The Limitations of Quasi-Experimental Studies, and Methods for Data Analysis When a Quasi-Experimental Research Design Is Unavoidable

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ABSTRACT

A quasi-experimental (QE) study is one that compares outcomes between intervention groups where, for reasons related to ethics or feasibility, participants are not randomized to their respective interventions; an example is the historical comparison of pregnancy outcomes in women who did versus did not receive antidepressant medication during pregnancy. QE designs are sometimes used in noninterventional research, as well; an example is the comparison of neuropsychological test performance between first degree relatives of schizophrenia patients and healthy controls. In QE studies, groups may differ systematically in several ways at baseline, itself; when these differences influence the outcome of interest, comparing outcomes between groups using univariable methods can generate misleading results. Multivariable regression is therefore suggested as a better approach to data analysis; because the effects of confounding variables can be adjusted for in multivariable regression, the unique effect of the grouping variable can be better understood. However, although multivariable regression is better than univariable analyses, there are inevitably inadequately measured, unmeasured, and unknown confounds that may limit the validity of the conclusions drawn. Investigators should therefore employ QE designs sparingly, and only if no other option is available to answer an important research question.

Keywords: Quasi-experimental study, research design, univariable analysis, multivariable regression, confounding variables

If we wish to study how antidepressant drug treatment affects outcomes in pregnancy, we should ideally randomize depressed pregnant women to receive an antidepressant drug or placebo; this is a randomized controlled trial (RCT) research design. However, because ethics committees are unlikely to approve such RCTs, researchers can only examine pregnancy outcomes (prospectively or retrospectively) in women who did versus did not receive antidepressant drugs; this is a quasi-experimental (QE) research design. A QE study is one that compares outcomes between intervention groups where, for reasons related to ethics or feasibility, participants are not randomized to their respective interventions.

QE studies are problematic because, when participants are not randomized to intervention versus control groups, systematic biases may influence group membership. For example, women who are prescribed and who accept antidepressant medications during pregnancy are likely to be more severely ill than those who are not prescribed or those who do not accept antidepressant medications during pregnancy. So, if adverse

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pregnancy outcomes are commoner in the antidepressant group, they may be consequences of genetic, physiological, and/or behavioral features that characterize severe depression rather than the antidepressant treatment, itself.

A statistical approach to dealing with such confounds is to perform a regression analysis where pregnancy outcome is the dependent variable and antidepressant treatment, age, sex, socioeconomic status, medical history, family history, smoking history, drinking history, history of use of other substances, nutrition, history of infection during pregnancy, and dozens of other important variables that can influence pregnancy outcomes are independent variables. In such a regression, antidepressant treatment is the independent variable of interest, and the remaining independent variables are confounders that are adjusted for in the regression so that the unique effect of antidepressant treatment on pregnancy outcomes can be better identified. Propensity score matching refines the approach to analysis.[1]

Many investigators use QE designs to answer their research questions, though not necessarily as an "experiment" with an intervention. For example, Thomas et al.[2] compared psychosocial dysfunction and family burden between outpatients diagnosed with schizophrenia and those diagnosed with obsessive-compulsive disorder (OCD). Obviously, it is not feasible to randomize patients to have schizophrenia or OCD. So, in their analysis, Thomas et al.[2] first examined whether the two groups were comparable on important sociodemographic and clinical variables. They found that the groups did not differ on, for example, age, family income, and duration of illness (but here, and in other QE studies, as well, these baseline comparisons would almost certainly have been underpowered); however, the schizophrenia group was overrepresented for males and for a history of substance abuse. In further analysis, Thomas et al.[2] used *t* tests to compare dysfunction and burden between the two groups; they found that both dysfunction and burden were greater in schizophrenia than in OCD.

Now, because patients had not been randomized to their respective diagnoses, it is obvious that the groups could have differed in many ways and not in diagnosis, alone. So, separate regressions should have been conducted with dysfunction and with burden as the dependent variable, and with diagnosis, age, sex, socioeconomic status, duration of illness, history of substance abuse, and others as the independent variables. Such an analysis would allow the investigators to understand not only the unique impact of the diagnosis but also the impact of the other sociodemographic and clinical variables on dysfunction and burden.

Note that inadequately measured, unmeasured, and unknown confounds would still have plagued the results. For example, in this study,[2] severity of illness was an unmeasured confound. What if the authors had, by chance, sampled more severely ill schizophrenia patients and less severely ill OCD patients? Then, illness severity rather than clinical diagnosis would have explained the greater dysfunction and burden observed in the schizophrenia group. Had they obtained a global rating of illness, they could have included it as an additional, important independent variable in the regression.

In another study with a QE design, Harave et al.,[3] like Thomas et al.,[2] used univariate tests to compare neurocognitive functioning between unaffected first-degree relatives of schizophrenia patients and healthy controls. More correctly, because there are likely to be systematic differences between schizophrenia relatives and healthy controls, they should have performed multivariable regressions with neurocognitive measures as the dependent variables, and with group and confounders as independent variables. Confounders that could have been considered include age, sex, education, family income, a measure of stress, history of smoking, drinking, other substance use, and so on, all of which can directly or indirectly influence neurocognitive performances.

This multivariable regression approach to data analysis in QE designs requires the a priori identification and measurement of all important confounding variables. In such analyses, the sample size for a continuous dependent variable should ideally be at least 10–15 times the number of independent variables.[4] Given that the number of confounding variables to be included is likely to be large, a very large sample will become necessary. Additionally, because studies are never perfect, it would be impossible to adjust for inadequately measured, unmeasured, and unknown confounds (but adjusting for whatever is known and measured is better than making no adjustments, at all). All said and done, the QE research design is best avoided because it is flawed and because even the best statistical approaches to data analysis would be imperfect. The QE design should be considered only when no other options are available. Readers are referred to Harris et al.[5] for a further discussion on QE studies.

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