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‘Mendelian randomization’ equals instrumental variable analysis with genetic instruments

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SUMMARY

Interest in instrumental variable (IV) analyses using genetic instruments has been growing over the past 4 years. The background, strength and weaknesses of this approach, which in the epidemiology literature has been referred to as ‘Mendelian randomization’, has been recently reviewed by Lawlor *et al.* (*Statist. Med.* 2007. DOI: 10.1002/sim.3034). We suggest a change in the nomenclature of ‘Mendelian randomization’ and discuss issues relevant to IV analysis including instrument validation, motivation of IV analysis and interpretation of IV estimates in order to motivate a more consistent and standard use of IV analysis across applications using genetic instruments.

Keywords

Mendelian randomization; instrumental variables; endogenous variables; self-selection; confounding

IV VERSUS ‘MENDELIAN RANDOMIZATION’

Instrumental variable (IV) analysis is a statistical tool that is extensively used by economists and others to account for the bias in estimating the effect of endogenous variables on outcomes. Common endogenous variables include choice of treatments, health-related behaviors and risks. Self-selection into these variables (referred to hereafter as endogenous selection) can result in bias due to correlations with unobserved variables that are also related to the studied outcome. The IV design uses variables, called instruments, that are known to be related to the endogenous variable (first assumption) but are otherwise assumed to be unrelated to the outcome either directly or indirectly through unobservable variables (second assumption). In other words, instruments are assumed to be related to the outcome only through the endogenous variable and any observable variables that are included in the analysis as covariates or explanatory variables.

There has been a growing interest over the past 4 years in the use of genetic variants as instruments for health behaviors and risk factors when studying their effects not only on disease

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and health outcomes but also on social and economic outcomes. These applications are expected to grow significantly especially with the increase in large-sample genome-wide studies, which provide data on multiple genetic instruments that could be used in various research questions [1]. This novel application of the IV technique became known in the epidemiology field as ‘Mendelian randomization’ due to the random assignment of alleles from parents to children. Yet describing the application under this concept is restrictive and rather narrow for several reasons.

It is important to emphasize that the assumption of randomization is not unique to genetic instruments. The second IV assumption implies that unobservable factors that confound the estimation of the effect of the endogenous variable on the outcome (i.e. the unobserved confounders) are ‘randomized’ by or unrelated to the instruments after adjusting for all the relevant observable factors regardless of whether genetic or non-genetic instruments are used. The IV estimation is a standard technique in health economics applications that evaluate the effects of treatments and health behaviors on outcomes. Instruments typically include availability (e.g. prices, geographic availability, etc.) or enabling/access (e.g. income, insurance, etc.) variables. The ‘geographic’, ‘price’ or ‘distance’ randomization did not emerge as an independent concept given that they are merely different instruments used under the same IV technique.

Genetic instruments are used for the same purpose as non-genetic instruments, are subject to the same IV assumptions and may satisfy these assumptions better or worse than non-genetic instruments depending on the specific instruments and research question (endogenous and outcome variables). Publicizing the application of IV analysis with genetic variants as instruments under the term ‘Mendelian randomization’ seems unnecessary and might lead to an unintended communication barrier between researchers in the fields of epidemiology, health economics, health services research and other health science fields where the IV technique is employed. Some health economists have begun to apply IV methods with genetic variants as instruments to evaluate the effects of health risks and behaviors on health and socioeconomic outcomes [2-4]. The application of genetic IV analysis is expected to grow significantly in the health economics field to study the effects of health behaviors and risks with fully or somewhat known genetic etiology on various outcomes. Using common language between disciplines applying IV analysis with genetic variants is essential to increasing collaborations and fostering the application of this method.

We suggest that the term ‘Mendelian randomization’ is replaced in future papers with ‘instrumental variable analysis with genetic instruments’ where the emphasis is placed on the IV method with a clear reference to the use of genetic variants. Some papers have clearly described ‘Mendelian randomization’ as an IV analysis [5-7]. However, there is still a special treatment of the concept as a new method. For instance, when discussing the non-linearity challenges imposed by binary outcomes and endogenous variables in the paper by Lawlor *et al.* [7, Section 4.9], there seemed to be (perhaps an unintended) indication that ‘Mendelian randomization’ might have specific sensitivities to these challenges compared with an IV analysis with non-genetic instruments, which obviously is not the case. These challenges are unrelated to the type of the instrument.

It is true that the term ‘Mendelian randomization’ describes an important strength of the application in that alleles predicting the endogenous variable are randomly assigned, yet this strength is not sufficient for the genetic variant to satisfy the IV assumption of randomizing the relevant unobservable confounders (second assumption). A certain genetic instrument might satisfy the first assumption of being related to the endogenous variable, but it might also be correlated to other unobservable variables such as other health risks, which would confound the IV estimation.

Epidemiologists and others who are interested in IV analysis with genetic instruments are encouraged to learn more about the methodological issues of IV estimation that are common to all IV studies including those using genes as instruments. Econometric books and seminal methodological papers on IV provide a great venue to study IV methods [8-10].

OVER-IDENTIFICATION TESTS FOR THE SECOND IV ASSUMPTION

Lawlor *et al.* [7] described well using genetic terms ('linkage disequilibrium' and 'pleiotropy') how genetic variants might violate the second IV assumption, but no tests are described for this problem. It is econometrically impossible to fully test for violation of this assumption, but it is possible to test for it at least partially. One approach involves comparing the distribution of the observable covariates by subgroups of the instruments and using bivariate to test for differences. If the instrument is unrelated to unobservable confounders, it is expected to have no consistent pattern of correlations with observable confounders. Some correlations might be inevitable due to sample size or selection without necessarily suggesting that the instruments are invalid after adjusting for all the observable confounders. Yet a systematic pattern of correlations between the instruments and the observable confounders such as when a certain instrument group seems to be related to several measures of poor health, health behaviors or socioeconomics likely suggests that unobserved confounders may also be related to the instrument.

When the number of instruments exceeds the number of endogenous variables, an over-identification test can be conducted, which partially evaluates the second IV assumption. These tests essentially evaluate whether the additional instruments used to estimate the IV model (a minimum of one instrument per endogenous variable is needed) can be excluded from the outcome equation after identifying the model with the minimum number of instruments. In other words, these tests evaluate whether the extra instruments have significant joint effects on the outcome after accounting for the endogenous selection of the primary variable(s) of interest. Several test versions are available including the common Basman and Hausman tests [11,12]. These tests have power limitations but are very useful and their use is standard in IV applications to evaluate the validity of the instruments. As several of the studied health behaviors and risks are complex with multiple related genes, IV analysis using genetic instruments will likely have access to more than one instrument and the over-identification tests should be applied in those scenarios.

MOTIVATION OF THE IV ANALYSIS

The IV model is applied after establishing theoretically the endogenous selection of the variable of interest. Non-random self-selection, omitted variables (or confounders) and systematic measurement error are typical problems that can benefit from the use of IV analysis. Establishing the need for IV use is important for justifying the applications given the challenge in identifying appropriate instruments.

Health behaviors such as smoking, drinking, drug use, eating habits, exercise, etc., risks and illnesses such as obesity, stress, depression, etc. and health-care treatments are theoretically endogenous given the roles of preferences for health and risk taking and health endowments, which induce correlations between these variables but may also have direct effects on outcomes (especially in the case of health endowments). On the other hand, the endogenous selection of biologic markers or exposures such as plasma folate levels, C-reactive proteins or others is less intuitive. It is true that these are in part a function of behavioral factors such as nutrition and vitamin use (which are endogenous), but they are also a function of many other variables including likely "random" factors. This might dilute the correlation between these biologic markers and unobserved confounders that will bias the estimation of their effects. When considering IV models to evaluate the effects of biologic markers, it is important to highlight

the theoretical reasoning for endogenous selection and to assess the potential biases of regular *versus* IV estimations.

INTERPRETATION OF THE IV ESTIMATE

The IV estimate will depend on the set of instruments used to identify the model. The estimates of traditional IV models such as two-stage least squares are applicable to those whose assignment or choice of the endogenous variable is dependent on the used instrument and who would have changed this assignment had they switched between the different groups defined by the instrument [13], such as between genotypic variants of a single nucleotide polymorphism instrument. Given that different genes might be related to different specifications of the endogenous variable (such as smoking initiation *versus* addiction or having certain genes involved in more intensive smoking), it is important to interpret the IV estimate in relation to the specific instrument used and describe the implications of different instruments for generalizability. For instance, when evaluating the effects of smoking using genetic IVs, it is interesting to compare the estimates using detoxification *versus* addiction IVs given that these might theoretically identify different smoking patterns.

Stratifying the IV estimation by relevant covariates such as sociodemographic characteristics might also help gauge the generalizability of the IV estimate. For instance, when evaluating the effects of smoking using genetic variants that predispose to addiction as instruments, stratifying by education might be relevant if the effects of the addiction variants on smoking might vary by education (e.g. might be stronger with lower education). It is also useful to evaluate several combinations of instruments when possible to evaluate the sensitivity of the IV estimate to different instrument specifications.

SUMMARY

The application of IV analysis using genetic instruments provides a powerful approach to address several important questions related to identification of disease etiology as well as the health and socioeconomic ramifications of disease. It is however important to emphasize that this constitutes a novel application of an old and commonly used method rather than a new method. Therefore, referring to this application as an IV analysis with genetic instruments might be more appropriate than publicizing this application under the term ‘Mendelian randomization’. Researchers who are considering this application should follow the standards used in IV analysis including the full validation of the instruments using the available methods and tests.

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