SELF-SELECTION—A MAJOR PROBLEM IN OBSERVATIONAL STUDIES

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1. Introduction

I am pleased to have been asked to participate in the Sixth Berkeley Symposium on Mathematical Statistics. It provides an opportunity for an exchange of information and ideas on some methodologic problems encountered in observational studies of etiologic factors in chronic diseases. These problems present different aspects than those ordinarily involved in experimental studies usually encountered in statistical investigations. In the latter, especially in those on inferences derived from comparisons of two samples, there is a tacit assumption that the samples have been equalized usually through a procedure of randomization.

In studies on human beings, experimentations are difficult, if not impossible. In attempts to determine the roles of environmental factors in development of disease, one must depend on observation of phenomena as they occur in nature. Often factors such as emotional stress, physical conditions, certain components in the diet, cigarette smoking, sedentary occupations, and other characteristics require prolonged periods of observation between the exposure to the environmental factor and the development of disease. In many cases the period is measured in years and sometimes decades. Consequently, a manipulative study would involve major changes in modes of life of large groups of people over prolonged periods of time. Such experimentations are impractical, if not impossible. Of necessity, therefore, the main methods are those of observations of associations between prevalence of a given disease or condition and environmental factors as they occur in nature without interference on the part of the investigator.

The most elementary and least desirable of these observational studies are the so-called “indirect studies.” In these, the unit of investigation is the group rather than the individual. Often mortality or morbidity data derived from vital statistics are compared with indices of suspected environmental characteristics. Such studies are useful to provide leads for further investigations. They have,

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however, great weaknesses in that the groups differ along many other characteristics in addition to the variables of discourse.

More desirable are studies which focus on the individual. These are mainly of two types: retrospective and prospective. The former start with a group of individuals, each of whom experienced a certain disease or condition and a selected group of controls, matched on a number of pertinent characteristics. The two groups are then compared for a number of variables. The prospective study starts with the selection of a sample of the population in which individuals are identified as those possessing and those not possessing the suspected environmental variable. The two groups are followed for a length of time sufficient to detect differences in incidences of the disease or condition.

It is clear that these methods are also not free from the major difficulty of lack of group comparability since the groups have been self-selected. They therefore do not satisfy the basic rule for valid scientific inference—that, \textit{a priori}, groups being compared be alike in all pertinent characteristics. Unfortunately, the inherent weaknesses of the methods are often escalated by deficiencies and carelessness in study design.

Before proceeding to discuss the major problem of self-selection, it is desirable to illustrate some of the more simple pitfalls in investigations of etiologic factors in chronic diseases. These errors are relatively simple and should not have to be mentioned. They are, however, important because of the frequency with which they are encountered in the literature. Examples are the recent studies which attempt to correlate radiation effects with the infant mortality rates [1], [2]. These suffer not only from noncomparabilities of the groups, but the method employed has the additional weakness that the comparisons are made not with current and past trend of the infant mortality rates, but with hypothetical rates derived from extrapolation of current and past rates into the future; a procedure based on the speculative assumption that if it were not for the radiation effect the past trend would continue into the future with the absurd consequence that a zero rate would have been reached.

Another important error often encountered in the literature is the fallacy of utilizing evidence supporting a given hypothesis and neglecting evidence contradicting it. An illustration is shown in Figure 1. In this case, the investigator selected six countries and correlated the per cent of fat in the diet with the mortality of coronary heart disease in these six countries [3]. On the face of it, the correlation appears very striking and indeed the author in reviewing the data in Figure 1 makes the following strong statement: "The analysis of international vital statistics shows a striking feature when the national food consumption statistics are studied in parallel. Then it appears that for men aged 40 to 60 or 70, that is, at the ages when the fatal result of atherosclerosis are most prominent, there is a remarkable relationship between the death rate from degenerative heart disease and the proportion of fat calories in the national diet. A regular progression exists from Japan through Italy, Sweden, England and Wales, Canada, and Australia to the United States. No other variable in the

The question arises how were these six countries selected. Further investigation reveals that these six countries are not representative of all countries for which the data are available. For example, it is easy enough to select six other countries which differ greatly in their dietary fat consumptions, but have nearly equal death rates from coronary heart disease (Figure 2). Similarly, six other countries were easily selected which consumed nearly equal proportions of dietary fat, but which differed widely in their death rates from coronary heart disease (Figure 3). This tendency of selecting evidence biased for a favorable hypothesis is very common. For example, investigations among the Bantu in Africa are often mentioned in support of the dietary fat hypothesis of coronary
Six countries selected for equality in mortality from coronary heart disease, but differing greatly in consumption of fat calories in per cent of total calories.

heart disease, while observations on other African tribes, Eskimos, and other groups which do not support the hypothesis are generally ignored.

However, even when these errors are avoided and the studies are well conducted, the conclusions which may be derived from observational studies have great limitations stemming primarily from noncomparability of the self-formed groups. The phenomenon of self-selection is the root of many of the difficulties. Were all other complications eliminated, the inequalities between groups which result from self-selection would still leave in doubt inferences on causality. For example, in the study of the relationship of cigarette smoking to health, if we assume well conducted investigations in which (a) large random samples of the population have been selected and the individuals correctly identified as smokers, nonsmokers, or past smokers, (b) the problem of nonresponse did not exist, (c) the population had been followed long enough to identify all cases of the disease in question, (d) no problems of misdiagnosis and misclassification existed, (e) and no one in the population had been lost from observation, then even under these ideal conditions, the inferences that may be drawn from
Six countries selected for equality in consumption of fat calories in per cent of total calories, but differing greatly in mortality from coronary heart disease.

the study are limited because the individuals being observed, rather than the investigator, made for themselves the crucial choice: smoker, nonsmoker, or past smoker.

Faced with these difficulties, it becomes necessary to develop auxiliary and supplementary methods of study which would help overcome their built-in limitations, and increase the probability of arriving at correct conclusions. This, unfortunately, has so far not been seriously tackled. To date, epidemiologists and statisticians have not responded fully to this challenge. We have made only a meager beginning in refining the tools and redefining the standards that would aid the process of inferring causation from observed associations.

A helpful first step is to determine whether the observed association is specific to the disease under study. For it is intuitively recognized that if the association is specific there is a greater likelihood of an etiologic relationship than when it is not. An association which is nonspecific, diffuse, manifesting itself in a large and varied number of diseases, increases the probability that the observed differences may be due to extraneous factors which differentiate the self-formed subgroups.
Another important activity in evaluating the significance of observed associations is to investigate whether the findings fit with other known phenomena. For, again, it is intuitively apparent that if the observed association contradicts other aspects of an overall phenomenon, doubts are raised concerning the causation hypothesis, and it becomes necessary to dig and explore further in an attempt to derive at a more reasonable evaluation of the meaning of the observed association.

In the following, I will attempt to demonstrate the usefulness of exploring additional leads in order to arrive at a sharper judgment and evaluation of whether an observed association may be interpreted as indicating a cause and effect relationship. I will use for this exercise two recent studies on the association of cigarette smoking and premature birth [4], [5].

2. Cigarette smoking during pregnancy and "premature birth"

A large number of investigators have demonstrated that women who smoke cigarettes during pregnancy have a larger proportion of "premature births," than women who do not smoke [5]–[37]. Prematurity in this case is defined by the birth weight criterion and refers to low birth weight infants (weighing 2,500 grams or less). In our Child Health and Development Studies, we also investigated this problem in 1964 and found the same phenomenon. Women who smoked cigarettes have nearly twice as many low birth weight infants as women who do not smoke. An increase in low birth weight infants has very serious implications, for the neonatal mortality rate (the risk of dying in the first month of life) is more than 20 times higher than the neonatal mortality rate of heavier infants [38]. The expectation is, therefore, that the perinatal mortality rate should be considerably higher for infants of smoking than for those of nonsmoking mothers. (The perinatal mortality rate is the number of stillborn infants of at least 28 weeks gestation and liveborn infants who died within seven days after birth per 1,000 total births.) However, we found that the mortality rate was nearly identical for infants of smokers and nonsmokers. Thus, the findings from this observational study did not fit with other known phenomena.

The next step therefore was to consider the mortality of the low birth weight infants. The surprising finding was that the neonatal mortality rate of low birth weight infants of smoking mothers was substantially and significantly lower than that of low birth weight infants of nonsmoking mothers. Our findings were later corroborated by several other investigators [35], [36].

To date, there are some 33 studies on the subject. Fifteen of these did not investigate mortality [6]–[20], fourteen others were based on relatively small samples of approximately 2,000 births. Of these, seven found no increase in mortality [21]–[27], and seven found some increase [28]–[34]. But even the increase in most of the latter were of relatively small magnitude. Moreover, it can be shown that if the perinatal mortality rate of infants of smoking mothers is indeed greater by 35 per cent than that of nonsmoking mothers, (the figure 35 per cent
was selected because such an increase is to be expected from a doubling of the incidence of low birth weight infants) then the probability that seven of fourteen such studies should fail to detect such increases is very small \( (p < 0.005) \). More important is the fact that there are several studies based on large samples. In addition to our 1964 studies, which we recently enlarged [5], there appeared three other studies based on relatively large samples (Table I) [35]–[37]. The

**Table I**

**Perinatal Mortality Among All Infants and Among Low Birth Weight Infants by Mother's Smoking Status in Five Large Studies**

Numbers 1 and 5 refer to neonatal mortality only.

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Number of births</th>
<th>Perinatal mortality per 1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonsmoker</td>
</tr>
<tr>
<td>1. Yerushalmy 1964</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>5,381</td>
<td>12.4</td>
</tr>
<tr>
<td>Black</td>
<td>1,419</td>
<td>23.4</td>
</tr>
<tr>
<td>2. Underwood, et al.</td>
<td>48,505</td>
<td>19.7</td>
</tr>
<tr>
<td>3. Rantakallio 1969</td>
<td>11,931</td>
<td>23.2</td>
</tr>
<tr>
<td>4. Butler, et al.</td>
<td>16,994</td>
<td>32.4</td>
</tr>
<tr>
<td>5. Yerushalmy 1971</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>9,793</td>
<td>11.0</td>
</tr>
<tr>
<td>Black</td>
<td>3,290</td>
<td>17.1</td>
</tr>
</tbody>
</table>

study by Underwood is based on 48,000 births, by Rantakallio on 12,000 and by Butler on some 17,000 births. Butler's study was retrospective, the others were prospective. Only Butler's study showed an increase in perinatal mortality. The others did not. It is of great interest that the large prospective studies confirmed our interesting findings that the perinatal mortality rate of low birth weight infants of smokers was substantially and significantly lower than that of infants of nonsmoking mothers.

In addition, in an extensive study on etiological factors in prematurity, Jansson [27] considered also the question of smoking. He states: "Recently Yerushalmy (1964) in an extensive prospective study found the same relationship, but he was unable to confirm a higher perinatal mortality in infants of smoking mothers. On the contrary he made the surprising observation that in single live births, which fulfilled both criteria of prematurity, i.e. birthweight 2,500 g or less and gestational age less than 37 weeks, the neonatal mortality was significantly lower in infants of smoking than of nonsmoking mothers. Yerushalmy could not explain the apparently higher survival rate for those prematures whose mothers were smoking during pregnancy.

"In our series we made observations of a similar kind. If the malformed infants are not included, the perinatal mortality in premature infants of nonsmoking mothers was 29 per cent, while the corresponding figure for infants of smoking mothers was 8 per cent. . . ."
"Another observation in our series was that the number of smoking mothers of premature infants was higher in social class III than in classes I and II. It is a well established fact that premature birth is considerably more common in the lower social classes. Thus, the relationship of smoking to prematurity may be indirect. As Yerushalmy points out, it may be the smoker, not the smoking in itself, which offers an explanation of the differences observed."

It is thus abundantly clear that we are presented with phenomena which do not fit and contradict each other. The proportion of low birth weight infants born to smoking mothers is much higher than that of infants of nonsmokers, but the perinatal mortality of infants of smokers is not higher. Especially surprising is the fact that low birth weight infants of smokers have substantially lower perinatal mortality rates than infants of nonsmoking mothers. Other paradoxical phenomena were noted in our more detailed study. A number of variables such as parity, age of mother, length of pregnancy, and other factors were investigated and none of them could offer a reasonable explanation for the paradoxical findings [5].

It was next necessary to investigate differences between smokers and nonsmokers. A number of investigators demonstrated great differences in smokers and nonsmokers in many characteristics. For example, smokers were found to be significantly different from nonsmokers in morphologic dimensions and proportions [39]. Smokers were found to be more neurotic and changed jobs and spouses more often than nonsmokers [40]-[43]. When we investigated and compared our smokers and nonsmokers, we found striking differences in mode of life characteristics between the two groups. Smokers were less likely to use contraceptive methods than nonsmokers. They were less likely to plan the pregnancy. They were more likely to drink hard liquor, beer, and coffee, while nonsmokers were more likely to drink tea, milk, and wine. The smoker was more likely to indulge in these habits to a greater extreme than the nonsmoker. We also found some differences in biologic characteristics. For example, the age of menarche was significantly lower for women who subsequently became smokers than for nonsmokers. These differences bring into sharp focus the fact that inferences concerning etiology from observational studies are derived from comparison of groups which violate the principle of group comparability.

These findings raised doubts and argued against the proposition that cigarette smoking acts as an exogenous factor which interferes with the intrauterine growth and development of the fetus. It appears that these findings give support also to the hypothesis that smokers may represent a group of people whose reproductive experience would have duplicated the observed pattern whether or not they smoked. Smoking may be considered an index which characterizes the smoker, but smoking per se is only incidental as a causal factor in the observed phenomena. The difference in incidence of low birth weight may be due to the smoker not the smoking.

We explored this suggestion in two ways, one indirectly, namely, we investigated whether it would be possible to duplicate some of the findings between
smokers and nonsmokers in groups of women who were differentiated along a selected biologic characteristic. The height variable was selected because it is known that infants of short women are, on the average, smaller than those of tall women. We found that short and tall women showed differences in incidence and mortality of low birth weight infants very similar to those of smoking and nonsmoking women. Thus, short women have higher proportion of low birth weight infants, but these low birth weight infants of short women had lower neonatal mortality rates than low birth weight infants of tall women (Figure 4).

In a recent paper [44], we investigated this problem more directly. In our Child Health and Development Studies, we obtained detailed information about the women's previous births, including the birth weight. Much later in the interview, we obtained from the woman a history of her smoking habits, including the age at which she started to smoke. We tested the reliability of the answers to these questions and found that they were reliable and not biased one by the other. From this information, we were able to divide the women into four groups: (1) women who never smoked, (2) women all of whose previous children were born under smoking conditions, (3) women who subsequently became smokers but who produced infants during the period before they acquired the smoking habit, and (4) women who quit smoking but who produced liveborn infants before they quit. It is therefore possible to investigate the reproductive performance of the women in group 3 during their nonsmoking periods and women in group 4 during periods of smoking.

If it is the smoking that causes the increase in low birth weight, then women in group 3 should have had relatively few infants of low birth weight during the period before they started to smoke. On the other hand, if it is the smoker not the smoking, then we would expect that women who eventually became smokers should have already a high incidence of low birth weight infants even in the period before they started to smoke. Similarly, the data may be used to test the proposition that women who quit smoking are basically nonsmokers, and thus, should have relatively low incidence of low birth weights even before they quit smoking. In order to narrow the age gap between the women in the four groups, the incidence of low birth weight infants is compared only for those born when the women were 25 years of age or younger.

Figure 5 shows that the reproductive performance of smokers before they started to smoke was much like that of smokers, and that of past smokers before they quit smoking was much like that of nonsmokers. The differences are statistically significant in both groups. The evidence appears, therefore, to support the proposition that the incidence of low birth weight infants is due to the smoker and not the smoking.

3. Comment

While the results of this study have inherent value in themselves and are very suggestive, it is, nevertheless, only a single study and the results must be
Figure 4

Reproductive performance of non-smoking and smoking gravidas contrasted with that of tall and short gravidas.
GRAVIDAS' SMOKING HABITS
IN PREVIOUS PREGNANCIES

NONSMOKER

SMOKER
DURING ALL PREGNANCIES

SMOKER
BEFORE SHE STARTED SMOKING

PAST SMOKER
BEFORE SHE QUIT SMOKING

WHITE
PERCENT
LOW-BIRTHWEIGHT INFANTS
N

5.3
2529

8.9
2076

9.5
210

6.0
651

O O statistically significant P<.02

FIGURE 5
Per cent of low birth weight infants by smoking status of their mothers.
considered tentative until confirmed by more studies based on larger samples in other population groups. The study, however, makes a strong point that observational studies have a number of weaknesses and the results of studies must be explored along a number of additional areas before they can be accepted.

Most important is the suggestion that the profession must devote serious study and develop methodologies which are especially applicable to investigations on human beings, where the basic assumption of statistical inferences do not hold. It is necessary to develop supplementary and complimentary methods of study which would be helpful in the difficult area of inferring causation from observed associations.

REFERENCES


