal inference using observational data.[30,31] It involves defining the research question and study protocol to mimic a hypothetical randomized controlled trial (RCT) (the "target trial"), and emulating the protocol using observational data.[30,32] This process helps avoid common biases arising in observational analyses.[33] Target trial emulation has yielded results comparable to RCTs,[34,35] and is recommended by researchers as a "best practice" for conducting observational studies.[32,36–38] Despite being increasingly used in epidemiologic research, it has not been commonly applied to sport injury epidemiology. We refer readers to a methodological article for more information on this framework and its potential application to this research area.[31]

RCTs can be analyzed to obtain an "intention-to-treat" or "per-protocol" effect.[39] The intention-to-treat effect compares participants based on the intervention they were assigned, whereas the per-protocol effect compares participants based on the intervention they actually received.[39] Whereas the intention-to-treat effect is unbiased in an RCT assuming successful randomization, the per-protocol effect can be biased if reasons for non-adherence are not appropriately controlled for. Intention-to-treat effects can be estimated under the target trial framework by using planned loads and adjusting for baseline confounders to emulate randomization.[31]

The objective of this study is to conduct target trial emulation to estimate the intention-to-treat effect of relative changes in planned participation in practices and games on injury and concussion risk among adolescent ice hockey players without recent injuries. Additionally, we examine differences in effects between bodychecking and non-bodychecking leagues.

Methods

Data Source

The data source for this study was Safe2Play, a 5-year (2013 to 2018) longitudinal prospective cohort study of adolescent ice hockey players in Alberta and British Columbia, Canada. Safe2Play included male and female players on co-ed teams across all levels of play in Under-13 (ages 11 to 12), Under-15 (ages 13 to 14), and Under-18 (ages 15 to 17) age-groups, in leagues

that allowed or disallowed bodychecking. All hockey associations within their respective regions were invited to participate, and individual teams were recruited if they could identify a team designate (e.g. manager, coach, parent) to report participation in games and practices on a weekly exposure sheet (WES). Injury report forms (IRF) were initiated by study personnel based on self-report, team designate report on WES, or team therapist report. Individual players (≥14 years for mature minor consent) providing written consent and parents (children <14 years) providing written consent (child providing written assent) were included in the study. Participants could enter the study at any time in the hockey season (October to April), but most were recruited at the beginning of the season. Participants could be followed for multiple seasons.

During each season, weekly exposure data were recorded by the team designate, including practice and game durations in minutes, participation for each player (full, partial, or none), and reasons for missed participation (hockey-related injury, non-hockey-related injury, sickness, or other). Hockey-related injuries resulting in medical attention, inability to complete the session, or missed participation from subsequent sessions (i.e. time-loss) were recorded on an IRF by the team designate. The Safe2Play study has resulted in numerous secondary analyses and publications; more details about its procedures can be found elsewhere.[40–44]

Target Trial Specification and Emulation

We specified the protocol of hypothetical target trials to estimate the intention-to-treat effect of changing participation by different amounts on injury risk and emulated this protocol using data from the Safe2Play study. Components of the target trials are summarized in Table 1.

Eligibility Criteria

The target trials would include adolescent ice hockey players who were participating in hockey practices and games and had not been injured or recovering from injury in the 4 weeks leading up to the study.

Our observational study included participants from the Safe2Play parent cohort study followed in the 2013-2014 through 2016-2017 playing seasons. The 2017-2018 season was excluded due to

significant missing exposure data. Participants were excluded if they had missing data on whether they played in a league that allowed or disallowed bodychecking. Those in the Under-13 age group were excluded as bodychecking was banned for this group in Canada in 2013, and including this group would violate the positivity assumption required for causal inference.[45]

Individuals must have been participating in hockey practices and games for the previous 4 weeks and must not have been injured or recovering from injury in the previous 4 weeks. As such, individuals must have had data for at least 5 weeks within a season to be eligible (4 weeks for eligibility criteria and 1 week for follow-up). Within the Safe2Play data, individuals may have been eligible at multiple time points. To maximize sample size and power, individuals at each eligible time point were considered as separate units of analysis (player-trials),[33] with adjustment for clustering in the analyses. An individual could have been eligible the day after the previous player-trial, and therefore have contributed multiple overlapping player-trials (Supplementary Material, Figure S1).[31]

Intervention

Because we were interested in intention-to-treat effects, interventions were expressed as X-fold changes (ranging from 0.1- to 5-fold) in planned participation for the upcoming week, measured using the ACWR (acute load divided by chronic load). The acute load was calculated as the daily average planned participation duration over 7 days, starting at time zero. Planned participation duration was defined as the number of minutes of hockey practices and games in a team's schedule, as reported by the team designate, and did not account for individuals' absences from practices or games. As would occur in an RCT accounting for previous activity, the chronic load was calculated as the daily average participation duration over the previous 28 days, ending at time zero (Supplementary Material, Figure S1). The chronic load was measured using observed rather than planned participation, accounting for absences from practices or games. Individuals who were completely absent from a practice or game were assigned a session duration of 0, whereas individuals who partially participated in a practice or game were assigned 50% of the session duration.

Outcome

The outcome was any ice hockey-related injury occurring during participation in practices or games resulting in medical attention, inability to complete the session, or missed participation from subsequent sessions (i.e. time-loss). In a secondary analysis, we limited the outcome to concussions.

Intervention Assignment

In our target trials, participants would be randomly assigned to an X-fold change in participation duration (ACWR value) ranging from 0.1 (10-fold decrease in activity) to 5.0 (5-fold increase in activity). Their assigned participation duration (planned acute load) would be equal to their chronic load multiplied by their assigned X-fold change or ACWR.

In our observational study, the observed X-fold changes in participation duration were calculated for each individual at each eligible time point. To emulate exchangeability obtained by randomization in an RCT, we identified baseline confounders based on background knowledge of factors that may be common causes of changes in planned participation and injury risk. We identified chronic load, age group (Under-15/Under-17), and league bodychecking status (allows bodychecking/disallows bodychecking) as potential confounders. A causal directed acyclic graph displaying our assumptions about the causal relationships between our variables of interest can be found in Supplementary Material, Figure S2. We assumed that chronic load affects the change in planned participation, and might differentially affect current injury risk (e.g. by impacting fitness). We also assumed that teams with older and more experienced players as well as those in bodychecking leagues might have more variation in session durations, and that these factors may also impact injury risk. We did not identify sex as a confounder because the large majority of participants were male, and sex was unlikely to affect planned participation as teams were co-ed. We acknowledge that there may be other important factors that we did not identify or have data on, and that other researchers may have different assumptions regarding the causal relationships between these factors.

We then assigned all individuals at each eligible time zero to the same fold change in participation duration. This was done for a range of ACWRs from 0.1 to 5.0 in 0.1-unit increments.

Follow-Up Period

In the target trials, participants would be followed up from time zero for one week to determine whether they became injured. In our observational study, we determined whether or not a participant became injured over the next 7-day window starting at time zero for each player-trial (5-week unit of analysis including 4-week eligibility period [chronic load] and 1-week follow-up [acute load]).

Causal Contrasts of Interest

Our causal contrasts of interest were the intention-to-treat effects of changing participation duration on injury risk. In the target trial, this would be the effect of being assigned to a particular X-fold change in participation duration compared to no change (ACWR=1). In our observational study, this was the effect of planned changes in participation duration compared to no change, based on a team's practice and game schedule, adjusted for baseline confounders.

Subgroup Analyses

We pre-specified subgroup analyses by league bodychecking status as ice hockey players in leagues that allow bodychecking have higher injury risks.[41,46]

Statistical Analysis

We modelled the relationship between X-fold changes in participation duration and injury using pooled data across eligible person-trials. We fit a generalized additive model (GAM) with injury as the outcome and ACWR as the exposure, with a logit link function for the binomial outcome. We applied a smoothing term to the ACWR using a cubic regression spline with 8 degrees of freedom. We included chronic load, age group, and bodychecking status as covariates.

We then predicted injury risks for each player-trial using our fitted model under interventions where the ACWR was set to values ranging from 0.1 to 5.0, in increments of 0.1. We calculated marginal injury risks and risk ratios (RRs) relative to no change in participation duration (ACWR=1). We conducted separate analyses stratified by league bodychecking status, and with concussion as the outcome. We applied cluster bootstrapping with 300 replicates to account for

repeated measures within players when estimating 95% confidence intervals. Analyses were conducted in RStudio.[47] GAMs were fit using the *mgcv* package.[48]

Results

A total of 2,633 players were eligible for target trial emulation, contributing 115,821 player-trials over 3,034 player-seasons (Figure 1). Males accounted for 2,406 (91.4%) participants. Most eligible player-trials were contributed by the Under-15 age group, and in leagues that allowed bodychecking (Table 2). Among eligible player-trials, the median planned participation duration was 5 hours/week or 41 minutes/day (IQR: 30 to 54 minutes/day), while the median observed participation duration was 4.5 hours/week or 39 minutes/day (IQR: 26 to 51 minutes/day). The mean difference between planned and observed participation duration was 4 minutes/day (95% CI: -12 to 19 minutes/day). Injuries occurred in 2,588 (2.2%) of eligible player-trials, of which 507 (19.6%) were concussions.

The estimated injury risk for a 1.0-fold (no) change in participation duration was 1.9% (95% CI: 1.7%-2.3%). The largest increases in injury risk occurred with increases in participation duration up to 2.0-fold (RR = 1.62, 95% CI: 1.33-1.98). Injury risk increased further with increases in participation duration up to 5.0-fold (RR = 2.35, 95% CI: 1.68-3.26). Injury risk decreased largely for decreases in participation up to 0.5-fold (RR = 0.43, 95% CI: 0.31-0.54), but was stable for further decreases in participation, with large uncertainty and wide CI's (Figure 2; Supplementary Material, Figure S3 shows 95% CIs for RRs).

Injury risks were higher for leagues allowing bodychecking compared to leagues disallowing bodychecking for increases in participation up to 2-fold and decreases down to 0.8-fold (Figure 3). RRs relative to no change in participation did not differ meaningfully by bodychecking status, except between 0.6-fold and 1-fold, where decreases in participation resulted in lower injury RRs among leagues allowing bodychecking (Supplementary Material, Figure S4).

Concussion risk did not change for increases in participation from 1.0- to 1.5-fold; however, it increased for further increases in participation (Figure 4). Concussion RRs associated with increases in participation beyond 2-fold were greater than observed for all injuries.

Discussion

We found that injury risk increased consistently for planned increases in participation duration relative to the previous 4 weeks, while injury risk decreased for planned decreases in participation duration relative to the previous 4 weeks. Increases in injury risk were less than would be expected for the increase in exposure time at risk, suggesting beneficial effects of increasing participation that partially counteract the increased exposure time at risk. For example, 2-fold, 3-fold, and 5-fold increases in planned participation resulted in 1.5-fold, 2-fold, and 2.5-fold increases in injury risk, respectively. Increases in planned participation relative to the previous 4 weeks resulted in larger increases in concussion risk than any injury, but still less than would be expected for the increased exposure time (1.6-fold, 2.4-fold, and 3.2-fold increase in concussion risk for 2-, 3-, and 5-fold increases in participation, respectively). While injury risks were higher among leagues allowing bodychecking, intention-to-treat effects of changing participation duration on injury risk did not differ substantially by league bodychecking status.

The observed relationship between planned changes in participation and injury risk is likely due to a mixing of mechanisms. Increasing participation results in increased exposure time at risk.[12] It can also result in increased load on tissues without sufficient recovery, resulting in overuse injuries,[3] and increased physical and mental fatigue affecting balance, proprioception, spatial awareness, and reaction time, resulting in acute injuries.[13–18] Increased participation can also have beneficial effects for injury prevention, including increased tissue load capacity given sufficient recovery,[3] improved skills and confidence,[49,50] and improved fitness.[51,52] Separating these different mechanisms is complex, and not necessarily of interest to coaches, players, and parents whose goal is to increase participation while minimizing risk of all injuries.

Some previous studies looking at associations between changes in load and injury risk identified "sweet spots" where load can be increased without increasing injury risk.[21,53] For instance, studies have identified ACWRs between 0.8-1.3 to be associated with decreased injury risk compared to ACWRs below or above this range.[53] Our results using target trial emulation suggest no such "sweet spot" for changing participation while minimizing injury risk in adolescent ice hockey, although concussion risk was stable for increases in participation between

1.0- to 1.5-fold. Participation decisions in this setting should balance the benefits of increased participation with the consequences of increased injury risk.

Strengths

Our study is the first to our knowledge to apply target trial emulation to assess the relationship between changes in load and injury risk. This framework requires defining a study protocol in a way that mimics a hypothetical RCT, helping avoid common errors in biases in conventional observational analyses.[30]

For instance, researchers have often categorized load into weekly blocks by calendar time and calculated the ACWR exposure within these blocks.[54–56] This creates an issue where the exposure assignment is not aligned with the start of follow-up and measurement of baseline confounders (time zero), resulting in bias where increased injury risks are observed for decreases in load.[27,33] In our study, we aligned exposure assignment with the start of follow-up by using planned participation durations rather than observed participation to calculate the acute load.

Few studies have considered whether individuals were recently injured in analyses of changes in load and injury risk.[25] Instead, analyses often pool initial and subsequent injuries,[57] which assumes that they have similar relationships with changes in load. However, initial injuries are an important confounder, affecting both subsequent activity and injury risk.[58] In RCTs, this confounding is avoided by 1) restricting eligibility to uninjured participants at baseline, or 2) randomization of intervention assignment so that groups have similar distributions of injured versus uninjured participants. We avoided confounding by recent injuries in our target trial emulation by restricting participation to players who were uninjured in the previous 4 weeks. Although adjusting for recent injuries at baseline (emulating randomization) would also avoid confounding, we chose not to because there may be important differences in the effects of increasing planned participation on initial versus subsequent injury risk that would be masked by regression adjustment.

We employed a large data source, allowing the use of flexible modelling strategies. The current study and previous studies have suggested that the relationship between changes in load and

injury risk does not follow a simple exponential or polynomial curve.[59–61] Future research should also employ non-linear modelling approaches.

Limitations

Our study had several limitations. We did not have data on potentially important confounders of fatigue or soreness,[62] which may have biased our findings. However, we assume that fatigue or soreness would only affect changes in planned participation by affecting the chronic load (as planned participation is based on the team schedule); therefore, by adjusting for chronic load, any bias from ignoring fatigue or soreness for our intention-to-treat estimate is likely to be minimal. We also did not adjust for division skill level. Participants in higher level divisions may have larger increases in planned participation during the season (e.g. due to more tournament play) and may be at higher risk of injury due to increased intensity and speed of play.[2,63] Although bodychecking generally occurred in higher level divisions, and was included as a confounder, we would still expect some residual confounding that may have resulted in an apparently larger association between changes in planned participation and injury risk.

We operationalized changes in participation duration using the ACWR, a measure that has been criticized for assessing causal effects.[27,28,62] Although we use an "uncoupled" measure (excluding acute load from calculations of chronic load) that avoids more serious limitations of the ACWR,[27,64] some authors have suggested that even the uncoupled measure is prone to erroneous inferences.[28] We used a ratio as our exposure variable, rather than assessing the acute and chronic loads as separate variables.[65] This was to be consistent with our research question which concerned the effect of changes in planned participation on injury risk rather than the separate effects of current planned participation and previous participation. We combined acute and overuse injuries in our outcome of interest, assuming that changes in planned participation would impact both acute and overuse injury risk. Our findings are likely due to a mixing of mechanisms as relationships may differ between injury subtypes, and our results only apply under our assumptions. Finally, we did not differentiate between practices and games. Studies have shown that injury incidence is higher during games than practices in team sports,[66] and the relationship between changes in load and injury risk may differ between practices and games.[67]

Future Directions

Our research question focused on the intention-to-treat effects of changing participation duration at one point in time on injury risk. This aligns with the current application of the ACWR to quantify and reduce injury risk.[26] Future directions include determining the effects of participation duration on injury risk at different times throughout the season,[68] and estimating per-protocol effects based on observed rather than planned participation.[69] More advanced causal inference methods are required (1) to assess injury risk at multiple timepoints, which requires adjusting for time-varying confounding,[69] and (2) to estimate per-protocol effects, which requires adjusting for factors related to non-adherence to participation schedules.[69]

Conclusion

Using target trial emulation, we found that injury risk increased consistently with planned changes in duration of participation in practices and games compared to the previous 4 weeks among adolescent ice hockey players without recent injuries, but by less than would be expected for the increase in exposure time at risk. Target trial emulation is easily extended to other study populations and should be considered by sport injury researchers as a valuable tool to explicitly define their study protocols and avoid common errors in observational analyses.

Practical Implications

- Injury risk increased consistently with planned increases in participation among adolescent ice hockey players without recent injuries, but by less than would be expected for the increase in exposure time at risk
- This study did not find a “sweet spot” for increasing ice hockey participation without increasing injury risk
- Participation decisions should balance the benefits of increased participation with the consequences of increased injury risk

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Table 1. Target trial specification and emulation to estimate the intention-to-treat effect of changing participation duration on injury risk among adolescent ice hockey players without recent injuries.

Protocol Component	Hypothetical Target Trial	Observational Study
Eligibility Criteria	- Adolescent ice hockey players aged 13 to 17 years in British Columbia and Alberta - Have been participating in ice hockey practices and games for at least 4 weeks - Not injured or recovering from injury in the previous 4 weeks - Individuals are eligible at one time point	- Same as for target trial, but participants must have been part of the Safe2Play parent study and have 5 weeks of participation data (previous 4 weeks and current week) - Individuals can be eligible at multiple time points
Intervention	- Relative changes in participation duration (number of minutes of ice hockey practices and games) defined by the ACWR o Chronic load: daily average participation duration over the previous 4 weeks o Acute load: daily average planned participation duration over the next 7 days o Assigned participation duration for the next 7 days is calculated as the participant's chronic load multiplied by their assigned ACWR - Comparison is an ACWR of 1, where the acute load (daily average participation duration over the next 7 days) is equal to the chronic load (daily average participation duration over the previous 4 weeks)	- Same as target trial
Intervention Assignment	- Participants randomly assigned at baseline to a particular ACWR value ranging from 0.1 to 5.0, in 0.1-unit increments	- Observed ACWRs calculated for each individual at each eligible time point - Modelled ACWR-injury relationship adjusted for baseline confounders (chronic load, age group) to emulate randomization - Assigned all individuals at each eligible time point to the same

		ACWR, and estimated injury risks using model o Done for ACWR values ranging from 0.1 to 5.0, in 0.1-unit increments
Outcome	- Any ice hockey-related injury occurring during participation in practices or games resulting in medical attention, inability to complete the session, or missed participation from subsequent sessions	- Same as target trial
Follow-Up Period	- 7 days starting from eligibility assessment and randomization	- 7 days starting from eligibility assessment
Causal Contrasts of Interest	- Intention-to-treat effect (effect of assigning a X-fold change in planned participation duration)	- Intention-to-treat effect (effect of a X-fold change in planned participation duration as determined by the team's planned participation schedule)
Subgroup Analyses	- Stratification by league bodychecking status	- Same as target trial
Statistical Analyses	- Compare injury risks for each intervention group to the injury risk for the group where ACWR was assigned as 1.0	- Compare predicted injury risks among all eligible individuals under each hypothetical intervention to the injury risk for the hypothetical intervention where ACWR was assigned as 1.0

Abbreviations: ACWR, acute:chronic workload ratio

Table 2. Characteristics of participants and player-trials included in a target trial emulation to estimate the intention-to-treat effect of changing participation duration on injury risk among adolescent ice hockey players without recent injuries. Participants were from the Safe2Play parent study (2013-2017). There was a total of 2,633 eligible participants.

	No. of player-trials (%) (n=133,332)	
Characteristic	**Eligible player-trials (n=115,821; 86.9%)**	**Ineligible player-trials[a] (n=17,511; 11.3%)**
Age group		
Under-15 (13 to 14 years)	72,137 (62.3%)	9,385 (53.6%)
Under-18 (15 to 17 years)	43,684 (37.7%)	8,225 (46.4%)
Sex		
Male	101,040 (87.2%)	15,316 (87.5%)
Female	14,781 (12.8%)	2,195 (12.5%)
League bodychecking status		
Allows bodychecking	78,102 (67.4%)	13,291 (75.3%)
Disallows bodychecking	37,719 (32.6%)	4,319 (24.7%)

[a] Ineligible player-trials were those where the player was injured or recovering from injury in the previous 4 weeks, or had been absent from all hockey practices and games in the previous 4 weeks.

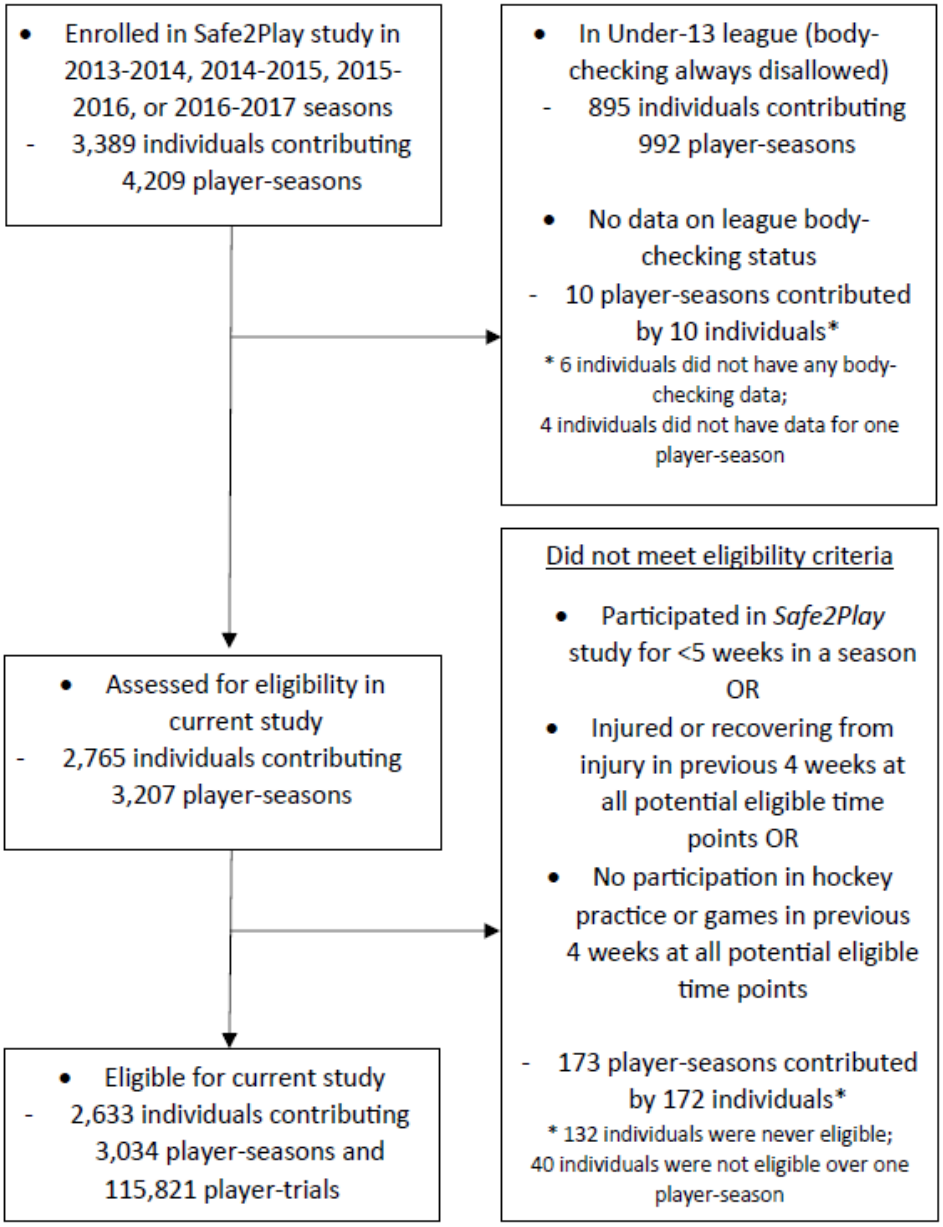

Figure 1. Participant flow chart for the emulation of a target trial assessing the effect of changing participation duration on injury risk among adolescent ice hockey players without recent injuries.

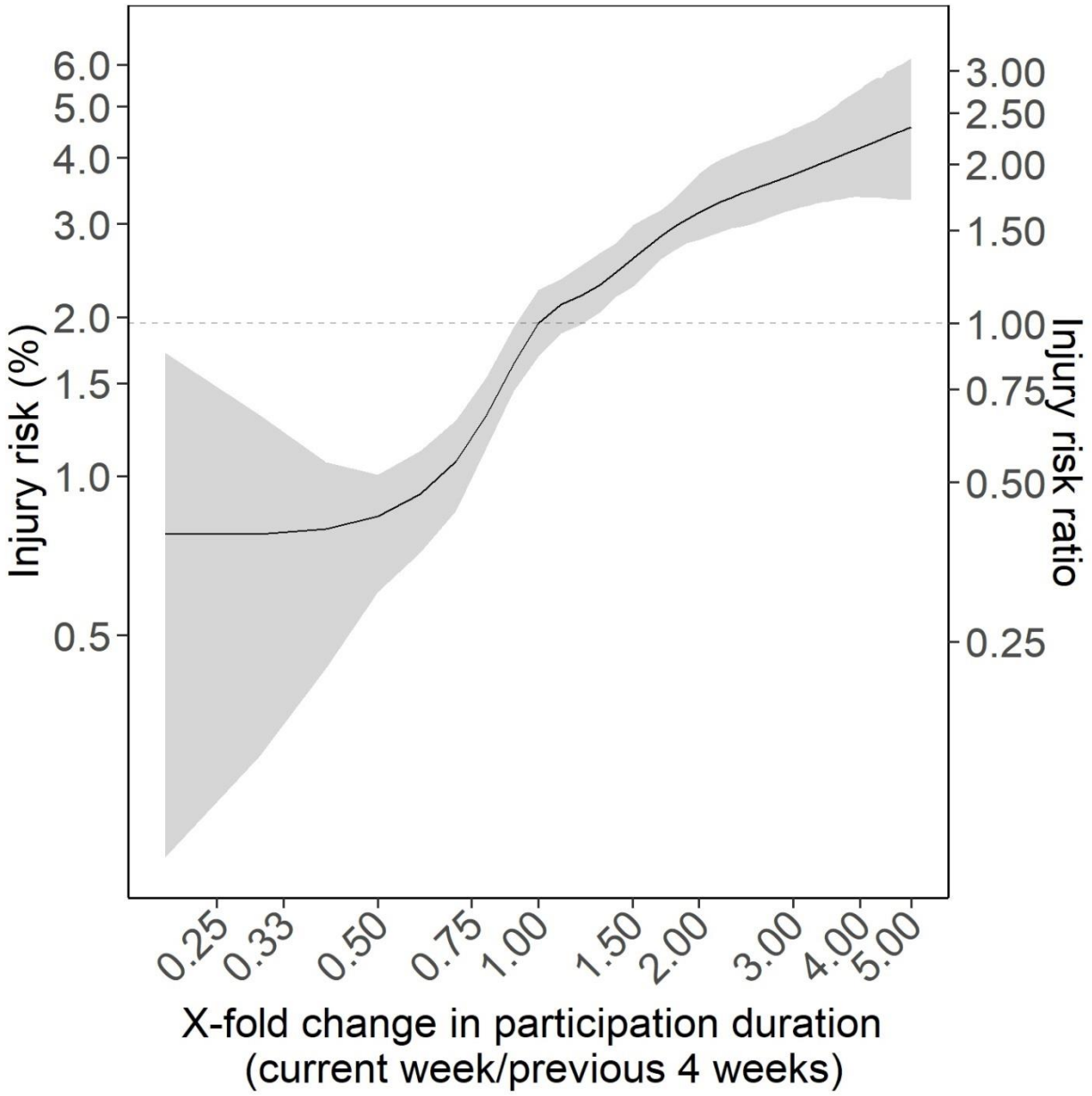

Figure 2. Intention-to-treat effect of changing participation duration on injury risk among adolescent ice hockey players without recent injuries. Participation duration was measured as minutes of hockey practices and games. X-fold changes were measured as the ratio of the planned average daily participation duration in the current week to the average daily participation duration over the previous 4 weeks (uncoupled ACWR). Risk ratios were calculated relative to no change in participation duration (1.0-fold). The line represents estimated effects for the study population; the shaded area represents 95% confidence intervals for injury risk. All axes are on the log-scale.

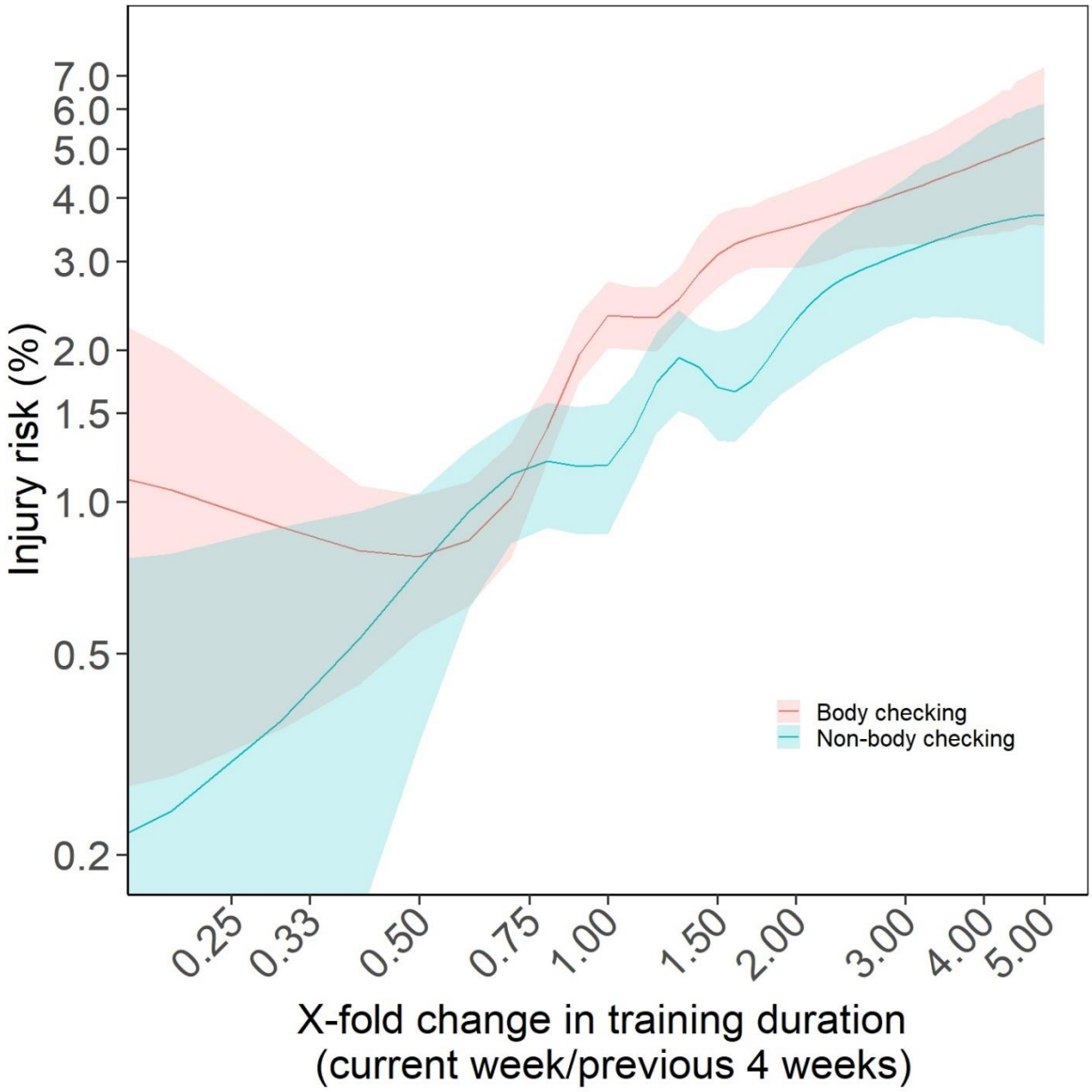

Figure 3. Intention-to-treat effect of changing participation duration on injury risk among adolescent ice hockey players without recent injuries, by league bodychecking status. Participation duration was measured as minutes of hockey practices and games. X-fold changes were measured as the ratio of the planned average daily participation duration in the current week to the average daily participation duration over the previous 4 weeks. Risk ratios were calculated relative to no change in participation duration (1.0-fold). The lines represent estimated effects for the study population stratified by league bodychecking status; the shaded areas represent 95% confidence intervals for injury risk. All axes are on the log-scale.

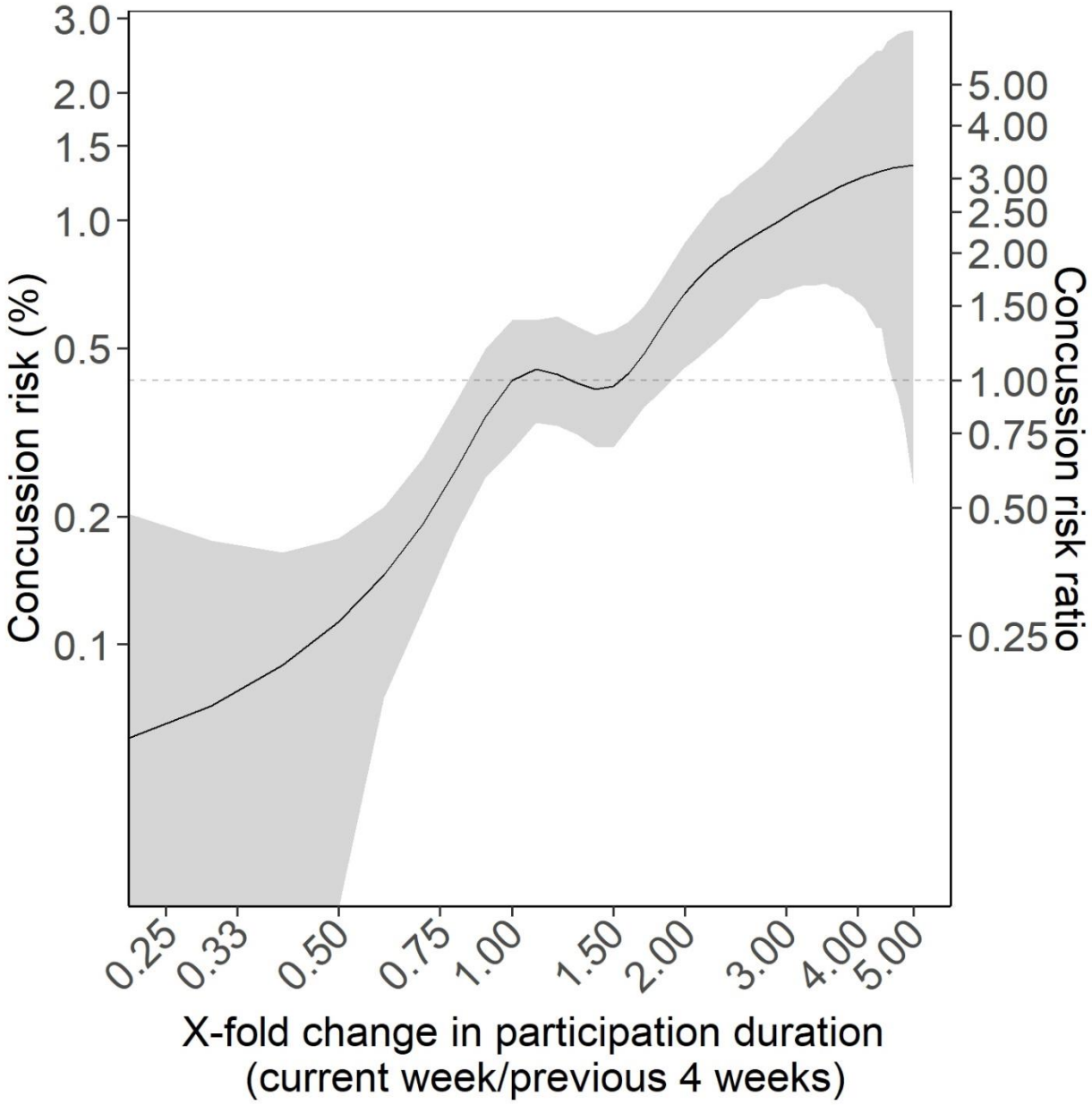

Figure 4. Intention-to-treat effect of changing participation duration on concussion risk among adolescent ice hockey players without recent injuries. Participation duration was measured as minutes of hockey practices and games. X-fold changes were measured as the ratio of the planned average daily participation duration in the current week to the average daily participation duration over the previous 4 weeks (uncoupled ACWR). Risk ratios were calculated relative to no change in participation duration (1.0-fold). The line represents estimated effects for the study population; the shaded area represents 95% confidence intervals for injury risk. All axes are on the log-scale.

Supplementary Material

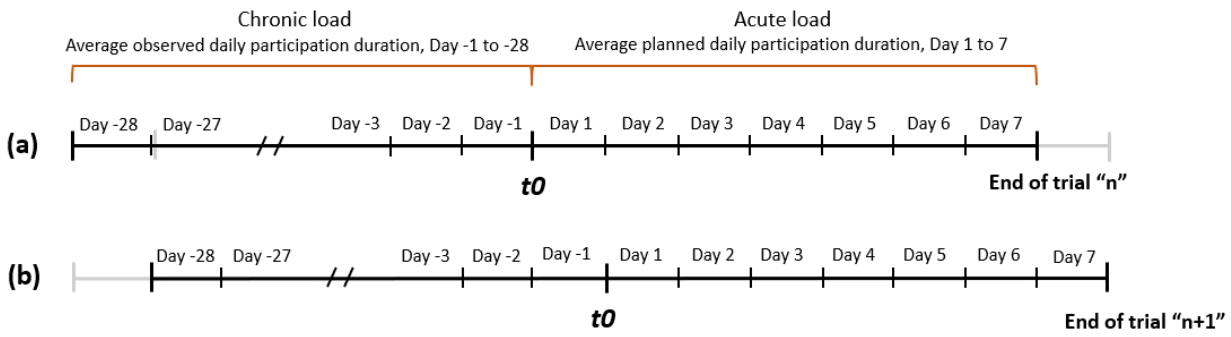

Figure S1. Schematic displaying the specification of the intervention in a target trial estimating the intention-to-treat effect of changing participation duration on injury risk. (a) The intervention is a change in participation duration defined by the uncoupled acute:chronic workload ratio (ACWR). The uncoupled ACWR is calculated as the acute load divided by the chronic load. (b) Participants can contribute multiple overlapping player-trials (trials "n" and "n+1") as long as they meet eligibility criteria at time zero (*t0*).

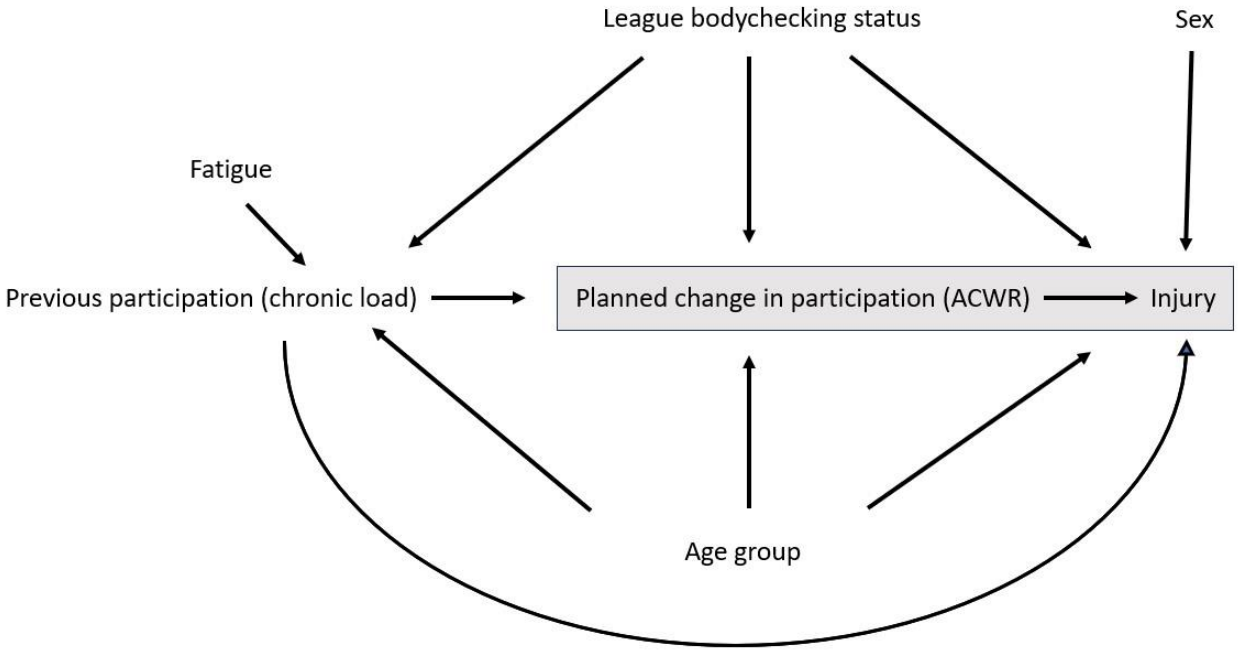

Figure S2. Directed acyclic graph for the relationship between planned changes in participation and injury among adolescent ice hockey players. Previous participation, age group, and league bodychecking status are identified as baseline confounders because they are upstream of both the exposure and outcome. Sex is not a baseline confounder because it is only upstream of the outcome.

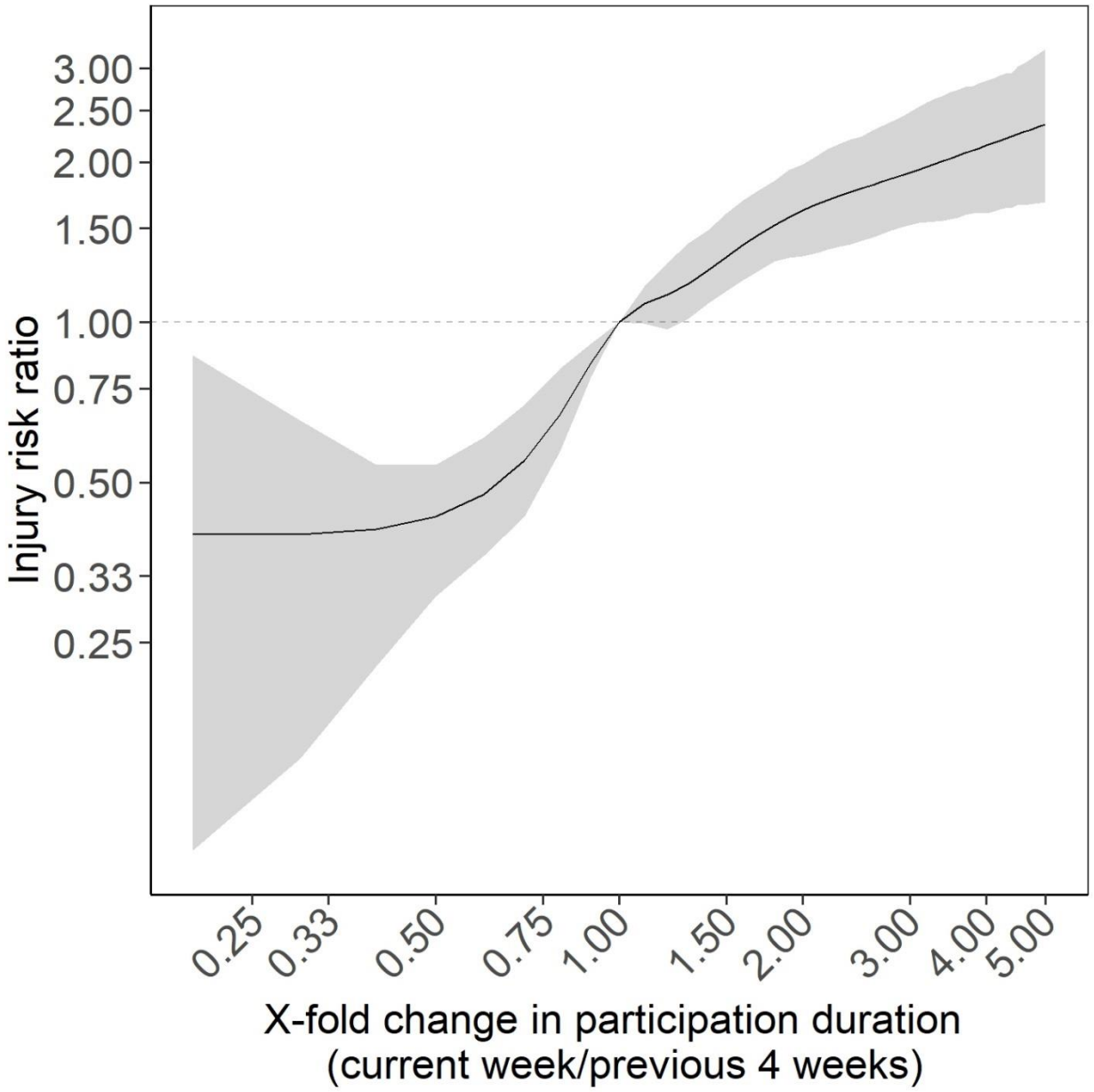

Figure S3. Risk ratios for the intention-to-treat effect of changing participation duration on injury risk among adolescent ice hockey players without recent injuries. Participation duration was measured as minutes of hockey practices and games. X-fold changes were measured as the ratio of the planned average daily participation duration in the current week to the average daily participation duration over the previous 4 weeks. Risk ratios were calculated relative to no change in participation duration (1.0-fold). The line represents estimated effects for the study population; the shaded area represents 95% confidence intervals for injury risk ratios. All axes are on the log-scale.

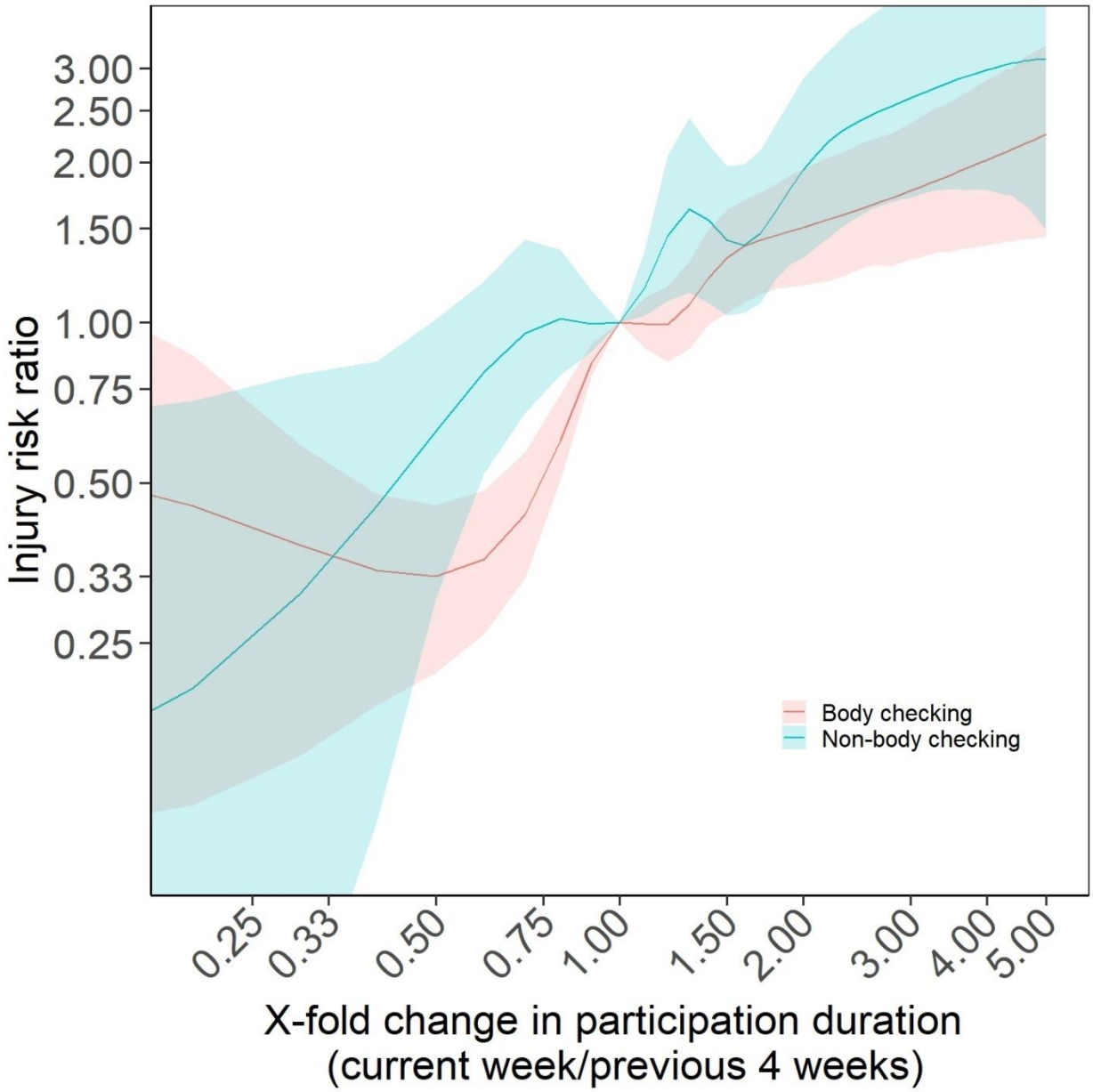

Figure S4. Risk ratios for the intention-to-treat effect of changing participation duration on injury risk among adolescent ice hockey players without recent injuries, by league bodychecking status. Participation duration was measured as minutes of hockey practices and games. X-fold changes were measured as the ratio of the planned average daily participation duration in the current week to the average daily participation duration over the previous 4 weeks. Risk ratios were calculated relative to no change in participation duration (1.0-fold) by league bodychecking status. The lines represent estimated effects for the study population stratified by league bodychecking status; the shaded areas represent 95% confidence intervals for injury risk ratios. All axes are on the log-scale.

Chapter 9: Discussion

Preface

In this chapter, I provide a summary of the findings in this thesis and their significance, discuss the limitations of the included manuscripts, and discuss future directions regarding research on the relationship between changes in physical activity and injury.

Summary of Findings

Although physical activity plays a crucial role in the healthy development and socialization of children and adolescents,[2] participation in physical activity and sport has an inherent risk of injury.[4] Maximizing the benefits of physical activity while minimizing injury risk is an important goal for athletes, parents, coaches, and clinicians. The objectives of this thesis were to assess the relationship between changes in physical activity levels and injury risk among children and adolescents, and to inform the methodology for future research in this area.

In Chapter 4 (Manuscript 1), I provided an overview of musculoskeletal sport injuries targeted towards epidemiologists who might not have substantive or clinical expertise in this area. I reviewed the definition of a sport injury from both biological and epidemiological aspects, and explained how these relate to common categorizations of sport injuries in epidemiologic research. I summarized the tissues and organs of the musculoskeletal system and common injuries that occur to them, and covered the principles of healing and rehabilitation of sport injuries.

In Chapter 5 (Manuscript 2), I employed flexible weighted cumulative exposure methods to assess the relative importance of activity done in past weeks on current injury risk in a cohort of Danish schoolchildren. I showed that high levels of activity done in the recent past (2 to 9 weeks ago) were associated with increased injury risk, conditional on the activity level in the current week, whereas activity done further in the past (11 to 20 weeks ago) were associated with decreased injury risk. For instance, being minimally active 11 to 20 weeks ago but highly active 1 to 10 weeks ago was associated with a 40% greater hazard of first injury than being minimally active for the previous 20 weeks (HR = 1.63, 95% CI: 1.18-2.23), whereas being highly active 11

to 20 weeks ago but minimally active 1 to 10 weeks ago was associated with a 20% lower hazard of first injury than being minimally active for the previous 20 weeks (HR = 0.81, 95% CI: 0.62-1.00). Although patterns were similar between girls and boys, the association between activity and injury appeared to be stronger among girls.

In Chapter 6 (Manuscript 3), I explored the problem of immortal time bias in observational studies assessing the relationship between activity and injury risk. I illustrated how immortal time bias may occur when the assessment of activity is not aligned with the start of follow-up for injury. I provide several options to mitigate this bias, including assessing injury risk subsequent to the time window over which activity is assessed, using planned activity rather than observed activity as the exposure of interest, or through cloning and censoring when activity is defined as a categorical exposure.

In Chapter 7 (Manuscript 4), I illustrated how the target trial framework might be applied to studies of activity and injury. I discussed the major components of a target trial protocol and specific considerations for designing a protocol to assess the relationship between changes in activity and injury risk.

In Chapter 8 (Manuscript 5), I applied the target trial framework to estimate the intention-to-treat effect of changes in activity on injury risk among adolescent ice hockey players. I found that while injury risk increased consistently with planned increases in hockey participation duration, increases in risk were less than would be expected for the increase in exposure time at risk. For instance, a 2-fold increase in participation resulted in a 1.6-fold increase in risk (RR = 1.62, 95% CI: 1.33-1.98), whereas a 5-fold increase in participation resulted in a 2.4-fold increase in risk (RR = 2.35, 95% CI: 1.68-3.26). I found that decreases in participation resulted in decreases in injury risk, with a 0.4-fold injury risk for a 0.5-fold decrease in activity (RR = 0.43, 95% CI: 0.31-0.54)

Significance of Findings

This thesis contributes to the literature by providing insights into the relationship between changes in physical activity and injury risk in children and adolescents, and informing how these relationships might be analyzed in future studies to estimate causal effects.

Although there is a breadth of information available on the biological and clinical aspects of sport injuries, few texts link these aspects to the design of epidemiologic research in a concise and accessible manner. Manuscript 1 may act as an important resource for epidemiologists without substantive background in anatomy, injury definitions, mechanisms, and clinical care who are interested in conducting research relating to sport injuries.

Manuscript 2 is the first study to our knowledge that applied flexible WCE methods to sport injury epidemiology. The vast majority of studies in this area have summarized past activity patterns using unweighted or exponentially weighted moving averages.[63,64] Further, the majority of studies have arbitrarily assumed that any activity done in the previous 3 to 4 weeks is protectively associated with injury.[63,64] We are not aware of any other studies that have applied a data-driven approach to identify the relevant time window over which previous activity might influence injury risk. Flexible WCE methods are a promising approach to assign weights to previous activity using a data-driven method, and to identify etiologically relevant time windows for specific sporting contexts in future studies.

Manuscript 3 describes the bias resulting from measuring injury incidence during the same time window as exposure assessment. Although other authors have noted issues with temporality and the potential for artificially low loads for athletes injured early in the week,[52,81] Manuscript 3 is the first to explicitly describe this issue as a form of immortal time bias. Immortal time bias is a commonly acknowledged problem in other areas of epidemiology,[149] and several design and analytic solutions have been outlined to avoid this bias.[149,150] By identifying the source of immortal time bias in studies of activity and injury and outlining how it can be avoided in future studies, we hope to strengthen the methodology of future research in this area.

Manuscript 4 is the first commentary to our knowledge that describes how the target trial framework can be applied to observational studies of activity and injury. Despite being used to generate training recommendations, many existing studies are of a descriptive or predictive nature and suffer from methodological flaws that impact the validity of these recommendations.[12,95] To provide valid recommendations, researchers should aim for causal inferences.[95,151] As a conceptual framework for conducting causal inference using observational data,[152] the target trial framework has potential to be a valuable tool for researchers aiming to

estimate the causal effect of changing physical activity levels on injury risk. Our hope is that this manuscript can provide researchers in sport injury epidemiology the necessary background and guidance to employ target trial emulation, thereby strengthening the methodology of future research which may be used to generate valid training recommendations.

Manuscript 5 applies the target trial framework to a study of adolescent ice hockey players to determine the relationship between changes in duration of hockey participation and injury risk. It is the first study to our knowledge in the sport injury field to explicitly utilize the target trial framework. It is also one of few studies to employ flexible non-linear methods to model the relationship between activity and injury.[79] Our findings provide insight into the relationship between activity and injury in this study population.

Limitations

The studies included in this thesis (Manuscripts 2 and 5) have several limitations that require caution before concluding causal effects and generating training recommendations from our findings.

Measurement of physical activity

Based on the data available, we assessed physical activity as the number of recreational activity sessions per week in Manuscript 2, and the total duration of participation in ice hockey games and practices in Manuscript 5. As we did not assess any measures of intensity, nor did we assess duration of activity in Manuscript 2, there is likely to be heterogeneity in the actual loads experienced by participants. This heterogeneity may have decreased the precision of effect estimates. Further, the study population in Manuscript 2 engaged in a variety of different sports (e.g. soccer, handball, gymnastics). Our results represent an average across different sports, and results may not be generalizable to specific sports or to children outside Denmark who may participate in other types of sports. Finally, because our exposures are not precisely defined (i.e. may vary in activity frequency, duration, intensity, and/or type) and may result in different potential outcomes in the same person, we are likely to violate the consistency assumption of causal inference.[153,154]

There is the possibility of measurement error in the assessment of physical activity. We made several assumptions regarding physical activity levels. In Manuscript 2, the number of physical activity sessions per week was the sum of physical education classes and parent-reported extracurricular activities. As we did not have data on school attendance, we assumed that participants always attended physical education classes. As such, physical activity may be overestimated in those who were absent from school. If reasons for absences were related to injury risk (e.g. individuals with an injury history did not participate), this could have biased estimates. However, we only assessed the time to first injury in a school year, so it is unlikely that previous injuries would have affected absences. Further, a sensitivity analysis where we included recent musculoskeletal pain as a covariate (accounting for the fact that individuals with pain may have decreased participation in physical education classes) did not affect findings. As such, any measurement error is likely to be non-differential and have resulted in attenuation of effect estimates.[155]

In Manuscript 5, individuals who were reported as having partially participated in a game or practice were assigned a participation duration of 50% the session duration. This may have created error in the measurement of previous activity (current activity was based on planned participation). As we restricted eligibility to individuals who were uninjured in the previous 4 weeks, this error is unlikely to be differential by injured status. However, it may have caused non-differential measurement error and resulted in attenuation of effect estimates.[155]

Selection bias

Selection affecting internal validity

There are multiple sources of potential selection bias in Manuscript 2. Firstly, we identified a protective association between activity done 11 to 20 weeks ago and injury risk. This association may be partially attributed to survivor bias,[156] where only those who were uninjured for a 20-week interval were observed for the entire 20-week time window. Participants who became injured before the 11- to 20-week interval would not have contributed to the association that was observed in this window. This is a known limitation of survival analyses, and could be mitigated with inverse probability of censoring weighting.[157,158]

There is also the possibility of selection bias through loss-to-follow up. Participants were able to enter and leave the study at any point. It may be that individuals who experienced symptoms of injury (e.g. pain) were less likely to remain in the study, and were thus censored prior to recording a clinician-diagnosed injury. This could similarly be mitigated with IPCW.

Selection bias is less likely to affect findings from Manuscript 5, as participants were followed throughout the season. Reasons for non-participation were primarily due to the inability to identify a team designate to record participation and injuries,[159] rather than factors related to participation and injury risk.

Selection affecting generalizability

Selection of study participants might also affect generalizability of results. In Manuscript 2, participants were able to enter and leave the study at any point. Parents of children who were heavily involved in extracurricular physical activity may have been enthusiastic about study participation and more likely to be retained in the study, whereas parents of children who did minimal amounts of activity may have been less inclined to participate.

In Manuscript 5, we excluded individuals who were playing in Under-13 leagues because bodychecking is banned in these leagues. As such, our results are not generalizable to younger hockey participants.

Grouping acute and overuse injuries

We combined acute and overuse injuries as the outcome of interest in Manuscripts 2 and 5, although we performed a separate analysis restricted to concussions in Manuscript 5. We made this decision because stakeholders (e.g. athletes, parents, coaches) are concerned about injuries of all types, rather than preventing a certain type of injury. For instance, it would be ill-advised to provide recommendations for decreasing risk of overuse injuries (e.g. stress fractures) if the same recommendations would increase risk of acute injuries (e.g. concussions). Further, the mechanisms behind which unaccustomed activity causes acute and overuse injuries are likely to differ.[94] Whereas overuse injuries result from tissue fatigue causing decreased load capacity, acute injuries can occur at normal load capacities (although tissue and mental fatigue may play a

role).[14,15,23,94] To advance our understanding of the causal mechanisms between changes in activity and injury, acute and overuse injuries should be studied separately.

Initial versus subsequent injuries

In Manuscript 2, we only included the first injury occurring for an individual within a given school year in analyses (individuals were censored after the first injury). We did not study subsequent injuries because subsequent injury risk is thought to be influenced by initial injuries,[19,20] and activity patterns are likely to change after an initial injury (e.g. to give time for recovery). As such, the relationship between cumulative activity and injury risk is likely to differ between initial and subsequent injuries, and our results are not generalizable to subsequent injuries.

In Manuscript 5, we imposed eligibility criteria which required that individuals were uninjured and not recovering from injury in the previous 4 weeks. This was done to restrict analyses to initial injuries. This is similar to imposing a "washout" period to ensure that analyses are not confounded by previous exposures or outcomes.[160] We assumed that any influence of a previous injury on current injury risk would be minimal after having been uninjured (defined as being medically cleared to return to full participation and/or having returned to full participation) for 4 weeks. If this assumption is not valid, our results may be confounded by injury history.

Unmeasured confounding and exchangeability assumption

We did not have data on important indications for changes in activity patterns, including tiredness and soreness,[23,94] in Manuscripts 2 and 5. These factors may also affect risk of injury, and are sources of unmeasured confounding. Individuals who performed different patterns of activity may not be considered exchangeable (i.e. have the same distribution of injury risk factors) even conditional on measured covariates, and as such we may violate the exchangeability condition of causal inference.[154]

Positivity assumption

Under the positivity condition of causal inference, each participant should have a theoretically positive probability of receiving each level of treatment.[154,161] In the context of Manuscript 5, this

means that each participant should theoretically be able to increase their physical activity across the range of ACWR values. We only assessed injury risk for ACWRs up to 5, based on the distribution of calculated ACWRs in the observed data. However, individuals who already have high amounts of hockey participation may not be able to increase their participation by up to 5-fold. For instance, a team with an average past participation duration of 1.5 hours per day (the highest value observed in the dataset) would have to be able to increase their participation up to 7.5 hours per day, which while theoretically possible, may be implausible given other demands during the hockey season (e.g. school).

Accounting for repeated measures

In Manuscripts 2 and 5, we accounted for repeated measures solely using cluster bootstrapping.[137] This is a computationally inefficient method, but was necessary to derive risk ratios from logistic regression in Manuscript 5.[137]

Although we explored using a random intercept applying GAMMs in the analyses for Manuscript 5 of this thesis, the predicted injury risks were extremely low and implausible. This may have occurred because the random effects could not be well estimated due to the flexibility of the non-parametric fixed effect for activity. Random effect estimation was likely affected by an imbalance of the number of observations per individual and/or the large number of individuals with no injuries. Further, we were unable to use GEE to account for repeated measures in GAMs because the structure of the GAMs did not allow a straightforward computation of robust standard errors using standard statistical packages. Applying mixed effect models and GEE in our analyses could have provided more robust estimates, and provided further insight into the relationship between changes in physical activity and injury risk.

Future Directions

Currently, there is a lack of evidence regarding the causal relationship between changes in activity and injury. Current training recommendations are based largely on statistical associations that are likely to be biased for causal effects, and are unlikely to be generalizable to all sporting contexts. Future research in this area should expand on the work presented in this thesis and employ methods that can be used to estimate causal effects.

In Manuscript 2, we demonstrated that previous physical activity patterns can be represented using flexible WCE methods within a Cox PH model. An extension would be to incorporate flexible WCE methods within generalized linear models (e.g. logistic models) to make inferences about injury risks. For instance, rather than arbitrarily defining change in activity as the ratio of current activity to the unweighted average activity over the previous 4 weeks, change in activity could be represented as the ratio of current activity to a WCE-determined weighted average of previous activity. Flexible WCE methods have been extended to allow the use of weight functions within linear mixed effect models.[162]

In Manuscript 5, we estimated the intention-to-treat effects of relative changes in activity at single timepoints on injury risk. As such, we were not worried about time-varying confounding by previous activity or injury, and avoided introducing immortal time bias as outlined in Manuscript 3. Future research might investigate the per-protocol causal effect of cumulative physical activity as a time-varying treatment on injury risk (e.g. determining the injury risks associated with different week-to-week patterns of activity). This would require adjusting for time-varying confounding by activity and injury history, as well as other important confounders such as fatigue, soreness, or tiredness. This could be done using g-methods,[154,163] keeping in mind that extensions may be needed to accommodate continuous exposures such as physical activity.[164] Proper estimation of per-protocol effects also requires obtaining an unbiased measure of an individual's observed activity, as touched on in Manuscripts 3 and 4. This can be done for categorical exposures (e.g. increase in activity by more than 1.5-fold vs. less than 1.5-fold) through cloning and censoring, as discussed in Manuscript 3. However, the only solution we have up to this point for estimating per-protocol effects of continuous exposures of changes in activity is to impose an injury lag period. This obscures variations in activity leading directly up to an injury that are likely to affect injury risk. Finer data on the timing of injury (e.g. the exact minute within a practice session that an injury occurred) is needed to reduce bias in the measurement of exposure. Estimating per-protocol effects in this context remains a future challenge.

We only examined initial injuries in our analyses. However, subsequent injuries account for a considerable proportion of all injuries (10-25% of injuries are subsequent injuries to the same body location).[165] Risk factors for a subsequent injury are likely to differ from that of the initial

injury,[166] and it may be inappropriate to analyze initial and subsequent injuries together as a single outcome. Future research might employ recurrent event methods.[167,168]

We note that in order to elucidate causal relationships, we must appropriately control for confounders between changes in physical activity and injury risk. This requires data on important confounders (e.g. soreness, tiredness, fatigue). Methods that control for unmeasured confounding such as instrumental variable approaches could also be explored.[169,170] We previously suggested that an athlete's proposed training schedule might be a valid instrument for their actual activity performed.[12] However, there may be confounders that affect one's proposed training schedule as well as injury risk, such as fatigue. Proposed training schedule is only a valid instrumental variable if these factors are controlled for in analyses.[12]

Conclusion

Assessing the relationship between changes in physical activity and injury among children and adolescents is an important step in developing valid recommendations for injury prevention. In this thesis, I demonstrated how approaches employed in other substantive areas of epidemiology can be used in sport injury epidemiology, including using flexible weighted cumulative exposure methods to represent cumulative physical activity, and employing the target trial framework to minimize biases in observational analyses for causal effects. Although limitations in our data sources and analyses precluded us from definitively concluding causal effects, this thesis is a valuable resource for informing future research in this field.

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