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Introduction to epidemiologic research methods

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1.1 What is epidemiology?

Epidemiology, according to *Last's Dictionary of Epidemiology*, is 'The study of the distribution and determinants of health-related states or events in specified populations and the application of this study to control of health problems' [1]. Wikipedia states 'Epidemiology is the study of factors affecting the health and illness of populations, and serves as the foundation of interventions made in the interest of public health and preventive medicine'. Rothman and Greenland [2] after observing 'there seem to be more definitions of epidemiology than epidemiologists' fulfil their own observation by creating a new definition: 'the ultimate goal of most epidemiologic research is the elaboration of causes that can explain patterns of disease occurrence' [2], thereby narrowing the focus of the subject on aetiology.

John Snow is usually credited with creating epidemiology as a result of his work in the 1840s associating cholera with contaminated water from the River Thames in London [3]. It was only in the second half of the twentieth century that epidemiological methods began to be consistently applied to the whole range of health problems. Before that time, most of the focus was on infectious disease, though there were exceptions, such as pellagra [4]. Rothman coined the term 'modern epidemiology' [5] to reflect the increasing understanding of population based research after the second world war and the increase in its application. The Framingham Heart Study was started in 1949 and Bradford Hill,

amongst his other contributions, conducted the first randomised controlled trial (RCT) in medicine in 1948 [4]. This postwar era is the most important from the perspective of psychiatry. In this period the terms 'chronic disease epidemiology' or 'risk factor epidemiology' have been used to describe the extension of epidemiological methods to non-infectious disease. It is during this period that, in the main, psychiatric epidemiology has developed, often learning from epidemiologists studying heart disease and cancer.

Epidemiologists get involved in studies with a variety of uses [6] including straightforward description, as well as the studies of aetiology that Rothman and Greenland mention in their definition. However, most definitions of epidemiology appear, at least at first sight, to leave out RCTs and systematic reviews yet many epidemiologists also carry out such studies. The use of the term clinical epidemiology [5] reflects this broadening of epidemiological methods into the care of patients, the validity of diagnostic tests and clinical decision making [7]. Epidemiologists have been at the heart of the evidence-based medicine movement [8] and thinking about how research findings are best transferred to clinical practice. And finally, 'genetic epidemiology' [6] is the creation of a marriage between epidemiology and genetics. It is designed to exploit molecular genetics and the technological advances that have enabled rapid characterisation of a person's genetic makeup.

Epidemiology has increased its scope and remit within medicine and psychiatric epidemiology is

a reflection of these imperialistic tendencies. At times, it is difficult to decide where epidemiology ends and ‘other’ clinical research begins; it is a matter of emphasis. Epidemiologists tend to be more oriented towards the study of common conditions of public health importance and are more interested in making inferences about whole populations. In epidemiology, there is more emphasis on establishing causal relationships than understanding the mechanisms that might underpin those relationships. Even though, when possible, epidemiological methods are also needed for investigating mechanisms. This concern with causation has led epidemiologists to emphasise the importance of RCTs to evaluate treatments and to summarise evidence using systematic reviews. So perhaps, those definitions of epidemiology quoted above are sufficient and adequately cover the remit and scope of the discipline.

1.1.1 Psychiatric epidemiology

Psychiatric epidemiology is simply the epidemiology of psychiatric disorders – no more, no less. The principles and practice are the same when studying psychiatric disorder as they are when studying other medical conditions. Understanding the epidemiological principles and methods developed for physical disease will inform our epidemiological study of psychiatric disorder.

Good psychiatric practice requires attention paid to biological, psychological and social factors. The same can be said for psychiatric epidemiology. When studying aetiology or evaluating treatments, epidemiological research is testing hypotheses about cause or treatment based upon a theory relating biological, psychological or social factors to illness or recovery. Understanding the mechanisms underlying disease and treatment is therefore critical in interpreting data from epidemiological and clinical studies. However, it is important to acknowledge that epidemiology is often limited in investigating mechanisms as epidemiological studies often involve measurements that are remote from the mechanisms that are likely to be important.

This is an especial problem in psychiatry as it is difficult to carry out intensive biological and psychological assessments in the context of large scale epidemiological studies. A recent exception is

the collection of DNA in epidemiological studies, which is now useful thanks to the massive technological progress in genetics. But for other areas of neuroscience, this is still mostly a challenge for the future. There are examples of population-based studies of brain imaging [9] and neuroendocrinology [10] but epidemiologists will need further assistance from scientists engaged in imaging, psychology and other areas of basic science in order to develop quicker and easier tests to use in population studies and improve understanding of the neuroscientific basis of psychiatric disorder. We should also not forget about social science. Social scientists will also help in understanding the social context of psychiatric disorder, for example the ideas about social capital have been influential [11] though the advances in social science appear less rapid than those in neuroscience.

1.2 Causation in medicine

One of the most important functions of epidemiology, as suggested by Rothman and Greenland [2] is to investigate factors that might cause disease and treatments or interventions that might cause recovery. Causal inference is the label for a process of reasoning that provides some structure to this difficult and often rather subjective task. ‘Risk factor’ is often used by epidemiologists, in part, to show that there is always some doubt about causal relationships. However, we are only really interested in ‘risk factors’ if they are causal. The first issue to address, then, is what is meant by ‘cause’.

Cause is a word, that is used in everyday language but in medicine it is important that this word is defined and understood in a way that distinguishes it from its usual use in language. Rothman [5] has provided one of the most reasoned and influential approaches towards thinking about cause in medicine. He defines cause (of disease) as ‘an event, condition or characteristic that plays an essential role in producing an occurrence of a disease’. In other words, that a particular occurrence of disease would not have occurred without that event/condition/characteristic having happened first. Rothman has also argued that causes have to occur *before* outcomes. This is a *sine qua non* of any causal

relationship and so any consideration of cause has to include this criterion.

Rothman [5] emphasises that causation implies a comparison. Smoking one pack of cigarettes a day is not a cause if it is compared to two packs, but is a cause when compared to a person who smokes no cigarettes. This comparison is usually measured in epidemiology by calculating an index of association, such as an odds ratio, between a possible causal factor and the disease or outcome of interest. For example, smoking cannabis regularly doubles the risk of schizophrenia compared to people who do not smoke cannabis [12] (though whether this is a causal relationship is still uncertain).

In everyday talk, people often think of causes as though they have a one-to-one relationship with an outcome. The smashed china was caused by the ball kicked by your son. This approach is also attuned to the deterministic model common in basic science, in which, for example, a neurotransmitter acts on a receptor, that is coupled with a G protein that in turn activates a signal transduction pathway. However, the model of causation in clinical medicine has increasingly regarded causes as neither necessary nor sufficient for the majority of non-infectious medical conditions. Smoking cigarettes increases the risk of lung cancer, but many people who smoke do not develop lung cancer and some people develop lung cancer without smoking. It is possible to think of some exceptions to this rule, but in the main these are single gene disorders with high penetrance such as Huntington's disease. In infectious disease, the infectious agent is necessary, but not always sufficient for the clinical disease. Nevertheless, for most non-infectious disease, there has grown a consensus that causal factors are likely to be neither necessary nor sufficient. This has also encouraged use of the term 'risk factor' in epidemiology as the causal factors that are identified in human populations increase the risk of disease but do not confer any certainty about future events.

At first sight there appears to be a conflict between the deterministic models used in biological science and the more probabilistic models that seem to apply to disease in human populations. There are two ways in which this apparent conflict has been resolved. First, that most diseases have multiple causes and this would seem particularly true for psychiatric

disorder. The evidence from heart disease and cancer provides ample evidence that this can be the case. The other suggestion, again made by Rothman [13], is the idea of multiple sufficient causes for a single disease, and that each of these sufficient causes are in turn multifactorial and with overlapping sets of causal factors. If we accept this model, it is possible to understand that in a circumstance of partial knowledge, each element of those sufficient causes will appear neither necessary nor sufficient. This is an important argument that enables us to link epidemiology to the underlying mechanisms that underpin the associations that epidemiologists will observe in human populations.

1.2.1 Alternative explanations

Epidemiological studies estimate the association between a possible causal factor and a disease or a treatment and recovery. In human populations, this is the only approach that is feasible. We also have to understand that the tight experimental controls that can occur in basic science and in experimental animals are impossible in epidemiological studies of human populations. Participants in epidemiological studies or clinical trials will change their behaviour, change their treatment, and may refuse to continue to take part in a study. On occasions, these changes will be influenced by the study itself, public health campaigns or changes to health policy. There will always be difficulties therefore, in interpreting data from epidemiological studies. There are no perfect studies in epidemiology and this leads to more emphasis upon interpretation of any finding of association. It also implies that single studies are rarely sufficient, on their own, to draw conclusions. It is common for RCTs to be described as the 'gold standard' but this ignores the difficulties in interpreting even that most rigorous of the designs at our availability. Patients drop out of RCTs, stop taking their medication, start taking non-trial medication or make other changes to their lifestyle and health care use, sometimes as a result of the randomised intervention. RCTs might reduce the controversy surrounding interventions but they do not eliminate them [14, 15]. If this is epidemiological gold, it has less lustre than its counterpart in government vaults.

One approach towards causal inference is therefore to consider the alternative explanations for an association, apart from causation and it is usual to consider at least these four alternatives: sampling variation and chance, confounding, bias and reverse causality.

1.2.1.1 Sampling variation and chance

Epidemiologists have been at the forefront of considering statistical issues in relation to medical research. There is marked variation within human populations and so sampling variation is usually important to consider. It is difficult to imagine the days when medical journals did not include any statistical tests, but at least in the United Kingdom, Bradford Hill's series of articles in *The Lancet* in the 1930s were very influential in introducing statistical tests into medicine [16].

Many studies are completed and many statistical tests are carried out, even within a single study. Every article in a scientific journal will usually contain dozens of statistical tests. Type 1 errors in which results are statistically significant by chance are therefore common. Statistical tests can be very useful when an analysis was planned as part of a hypothesis driven investigation. However, carrying out repeated tests during exploratory analyses or 'data mining' can lead to results that will often be due to chance. Results from exploratory analyses are best thought of as 'hypothesis generating' that require replication. It is particularly difficult when unscrupulous investigators report such analyses as though they were testing a priori hypotheses. In the light of these concerns, the conventional 5% threshold for statistical significance is almost certainly too high [17], and for most decisions, one needs much better statistical evidence.

Type 2 errors, in which non-significant findings are interpreted as reflecting no association, are very common in the psychiatric literature given the relatively small size of many studies. Confidence intervals can help you decide upon the accuracy with which an association is estimated and help to decide if the investigators have excluded an important result. This is a common circumstance in treatment research in psychiatry [18].

1.2.1.2 Confounding

Factors of aetiological importance are not randomly allocated in human populations. In RCTs of sufficient size there should be a complete balance between the groups in confounding factors, including those that the investigator does not know about. In observational studies, however, confounding can occur. For example, cannabis users will differ in many ways from people who do not use cannabis. In the Swedish conscript study, cannabis users were more likely to live in cities, were more sociable and were more likely to get into trouble with the police [19]. It is possible that these other characteristics could alter risk of subsequent psychosis. These 'other characteristics' are potential confounding variables.

A confounder is defined as an independent risk factor (or protective factor) for the outcome at each level of the exposure, that is also associated with the exposure. A confounding factor can lead to a spurious association or can eliminate a real association between exposure and disease. In the case of cannabis and psychosis, there is good evidence that confounding occurs [12]. In other words, much of the increased risk of psychosis in cannabis users can be attributed to their other characteristics. Statistical adjustment for confounders accounted for about half, but only half, of the observed association.

1.2.1.3 Bias

Bias is another epidemiological term that is borrowed from normal every day use. In epidemiology, bias refers to the possibility that the estimate of association that is obtained is not the 'true' association that would pertain if one could carry out a perfect study. It can be contrasted with confounding, that is, a real explanation for an association that would be present even if your study had perfectly estimated the association in the population. In contrast, bias is introduced by the investigator or is a consequence of the investigation.

The distinction between confounding and bias can be illustrated using the example given above of the link between cannabis and schizophrenia. Even if the measurement of cannabis and schizophrenia were

done perfectly and everyone in a study was followed up, confounding would still exist and have to be considered. Bias will only be introduced as one departs from this utopian state.

There are two main types of bias: selection and measurement bias. Selection bias is to do with the selection of subjects for the study while measurement or information bias is concerned with bias in measurement, diagnosis and ascertainment of outcome and confounders. There are more comprehensive classifications of bias [7], but in the main these two types are the most important to consider.

Selection bias is often described in relation to case-control studies that are very susceptible to this bias. It occurs when the cases and controls in a case-control study are drawn from different populations that differ with respect to the exposure variable. In case-control studies, controls estimate the frequency of exposure in the population from which the cases were drawn. If the control were to become diseased the control should be in the sampling frame for the cases. Case-control studies are therefore population based studies and it is this aspect of case-control design, that is often overlooked.

For example, Mulvany and colleagues [20] carried out a case-control study in which people with schizophrenia (the cases) were selected from a hospital in Dublin who had birth records in the local maternity hospitals. The controls were the next birth in that hospital. There was no way of knowing whether the controls were still resident in Dublin when adult so might not have been in the population 'at risk' of being cases in the study. Some of the controls will have moved away from Dublin. This mismatch could lead to selection bias. This study reported that people of higher socioeconomic status were more likely to develop schizophrenia but this might have been because wealthier people were less likely to move away between birth and adulthood. This result is the opposite of the findings from a cohort study [21] and a case-control study with less risk of selection bias [22] that both found that people of lower socioeconomic status were at increased risk of schizophrenia. On balance, the Mulvany study does not support the idea that higher social classes

are at risk of developing schizophrenia; if anything, the reverse is the case.

Selection bias can also be used to describe the bias introduced by partial follow-up in cohort studies and RCTs. Cohort studies are relatively insensitive to the selection of participants in the cohort, for example the British doctors' cohort of Doll and Hill [23] has produced some robust and reproducible findings even though British doctors are a highly selected group. Likewise, Framingham is far from a representative town. However, bias is more likely to be introduced by differential drop out from the cohort than from the initial selection of the subjects in the cohort, at least in this kind of design. Many cohort studies have quite marked attrition, particularly for longer term follow-up and statistical methods for dealing with such missing data (see www.missingdata.org.uk) are designed to reduce this form of bias.

Measurement or information bias occurs when measurement of exposure or ascertainment of disease is influenced by knowledge of the exposure (longitudinal designs or cross-sectional designs) or of the outcome (case-control and cross-sectional designs).

Recall bias can be a problem if the presence of disease influences the measurement of exposure, as might occur in case-control studies and cross-sectional surveys. People with an illness, or their relatives, are likely to be more aware of past events that might be relevant to illness. The mental state of people with psychiatric disorder might increase or reduce the chance that past events are remembered. For example, people with depression have well-documented information processing biases that make it more likely that negative events are recalled [24]. There are many examples of studies that ask people with depression to record negative adverse experiences [25]. The strong associations that have been observed between depression and these measures may be partly as a result of such a recall bias. It is always difficult or impossible to estimate the likely influence of bias on results.

The high chance of recall bias when measuring factors of potential aetiological importance in psychiatry is a powerful argument for using longitudinal designs to study causation. Using data sources gathered before the onset of disease will

also reduce measurement bias. Other strategies to reduce measurement bias include using structured questionnaires and restricting retrospective inquiry to events that are unlikely to be forgotten.

Bias can also be introduced by the researcher who is interviewing the participant, so-called observer bias. If possible, this source of bias can be eliminated by using self-administered questionnaires. However, there are occasions when participants might find the questions in self-administered form difficult to understand or when they might be misinterpreted. This seems particularly likely when asking about psychotic symptoms [26]. Many assessments of psychiatric disorder are semistructured and rely upon ‘cross-examination’ of the participant. There has been a vigorous debate comparing the validity and reliability of self-reported and semistructured interviews in assessing psychiatric disorder [27]. One has to balance the danger that questions can be misinterpreted with the risk that the observer can influence findings according to preconceived views. The balance of these arguments differs according to the diagnoses that are being studied. For most depression and anxiety disorders where insight is retained, self-reported information would seem to be an advantage. In contrast, for psychotic disorders the cross-examination style of semistructured interviews would seem necessary.

1.2.1.4 Reverse causality

Finally, the disease may cause the exposure. This might occur in case-control studies and cross-sectional surveys because data on exposure is usually collected retrospectively. In contrast, longitudinal studies should ensure that exposures occur before the onset of disease. Many biological aspects of psychiatric disorder are studied using case-control methods. For example, in imaging studies the abnormalities described in people with schizophrenia could result from the illness rather than being a marker of possible causes. Studies of first episode psychosis [28] go some way to address this possibility, but longitudinal studies are required in order to establish abnormalities that are present before the onset of psychosis.

1.3 Causal inference

A number of criteria have been suggested that might encourage a conclusion that exposures have a causal role in disease [13, 29, 30]. These usually require evidence from a variety of sources and one would expect a number of different studies using different approaches all to produce consistent results before coming to a conclusion about causality. The criteria usually suggested include:

- 1 **Timing.** The cause has to occur before the disease.
- 2 **Strength of relationship measured by relative risk.** Large relative risks are more likely to be causal. A relative risk below about 1.5 should be treated with more caution.
- 3 **Consistency of findings across studies.** One would want a variety of different studies in different populations and with different strengths and weaknesses in the design all to produce the same results.
- 4 **Dose-response relation.** Does the evidence support a ‘dose-response’ relation in that the more exposure to a risk factor the more likely the disease.
- 5 **Biological plausibility.** Is the relationship biologically plausible and underpinned by a reasonable mechanism?

One advantage of epidemiology is that it can work in isolation of knowledge of mechanisms. For example, John Snow argued that contaminated water led to cholera many decades before the cholera *Vibrio* was identified or the molecular basis of that disease was established. This should be especially useful for psychiatric epidemiology given the complexity of brain structure and function and the limits of our basic neuroscientific knowledge. None of the criteria listed above are essential, except perhaps for the issue of timing – causes have to occur before the onset of disease. These criteria are a guide, but often the final conclusion relies upon a matter of judgement.

One important principle to consider is whether the evidence is good enough to justify any policy decisions that might be taken. For example, if cannabis

had a causal relationship to schizophrenia then the main policy implication would be to carry out a public health campaign to alert young people to the possible dangers. The amount of evidence required to justify this would be less than that needed to justify a more expensive or risky intervention. For example, suggestions to recommend widespread use of cholesterol-lowering agents has to take account of the greater financial cost and potential for adverse effects. The strength of evidence required for such an intervention would be greater than that needed for a publicity campaign.

1.4 The future for psychiatric epidemiology

Studying the causes of psychiatric disorder in human populations has to be carried out using epidemiological methods. Basic science experiments can often suggest likely causal mechanisms and generate hypotheses about the risk factors for psychiatric disorder but cannot support that such mechanisms are operating in humans. Small-scale experimental studies in humans can illustrate if these mechanisms are occurring in humans with disease but they cannot argue if they are causing the disease in human populations. For example, the work of Meaney and others [31] has suggested possible influences on stress reactivity based upon work on experimental animals. Small-scale experimental work on humans can investigate possible mechanisms further. However, it is only by studying humans in population-based studies that allow us to infer whether the kind of stresses that exist in human life could lead to permanent changes in hypothalamo–pituitary–adrenal axis responsivity and thus lead to human disease.

The future of psychiatric epidemiology will rest upon advances in neuroscience and will increasingly need to measure psychological and biological processes in population based studies. Likewise, epidemiology can generate hypotheses that will need to be investigated by basic scientists and in smaller scale experimental studies in humans. This approach is often described as ‘translational medicine’ [32] and epidemiology will remain one of its key building

blocks if this vision is to be realised and the benefits of medical research to human health will be achieved.

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