UNIVERSITY OF
LEICESTER

Analysing Longitudinal Data Originating from Electronic Health Records

Alessandro Gasparini

ag475@leicester.ac.uk

@ellessenne

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Work in collaboration with Michael Crowther, Keith Abrams, Jessica Barrett, Rupert Major, Michael Sweeting, Nigel Brunskill (in no particular order).

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Outline

Background (1)

Electronic Health Records [EHRs] are medical records of patients attending medical care (e.g. visiting the GP) and recorded in a digital format.

We can construct data cohorts for research use by extracting and linking:

- EHRs from primary, specialist, and hospital care;
- nationwide registries;
- any other data source that could be linked to the above.

This kind of data (sometimes referred to as *health care consumption data*) is being increasingly used in medical research. For instance:

- Kidney disease;
- Cardiovascular disease;
- End-of-life healthcare.

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Health care consumption data cohorts have thousands - if not millions - of individuals with hundreds of measurements each.

The availability to researchers of such a vast amount of data allows answering more relevant and detailed clinical questions but poses new challenges:

1. Informative censoring;
2. Informative observation process;
3. Reporting (REPORT guidelines, Benchimol *et al*., 2015);
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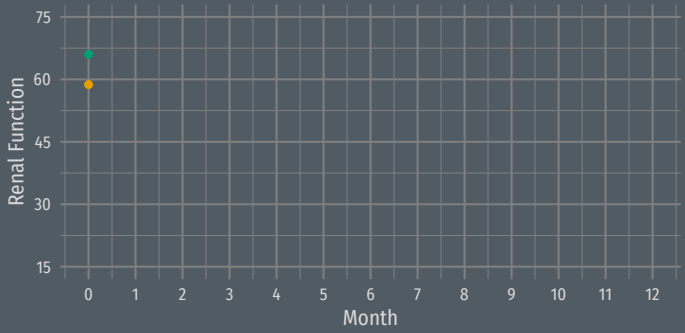
1. Observation times are likely correlated with disease severity;
2. Dropout (censoring) is likely informative.

Visit times are likely not at random!



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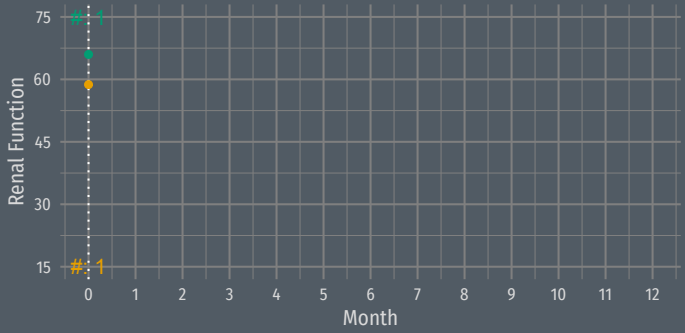

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Common assumption with traditional methods for analysing longitudinal data:

> *The mechanism that controls the observation time is independent of disease severity*

- Joint models for longitudinal-survival data can account for an informative censoring process;
- Research is scarce on whether inference is valid when the observation process is informative.

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Bias structure

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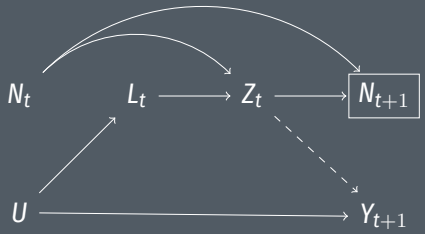

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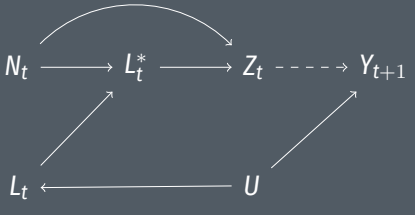

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Based on Hernán *et al*., 2009.

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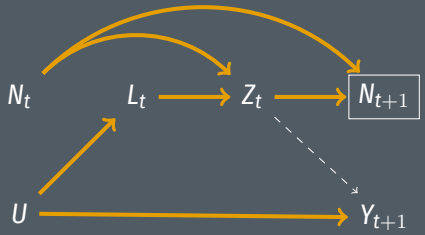

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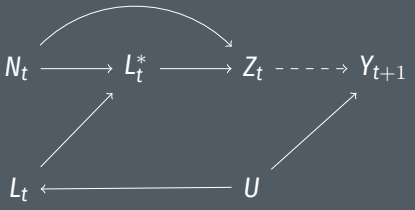

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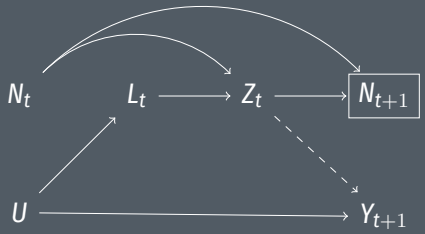

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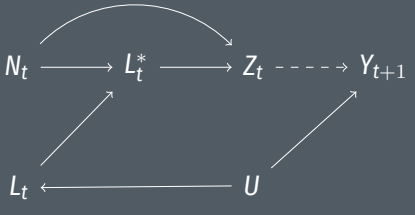

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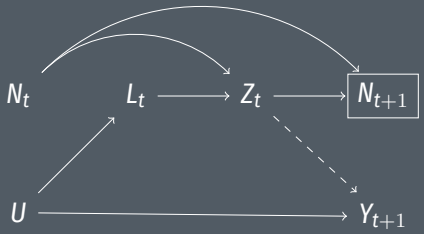

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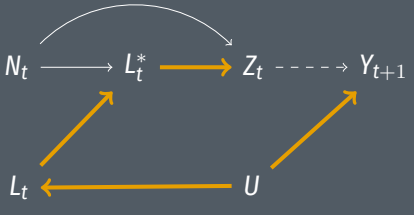

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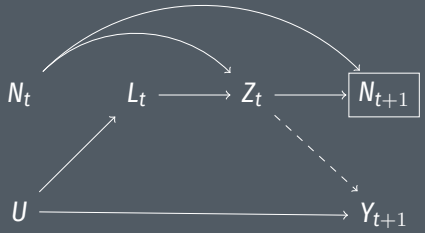

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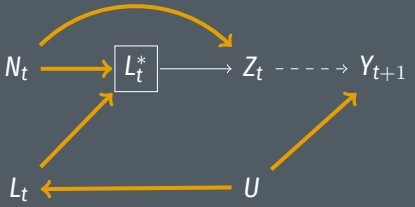

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We can identify sources of bias in EHRs-related settings on the basis of theoretical considerations.

The question is:

1. What can we do about it?
2. Does it really matter?

Outline

Joint modelling (1)

We can fit a generalised multi-equation joint model (Crowther, 2017) to model informative visit times and the longitudinal outcome jointly:

$$r_i = r_0(t)\exp(w_i\beta + u_i) \quad (1)$$

$$y_{ij}|(N_{ij}(t) = 1) = z_{ij}\alpha + \gamma u_i + v_i + \epsilon_{ij} \quad (2)$$

- i and j index individuals and observations, respectively;
- observations of Y_{ij} recorded at each $N_{ij}(t) = 1$;
- z_{ij} and w_i covariate vectors;
- u_i, v_i normally distributed random effects with E(u) = E(v) = 0;
- γ association parameter.

Joint modelling (2)

The method we implement is a generalisation of Liu *et al*, 2008.
The joint model from the previous slide is one of the most simple models we can fit with readily available software.

Current work on extending the model within a general framework:

- Modelling the dropout process as well;
- Modelling any number of longitudinal outcomes, each with its observation process;
- Any baseline hazard for the recurrent events model;
- Any (sort of) association structure between each longitudinal outcome and its observation process.

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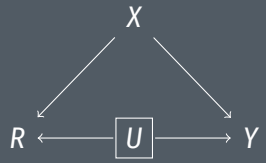

Y is the longitudinal outcome, *R* the observation process, *U* the random effect linking the two sub-models, *X* a covariate.

- *Y* and *R* are independent conditioning on the random effect *U*;
- by conditioning on *U*, the backdoor path between *X* and *Y* via *R* is blocked and the estimated association between *X* and *Y* has a causal interpretation.

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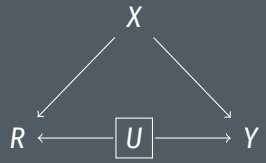

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Adjusting for the number of measurements

Methods of this kind are based on work by Goldstein *et al.* (2016). They investigate *informed presence bias* and show that:

1. conditioning on the number of health-care encounters it is possible to remove bias due to an informative observation process;
2. in doing so, such approach can result in selection bias under some settings.

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Inverse intensity of visit weighting (1)

Inverse intensity of visiting weighting [IIVW] is an approach first introduced by Robins *et al.* (1995) and further generalised by Hernán *et al.* (2009).
Relevant papers describing the method in practice: Van Ness *et al.* (2009), Bůžková *et al.* (2010).

The method is based on:

1. estimating weights based on the probability that individual *i* has an observation at time *t*;
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Inverse intensity of visit weighting (2)

In more detail:

1. (Stabilised) weights create a pseudo-population where the outcome (and/or the exposure) does not depend on the observation process;
2. A weighted marginal mean model for a longitudinal outcome Y and a vector of covariates X has the form:

$$E(Y) = g(\bar{X}; B),$$

where $\bar{X}$ is the weighted data and B is a vector of regression coefficients. The marginal model is fitted e.g. using the generalised estimating equations [GEE] method.

Do nothing...

...with appropriate caution.

Neuhaus *et al.* (2018) showed that in their settings the standard mixed model analyses had essentially no bias for covariates that did not have associated random effects in the model and little bias otherwise.

Their advice on study design:

> *Combining a small number of regular visits with the irregular (and highly outcome dependent) visits greatly reduced even this small bias.*

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A simulation study

- Comprehensive comparisons of the performance of different methods are (very) scarce in the literature;
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Aims:

1. What are the consequences of ignoring the visiting process in practice?
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Data-generating mechanism (1)

Simulating data from the joint model:

$$r_i = r_0(t)\exp(Z_i\beta + u_i)$$
$$y_{ij}|(dN_{ij}(t) = 1) = \alpha_0 + Z_i\alpha_1 + t_{ij}\alpha_2 + \gamma u_i + v_i + \epsilon_{ij}$$

- binary treatment Z_i;
- β = 1, α_0 = 0, α_1 = 1, α_2 = 0.2;
- σ_u^2 = 1, σ_v^2 = 0.5, σ_ϵ^2 = 1;
- $r_0(t)$: Weibull with shape p = 1.05 and scale λ = {0.10, 0.30, 1.00};
- γ = {0.00, 1.50};
- 200 individuals, with independent censoring from Unif(6, 12).

Data-generating mechanism (2)

Simulating observation times from a Γ distribution with shape = 2.0 and scale = $\exp(-\beta\theta Z_i + \rho Y_{i,j-1} + \xi_i)$; ξ_i is random noise from a Normal distribution.
Scenarios:

1. θ = 0.00 and ρ = 0.00
2. θ = 2.00 and ρ = 0.00
3. θ = 2.00 and ρ = 0.20

After generating the observation process, the longitudinal process is simulated from the same model as before:

$$y_{ij}|(dN_{ij}(t) = 1) = \alpha_0 + Z_i\alpha_1 + t_{ij}\alpha_2 + \gamma u_i + v_i + \epsilon_{ij},$$

All the rest is the same as before: model coefficients, sample size, censoring, ...

Estimands

The main estimands of interest are the regression coefficients of the longitudinal model:

1. α_0, the intercept;
2. α_1, the treatment effect;
3. α_2, the effect of time.

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2. α_1, the treatment effect;
3. α_2, the effect of time.

Models included in this comparison

1. The joint model used to simulate data;
2. A mixed-effects model disregarding the observation process;
3. A mixed-effects model, adjusting for the total number of measurements;
4. A mixed-effects model, adjusting for the cumulative number of measurements (as a time-varying covariate);
5. A model fit using generalised estimating equations [GEE] and IIVW, following the approach of Van Ness *et al*. (2009).

Performance measures and number of replications

We focus on the following performance measures:

1. bias, i.e. whether an estimator targets the true value on average;
2. coverage, i.e. the proportion of times that a confidence interval around each estimated value contains the true value.

Assuming (1) a variance of each estimate of 0.1 or lower and (2) a Monte Carlo standard error for bias of 0.01 or lower, we require 1,000 replications.
The expected Monte Carlo standard error for coverage, assuming a worst case scenario of coverage = 0.50, would be 0.02.

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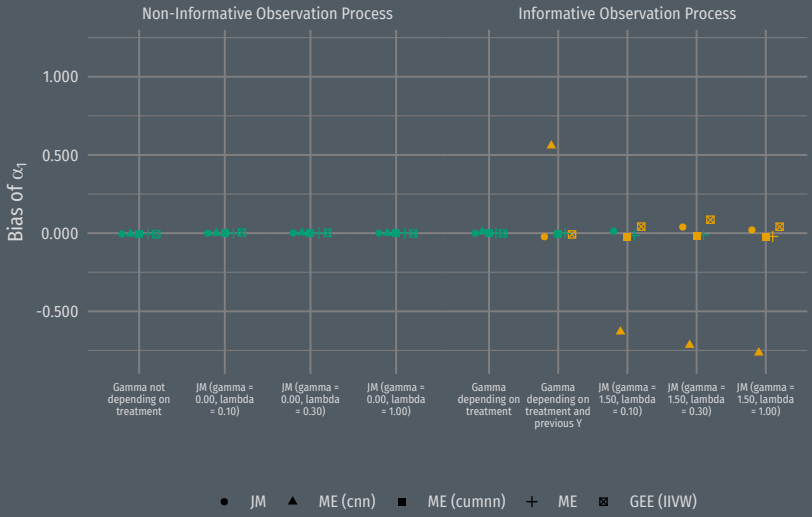

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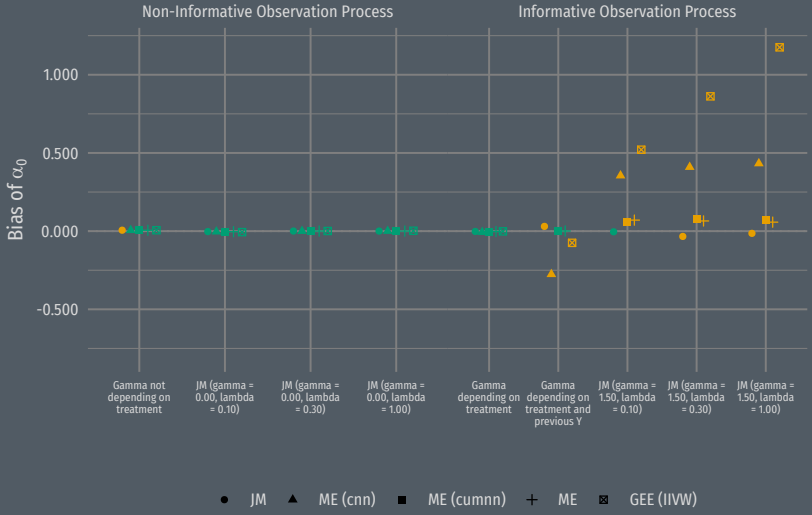
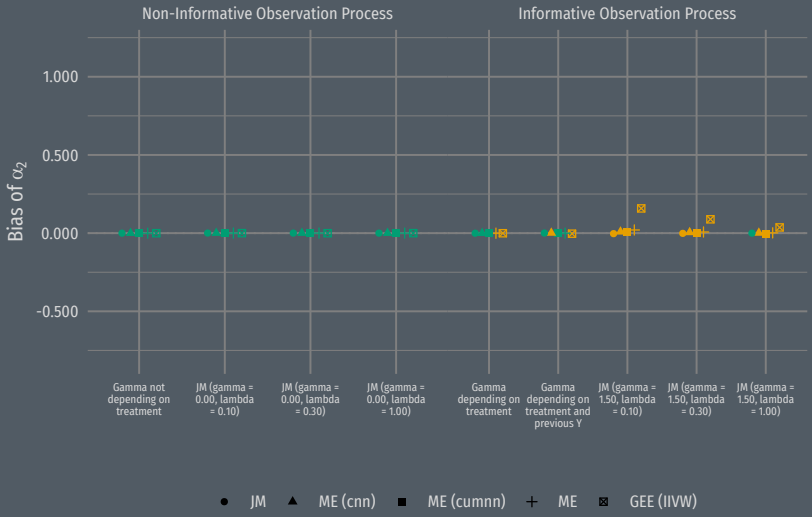


Results: bias of time coefficient



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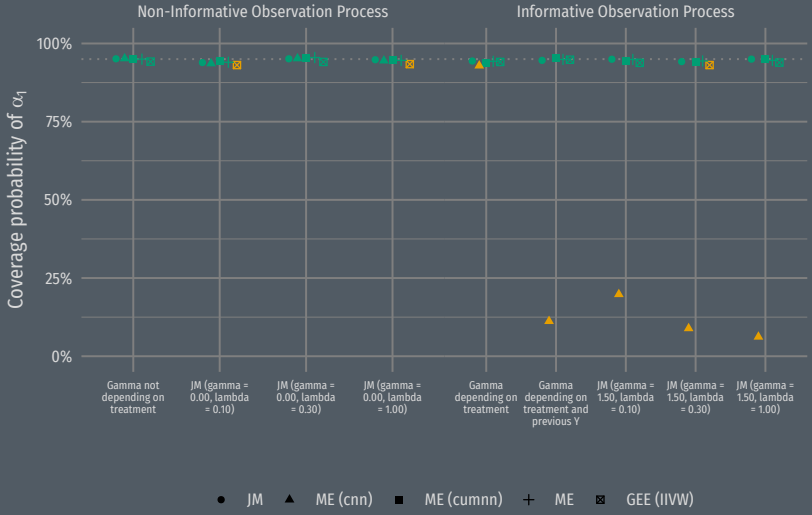

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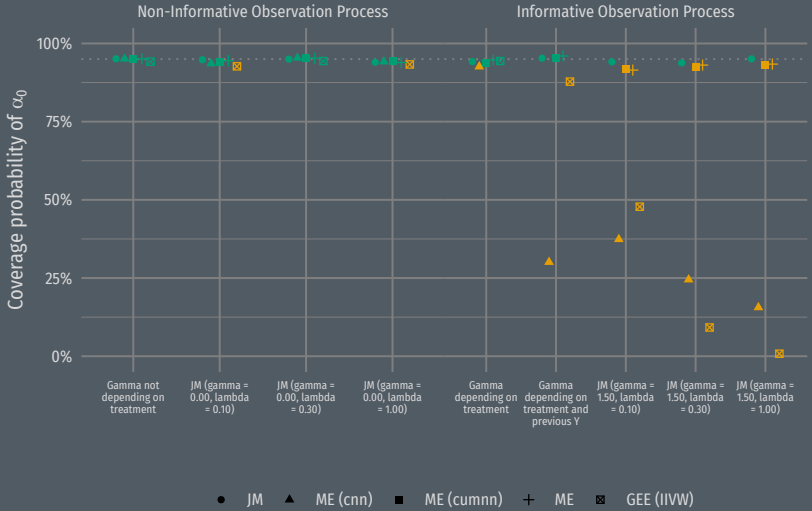

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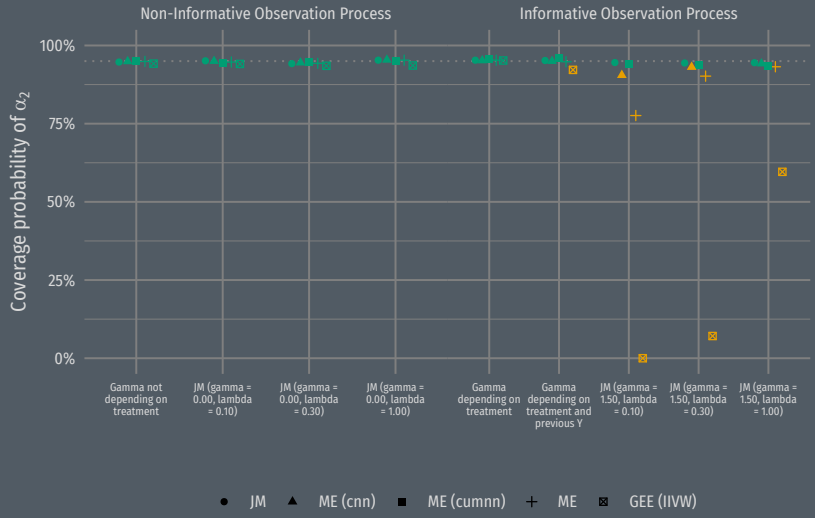

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Application data: PSP-CKD

- PSP-CKD is a cluster randomised controlled pragmatic trial of enhanced chronic kidney disease (CKD) care against usual primary care management.
- 49 primary care practices from Northamptonshire, United Kingdom, were randomised to either enhanced care or usual care; informed consent was provided at the practice level.
- We extracted baseline data collected retrospectively at the date of randomisation (up to 5 years prior) from the PSP-CKD study consisting of all longitudinal eGFR measurements pre-randomisation and demographics data.
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Data

```
. list id practice egfr egfr_date date_rand sex n nn cumnn cnn if id == 1
```

	id	practice	egfr	egfr_date	date_rand	sex	n	nn	cumnn	cnn
1.	00001	26	49	26feb2009	05oct2010	M	8	8	1	1.444082
2.	00001	26	54	15apr2009	05oct2010	M	8	8	2	1.444082
3.	00001	26	56	12may2009	05oct2010	M	8	8	3	1.444082
4.	00001	26	55	02oct2009	05oct2010	M	8	8	4	1.444082
5.	00001	26	55	20oct2009	05oct2010	M	8	8	5	1.444082
6.	00001	26	53	21jan2010	05oct2010	M	8	8	6	1.444082
7.	00001	26	53	12mar2010	05oct2010	M	8	8	7	1.444082
8.	00001	26	55	30mar2010	05oct2010	M	8	8	8	1.444082

```
. list id tY tY1 tYr tYr1 gaptY obs if id == 1
```

	id	tY	tY1	tYr	tYr1	gaptY	obs
1.	00001	-1.6044157	-1.472996	0	.13141972	.13141972	1
2.	00001	-1.472996	-1.3990724	.13141972	.20534331	.07392359	1
3.	00001	-1.3990724	-1.0075512	.20534331	.59686454	.39152124	1
4.	00001	-1.0075512	-.95826876	.59686454	.64614694	.04928239	1
5.	00001	-.95826876	-.70364306	.64614694	.90077264	.2546257	1
6.	00001	-.70364306	-.56674753	.90077264	1.0376682	.13689554	1
7.	00001	-.56674753	-.51746513	1.0376682	1.0869506	.04928239	1
8.	00001	-.51746513	0	1.0869506	1.6044157	.51746513	0

Descriptive characteristics

Number of individuals / measurements:

- 264,586 eGFR measurements;
- 38,239 individuals;

Sex:

- 14,905 (39%) males, 23,334 (61%) females;

Gap time between measurements:

- Median: 0.35 years (129 days);
- Inter-quartile interval (IQI): 0.11 – 0.74 years (39 – 272 days).

Is the observation process informative?

```
. spearman gaptY sex

 Number of obs =  239468
Spearman's rho =  0.0132

Test of Ho: gaptY and sex are independent
    Prob > |t| =  0.0000
```

```
. quietly mixed gaptY i.sex || id: R.sex if obs == 1
. nlcom _b[2.sex] * 365.242
       _nl_1:  _b[2.sex] * 365.242
------------------------------------------------------------------------------
      gaptY |      Coef.  Std. Err.      z    P>|z|     [95% Conf. Interval]
------------+-----------------------------------------------------------------
      _nl_1 |   8.561543   1.521358     5.63   0.000     5.579737    11.54335
------------------------------------------------------------------------------
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------------------------------------------------------------------
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Stata code to fit models (1)

- Joint model:

```
gsem (egfr ← i.sex##c.tY M1[id] M2[id]@1, family(gaussian)) ///
     (gaptY ← i.sex M1[id]@1, family(weibull, failure(obs))) ///
     , covstruct(M1[id] M2[id], diag)
```

- Mixed effects model:

```
mixed egfr i.sex##c.tY || id:
```

- Mixed effects model adjusted for the total number of observations:

```
mixed egfr i.sex##c.tY cnn || id:
```

- Mixed effects model adjusted for the cumulative number of measurements:

```
mixed egfr i.sex##c.tY cumnn || id:
```

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```
mixed egfr i.sex##c.tY cumnn || id:
```

Stata code to fit models (2)

- GEE (IIVW) model:

```
stset tYr1, fail(obs == 1) enter(tYr) exit(time .) id(id)
stcox sex, nohr vce(cluster id)
stset, clear
predict lp, xb
generate w = 1 / exp(lp)
summarize w
generate wn = w - r(mean) + 1
bysort id: generate iivw = wn[_n - 1]
replace iivw = 1 if iivw == .

glm egfr i.sex##c.tY [pw = iivw] ///
    , family(gaussian) link(identity) vce(cluster id)
```

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    , family(gaussian) link(identity) vce(cluster id)
```

Estimated coefficients

Coefficient	A	B	C	D	E
Intercept	55.90	55.77	55.90	56.14	54.14
Time	-0.70	-0.71	-0.72	-0.61	-0.67
Gender	0.11	0.11	0.02	0.11	0.74
Time $\times$ Gender	0.47	0.47	0.47	0.47	0.52

1. Model A: Joint model, `JM`
2. Model B: Mixed-effects model, `ME`
3. Model C: Mixed-effects model adjusted for total number of measurements, `ME (cnn)`
4. Model D: Mixed-effects model adjusted for cumulative number of measurements, `ME (cumnn)`
5. Model E: Inverse intensity of visiting weighting model, `GEE (IIVW)`

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1. Model A: Joint model, `JM`
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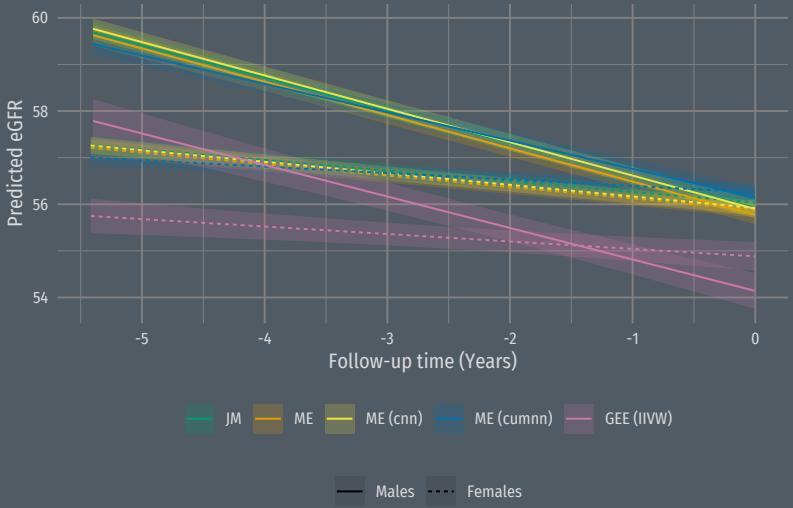
Comparing estimated trajectories



Outline

Take-home messages

1. Failing to account for a dynamic visiting process can yield biased results because of selection bias or confounding;
2. There is a variety of methods that can be utilised to account for an informative visiting process, but they are severely underutilised (as highlighted by Farzanfar *et al.*);
3. Simulating data that is biologically and clinically plausible in these settings is a challenge - any idea, suggestion, or feedback is very welcome;
4. Further extension to this work are coming soon(-ish).

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Work in collaboration with Michael Crowther, Keith Abrams, Jessica Barrett, Rupert Major, Michael Sweeting, Nigel Brunskill (in no particular order).

Preprint available at: `https://arxiv.org/abs/1808.00419`

Outline

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