Statistical aspects of health and medical research & policy

Keith R Abrams, *Department of Statistics*

October 04, 2024

WARWICK
THE UNIVERSITY OF WARWICK

About me …

- BSc MORSE in mid-1980s

- MSc in Medical Statistics (U of Leicester)

- PhD in Medical Statistics (U of Liverpool)

- Post-doctoral Fellow - King's College London & London School of Hygiene & Tropical Medicine

- Academic at U of Leicester for 27 years (joined UoW in June 2021)

- Teaching – Medical Statistics module to 3rd/4th UG & MSc Statistics

- Research – developing & applying statistical methods in medical applications

- Consultancy with pharmaceutical companies

- External roles, mainly National Institute for health & Care Excellence (NICE)

Joint Modelling – 1
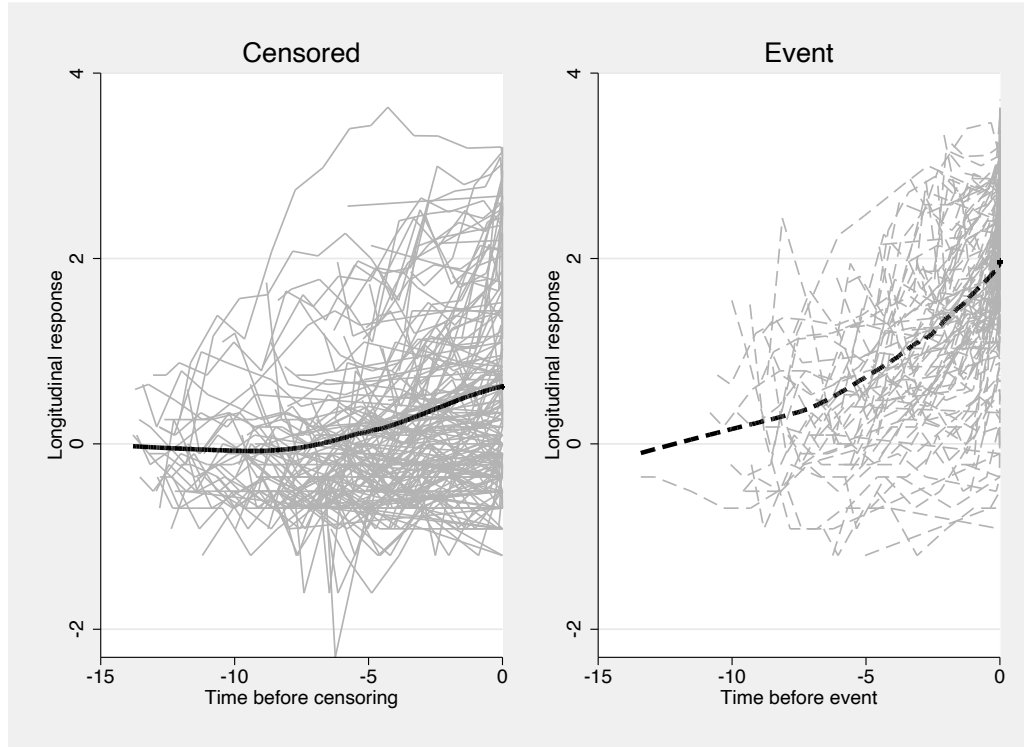
- 312 patients with primary biliary cirrhosis
- Cirrhosis is a slowly progressing disease in which healthy liver tissue is replaced with scar tissue, eventually preventing the liver from functioning properly
- 1945 repeated measures of serum bilirubin, a measure of liver function
- Outcome of all-cause death, where 140 (44.8%) patients died

Joint Modelling – 2
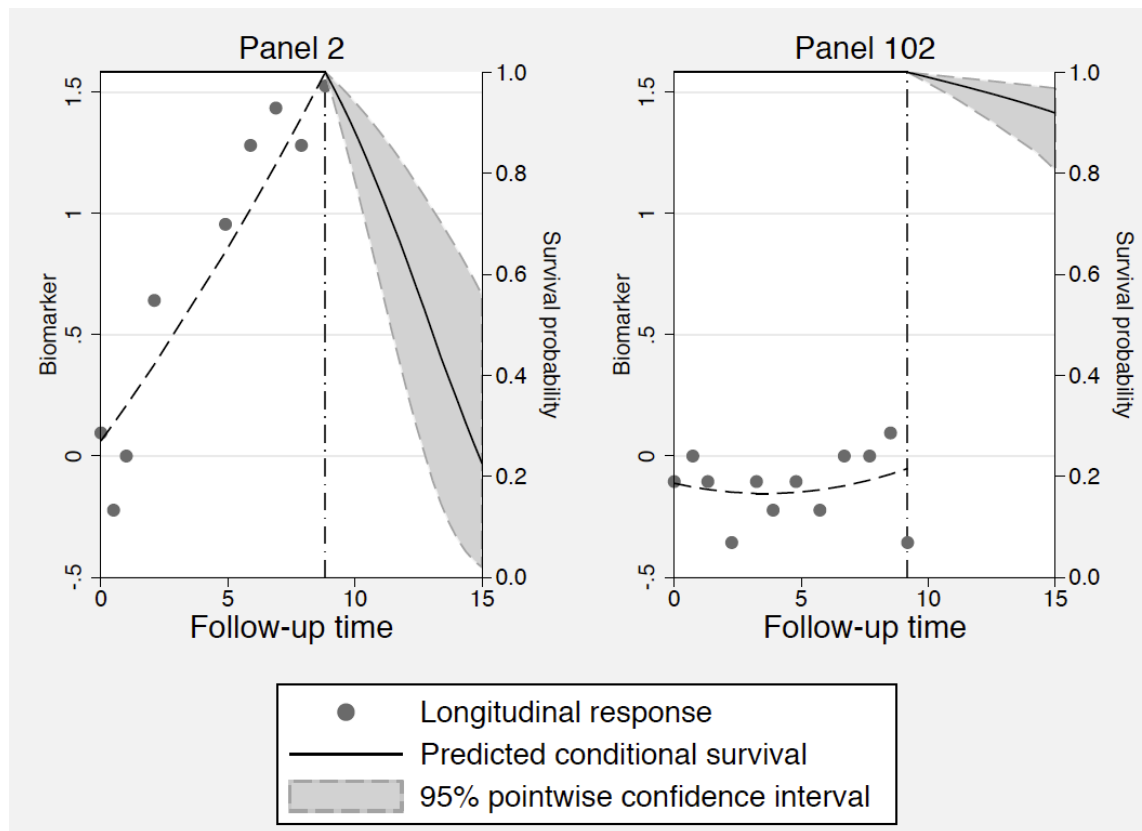
UK TAVI Trial – Intermittent Missing Data & Missing Data due to Death

Effect of Transcatheter Aortic Valve Implantation vs Surgical Aortic Valve Replacement on All-Cause Mortality in Patients With Aortic Stenosis
A Randomized Clinical Trial

The UK TAVI Trial Investigators

IMPORTANCE Transcatheter aortic valve implantation (TAVI) is a less invasive alternative to surgical aortic valve replacement and is the treatment of choice for patients at high operative risk. The role of TAVI in patients at lower risk is unclear.

OBJECTIVE To determine whether TAVI is noninferior to surgery in patients at moderately increased operative risk.
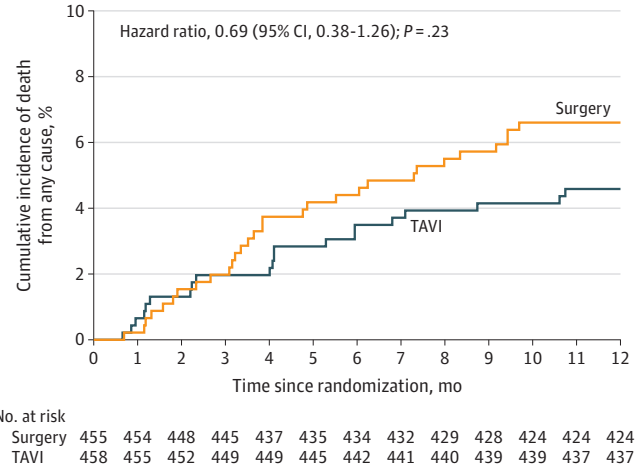
DESIGN, SETTING, AND PARTICIPANTS In this randomized clinical trial conducted at 34 UK centers, 913 patients aged 70 years or older with severe, symptomatic aortic stenosis and moderately increased operative risk due to age or comorbidity were enrolled between April 2014 and April 2018 and followed up through April 2019.

INTERVENTIONS TAVI using any valve with a CE mark (indicating conformity of the valve with all legal and safety requirements for sale throughout the European Economic Area) and any access route (n = 458) or surgical aortic valve replacement (surgery; n = 455).

MAIN OUTCOMES AND MEASURES The primary outcome was all-cause mortality at 1 year. The primary hypothesis was that TAVI was noninferior to surgery, with a noninferiority margin of 5% for the upper limit of the 1-sided 97.5% CI for the absolute between-group difference in mortality. There were 36 secondary outcomes (30 reported herein), including duration of hospital stay, major bleeding events, vascular complications, conduction disturbance requiring pacemaker implantation, and aortic regurgitation.

RESULTS Among 913 patients randomized (median age, 81 years [IQR, 78 to 84 years]; 424 [46%] were female; median Society of Thoracic Surgeons mortality risk score, 2.6% [IQR, 2.0% to 3.4%]), 912 (99.9%) completed follow-up and were included in the noninferiority analysis. At 1 year, there were 21 deaths (4.6%) in the TAVI group and 30 deaths (6.6%) in the surgery group, with an adjusted absolute risk difference of −2.0% (1-sided 97.5% CI, −∞ to 1.2%; P < .001 for noninferiority). Of 30 prespecified secondary outcomes reported herein, 24 showed no significant difference at 1 year. TAVI was associated with significantly shorter postprocedural hospitalization (median of 3 days [IQR, 2 to 5 days] vs 8 days [IQR, 6 to 13 days] in the surgery group). At 1 year, there were significantly fewer major bleeding events after TAVI compared with surgery (7.2% vs 20.2%, respectively; adjusted hazard ratio [HR], 0.33 [95% CI, 0.24 to 0.45]) but significantly more vascular complications (10.3% vs 2.4%; adjusted HR, 4.42 [95% CI, 2.54 to 7.71]), conduction disturbances requiring pacemaker implantation (14.2% vs 7.3%; adjusted HR, 2.05 [95% CI, 1.43 to 2.94]), and mild (38.3% vs 11.7%) or moderate (2.3% vs 0.6%) aortic regurgitation (adjusted odds ratio for mild, moderate, or severe [no instance of severe reported] aortic regurgitation combined vs none, 4.89 [95% CI, 3.08 to 7.75]).

A Death from any cause

Hazard ratio, 0.69 (95% CI, 0.38-1.26); P = .23

No. at risk												
Surgery	455	454	448	445	437	435	434	432	429	428	424	424	424
TAVI	458	455	452	449	449	445	442	441	440	439	439	437	437

- Used a Joint Model to adjust longitudinal Patient Reported Outcomes (e.g. Health-related Quality of Life) for both intermittent missing data and all-cause mortality

Modelling trajectories of disease in multimorbidity using "Big Data"

Effect on life expectancy of temporal sequence in a multimorbidity cluster of psychosis, diabetes, and congestive heart failure among 1·7 million individuals in Wales with 20-year follow-up: a retrospective cohort study using linked data

Rhiannon K Owen, Jane Lyons, Ashley Akbari, Bruce Guthrie, Utkarsh Agrawal, Daniel C Alexander, Amaya Azcoaga-Lorenzo, Anthony J Brookes, Spiros Denaxas, Carol Dezateux, Adeniyi Francis Fagbamigbe, Gill Harper, Paul D W Kirk, Eda Bilici Özyiğit, Sylvia Richardson, Sophie Staniszewska, Colin McCowan, Ronan A Lyons, Keith R Abrams

Summary

Background To inform targeted public health strategies, it is crucial to understand how coexisting diseases develop over time and their associated impacts on patient outcomes and health-care resources. This study aimed to examine how psychosis, diabetes, and congestive heart failure, in a cluster of physical–mental health multimorbidity, develop and coexist over time, and to assess the associated effects of different temporal sequences of these diseases on life expectancy in Wales.

Methods In this retrospective cohort study, we used population-scale, individual-level, anonymised, linked, demographic, administrative, and electronic health record data from the Wales Multimorbidity e-Cohort. We included data on all individuals aged 25 years and older who were living in Wales on Jan 1, 2000 (the start of follow-up), with follow-up continuing until Dec 31, 2019, first break in Welsh residency, or death. Multistate models were applied to these data to model trajectories of disease in multimorbidity and their associated effect on all-cause mortality, accounting for competing risks. Life expectancy was calculated as the restricted mean survival time (bound by the maximum follow-up of 20 years) for each of the transitions from the health states to death. Cox regression models were used to estimate baseline hazards for transitions between health states, adjusted for sex, age, and area-level deprivation (Welsh Index of Multiple Deprivation [WIMD] quintile).

# Example in Diabetes, Hypertension and Peripheral Vascular Disease (PVD)
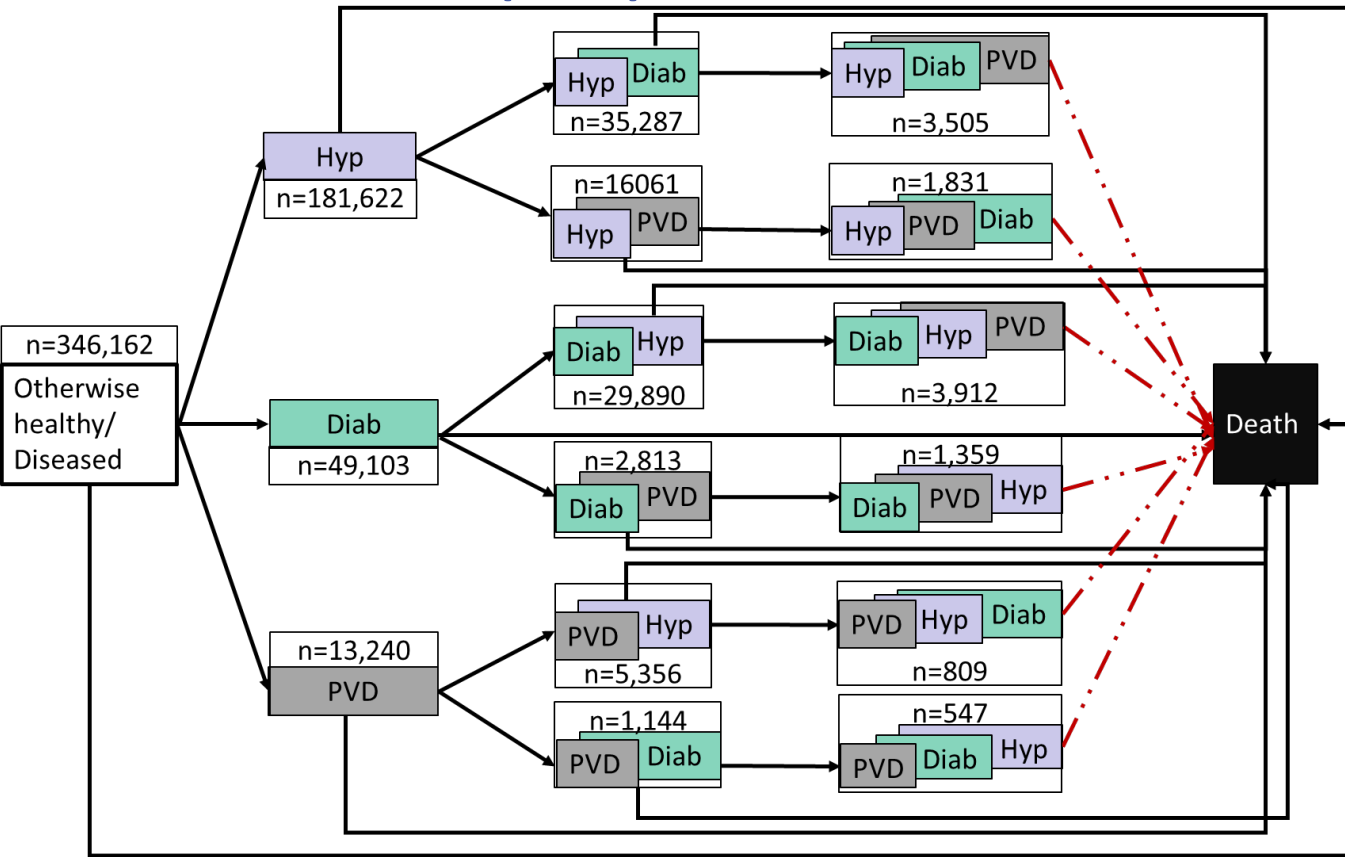
Mortality from transition	n
Otherwise healthy/diseased	72,232
Hypertension	88,867
Diabetes	12,398
PVD	5,816
Hyp->Diab	19,381
Hyp->PVD	11,116
Diab->Hyp	19,020
Diab->PVD	1,286
PVD->Hyp	3,674
PVD->Diab	510
Hyp->Diab->PVD	2,513
Hyp->PVD->Diab	1,272
Diab->Hyp->PVD	3,171
Diab->PVD->Hyp	1,141
PVD->Hyp->Diab	593
PVD->Diab->Hyp	446

Diab; Diabetes, Hyp; Hypertension, PVD; Peripheral Vascular Disease

Example in Diabetes, Hypertension and Peripheral Vascular Disease (PVD): Survival probabilities

Diab; Diabetes, Hyp; Hypertension, PVD; Peripheral Vascular Disease
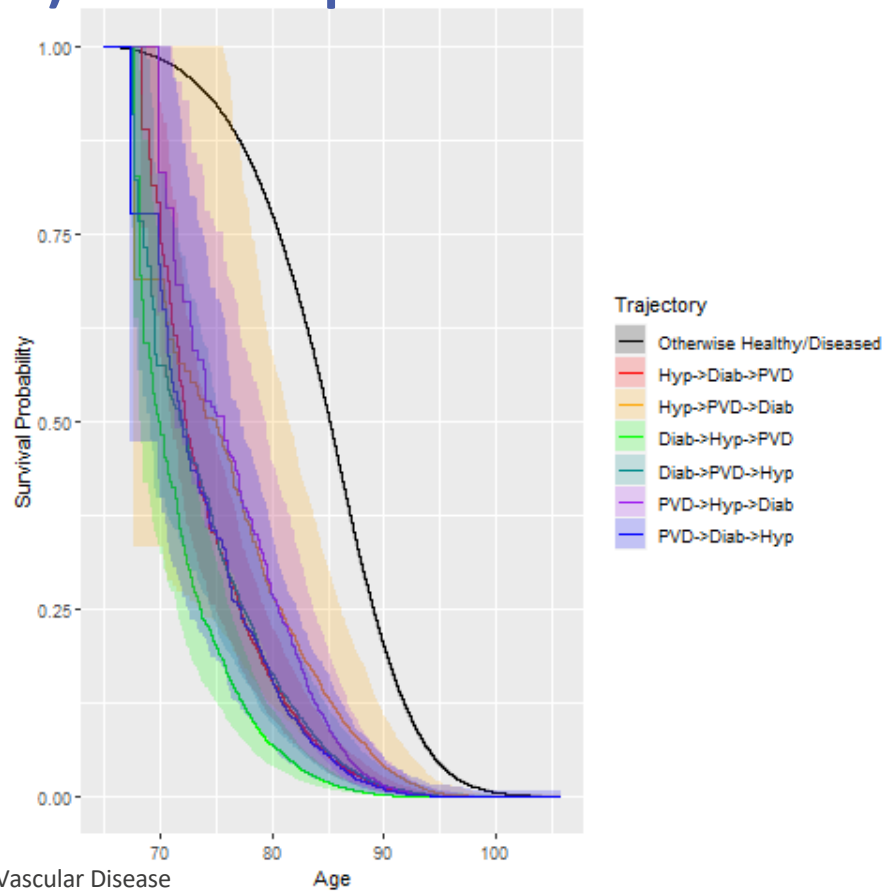
Extensions – Informative Observations

WILEY

Mixed-effects models for health care longitudinal data with an informative visiting process: A Monte Carlo simulation study

Alessandro Gasparini[1] | Keith R. Abrams[1] | Jessica K. Barrett[2] | Rupert W. Major[1,3] | Michael J. Sweeting[1,4] | Nigel J. Brunskill[3,5] | Michael J. Crowther[1]

[1]Biostatistics Research Group, Department of Health Sciences, University of Leicester, Leicester, UK

[2]MRC Biostatistics Unit, University of Cambridge, Cambridge, UK

[3]Department of Nephrology, University Hospitals of Leicester NHS Trust, Leicester, UK

[4]Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

[5]Department of Infection Immunity and Inflammation, University of Leicester, Leicester, UK

Correspondence
Alessandro Gasparini, Biostatistics Research Group, Department of Health Sciences, University of Leicester, Centre for Medicine, University Road, Leicester LE1 7RH, UK.
Email: ag475@leicester.ac.uk

Funding information
NIHR CLAHRC East Midlands and Kidney Research UK, Grant/Award Number: TF2/2015; MRC Unit

Electronic health records are being increasingly used in medical research to answer more relevant and detailed clinical questions; however, they pose new and significant methodological challenges. For instance, observation times are likely correlated with the underlying disease severity: Patients with worse conditions utilise health care more and may have worse biomarker values recorded. Traditional methods for analysing longitudinal data assume independence between observation times and disease severity; yet, with health care data, such assumptions unlikely hold. Through Monte Carlo simulation, we compare different analytical approaches proposed to account for an informative visiting process to assess whether they lead to unbiased results. Furthermore, we formalise a joint model for the observation process and the longitudinal outcome within an extended joint modelling framework. We illustrate our results using data from a pragmatic trial on enhanced care for individuals with chronic kidney disease, and we introduce user-friendly software that can be used
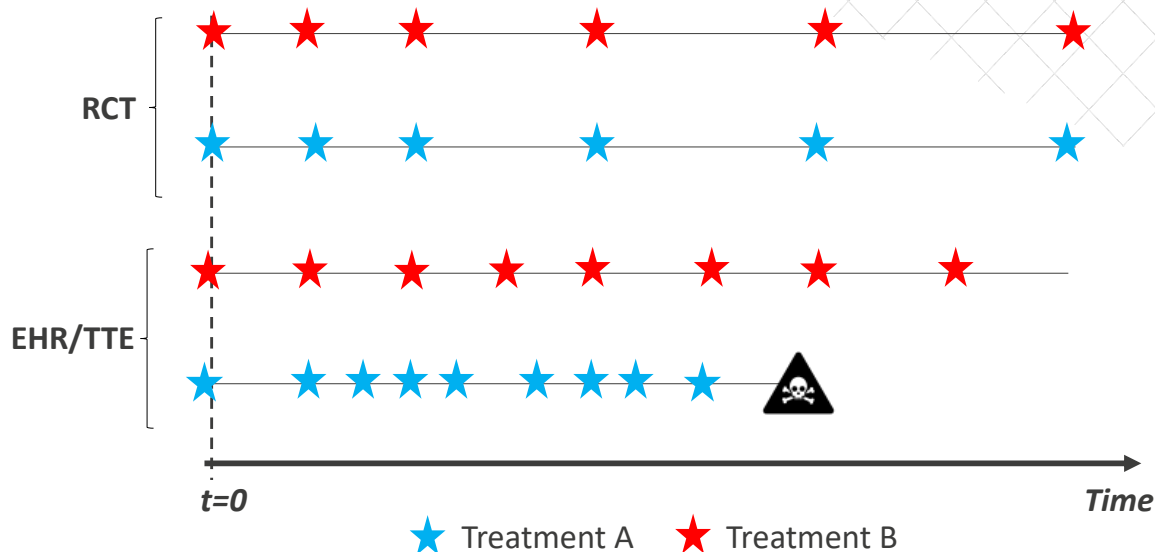
Issue of applying adjustment using a Bayesian Joint Modelling approach in very large-scale population data (e.g. SAIL ~ 1.7M pop) using MCMC – investigating Bayesian approximation methods, e.g. `INLA`

Other areas of research/interest …

- Meta-Analysis/Evidence Synthesis
    - (Hierarchical) Network Meta-Analysis Models
    - Allowing for heterogeneity in populations and study design (e.g. RWD)
    - Diagnostic and survival/time-to-event outcomes

- Treatment Switching in RCTs
    - Bayesian methods
    - Use of external data
    - Impact on longitudinal outcomes, e.g. HRQoL

Thank you

Email: Keith.Abrams@warwick.ac.uk

Webpage: www.warwick.ac.uk/krabrams

A pdf copy of these slides is available via **QR code**