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Case-crossover studies of occupational trauma: methodological caveats

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Abstract

***Objectives*—The case-crossover study design was developed to examine triggers for the onset of myocardial infarction. This paper seeks to examine selected methodological issues when applying the case-crossover method to the study of traumatic injuries in the work environment.**

***Methods*—Researchers known to be working on occupational case-crossover studies were invited to present at a workshop held at the National Occupational Injury Research Symposium in October 2000. Data from ongoing studies were used to illustrate various methodological issues involved in case-crossover studies of occupational injury.**

***Key findings and issues identified*—To utilize the case-crossover design, investigators must clearly define the time during which a worker is at risk of injury, the period of time during which a particular transient exposure could cause an injury and carefully select control time periods that estimate the expected frequency of exposure. Other issues of concern are changing work tasks over time, correlated exposures over time and information bias.**

***Conclusions and future research needs*—More case-crossover studies of occupational injury are needed to compare results from multiple studies. The validation of the timing of transient exposures relative to injury onset, whether done in a laboratory or field setting, should be conducted. Nested case-crossover designs in other epidemiological studies (case-control or cohort) can examine both transient and fixed risk factors for occupational injury, and should be attempted.**

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The case-crossover methodology is gaining increasing acceptance as a means of investigating the risk associated with transient exposures or triggers for disease. The methodology was developed initially to study transient factors that may trigger a myocardial infarction in someone with underlying atherosclerosis.[1 2] The key question it seeks to answer is what is different about the time period just before an incident occurs compared with other time periods for the same individual when the incident did not occur? It is similar to the case-control study, except individuals act as their own controls.

The case-crossover approach has also been proposed as an ideal way to examine many of the transient risk factors related to injury causation. For example, investigators have used this method to study cell phone use and car crash risk[3] and alcohol use and risk of injury presenting to hospital emergency departments.[4] More recent results of other case-crossover studies have been presented at national meetings.[5–9] Several of these recent studies have proposed using the method to study occupational injuries.[5 6 8 9] However, there are a number of difficult methodological issues to consider when studying the immediate precipitants of injury. For example, the investigator must clearly define the time during which a worker is at risk of injury, and the period of time during which a particular transient exposure could cause an injury. These design features must be clearly defined whether the investigator is planning a cohort, case-control, or a case-crossover study. This paper seeks to examine selected methodological issues when applying the case-crossover method to the study of traumatic injuries in the occupational environment.

Methods

Researchers known to be working on occupational case-crossover studies were invited to present at a workshop held at the National Occupational Injury Research Symposium in October 2000.[10] The workshop sought to examine the issues involved in using case-crossover methods to study injury in the workplace. Data from three ongoing studies were used to illustrate various methodological issues involved in case-crossover studies and each one is described in more detail elsewhere. The first study examined the risk of sharps related injuries to health care workers.[9 10] The second study evaluated transient risk factors for occupational traumatic hand injury in patients presenting to occupational health clinics in New England.[6 11] The last study was a cross sectional study of risk factors for animal related injuries to practicing veterinarians in Minnesota,[5] which included a case-control and case-crossover study nested within it.

The findings from the above studies were used to illustrate some key issues to consider when planning a case-crossover study of occupational injury. The issues include (1) determining the person-time at risk of injury and exposure, (2) defining the transient exposures and the hazard and control periods, (3) considering the correlation of work related exposures over time, (4) controlling for potential confounding by between and within subject

factors, (5) considering how changing tasks in the work environment may influence the study results, and (6) taking into account potential recall bias. Finally, the study of temporal factors in occupational injury using this design[8] and nesting case-crossover studies in other epidemiological designs are discussed.[5] Some suggested areas for future research are noted in the conclusion.

Key findings and issues identified

PERSON-TIME AT RISK OF INJURY AND EXPOSURE

In conducting an empirical study of occupational injury, exposure and injury must be ascertained during person-time at risk of an injury. Whether conducting a cohort, case-control or case-crossover study, only person-time during which an individual is at risk of the outcome ought to be considered. Unlike chronic disease outcomes, which can occur at any time, occupational injuries require special circumstances. Consider a study of rushing as a transient risk factor for sharps related injuries in healthcare workers.[9] Because the worker is only at risk while handling sharps on the job, exposure (rushing or not) while handling sharps when working, is the only person-time that is relevant. For instance, sharps related injuries or episodes of rushing outside of work should be excluded. Whether the subject was rushing during the hazard period (shortly before the injury) also needs to be ascertained. Finally, the expected frequency of rushing while performing medical procedures with a sharp instrument needs to be determined. Rushing while not handling a sharp instrument should not be counted in the study base. The person-time at risk needs to be worked out during the planning phase of a case-crossover study of occupational trauma.

TRIGGERS (EXPOSURES) AND HAZARD PERIOD: DEFINITIONS

Injury is associated with multiple component causes, some of which are present for a relatively long time period, and others occur just before it and are thought to trigger the onset of the injury producing event.[12] A trigger (exposure) may be transient in nature and have a short effect period (such as an object falling near a worker) or can be transient but have longer effects (such as a disturbing telephone conversation that distracts a worker for hours afterwards). The hazard period is the time segment during which the exposure is likely to have its etiological effect on the injury, and must be carefully specified to capture the etiologically relevant exposures. The hazard period can vary depending on the nature and duration of the exposure under study. For example, on the one hand, malfunctioning equipment can influence injury risk during the entire period of the malfunction, lasting several seconds up to several hours. On the other hand, the sedating effects of antihistamines may have their onset of effect after 30–60 minutes of ingestion and can be expected to affect injury risk for several hours. Misspecification of the hazard period is likely to lead to null biased results, for example, antihistamine use in the past month may be less relevant to the risk of injury than its use in the four hours before the injury.

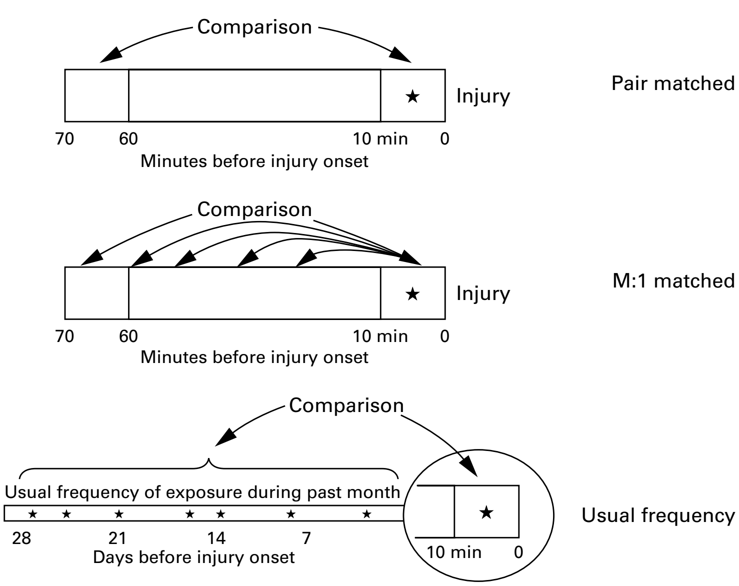

Figure 1 Case-crossover study design (= episode of exposure).*

EXPECTED FREQUENCY OF EXPOSURE AND SELECTION OF CONTROL TIME PERIODS

The extent to which an exposure is "unusual" can be estimated using various control time periods,[13] during which an injury is not reported to have occurred. These time periods may be sampled from other workers, such as in a case-control study, or from the previous exposure experience of the injured worker (case-crossover study). An investigator might choose the average frequency and duration of reported transient exposures in the work-month before the injury. This approach is termed the usual frequency of analysis (UFA). Other control time periods however could also be used, such as an earlier equivalent time period one hour before the injury (pair matched interval approach) (fig 1). The UFA approach is more powerful for finding effects if they exist than is the pair matched interval approach.[13] The UFA is comparable to a retrospective cohort study that is highly stratified (each subject forms his or her own stratum).[14]

CORRELATION OF WORK RELATED EXPOSURES OVER TIME

The correlation of exposures over time is also a concern. For example, in the study of transient risk factors for hand injuries, four of eight factors were correlated over the 90 minute exposure window before the injury (table 1).[11] That is, the median duration of these four exposures, when they did occur, covered almost all of the 90 minute time period before the injury (working overtime, wearing gloves, rushing, and feeling ill). Thus, it was not possible to detect a change in these four exposures between the hazard period 10 minutes before the injury and the 60–70 minute pair matched interval period before the injury. In choosing

*Table 1 Reported duration of exposure in minutes to each transient factor in the month before injury shown as the 25th, 50th, and 75th percentiles in hand injured subjects**

Factor	No exposed†	Exposure duration (min) 25%	Median 50%	75%
Working overtime	160	90	180	390
Wearing gloves	155	60	258	480
Rushing	151	60	120	300
Distracted	118	2	8	20
Unusual task	86	18	60	150
Equipment/materials or performed differently	71	1	5	60
Feeling ill	65	60	240	480
Different work method	64	9	30	120

*Adapted from Sorock *et al.*[11]
†Number of subjects (n=232) reporting any exposure during the past work-month to each of eight transient risk factors. For instance, 118 subjects reported a median of 8 minutes of distraction time, on average, during episodes of distraction in the month before the injury.

control periods, it is imperative that the investigator choose time intervals during which exposure is independent of the hazard and other control periods. Investigators ought to evaluate the average duration of each suspected transient risk factor in a pilot study so the control periods can be chosen judiciously.

CONFOUNDING

Between subjects

One way to control for between subject confounding in a case-control study is to match on factors that are thought to be associated with the injury among the unexposed (for example, age, gender, occupation, and job experience). In a case-crossover study, the self matched design permits control of all measured and unmeasured confounders that are fixed and will not vary within an individual over a short time period. Just as in any epidemiological design, matching does not permit evaluation of the matched variable as a risk factor for the study outcome. However, provided there are enough subjects in each level of a matched factor, one can evaluate how the "matched" factor modifies the risk of injury when exposed or unexposed to the transient risk factor of interest. Thus, by design, the case-crossover study only permits evaluation of effect modification by fixed risk factors.

Within subjects

Within subject confounding is still possible especially for multiple, correlated, transient factors which change over time within a subject (such as being distracted while wearing gloves). In the hand injury study, the pair matched interval approach was initially planned to contrast exposure (that is, glove wearing) in the hazard period (defined as the 10 minutes preceding the hand injury) and exposure in a 10 minute control period sampled 60–70 minutes before the injury on the same day. However, the median exposure to wearing gloves was 258 minutes. Thus, exposure in the hazard and control periods were not likely to be independent since the difference in time between the planned hazard (10 minutes before the injury) and control period (60–70 minutes before the injury) was exceeded (table 1). This would violate the assumption of independence of the case-crossover design.

Had it been possible to use the pair matched interval approach, an evaluation of the relationship between glove wearing and other transient exposures that may be correlated and change over time (within subject confounding) could have been made. For example, since data were collected on the temporal relationship between wearing gloves and rushing within the 90 minute period before the injury, we could control for within subject confounding of these two variables using conditional logistic regression. This would be more likely to go undetected while utilizing the usual frequency approach since data were not collected on the co-occurrence of rushing while wearing gloves in the past work month, only the average frequency and duration of glove use. Because of the difficulties mentioned above, it is important to carefully consider the choice of control period selection, and take into account correlation of transient exposures over time and the need to control for within person confounding.

CHANGING TASKS IN THE WORK ENVIRONMENT

One major challenge in conducting case-control or case-crossover studies in the work environment is identifying control periods that are similar to the time at which the injury occurred. For instance, workers may change tasks considerably over a 90 minute time period. If the work task done 10 minutes before the injury is vastly different from the task(s) done over the previous 80 minutes, then the nature of the work has changed and perhaps the risk of injury as well. This would affect the pair matched analytic approach if one used the 60–70 minute earlier period as the control period. However, when considering traumatic hand injury, there are many ways that a laceration, crush, or puncture can occur so excluding certain tasks as "zero risk" may be ill advised.

RECALL BIAS

The reliability and validity of self reported transient exposures has been another important criticism of case-crossover studies.[15] For the hand injury study, there are now test-retest reliability data available which may suggest that injured subjects can reliably report the frequency and duration of transient exposures in the month before the injury up to four days after the initial interview.[16] This implies that recall of such exposures may be reliable, but does not answer the question of the validity of the recall, that is: can the timing of the transient exposure in the hazard period be recalled correctly? Was the subject truly rushing in the 10 minute interval before the injury or was it 20–30 minutes before the injury? Answering this question may require methods such as sampling observation periods for factors such as rushing or working with malfunctioning machinery.[17] This may not be feasible however given the infrequent nature of exposures and work injuries. Another example might be to use the occurrence of documented assembly line speed-ups seen in manufacturing production as a gold standard for rushing with respect to the recalled period of rushing.

The accuracy of the exposure timing is another potential source of information bias. Memory recall of the timing of an exposure after a salient event such as an injury may be "telescoped" closer to the injury time than it actually occurred. This has been found for recall of personal events more than two months old.[18] Memory telescoping may not affect studies where the time interval between exposure and injury is on the order of a few seconds to hours, and the interview occurs within a few days after the injury. If subjects overestimate exposure in the hazard period, just before the injury, and underestimate exposure in the past work month, effect estimates may be biased upwards. The degree to which this recall bias may be operating in case-crossover studies of injury is currently unknown.

TEMPORAL RISK FACTORS FOR OCCUPATIONAL TRAUMATIC HAND INJURIES

Temporal factors are receiving increased attention in the etiology of workplace injury.[19–21] Data from the case-crossover study of occupational hand injuries were used to evaluate associations between traumatic hand injuries and various temporal factors or "markers for fatigue". Descriptive data relating to each hand injury were used to examine temporal determinants of the injuries[8] including the distribution of the time of day of the injuries and the elapsed time between the start of a shift and the time of the injury. Moreover, using the case-crossover data it was possible to evaluate overtime status at the time of injury, and the number of hours of sleep on the night before the injury as compared to the usual number of hours of sleep as risk factors for a traumatic hand injury.

Selection bias was largely avoided since cases served as their own controls in this study. However, subjects could self select themselves into this study based upon their exposures. One concern was the possibility of a "harvesting effect" or whether clinics might have been closed during the hours when workers were likely to be working overtime. This may lead to the inclusion of primarily non-overtime working injured subjects into the study. Although the evaluation was limited, the two major clinic organizations used to recruit the study subjects had different hours of operation. Organization #1 was open primarily from 08:00 am to 08:00 pm, whereas organization #2 was open primarily from 08:00 am to 04:30 pm. This allowed a comparison of the risks of a hand injury during overtime among the subjects from each of the two organizations.

Other problems, such as information bias may have also affected the assessment of exposure timing. For example, work during overtime was retrospectively self reported for the hazard and control time intervals. If there was differential accuracy in the reporting of overtime exposure during the hazard period or the usual frequency of exposure (that is, the control period), biased results would be obtained depending on the direction and strength of the error in reporting.[15] For example, injuries during overtime work may be under-reported compared to regular work hours. Since workers are a dynamic study population, a prospective cohort study may be the only way to enumerate person-time at risk and person-time exposed.[22] This may be the most accurate and useful approach to determine whether extended work hours is a contributing causal factor for acute traumatic hand injury in the workplace.

CASE-CROSSOVER STUDIES NESTED IN OTHER STUDIES

Case-crossover studies can also be conducted in the context of other epidemiological studies (cross sectional, case-control, and cohort studies). In the study of risk factors for animal-related injuries among veterinarians,[5] several questions were included in a cross sectional questionnaire to enable conduct of a case-crossover study within a nested case-control study. In the case-crossover study, the hours of sleep the night before the injury were compared with the usual hours of sleep during the prior month for the injured person. In the case-control study, the average hours of sleep the month before the injury for cases were compared with a randomly selected month for controls (table 2). While the case-crossover study examined acute sleep deficit (last night), the case-control study examined chronic sleep deficit (hours of sleep in the last month).

Case-crossover studies conducted in the context of case-control studies have considerable utility. Both fixed and transient risk factors for injury can best be evaluated by conducting a case-crossover study using the cases from a case-control study. In a pair matched case-control study of occupational hand injury, the number of hours of sleep the night before the injury and the average number of hours of sleep were asked of both cases and controls (uninjured persons were matched by date of injury to the cases).[23] In that study, a case-crossover analysis using the cases only could also have been done permitting comparison of the same question (acute sleep deficit as a risk factor for hand injury), using both study designs. Where case-crossover studies have been conducted in

Table 2 Comparison of case-crossover and case-control features for examining sleep deficit as a risk factor for animal related injuries to veterinarians, Minnesota

Study type	*Case definition*	*Exposure assessment*	*Control selection*	*Factors potentially evaluable*
Case-crossover	Animal related injury in past year	Hours of sleep the night before the injury	Usual hours of sleep at night the month before the injury for the injured vets	Transient factors like hours of sleep
Case-control	Animal related injury in past year	Hours of sleep the month before the injury	Hours of sleep for a randomly selected month for uninjured vets	Transient factors like hours of sleep and fixed factors like age, gender, practice style, etc

tandem with case-control studies, the results have been consistent in the direction of effects.[2 24 25] Furthermore, this approach would allow the investigator to also conduct a case-time-control study to adjust for possible temporal trends in exposure.[26 27]

Conclusions and recommendations for future research

The following recommendations for future research were made based on our analyses and discussions with workshop participants.

(1) More case-crossover studies of occupational trauma should be conducted that compare results for the same injury type and across injury types, especially where and when interviews of injured workers can be done shortly after the injury (in company medical departments, outpatient clinics, hospitals, by telephone at home, or in doctors' offices). Questions regarding exposures in a hazard period and during the previous work month can also be added to company incident investigations on site.

(2) The examination of the validity of exposure timing compared with self reported exposure timing should be given high research priority. This may be most feasible for transient factors that are external such as malfunctioning equipment, or wearing gloves, compared with internal factors such as distraction due to thinking about other people or rushing where there are no witnesses or external processes to corroborate or refute the self reported exposure.

(3) In work settings, where it is possible, an effort should be made to launch cohort studies perhaps using pre-employment data or new baseline data on fixed risk factors such as age, gender, work tasks, occupation, job experience, and safety training. A case-crossover study nested in a cohort could evaluate both fixed and transient risk factors. A study in a large manufacturing company that targets all acute traumatic injuries might be successful, provided adequate pilot studies were done first to help identify appropriate person-time at risk, hazard period duration, and eligible control periods.

In summary, the case-crossover design is useful for the evaluation of transient risk factors that may trigger injury at the workplace. This approach leads to freedom from confounding by differences between workers that would be difficult if not impossible to overcome with more traditional approaches. Implementing such studies involves overcoming several important challenges just as in any other observational design.

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