

A conversation with David Madigan on 03/07/13

Participants

- David Madigan — Professor and Chair, Department of Statistics, Columbia University
- Alexander Berger — Senior Research Analyst, GiveWell

Note: This set of notes was compiled by GiveWell and gives an overview of the major points made by David Madigan. David Madigan was representing himself and his statements are not meant to represent his employer or the Foundation for the National Institutes of Health.

Summary

David Madigan works as a principal investigator on the Observational Medical Outcomes Partnership (OMOP) research program. He has done research on the reliability of the methodologies used in observational epidemiological studies. GiveWell spoke with him as part of our investigation of opportunities to improve biomedical research. The main subjects discussed were observational epidemiology and Professor Madigan's research at OMOP.

Observational epidemiology studies

Epidemiological studies of adverse events

The question of whether using a given medical drug has a particular negative impact on one's health (such as causing cancer or liver failure) later in life cannot always be answered by randomized controlled trials, both for ethical and for practical reasons.

Medical researchers typically attempt to address these sorts of questions via observational studies that look at massive databases of patient medical records and study whether (after controlling for various factors) there is a correlation between having taken the drug and the negative impact.

There are many decisions (perhaps 40 or 50 decisions) that go into this sort of analysis, such as those pertaining to:

- What data to examine
- What group to compare with those who took the drug
- How to precisely define the outcome of interest.

The decisions that are made are entirely subjective and testing whether they've been made correctly is very challenging.

Observational Medical Outcomes Partnership's work

The Observational Medical Outcomes Partnership (OMOP) has studied whether the methodologies that are used in epidemiological studies yield the right results when applied to questions to which the answers are already known.

For this project, OMOP:

- Restricted its study to questions about drug safety.
- Examined 150 examples where it's known that a drug has a particular negative health impact and 250 examples where it's known that a drug doesn't have particular negative impact.
- Applied approximately 3000 particular analyses that researchers have used for various epidemiological studies to the 400 examples.

OMOP found that many analyses did not yield correct results, and that in many cases, different methodologies that researchers commonly use produce contradictory results.

This largely corroborates John Ioannidis' work finding that most published medical research findings are false.

Which methodologies work best? — OMOP found that for the examples studied, some methodologies seem to work systematically better than others. This raises the possibility of using machine learning to identify methodologies that produce systematically better results in epidemiological studies than others. OMOP hopes to improve on the status quo by doing further work along these lines.

Resistance to OMOP's perspective — OMOP's findings approach epidemiology from a new perspective and challenge much of the research that's been done in epidemiology. The research community has been slow to adopt the new approach.

Funding — So far OMOP has received a considerable amount of funding from a pharmaceutical consortium, but substantial future funding remains uncertain.

Sentinel System — Under the auspices of the "Sentinel Initiative," the Food and Drug Administration gave a contract to Harvard Pilgrim Health Care in 2010 to create the "mini-sentinel system" that monitors the safety of drugs by using large-scale patient-level administrative claims data. OMOP hopes to have more involvement in mini-sentinel going forward, and efforts are underway to have more joint OMOP-mini sentinel projects.

The availability of code

The code that's used for epidemiological studies is seldom made public, and so the analyses that the authors of a paper did are not replicable by others. All the code underlying the OMOP methods is freely available at <http://omop.fnih.org>.

Clinical Trials

Very often, clinical trials don't reproduce, a problem that is exacerbated by the lack of data sharing by pharmaceutical companies.

The need for data from clinical trials by drug companies

It's important that data from clinical trials of drugs that are funded by drug companies be made public. There has been some progress on this dimension in Europe. There's a drug called Vioxx (generic name Rofecoxib), which increases the risk of heart attack and stroke. It should have been possible for the research community to foresee this ahead of time. The studies that reported that it was safe didn't use false data, but a number of papers made errors of omission. The drug was withdrawn in 2004, but the system that allowed it to be approved by the FDA is still largely the same as it was.

Others for GiveWell to talk to

- Victoria Stodden: A professor in the Department of Statistics at Columbia University. Dr. Stodden designed a website called RunMyCode, which is a tool for authors of research papers to upload the computer code that they used to analyze their data so that others can use them to replicate their findings.
- David Donoho: A professor in the Department of Statistics at Stanford University. Dr. Donoho is a member of the National Academy of Sciences. He was Victoria Stodden's advisor, and has thought about issues related to the reliability of academic research, including the multiple testing problem in statistics.
- S. Stanley Young: The Assistant Director for Bioinformatics at the National Institute for Statistical Sciences. He has written about reproducibility and about the issue of authors performing many analyses of a given data set and selectively reporting on those that yield particularly favorable results.

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