Practice of Epidemiology

Past Injury as a Risk Factor: An Illustrative Example Where Appearances Are Deceiving

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Initially submitted June 19, 2010; accepted for publication November 30, 2010.

Previous injury is believed to be a causal risk factor for subsequent injury. Using empirical data on circus artists (n = 1,281 artists) between 2004 and 2008 in Montreal, Canada, as a motivating example, the authors use patient vector plots to demonstrate that a bias away from the null must always occur in the typical analyses cited as evidence (i.e., survival analysis, Poisson regression), except in the improbable context where all subjects have the same inherent risk independent of previous injury. In addition, using simulated data, the authors demonstrate that a simple method that conditions on the individual will approximate conclusions from more complex analytical methods. By using the typical analysis of the authors’ empirical data, Kaplan-Meier curves and Cox regression suggested increasing injury rates for both the second and third injuries compared with the first injury. However, conditional analyses using a matched population (i.e., time to first, second, and third injuries among artists with 3 or more injuries) showed that injury rates were unchanged for both the second and third injuries compared with the first injury. These results suggest that previous injury should not be evaluated as a causal risk factor unless one conditions on the individual in some way.

bias (epidemiology); causality; survival analysis; wounds and injuries

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

Authors of systematic reviews have suggested that a previous injury increases the risk of future injuries (1–3). Most of the original research cited was conducted in prospective cohort studies and compared the injury rate ratios among those with and without a previous injury, as defined by self-report at baseline. Five specific studies were found that followed subjects after an initial index injury and prospectively calculated subsequent injury rates (4–8). Highlighting the 3 most recent studies, in 2001, Orchard (6) reported that previous injuries (either within an 8-week time interval or not) increased the risk of sustaining a muscle strain to the same location for the hamstrings, quadriceps, and calf muscles. In 2006, Hagglund et al. (7) studied 12 Swedish male football teams over 2 seasons and found that players who were injured in the first study year were at greater risk of any injury (i.e., their subsequent injury) in the following season compared with noninjured players (hazard ratio (HR) = 2.7, 95% confidence interval (CI): 1.7, 4.3). In addition, the injury risk increased with the number of injuries that occurred in the previous season. In 2007 in an observational cohort study including 5 female high school sports over 3 years, Rauh et al. (8) found that the risk of a second injury to the same location (subsequent injury) was greater than the risk of the index injury (risk ratio (RR) = 2.8, 95% CI: 2.6, 2.9). Similarly, the injury risk to a different body part was also increased (RR = 1.7, 95% CI: 1.6, 1.8).

There are 2 plausible theories to explain the relation between previous injury and subsequent injury risk: 1) a causality theory (1, 7, 9–11) and 2) a “noncausal marker” theory (7, 12). In the causality theory, inadequate rehabilitation leads to increased risk of the previously injured tissue due to incomplete healing and weakness, and to increased risk of injury to the surrounding and anatomically unrelated areas due to altered movement patterns, loss of balance, or
other functional/psychological impairments. If true, injury risk would return to normal after adequate rehabilitation. In the “noncausal marker” theory, the previous injury is simply a marker for other traits that would cause an individual to be at a higher risk of injury. Certain individuals might be at higher risk of injury due to genetic factors, risk-taking behavior, or other nongenetic injury-prone characteristics (e.g., training, playing position, psychological). If true, the previous injury does not causally increase the risk of a subsequent or new injury but rather is simply a marker for a common cause of both previous injury and subsequent/new injury; that is, confounding bias is present for the parameter of an increased injury risk as defined by the structural approach to bias (13, 14).

Although complex statistical techniques exist to analyze data that include repeated events such as injury (15–19), the underlying assumptions are complex (20), it can be difficult to estimate marginal distributions of event times (17), and one cannot easily assess when important model assumptions are violated. The purpose of this study is to 1) illustrate that bias must occur in analyses commonly cited in the literature (typical analyses) to infer that previous injury increases the risk of subsequent injury and 2) demonstrate a simple and transparent method of analysis that allows those without specific expertise in advanced analysis of repeated events to approximate the causal effect of previous injury on the risk of subsequent injury (i.e., to minimize bias). We use data from a population of individuals with multiple injuries (a prospective cohort study on circus artists (21)) and compare typical analyses examining subsequent injury risk with analyses where one condition on the individual. Although a formal statistical proof of the method is beyond the scope of this paper, we have included some simulations in a Web Appendix, which is posted on the Journal’s Web site (http://aje.oxfordjournals.org/), that compare our method with one of the more complex methods that have been proposed to address this issue (17, 19).

MATERIALS AND METHODS

This paper describes analyses to determine if previous injury increases the risk of subsequent injury. We first describe the data set we used and then describe the different types of analyses.

The motivating example represents a secondary analysis of data collected to report on injury patterns and injury rates of circus performers, and the details of the cohort study are presented elsewhere (21). One author’s institution stated that formal ethics approval was not required, because historical data were gathered as part of routine business practice and therefore fell under a category of quality assurance. For the other institution, the Office of Medical Bioethics provided approval. Subjects were included if they were 1) a circus artist between August 2004 and March 2008 and 2) had at least 3 performances of exposure data recorded. The circus company performs shows with artistic and gymnastic elements that are considered highly athletic in nature. Exposure data were recorded electronically for each performance, and all therapists used an electronic database as their sole charting procedure for injuries and associated treatments. Duplicate injuries were removed, exacerbations were considered as part of the original injury, and an injury was considered healed if the artist did not have a treatment for 3 months. If an event resulted in multiple injuries (i.e., multiple locations or multiple injury types), each injury was recorded separately. An injury was included in the current analysis if it 1) occurred during a performance within the study period, 2) was reported to a therapist, and 3) resulted in a completely missed subsequent performance (time loss injury). We restricted ourselves to time loss injuries because these are considered more likely to be causal factors for subsequent injury. Finally, an injury was defined as fully healed on the date the artist returned to full participation (22, 23).

Concerning analyses, we first used survival analysis on the empirical data to obtain the (biased) estimate that has been reported more typically in injury epidemiology studies (7). In brief, we considered the artist to have no previous injuries when he/she entered the cohort and compared the Kaplan-Meier curves and hazards using Cox regression if the proportional hazards assumption was considered reasonable (R package, “survival version 2.35-7†”). The time to first injury among all artists (those with no injuries were censored at end of follow-up) was compared with the time to second injury among all artists with 1 injury, time to third injury among all artists with 2 injuries, and so on.

Next, we used a simple patient vector plot (24) to illustrate why these types of analyses (survival analysis or rate ratios) introduce a large bias when estimating the causal effect of previous injury on the risk of subsequent injury. In brief, these typical analyses compare the injury risk of an entire group with the injury risk after removing individuals with a particular predisposition toward injury (e.g., excluding subjects with a very low risk of injury). To remove this bias, one can simply compare injury risk within the individual (subset analysis). Simply put, one conducts survival analyses but restricts the population to those individuals with a specified number of injuries (e.g., 3 or more, 5 or more, and so on). In this subset approach analysis, the subsample of subjects is the same for time to first, second, and third injuries. Essentially, this matched analysis conditions on the individual, and therefore noninjury individual predisposition to risk is controlled for (assuming it is constant over time). The Web Appendix shows the comparison of our results with one of the more complex methods proposed in the literature (17, 19). Although both the subset approach and the more complex method can be used to estimate time to injury, it is not appropriate to directly compare the numerical results as they are not using the same data nor comparing the same distributions.

Finally, we illustrate the effect of our subset approach using the empirical injury data from circus artists. We conducted the subset approach restricted to individuals with 3 or more injuries. We also conducted the subset approach on subjects with 5 or more injuries (time to first, second, third, fourth, and fifth injuries) and 2 or more injuries to explore for potential biases due to conditioning on individuals with only a specific number of injuries.

All statistical analyses were conducted by using R Foundation for Statistical Computing, version 2.7.1 (25).
Results

Of the 1,281 artists that met our inclusion criteria, 180 artists (14.1%) incurred 3 or more time-loss injuries, and 65 artists (5.1%) incurred 5 or more time-loss injuries. In total, there were 1,230 time-loss injuries that resulted in 1 completely missed performance.

Figure 1 shows the comparison of time to injury according to typical analyses to determine if a previous injury increases the risk of subsequent injury. As previous authors have shown, the time to injury is decreased (risk was increased) among those with a previous injury compared with those without a previous injury, and the time to injury decreases further (the Kaplan-Meier curves are steeper) as the number of previous injuries increases. Using time to first injury as a reference, we found increased risk comparing the time to first injury with the time to second injury (HR = 1.99, 95% CI: 1.72, 2.30), as well as time to third injury (HR = 2.41, 95% CI: 2.03, 2.87).

Causal inferences on this analysis are problematic because each line represents different groups of subjects, and therefore the different risk profiles may occur simply because previous injury is a marker for some other common cause of both previous injury and subsequent injury. Figure 2 uses a patient vector plot (24) to schematically illustrate that typical analyses for estimating risk with repeated events data (both in survival analysis and Poisson regression) are always biased away from the null. We have created a patient vector plot assuming that each subject has never been previously injured and has a constant injury rate that would be unaffected by previous injury; that is, the time to injury is identical for the first and all subsequent injuries. The parameter of interest is injury risk, and an unbiased estimate would show that injury risk does not increase with previous injury. In the typical analysis illustrated in Figure 1, the time to injury for those with no previous injury is simply an average of the time to injury across all individuals (Figure 2A). However, the time to third injury requires that 2 previous injuries have occurred, which means that subjects 1 and 2 are excluded from this analysis because they have 0 and 1 injury, respectively (Figure 2B). Therefore, the average of the time to injury for subjects 3–6 must be shorter than for subjects 1–6, because the individuals that have been eliminated are those with the longest time to injury. The same principle is applied for the analysis on time to fifth injury, and one now averages only subjects 5 and 6 (Figure 2C).
Using Poisson regression does not avoid the bias, because one is still comparing individuals with an inherently higher injury risk with individuals with an inherently lower injury risk; there is no comparison of change in risk within an individual following an injury.

Figure 3 shows the comparisons in our empirical data when we directly measure the time between each injury (i.e., our parameter of interest) for those individuals with 3 or more injuries (Figure 3A) and 5 or more injuries (Figure 3B). Unlike Figure 1, the lines that denote the time to injury are now practically superimposed for both Figure 3A and Figure 3B. For artists with 3 or more injuries, the hazard ratios were 1.08 (95% CI: 0.88, 1.33) for time to second injury and 1.08 (95% CI: 0.88, 1.32) for time to third injury (using time to first injury as reference). The hazard ratio for artists with 5 or more injuries (Figure 3B) could not be calculated as the curves crossed at several points and the proportional hazards assumption was violated. As a sensitivity analysis, we also ran the analysis for artists with 2 or more injuries and obtained the same result (data not shown). Therefore, one must see an overall reduced time to injury even though previous injury does not actually increase the risk of subsequent injury. The same principle applies for the time to fifth injury (C).
To further illustrate the bias, we plotted the time to first injury stratified by the number of injuries that a subject had (i.e., a different line for subjects with a total of 2 injuries, 3 injuries, and 5 injuries) (Figure 4). Although the results appear similar to those of Figure 1, they illustrate a very different point. First, Figure 1 compares the time to first injury among all subjects, the time to second injury among artists with 1 injury, the time to third injury among artists with 2 injuries, and so on. However, Figure 4 compares time to first injury for each of the groups (artists with 1 injury, artists with 2 injuries, and so on). The time to first injury for subjects with 2 injuries was slightly longer than the time to first injury for subjects with 3 injuries, which was longer than the time to first injury for subjects with 5 injuries. These results suggest that subjects who had incurred a greater number of injuries during the entire study period had a shorter time to their first injury, or increased risk of their index injury. Because a subsequent injury after the index injury cannot possibly cause an increased risk for the index injury, the differences in time to first injury must represent a bias. If previous injury did cause an increase in subsequent injury risk, one would expect to observe shorter times between injuries in the previously injured group, but the time to first injury should have been the same.

**DISCUSSION**

Our results illustrate that typical epidemiologic analyses examining previous injury as a causal risk factor must be biased. Using empirical data, as well as simulated data where time to injury is unaffected by previous injury, we demonstrate how and why this bias occurs and that conditioning on the individual is one simple and transparent method that can minimize the bias.

To date, authors have examined only previous injury as a “risk factor” and have not adequately considered adjusting for the bias created when different individuals have different predispositions toward injury. For example, in 2006, Hagglund et al. (7) published a study of elite football in 12 Swedish male teams over 2 seasons and found that the risk of an injury was higher for individuals with 1–2 injuries in the previous season compared with uninjured players in the previous season (HR = 2.2, 95% CI: 1.4, 3.6). Those
who had 3–4 injuries or ≥5 injuries in the previous season had an even higher risk of injury compared with uninjured players in the previous season (HR = 3.0, 95% CI: 1.8, 5.3 or HR = 5.2, 95% CI: 2.9, 9.0), respectively. Using the same type of analysis for our empirical data on circus artists, we obtained a similar result for time to second injury (HR = 1.99, 95% CI: 1.72, 2.30) and for time to third injury (HR = 2.41, 95% CI: 2.03, 2.87). These results confirm that previous injury is associated with higher injury rates. However, minimizing the bias by restricting the population and conditioning on the individual so that we compare the results of each individual with him or herself, we demonstrated that previous injury is not associated with an increased risk of subsequent injury for an individual in our sample.

Although our patient-vector plot uses a static cohort with no previous injury to demonstrate that bias must occur, the results are generalizable to all situations. In a large dynamic cohort, the specifics are different, but the principles are the same; there are many more individuals, individuals enter and leave the cohort at different times, the duration of each injury may be different, and there may be periods of non-exposure due to illness or other noninjury reasons. However, the typical analyses still eliminate subjects with lower fixed injury rates, resulting in the appearance of increased injury risk with previous injury. We considered the index injury in our cohort to be the first injury that is observed in the data obtained, and that all subjects were considered free of previous injury before then. All adults who participate in sport have likely been injured at least once in their lifetime, so no one is truly “injury free.” To account for previous injury, some authors have restricted (or stratified) analyses to subjects who have had no injury within a certain period of time (e.g., 1 year). This practice just eliminates (or stratifies) those individuals with the highest fixed injury rates; for example, subjects injured every 6 months never enter the study, and the problems we outlined still exist for the remaining subjects (or within the stratified subgroups). There are additional problems related to this type of left-truncating of data (26, 27) and interpretations of hazard ratios in general (28) that are often unrecognized in the injury epidemiologic literature. Although important, these are beyond the scope of this paper and do not affect the general principles.
we have outlined. Finally, in the simulated data shown in the Web Appendix where previous injury was a causal risk factor, the typical analyses would still overestimate the true causal relation because the above biases are external to any method of simulating the data and, therefore, continue to be present.

Although our results strongly suggest that previous injury was not a causal risk factor in our data (i.e., support the “noncausal marker” theory over the causality theory) and that our explanation of the effect using patient vector plots shows that bias must have been present in previous studies and will in fact always be present in the typical analyses, this does not mean that previous injury is never a causal risk factor for subsequent injury. The circus company that provided the data is a unique setting, and the injury rates and types of injuries may not be similar to injuries in other sports. In addition, the artists are closely monitored after an injury occurs, and rehabilitation is strongly encouraged. In considering a dynamic model of etiology in sport injury that defines injury risk as the cyclic nature of changing risk factors (29), our results suggest only that, after an injury, the circus artists studied here appear to return to the baseline risk that they had before their injury. In a different population where appropriate rehabilitation does not occur, results could indeed indicate that previous injury is a causal risk factor. Therefore, we suggest that our method of analysis could be used to determine if adequate rehabilitation has occurred (i.e., a type of quality assurance) within large-scale studies across leagues and sports. In addition, the same method should be encouraged for any study with multiple event outcomes because the same principles apply (e.g., recurrent exacerbations in patients with chronic obstructive pulmonary disease). Finally, our subset approach is helpful when investigators wish to establish a causal relation between previous injury and subsequent injury. In some contexts, authors might be concerned only about whether a previous injury predicts subsequent injury even if it is not causally related. Of course, our theoretical analysis using patient vector plots illustrates that previous injury must predict subsequent injury under realistic assumptions. Therefore, these specific contexts should be limited to a comparison of the magnitude of the prediction under different scenarios.

Limitations

Our analysis is based on the assumption that there are different underlying risks for different individuals or groups of individuals. We believe this to be valid because, in most sports, different positions (e.g., a football lineman vs. a defensive safety) are associated with different injury risks, and different players have different levels of aggressive play. If one were able to precisely control for all of these covariates (which we believe is impossible due to unknown effect modifiers and measurement error), the typical analyses would yield an unbiased result.

The proposed analysis can only be done if one has longitudinal information on each subject, including precise data on all subsequent injuries. Thus, it cannot be used with injury surveillance methods that do not link injuries to specific individuals over time. As such, our theoretical analysis demonstrates that examining the role of previous injury using data that do not link injuries to specific individuals does not provide useful information about previous injury as a causal risk factor because the analysis will always show an increased risk. These analyses should not be included in articles using these types of data. In addition, the analysis cannot include subjects who were censored at the time of the last injury, or a bias will be introduced (17, 30). For example, Figure 3A specifically includes time to third injury only among subjects with 3 injuries. It specifically excludes subjects with 2 injuries who would normally be censored but included in a survival plot for time to third injury.

The purpose of this article was to clearly illustrate the epidemiologic concept underlying the bias with the typical analyses. Although we restricted our population to obtain a “matched-analysis,” we did not actually account for the matching in the statistical model, because we felt it would unnecessarily introduce another level of complexity. This means that our variance calculation (which assumed an unmatched population) would be expected to overestimate the true variance of the matched population, just as using an unpaired t test with matched data would usually (but not always) overestimate the variance. Although variance estimates in our analysis are inaccurate, the hazard ratio point estimates, Kaplan-Meier curves, and the interpretation of the results would not change. Using one of the more complex survival-analysis-for-repeated-events-data approaches such as the one described in the Web Appendix is possible, but these require specialized expertise to verify the underlying assumptions of the model and to include other limitations (15, 16, 20, 28). An alternative variance calculation for our subset approach that might be more accessible is a bootstrap method (31, 32). We believe that the rough approximation obtained using our method is acceptable given that it will be accessible to a much greater number of researchers compared with the more complex methods.

Finally, our analyses were restricted to time-loss injuries for performances in artists with at least 3 exposures and defined an injury to be fully healed when the artist returned to full participation, which may affect the generalizability of the results. In addition, exposure information for performances was the only exposure information recorded. Although the numerical results would be different for other injury definitions (e.g., medical attention injuries) and fully healed injuries, as well as different levels of exposure (performance vs. training), this would not affect the conclusion that the typical analysis is always biased away from the null.

Conclusion

Using both simulated and empirical data, we have demonstrated that the typical analysis examining previous injury as a causal risk factor will always bias the results away from the null unless it were possible to precisely measure and condition on all other injury risk factors in the statistical model. Although previous injury was not a causal risk factor for subsequent injury in our empirical data, it may still be a causal factor in other studies. Researchers who are interested in the causal effects of previous injury need to conduct.
some type of matched analysis in order to obtain approximate estimates of effect.

ACKNOWLEDGMENTS

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This work was supported by the Canadian Academy of Sport and Exercise Medicine. I. S. was supported by the Senior Clinician Scientist Award from the Fonds de la Recherche en Santé du Quebec. C. E. was supported by a Population Health Investigator Award from the Alberta Heritage Foundation for Medical Research, a New Investigator Award from the Canadian Institutes of Health Research, and a Professorship in Pediatric Rehabilitation funded through the Alberta Children’s Hospital Foundation.

I. S. is also the consulting medical director for the circus company, which could be considered to represent an apparent conflict of interest.

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