Using natural experiments to evaluate population health interventions: new Medical Research Council guidance

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ABSTRACT
Natural experimental studies are often recommended as a way of understanding the health impact of policies and other large scale interventions. Although they have certain advantages over planned experiments, and may be the only option when it is impossible to manipulate exposure to the intervention, natural experimental studies are more susceptible to bias. This paper introduces new guidance from the Medical Research Council to help researchers and users, funders and publishers of research evidence make the best use of natural experimental approaches to evaluating population health interventions. The guidance emphasises that natural experiments can provide convincing evidence of impact even when effects are small or take time to appear. However, a good understanding is needed of the process determining exposure to the intervention, and careful choice and combination of methods, testing of assumptions and transparent reporting is vital. More could be learnt from natural experiments in future as experience of promising but lesser used methods accumulates.

INTRODUCTION
Natural experimental studies are often recommended as a way of understanding the impact of population-level policies on health outcomes or health inequalities.8–10 Within epidemiology there is a long tradition, stretching back to John Snow in the mid nineteenth century,5 of using major external shocks such as epidemics, famines or economic crises to study the causes of disease. A difficulty in applying similar methods to the evaluation of population health policies and interventions, such as a ‘fat tax’ or a legal minimum price per unit of alcohol, is that very often the change in exposure is much less extreme, and its effects may be subtle or take time to emerge. Although they have certain advantages over planned experiments, for example by enabling effects to be studied in whole populations,6 and may be the only option when it is impossible to manipulate exposure to the intervention, natural experimental studies are more susceptible to bias and confounding. It is therefore important to be able to distinguish situations in which natural experimental approaches are likely to be informative from those in which some form of fully experimental method such as a randomised controlled trial (RCT) is needed, and from those in which the research questions are genuinely intractable.

WHAT ARE NATURAL EXPERIMENTS?
The term ‘natural experiment’ lacks an exact definition, and many variants are found in the literature.5–10 The common thread in most definitions is that exposure to the event or intervention of interest has not been manipulated by the researcher. Outside an RCT it is rare for variation in exposure to an intervention to be random, so special care is needed in the design, reporting and interpretation of evidence from natural experimental studies, and causal inferences must be drawn with care.

WHY ARE NATURAL EXPERIMENTS IMPORTANT?
Alternatives to RCTs have been advocated by policymakers and researchers interested in evaluating population-level environmental and non-health sector interventions11 and their impact on health inequalities.5 Such interventions may be intrinsically difficult to manipulate experimentally—as in the case of national legislation to improve air quality, or major changes in transport infrastructure12—or be implemented in ways that make a planned experiment difficult or impossible, for example with short timescales or extreme variability in implementation.13 It may also be unethical to manipulate exposure in order to study effects on...
where the factors that determine exposure can be measured accurately at population level and can be measured accurately at population level using routinely available data. This combination of circumstances is rare, and more complex designs are usually required.

Natural experiments can also be used to study more subtle effects, so long as a suitable source of variation in exposure can be found, but the design and analysis of such studies is more challenging. In any case, what is often required is an estimate of effect size, and a large observed effect may incorporate a large element of bias due to selective exposure to the intervention. Whatever the expected effect size, care should be taken to minimise bias in the design and analysis of natural experiments.

Design elements that can strengthen causal inferences from natural experimental studies include the use of multiple pre/post measures to control for secular changes, as in an interrupted time series design;27 multiple exposed/unexposed groups that differ according to some variable that may affect exposure and outcome to assess whether selection on that variable is likely to be an important source of bias; accurate measurement of multiple potential confounders and combinations of methods to address different sources of bias. In a study that exemplifies many of the features of a rigorous approach to identifying relatively small effects, Ludwig and Miller28 used variation in head start funding to model exposure, and compared a variety of outcomes among children who were above or below the age cut-off for access to Headstart services (box 1; supplemental table 1).

Analysis
The defining feature of a natural experiment is that manipulating exposure to the intervention is impossible. There are a few examples where assignment is by a ‘real life’ lottery, but selection is the rule and a range of methods is available for dealing with the resulting bias.

Where the factors that determine exposure can be measured accurately and comprehensively, matching, regression and
Theory and methods

Box 1 Selection on unobservables

**Difference in differences**
This method compares change over time in exposed and unexposed groups. The differencing procedure controls for unobserved individual differences, and for common trends. It assumes that the unobserved characteristics are fixed, and that the outcomes in each group would change in the same way in the absence of the intervention, so is vulnerable to changes in the composition of the groups and to external influences that differentially affect the exposed and unexposed groups.

**Instrumental variables**
An instrumental variable is a factor, such as treatment assignment in a well-designed randomised controlled trial, which is associated with outcomes only via its association with exposure to the intervention and is independent of other factors associated with exposure. Instrumental variables have been used to identify the impact of treatment from routine data. In these studies, variables such as distance from a specialised centre have been used to evaluate novel treatments, the assumption being that patients living close to a specialised centre are more likely to receive the novel treatment, but are otherwise similar to other patients.

**Regression discontinuity designs**
This approach exploits a step change or ‘cut-off’ in a continuous variable used to assign treatment or otherwise determine exposure to an intervention. The assumption is that units (individuals, areas, etc) just below and just above this threshold will otherwise be similar in terms of characteristics that may influence outcomes, so that an estimate of treatment effect can be obtained by comparing regression slopes on either side of the cut-off. When the Headstart programme to improve the health of disadvantaged children was first implemented in the USA, help with applying for funding was targeted on the 300 poorest counties, and a higher proportion of those counties received funding. Ludwig and Miller compared regressions of child mortality on poverty for counties either side of the cut-off, and a conditional cash transfer scheme to encourage women to use contraception was first implemented in the USA, help with applying for funding was targeted on the 300 poorest counties, and a higher proportion of those counties received funding. Ludwig and Miller compared regressions of child mortality on poverty for counties either side of the cut-off, and found lower than expected mortality in those that qualified for assistance.

Combining methods that address different sources of bias and comparing the results is one such approach and there are several examples in supplemental table 1. In their evaluation of a conditional cash transfer scheme to encourage women to use health facilities to give birth, Lim et al combined methods for dealing with selection on both observable and non-observable characteristics. Another useful technique is to analyse outcomes that are not expected to change. Dusheiko et al used trends in emergency admissions as a non-equivalent dependent variable to test whether changes in elective admissions could plausibly be attributed to GP fundholding, while Ludwig and Miller compared mortality from causes that were likely or unlikely to respond to Headstart services.

Given the difficulty of eliminating bias, single studies are unlikely to be definitive. Replication and careful synthesis of evidence across studies will be needed to support confident inferences about effectiveness. Exact replication of a natural experiment is unlikely, but partial replication is often possible and may be more informative. Consistent findings from studies using varying designs makes it less likely that common biases are present, and consistent findings across settings or populations increase confidence in the generalisability of causal inferences. For example, a number of studies in different countries have shown that legal restrictions on smoking in public places reduce hospital admissions for heart attacks. Although the size of the effect varies widely, as might be expected given variation in smoking rates and the extent of partial restrictions prior to outright bans, the balance of evidence suggests a real effect.

**Box 2 Selection on observables**

**Matching**
This involves finding unexposed individuals (or clusters of individuals) which are similar to those receiving the intervention, and comparing outcomes in the two groups.

**Regression adjustment**
Measured characteristics that differ between those receiving the intervention and others can be taken into account in multiple regression analyses.

**Propensity scores**
The likelihood of being exposed to an intervention given a set of covariates can be estimated by logistic regression and used to match exposed with unexposed cases, or for covariate adjustment.

Reporting
Transparent reporting of natural experimental studies is vital. Established guidelines such as STROBE should be followed, with particular attention to: clearly identifying the approach as a study of a natural experiment; providing a clear description of the intervention and the assignment process; and explicitly stating the methods used to estimate impact. Procedures used to reduce bias should be discussed in a detailed and balanced way. Ideally, qualitative judgements about the risk of bias, and how well it has been dealt with, should be supplemented by a quantitative assessment. If a study has used multiple methods, variation in the estimates should be highlighted. The context within which the intervention was implemented should be described as this may affect interpretation and help users assess the generalisability of the findings. Wherever possible, the results...
CONCLUSION

There are important areas of public health policy—such as suicide prevention, air pollution control, public smoking bans and alcohol taxation—where natural experimental studies have already contributed a convincing body of evidence. Such approaches are most readily applied where an intervention is implemented on a large scale, the effects are substantial and good population data on exposure and outcome are available. But they can also be used to detect more subtle effects where there is a suitable source of variation in exposure.

Even so, it would be unwise to assume that a particular policy or intervention could be evaluated as a natural experiment without very detailed consideration of the methodological challenges. Optimism about the use of a natural experimental approach should not be a pretext for discounting the option of conducting a planned experiment, where this would be possible and more robust.

Research effort should focus on addressing important and answerable questions, taking a pragmatic approach based on combinations of research methods and the explicit recognition and careful testing of assumptions. Priorities for the future are to build up experience of promising but lesser used methods, and to improve the infrastructure that enables research opportunities presented by natural experiments to be seized.