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Causal Mediation Analysis in a Survival Context

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The importance of mediation analysis in health and medical research relies on the need to illuminate the mechanisms by which an exposure exerts a causal effect on an outcome variable. In practice, a mediational model hypothesizes that the exposure variable causes one or more measured intermediate variables (mediators), which in turn affects the outcome variable. Traditionally, causal mediation analysis has been implemented within the framework of linear structural equation modeling (LSEM) [1] involving a series of liner regression models and two approaches have been proposed to quantify mediation as difference in coefficients method [2] and product of coefficients method [3]. For regression models using standard least squares without missing data, the estimators from both approaches are identical [4]. Recently, the methods developed in the LSEM framework were generalized to nonlinear models, e.g. proportional hazards model for survival data. Warner et al. [5] and Lu et al. [6] compared the hazard ratios of the exposure from Cox model both with and without adjusting for the potential mediators and a change in hazard ratios is taken as evidence of mediation through the mediators. Lange and Hansen argued that, such mediation analysis for survival data has severe shortcomings [7]. First of all, the observed changes in hazard ratios cannot be given a causal interpretation, and also it cannot be satisfied that the proportional hazards assumption holds for both models with and without the mediator.

More recently, researchers have addressed causal mediation analysis using the potential outcomes framework, which allows definition of mediation effects in causal terms and clear specification of assumptions required for a causal inference [8-10]. One very general approach for causal mediation analysis based on the potential outcomes framework is what Pearl refers to as the 'mediation formula' [11]. This approach allows the estimation of expected potential outcomes, used in the definition of causal mediation effects, to be estimated as a function of association parameters for the outcome model that are directly estimable from the observed data. The assumptions required by the mediation formula approach is that of 'sequential ignorability' [10], in which the exposure is first assumed to be ignorable given the baseline covariates, and then the mediator variable is assumed to be ignorable given observed values of exposure status and the baseline covariates. Imai et al. provided a general approach based on the mediation formula that can be applied to linear and nonlinear relationship, parametric and nonparametric models, continuous and discrete mediators, and various types of outcome variables [12]. One missing component in Imai et al.'s approach is the mediation analysis for the survival data. Lange and Hansen gave formal counterfactual definitions of the causal direct and indirect effects for the Aalen's additive hazard model, and proved that the 'product of coefficient' mediation effect estimate is mathematically consistent and allows a causal interpretation [7]. For the survival data mediation analysis, VanderWeele stated that there are multiple ways or scales by which a total effect might be decomposed into direct and indirect effects, for example, mediation effects on survival functions, hazard functions, mean or median survival time [13]. In the same paper, VanderWeele extended Lange and Hansen's approach to proportional hazards model assuming a rare outcome or accelerated failure time models generally. A SAS macro is compiled and provided to apply VanderWeele's method for the survival mediation analysis [14]. In addition, TchetgenTchetgen proposed theory to deliver the robust estimators for the natural direct and indirect effects under proportional hazards models and additive hazards models, as well as sensitivity analysis techniques for assessing the impact of the violation of the mediator's ignorability assumption [15].TchetgenTchetgen also described a new inverse odds ratio-weighted approach to estimate the natural direct and indirect effects in a number of commonly used models including the Cox proportional hazards regression for a survival outcome. An additional advantage of TchetgenTchetgen's new method is that it can easily incorporate multiple categorical, discrete or continuous mediators [16].

Although we now have, at least some methods as described above for the causal mediation analysis in a survival context, a number of challenges still exist. First of all, survival data in biomedical research are often modelled with semi-parametric models, as Cox proportional hazards model or accelerated failure time model, which has the advantage of estimating covariate effects without the need to estimate the baseline hazard, and on the other hand, the parametric

baseline hazard is necessary for the application of mediation formula-based causal mediation analysis. Secondly, the extensive computation issue due to multiple integration is another challenge for survival mediation analysis in complex causal models with multiple and/or multiple-stage mediators. Finally, corresponding sensitivity analysis approaches must be developed to assess the robustness of the conclusion regarding the survival mediation effects when the untestable no mediator-outcome confounder assumption is violated.

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Curriculum Vitae

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Visa Status

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Education

Ph.D. in Biostatistics
Case Western Reserve University, Cleveland, OH, May 2012

M.S. in Pathology
Case Western Reserve University, Cleveland, OH, August 2007

B.S. in Biology
Peking University, Beijing, China, May 2001

Professional Experience:

University of Mississippi Medical Center, Center of Biostatistics and Bioinformatics, Jackson, MS

Assistant Professor — October 2013 - Present

- Conducting mixture regression model analysis and causal inference methodology research
- Consultation and collaboration with biomedical, epidemiologic, and public health researchers to design studies, perform data analysis, interpret analysis results, prepare manuscript and external grant applications focusing on cardiology, nephrology, geriatrics, and neurodegenerative dementia fields
- Providing statistical support for the Heart Failure/Stroke and Chronic Kidney Disease Working Groups of the Jackson Heart Study
- Serving on the Events Monitoring Subcommittee of the Jackson Heart Study

Global Eye Health Center, Bausch and Lomb Inc., Rochester, NY

Statistician — June 2012 - August 2013

- Served as lead statistician on medical device clinical trials: aiding in development of protocols by defining study design, writing the statistical section and providing sample size calculations, writing statistical analysis plans, preparing analysis files and reviewing clinical statistical reports
- Performed analysis for internal clinic studies and programmed statistical output with corresponding sas procedures
- Prepared statistical files/programs for regulatory submission

University Hospitals, Cardiovascular Imaging Core Laboratory, Cleveland, OH

Biostatistician — July 2008 - June 2012

- Conducted statistical analysis using SAS, and provided interpretation of analysis results for research studies in collaboration with medical researchers
- Design and analysis for clinical trials evaluating coronary artery response to new stents with optical coherence tomography, intravascular ultrasound and quantitative coronary arteriography methodology
- Processed, manipulated and organized data in preparation for analysis
- Developed SAS macros to expedite SAS programming activities
- Assisted the investigators with writing the statistical consideration for research proposals and manuscript presentations

Teaching Experience:

University of Mississippi Medical Center, Department of Otolaryngology, Jackson, MS
Lecturer for Systematic Review and Meta-Analysis — Spring 2014

University of Mississippi Medical Center, School of Medicine, Jackson, MS
Teaching Assistant for Fundamentals of Epidemiology & Biostatistics — Spring 2014

Case Western Reserve University, Department of Epidemiology and Biostatistics, Cleveland, OH
Teaching Assistant for Introduction to Statistical Computing — Fall 2009

Cleveland Clinic Lerner College of Medicine, Cleveland, OH
Teaching Assistant for Statistical Methods for Medical Research — Summer 2009

Research Interests:

Causal inference, mixture regression model analysis, joint modelling of longitudinal and competing risks data, crossover trial analysis

Computer Skills:

Statistical Software: SAS 9.2 with SAS/IML programming, R/S-plus, JMP
Others: Microsoft office (Word, Excel, Access, PowerPoint), LaTex and GraphPad Prism

Publications

Statistical Methodology

1. Albert J.M. and Wang W. (2015) Sensitivity analyses for parametric causal mediation effect estimation. Biostatistics 16:339-51.
2. Wang W., Nelson S. and Albert J.M. (2013) Estimation of causal mediation effects for a dichotomous outcome in multiple-mediator models using the mediation formula. Statistics in Medicine 32:4211-4228.
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Statistical Collaboration and Application

5. Wang W., Young B.A., Fulop T., de Boer I.H., Boulware L.E., Katz R., Correa A. and Griswold M.E. (2015) Effects of serum creatinine calibration on estimated renal function in African Americans: the Jackson Heart Study. The American Journal of Medical Sciences. 349:379-384.
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Journal Reviewer:

Statistics in Medicine	2013 - Present
Statistical Methods and Applications	2014 - Present
REVSTAT	2013 - Present
Biomedical and Environmental Sciences	2013 - Present
Osteoporosis International	2013 - Present