The possibility of unmeasured confounding variables in observational studies: a forgotten fact?

James Brian Byrd,[1] P Michael Ho[2]

"For a forgotten fact is news when it comes again"

—Samuel Clemens

Despite oft-repeated caveats about the proper interpretation of data from observational studies, the implications of such studies are subject to being misunderstood. In recent years, a rich body of observational data has illuminated an association between poor adherence to medication and adverse outcomes. A simple explanation for this relationship is that patients who do not take their medication fail to obtain the beneficial effects of the drugs. However, the confounding of such associations by unmeasured variables is another possibility. In their paper published in *Heart*, LaFleur *et al* report on the association between adherence to anti-hypertensive treatment and cardiovascular outcomes and argue that because the benefit found in their observational study did not disappear after controlling for longitudinal blood pressure measurements, unmeasured confounders must be the explanation for the difference found.[1] This work reminds us of the need for careful interpretation of findings from observational studies, and, indeed, from studies of all designs. At the time of publication of these data, it is appropriate to reflect upon the implications of this publication, as well as the authors' assumptions and conclusions.

The main strength of the approach taken by Lafleur *et al* is their rigorous approach in assessing the association between adherence to anti-hypertensive medication and adverse outcomes. The authors used previously validated approaches to measure adherence and examined its association with cardiovascular outcomes after controlling for follow-up blood pressure measurements. In this way, they demonstrated that blood pressure reduction is not the sole factor accounting for the improved outcomes among patients who adhere to their anti-hypertensive regimen. They hypothesise that there are unmeasured confounding variables, including one known as the healthy user (or adherer) effect. The strengths of the work include the large sample size drawn from all veterans with hypertension starting treatment with anti-hypertensive drugs, and the longitudinal pharmacy and blood pressure data used to assess medication adherence and hypertension control. Overall, the analysis is well done and the findings are consistent with previous publications assessing the association between adherence to anti-hypertensive drugs and outcomes.

Despite these strengths, the study has some potential limitations, which should be acknowledged. The authors chose to include among the three outcomes examined, all-cause hospitalisations, which is a non-specific outcome and may not be related to uncontrolled hypertension. Outcomes such as cerebrovascular accident, chronic kidney disease and congestive heart failure can result from poor hypertension control and would be the preferred outcomes of interest, rather than all-cause hospitalisations.

Another important limitation is the failure to attempt to adjust for the healthy user effect, to which the authors ascribed some of the unexplained minimisation of adverse outcomes among adherent patients. The authors conclude that the recent observational studies of medication adherence and outcomes are 'impossibly confounded' by this bias. The healthy user effect, which might be more precisely called the healthy adherer effect in this context, is observed when patients who adhere to a drug regimen have healthier habits in general than non-adherent patients. Somewhat surprisingly, the authors did not report the relationship between adherence and cardiovascular outcomes after controlling for this effect, though methods to control for it exist. For example, one can include in the statistical model adherence to a drug thought to be irrelevant to the outcomes of interest.[2] Another method which allows investigators to assess whether the healthy adherer is biasing their results is to study several outcomes that are not plausibly related to the drugs of interest. For example, Rasmussen *et al* examined the association between adherence to cardiovascular drugs after myocardial infarction and cancer-related admissions[3] and found no association. However, adherence to drugs (β blockers and statins) shown in clinical trials to provide benefit after myocardial infarction was associated with improved mortality, while adherence to calcium channel blockers was not, suggesting that the healthy adherer effect was not an important confounding variable in their study. Implementing one or more of these methodologies would have allowed the authors to demonstrate more convincingly the presence of the healthy adherer effect, if it did indeed bias their findings.

In addition to the concerns about the study itself, there are many important caveats in the interpretation of the study findings by LaFleur *et al*. The conclusions reached by the authors based on these results highlight important limitations of the study as well as their framing of the findings in relation to the literature. The authors designed their study to challenge a model in which blood pressure reduction mediates any effect of adherence on cardiovascular outcomes. However, it is not clear that this model, which they successfully deconstructed, is widely accepted in the first place. For example, many hypertension experts believe ACE inhibitors confer health benefits beyond those attributable to blood pressure reduction.[4 5] In the discussion of their data, the authors acknowledge that the conceptual model they set out to challenge is oversimplified.

Moreover, Lafleur *et al* seem concerned that readers may fail to understand the proper interpretation of observational studies—in particular, the possibility of bias from unmeasured confounders. This concern has been addressed not infrequently in the medical literature. For example, several authors have proposed hierarchies of evidence, ranking the weight to be given to data from various types

[1]Division of Cardiology, University of Colorado, Denver, Colorado, USA; [2]Cardiology Section, Denver VA Medical Center, Denver, Colorado

Correspondence to P Michael Ho, 1055 Clermont St. Denver, CO 80220, USA; michael.ho@coloradooutcomes.org

of studies.[6] There is general agreement that randomised controlled trials provide a stronger type of evidence for or against clinical interventions than do individual observational studies. Because of the possible presence of unmeasured confounding variables, conclusions about causality usually cannot safely be drawn from observational study designs. This axiom is stated explicitly in the observational literature describing medication adherence and cardiovascular adverse outcomes.[7–9] In 1965, Hill described nine now-classic criteria for concluding that an association is casual, the seventh of which involves experimentation.[10] Without controlled intervention, it is not typically possible to draw strong inferences about causality, although Hill points out the strong, consistent link between smoking and lung cancer as a notable exception. In instances in which experiments would be impractical or unethical, as in many matters dealing with drug safety, observational studies are the best method available. For example, it would be unthinkable or unethical to randomise patients to varying levels of adherence to directly assess harms inflicted by poor adherence to a drug with proven efficacy. Accordingly, observational studies that deal with issues of drug safety can sometimes influence clinical practice guidelines while recommendations about the efficacy of specific drugs are derived from findings of randomised controlled clinical trials. Observational studies also play an important role in generating hypotheses to inform future randomised clinical trials evaluating the efficacy of treatments in real-world settings, and studying problems which occur rarely or in under-represented patient populations.

In the final analysis, the message of the observational literature about outcomes and medication adherence is clear: adherence in general is poor, and patients generally do better if they adhere to drugs that have been shown in clinical trials to improve outcomes. Studies of adherence and associated outcomes involving drugs previously demonstrated to be effective in randomised controlled trials are appropriate, but must be carefully interpreted; this is a fact that should not be forgotten. The biggest question is how to move the adherence literature forward. Interventional studies are needed to improve adherence and outcomes. The results of such experiments will come as true news and inform clinical decision-making.

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