

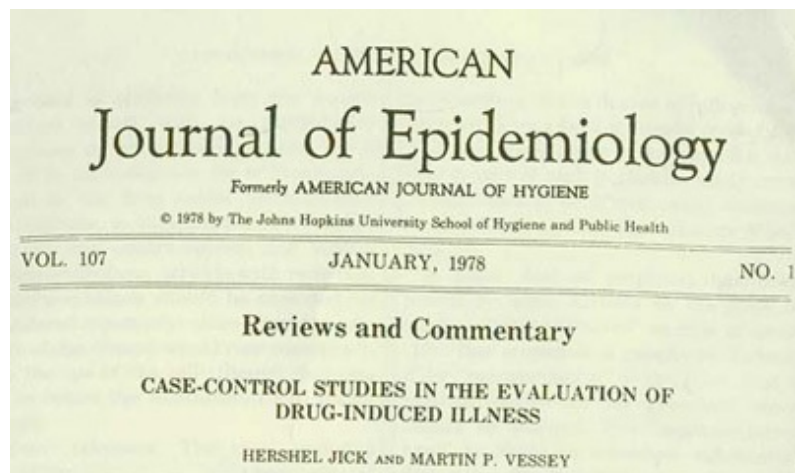
## Records

[Key Passage\(s\)](#)   [JLL Article\(s\)](#)   [Context](#)

[Download key passages/title pages as a PDF](#)

**[Jick H, Vessey M \(1978\)](#)**. Case-control studies in the evaluation of drug-induced illness. *Am J Epidemiol* 1978;107:1-7.

### Key passages



### *Selection of the cases*

The following considerations should be kept in mind:

*Definition of illness.* The illness under investigation should normally be clearly defined. This point is particularly important when studying illnesses such as coronary artery disease which have a multifactorial etiology and many manifestations. Cigarette smoking, for example, is strongly associated with the risk of acute myocardial infarction in young people, but shows a much less clear relationship with angina pectoris (11).

*Accuracy of diagnosis of illness.* The diagnosis of the illness should be as accurate as possible. In some instances, e.g., most cancers proven by biopsy, the accuracy of the diagnosis may be readily confirmed. However, when dealing with less well-defined illnesses such as subacute myelo-optic neuropathy (12) (SMON—a drug-related neurologic disorder) or those involving acute disturbance of liver function, misdiagnosis may produce substantial distortion.

*Illness-drug relationship.* The course of the illness under study should not influence the probability of being exposed to the drug of interest. This generally calls for admitting people who have been newly-

diagnosed as suffering from the disease (incident cases) with no premonitory symptoms or predisposing factors which would be an indication for or contraindication to the drug under investigation. For example, in studying the relationship between oral contraceptives and venous thromboembolism, subjects with recurrent thromboembolism should be excluded (or considered separately) since a previous episode of the disease would now contraindi-

cate the use of the pill (though this was not so before the relationship was established).

*Illness relevance.* The cases included should have some reasonable possibility of having been induced by the drug of concern. For example, cases of thromboembolism occurring during pregnancy or immediately post-partum should be excluded from a study of the pill and thromboembolism since such cases could not possibly be pill induced. Similarly, post-operative thromboembolism should be considered separately from "idiopathic" disease since surgery is a sufficient cause for the event, and the presence of oral contraceptive use may not play the same role in the etiology of post-operative disease. Inclusion of cases which do not relate to a reasonable hypothesis will, of course, dilute any association which may be present.

*Selection bias.* Finally, it is important to be aware of possible selection biases among diagnosed cases. Such biases are of particular concern when the hypothesis being tested has previously been entertained. In these circumstances, a history of drug use may tend to increase suspicion of, or hospitalization for, an illness. For example, in regard to the pill and thromboembolism, any interpretation of the results of a current study should take into account the possibility that the illness may be selectively diagnosed (with subsequent hospitalization) in pill users as a result of a high index of suspicion in the physician. The extent of the bias introduced in such instances is usually difficult

to estimate and the degree of influence on the results may be a matter of conjecture. As in all other areas of concern, the specific details of each particular study must

the details of each particular study must be examined to determine what evidence there is for or against the influence of this bias.

A great deal of emphasis has been placed by some authors on the need to study a "representative" sample of cases (10). This emphasis is misplaced. Indeed, if by "representative" it is meant that a random sample of all prevalent cases should be selected, this "representativeness" is likely to introduce substantial distortion. For example, in studying the relation between oral contraceptives and venous thromboembolism, a "representative" group of cases might be considered to include women with recurrent thromboembolism (10), and those who developed the illness while pregnant or after the menopause. In fact, as indicated above, such women should expressly be excluded from the study.

Furthermore, a valid study may be carried out in a highly "selected" group of people. For example, a study of the relationship of oral contraceptives and benign liver tumors could be restricted to cases occurring in nurses. The control group would most likely have to consist of nurses as well, since this occupational group may have distinctive contraceptive habits. Furthermore, the results would, strictly speaking, apply only to nurses. Nevertheless, the results themselves would be valid, if confounding were adequately controlled, despite the highly selected nature of the case and control series.

#### *Selection of the controls*

The series of control subjects should be chosen in such a way that when a proper analysis is made, i.e., statistical adjustment is made for confounding factors, they are comparable with the cases in all rele-

vant ways, except that they do not have the illness under study. When this is

achieved, the controls are as likely to be users of the drug being studied as the cases (assuming that no association exists). To achieve comparability, subjects who are identified by a condition which is known to be associated with the drug under study should be excluded from the control series. Thus, when the control series consists of hospitalized patients, the following exclusions are mandatory:

- 1) Patients *admitted* for conditions which are an indication for or contraindication to the drug of interest. For example, in studying the relationship of aspirin to a particular illness such as acute myocardial infarction, it would be necessary to exclude from the control series patients *admitted* to hospital because of chronic arthritis (who would be likely to have excessive aspirin use) and those *admitted* because of chronic peptic ulcer disease (who would be likely to have decreased aspirin use).

- 2) Patients *admitted* for conditions which are caused or prevented by the drug under study. For example, in studying the relationship between oral contraceptives and breast disease, it would be necessary to exclude from the control series women admitted to hospital for thromboembolic disease (who would be likely to have excessive pill use) and those admitted for ovarian cyst (who would be likely to have decreased pill use).

The probability of being admitted to hospital for a given illness tends to depend on whether the condition requires mandatory hospitalization (e.g., acute myocardial infarction, severe trauma) or whether the condition is such that hospitalization is elective (e.g., hernia repair). The nature of the particular illness under study in terms of these two categories ideally calls

terms of these two categories ideally calls for a control series which falls into the same category, since the likelihood of hospitalization and the likelihood of having had a drug prescribed may be correlated. In practice, this potential bias may not be of much importance. In a very large series

of hospitalized patients, the age-sex standardized rates of regular drug use were closely similar in patients with mandatory admissions in comparison with those with elective admissions (13).

The decision as to the source of the control series is generally influenced by practical considerations. Where a case series is derived from a large defined group (such as a group health plan), the control series may easily and efficiently be drawn from that group (14). When such a defined population is not available, hospital controls are generally most convenient to study. When hospital controls are used, they should be drawn from a variety of diagnostic groups so as to minimize the impact of inadvertently including an admitting illness which (unknown to the investigator) is associated either positively or negatively with the drug under study. Exposure rates for each of the control illnesses should be calculated. If the different categories are, in fact, unassociated with the exposure, the exposure rates, appropriately standardized, should be similar. "Community controls," despite their popularity, generally confer little advantage and may have considerable disadvantage in case-control studies on drug-induced illness since it is frequently difficult to obtain information from cases and controls in a comparable manner. Other factors influencing comparability may be present and, therefore, when community controls are used, they should be chosen so as to optimize the probability that they will be comparable to cases in terms of the likelihood of being hospitalized, the likelihood of being a drug user, and the likelihood of encompassing the range of confounding factors.