

# The Use of the Case-Crossover Design in Studying Illicit Drug Use

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## ABSTRACT

The case-crossover design was developed to study time-varying exposures that cause transient excess risk of acute health events. It is a variant of case-control and subject-as-own-control research designs, involving use of information about exposure history of each case to estimate the transient effect. This kind of self-control design can help to reduce sampling bias otherwise introduced in the selection of controls, as well as confounding bias that might be derived from enduring individual characteristics, especially personality traits and other long-standing inherited or acquired vulnerabilities. When the subject is used as his or her own control, these personal vulnerabilities are matched. In this paper we discuss strengths and weaknesses of the case-crossover design and suggest applications of the case-crossover design in epidemiologic studies on suspected hazards of illicit drug use, and in studies of drug use and co-occurring psychiatric disturbances. We conclude that the case-crossover design can play a useful role, but it discloses a need to secure fine-grained measurements in epidemiologic research

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on psychiatric comorbidity. As explained in the paper, we also believe the case-crossover method may be of use to criminologists who study the drugs–crime nexus, to services researchers and clinicians who seek to understand treatment entry and compliance behavior, and to etiologists interested in polydrug use. [Translations are provided in the International Abstracts Section of this issue.]

*Key words.* Case-crossover; Comorbidity; Epidemiology; Methodology; Substance use

## INTRODUCTION

Epidemiologists search for evidence of determinants of disease by asking questions such as “Where are cases of disease more likely to be found, with respect to characteristics of person, place, and time?” (Anthony and Van Etten, 1998). Within this framework, epidemiologists often start their search with basic tests of alternative theories by estimating associations between the disease of interest and the past history of suspected causal exposures or characteristics. Recently, a new epidemiologic research design, the case-crossover design (Maclure, 1991), was developed to estimate the effects of a transient exposure, such as might occur just before an acute-onset event such as a car crash, heart attack, or panic attack. In essence, the case-crossover design poses a question that clinicians often ask their patients: “Were you doing anything unusual just before this episode?” (Maclure, 1991). As such, the case-crossover design is a special instance of applying experience sampling methods to assess alternative hypotheses about one or more elements in an array of possible unusual behaviors or characteristics that might have caused an adverse health outcome.

In this paper we discuss strengths and weaknesses of the case-crossover design and suggest the application of the case-crossover design in epidemiologic studies on suspected hazards of illicit drug use and in studies of illicit drug use, including nonmedical use of psychotherapeutics, and co-occurring psychiatric disturbances. We also surmise a possible utility in research on other topics such as the drugs–crime nexus, treatment entry, premature termination of treatment, and polydrug use.

## BACKGROUND

Traditionally, case-control studies have been used at early stages of research on the possible causal associations between a suspected risk-promoting factor (e.g., tobacco smoking) and a subsequent health event (e.g.,

lung cancer). Design of a case-control study often involves ascertainment of "cases" (those suffering the event) and securing an appropriate set of non-case "controls" who have not become cases during the observation interval under scrutiny. Alternative case-control designs involve a comparison of "observed" case values on risk-promoting factors with "expected" values from the population base out of which the cases are sampled. Comparisons with respect to past exposure history are made in order to obtain a relative risk estimate as a measure of strength of association between the exposure and the outcome under study. However, one of the fundamental issues in case-control methodology is whether the controls provide adequate expected values (Lilienfeld and Stolley, 1994). The selection processes for controls also may be time-consuming and costly.

As in essentially all research, especially nonexperimental research, the case-control design must control for suspected distorting influences, such as sex, age, genetic vulnerability, personality traits, and alternative social and environmental exposures, and experiences. When these characteristics are associated with both the suspected risk factor under study and the outcome, they may "confound" any attempt to estimate the factor-outcome association. To reduce these potentially distorting influences, epidemiologists most often turn to an array of procedures such as fine-grained stratification or matching, statistical adjustments, and statistical models which substitute for constraints imposed by randomization in controlled trials (e.g., see Schlesselman, 1982; Anthony and Van Etten, 1998; Anthony et al., 1989; Anthony and Petronis, 1991). For example, in epidemiologic research to estimate a suspected causal association between illicit drug use and risk of suicide attempts (Petronis et al., 1990), one of the matching variables has been the local area of residence because both illicit drug use and suicidal behaviors might be influenced by shared local neighborhood characteristics (e.g., community disorganization, community norms or attitudes, "anomie" as a socially shared construct). Unless constrained by matching, stratification, modeling, or randomization, these differences in neighborhood characteristics might account for any observed association between illicit drug use and suicidal behaviors (Petronis et al., 1990).

The prospective or cohort design also is commonly used in epidemiologic research. Here, the risk of disease is compared across levels of an antecedent variable such as an exposure to a toxic agent (e.g., Agent Orange; low-level microwave irradiation). Despite multiple strengths (Breslow and Day, 1987), the prospective cohort design also has some limitations, including the possibility that distorting influences are not fully controlled as they might be in a randomized controlled trial.

As implied in this brief review of case-control and prospective cohort studies, randomized controlled trials represent a major advance in the con-

trol of potentially distorting influences due to confounding variables. However, for studies that involve testing suspected hazards of illicit drug use among human beings, randomized controlled trials often can be infeasible or even unethical to conduct. For example, both theory and primarily clinical evidence support the idea that cocaine precipitates panic attacks among illicit drug users (e.g., see Louie et al., 1989), but it is quite possible that these clinical observations about the cocaine-panic association are distorted by uncontrolled confounding factors such as genetic vulnerability and preexisting personality traits. In addition, as with many hypotheses in psychiatric comorbidity research, the cocaine-panic linkage has not been tested in controlled laboratory experiments with human subjects due to issues of feasibility and ethical concerns about administering cocaine to the point of inducing psychiatric disturbances.

In this type of situation, when the burdens of randomized controlled trials are impossible or difficult to bear, or are premature, epidemiology sometimes can be called upon as a source of new evidence. This is part of our rationale for proposing the use of a case-crossover design to augment other epidemiologic research designs when the goal is to assess suspected hazards of illicit drug use or when the exposure of interest tends to vary with time (such as alcohol or illicit drug use) and is thought to have a transient effect on an acute event.

The case-crossover design was developed to study transient effects of an intermittent exposure on the risk of an acute event (Maclure 1991; Mittleman et al., 1995). The term "crossover" is used to describe the design feature in which all subjects serve as their own controls. Specifically, for each case, control information is based on his or her own past exposure experience. Use of subjects as their own self-matched controls constrains the potentially distorting influences of confounding characteristics, which might be time-invariant or fixed individual characteristics, such as sex, race, and long-standing vulnerabilities, whether inherited or acquired. Analogous to research on matched pairs of monozygotic twins, where genetic vulnerabilities are held constant, self-matching also constrains these and other vulnerabilities, and this is the main advantage of using the case-crossover design. Additionally, this design requires fewer subjects than alternative epidemiologic designs and can be used to study rarely occurring outcomes. However, it also should be noted that potential distortions due to characteristics that tend to change over time are not constrained by a case-crossover design. This sort of within-person confounding occurs when multiple transient exposures are correlated in time within the same individual (Mittleman et al., 1995).

To assess a suspected change in risk of an acute-onset event following a brief exposure to the suspected determinant of the event, the case-crossover

design compares the frequency of exposure during a brief “hazard interval” for an individual subject with the frequency of exposure during an appropriately selected “control interval” for that same subject. A significant increase in risk is identified when the frequency of exposure observed during the hazard interval is greater than is estimated for the control interval. Because a self-matching strategy is used, the matching needs to be taken into account in the statistical analysis, as also is true for monozygotic twin studies or other matched designs (e.g., see Schlesselman, 1982). Depending on the sampling strategy, the case-crossover data can be analyzed by using standard matched pair methods, such as the matched-pair analysis offered by the conditional logistic regression model (Mittleman et al., 1995), or Mantel–Haenszel methods for follow-up studies with sparse data in each stratum (Greenland and Robins, 1985).

A selection of examples from these past studies might help to clarify the nature of the design and its potential utility in research on drug-taking.

### **Example 1: Use of Cellular Phones and Car Collisions**

Redelmeier and Tibshirani (1997a) sought to test whether drivers’ use of cellular phones might increase the risk of a car crash. To identify their cases, they approached drivers who came to the attention of the New York Collision Reporting Center because of a collision with substantial property damage. A total of 699 drivers who had a cellular phone and accessible billing records of cellular phone calls were included in the study. For the “hazard interval” they designated a 10-minute interval just prior to the official recorded or estimated time of the crash, and they obtained cellular phone company records to show whether the driver had used the cellular phone within the 10-minute interval prior to the collision. For the “control interval” they designated the same period as the hazard interval, but on the day before the collision. They compared each person’s telephone activity during the hazard interval to his or her activity during the control interval. They found that cellular-telephone activity was associated with an estimated 4.3 excess risk of a motor vehicle collision; they also showed the robustness of the result by analyzing hazard intervals of 1, 5, and 15 minutes, with similar conclusions.

### **Example 2: Alcohol Consumption and Injury**

Vinson et al. (1995) used the case-crossover design to study the transient risk of alcohol consumption on injury. Adults 18 years of age or older presenting with acute trauma to emergency centers at two hospitals were approached and recruited for the investigation. Information on alcohol

consumption was then derived from two timeline follow-back interviews covering alcohol consumption during the past 28 days prior to injury. These investigators compared alcohol use during the "hazard" or "case" period (i.e., 6 hours prior to injury) with alcohol use during a "control" period (i.e., the same 6-hour time window on the prior-to-admission day). The matched-pair analysis, based on pairs of observation that were discordant for alcohol use in the 6 hours prior to injury and the same 6-hour window on the previous day, yielded estimates of injury risk associated with alcohol consumption. Two additional analyses with different estimation procedures also yielded consistent (yet higher) odds ratio estimates.

### **Example 3: Heavy Physical Exertion and the Onset of Acute Myocardial Infarction**

The case-crossover method has a unique advantage in testing hypotheses about important health events that can be infeasible or unethical for study under controlled designs. Mittleman et al. (1993) first used a case-crossover design to investigate a suspected link between heavy physical exertion and onset of acute myocardial infarction. A total of 1,228 patients with myocardial infarction (MI) were interviewed to secure information on the time and the place of the MI as well as their frequencies of physical exertion during the previous year. The relative risk estimate was obtained by comparing heavy physical exertion during a 1-hour hazard interval immediately before the onset of MI with heavy physical exertion during the same 1-hour control interval on the day prior to the MI. They found 50 patients who reported heavy exertion only during the 1-hour hazard period as compared with 9 who reported heavy exertion only during the control period. The standard matched-pair analysis yielded a relative risk of myocardial infarction of 5.6 (95% confidence interval, 2.7 to 12.8).

Using the case-crossover design, Willich et al. (1993) reported a consistent finding on the association between physical exertion and the onset of myocardial infarction. Subsequent researchers also reported the utility of the case-crossover design in investigating suspected triggers of acute myocardial infarction or myocardial ischemia such as sexual activity and negative emotions (Muller et al., 1996; Mittleman et al., 1997; Gullette et al., 1996).

Dixon (1997) made an interesting comparison of results from the case-crossover design with corresponding results from a case-control design in research on risk factors for hemorrhagic fever with renal syndrome. Both the case-crossover and the case-control analyses showed generally consistent results, but the relative risk estimates for the case-crossover analyses were stronger in magnitude. Dixon concluded that the case-crossover design is a

valuable adjunct to traditional case-control studies when interest is in the effects of transient exposures on the risk of acute disease episodes.

## METHODOLOGICAL ISSUES

The case-crossover method addresses the issue of selecting controls quite simply. It allows the use of all identified cases, rather than a restricted sample, and no additional controls need to be identified or interviewed, although for each case a "hazard" interval and a suitable "control" interval must be designated. The self-matching feature of the design has a particular value when the outcome is rare or when subjects might be reluctant to participate as controls (Redelmeier and Tibshirani, 1997b). Moreover, by using this new design, epidemiologists are able to constrain variables (both measured or unmeasured) that have made previous case-control studies difficult to interpret (e.g., Vinson et al., 1995), especially personality variables (e.g., sensation seeking or risk aversion), as well as genetic vulnerabilities that are important in alcohol or illicit drug use research. The case-crossover design constrains the influences of these potentially confounding variables to the extent that these traits are constant across the "hazard" and "control" intervals.

Nonetheless, as Redelmeier and Tibshirani (1997b) indicate, the case-crossover design is a powerful method applicable only to a narrow range of scientific questions. Greater understanding of strengths and biases in case-crossover studies may help investigators explore selected questions in behavioral medical research. For example, potential biases may occur from the following sources: selection of cases under study, selection of hazard and control intervals, and correlation of exposures over time.

First, although bias in control selection is eliminated, there is possible bias in selecting cases. As with other epidemiologic methods, judgments about the generalizability of a study's results depend upon discovery of replications elsewhere. For example, in the cellular telephone and car crash study (Redelmeier and Tibshirani, 1997a), respondents were recruited from a single region over a time span of a few months. The estimated relative risks hence may not be applicable to other settings to the extent that driving conditions vary from place to place or time to time. In addition, proficiency with cellular telephone usage while driving might change with time or increasing experience and practice (Redelmeier and Tibshirani, 1997b). Likewise, in Vinson's alcohol and injury study (Vinson et al., 1995), all cases were injured during late spring and early summer; the results might not generalize to other seasons.

A second methodological issue is that the relative risk estimates depend directly on the duration of the hazard and control intervals (Maclure, 1991). The case-crossover method requires a good estimate or specification for the duration and timing of an interval during which effects might be expected to occur. This “lag” or “induction” interval must be specified on the basis of theory or prior evidence, as in the case of longitudinal research generally. Fortunately, the effect period can be studied empirically by examining the change in magnitude of the relative risk estimate under different assumptions (Maclure, 1991).

There also might be bias in the selection of control periods. In practice, selecting an appropriate comparison period is difficult and might rival the difficulty of selecting appropriate control subjects in case-control studies. As a check on validity, it is possible to examine multiple control intervals and to check the robustness of the final results (Redelmeier and Tibshirani, 1997b).

A third methodological issue is that the case-crossover design cannot control for individual characteristics that tend to change over time (i.e., within-person confounding). That is, time trends in exposure or a correlation of exposures over time can bias the relative risk estimate from case-crossover designs. Hence, the case-crossover design is best-suited for exposures that exert a transient effect on a health outcome. This design is not well-suited for exposures that have a chronic or cumulative effect on the outcome.

A final methodological issue involves what we call coarse- and fine-grained measurements on the timing of health events. For the case-crossover design to work well, the measurement of the timing and sequencing of the exposure and the outcome must be relatively fine-grained rather than coarse-grained. For example, in Redelmeier and Tibshirani's study (1997b) it was necessary to specify the “hazard” interval so that it did not encompass the postcrash period when the driver might have used the cellular phone to call the police, ambulance, or tow truck. Minute-by-minute resolution in the measurement was necessary to keep the temporal sequencing in order; i.e., the call-crash sequence rather than the crash-call sequence. We will return to this issue of fine-grained measurement when we consider the use of the case-crossover method in research on psychiatric comorbidity and other suspected effects of illicit drug use.

## PSYCHIATRIC COMORBIDITY HYPOTHESES

Our research group has used epidemiological procedures to test an array of psychiatric comorbidity hypotheses that involve use of illicit drugs. In this

research, distorting influences by confounding factors have been controlled mainly via case-control matching strategies, case-base sampling, and statistical adjustments or modeling (e.g., Anthony and Petronis, 1991; Petronis and Anthony, 1989; Tien and Anthony, 1990; Petronis et al., 1990; Crum and Anthony, 1993). For example, Anthony et al. (1989) studied first-time panic attack cases and neighborhood-matched community controls, and then used multiple logistic regression modeling to estimate relative risks based upon prospectively gathered data from almost 9,000 young adult household residents who had completed Diagnostic Interview Schedule (DIS) assessments as part of the multisite collaborative Epidemiologic Catchment Area (ECA) Program. Risk of developing panic attacks for the first time was estimated 3.4 times greater among cocaine users versus nonusers; the level of excess risk of becoming an incident case of panic attack was markedly greater among adults who recently had used cocaine but not marijuana.

A similar approach was used to study marijuana and cocaine effects on risk of making a suicide attempt, also among ECA participants. By using matching and multiple regression modeling techniques, Petronis et al. (1990) prospectively estimated excess risk of suicide attempts among cocaine users. They found that individuals who used cocaine were much more likely to make a suicide attempt.

What is similar about these examples is that large-sample epidemiological research designs have been used to shed new light upon suspected causal associations between illicit drug use and the risk of specific psychiatric disturbances. In addition, in each instance, these investigators have had to face a limitation: namely, they were unable to constrain all possible long-standing individual-level personality traits or other vulnerabilities that might have caused illicit drug use to co-occur with psychiatric disturbances. That is, confounding by long-standing individual-level vulnerabilities could not be ruled out. Further, at present, we do not know these vulnerabilities well enough to measure all of them.

In theory, a randomized controlled trial might be used to test for cocaine or marijuana effects on anxiousness, depressed mood, or other suspected psychiatric disturbances, with random assignment used to constrain possible confounding by long-standing vulnerabilities. However, it arguably is unethical to expose humans to cocaine in order to induce psychiatric disturbances as severe as panic attacks or suicidal ideation, even if logistical issues were resolved.

When randomization is unethical or infeasible to test hypotheses about drug effects, we must turn to nonexperimental observational research designs of the type illustrated by Anthony et al. (1989), Petronis et al. (1990), and Crum and Anthony (1993). We now can add the case-crossover

design to this array of nonexperimental approaches, and this design is ripe for use in research on psychiatric comorbidity hypotheses precisely because the case-crossover method effectively matches on vulnerabilities of the type previously left uncontrolled.

The use of case-crossover methods in psychiatric comorbidity research is not without difficulty, however. A major challenge involves what we have discussed as an issue of "fine-grained measurement" with respect to temporal sequencing. To date, most psychiatric comorbidity research has rested upon recall of age of onset of different events over an entire life history up to the point of assessment (e.g., Kessler et al., 1996, 1997), or at least a restriction to a 1-year interval of recent memory (e.g., Anthony et al., 1989; Crum and Anthony, 1993). However, in our most recent work we have been working with recall of events of the month prior to assessment, and even in the context of "fine-grained measurement" we cannot always be sure that the drug use precedes the adverse health event or vice versa. We note that this is not a consequence of using the case-crossover design; it applies equally to almost all of the nonexperimental research designs used to study psychiatric comorbidity. What is needed in these studies is a much more deliberate effort to assess temporal sequencing and to determine which came first. For some hypotheses, minute-by-minute resolution might be required such as can be obtained only by using experience sampling methods (e.g., see Larson and Csikszentmihalyi, 1983; Stone and Shiffman, 1994; Shiffman et al., 1996; Kaplan and Lambert, 1995). [Note: The experience sampling method was developed primarily by Larson and Csikszentmihalyi in response to a need for more accurate assessment of the subjective experience of individuals in their natural environments. A recent adaptation of this method has been described with the term ecological momentary assessment (EMA). Components of EMA are (a) phenomena are assessed as they occurred; (b) assessments are dependent upon careful time-sampling; (c) assessment protocols involve repeated longitudinal observations of individual subjects; and (d) assessments are made in the environment inhabited by the research subjects (Stone and Shiffman, 1994).]

## OTHER APPLICATIONS

Whereas our own focus has been upon the potential utility of the case-crossover design in psychiatric comorbidity research, we believe that this methodological innovation from epidemiology might also have value for criminologists interested in the drugs-crime nexus, for health service

researchers who seek to understand the determinants of entry into treatment or premature termination of treatment, and for clinicians or etiologists who wish to look into polydrug use. For example, with respect to drugs and crime, we note that many observers interpret the DUF and ADAM data on arrestees' drug use as an indication of the causal association between drug use and criminal activity (US Department Justice, 1996, 1998). In fact, it is possible that drug taking impairs a criminal during a postcrime interval, and this impairment leads to arrests, followed by enrollment in the DUF and ADAM studies. The case-crossover design can be used to sort out the drug–arrest association from the drug–crime association via a focus on drug taking in three intervals: the “hazard” interval just prior to arrest (now assessed via DUF/ADAM interview and bioassay methods), an additional “hazard” interval just prior to the crime that precipitated the arrest (via an interview assessment about the hours prior to the crime), and a “control” interval of equal duration, totally unconnected with either the crime or the arrest. Here, the selection of hazard and control intervals for case-crossover research on drugs and crime might be guided by the experience of past researchers who have investigated car crashes, injuries, and myocardial infarctions by using this new method. We are aware that some criminologists have investigated the drugs–crime nexus with a qualitative orientation to the same type of study data; the case-crossover design merits attention to its capacity for quantitative estimation of the suspected risk relationships.

With respect to health services research, we note an array of possible applications of the case-crossover design. For example, Schutz and colleagues (1994) analyzed data from the Baltimore ALIVE study and found that the experience of an overdose might be an important determinant of entry into treatment for opioid dependence. However, in this observational research, the investigators were unable to constrain potential confounding by long-standing vulnerabilities that might prompt both overdose and treatment entry. In order to pursue this line of inquiry, future services researchers might study the time-varying overdose experience of treatment entrants, not only in the few days just prior to treatment entry (i.e., a “hazard” interval), but also in appropriately selected “control” intervals.

The vexing problem of premature termination of drug treatment also merits attention via case-crossover methods. For example, child-care crises are among the long-suspected determinants of female clients' early departure from long-term treatment programs such as therapeutic communities (e.g., see Hughes et al., 1995). If the women in the therapeutic communities were to keep standardized daily diaries of life stressors and other time-varying suspected influences on premature discharge (including worries

about care of their children), it would be possible to compare the entries for the "hazard interval" just prior to departure with sampled entries for "control intervals" prior to departure. Separate measurements might be taken to gauge the array of reinforcers in the therapeutic community environment and other time-varying aspects of its reinforcement contingencies. The same kind of approach also could be used to study the causes of drop-out from other treatment modalities (e.g., methadone maintenance), or from participation in controlled trials being conducted as part of the current NIDA medications development program.

With respect to clinical and etiological research on polydrug use, we offer as an example a recently reported association between daily alcohol intoxication and the "smoking" of methamphetamine (i.e., "ice smoking") in the United States (Furr et al., in press). Furr and colleagues surmise that becoming intoxicated with alcohol on a daily basis might promote the initiation and persistence of "ice smoking," but the investigators acknowledge that some long-standing vulnerability might be creating a spuriously high association between these two manifestations of drug involvement. One of the next steps in this line of research might be a case-crossover study in which experience sampling methods are used with samples of "ice smokers" in order to study whether becoming alcohol-intoxicated precipitates the start of an ice smoking spree, or vice versa.

## CONCLUSIONS

In conclusion, the new case-crossover method is a powerful design in studying a transient risk factor on occurrence of an acute event. It may prove to be a useful and important adjunct to current epidemiologic studies. This new method also highlights a need to develop assessment procedures with fine-grained measurement of the temporal sequencing of respondents' drug use and related problems.

In this introduction to the case-crossover design, we have provided numerous past examples outside the realm of research on illicit drug use. Our initial case-crossover research will address hypotheses about psychiatric comorbidity, such as the cocaine-panic association first estimated via the case-control method by Anthony et al. (1989). We leave to other investigators the opportunity to apply the case-crossover design in studies of the drugs-crime nexus, in services research, and in clinical etiological research or issues such as polydrug use.

## GLOSSARY\*

**Case** - A term most often used in epidemiology for a person in the population or study group identified as having the disease or condition of interest.

**Case-Control Study** - A study design in which comparisons are made between individuals who have a particular disease or condition (the cases) and individuals who do not have the disease (the controls).

**Cohort Study** - An investigation in which a group of individuals (the cohort) is identified and followed prospectively, perhaps for many years, and their subsequent medical history recorded. The cohort may be subdivided at the onset into groups with different characteristics; for example, exposed and not exposed to some risk factors, and at some later stage a comparison made of incidence of a particular disease in each group.

**Epidemiology** - The study of the distribution and size of disease problems in human populations, in particular to identify etiological factors in the pathogenesis of disease, and to provide the data essential for the management, evaluation, and planning of services for the prevention, control, and treatment of disease.

**Matched Pairs** - A term used for observation arising from either two individuals who are individually matched on a number of variables; for example, age and sex, or where two observations are taken on the same individuals on two separate occasions.

**Randomized Clinical Trial** - A clinical trial that involves formation of treatment groups by the process of random allocation.

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## REFERENCES

- ANTHONY, J. C., and PETRONIS, K. R. (1991). Suspected risk factors for depression among adults 18–44 years old. *Epidemiology* 2: 123–132.
- ANTHONY, J. C., TIEN, A. Y., and PETRONIS, K. R. (1989). Epidemiologic evidence on cocaine use and panic attacks. *Am. J. Epidemiol.* 129: 543–549.

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- ANTHONY, J. C., and VAN ETTEN, M. L. (1998). Epidemiology and its rubrics. In A. Bellack and M. Hersen (Eds), *Comprehensive Clinical Psychology, Vol. 1*, Chapter 12. Oxford, UK: Elsevier.
- BRESLOW, N. E., and DAY, N. E. (1987). *Statistical Methods in Cancer Research* (IARC Scientific Publication 82) Lyon: International Agency for Research on Cancer.
- CRUM, R. M., and ANTHONY, J. C. (1993). Cocaine use and other suspected risk factors for obsessive-compulsive disorder: A prospective study with data from the epidemiologic catchment area surveys. *Drug Alcohol Depend.* 31: 281-295.
- DIXON, K. E. (1997). A comparison of case-crossover and case-control designs in a study of risk factors for hemorrhagic fever with renal syndrome. *Epidemiology* 8: 243-246.
- FURR, C. D. M., DELVA, J., and ANTHONY, J. C. (in press). The suspected association between methamphetamine ("ice") smoking and frequent episodes of alcohol intoxication: Data from the 1993 National Household Survey on Drug Abuse. *Drug Alcohol Depend.*
- GREENLAND, S., and ROBIN, J. M. (1985). Estimation of a common effect parameter from sparse follow-up data. *Biometrics* 41: 55-68.
- GULLETTE, E. C., BLUMENTHAL, J. A., BABYAK, M., JIANG, W., WAUGH, R. A., FRID, D. J., O'CONNOR, C. M., MORRIS, J. J., and KRANTZ, D. S. (1996). Effects of mental stress on myocardial ischemia during daily life. *JAMA* 275: 1405-1409.
- HUGHES, P. H., COLETTI, S. D., NERI, R. L., URMANN, C. F., STAHL, S., SICILIAN, D. M., and ANTHONY, J. C. (1995). Retaining cocaine-abusing women in a therapeutic community: The effect of a child live-in program. *Am. J. Public Health* 85: 1149-1152.
- KAPLAN, C. D., and LAMBERT, E. Y. (1995). The daily life of heroin-addicted persons: the biography of specific methodology. *NIDA Res. Monogr.* 157: 100-116.
- KESSLER, R. C., CRUM, R. M., WARNER, L. A., NELSON, C. B., SCHULENBERG, J., and ANTHONY, J. C. (1997). Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. *Arch. Gen Psychiatry* 54: 313-321.
- KESSLER, R. C., NELSON, C. B., MCGONAGLE, K. A., LIU, J., SWARTZ, M., and BLAZER, D. G. (1996). Comorbidity of DSM-III-R major depressive disorder in the general population: Results from the U.S. National Comorbidity Survey. *Br. J. Psychiatry Suppl.* 30: 17-30.
- LARSON, R., and CSIKSZENTMIHALYI, M. (1983). The experience sampling method. *New Dir. Method. Soc. Behav. Sci.* 15: 14-56.
- LILIENFELD, D. E., and STOLLEY, P. D. (1994). *Foundations of Epidemiology*. Oxford: Oxford University Press.
- LOUIE, A. K., LANNON, R. A., and KETTER, R. A. (1989). Treatment of cocaine-induced panic disorder. *Am. J. Psychiatry* 146: 40-44.
- MACLURE, M. (1991). The case-crossover design: A method for studying transient effects on the risk of acute events. *Am. J. Epidemiol.* 133: 144-153.
- MITTLEMAN, M. A., MACLURE, M., NACHNANI, M., SHERWOOD, J. B., and MULLER, J. E. (1997). Educational attainment, anger, and the risk of triggering myocardial infarction onset. *Arch. Intern. Med.* 157: 769-775.
- MITTLEMAN, M. A., MACLURE, M., and ROBINS, J. M. (1995). Control sampling strategies for case-crossover studies: An assessment of relative efficiency. *Am. J. Epidemiol.* 142: 91-98.
- MITTLEMAN, M. A., MACLURE, M., TOFLER, G. H., SHERWOOD, J. B., GOLDBERG, R. J., and MULLER, J. E. (1993). Triggering of acute myocardial infarction by heavy physical exertion. *New Engl. J. Med.* 329: 1677-1683.

- MULLER, J. E., MITTLEMAN, M. A., MACLURE, M., SHERWOOD, J. B., and TOFLER, G. H. (1996). Triggering myocardial infarction by sexual activity. *JAMA* 275: 1405-1406.
- PETRONIS, K. R., and ANTHONY, J. C. (1989). An epidemiologic investigation of marijuana- and cocaine-related palpitations. *Drug Alcohol Depend.* 23: 219-226.
- PETRONIS, K. R., SAMUELS, J., MOSCICKI, E., and ANTHONY, J. C. (1990). An epidemiologic investigation of potential risk factors for suicide attempts. *Soc. Psychiatry Psychiatr. Epidemiol.* 25: 193-199.
- REDELMEIER, D. A., and TIBSHIRANI, R. J. (1997a). Association between cellular telephone calls and motor vehicle collisions. *New Engl. J. Med.* 336: 453-458.
- REDELMEIER, D. A., and TIBSHIRANI, R. J. (1997b). Interpretation and bias in case-crossover studies. *J. Clin. Epidemiol.* 50: 1281-1287.
- SCHLESSELMAN, J. J. (1982). *Case-Control Studies*. New York, NY: Oxford University Press.
- SCHUTZ, C. G., RAPITI, E., VLAHOV, D., and ANTHONY, J. C. (1994). Suspected determinants of enrollment into detoxification and methadone maintenance treatment among injecting drug users. *Drug Alcohol Depend.* 36: 129-138.
- SHIFFMAN, S., PATY, J. A., GNYS, M., and KASSLE, J. A. (1996). First lapses in smoking: Within-subjects analysis of real-time reports. *J. Consult. Clin. Psychol.* 64: 366-379.
- STONE, A. A., and SHIFFMAN, S. (1994). Ecological momentary assessment (EMA) in behavior medicine. *Ann. Behav. Med.* 16: 199-202.
- TIEN, A. Y., and ANTHONY, J. C. (1990). Epidemiological analysis of alcohol and drug use as risk factors for psychotic experiences. *J. Nerv. Ment. Dis.* 178: 473-480.
- US DEPARTMENT OF JUSTICE (1996). *Drug Use Forecasting 1996 Annual Report on Adult and Juvenile Arrestees*. Washington, DC: Office of Justice Program. (National Institute of Justice Series).
- US DEPARTMENT OF JUSTICE (1998). *1997 Arrestee Drug Abuse Monitoring (ADAM) Report* (National Institute of Justice Series). Washington, DC: Office of Justice Program.
- VINSON, D. C., MABE, N., LEONARD, L. L., ALEXANDER, J., BECKER, J., and MOLL, J. (1995). Alcohol and injury: A case-crossover study. *Arch. Fam. Med.* 4: 505-511.
- WILLICH, S. N., LEWIS, M., LOWEL, H., ARNTZ, H-R., SCHUBERT, F., and SCHRODER, R. (1993). Physical exertion as a trigger of acute myocardial infarction. *New Engl. J. Med.* 329: 1684-1690.

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