Confounding by indication is a commonly used term that refers to an extraneous determinant of the outcome parameter that is present if a perceived high risk or poor prognosis is an indication for intervention (1). The indication is a confounder because it correlates with the intervention and is a risk indicator for the illness. Thus, it produces an imbalance in prognostic factors between compared treatment groups. For example, in a study of the association of L-tryptophan with eosinophilia-myalgia syndrome, confounding by indication may occur because L-tryptophan is indicated to treat insomnia and depression, two disorders commonly associated with myalgias, particularly eosinophilia-myalgia syndrome (2). However, confounding by indication also is often used to emphasize the confounding role of disease severity or prognosis and the drugs consequently used to treat the disease. Furthermore, confounding by indication sometimes is used interchangeably with selection bias. The theoretical definition of confounding by indication is straightforward. However, in daily epidemiologic practice, the term is not always used consistently. Apart from the strict interpretation, we found three different situations in which the term has been applied or where it might have been used but was not: confounding by indication as protopathic bias, as confounding by severity, or as a form of selection bias. Protopathic bias and selection bias should not be confused with these terms. The use of appropriate terms ultimately will improve communication among researchers and contribute to the clarity of their papers. Am J Epidemiol 1999;149:981–3.

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the exposure and the disease (3). The implication is that confounding by indication should refer to those situations in which the indication for treatment acts as a confounder. Here, the indication should be a disease per se and not its prognosis or the severity of its manifestation. For example, when the association between antidepressant drugs and an increased risk of infarction is studied, the indication depression is considered the potential confounder (4). Sometimes, confounding by indication may occur as part of a diagnostic procedure. An example is the association between thyroid nodularity and a history of administration of iodine-131, as the underlying thyroid indication for this diagnostic procedure might be an independent risk factor for nodularity (5).

Confounding by indication is sometimes confused with protopathic bias (6). The latter term is used if the first symptoms of the outcome of interest are the reasons for use of treatment (7). For instance, a drug given for abdominal pain may be associated erroneously with hepatic injury, as abdominal pain may be one of the prodromal symptoms. In such a situation, use of the term confounding by indication is incorrect. Protopathic bias has been suggested in the association between aspirin use and Reye's syndrome and could occur if aspirin is prescribed preferentially to children who have a particular cluster of prodromal symptoms that precedes Reye's syndrome (8). Sometimes it may be difficult to distinguish protopathic bias from confounding by indication. For instance, in the demonstrated association between the use of cimetidine and subsequent gastric carcinoma (9), both issues may play a role.

Confounding by indication as confounding by severity

Confounding by severity is considered a type of confounding by indication (10), in which not only the disease that forms the indication but also its severity is the potential confounder. If one controls for the disease but not for its severity, the possibility of residual confounding remains. Here, the stage of the disease and its corresponding severity and complications are important. For example, when studying the mortality rate of patients who have rheumatoid arthritis that is being treated with gold salts, one should be aware of the stage of the disease at baseline. Gold salts are indicated to delay the evolution of rheumatoid arthritis, but patients who have an advanced stage of the disease will have the worst prognoses and will be treated preferentially with these drugs (11). Other examples pertain to recent discussions concerning the associations between use of diuretics and sudden death of hypertensive patients (12–15) and between use of fenoterol and mortality from asthma (10, 16–18). In the debate regarding asthma, some authors have suggested that the findings could be explained by confounding by severity if patients for whom fenoterol was prescribed for severe asthma have a higher risk of death (16, 17).

Some authors have applied the terms confounding by prognosis or confounding by comorbidity to describe vigorous treatment of patients who have a poor prognosis as a manifestation of physicians' perceptions of the prognosis (18). Although this situation may be regarded as identical to confounding by severity, there is a subtle difference; the physician's perception of the patient's prognosis, rather than the actual severity of the disease, acts as the confounder.

Confounding by indication as a form of selection bias

Selection bias is defined as a distorted estimate of the effect that results from the way in which subjects are ascertained or selected for the study population and includes factors such as differential surveillance, diagnosis, and referral of persons into the study (19). Some authors use selection bias interchangeably with confounding by indication. For example, regarding the relation between cimetidine and lung cancer, some authors have reported that a spurious relation is observed because lung cancer patients have a higher frequency of peptic ulcer and may be subject to selection bias because they have a higher probability of participating in the study (9). In this instance, confounding may be present because both peptic ulcer and lung cancer have been associated with smoking. Hence, if cimetidine is prescribed, a spurious association with lung cancer might occur. In a strict sense this is not confounding by indication, as peptic ulcer itself is not considered an independent risk factor for lung cancer. Another example concerns the association between an increased risk of falls and use of benzodiazepine hypnotics. Both medication use and fall rates increase with advancing age. The increased risk of falls associated with drug use is most marked for psychoactive agents such as benzodiazepines. The most frail patients also receive the largest drug burden (20), which is the result of selection bias rather than confounding by indication; insomnia is not necessarily an independent risk factor for falling, although it may be related indirectly. Similarly, the associations between acetaminophen use and chronic renal failure (21) and between lindane and cancer (22) consist of selection and indirect associations with the outcomes of interest but are not confounding by indication.

Discussion

There is variation in how the term confounding by indication is interpreted. This paper has presented
some of these interpretations, often as part of other types of confounding bias and sometimes as part of selection bias. Although confounding by severity should be considered a special form of confounding by indication, there may be two reasons for distinguishing both types of confounding when dealing with epidemiologic issues. First, controlling for disease as the indication for treatment does not exclude the possibility of residual confounding by severity. This issue played a role in discussions of the associations between myocardial infarction and calcium antagonists (23) and between fenoterol and mortality from asthma (16, 17). The subtlety of such a discussion would be lost if confounding by severity were completely covered by the term confounding by indication. Second, in the product information of registered medicines, the indications for treatment pertain to diagnoses per se rather than to the severity of the manifestation of their clinical pattern. Hence, when drug treatments are compared, controlling for these indications does not preclude confounding by severity. It may be helpful to limit use of the term confounding by indication to the situation in which the disease itself acts as a confounder irrespective of its severity and to apply the term confounding by severity if the severity of this disease acts as a confounder. Protopathic bias and selection bias should not be confused with these terms. The use of appropriate terms ultimately will improve communication among researchers and contribute to the clarity of their papers.

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