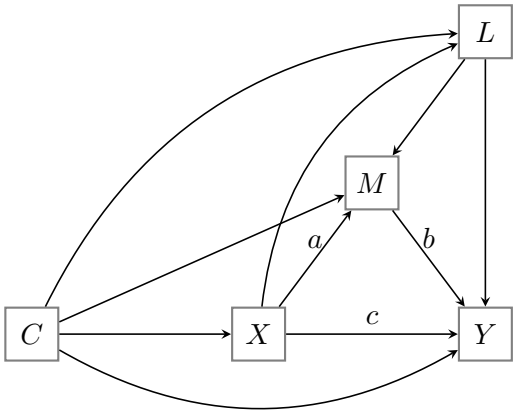
Causal Mediation Analysis.



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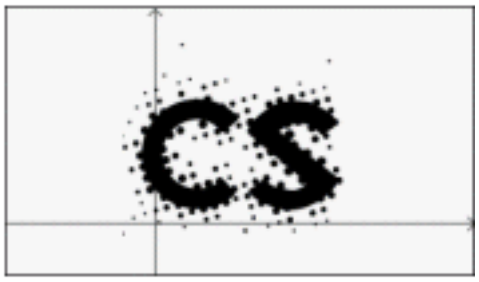

Ghent University

Ghent — January 28 and 29, 2013

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You are kindly invited to prepare a *question for the panel* discussion at the end of the 2nd day. You can drop your written question in the designated dropbox before the end of the 1st day.

Program Causal Mediation Analysis

Monday January 28th 2013

09h45 - 10h15 Registration and coffee

10h15 - 10h30 Welcoming

10h30 - 11h30 David Kenny (University of Connecticut, US)
Mediation Analysis: Background and Basics.

11h30 - 12h20 Contributed Session 1

- Wim Beyers (Ghent University, Belgium)
  The iceberg beneath the surface: Impact of stuttering on self-esteem in adolescents through mediating processes. A comparison of stuttering and non-stuttering adolescents.
- Meriam Belkhir (University of Sfax, Tunesia)
  Mediation analysis approach to highlight a new consumer behavior concept: the akratic spending behavior.
- Kimberley Goldsmith (Kings College London, UK)
  Exploration of instrumental variable methods for estimation of causal mediation effects in the PACE trial of complex treatments for chronic fatigue syndrome.

12h20 - 13h30 Sandwich lunch

13h30 - 14h15 Yves Rosseel (Ghent University, Belgium)
Software for Mediation Analysis.

14h15 - 15h00 Vanessa Didelez (University of Bristol, UK)
Basic concepts of causal mediation analysis and some extensions.

15h00 - 15h30 Coffee break

15h30 - 16h15 Contributed Session 2

- Helene Nordahl (University of Copenhagen, Denmark)
  Education and risk of coronary heart disease: Assessment of mediation by behavioral risk factors using the additive hazards modelling.
- Saskia Le Cessie (Leiden University Medical Centre, the Netherlands)
  Unmeasured confounding and measurement error in mediation analysis.

16h15 - 17h15 David MacKinnon (Arizona State University, US)
A Longitudinal Look at Longitudinal Mediation Models.

17h15 - 18h30 Poster Reception

19h00 - 22h00 Conference Dinner

Tuesday January 29th 2013

09h00 - 10h00 Tyler VanderWeele (Harvard University, US)
Varieties of sensitivity analysis for direct and indirect effects.

10h00 - 10h45 Richard Emsley (University of Manchester, UK)
How do treatments work and who for? Efficacy and mechanisms evaluation in complex interventions and personalised medicine.

10h45 - 11h15 Coffee break

11h15 - 12h15 Contributed Session 3

- Donna Coffman (Pennsylvania State University, US)
  Comparison of Three Approaches to Causal Mediation Analysis.
- Alessandra Mattei (University of Florence, Italy)
  Understanding Causal Mechanisms through Principal Stratification: Definitions and Assumptions.
- Rhian Daniel (London School of Hygiene and Tropical Medicine, UK)
  Causal mediation analysis with multiple causally-ordered mediators.

12h15 - 13h30 Sandwich lunch

13h30 - 14h15 Stijn Vansteelandt (Ghent University, Belgium)
Flexible mediation analysis in the presence of non-linear relations using natural effect models.

14h15 - 15h15 Contributed Session 4

- Carlo Berzuini (University of Manchester, UK)
  Mechanistic interaction in presence of stochastic mediators.
- Axel Mayer (Friedrich Schiller University Jena, Germany)
  A stochastic approach to atomic total, direct and indirect effects.
- Michel Mouchart (UCL, Belgium)
  A structural modelling approach to mediators, moderators and confounders. A counterfactual-free approach.

15h15 - 15h45 Coffee break

15h45 - 17h15 Panel Discussion with Invited Speakers
Discussant: Niels Keiding (University of Cophenhagen, Denmark)
Moderator: Els Goetghebeur (Ghent University, Belgium)

Invited Talks

Mediation Analysis: Background and Basics

David A. Kenny
University of Connecticut

Mediation is an incredibly popular topic in research in the social and behavioral sciences. Although there are several reasons for this popularity, the most important reason is that mediational analyses allow for the study of process. The history of mediation analysis is reviewed and three major stages are discussed: Steps in Determining Mediation, Testing the Indirect Effect, and Probing Mediational Assumptions. Finally, I discuss three areas of current interest to me: DataToText using R, relative power, and longitudinal modeling of mediation.

Software for Mediation Analysis

Yves Rosseel
Ghent University

In the first part of the presentation, a brief overview is given of different software packages that can be used for mediation analysis. We focus on software that is commonly used in the social and behavioural sciences. In the second part of the presentation, we introduce the R package 'lavaan': a free and easy to use open-source package for structural equation modeling and related methods. Several examples will be given to illustrate how lavaan can used for mediation analysis. We start with some basic setups, and then proceed to some more advanced examples.

Basic concepts of causal mediation analysis and some extensions

Vanessa Didelez
University of Bristol

In the context of linear structural models it is relatively straightforward to compute path specific effects with the aim to quantify effects along direct or specific indirect causal pathways. However, it is clear that the simplistic assumptions of linearity and additivity are often not appropriate. Proposals for the definition of direct/indirect effects that are not linked to linearity and additivity have been made by Robins & Greenland (1996) and Pearl (2001). These are based on a formulation where the nested counterfactual Y(x,M(x*)) when X is set to x and M is set to its value if X were x* is a central quantity. I will review and discuss the assumptions required to be able to identify these measures of (in)direct effects from empirical data. Further I will follow an interpretation of Robins and Richardson (2010), who show that under an augmented version of a directed acyclic graph model, such counterfactual quantities can be seen as a so-called manipulable parameter, in which case they are compatible with a decision-theoretic approach to statistical causality (Didelez et al, 2006). The augmentation means that the node representing the exposure or treatment of interest is separated into two nodes with different pathways leading to the outcome of interest. I will consider this augmented system as the target of inference, and discuss under what assumptions we can estimate interesting aspects of this system, such as path-specific effects. The idea of augmentation can also be used to fit the model and obtain the desired effects along separated pathways; Lange et al (2012) have suggested this in the context of marginal structural models, while we here follow an approach that is comparable to G-computation (Kreiner, 2002). The methodology will be illustrated with sociological data addressing the question of childhood environment and fear of violence in adults; the data contain only categorical and ordinal variables so that general loglinear models are used, as linear additive models are not appropriate (joint work with Svend Kreiner, Biostatistics, Uni Copenhagen).

A Longitudinal Look at Longitudinal Mediation Models

David P. MacKinnon
Arizona State University

The purpose of this talk is to provide a historical perspective on longitudinal mediation. The mediation model is a longitudinal model that specifies a temporal sequence such that X causes M and M causes Y. When X represents randomization to conditions, the temporal sequence is that X comes before M and Y but the causal direction from M and Y may not be as predicted. Longitudinal data may shed light on the relation between M and Y. With two waves of longitudinal data, more detail can be assessed about longitudinal mediation but several complications arise including regression to the mean and the different meaning of cross-sectional versus longitudinal relations between variables. Generally, more convincing evidence is obtained when change in M precedes and predicts subsequent change in Y. For two-waves of data, several alternative models are available including difference score and analysis of covariance models. With more than two waves of data, a large number of models are applicable including latent growth, autoregressive, latent change, and continuous time models. The models make different assumptions about change over time and can add credibility to the claim that M is a mediator of the effect of randomized X on Y. Recent developments in causal inference for longitudinal data show that X induced change at earlier waves may confound long term relations. Mediation models are applied to a longitudinal study of a randomized intervention to promote healthy behavior among police officers.

Varieties of sensitivity analysis for direct and indirect effects

Tyler VanderWeele
Harvard University

Methods for direct and indirect effects have been popular within the social sciences for decades and have recently been receiving increasing attention from the statistics community. To interpret estimates of direct and indirect effects causally several strong identification assumptions are required. In most application settings these will not hold. Sensitivity analysis techniques can be useful in assessing the extent to which violations in the assumptions would changes substantive conclusions. Several sensitivity analysis techniques will be presented and illustrated including sensitivity analysis for unmeasured mediator-outcome confounding, for time-dependent confounding, and for measurement error of the mediator. Several applications will be presented in which such sensitivity analysis reasoning sheds considerable light on the applications in question. Examples will be presented from perinatal epidemiology, psychiatric epidemiology and genetic epidemiology.

How do treatments work and who for? Efficacy and mechanisms evaluation in complex interventions and personalised medicine

Richard Emsley
University of Manchester

Analysing randomised trials of complex interventions involves estimating different pathways to judge whether the putative intermediate variables are the true mechanistic components underpinning the intervention. The development of personalised (stratified) medicine is intrinsically dependent on an understanding of these treatment-effect mechanisms to target the right treatment to the right patient at the right time. Mediation analysis is the obvious approach for these questions, but there are several limitations when applying it. Firstly, we classify these intermediate variables into three groups (true mediators, incidental mediators, and post-randomisation effect modifiers), and show that questions of treatment efficacy usually involve effect modifiers rather than mediators. We review the problem of confounding for the drawing of valid inferences concerning treatment-effect mechanisms, even when the data has been generated using a randomised trial. We show how instrumental variable procedures can be applied to estimate controlled direct effects and produce unbiased estimates of the mediator-outcome relationship. Secondly, by building on this instrumental variable procedure, we illustrate the potential of a biomarker-stratified design to enable us to evaluate both the utility of the predictive biomarker in such a stratification and, perhaps more importantly, to estimate how much of the treatment's effect is actually explained by changes in the putative mediator. We call this a biomarker stratified efficacy and mechanisms evaluation (BS-EME) trial. We illustrate these concepts with examples from complex interventions in mental health.

Flexible mediation analysis in the presence of non-linear relations using natural effect models.

Stijn Vansteelandt
Ghent University

Traditional mediation analysis approaches build on standard regression models for the outcome and mediator, but easily result in difficult-to-interpret or difficult-to-report results when some of these models involve non-linearities. We will overcome this via a novel class of natural effect models, which directly parameterize the (natural) direct and indirect effects of interest. We propose flexible imputation-based estimation strategies for these direct and indirect effect parameters, which are easy to perform with standard statistical software. Data illustrations will be given and challenges will be discussed for handling multiple mediators when some confound the relationship between the remaining mediators and outcome.

Contributed Talks

The iceberg beneath the surface: Impact of stuttering on self-esteem in adolescents through mediating processes. A comparison of stuttering and non-stuttering adolescents

Wim Beyers & S. Adriaensens
Ghent University

The total number of people that stutter is estimated to be approximately one percent of the total population (Bloodstein, 1995). When defining stuttering, it is often forgotten that under external stuttering a large number of hidden feelings and thoughts reside. People who stutter often do this in a hidden way, not visible for others, and often experience anxiety, shame or cognitive distortions (Vuylsteke, Reunes, & Van Borsel, 2001). In this research, we use a definition of stuttering that focuses both on external and internal aspects, as such looking for the iceberg beneath the surface.

The main question we considered was the influence of these hidden thoughts and feelings on people who stutter. Do people who stutter have a negative self-esteem? Moreover, does this negative self-esteem express itself on each aspect of the self-concept, particularly in adolescence? We studied the influence of stuttering on self-esteem by using a multifactor scale, to investigate the different domains of the self. Moreover, we compared two age categories within adolescence, namely early and late adolescence. We expected to find, in line with Green (1998, 1999), that late adolescent stutterers have a more negative evaluation of the self, compared to their younger peers, because of more negative experiences with their speech. In the next phase we investigated the possible mediation role of internal processes on the relation between stutter severity and self-esteem, namely negative communication attitudes, experienced stigma, introversion about stuttering and perfectionism. Previ ous research linked these processes to stuttering.

Our sample comprised 55 stuttering adolescents and 76 non-stuttering adolescents, split up into two age groups (early adolescents, mean age 13 years and 3 months; late adolescents, mean age 19 years and 4 months). They were asked to fill in a battery of standardized questionnaires. Multiple regression showed that stuttering has a negative influence on the self-image of adolescents ($F(7,108)= 4.00$; $p < .001$; $R^2 = .21$). Social acceptance, school capacities, the capacity to experience a close friendship and global self-image are influenced negatively by stuttering severity. To investigate the mediation processes between stuttering severity and negative self-images, we used a four-step procedure of regression analyses (Baron & Kenny, 1986; Holmbeck, 1997) and the Sobel test. This was followed by a SEM analysis and bootstrap estimation of the indirect effects to find the strongest mediator. These analyses proved that maladaptive perfectionism, and even more negative communication attitudes, fully mediate the relation between stuttering severity and the evaluation of social and school capacities and global self-esteem.

These results offer support for the hypothesis of Green: in comparison to children, adolescents experience a significant negative influence of stuttering on their self-esteem, most likely due to more negative speech experiences (conform negative communication attitudes). Furthermore, the results provide support for a definition of stuttering that underlines internal processes like anxiety, perfectionism and cognitive distortions. Researchers and practitioners should pay more attention to the internal psychological processes in their stuttering clients, because the iceberg beneath the surface is large and determines the stability of the top!

Mediation analysis approach to highlight a new consumer behavior concept: the akratic spending behavior.

Meriam Belkhir, J.Jallais, & F.Akrout
University of economic sciences and management of Sfax- University of Sfax- Tunisia

Mediation analysis approach to highlight a new consumer behavior concept : the akratic spending behavior In this research, we illustrate the potential of mediation analysis to highlight the relevance of a new theoretical concept in consumer behavior literature. It deals with spending and buying behavior during which the consumer knowingly deviates from his activated personal standards. These behaviors refer to akrasia, a philosophical concept discussed by Aristotle to describe situations where the agent freely and deliberately acts contrary to his better judgment. A preliminary study (n=816) revealed a hierarchical structure of akratic spending behavior being a second order reflexive construct with three facets: priority subversion, product constellation deviation, and transgression of one's own principles according to appropriate funding. In order to test the ability of the new concept to belong to theoretical network of established concepts, we conducted a second field study (n=713). To achieve this second goal, we proceeded in two steps by using structural equation modeling through ML estimation method. We estimated the hypothesized model by using Amos16 software (Arbuckle).

At first, we tested two hierarchical nested models where the concept has a status of a full versus partial mediator. Results conclude to the superiority of the model where the new construct has partial mediation as evidenced by significant $\Delta\chi^2$ and better fit indexes (TLI=,913 CFI=,921 RMSEA=,047 SRMR= ,070 χ^2/df=1 ,982)

Second, we explored the mediating role played by our new concept following Zaho and al. (2010) approach. Indirect effects significance was tested via Sobel test by using online available program developed by Preacher and Leonardelli. The choice of Zaho and al. approach is justified by recent developments made by Rucker et al. (2011), zaho and al. (2010) calling to the abandon of Baron and Kenny (1986) dominant approach when it comes to studying mediation. Results demonstrated that mediating role of akratic spending behavior is manifested in three different forms, according to the set of antecedents/consequences involved. Akrasia has alternately.

Indirect only mediation in six cases: conspicuous motivation, possession centrality (as dimension of materialism), and use of positive financial practice has only indirect significant effect on the three predicted consequences (experienced financial stress, perceived financial self-efficacy and financial problems frequency) through akratic spending behavior. The prevalence of indirect only mediation, which corresponds to complete mediation according to Baron and Kenny (1986) is a good indicator of the important place of the proposed concept and a proof of conceptual framework consistency as suggested by Zaho and al. (2010, p.201).

Complementary mediation in four cases: consideration for future consequences has simultaneously direct and indirect significant effects on the three studied consequences. These effects are in the same direction. The use of positive financial practice has significant direct and indirect effects only on the perceived financial self-efficacy. However, the magnitude of these significant indirect effects is relatively low compared to direct ones. This result may points to the presence of other possible mediators not incorporated in

the model as suggested by Zaho et al. (2010, p.201).
Competitive mediation in two cases: possession centrality and use of positive financial practice have significant direct and indirect effects on financial problems frequency and experienced stress. However, direct and indirect effects are in opposite directions. This intriguing result signifies that akratic behavior may contribute to reverse the direction of direct effect. Thus, centrality possession generates financial problems only if it involves akratic spending. Otherwise, the consumer may continue to attach great importance to possessions and behave in accordance without feeling the need to change his spending pattern. Thus, akratic behavior, by displaying a competitive mediation, may trigger within the consumer the need to moderate the importance he assigns to material possessions. Besides, the use of positive financial practice is effective in reducing financial stress only by reducing akratic behaviors.
To conclude, we can say that the use of Zaho and al. (2010) approach allowed us to scrutinize the mediating role played by the new concept of "akratic spending behavior" in nomological network of theoretical established concepts in marketing, psychological and financial education literature.

Exploration of instrumental variable methods for estimation of causal mediation effects in the PACE trial of complex treatments for chronic fatigue syndrome

Kimberley Goldsmith, T. Chalder, P. White, M. Sharpe, A. Pickles
Institute of Psychiatry, King's College London

Background: Chronic fatigue syndrome (CFS) is characterised by chronic disabling fatigue. The PACE trial compared four treatments for CFS and found cognitive behaviour therapy (CBT) and graded exercise therapy (GET) to be more effective in improving physical function and fatigue than two other treatments. It is of interest to study whether the effects of CBT and GET are mediated through cognitive measures such as fear avoidance and activity avoidance. The traditional Baron, Judd and Kenny (BJK) methods for studying mediation do not account for unmeasured confounders and so may provide incorrect mediation effects; instrumental variable methods (IV) from economics can address this problem.
Aim: to explore mediation in PACE using BJK and IV estimates.
Methods: BJK and IV methods were applied using linear regression models. IV methods require instrumental variables - variables not in the postulated mediation model. Several interaction terms between baseline variables and treatment were assessed as instruments using the R^2 change between models with main effects only and with the interaction term. Different IV estimators were compared. Collective instrument strength was assessed using recommended measures.
Results: Tests of instrument strength indicated these were weak (ie. poor predictors of the mediator). The IV estimators were different in magnitude and less precise than the BJK estimators. The relative precision of different IV estimators varied 10-18%. There is scope for modelling a common effect of the mediators across different treatments.
Conclusions: Interaction term IVs in PACE were found to be weak. Combining trial arms may allow for more efficient analysis.

Education and risk of coronary heart disease: Assessment of mediation by behavioral risk factors using the additive hazards model

Helene Nordahl, N.H. Rod, B.L. Frederiksen, I. Andersen, T. Lange, F. Diderichsen, E. Prescott, K. Overvad, M. Osler
University of Copenhagen, Department of Public Health, Social Medicine

Introduction: Previous evaluations of the mechanisms behind social inequalities in coronary heart disease (CHD) have primarily been based on reductions in relative risk by the use of proportional hazards model. In the present study we applied an alternative absolute risk approach to understand educational-related inequalities in CHD.
Method: Prospective data from seven well established population-based cohort studies in Denmark was brought together in a database, which represented an important innovation for increasing statistical power to estimate mediation by smoking, low physical activity, and body mass index (BMI) on the education-CHD relationship. A total of 69,513 subjects between 30 and 90 years of age were included in the analysis. We applied newly proposed methods for mediation based on the additive hazards model and compared results from the Cox proportional hazards model.
Results: Short (vs. long) education was associated with 277 (95% CI: 219, 336) additional cases of CHD per 100,000 person-years at risk among women, and 461 (95% CI: 368, 555) additional cases among men. Of these additional cases 17 (95% CI: 12, 22) for women and 37 (95% CI: 28, 46) for men could be ascribed to the pathway through smoking. Further, 39 (95% CI: 30, 49) cases for women and 94 (95% CI: 79, 110) cases for men could be ascribed to the pathway through BMI. The effects of low physical activity were negligible.
Conclusion: Using contemporary methods of the additive hazards model for mediation we indicated the absolute numbers of CHD cases prevented when modifying smoking and BMI. This study confirms previous claims based on the Cox proportional hazards model that behavioral risk factors partially mediates the effect of education on CHD, and the results seems not to be particularly model dependent.

Unmeasured confounding and measurement error in mediation analysis

Saskia Le Cessie, S. Cannegieter, & J.P. Vandenbroucke
Leiden University Medical Centre

Determining factors in the causal pathway between an exposure and a disease is often the aim of etiologic research. For example, if a gene is associated with a certain disease, one would like to know if this relation can be explained by one or more intermediary biochemical variables. Under certain regularity conditions (VanderWeele and Vansteelandt, 2010) this can be explored by performing logistic regression and conditioning on the intermediate factor.

Recently we have studied the effect of several types of measurement error on the estimates of direct and indirect effect in such an analysis (le Cessie et al., 2012). Unmeasured confounding is another cause of bias in the estimates of direct and indirect effects (Cole and Hernan, 2002; VanderWeele, 2010). In this presentation, we compare the size of bias caused by measurement error to the bias caused by unmeasured confounding. Bias formulas for unmeasured confounding have been derived by Vanderweele (2010). He estimates the bias by specifying the effect of the unmeasured confounder on the outcome, and the prevalence of the unmeasured confounder for specific values of the intermediate. In practice it is often easier to make assumptions about the effect of the confounder on the intermediate. Therefore we have rewritten some of the results of VanderWeele and obtained bias rules where the prevalence of the confounder and its effect on the intermediate can be specified directly.

As a practical example we consider data of the LETS study. In this case-control study the question was whether the relation between blood group and venous thrombosis was mediated through coagulation factor VIII. Here intra-individual variation over time likely is the major source of bias; the effect of an unmeasured confounder on the intermediate and outcome should be large to substantially alter the estimates of direct and indirect effects.

References:

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le Cessie S, Debeij J, Rosendaal FR, Cannegieter SC, Vandenbroucke JP. Epidemiology. 23(4):551-560.
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Comparison of Three Approaches to Causal Mediation Analysis

Donna Coffman, D. P. MacKinnon, Y. Zhu, & D. Ghosh
Pennsylvania State University

Introduction: Mediation occurs as part of a hypothesized causal chain of events: An intervention or treatment, T, has an effect on the mediator, M, which then affects an outcome variable, Y. Recently, three different approaches, all of which fall under the potential outcomes framework for causal inference, have been proposed for drawing more valid causal inference in mediation analyses. These approaches define the mediation effects as either principal strata effects (e.g., Rubin, 2004; Jo, 2008), natural effects (e.g., Pearl, 2001; Imai et al., 2010), or controlled effects (e.g., Robins & Greenland, 1992; VanderWeele, 2009).

Methods: In this talk, we illustrate that each of these definitions answer different scientific questions and that each makes different assumptions about the existence of direct effects (i.e., the effect of T on Y that is not due to M), iatrogenic effects of T on M, the existence of post-T confounders that have been influenced by T, and the existence of T*M interactions. We also describe how the traditional regression-based approach relates to the three approaches based on the potential outcomes framework. We assess the sensitivity of each of the three approaches to violations of the assumptions using a simulation study that systematically varies different aspects of these assumptions.

Results: We found that when no assumptions were violated, as may be expected, each approach was unbiased for its respective population value and 95% confidence interval (CI) coverage was maintained. When there was a direct effect of T on M or an interaction between T and M, the principal strata effects were severely biased and 95% CI coverage was unsatisfactory. Natural and controlled effects were unbiased and maintained 95% CI coverage. When there were possible iatrogenic effects of T on M, principal strata effects were slightly biased but the variance was very large and resulted in 95% CI coverage of 100%. In this situation, natural and controlled effects were unbiased and maintained 95% CI coverage. These are the results from a few of the simulation conditions, as there is not space to present all of them here.

Conclusions: We suggest that researchers need to choose the best approach based on the scientific question to be addressed and the assumptions that are plausible given their data.

Understanding Causal Mechanisms through Principal Stratification: Definitions and Assumptions

Alessandra Mattei, F. Li, & F. Mealli
Department of Statistics, University of Florence

Understanding causal mechanisms is just as attractive as it is challenging, and full agreement on how defining, identifying and estimating causal mechanisms is still debatable. Here we would like to shed some light on crucial issues that often give rise to fierce disputes in the causal inference community. We use potential outcomes to discuss (a) research questions, which motivate focus on understanding causal mechanisms; (b) alternative definitions of causal estimands; and (c) assumptions allowing one to identify and estimate those causal estimands. We clarify the role of the alternative (structural and distributional) assumptions, separating and critically discussing those allowing one to carry out extrapolation to recover *never observable quantities* and those on potentially observable sub-populations.

Some researchers focus on identifying and estimating natural direct and indirect effects, which are descriptive tools for explaining how part of the treatment effect is channelled by the mediating variable. This approach generally treats potential outcomes of the mediating variable asymmetrically by choosing only one of them as *natural condition*, and involves so-called 'a priori counterfactuals'. A priori counterfactuals may be very difficult to conceive and are also ill-defined unless we are willing to assume that the mediating variable could be at least potentially controlled by external interventions, by explicitly introducing an assignment mechanism for the mediating variable.

According to us, a *principal stratification* (PS) approach can provide a better description of the causal paths. PS focuses on principal causal effects (PCEs), which are always well-defined causal effects, and avoid a priori counterfactuals. PCEs for principal strata where the mediating variable is unaffected by the treatment, also named 'dissociative effects', *naturally* provide information on natural direct effects for units for whom the mediating variable does not change. Also the comparison between dissociative effects and the other PCEs (associative effects) may provide valuable information on the mediated effects, at least under specific assumptions.

Conducting a full principal stratification analysis may be a challenging task, due to latent nature of principal strata membership. Depending on the substantive empirical setting, alternative assumptions can be introduced, which however generally lead only to partial identification of PCEs unless coupled with distributional assumptions. Although these additional assumptions may be critical and arguable in some settings, they generally do not involve comparisons of units belonging to different strata, because they aim at identifying local causal effects rather than overall direct and indirect effects.

Our suggestion is therefore to preliminary conduct a principal stratification analysis, looking at the characteristics of each principal stratum and the distributions of potential outcomes in each principal stratum, in order to decide whether ignorability assumptions on the assignment mechanisms for the mediating variable, which justify mixing information across principal strata, may be reasonable.

Causal mediation analysis with multiple causally-ordered mediators

Rhian Daniel, & Bianca De Stavola
London School of Hygiene and Tropical Medicine

In many fields of empirical research, interest lies in decomposing the effect of an exposure on an outcome into its effect via a number of different pathways. For example, the effect of heavy alcohol consumption on systolic blood pressure (SBP) may be separated into an effect via body mass index (BMI), an effect via gamma-glutamyl transpeptidase (GGT), an effect via both BMI and GGT, and an effect via other pathways (not through BMI or GGT)—often called the direct effect. Much progress has been made, mainly due to contributions from the field of causal inference, in understanding the precise nature of estimands that capture these sorts of effects, the assumptions under which they can be estimated from data, and statistical methods for doing so. However, the focus has been mostly on the decomposition of an effect around and through a single mediator, or a set of mediators considered as a block, hence the two components: a direct and indirect effect. In this talk, we discuss path-specific estimands that permit the decomposition of the total effect of an exposure on an outcome into a sum of numerous path-specific effects through many mediators, where the mediators are permitted to have a causal effect on each other. We show that there are many ways in which this decomposition can be done, discuss assumptions that permit identification, and illustrate these decompositions using a real data example on alcohol consumption, SBP, BMI and GGT.

Mechanistic interaction in presence of stochastic mediators

Carlo Berzuini and A.Philip Dawid
Centre for Biostatistics, University of Manchester, UK

Given two variables, A and B, that causally influence a binary response, one often asks whether the effects of A and B upon the response interact in a *mechanistic* sense, that is, by virtue of the fact that they operate through a common mechanism. The problem has been frequently tackled in the literature. Yet, complications arise when the effects of A and B on the response are mediated by a stochastic variable, M, but not totally. In this case, one might ask the more specific question whether mechanistic interaction exists between the *direct* (as opposed to *total*) effects of A and B on the response. In other words, do we still have mechanistic interaction when we perform a (possibly hypothetical) intervention that fixes M to the same value in all individuals?

We tackle the problem from within a purely probabilistic framework, without using potential outcome concepts. We introduce a definition of *probabilistic mechanistic interaction* free from the usual assumptions of determinism (about either of the response or the mediator), in a way that invites a comparison with the recent s̈tochastic counterfactualsd̈evelopments by VanderWeele and Robins. Then we provide conditions and assumptions under which such probabilistic mechanistic interaction - between total or direct effects - can be assessed from observational data. The main conditions are expressed in terms of conditional independence relationships, that can be manipulated with the aid of causal diagrams. We shall consider generalizations to the case where A is continuous, and to the case of three interacting causal factors. We shall illustrate the method and its relevance with the aid of real studies in a variety of applied contexts.

A stochastic approach to atomic total, direct and indirect effects

Axel Mayer & Rolf Steyer
Friedrich Schiller University Jena

In mediation analysis, we typically distinguish between total, direct and indirect effects. Intuitively, direct effects represent those parts of total effects that are not transmitted through the intermediate variable(s). Indirect effects are those components that are not direct but may be transmitted through mediator variables. Several formal definitions of causal effects in mediation models have been recently presented in the literature (Didelez et al., 2006, Imai et al., 2010; Pearl, 2001; VanderWeele & Vansteelandt, 2009).

We offer an alternative definition based on a stochastic theory of causal effects (Steyer et al., 2012; Mayer et al., 2012). We define atomic causal effect variables as differences between true-outcome variables. These true-outcome variables are the conditional expectations of the outcome variable in a treatment condition, given all potential confounders. The true-outcome and causal effect variables are defined with respect to a time point in order to distinguish between total and direct effects. Based on atomic causal effect variables, we can define average and conditional causal effects as specific expectations and conditional expectations. Conditional effects, such as effects on the treated or causal effects conditional on a mediator, provide the researcher with additional insights about the effectiveness of the treatment. Conditional effects allow for a detailed inspection of the effectiveness of a treatment or an intervention.

We define unbiasedness of empirically estimable regressions and discuss conditions that imply unbiasedness. We propose (conditional) stochastic and regressive independence conditions (causality conditions) that allow for identifying causal mediation effects from estimable quantities.

We discuss several examples to illustrate how these theoretical definitions of total, direct and indirect causal effects apply to path analytic models. These examples include (1) a mediation model with pre-treatment variables, (2) causal mediation effects in structural equation models with latent variables, (3) models with multiple potential mediators and (4) an applied data example from psychotherapy research.

A structural modelling approach to mediators, moderators and confounders. A counterfactual-free approach.

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As long as statistical association, or correlation, does not imply causation, causal attribution requires understanding the mechanism underlying a data generating process.
Explaining a multivariate, or complex, process is most properly operated through a recursive decomposition of a multivariate distribution into a sequence of marginal and conditional distributions, each one representing a sub-mechanism of the global one.
A structural modeling approach endeavors at unfolding the structure underlying the data generating process and looks for sub-mechanisms congruent with field knowledge and enjoying a suitable stability, or invariance, relatively to a population of interest and, accordingly to a suitable class of interventions or of modification of the environment.
The effect of a (causing) variable on the outcome of a sub-mechanism is evaluated through the change, or variation, of the conditional distribution, representing a sub-mechanism, attributable to a change, or variation, of the causing variable of interest.
The classification of variables into mediators, moderators or confounding variables refers to the role of a variable on the working of a mechanism or of a sub-mechanism.
This paper shows that measuring the effect of a causing variable does not require the recourse to counterfactual concepts but also the counterfactual ideas may, in some contexts, provide a suitable starting point for an adequate structural model.

Posters

Eurosupport 6: Assessing mediators of a computer-assisted counseling intervention on safer sex for people living with HIV

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Due to medical treatment advances, greater numbers of people living with HIV (PLHIV) are living in good health for longer periods of time. The focus of health care has thus shifted from preventing death to increasing quality of life, of which sexual and reproductive health and rights are an important part. A randomized clinical trial is performed with the objective to evaluate a computer-assisted counseling intervention on safer sex (CISS) to reduce HIV and STI transmission risk behaviours among PLHIV, and thereby increase sexual and reproductive well-being. The CISS is based on the information-motivation-behavioural skills model (Fisher & Fisher, 2002), which was adapted to the specific needs of PLHIV in a previous study. According to these previous findings, HIV transmission risk behaviours are driven by deficits in motivation and in behavioural skills. In order to support PLHIV in preventive behaviour, the CISS intervention comprises an individualized prevention plan that aims at remediating such deficits. When assessing the effect of CISS on condom use, our goal is to evalua te whether this intervention effect is mediated through changes in attitudes, which are part of motivation, and/or self-efficacy, which is an important prerequisite of behavioural skills. Since CISS is tailored to a person's specific needs, the intervention-mediator association may differ between people. We suggest three possible approaches to account for this heterogeneity. First, add interaction with baseline covariates, e.g. baseline attitudes, self-efficacy, depression score, to the intervention-mediator model. Second, split the intervention in different types of intervention according to their individualized goal and assess the effect of the different intervention types. Third, account for heterogeneity by introducing random effects in the intervention-mediator relationship. We invite discussion on the feasibility, advantages and disadvantages of the different approaches.

Fisher JD & Fisher WA (2002). The information-motivation-behavioural skills model. In: Di Clemente R, Crosby R, Kegler R (eds). HIVPrevention Handbook. New York, Kluwer Academic, 3-55.

Testing treatment mediation in small uncontrolled samples: Product of coefficient test

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Mediation analysis can be a valuable tool in treatment outcome studies to investigate processes through which a certain treatment works. Small samples are one of the most important obstacles to studying mediation in treatment outcome studies. Traditional methods (i.e., Baron & Kenny, 1986) require rather large samples. The aim of this study is to illustrate how product of coefficient test (MacKinnon, 2008) can be used to test for treatment mediation in small uncontrolled samples. Study participants were 19 adolescents who completed cognitive-behavioural treatment. Outcome and mediator variables were assessed at pre-treatment, post-treatment and 2-month follow-up. Post-treatment increases in school attendance and decreases in fear about attending school the next day were found to be mediated by self-efficacy. Mediating effects were not observed at 2-month follow-up. These findings contribute to a small body of literature suggesting that cognitive change enhances CBT outcomes for young people with internalizing problems. The product of coefficient test appears to be a valuable way to study mediation in outcome studies involving small samples. Approaches to how confounding variables may have contributed to the observed results are described.

Identity Processes in Filipino Emerging Adults: Parental Influences and Mental Health Outcomes

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This study focused on a process-oriented approach to identity development (Luyckx et al., 2008) using a Filipino emerging adult sample, integrating mental health as identity outcomes and parental influences as antecedents. Furthermore, the role of identity as a mediator between parental influences and mental health outcomes was examined. Two types of parental influences (parental psychological control and parental support), two types of mental health outcomes (depression and psychological well-being), and five dimensions of identity development (commitment making, identification with commitment, exploration in breadth, exploration in depth, and ruminative exploration) were assessed. Respondents (N = 778) were asked to complete an online survey. Recursive path analysis showed that exploration in breadth, exploration in depth, ruminative exploration and identification with commitment mediated the relationship between parental influences and mental health outcomes. The mediation analysis suggests that identification with commitment, exploration in breadth, and exploration in depth could partially account for how parental support influences adult well-being. Similarly ruminative exploration could partially explain why and how parental psychological control carries over into depression and well-being. Relevance of the findings on identity development and parenting will be discussed.

Adult attachment and sexual satisfaction: An analysis of the mediating role of sexual communication

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In the current study we examined sexual communication and sexual satisfaction within intimate relationships from an attachment perspective. More specifically, we aimed to investigate the specific associations between individuals and attachment orientation (anxiety, avoidance), sexual communication with their partner (openness) and their level of sexual satisfaction. We hypothesized that sexual communication would partially mediate the association between individuals attachment orientation and sexual satisfaction. Gender differences were also explored. A sample of 507 participants, who were all involved in a committed intimate relationship, completed questionnaires that assessed sexual communication, sexual satisfaction and attachment. The mediating effects of sexual communication were assessed using regression equations and the Sobel-test. Our results indicated that more anxiously and avoidantly attached men reported lower levels of sexual satisfaction. For women, however, merely avoidant attachment was a significant predictor of sexual satisfaction. For both men and women avoidant attachment, relative to anxious attachment, was more detrimental to sexual satisfaction. Consistent with our predictions, sexual communication was positively associated with sexual satisfaction, with individuals who communicate more openly about sex, being more sexually satisfied. Furthermore, regarding men, we found that the association between individuals and insecure attachment and their level of sexual satisfaction was partially mediated by the openness of sexual communication. In contrast, for women, sexual communication was merely a partial mediator of the relation between avoidant attachment and sexual satisfaction. No significant gender differences were found in the associations between our key variables. Our findings thus suggest that people's attachment characteristics have an impact on their level of sexual satisfaction by means of the degree of openness of their sexual communication with their partner.

Modelling Treatment Processes in Parenting Programmes

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Parenting programmes are the most effective intervention to change persistent child anti-social behaviour and are widely used, but little is known about the mechanisms through which they work and hence how to improve them. The theory underlying parenting programmes and corresponding research literature suggests mediation pathways work through changing parenting practices which then change child outcomes. This project aims to bridge this gap by using data from existing randomised controlled trials (RCTs) of parenting programmes to explicitly evaluate mediation models for parenting treatments and partition the total effect of training programmes on child outcome into parts that can be attributed to the different hypothesized pathways.
Putative mediators were fitted into signal-mediation models and traditional Barren and Kenny regression approach was applied to analyzing mediation effects. Preliminary results indicate that harsh parenting, parental criticism and parental warmth mediated the treatment effects on child conduct problems ignoring the confounding between parenting mediator and child outcome relationship. The statistical evaluation of mediation poses a number of analytical challenges. First, traditional mediation analyses assume the absence of unmeasured confounders that are likely to be present in parenting trials. Second, reverse causation cannot be ruled out as the effect of child behaviour on subsequent parenting. Finally, the mediator maybe subject to measurement error. Thus the emphasis of this project will be on developing process analysis methods in the field of parenting treatments (e.g. instrumental variable methods) and increasing statistical power by combining several trials.