BASIC PROBLEMS IN EVALUATING THE RELATIONSHIP BETWEEN STRESS AND DISEASE BY EPIDEMIOLOGIC STUDIES

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ABSTRACT

There is an increasing interest in the possible role of psychosocial environment or life stress as an etiological factor of chronic diseases. When the relationship between psychological stress and a disease is to be studied in human populations, epidemiologic methods are most suitable. A case-control study is one of the most useful methods for such studies. However, the study might lead to a false conclusion, unless confounding variables are taken into consideration. In this paper, the natural history of an ill person who visits a medical facility with a disease caused by stress from psychosocial environment was discussed and two confounding variables were successfully identified, which might cause spurious association between stress and disease when a case-control study was conducted using these hospital patients. First, susceptibility to psychological stress might cause a spurious association if the difference in the psychological process of seeking-medical-aid behavior between cases and controls was not taken into consideration. Second, the study also leads to a false conclusion when psychological stress plays a role not in the biological process of the disease but in the psychological process of the diseased people, through which they decide to seek medical care. For these reasons, patients selected from the general population through health examinations are preferable to hospital patients. If the hospital patients are the only available source for the study, controls should be selected with great care so as to avoid such spurious associations.

INTRODUCTION

Psychosocial environment or life stress have been demonstrated in recent years to be one of the important etiological factors of some chronic diseases.1,2

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For example, the incidence of coronary heart disease was found through several studies to be related to the specific behavior pattern called "type A".\(^3,4\) The effect of stress on health is also becoming one of the most important problems in occupational medicine.\(^5,6\)

An epidemiologic study seems indispensable in studying the natural history of a disease in human populations. However, some methodological problems still remain unresolved when the effect of psychological stress on the disease process is studied. A case-control study is one of the most useful methods for such investigations. In a case-control study, the magnitude of stress of the patients concerned, measured by some method such as questionnaires, is compared with that of controls properly selected. However, even if a positive association between stress and disease is seen in such a case-control study, the interpretation of the results should be made very carefully, especially as to whether the observed association is a causal one or not. The observed association might be a spurious one if some variables act as confounders.

The author had an opportunity to study female clerical workers who visited the orthopedic outpatient clinic in their company with various symptoms of cervico-brachial regions.\(^7\) The study revealed that the personality distributed differently among the patients who complained of the symptoms of truncal regions, when compared with the patients who complained of the symptoms of peripheral regions. This finding suggested that the personality or psychological stress played a role in the natural history of these patients, but there remained some difficulties when the results were interpreted. The psychological stress might be the cause of their symptoms, but it could not be denied that the stress played a role in the psychological process through which they decided to seek medical care.

Since psychological stress might play a role in several different steps in the clinical course of an ill person as indicated through this example, it seems necessary to look into the natural history of an ill person, in order to avoid possible confounding effects. In this report, basic problems in evaluating the relationship between stress and disease by case-control studies are discussed. First, the natural history of an ill person who visits a medical facility with a disease caused by stress from psychosocial environment is studied with special interest in the behavioral aspect of the ill person. Then the case-control method is examined in order to avoid spurious associations which might be brought about when the relationship between psychosocial environment and disease is in question.

**NATURAL HISTORY OF AN ILL PERSON WITH A DISEASE CAUSED BY STRESS**

In order to develop a proper method for a case-control study on stress and
disease, it is necessary to examine not only the biological process of the disease but also the psychological process of the diseased person. Fig. 1 shows schematically a model for the natural history of an ill person who visits a medical facility with a disease caused by stress from psychosocial environment. The whole clinical course of the ill person can be divided into two different steps.

The first step can be called the biological or physiological process. In this process, excessive exposure to psychological stress causes a physiological reaction in the body and this reaction in turn gives rise to irreversible changes in tissue or a functional disturbance of the biological system, which is recognized as disease. According to the cognitive model of stress proposed by R. S. Lazarus, a stress reaction follows only when an individual “appraises” his current situation as stressful. Therefore, cognitive process cannot be ignored when the effect of psychological stress on health is studied. This fact is shown schematically in the left side of Fig. 1 ((A)-(B)-(C)).

The second step can be called the behavioral or psychological process. An ill person does not necessarily visit a medical facility even if a disease is developing in his body. Before he seeks medical aid, he should perceive a change in his body through his symptoms and appraises his current situation as stressful ((C)-(D)-(E) in Fig. 1). In both the physiological and psychological processes, stress cannot be defined exclusively by situations because the capacity of any situation to produce stress reactions depends on the characteristics of individuals. The stress might be appraised quite differently according to the individual susceptibility to psychological stress even if they are exposed to the same amount of psychological stress in similar situations ((X)-(B) and (X)-(D) in Fig. 1).

In 1962, D. Mechanic proposed a concept of illness behavior, suggesting that
the behavioral aspects of an ill person should be taken into consideration when psychosocial factors were studied in relation to a disease. The study might possibly lead to a false conclusion because the psychological stress under study is often the factor which brought the patient to the doctor, not the factor which brought on the disease. In fact, several studies have demonstrated that the psychological distress plays an important role when an ill person decided to seek medical care. This is shown as direct link of (A) with (D) in Fig. 1. This relationship is discussed in detail later.

In Fig. 2, the psychological process of seeking-medical-aid behavior is reviewed in more detail. In order to understand the relationship between stress and seeking-medical-aid behavior, it is necessary to identify the factors which might affect this relationship. As the cause of stress, symptoms seem to be most important. They can be the source of both physical and psychological stress. Here, the term ‘physical stress’ is used to represent the stress which is caused by symptoms themselves but does not include the psychological effect of symptoms. When ill people visit medical facilities, most of them do suffer from some symptoms. In some cases, they would say to the doctors that they have come to them because they cannot endure their symptoms. In these cases, the predominant stress affecting them is physical and the strength of stress might be influenced by several features of symptoms: the intensity and duration would be important, to say nothing of the nature of symptoms such as pain, dullness, and malaise. Symptoms can also be the cause of psychological stress by making a person believe that he might have a serious disease. In this

![Fig. 2 A model for the psychological process of an ill person when he decides to seek medical aid.](image-url)
case, the strength of psychological stress should be affected by whether the person has the correct knowledge of the disease or not ((II)-(IV)). The psychosocial environment of ill people can be considered as another major cause of psychological stress ((III)-(VI)). This is the same with the direct link of (A) with (D) in Fig. 1. For example, when a person suffers from interpersonal difficulties, it might urge a person to seek medical care, as some preceding studies have pointed out.9-12 If the ill person continues to be troubled with symptoms, the physical stress could also strengthen the psychological stress directly ((V)-(VI)).

According to this model, the psychological process of an ill person can be classified into three forms: (1) the case in which physical stress plays a predominant role, (2) the case in which both physical and psychological stress play a significant role and (3) the case in which psychological stress plays a predominant role.

Physical stress would play a predominant role when a person is bothered by rapidly developing symptoms, but does not feel anxious about serious diseases ((I)-(V)-(VIII)-(IX) in Fig. 2). This will occur, for example, when he suffers from an acute inflammation of the wrist caused by excessive use of his hand for writing.

Both physical and psychological stress might play a significant role in several instances in which the ill person appraises his situation as both physically and psychologically stressful. Symptoms such as abdominal pain can be the cause of both physical and psychological stress because such symptoms act as physical stress ((I)-(V) in Fig. 2) and at the same time as psychological stress by suggesting that he might be affected by a serious disease ((I)-(IV)-(VI) in Fig. 2). When the ill person suffers from the symptoms which last for a considerable period, psychological stress can be generated by the effect of physical stress itself ((V)-(VI) in Fig. 2).

Psychological stress would play a predominant role when the psychological stress exists in advance in ill people. This might occur when the ill person has been tortured with psychological stress caused by social situations such as interpersonal difficulties ((III)-(VI) in Fig. 2) or when he is affected by the fear of a disease ((II)-(IV)-(VI) in Fig. 2). When psychological stress plays an important part in the process, susceptibility to the psychological stress cannot be ignored. Those with higher susceptibility to psychological stress tend to evaluate their situations as more stressful than those with lower susceptibility ((VII)-(VIII) in Fig. 2) and are more likely to seek medical care.
CONFOUNDERS IN CASE-CONTROL STUDIES

When a case-control study is designed to investigate the relationship between stress and disease, the case group as well as the control group is often sampled from those who visited outpatient clinics. The hypothesis to be tested is the relationship shown in Fig. 1 as the direct link of (A) with (C) through (B). However, statistically significant association might be detected through the study although there is no direct relationship between psychosocial environment and the disease. There are two possible situations which might cause a spurious association in a case-control study.

First, it will occur when the case group as a whole is more susceptible to psychological stress than the control group. In this situation, the result of the questionnaire will probably show that cases suffer from stronger psychological stress than controls, even though, in fact, the case group is exposed to almost the same level of psychological stress as the control group. This difference in the susceptibility to psychological stress can be caused by the difference in the psychological process of seeking-medical-aid behavior between cases and controls. The following example is useful to understand this situation:

Example

A case-control study was designed to test the hypothesis that psychological stress was related to an outbreak of a gastric ulcer. To test this hypothesis, the magnitude of psychological stress, measured by a questionnaire, of patients who visited outpatient clinics and were diagnosed as having a gastric ulcer (cases) was compared with that of patients who visited the same outpatient clinics and were diagnosed as acute cholecystitis (controls). The result of the questionnaires successfully showed that the patients with gastric ulcers suffered from stronger psychological stress than the patients with acute cholecystitis.

In this example, the sampling of gastric ulcer cases is biased by the patients’ seeking-medical-aid behavior and those with higher susceptibility to psychological stress tend to be sampled in the case group compared with the control group. This might occur since the symptoms of acute cholecystitis would develop in a different manner from those of a gastric ulcer. In the instance of a gastric ulcer, symptoms tend to develop gradually over a long period, which can be the cause of both physical and psychological stress, whereas the symptoms usually develop more rapidly in the case of cholecystitis, where physical stress plays a greater part when the patients decide to seek medical aid. In this example, the patients with gastric ulcers would be more susceptible to psychological stress than the patients with acute cholecystitis and the result of the questionnaire would de-
monstrate that gastric ulcer cases suffer from more severe psychological stress than controls even if the case group was exposed to almost the same level of psychological stress as the control group. This fact is shown in Fig. 1 as the link of (A) with (C) through the (A)-(B)-(X)-(D)-(C) pathway.

Another situation which might cause a spurious association can be seen when the psychosocial situation of the case group is different from that of the control group. For example, this might occur when the cases are sampled from office workers whereas the controls are sampled from the general population. Office workers might suffer from more severe psychological stress when compared with the general population because their social and interpersonal situations are more specific. In this situation, the result of the case-control study will possibly show that the case group suffers from more severe psychological stress although stress is not directly related to the disease process. This fact is demonstrated in Fig. 1 as the link of (A) with (C) through the (A)-(D)-(C) pathway.

PLANNING OF A CASE-CONTROL STUDY

Through these considerations, two confounding variables were successfully identified: susceptibility to psychological stress and psychological stress as a motive for seeking-medical-aid behavior. The result of the case-control study would be seriously biased unless these variables are taken into consideration. The following discussion is aimed to propose the proper method for the selection of cases and controls, which can avoid these confounders.

Ideally, cases should be selected from a source of patients who were detected by chance through some opportunity such as health examinations. Controls should also be selected by a random sampling method from the general population. If these sampling methods are possible, no systematic difference in the susceptibility to psychological stress would be seen between cases and controls and the confounding effect could be avoided.

If hospital patients are the only available source for the study, efforts should be made to standardize the psychological process of seeking-medical-aid behavior between cases and controls. According to Fig. 2, there are three factors which might affect this process: (I) the effect of symptoms, (II) correct or incorrect knowledge of disease, and (III) the psychosocial environment of cases and controls. The control group should not be sampled from the general population if the case group is sampled from hospital patients. The case group will be more susceptible to psychological stress because cases are likely to be affected by psychological process through which they decide to seek medical care. The nature of symptoms should also be taken into consideration. Controls should be selected
from those patients who suffer from similar symptoms in nature, of similar intensity which occur in similar regions and last for similar durations, when compared with the case group ((I)-(V)-(VI) and (I)-(IV)-(VI) in Fig. 2). If possible, cases and controls should be selected before they know the diagnoses so as to avoid the effect of correct or incorrect knowledge of diseases ((II) in Fig. 2). The social environment of controls should also be made equal with cases ((III) in Fig. 1). If possible, the difference in the susceptibility to psychological stress between cases and controls should be checked by a psychological test ((VII) in Fig. 2). Personality can be characterized by several different viewpoints, and the author's previous study on the relationship between the patients' personality and the nature of symptoms of cervico-brachial regions indicated that social adaptability and emotional stability played an important part. It is also noteworthy if a difference in personality between cases and controls is detected in case-control studies. In such instances, we might be able to guess that psychological stress should play a role in the psychological process of the diseased person.

CONCLUSION

Through the theoretical consideration of the natural history of an ill person who visits a medical facility with a disease caused by stress from psychosocial environment, two confounding variables were successfully identified: susceptibility to psychological stress and psychological stress as a motive for seeking-medical-aid behavior. A case-control study might lead to a false conclusion, unless these confounding variables are taken into consideration. In order to avoid the effect of these confounders, the following guidelines seem to be useful:

(1) Hospital patients should be avoided if possible.
(2) If hospital cases are the only available source of the study, controls should also be selected from hospital patients who are suffering from similar symptoms in similar regions for similar durations compared with the cases.
(3) If possible, cases and controls should be sampled before they are informed of their diagnoses.

REFERENCES

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