COMMENTARY

The Case-Crossover Study: A Novel Design in Evaluating Transient Fatigue as a Risk Factor for Road Traffic Accidents

Commentary on Valent et al. A case-crossover study of sleep and work hours and the risk of road traffic accidents. SLEEP 2010;33:349-354.

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IN THIS ISSUE OF *SLEEP*, VALENT AND COLLEAGUES[1] PRESENT THEIR FINDINGS FROM A CASE-CROSSOVER STUDY OF TRANSIENT MEASURES OF FATIGUE that included acute sleep, wakefulness, and long working hours as triggers of road traffic accidents (RTAs) among patients presenting an injury to a hospital emergency room (ER). Although there was no statistically significant association between work hours and RTAs, and observed significant risk decreased for sleep duration in only the highest exposure group (>11 hours), this study provides valuable data to illustrate several strengths and limitations of the application of this unique and potentially useful design to the study the acute effects of fatigue.

The case-crossover study design is a relatively new analytical epidemiological approach, and is unique in that the case serves as his/her own control and is used to investigate the transient effects of an intermittent exposure on the onset of acute outcomes.[2] This design is most often contrasted with the retrospective case-control design. There are several important and distinguishing differences including the evaluation of transient versus fixed risk factors and the comparison of exposure at the time of the event to within-person control periods rather than to the same time period across individuals (i.e., separate controls). The seminal application of this design was in the investigation of the immediate determinants of myocardial infarction (MI) onset, such as physical, psychological, or chemical triggers.[3] The rationale for employing this new design over the more traditional case-control design was based upon several methodological challenges. For example, in investigating heavy physical exertion as a potential risk factor for MIs, one difficulty is in selecting and enrolling healthy or hospital-based controls who had similar periods of atypical activities and exposures as those experiencing the MI (the case).[3] The researchers concluded that to control for these potentially confounding factors, the best selection would be the cases themselves. The next challenge was to select an appropriate control period (or periods) in which the exposure distribution best represented the expected exposure distribution for the cases during the time at risk.[2] Two reference (control) period approaches were established, the patient's estimated usual annual frequency of heavy exertion and the frequency of heavy exertion in the control period on the day before the onset of symptoms.[3-5] The study established that heavy physical exertion is a significant risk factor for the onset of acute MIs, especially among subgroups who are most often sedentary.

The case-crossover method has also been advanced by its use in one of the first studies to report that the estimated risk of a collision when using a cellular telephone is four times higher than the risk when it is not being used.[6] Although this study has been critiqued regarding the selection of an appropriate person-time at risk period,[7] one of the many challenges in implementing this design, the findings have been widely published. The case-crossover design has further been used to evaluate a wide range of transient risk factors for accidents and injury, such as rushing and distraction.[9]

In the study by Valent et al.[1] the specific questions of interest (i.e., does having less than usual sleep or working more than usual hours increase the risk of being injured in a road traffic accident requiring a visit to a hospital ER) are compatible with the key question this study design is intended to address: "Did anything unusual or different take place before the onset of the event?"[2,3] The study question also satisfies the requirement that the exposures are intermittent and exhibit transient effects (i.e., the case moves across periods of varying exposure).[2] By choosing this self-matching design that requires data only on the injured driver involved in the crash, the investigators likely saved many valuable study resources, such as the cost and time associated with interviewing a separate control group and with finding a sample of non-cases whose exposure distribution represented the expected exposure distribution for the cases (those involved in the MVA) during the time at risk. In contrast, had they chosen the case-control design, the investigators would need to identify and interview a separate group of controls who were not involved in an MVA, but who also were treated at the ER. The use of cases as their own controls eliminates confounding associated with differences in stable characteristics (both measured and unmeasured) that differ between subjects[5]—in the study of fatigue as it relates to MVAs, this confounding cannot be underestimated. There are several potentially important between-person confounders that would have otherwise required measurement and been controlled for in the analysis using non-matched study designs. These would include, for example, driving ability or experience, visual acuity, comorbidity, age, and other factors.

Submitted for publication January, 2010
Accepted for publication January, 2010

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Selecting the most appropriate control period for comparing the observed exposure in the defined hazard (or case) period preceding the MVA to the expected exposure, estimated from one or more control periods, is often a challenge to the investigator. Another important feature of the case-crossover design is that the control period data can be collected using two approaches; the Pair-Matched Interval approach or the Usual Frequency approach.[5] In the current study,[1] the investigators chose to use the Pair-Matched Interval approach, in which two distinct time intervals for each case are selected, the hazard (referred to here as the case-exposure window) and the control period. These periods are then statistically compared using conditional methods to be either concordant or discordant with respect to the presence or absence of the exposure of interest at the time of the MVA. Two control periods were selected to evaluate the hypotheses in this study: for sleep duration and work hours, a matched comparison was made between the 24-hour interval immediately before the road traffic accident (hazard period) with the 24-hour interval of the previous day (control period), thus potentially controlling for day-to-day factors.

There were few significant findings reported by Valent and colleagues[1]; however, the study illustrates a number of important issues often encountered when conducting a case-crossover study. One challenge in matched designs is that the number of discordant pairs is a key driver of statistical power. To illustrate, although 574 subjects were enrolled in this study, which in many circumstances would be an adequate sample size, an examination of the analysis of daily duration of sleep in Table 3 and daily work hours in Table 4, suggests that the statistical power (the ability to reject the null hypothesis) was relatively low across most hourly categories in these matched-pair control period analyses. The estimated odds ratio (relative risk) in these tables is the ratio of the discordant pairs (N in column 1 divided by N in column 2). For example, in Table 3 for <5 hours, RR= 3/2 = 1.30. Thus, it is important when planning a case-crossover study to select exposures of interest that not only exhibit variability within a wide enough time window, but to also select control periods that are sufficiently distant in time from the case period to minimize their correlation.[4] Otherwise, concordance is likely to lead to reduced statistical power and an increased potential of a Type II error.

Although there is complete control of between-person confounders, another key limitation of this study design is in the control of within-person confounding, which is still possible for multiple, correlated transient factors that change over time within a subject.[4,10] For example, if an MVA driver in this study was fatigued and concurrently using a mobile phone (i.e., distraction) while moving through a hazardous road condition, this confounding would be uncontrolled and would be a threat to the internal validity of the findings. However, it is still possible to de-confound these multiple transient exposures depending on the level of detail of the data collected, the control selection approach used, and appropriate analyses.[5]

The study by Valent et al.[1] illustrates several key issues to consider when planning a case-crossover study of sleep and other measures of fatigue as risk factors for traumatic outcomes.

DISCLOSURE STATEMENT

Dr. Lombardi has indicated no financial conflicts of interest.

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