Mendelian Randomisation: Past Success and Future Challenges

Friday 14th November 2014

Slides from the presentations now available (please see programme below)

Overview

The IBS-BIR are pleased to announce a meeting on the topic of Mendelian Randomisation (MR) taking place on Friday 14th November at the London School of Hygiene and Tropical Medicine in the John Snow Lecture Theatre.

The main afternoon meeting will begin at 1.30pm, with the AGM of the IBS-BIR commencing at 1.00pm.

The meeting will be preceded in the morning by an introductory session specifically aimed at career-young researchers and students wishing to learn the basics of the MR approach, although anyone is welcome to attend. A buffet lunch will be provided for those attending the morning workshop, for which there is a small additional cost at registration.

Details

Date: Friday 14th November

Venue: John Snow Lecture Theatre, LSHTM, Keppel Street, London

Costs

Afternoon Session 13:30-17:00

IBS member: £25

IBS student or retired member: £10

Non-IBS member: £40

The registration fee includes afternoon tea and coffee.

Morning Introductory Workshop (including buffet lunch) 10:30-13:00

£10

Registration is now closed.

Programme

10.30 - 12.00	**Introductory workshop on Instrumental Variables and Mendelian Randomisation** Morning session specifically aimed at career-young statisticians, although all are welcome to join.
10.30 - 11.15	**An introduction to Instrumental Variable analysis** **Richard Emsley (University of Manchester)** In epidemiologic studies, a common approach to investigating the effect of an exposure on an outcome is to use a regression model. However, in a standard regression model, if an explanatory variable is correlated with the error term (known as endogeneity) its coefficient cannot be unbiasedly estimated. This correlation could arise through measurement error in the endogenous variable or through unmeasured confounders which are absent from the model. An instrumental variable (IV) is a variable that does not appear in the model, is uncorrelated with the error term and is correlated with the endogenous explanatory variable. If a valid instrument is available, a two stage least squares (2SLS) estimation procedure can then be used to unbiasedly estimate the coefficient of the endogenous variable. We will describe the statistical principles underlying this instrumental variable approach, explore its key assumptions and show how these can be tested. We will motivate the discussion using randomisation as an instrument when adjusting for non-adherence in a clinical trial, and the use of parent's education as an instrument for child's education when examining the effect of education on wages.
11.15 - 12.00	**An introduction to Mendelian Randomization** **Stephen Burgess (University of Cambridge)** Mendelian randomization is the use of genetic variants to make inferences on causal effects using observational data. The causal effect of a risk factor on a disease outcome can be inferred under the assumption that certain genetic variants are instrumental variables for the risk factor. Mendelian randomization represents a fast and inexpensive technique for prioritizing or de-prioritizing risk factors as targets for clinical intervention. I will give an introduction to the topic of Mendelian randomization, explaining why causal inference in an observational setting is an important (and a difficult) question, and how and why genetic variants are able to untangle this problem. The talk will be based around the four stages of conducting a Mendelian randomization analysis: 1) specification of the dataset(s) for analysis, 2) search for candidate genetic instrumental variables, 3) validation of the instrumental variable assumptions, and 4) estimation of the causal effect (if appropriate). Particular attention will be given to biological reasons why a genetic variant may or may not be a valid instrumental variable, and the interpretation of an instrumental variable estimate as compared to a clinical or pharmacological intervention on the risk factor under analysis. The talk will be illustrated by an analysis of the causal effect of LDL-cholesterol on coronary heart disease risk.
12.00 - 13.00	**Lunch for morning delegates**
13.00 - 13.30	**AGM: International Biometric Society British and Irish Region** Annual General Meeting of the IBS-BIR
13.30 - 14.15	**Some extensions to Mendelian Randomisation, and some surprises** **Simon Thompson (University of Cambridge)** Presidential Address The basic principle of Mendelian randomisation for estimating causal effects is most easily explained in terms of a single genetic variant that follows the assumptions of an instrumental variable. This can be extended for practical applications to handle multiple genetic variants using two-stage least squares or related methods, and to data in multiple studies using hierarchical models. The behaviour of weak instrument bias and of allele scores are amongst the surprises. Weak instrument bias depends on expected rather than observed F-statistics, so that conventional advice to control the bias is misleading. Naive weighting of allele scores can also introduce bias; deriving weights by cross-validation or using unweighted scores are preferable approaches.

14.15 - 15.00

Instrumental Variable analyses with covariates

Vanessa Didelez (University of Bristol)

Instrumental variables provide an approach for consistent inference on causal effects even in the presence of unmeasured confounding. Such methods have for instance been used in the context of Mendelian randomisation, as well as in pharmaco-epidemiological contexts. In these and other applications, it is common that covariates are available, even if deemed insufficient to adjust for all confounding.

As IVs allow inference when there is unobserved confounding, it appears that often the analyst assumes that even observed confounders / covariates do not need to or should not be taken into account. However, this is not generally the case. With view to the role of covariates, we here contrast two-stage least squares estimators, generalized methods of moment estimators and variants thereof with methods more common in biostatistics using G-estimation in so-called structural mean and distribution models.

When using covariates, there are structural aspects to be considered, e.g. whether the covariates are prior to or potentially affected by the instruments. But in addition, one has to worry even more about efficiency versus model misspecification when modelling covariates. We discuss this for the IV procedures mentioned above, especially for linear instrumental variable models. Our results motivate adaptive procedures that guarantee efficiency improvements through covariate adjustment, without the need for covariate selection strategies. Besides theoretical findings, simulation results will be shown to provide numerical insight.

(This is joint work with Stijn Vansteelandt)

15.00 - 15.30

Tea and coffee break

15.30 - 16.15

Cautionary notes when conducting Mendelian Randomization

John Thompson (University of Leicester)

Mendelian randomization (MR) is a neat way of establishing causation provided that its key assumptions hold. Unfortunately the growing popularity of MR has led to its use in situations where the assumptions are highly questionable. Even if we dismiss these examples as the misuse of MR, we are still left with the majority of applications that are characterised by uncertainty over whether the assumptions hold or not; in these cases, the only honest conclusion is that either the factor is causal or it isn't. In this talk I want to ask two questions: does a MR estimate have any interpretation when the assumptions do not hold? and when we read a report of a MR, how do we judge whether the assumptions are reasonable or not?

16.15 - 17.00

Mendelian Randomisation: What does the future hold?

George Davey-Smith (University of Bristol)

Future directions for Mendelian randomisation will involve incorporation of newly discovered sources of genetic variation influencing intermediate phenotypes (including rare variants and the ever-expanding lists of established common variants) together with high dimensional intermediate phenotype data, from epigenomic profiles, transcriptomics, proteomics and metabolomics. Use of such genetic data will increase the statistical power of Mendelian randomisation studies, will allow more nuanced evaluation of the assumptions on which a valid Mendelian randomisation analysis is based and will prepare the way for utilising genetic instruments for data mining and edge-orientation in networks of phenotypes.