EpiCause 2024 - Abstact Booklet

Thursday, May 2, 2024 **2**

Keynote: Tyler VanderWeele . . . 2

The Paradoxes, Perplexities, and Power of Factor Analysis . . . 2

Session 1 . . . 3

Causation in Epidemiology: An action-related approach . . . 3

A new light on causes in human health-associated microbiome studies by unearthing its ecological roots . . . 4

From Treating to Beating Cancer: A Critical Examination of Cancer Prevention, Nutrition, Treatment Methods, and the Production of Ignorance . . . 5

Session 2 . . . 6

Exploring Geneticists' Alternate Understandings of Causation . . . 6

The answer is right under your nose but the question never arose . . . 7

What's in an effect? . . . 8

Friday, May 3, 2024 **9**

Keynote: Miguel Hernan . . . 9

Why most causal diagrams are not causal: The implications of well-defined causal questions . . . 9

Session 3 . . . 9

The Logic of Counterfactuals and the Epistemology of Causal Inference: A Dose of Econometrics for Everyone . . . 9

Session 4 . . . 10

What are causal relations across the sciences? Towards a hybrid account merging difference-making and mechanistic intuitions about the ontology of causation . . . 10

Session 5 . . . 11

Epidemiological Evidence and SIngle-Case Evaluation in Forensic Medicine - The Example of the "Excited Delirium Syndrome" . . . 11

Epistemology of Epidemiology : Its Relevance for Efficacy of Pandemic Management - the Case of COVID-19 and its "theory-free" Modeling . . . 12

The evidential role of the key characteristics of carcinogens . . . 13

Session 6 . . . 14

Formalising extrapolation . . . 14

Artificial intelligence methods in Bayesian evidence evaluation . . . 15

Health Effects of Loneliness and Causal Pluralism . . . 16

Saturday, May 4, 2024 **17**

Keynote: Stefano Canali . . . 17

Rethinking Data and Evidence in Medicine, Rethinking Causality and Empiricism in Philosophy? 17

Session 7 . . . 17

Epistemological and practical challenges in using causal inference analyses in social epidemiology: developing a tool to support researchers . . . 17

Epidemiology, RCTs and Econometric Modelling . . . 18

Session 8 . . . 19

Individual-level and population-level causes in epidemiology: a stability account . . . 19

It's Biomedical Standard Time somewhere: Unsettling the framing of epigenetic aging as a causal mechanism linking social and environmental exposures to health . . . 20

Thursday, May 2, 2024

Keynote: Tyler VanderWeele

The Paradoxes, Perplexities, and Power of Factor Analysis

*Tyler VanderWeele (Harvard University)**

Factor analysis is often employed to evaluate the extent to which a single factor suffices to explain the variation in the individual indicators, or alternatively to identify clusters of indicators that are strongly correlated with one another. However, the conclusions drawn from factor analysis often extend beyond what statistical analyses have in fact established. Often the resulting factors are each interpreted as corresponding to a structural univariate latent variable that is itself causally efficacious. I show that this assumption is in fact so strong that it has empirically testable implications, even though the supposed latent variable is unobserved; statistical tests are proposed that can often reject this underlying assumption. Factor analysis also suffers from the inability to distinguish between associations arising from causal versus conceptual relations, and if two supposed factors were to causally affect one another then, in many settings, over time, the process will converge to a factor model wherein only a single factor can be detected if one uses a single wave of data. Factor analysis further suffers from the problem that if different indicators are used to assess different portions of the distribution of an underlying univariate latent variable (as might arise from the use of negatively worded items in surveys), then factor analysis can suggest that two factors are present even though the data are in fact generated by only one. Examples of each these various phenomena are given from the psychology and biomedical literature concerning causal relations between depression and anxiety, differential associations with mortality of various indicators of life satisfaction, and supposedly different factors corresponding to optimism and pessimism. Despite these severe limitations, factor analyses, perhaps paradoxically, can nevertheless often be very informative, but the phenomena above require an appropriate reinterpretation of factor analysis results as reflecting a combination of causal, conceptual, and distributional relations.

Session 1

Causation in Epidemiology: An action-related approach

*Atocha Aliseda (UNED)**

The question to be addressed in this presentation is what characterises the notion of causation in epidemiology. I shall argue that action-related approaches to causality are very appropriate, as they are characterized by interpreting causal laws as closely connected to actions, interventions and manipulation, all key elements in epidemiology. I illustrate this approach with a well-documented case, that of the relationship between the act of smoking and the condition of lung cancer. In the first half of the XXth century, in the United Kingdom where lung cancer disease had increased exponentially between the years of 1922 and 1947, there were two competing hypotheses: the causality hypothesis – smoking causes lung cancer– and the constitutive one, according to which there was an unknown third aspect, the real cause, explaining both the smoking habit and lung cancer. Each hypothesis points to an action and assumes a conception of causality. The causality hypothesis assumes an interpretation in which causes are the medium by which goals are obtained. In this case an intervention goes towards preventing the cause –smoking—to reduce its effect: an increase in the incidence of lung cancer in the population. In contrast, in the constitutive hypothesis, the goal is to discover another cause.

I will then expand on why action-related approaches to causality are successful for epidemiology. An intervention may solve a problem (high incidence of lung cancer in smokers) as well as corroborate a causal claim, what Gillies calls the principle of interventional evidence: "A causal law cannot be taken as established unless it has been confirmed by some interventional evidence" (Gillies, 2019). In this approach to causality, the emphasis is on agent's actions wishing to transform a state of the world rather that to explain it. I will argue that this aspect gives a pragmatist flavor to action-related causality theories.

References

- British Medical Research Council, (1958), "Tobacco smoking and cancer of the lung: statement of the British Medical Research Council", CA: A Cancer Journal for Clinicians, 8(2), pp. 66–68.
- Collingwood, R., (1940), An Essay on Metaphysics, Oxford University Press, Oxford. Gillies, D., (2019), Causality, Probability, and Medicine, Routledge, U.K.
- Doll, R., Hill, A. B., (1950), "Smoking and carcinoma of the Lung; preliminary report", British Medical Journal, 2(4682), pp. 739-748.
- Parascandola, M., (2004), "Two approaches to etiology: the debate over smoking and lung cancer in the 1950s", Endeavour, 28(2), pp. 81–86.
- Rothman, K., y Greenland, S., (2005), "Causation and causal inference in epidemiology", American Journal of Public Health, 95(1), pp. S144-150.
- Von Wright, G. H., (1974), Causality and Determinism, Columbia University Press, New York.

A new light on causes in human health-associated microbiome studies by unearthing its ecological roots

*Aline Potiron (Johannes Kepler University)**

Animals host microorganisms at various body sites like the gastrointestinal tract, skin, lungs, vagina, and urinary tract. The human gut microbiome has been associated with multiple health and disease phenotypes for the past twenty years. This tendency culminates with the integration of microbiomes in epidemiology studies.

The research of causes in health-associated microbiome studies is based on the original or variants of Koch's postulates (e.g., Lynch et al., 2019; Vonaesh et al., 2018). They are helpful for the detection of single and specific causal factors of diseases, e.g., microorganisms. They have been successful for some time, especially in the case of monocausal diseases, and gave rise to the germ theory of diseases. The ideas of specificity in terms of monocausality and homogeneity of causes are pervasive in contemporary medicine (Ross, 2018). They are also ubiquitous in microbiome studies, e.g., researching biomarkers for cancers or researching a curative "silver bullet" bacteria. As a result, the default assumptions in those researches are often a monocausal and specific cause for a disease or an intervention.

However, I argue that scientists in health-associated microbiome studies have forgotten their history. Microbiology and microbiome studies are also ecological disciplines, not only medical ones. The father of microbial ecology is Sergei Winogradsky. While younger than Robert Koch, he was one of his contemporaries. In Winogradsky's work, the research of causes is not focused on entities but on processes and interactions. He was studying the natural phenomena of the soil and the microorganismal community within it. He recognized at face values that those phenomena were complex by nature, i.e., multifactorial and non-entity specific.

In this work, I will explore the state of health-associated microbiome studies if the default position would have been "Winogradskian," i.e., looking for several factors and non-specific entities before looking for specific and unique causes. It might be then that the contemporary attempts at simplicity would be an exception rather than a rule and that more global and integrative approaches, such as the one defended in the OneHealth concept, would have come sooner, impacting epidemiology-related policies.

References

- Lynch, K. E., Parke, E. C., & O'Malley, M. A. (2019). How causal are microbiomes? A comparison with the Helicobacter pylori explanation of ulcers. Biology and Philosophy, 34(62), 1–24. https://doi.org/10.1007/s10539-019-9702-2
- Vonaesch, P., Anderson, M., & Sansonetti, P. J. (2018). Pathogens, microbiome, and the host: Emergence of the ecological Koch's postulates. In FEMS Microbiology Reviews (Vol. 42, Issue 3, pp. 273–292). Oxford University Press. https://doi.org/10.1093/femsre/fuy003
- Ross, L. N. (2018). The doctrine of specific etiology. Biology and Philosophy, 33(5–6). https://doi.org/10.1007/s10539-018-9647-x

From Treating to Beating Cancer: A Critical Examination of Cancer Prevention, Nutrition, Treatment Methods, and the Production of Ignorance

*Courtney E Foster (University of Notre Dame)**

Cancer prevention strategies vary largely depending on the expert source. Considering that the cause of cancer is multifaceted experts often refer to its prevention in terms of risk factors for developing the disease rather than definitive prevention methods. Although most experts agree that maintaining a healthy diet reduces the risk of developing cancer, there are disagreements about the exact diet to follow. This type of inconsistency produces ignorance and creates confusion among people who want to prevent or lower their risk of developing cancer through diet because they are uncertain about whether nutrition helps prevent it.

Without being able to establish the exact effects of diet on cancer risk, nutrition is underemphasized as a potential preventative measure. Instead, early detection options (i.e., mammograms, colonoscopies, etc.) are promoted as a means of preventing cancer despite the methods of detection and prevention being separate and distinct. Once cancer is detected, oncologists prescribe extensive, invasive, and expensive conventional treatments like surgery, radiation, and chemotherapy with varying complete response rates (e.g., effectiveness) depending on the type and stage of the cancer being treated. Thus, the emphasis lies in early detection and conventional treatments, and the public comes to conflate early detection and prevention. Ignorance is then produced when early detection methods and conventional treatments are promoted over preventative dietary measures as the only approaches to eradicating cancer.

In this paper, I will provide a philosophical analysis of cancer research through the lens of agnotology. Based on my research, I have concluded that inconsistent and ambiguous scientific nutritional claims associated with cancer risk produce ignorance. Although further scientific exploration regarding the viability of nutrition when it comes to preventing cancer would be less expensive and non-invasive, scientific claims about whether there is a link between nutrition and cancer risk are unclear which produces ignorance. In addition, I will examine how conventional cancer treatments are less effective and cause more serious side effects than the scientific community portrays to the public. This produces ignorance and leads the public into believing that the only means to combat cancer are early detection and conventional treatment methods which, in turn, impacts public health.

Session 2

Exploring Geneticists' Alternate Understandings of Causation

*Hannah S Allen (University of Utah)** Within various subdisciplines of genetics, researchers claim to have uncovered genetic causes of a wide range of human traits from diseases such as sickle cell anemia to social and behavioral traits such as educational attainment. Our survey- based study follows Nancy Cartwright (2014) who connects scientists' concepts of causation with their various methods of discovering causes and Helen Longino (2013) who points out that the various approaches to understanding behavior dictate the types of causes researchers uncover.

Taking direction from Cartwright and Longino, we have begun investigating what geneticists mean when they purport to have discovered a genetic cause for some trait, what kinds of evidence they think are sufficient to support such claims, and whether they are more willing to make causal claims on behalf of genes connected with some traits rather than others.

We tackle these questions via a survey-based study. Our pilot survey has been distributed to geneticists and allied researchers and clinicians at the University of Utah and we have begun to analyze preliminary data. We asked respondents several general questions about genetic causation and present them with a series of four vignettes about different human traits in order to gauge differences in willingness to attribute genetic causes for traits on the basis of different kinds of evidence. Responses to our pilot study have helped us judge the effectiveness of our approach, and set up a larger study, which we are beginning to circulate to genetics societies such as the Genetics Society of America, the Behavior Genetics Association, and the International Society of Psychiatric Genetics.

In this talk, we present preliminary data and discuss feedback from geneticists on the pilot survey. We anticipate finding alternate understandings of genetic causation across the subdisciplines of genetics and anticipate that these alternate understandings of genetic causation will cluster within different sub-disciplines of genetics. We assess the fit between alternate accounts of genetic causation presented by philosophers of science and biology and accounts adopted by geneticists to determine whether philosophical accounts of genetic causation help (or hinder) geneticists. The implications of this research will possibly expose potential harms (or goods) that might come from scientists' oversimplifications of genetic causes when used for different purposes.

References

- Cartwright, N. 2014. "Causal Inference." In Philosophy of Social Science: An Introduction, edited by N. Cartwright and E. Montuschi, 308–26. Oxford: Oxford University Press.
- Longino, H.2013. Studying Human Behavior. Chicago: University of Chicago Press.

The answer is right under your nose but the question never arose

Johan Steen (Ghent University); Sigrid Sterckx (Ghent Univeristy); Stijn Vansteelandt (Ghent University); Wim Van Biesen (Ghent University); Johan Decruyenaere (Ghent University Hospital)*

Why the way we analyze our data determines the questions that we are truly answering and why these are often very different from the ones we think we are answering

A recently proposed taxonomy classifies empirical research questions into three different classes: descriptive (e.g. to assess the incidence of a certain adverse event in a given population), predictive (e.g. to identify patients who are at increased risk of experiencing that event within the next 5 years), and causal (e.g. to decide which intervention to best provide to patients that are at increased risk) questions [1]. Answers to each type of question may have different implications for clinical and policy decisions, hence it is important to recognize and formulate the goal(s) of empirical studies as belonging to one of these distinct categories. Even so, the causal goal of empirical studies is often not explicitly stated and statements with explicit causal inferences from non-randomized observational studies are moreover commonly discouraged by journal editors [2]. For instance, studies that investigate prolonged hospitalization related to hospital complications, such as hospital-acquired infections or acute kidney injury, are often not explicit about whether the goal is to provide a purely descriptive measure, a risk prediction or a causally interpretable numerical measure. In addition, it has been highlighted that the distinction between descriptive and causal questions is not always clear-cut [3]. In this talk, we will explore this continuum and how it relates to different forms of bias, such as confounding bias and immortal time bias. When a descriptive analysis considers stratification factors with a time-dependent onset (such as hospital complications), certain key questions arise on what makes an 'associational' measure well-defined and when its corresponding numerical estimate carries an unambiguous interpretation. The importance of these questions is illustrated by means of a negative control exposure (e.g. patients with zodiac sign of Taurus and Pisces vs others) which is known not to be associated with the outcome of interest (neither causally nor in any other way). In addition, we will explain that some analytical approaches that aim to tackle bias in descriptive analyses (e.g. the extended Kaplan-Meier estimator [4]) may inadvertently change the nature of the research question being answered by that analysis, possibly turning a descriptive question into a causal question [5]. This may, in turn, add an extra layer to the confusion on the distinction between descriptive and causal questions. In this talk, we aim to provide more clarity and potential solutions on these issues.

References

1. Hernán MA, Hsu J, Healy B (2019) A Second Chance to Get Causal Inference Right: A Classification of Data Science Tasks. CHANCE 32:42–49. https://doi.org/10.1080/09332480.2019.1579578

2. Hernán MA (2018) The C-Word: Scientific Euphemisms Do Not Improve Causal Inference From Observational Data. Am J Public Health e1–e4. https://doi.org/10.2105/AJPH.2018.304337

3. Fox MP, Murray EJ, Lesko CR, Sealy-Jefferson S (2022) On the Need to Revitalize Descriptive Epidemiology. Am J Epidemiol 191:1174–1179. https://doi.org/10.1093/aje/kwac056

4. Snapinn SM, Jiang Q, Iglewicz B (2005) Illustrating the Impact of a Time-Varying Covariate With an Extended Kaplan-Meier Estimator. Am Stat 59:301–307. https://doi.org/10.1198/000313005X70371

5. Sjölander A (2020) A Cautionary Note on Extended Kaplan-Meier Curves for Time-varying Covariates. Epidemiology 31:517–522. https://doi.org/10.1097/EDE.0000000000001188

What's in an effect?

*Veli-Pekka Parkkinen (University of Bergen)**

Epidemiological effect measures can be absolute, like incidence rate or risk difference, or relative, such as risk, rate, or odds ratio. Philosophers have argued for preferentially calculating and reporting absolute measures, in particular risk difference, in virtue of their alleged cognitive salience, and superior policy- and clinical relevance (e.g. Broadbent, 2013; Sprenger & Stegenga, 2017; Stegenga, 2015; Worrall, 2010). Absolute measures are philosophically attractive also for being readily interpretable in light of almost any difference-making theory of causation. In practice though, the choice of an effect measure depends on the choice of study design, which depends on the specifics of the research question. The arguments favoring absolute measures apply to designs that allow estimation of baseline risks, paradigmatically a cohort study. Such designs may not always or even often be feasible. Hence, different effect measures, the problem of choosing one, and the consequences of such choices for causal inference deserve to be studied in their own right, rather than seeing relative measures as foil for the virtues of absolute ones. I reassess the arguments in favor of absolute measures in the broader context of the problem of choosing a study design. I then note some observations about how the choice of effect measure shapes our understanding of key causal concepts like transportability of effects, confounding, and interaction. All of these concepts are in their own way ambiguous with respect to scale. For example, an interaction effect measured on the risk-difference scale might be a sum of independent effects on the odds ratio scale. I assess the consequences of such ambiguities for the interpretability of various effect measures, and the philosophical merits of assuming the existence of a "natural" scale on which "natural" causal effects live, to which all modeled effects could be translated to avoid ambiguities. I conclude that such an assumption is probably not useful, and several key concepts of causal inference may not be completely univocal.

References

- Broadbent, A. (2013). Philosophy of epidemiology. Palgrave Macmillan.
- Stegenga, J. (2015). Measuring effectiveness. Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences, 54, 62-71.
- Sprenger, J., & Stegenga, J. (2017). Three arguments for absolute outcome measures. Philosophy of Science, 84(5), 840-852.
- Worrall, J. (2010). Do we need some large, simple randomized trials in medicine?. Epsa Philosophical Issues in the Sciences: Launch of the European Philosophy of Science Association, 289-301.

Friday, May 3, 2024

Keynote: Miguel Hernan

Why most causal diagrams are not causal: The implications of well-defined causal questions

Miguel Hernan (Harvard University)

Session 3

The Logic of Counterfactuals and the Epistemology of Causal Inference: A Dose of Econometrics for Everyone

*Hanti Lin (University of California, Davis)**

The Rubin causal model (Rubin 1974) has long been argued to be committed to determinism, which the statistician Dawid (2000) takes to be a key reason against it. Dawid also has a closely related reason against it. Some of the most successful applications of the Rubin causal model come from a result proved by the econometricians Imbens & Angrist (1994), which concerns the possibility of statistical estimation and non-experimental identification of a certain causal effect: the local average treatment effect (LATE). But this result about LATE relies on the concepts of so-called compliers and defiers, which Dawid argues cannot be made sensible in an indeterministic worldview. So, if Dawid is right, we will have to question 2/3 of the 2021 Nobel Prize in Economics, the part awarded to Angrist and Imbens. I will defend the Rubin causal model and reply to Dawid.

I will start by clarifying the debate between Dawid and Rubin's followers. In particular, I will show that Dawid's (2000) worry for the Rubin causal model is, in an important sense, equivalent to a long-standing debate in philosophy: Lewis' (1973) objection to Stalnaker's (1968) logic of counterfactuals, including especially the Principle of Counterfactual Excluded Middle. Then, I will defend the Rubin causal model by giving it a somewhat radical reformulation, with two important properties:

(1) My reformulation of the Rubin causal model is free from the commitment to Counterfactual Excluded Middle, orthogonal to the Lewis-Stalnaker debate, and uncontroversially compatible with both determinism and indeterminism (at least uncontroversially so for both parties in the present debate).

(2) My reformulation of the Rubin causal model *provably* preserves all successful applications of LATE. The trick is to turn the Rubin causal model into a "fictionalist" extension of causal Bayes nets (and stay away from Pearl's nonparametric structural equation models).

I take this to be a first step toward a new foundation of the Rubin causal model and the theory of LATE, a very influential causal model and theory of causal inference in the health and social sciences (including epidemiology). It is a foundation compatible with both determinism and indeterminism.

This result should be interesting not just for philosophers of science, but also for philosophers of language. The 2021 Nobel Prize in Economics could have been used by Stalnakerians to give an indispensability argument for Counterfactual Excluded Middle (one that parallels the indispensability for mathematical platonism). The present work anticipates, and undermines, that argument.

Session 4

What are causal relations across the sciences? Towards a hybrid account merging difference-making and mechanistic intuitions about the ontology of causation

*Mariusz Maziarz (Jagiellonian University)**

All three domains in the title make heavy use of statistics to inform causal conclusions. But everybody knows, 'Correlation isn't causation'. What more is needed? Antecedent causal knowledge! Epidemiology draws on a variety of different kinds of knowledge to bolster causal hypotheses suggested by correlational data: quasi-natural experiments, sophisticate models of how diseases spread, demographic data, theories of human behaviour …. But occasionally, in especially epistemically convenient cases, we can use our antecedent knowledge not just as other ways to reinforce statistical suggestions but actually to infer causal conclusions from the statistics. Results about econometric modelling can show when and how.

So, this talk aims to familiarise you with results that show conditions under which this can be done in econometrics since – with very good luck – the same kind of modelling can be employed in epidemiology. The good luck has to do with what antecedent knowledge is available. What you need to know for these results to apply is demanding. Nevertheless there are many cases when we might well know what is necessary, or at least take it to be a good bet. So it is important that these kinds of results are familiar in epidemiology – we need all the good tools we can get.

What has this to do with RCTs? RCTs claim to be the gold standard for inferring causal conclusions from statistics is based on the fact that it is provable that if the required probabilistic independencies hold in the experiment then the difference in mean outcome values between treatment and control groups is an unbiased estimate of the true average treatment effect in the experimental population. Two things matter for the discussion here. First, as I shall explain, contrary to popular myth, RCTs –like any other method – require antecedent knowledge – and lots of it – to draw causal conclusions. Whether to do an RCT or an econometric-like model in epidemiology depends on which required knowledge you can get in time. Second, the proof just mentioned supposes that the causal possibilities in a given setting can be represented in potential outcomes equations. These are just what make up econometric models. So you can't defend RCTs or ('wannabe' RCTs like natural experiments) and reject causal econometric models. Again, which is better depends on what you know.

Session 5

Epidemiological Evidence and SIngle-Case Evaluation in Forensic Medicine - The Example of the "Excited Delirium Syndrome"

Enno Fischer (Ruhr-Universität Bochum); Saana Jukola (Universiteit Twente)*

Russo and Williamson (2011) have suggested an account of inference in cause-of-death inquiry that is based on a distinction between general-to-singular inferences and singular-to-general inferences. According to Russo and Williamson, forensic autopsy employs single-case "non-causal" evidence and generic causal knowledge to make inferences about an individual's cause of death. This is to be distinguished, according to Russo and Williamson, from other forms of autopsy, such as academic autopsy, which looks at individual corpses to draw general lessons about potential causes of death. However, looking at case studies of cause-of-death inquiry, such a neat separation appears to be problematic, both on the level of causal inference and on the level of epistemic practitioners involved in cause-of-death inquiry. Here we provide a more detailed taxonomy of kinds of causal claims that are relevant in forensic inquiry. More precisely, we will distinguish causal claims along two independent dimensions: general vs particular and actual vs potential. We will employ this taxonomy to shed new light on potential epistemic pitfalls of causal inference in forensic medicine, with particular regard to the development and application of epidemiological evidence in individual cases of cause-of-death inquiry. Specifically, we will look at cases of supposed "Excited Delirium Syndrome" (ExDS). ExDS is a highly controversial diagnosis that is often employed to explain deaths in police custody. The evaluation of individual cases of supposed ExDS importantly depends upon causal background assumptions about the existence and epidemiology of ExDS. These background assumptions, in turn, depend on often dubious assumptions of past instances of deaths in custody. Moreover, a separation between practitioners advancing the ExDS hypothesis scientifically and those employing the diagnosis in individual cases is not always possible. Applying our framework of causal reasoning, we analyze epistemically problematic aspects of ExDS diagnoses, and we highlight more general challenges for causal reasoning at the medico-legal interface of forensic medicine.

Russo, F., Williamson, J. Generic versus single-case causality: the case of autopsy. Euro Jnl Phil Sci 1, 47–69 (2011).

Epistemology of Epidemiology : Its Relevance for Efficacy of Pandemic Management – the Case of COVID-19 and its "theory-free" Modeling

Felix Tretter, Bertalanffy Center for the Study of Systems Science; Vienna

"Nothing is more practical than a good theory." Kurt Lewin

Scientific progress is based on empirical research AND theory. Epidemiology/medicine, however, lacks "theory". In contrast, medicine today is dominated by biotechnology-based data collection and data-driven modeling (cf. "corona science"; reference: Germany). In principle, the effectiveness of the management of epidemics/pandemics largely depends on the epistemic quality of epidemiological models (EMs). In this context, "theoretical epidemiology" (TE) should be discussed critically.
A systems thinker maps pandemic management in a macrosocial control loop model in which the EM is part of the loop. This is because the "real" infection status of the population is "caused" by a circular cascade of a set of variables: the virus, the immunocompetence and social behavior of hosts, the quality of surveillance and of EMs, the efficiency of political decision-making, the quality of media reports and of administration in implementing public health measures, and finally the adherence of the population. Consequently, the "incidence" was a result of fluctuating variables, a fact that justifies modeling of epi-/pandemics as a "complex dynamic system" with internal and external dynamics. In contrast, in most systematic reviews of EMs not these aspects but formal and data-related issues are discussed [1]. Furthermore, EMs were rarely based on useful theoretical models such as the bio-psycho-social model (G. Engel), the infection triad (pathogen, host, environment; J. Snow), the socio-ecological rainbow model (G. Dahlgren & M. Whitehead) or the eco-social model (N. Krieger). In consequence, the talk criticizes EMs and calls for a TE [2]. In particular, TE should (1) extend epistemology to transdisciplinarity, (2) explicitly apply systems thinking, (3) use a socio-ecological framework, and (4) focus on individuals. However, new institutions are needed for this program of change.

Sources

1. Marion G, et al. Modelling: Understanding pandemics and how to control them. Epidemics. 2022 Jun;39:100588. doi: 10.1016/j.epidem.2022.100588. Epub 2022 May 31. PMID: 35679714.

2. Tretter F, Marcum J. 'Medical Corona Science': Philosophical and systemic issues: Re-thinking medicine? On the epistemology of Corona medicine. J Eval Clin Pract. 2023 Apr;29(3):405-414. doi: 10.1111/jep.13734. Epub 2022 Jul 11. PMID: 35818671.

Author: Academic qualifications in psychology, philosophy, socio-economics and medicine; practice in brain research, empirical social research, systems research, addiction research and treatment, hospital management.

The evidential role of the key characteristics of carcinogens

*Michael Wilde (University of Kent); Jon Williamson (University of Kent)**

The International Agency for Research on Cancer (IARC) Monographs evaluate the carcinogenicity of various environmental exposures. A working group that is charged with evaluating an agent or a group of agents is split into four subgroups that assess human epidemiological studies, animal studies, mechanistic studies and exposure data respectively. The results of these assessments yield an overall evaluation of carcinogenicity. The mechanistic subgroup structures their assessment by looking for the presence of what they call 'key characteristics of carcinogens' or KCCs. Examples include electrophilicity and genotoxicity. At this stage, interesting philosophical questions emerge: what are KCCs exactly and how should they structure an assessment of mechanistic studies?

We argue that Evidential Pluralism can help to answer these questions. Evidential Pluralism is a theory of the epistemology of causality: it holds that establishing causation requires establishing both the existence of a correlation and the existence of a mechanism ("object pluralism"), so evaluating causation requires assessing both association studies – including epidemiological studies – and mechanistic studies (study pluralism'). We argue that KCCs are best thought of as features of mechanisms, rather than features of carcinogens, and that Evidential Pluralism provides a very natural account of their evidential role in evaluating carcinogenicity. The conceptualisation offered by Evidential Pluralism can also help in the following ways: it can provide a clear account of the role of indicators of KCCs such as biomarkers and omic signatures; it can handle richer mechanistic hypotheses, showing how KCCs can combine; and it can provide an account of strength of mechanistic evidence, which is crucial for evaluating the extent to which evidence of KCCs confirms carcinogenicity.

Session 6

Formalising extrapolation

Alexander Gebharter (Marche Polytechnic University); Barbara Osimani(Marche Polytechnic University)*

The extrapolator's circle is an epistemic paradox that is pervasive in evidence-based policy and medicine. It regards the fact that in order to apply evidence about causal effects observed in a source domain to another target domain, one needs to be confident enough about the fact that the latter is sufficiently similar in a causally relevant way to the former (cf. Cartwright & Hardie, 2012). However, in order to know that this assumption is met, one would need to have sufficient causal knowledge about the target setting, which would make the extrapolation redundant. There has been several attempts to solve the circle, all relying on partial knowledge about the source and target structures complemented by indirect evidence about the similarity assumption itself (Steel, 2007). Khosrowi (2019) in particular advances the importance of integrating qualitative evidence about the similarity of the two systems at stake with quantitative methods developed in econometrics to account for the role of interactive covariates. We propose a Bayesian formalization of extrapolation that provides the required epistemic justificatory underpinning for this sort of inferential procedures. It takes a middle ground between the two horns of the dilemma. In other words, it neither requires full causal knowledge of the structure underlying one's target system, nor that the inference procedure is free from uncertainty. By relying on a causal model in the background to support one's inference from the source to the target domain, we identify several factors relevant for extrapolation (such as the policy maker's degree of confidence in the causal model, the minimal likelihood that the policy will work acceptable to them, etc.) and formally investigate how they are related to each other. The model shows how the extrapolator's circle could be broken by being able to predict the expected likelihood of the policy's success in the target domain while, at the same time, giving full acknowledgement to one's degree of uncertainty about the causal structure as well as the fallibility of the inference.

References

- Cartwright, N., & Hardie, J. (2012). Evidence-based policy: A practical guide to doing it better. Oxford University Press.
- Khosrowi, D. (2019). Extrapolation of causal effects–hopes, assumptions, and the extrapolator's circle. Journal of economic methodology, 26(1), 45-58.
- Steel, D. (2007). Across the boundaries: Extrapolation in biology and social science. Oxford University Press.

Artificial intelligence methods in Bayesian evidence evaluation

*Francesco De Pretis (University of Modena and Reggio Emilia); Juergen Landes (University of Milan); William Peden (Johannes Kepler University)**

New pharmaceutical treatments are a key tool for improving public health. However, they also sometimes create insidious yet harmful effects. Adverse drug reactions (ADRs) are harms caused by pharmaceutical treatments. These reactions can be immediate, gradual, or occur after treatment ends (such as opioid withdrawal symptoms). Often, particular groups are at risk: consider the examples of Thalidomide for pregnant women or prophylactic therapy for lupus patients.

Clinical trials can sometimes identify ADR causal relations, but often the evidence only emerges gradually post-trial, via "pharmacovigilance." The evidence consists of heterogeneous data with various sources, modalities (observational, experimental) and different degrees of external and internal validity. How can these diverse sources of evidence be synthesised into overall assessments of drug safety?

We describe how a new approach, E-Synthesis, uses the methods of Bayesian epistemology, such as Bayesian networks, to formalise methodological principles of causal identification in medicine, like the Bradford Hill Guidelines. Unlike traditional statistical or qualitative methodologies, E-Synthesis enables quantitative hypothesis assessment using heterogeneous evidence.

However, for real-world complex problems, E-Synthesis is very computationally and cognitively demanding. We explain how recent developments in AI seem promising for making E-Synthesis more applicable in pharmacovigilance.

We also explore some challenges for AI E-Synthesis. First, Bayesian statistics requires judgements about the possibilities to be considered. The probabilities of these possibilities must sum to one for Bayesian reasoning to work. In practice, we never know or can articulate all the possibilities, so we must simplify by excluding some. Thus, higher-order judgements are required about which possibilities to take seriously enough to include in the Bayesian modelling.

We make a positive suggestion on this line, by building on Jon Williamson's "Objective Bayesianism." We explain how frequentist reasoning can help guide these higher-order judgements in Bayesian modelling. While frequentist statistics and Bayesian statistics are often regarded as rivals, we show how they can usefully collaborate for applying E-Synthesis.

Second, insofar as AI systems use common algorithms and datasets, there is a risk of groupthink. This herd behaviour undermines pharmacological science's robustness, by removing the subjectivities that characterise human evaluations of evidence and uncertainties. Social epistemologists like Philip Kitcher and Helen Longino have argued that the robustness of diverse evidence evaluations is part of science's success. We explain how the greater awareness of "justification for pursuit" could mitigate groupthink in AI pharmacovigilance, so that approaches like E-Synthesis can benefit from AI's computational power while not increasing groupthink.

Health Effects of Loneliness and Causal Pluralism

*Elena Popa (Jagiellonian University)**

This paper will explore causal pluralism in connection to causal claims about the health impact of loneliness. Loneliness has been singled out as a public health problem through its impact on both mental and physical health (Holt-Lunstad 2017; Miller 2020). While claims about a 'loneliness epidemic' have been employed in both public health and policy context, the philosophical underpinnings of this have attracted comparatively little philosophical attention thus far (see Popa 2021, 2023). This paper will bring together philosophical conceptualizations of loneliness with specific causal concepts and inference methods making a case for pluralism regarding capturing loneliness as a multifaceted phenomenon. This raises the question of what concepts and methods to use and why. The main analyses of loneliness will be brought together with causal concepts and methods as follows:

- Objectivism - loneliness is defined in relation to an intentional object— absence of specific social goods (Roberts and Krueger 2021). This can be connected with difference-making concepts of causation such as probabilistic and interventionist ones assumed in epidemiological studies.
- Subjectivism loneliness is experienced as a mood. This can be connected to psychological studies on the spiral between loneliness and defensiveness, which are self-reinforcing. Relevant causal concepts are mechanistic (applied to psychological processes) and dispositional.
- Relational views – objective lack of social interaction and subjective narrative of being disconnected from one's social environment (Seemann 2022). Qualitative studies can help reveal these patterns, which can be connected to mechanistic (applied to psychological and social processes) or dispositional causal concepts.

Regardless to how one defines loneliness, there are also lower-level physical mechanisms involving top-down dysregulation and inflammation that are used to explain its physical health effects. The resulting pluralism can be defined along the way of Longino's (2013) causal space – different operationalizations may yield different conclusions regarding what causes what. Nevertheless, given the current state of empirical research, I will argue that something along the lines of Mitchell's (2009) less radical integrative pluralism may be feasible, as these conclusions do not contradict one another (though questions about incommensurability may arise – see Maung 2020 on causes of suicide). Regarding criteria for choosing concepts and approaches, I will argue for a pragmatic stance emphasizing human needs: health advice and interventions looking at objective or relational aspects may help move beyond current critiques of advice that only targets the individuals affected (Wilkinson 2022) and neglecting political aspects.

Saturday, May 4, 2024

Keynote: Stefano Canali

Rethinking Data and Evidence in Medicine, Rethinking Causality and Empiricism in Philosophy?

Stefano Canali (Polytechnic University of Milan)

Session 7

Epistemological and practical challenges in using causal inference analyses in social epidemiology: developing a tool to support researchers

Léna Bonin (Equity team, CERPOP, UMR1295 Inserm-Université de Toulouse); Hélène Colineaux (Equity team, CERPOP, UMR1295 Inserm-Université de Toulouse); Benoit Lepage (Equity team, CERPOP, UMR1295 Inserm-Université de Toulouse); Michelle Kelly-Irving (Equity team, CERPOP, UMR1295 Inserm-Université de Toulouse)*

Background The last decade has seen considerable development in causal inference, with the conception of new methods. In practice causal inference remains poorly understood by researchers, especially those from the social sciences and social epidemiology. Thus, it may not be applied as often as it could be when dealing with observational data. Two challenges deserve attention: the epistemological differences between causal inference and classic prediction analyses in epidemiology, and difficulties in choosing an appropriate method. The objective of this work is to develop a user-friendly application that supports researchers in selecting a relevant method for their analyses.

Method We developed an application to help beginners in causal inference and mediation analyses, assuming they had already prepared a directed acyclic graph (DAG). Using Shiny App a series of questions were carefully developed with causal inference researchers in epidemiology to guide users towards determining which estimand they need and which method is the simpler to use, given their objective and the nature of their data.

Results The questionnaire uses simple epidemiological language and begins by separating situations where a total effect is desired from situations where mediation analysis is desired. If mediation is selected several potential options are offered. Questions are posed to determine the nature and characteristics of each variable, to check and improve the user's assumptions, and detect violations. Once the questionnaire is completed, a list of effects to be estimated and their corresponding objectives is displayed. The most parsimonious methods are advised, followed by a list of identifying assumptions, other comments and relevant R packages. The first version of the application includes regression-based and counterfactual approaches. It is currently being tested on users, who will provide feedback, allowing us to improve the app and reflect upon the challenges of causal inference in practice.

Discussion and conclusion Our application aims to support researchers starting out in causal analysis, by helping them clarify their research question, and suggesting appropriate statistical methods and packages. There are several limitations to this pilot project, namely, the assumption that users previously developed a DAG and restrictions on the types of methods offered, limiting the nature of the possible mediation analyses suggested. We hope to pursue the development of this app further with the help of user feedback.

Epidemiology, RCTs and Econometric Modelling

*Nancy Cartwright (UCSD & Durham Univ)**

All three domains in the title make heavy use of statistics to inform causal conclusions. But everybody knows, 'Correlation isn't causation'. What more is needed? Antecedent causal knowledge! Epidemiology draws on a variety of different kinds of knowledge to bolster causal hypotheses suggested by correlational data: quasi-natural experiments, sophisticate models of how diseases spread, demographic data, theories of human behaviour .... But occasionally, in especially epistemically convenient cases, we can use our antecedent knowledge not just as other ways to reinforce statistical suggestions but actually to infer causal conclusions from the statistics. Results about econometric modelling can show when and how.

So, this talk aims to familiarise you with results that show conditions under which this can be done in econometrics since – with very good luck – the same kind of modelling can be employed in epidemiology. The good luck has to do with what antecedent knowledge is available. What you need to know for these results to apply is demanding. Nevertheless there are many cases when we might well know what is necessary, or at least take it to be a good bet. So it is important that these kinds of results are familiar in epidemiology – we need all the good tools we can get.

What has this to do with RCTs? RCTs claim to be the gold standard for inferring causal conclusions from statistics is based on the fact that it is provable that if the required probabilistic independencies hold in the experiment then the difference in mean outcome values between treatment and control groups is an unbiased estimate of the true average treatment effect in the experimental population. Two things matter for the discussion here. First, as I shall explain, contrary to popular myth, RCTs –like any other method – require antecedent knowledge – and lots of it – to draw causal conclusions. Whether to do an RCT or an econometric-like model in epidemiology depends on which required knowledge you can get in time. Second, the proof just mentioned supposes that the causal possibilities in a given setting can be represented in potential outcomes equations. These are just what make up econometric models. So you can't defend RCTs or ('wannabe' RCTs like natural experiments) and reject causal econometric models. Again, which is better depends on what you know.

Session 8

Individual-level and population-level causes in epidemiology: a stability account

*Thomas Blanchard (University of Cologne)**

In a seminal paper, the epidemiologist G. Rose (1985) claimed that the causes of disease in individuals differ from causes of disease in populations. This principle is widely regarded as foundational for population health epidemiology, and yet needs clarification: since populations are composed of individuals, it is hard to see how causes of disease in individuals could fail to be causes of disease in the populations they compose, or vice versa. One way to understand Rose's principle is in terms of causal selection, i.e. as stating that the causes that best explain diseases in individuals are not (or at least need not be) the same as the causes that best explain diseases in populations. A version of this claim has recently been defended by Jonathan Fuller (2022), who proposes a contrastive model of causal selection: individual causes differ from population causes in that the former explain why some individual has the disease while some other doesn't, whereas the latter explain why disease incidence is higher for some population compared to another. My talk will raise some issues with Fuller's account, and propose another, in my view more illuminating way to understand Rose's principle in terms of causal selection. My account will rely on an approach to causal selection developed by Jim Woodward (2010) and others, according to which our explanatory practices favor stable causes – i.e., causes that are robustly associated with their effects insofar as they would continue to produce their effects under a wide variety of changes in background circumstances. I will argue that stable causes of disease at the population level need not be stable causes at the individual level: for example, restriction relaxation might be a stable cause of general Covid increase, but not a cause of why Alice caught Covid on a particular occasion. Because the distinction between stable and unstable causes has important pragmatic implications, the resulting account not only clarifies Rose's distinction, but also explains why the distinction has a central role to play in population epidemiology, and can help better identify effective disease-preventing interventions at the population level.

References

- Fuller, J. (2022). Epidemics From the Population Perspective. Philosophy of Science, 89, 232–251. Rose, G. (1985). Sick individuals and sick populations. International Journal of Epidemiology, 30, 427–432; discussion 433-434.
- Woodward, J. (2010). Causation in Biology: Stability, Specificity, and the Choice of Levels of Explanation. Biology& Philosophy, 25, 287–318.

It's Biomedical Standard Time somewhere: Unsettling the framing of epigenetic aging as a causal mechanism linking social and environmental exposures to health

*Elijah J Watson (Northwestern University)**

Epigenetic clocks are being heralded as a revolution in the monitoring of biological aging. They are simultaneously interpreted and conceptualized as a summary measure of past harmful exposures contributing to aging, a powerful tool for predicting future health, and a potential mechanism that causally links the social and physical environment to health outcomes. DNA methylation (DNAm), an epigenetic process involving the addition of a methyl group at the fifth carbon position of the cytosine base, is important for cellular differentiation and gene regulatory control. DNAm at a subset of loci changes predictably with age, which has allowed for the development of algorithms that act as "epigenetic clocks" capable of estimating chronological age with high accuracy. Notably, the deviation between an individual's predicted epigenetic age (from a given epigenetic clock algorithm) and their actual chronological age is referred to as "epigenetic age acceleration." Measures of epigenetic age acceleration across epigenetic clocks have been shown to be predictive of age-related functional decline, metabolic and immunological dysregulation, and mortality. However, tempering their allure, epigenetic clock algorithms are usually trained on data from Western countries and thus may not generalize to all populations. Drawing on Nancy Krieger's ecosocial theory from social epidemiology and Lock and Niewöhner's notion of situated biologies from medical anthropology, this paper aims to unsettle the causal claims implicitly made when the notions of generalizability and mechanism are invoked by wellness industry companies and biomedical researchers in relation to epigenetic clocks. I argue that 1) the marketing of epigenetic clocks as generalizable estimators of biological age assumes a universal biomedical standard body"which ticks at its own biomedical standard pace of biological time"against which all are compared and 2) the causal assumptions required to rigorously conceptualize and study epigenetic aging as a mechanism linking social environment or lifestyle to health are often ignored or glossed over by both anti-aging companies and biomedical researchers. I discuss how these two issues complicate calls for the use of epigenetic clocks in causal mediation analyses that aim to illuminate the embodiment of health inequities. I suggest that engaging with causal inference can enrich not only social epidemiology but also science and technology studies research that seeks to generate truthful, but always partial, understandings of biological pathways from social exposures to population health.