Irregular Assessment Times in Randomized Controlled Trials

Eleanor Pullenayegum, Ph.D.
Division of Biostatistics
Dalla Lana School of Public Health
University of Toronto
eleanor.pullenayegum@sickkids.ca

Daniel Scharfstein, Sc.D.
Department of Population Health Sciences
University of Utah School of Medicine
daniel.scharfstein@hsc.utah.edu

(Please cite appropriately)

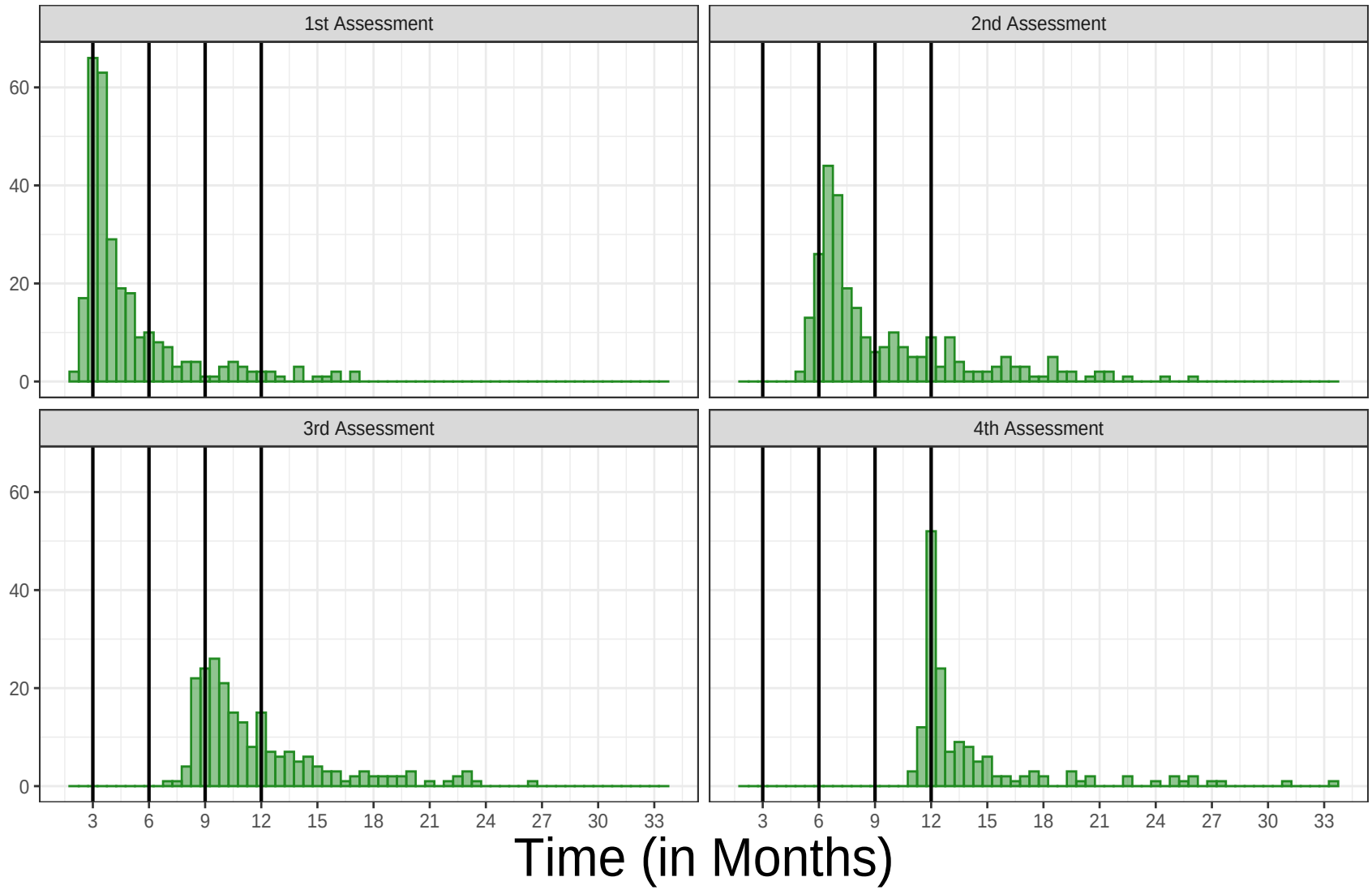
Introduction

- Randomized trials are often designed to collect outcomes at certain pre-specified times after randomization.
- In practice, there can be substantial variability in the times at which participants are actually assessed (i.e., *irregular*).
- In addition, the timing of assessments may be associated with the outcome of interest (i.e., *informative*).

Asthma Research for the Community (ARC) Study

- Randomized trial of 301 low-income participants with uncontrolled asthma.
- Control group: usual care plus access to and training in a web-based portal designed to improve communication with healthcare providers.
- Intervention group: home visits by community health workers, in addition to usual care and portal training.
- Primary outcome was Asthma Control score, reflecting symptoms over the week prior to assessment on a scale from 0 (completely controlled) to 6 (extremely uncontrolled).
- Study protocol called for outcome data to be collected at 3, 6, 9, and 12 months after randomization.
- Research coordinators were often unable to schedule data collection appointments until substantially later than these targeted times.

Asthma Research for the Community Study



Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial

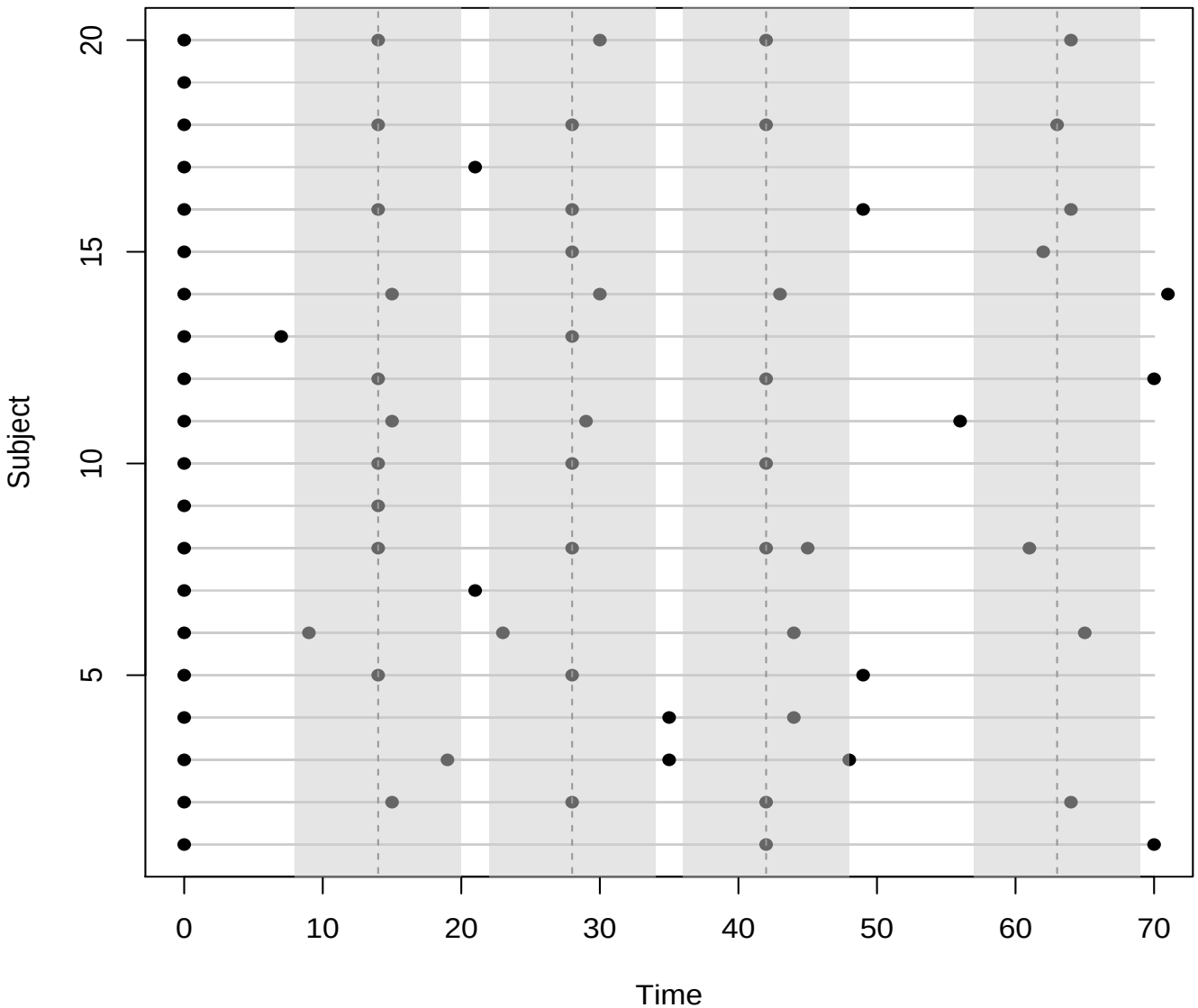
- Designed to evaluate the efficacy of treatments for major depressive disorder.
- Trial involved four stages, with randomization to an appropriate set of treatments among participants entering each stage.
- Each stage had a target treatment period of 12 weeks, however participants could exit early or remain longer based on their response to treatment.
- Within each stage, clinical visits were scheduled to occur at weeks 0, 2, 4, 6, 9, and 12; extra visits were allowed if clinically indicated.
- At each visit, the Quick Inventory of Depressive Symptomology (QIDS), was scheduled to be administered, both self-reported (QIDS-SR) and clinician rated (QIDS-CR).

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial

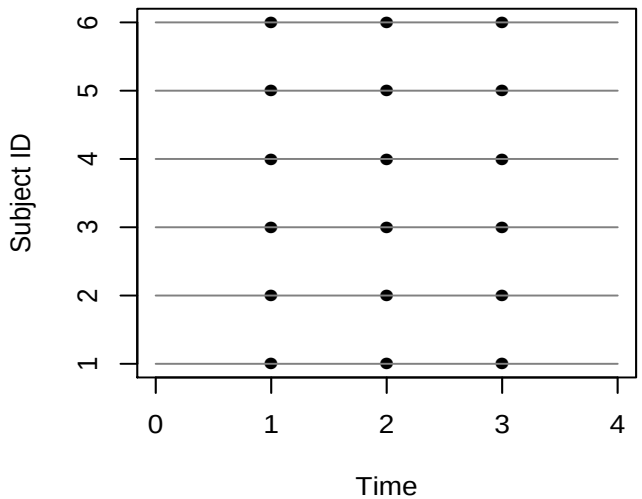
We focus on:

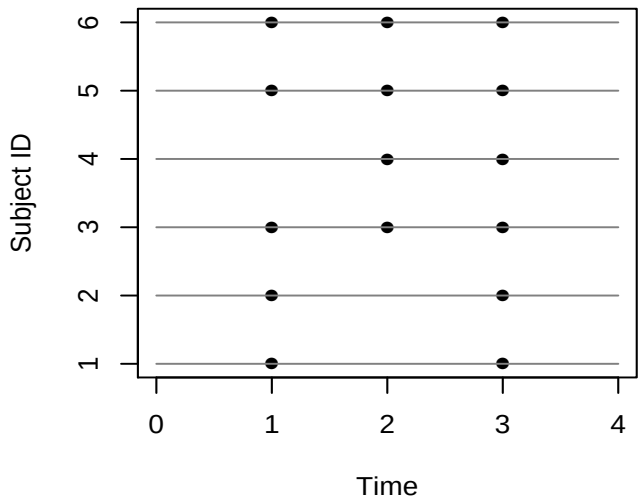
- 661 patients who entered phase 2 and were randomized to Bupriopion, Sertraline or Venlafaxine;
- longitudinal data through day 69 (all patients could stay through this day before exiting),
- change from baseline in the QIDS-SR.

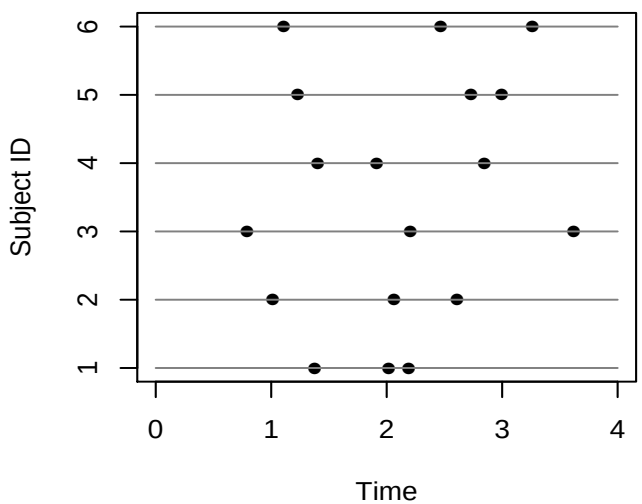
Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial

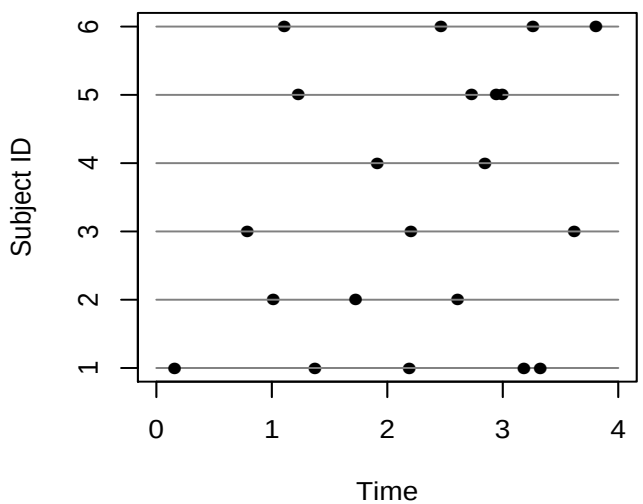


Distinction Between Irregular and Missing Data





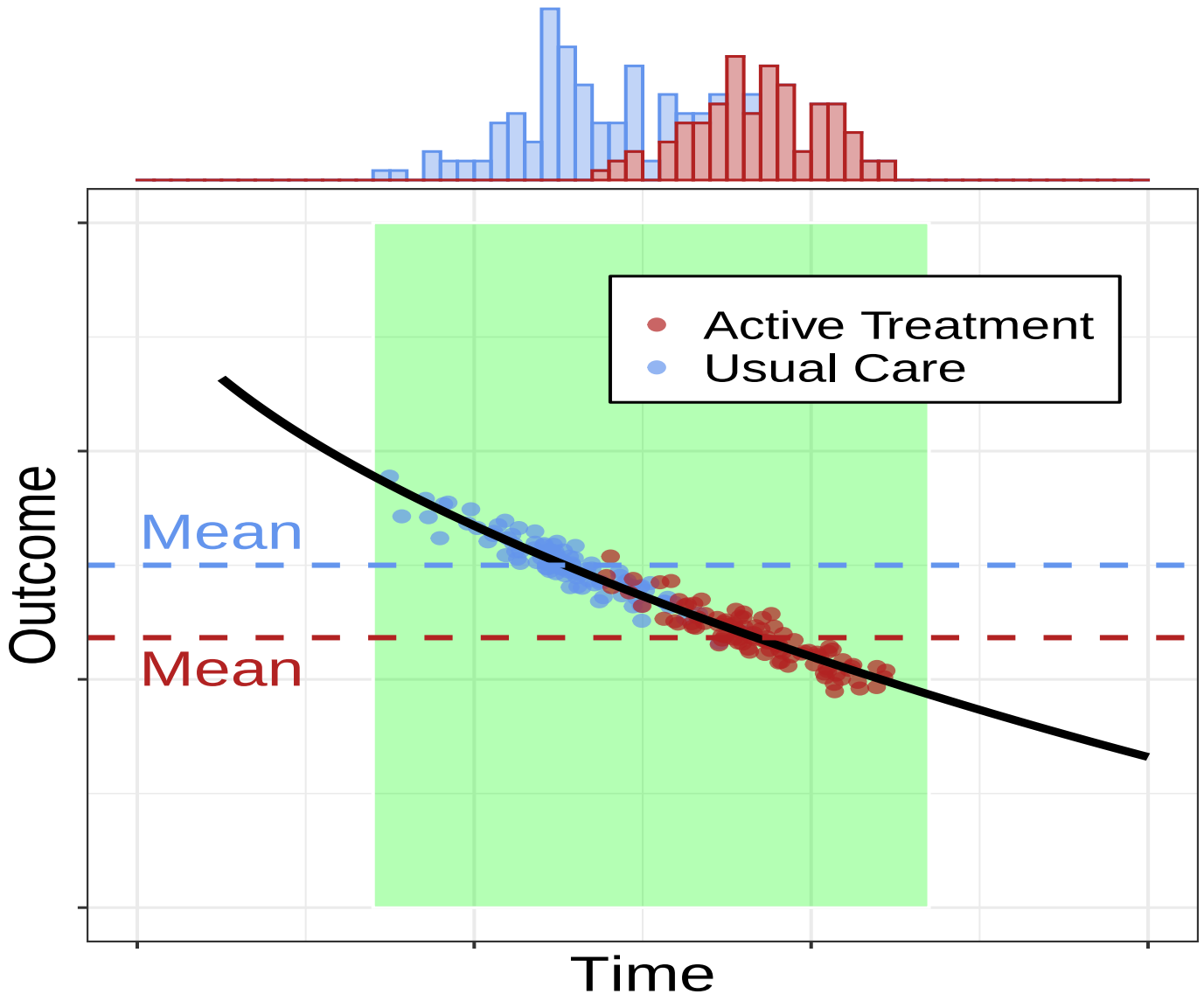




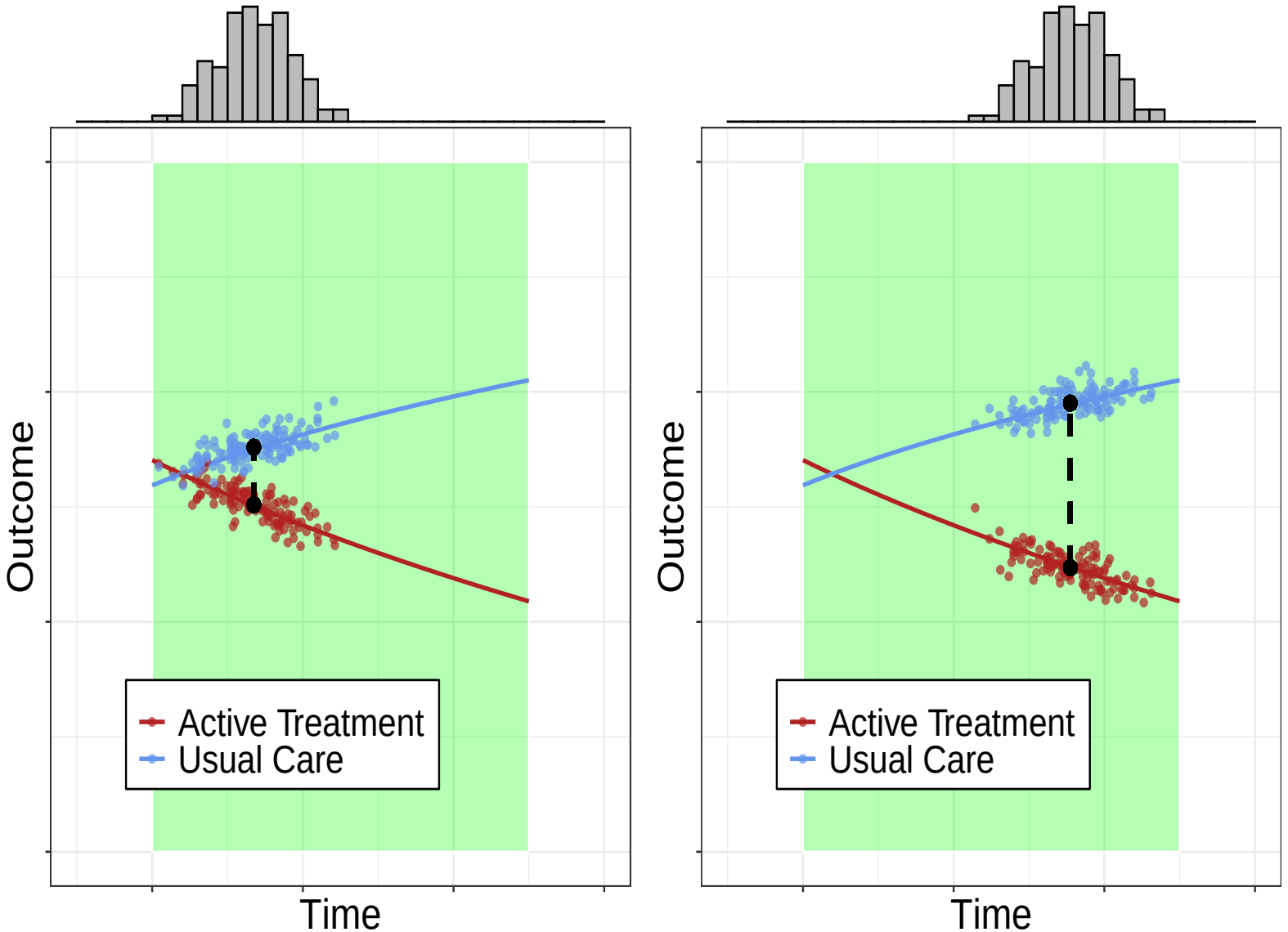
Problem

- When analyzing trials with irregular assessment times, researchers often focus on the outcome at the (random) time of assessment in each treatment arm.
- However, differences in this endpoint between treatment arms can be driven by the timing of assessments, rather than by an effect of treatment on participants' underlying outcome trajectories.
- Basing inference on the means of the observed outcomes can be problematic (even in trials without missing data).
- Examples include trials where the treatment effect changes with time, or where the times of assessments are different between treatment arms.

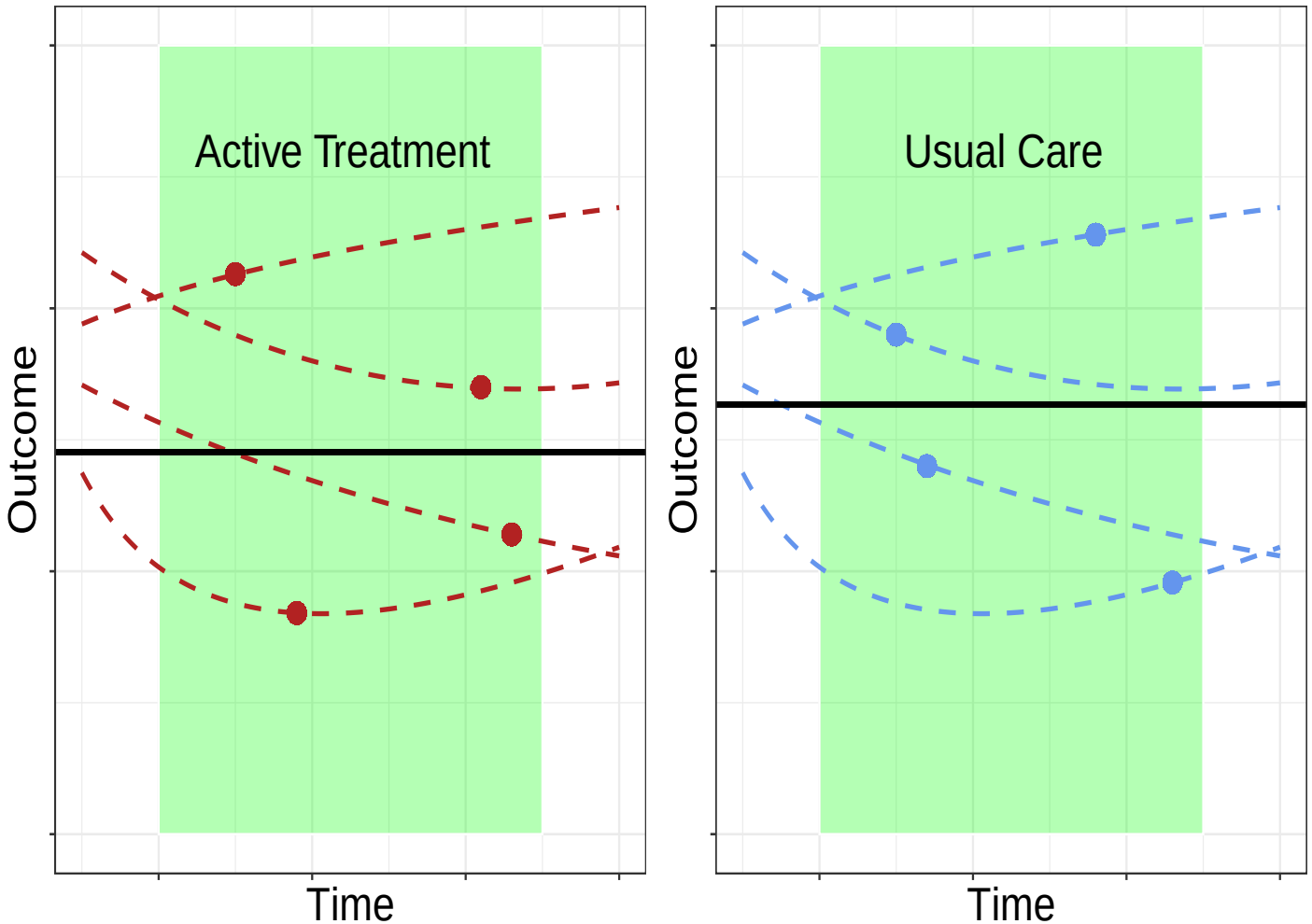
Differences in Distribution of Assessment Times



Two Studies


Outcome
Time
Active Treatment
Usual Care
Outcome
Time
Active Treatment
Usual Care

Timing of Assessments Related to Outcomes



Fixed Assessment Times

- One way to deal with this problem is to target the treatment effect at each of the (fixed) targeted assessment times stipulated in the protocol.
- What would be the treatment effect had everyone been assessed at these times?

Windows

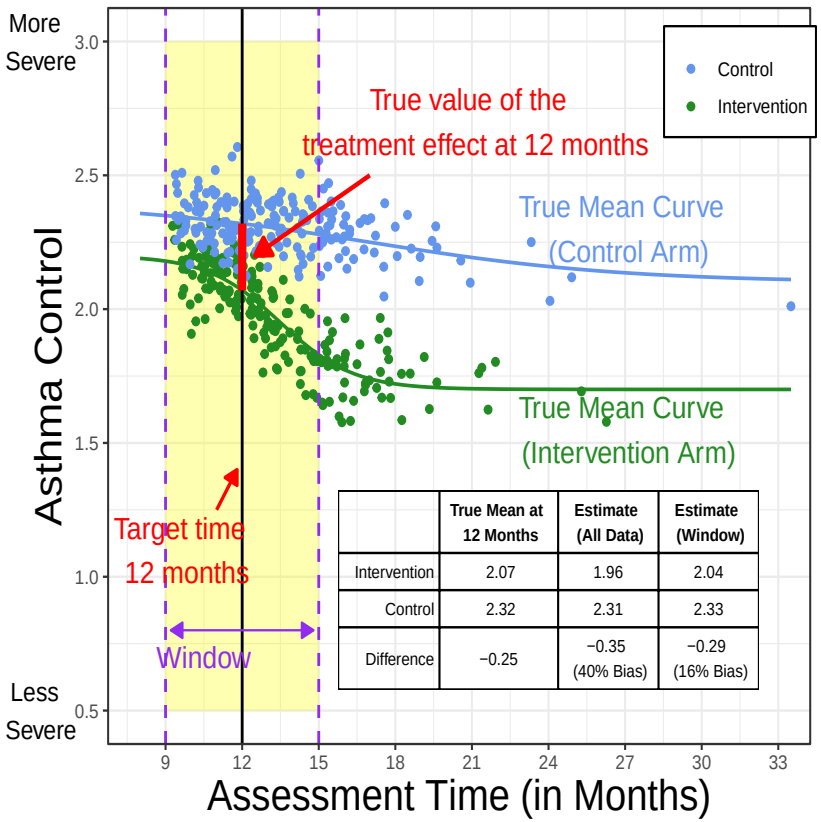
- A common approach to handling irregular longitudinal data is to convert them into repeated measures data subject to missingness.
- This might be done by specifying windows around the protocolized assessment times and, for each participant in each window, selecting the closest observation to the time point of interest, setting the outcome value to be missing for those participants with no assessments in a given window.

Windows

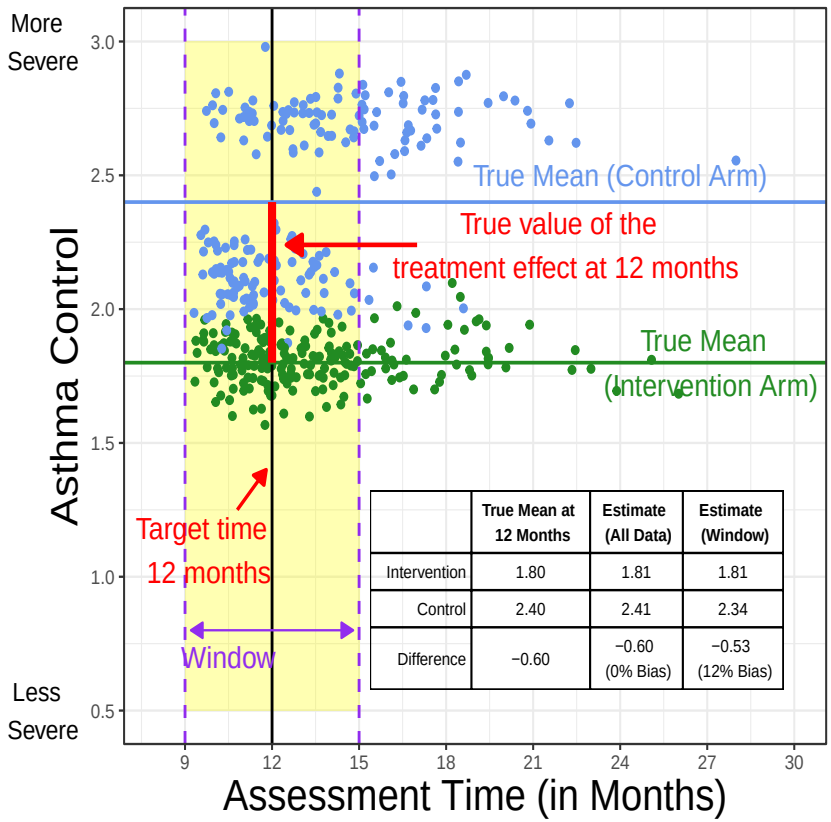
Why not?

- The width of the assessment windows is usually arbitrary.
- Using at most one observation per window means discarding information.
- Two individuals who are assessed only one day apart could be treated differently, one yielding an observed value and one yielding a missing value.
- Creating windows is unnecessary: longitudinal data subject to irregular assessment times is a generalization of repeated measures subject to missingness.

Windows



	True Mean at 12 Months	Estimate (All Data)	Estimate (Window)
Intervention	2.07	1.96	2.04
Control	2.32	2.31	2.33
Difference	−0.25	−0.35 (40% Bias)	−0.29 (16% Bias)



	True Mean at 12 Months	Estimate (All Data)	Estimate (Window)
Intervention	1.80	1.81	1.81
Control	2.40	2.41	2.34
Difference	−0.60	−0.60 (0% Bias)	−0.53 (12% Bias)

Course Outline and Objectives

Part I. **Characterizing the Assessment Process (Eleanor)**

- Quantifying the extent of irregularity
- Characterize the assessment process

Part II. **Analysis (Eleanor)**

- IIW-GEE
- Multiple outputation
- Semi-parametric joint models
- Fully parametric joint models
- Application to STAR*D

Part III. **Sensitivity Analysis (Dan)**

- Augmented IIW-GEE
- Application to ARC

Part 1. Characterizing the Assessment Process

Learning Objectives

By the end of this module, you should be able to

- quantify the extent of irregularity in a dataset
- explain why assumed relationships among outcomes, covariates, and assessment times are important
- use DAGs to describe hypothesized relationships
- describe models for the assessment intensity process

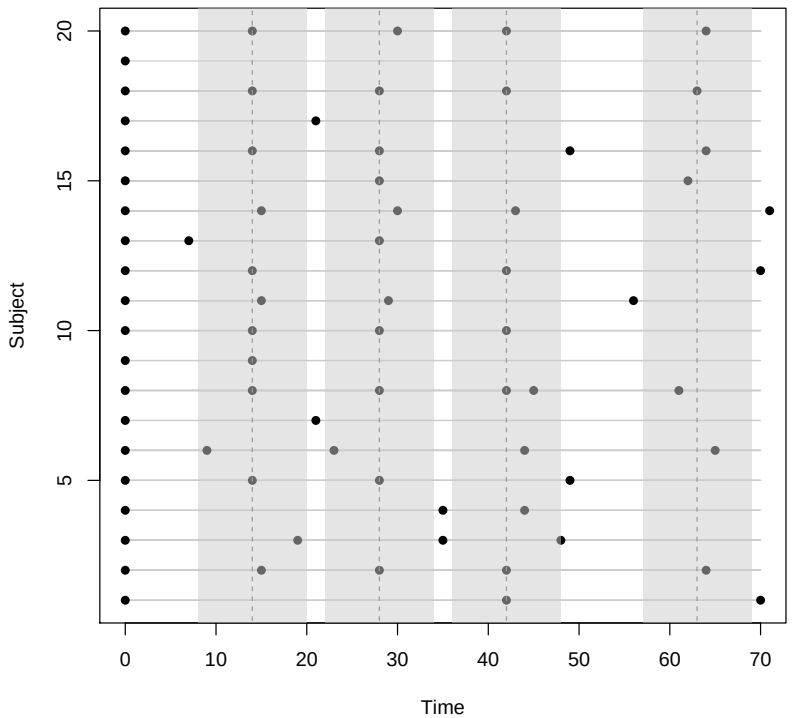
Extent of Irregularity

More irregularity $\rightarrow$ greater scope for bias

Measures of Irregularity

- Abacus plot
- Descriptives on number of visits
- Descriptives on gaps between visits

Abacus Plot & Descriptives



- R library `IrregLong`
- `abacus.plot` function

Group	No. of visits (SD)	Mean gap in days (SD)
Bupropion	3.8 (1.8)	19 (9)
Sertraline	4.0 (1.7)	19 (9)
Venlafaxine	4.2 (1.8)	20 (10)

- Gaps may be helpful when there is loss to follow-up
- No. of visits helpful when protocol has varying visit frequencies

Why Does Type of Dependence Matter?

For the same reason that missingness mechanism (MCAR/MAR/MNAR) matters

- no bias if assessment times are unrelated to outcomes
- potential for bias if assessment times are related to outcomes
  - choose analysis carefully
- Sensitivity analysis will be required for some types of dependence

Types of Dependence

- For **parametric** inference
  - *ignorability*
- For **non-** or **semi-parametric** inference
  - *ACAR*
  - *AAR*
  - *ANAR*

Ignorability

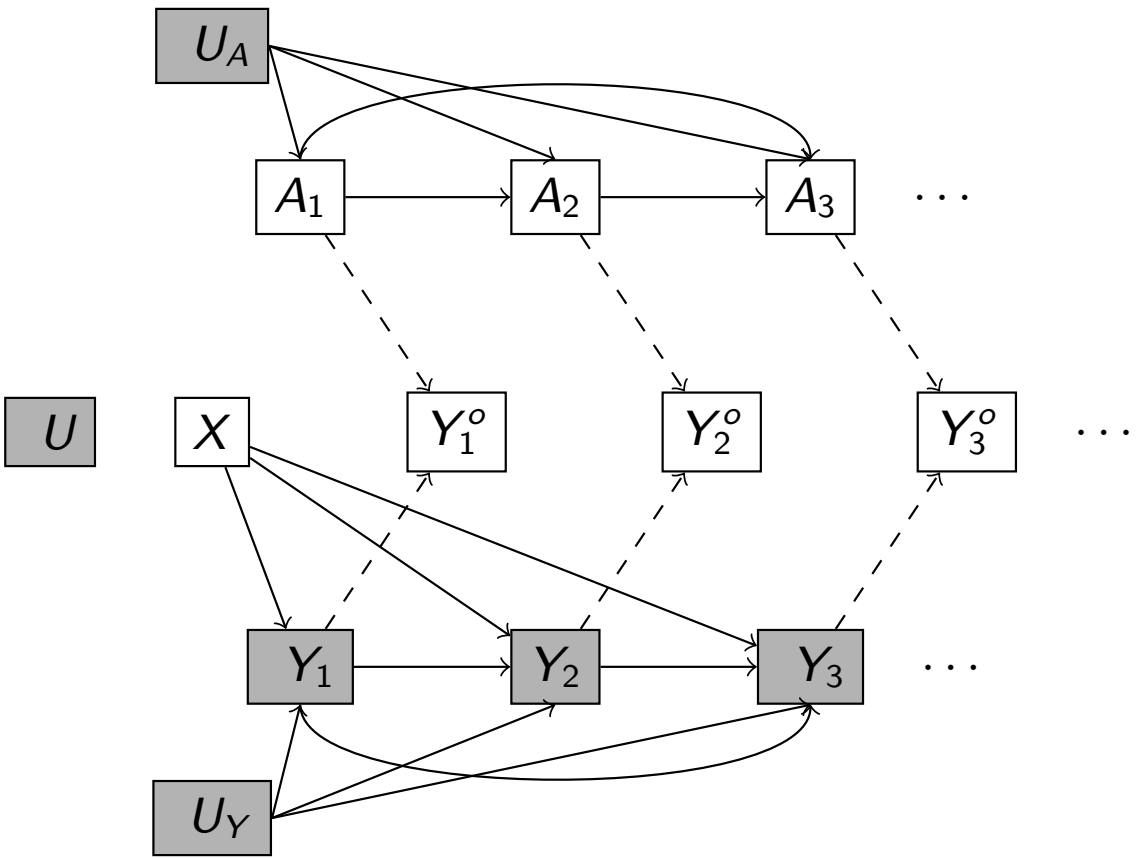
Suppose we have an outcome $Y(t)$ which, by time τ, is observed $N(\tau)$ times at time points $T_1, \ldots, T_{N(\tau)}$, where T_j are random variables

Assessment times are *ignorable* if

- $f(Y_1, \ldots, Y_{N(\tau)}, T_1, \ldots, T_{N(\tau)}) = f(Y_1, \ldots, Y_{N(\tau)}) f(T_1, \ldots, T_{N(\tau)})$
- *i.e.*, if the joint likelihood for assessment times and outcomes factorizes

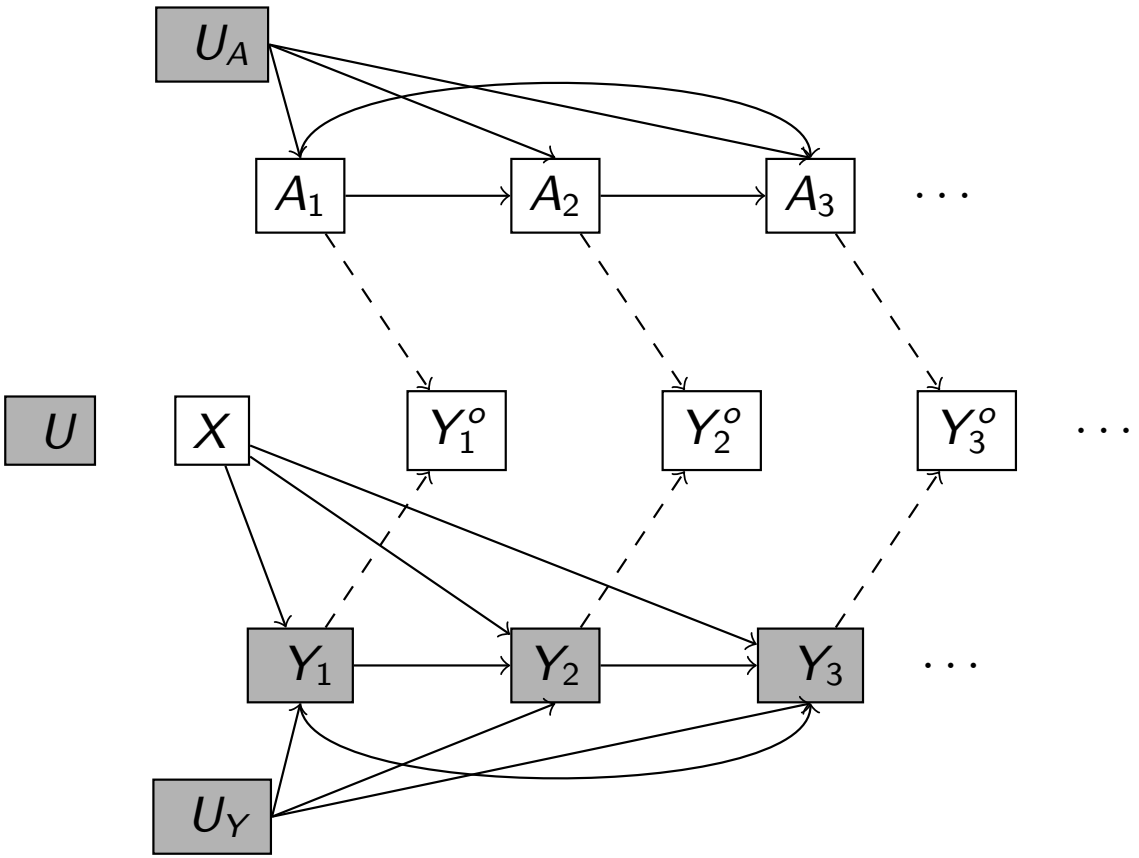
If you have ignorabiity, you can fit a mixed model to the outcomes alone
If you have simple stability, then you have ignorability

Simple Stability via DAGs



- Y_1, Y_2, Y_3: outcomes at times 1, 2, 3 ...
- A_1, A_2, A_3: indicators for whether the outcome was assessed
- $Y_j^o = Y_j$ if $A_j = 1$, missing o/w
- X: baseline covariates
- U, U_A, U_Y: random effects
- white boxes: observed
- grey boxes: unobserved

Simple Stability via DAGs



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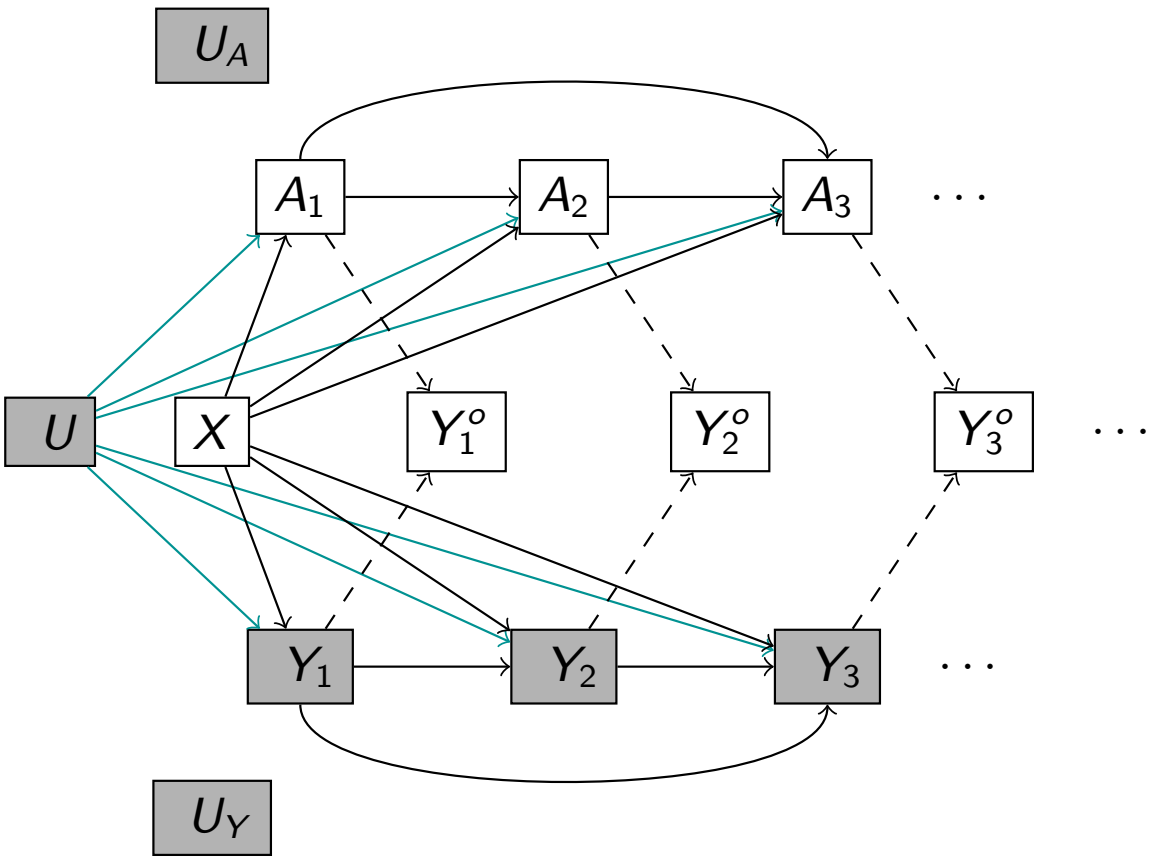
- A_1, A_2, A_3: indicators for whether the outcome was assessed
- $Y_j^o = Y_j$ if $A_j = 1$, missing o/w
- X: baseline covariates
- U, U_A, U_Y: random effects
- white boxes: observed
- grey boxes: unobserved

Simple stability holds if there is no backdoor path from Y_j^o to A_j that does not pass through previously observed data (A_k, Y_k^o $(k < j)$ or X).

Simple Stability via DAGs: Random Effect/Baseline Covariate Dependence



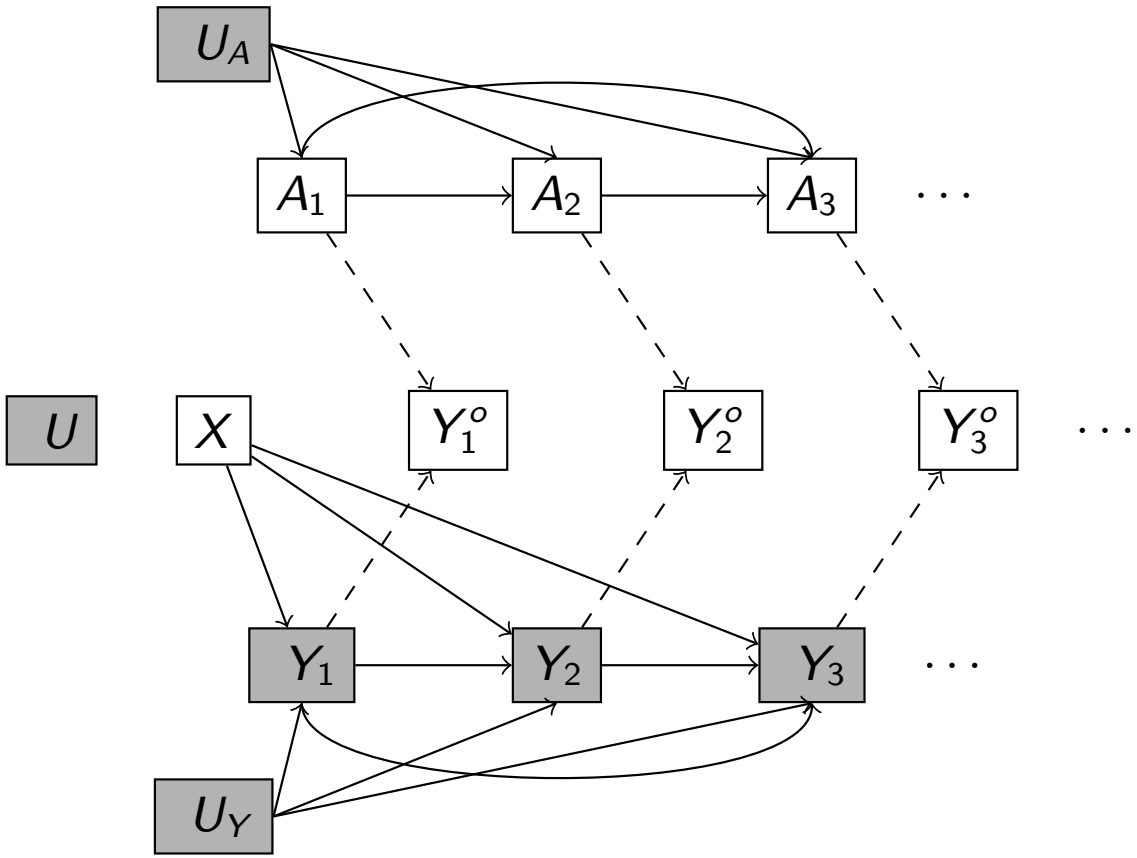
- Not Ignorable
- Need a joint model for outcomes & assessment times

Assessment Mechanisms for Non- and Semi-Parametric Inference

Type of Irregularity		Assessment & outcome...	
Assessment Completely at Random	(ACAR)	independent	$Y_j \perp\!\!\!\perp A_j$
Assessment Completely at Random with baseline covariates	(ACAR-X)	conditionally independent given baseline covariates	$Y_j \perp\!\!\!\perp A_j \mid X$
Assessment at Random	(AAR)	conditionally independent given past observed data	$Y_j \perp\!\!\!\perp A_j \mid \bar{O}_j$
Assessment Not at Random	(ANAR)	conditionally dependent given past observed data	$Y_j \not\perp\!\!\!\perp A_j \mid \bar{O}_j$

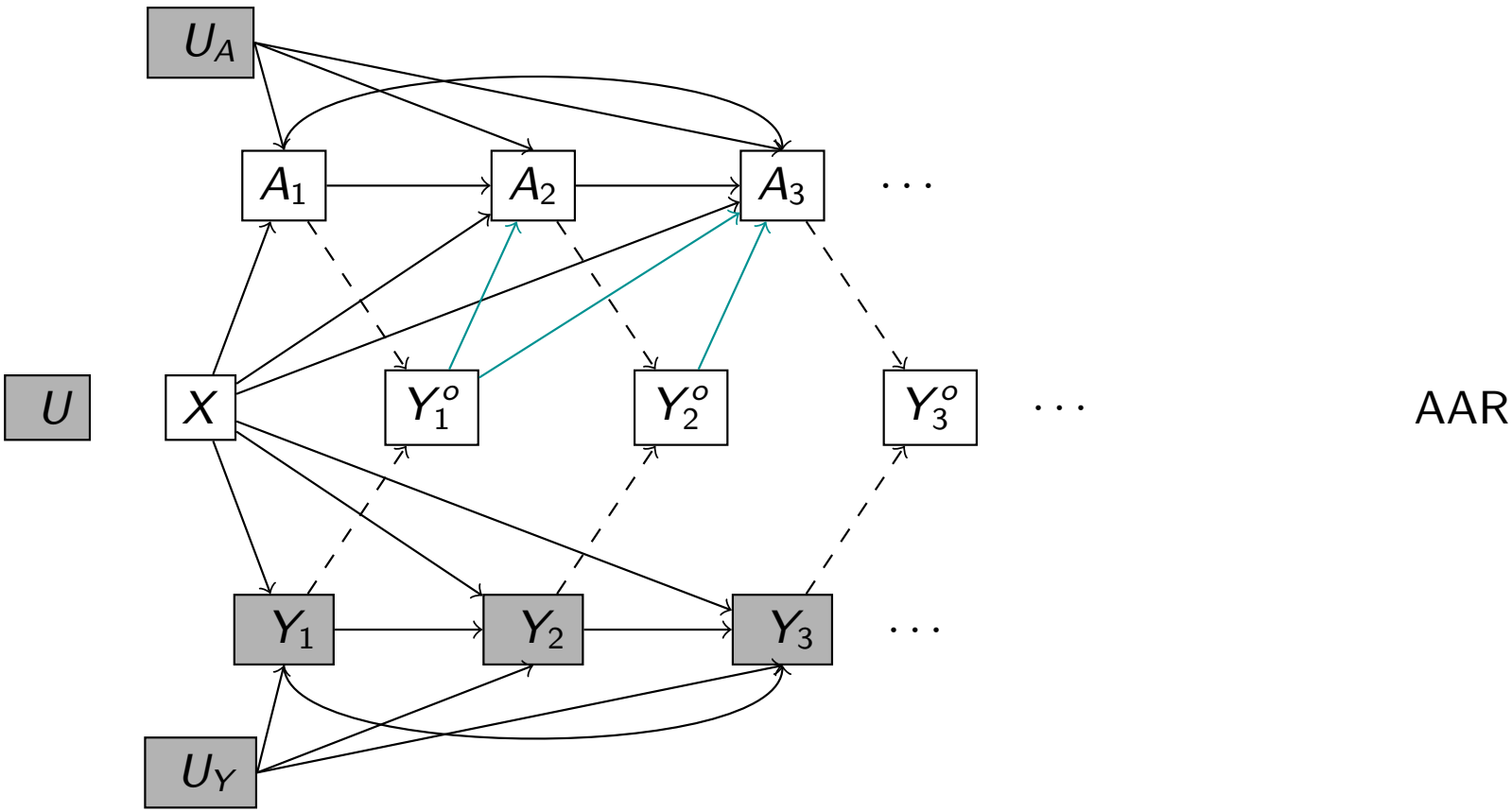
Table: Past observed data at time j includes previous assessment indicators, outcome assessments, baseline covariates, and, if available, auxiliary time-dependent covariates. Thus in the absence of time-dependent auxilaries $\bar{O}_j = \{Y_k^o, A_k, X \text{ for } k < j\}$; when time-dependent auxiliaries are included, $\bar{O}_j = \{Y_k^o, A_k, W_k^o, X \text{ for } k < j\}$

Assessment Mechanism: Independence

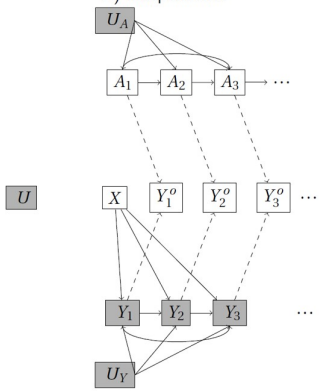


ACAR

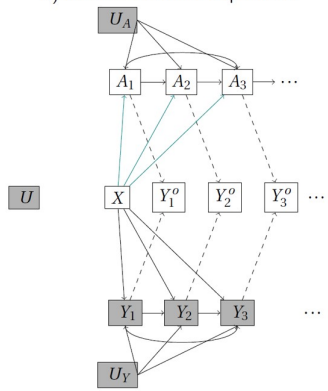
Assessment Mechanism: Past Outcome Dependence



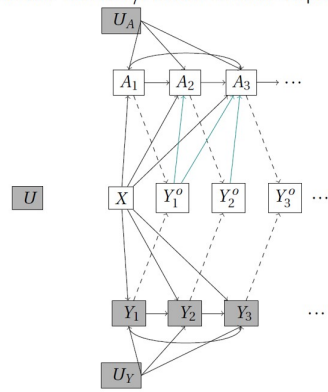
A) Independence



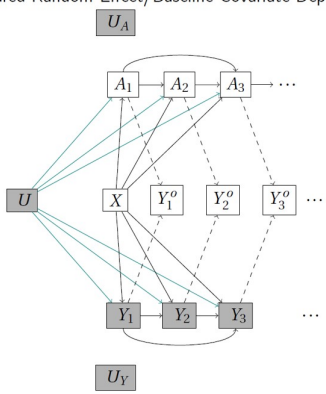
B) Baseline Covariate Dependence



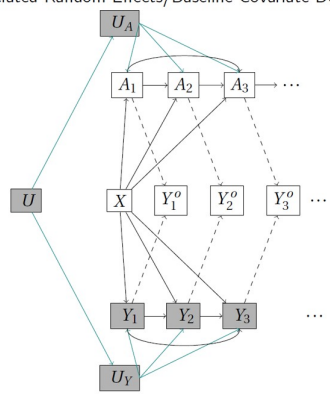
C) Baseline Covariate/Previous Outcome Dependence



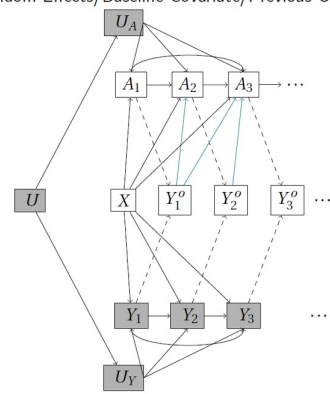
D) Shared Random Effect/Baseline Covariate Dependence



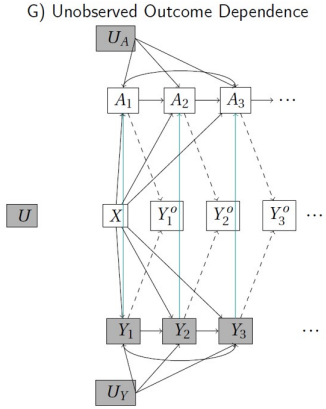
E) Correlated Random Effects/Baseline Covariate Dependence



F) Correlated Random Effects/Baseline Covariate/Previous Outcome Dependence



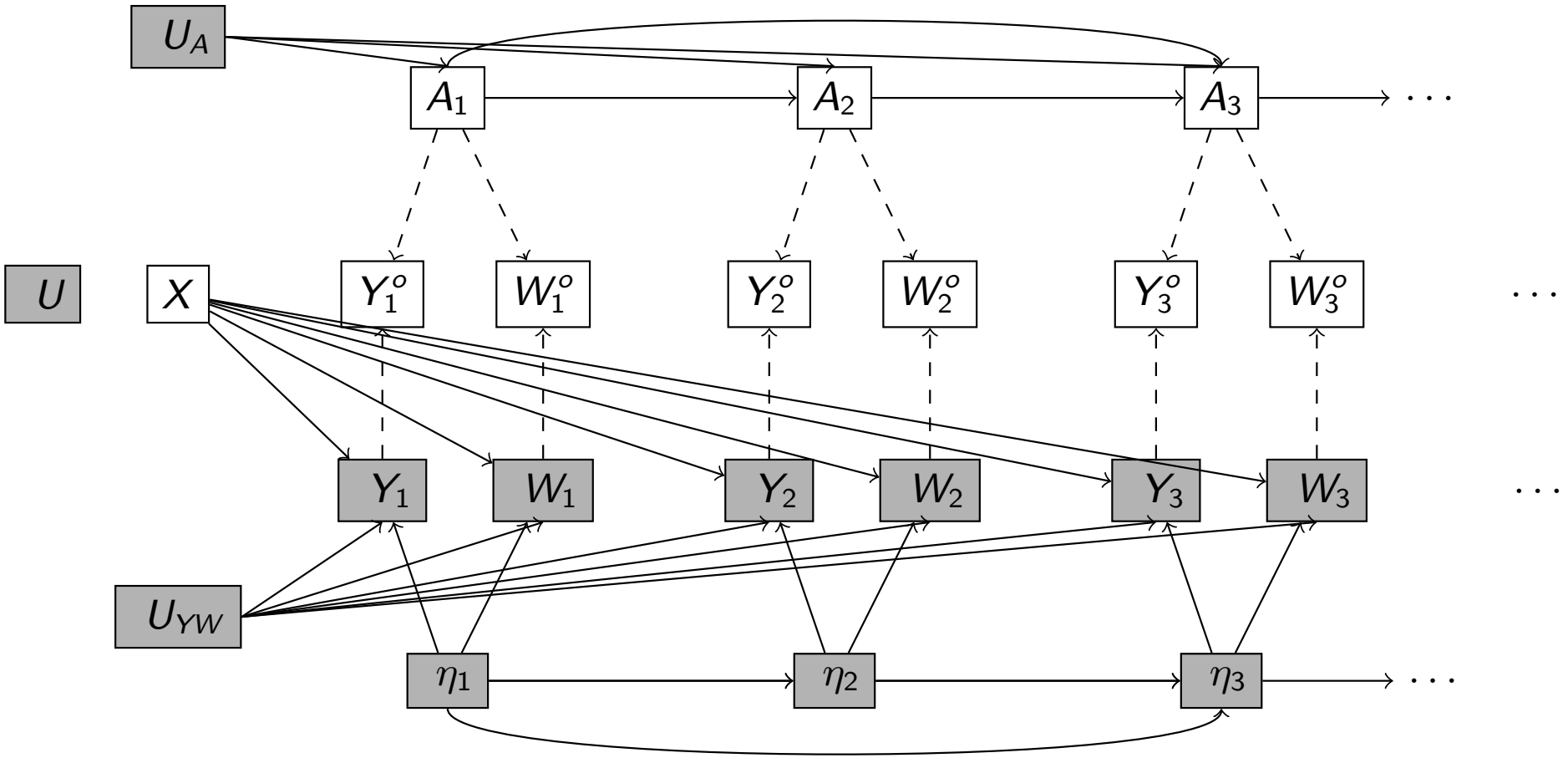
G) Unobserved Outcome Dependence



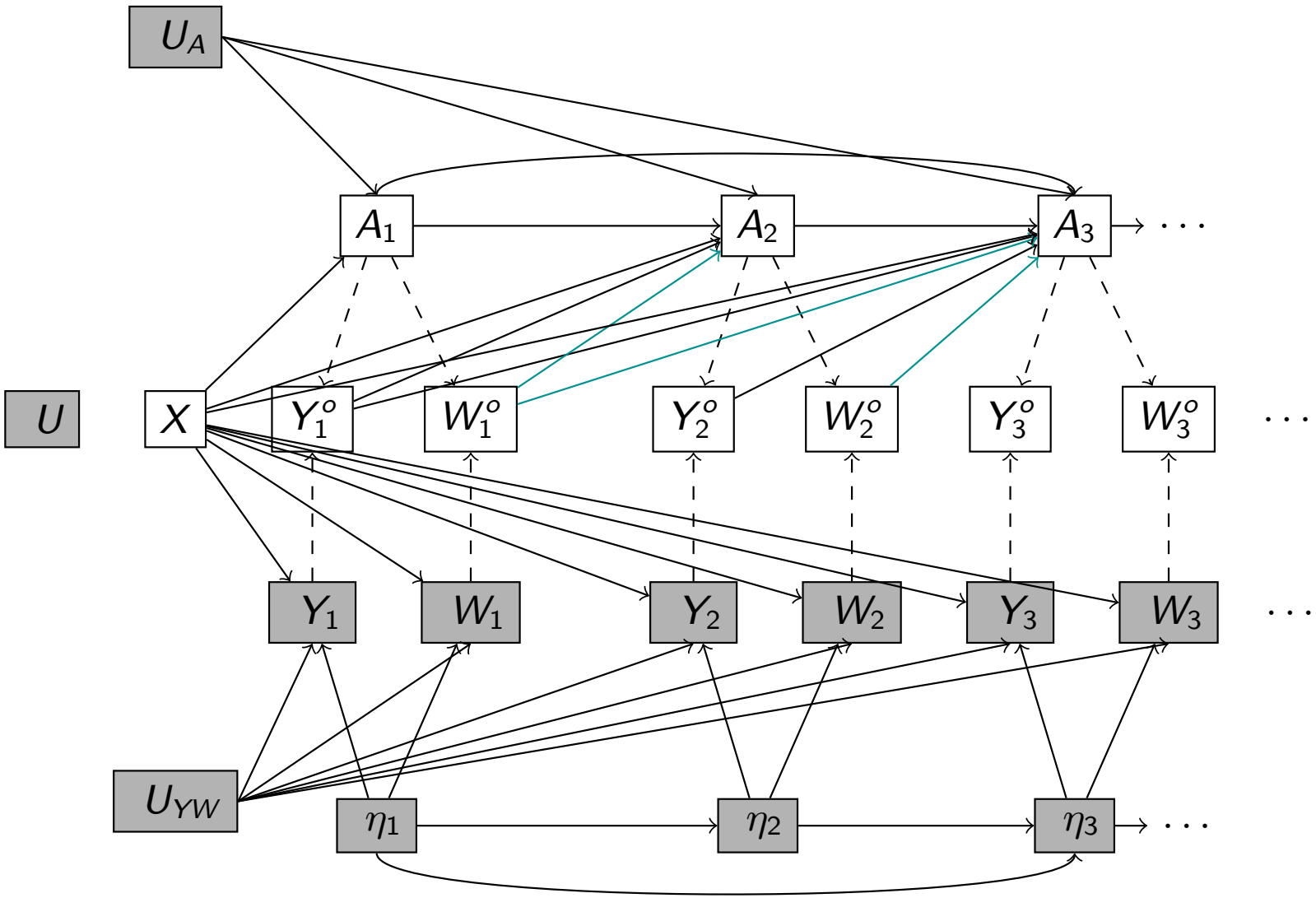
Time-dependent Auxiliary Covariates

- So far our DAGs have had no time-dependent covariates
- Any time-dependent covariates assumed to be **auxiliary**
  - outcome model does not condition on them
  - b/c they are post-randomization covariates
- Simple stability extends to time-dependent covariates
  - no backdoor paths that are not blocked by previously observed outcomes, *previously observed auxiliary covariates*, observation times, or baseline covariates
- ACAR, ACAR-X, AAR, ANAR continue to apply with observed auxiliries incorporated in the histories $\bar{O}_j$

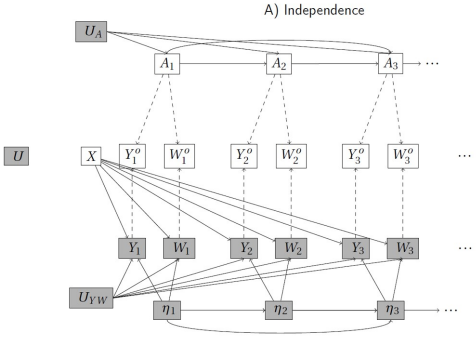
DAGs with Auxiliary Covariates: Independence



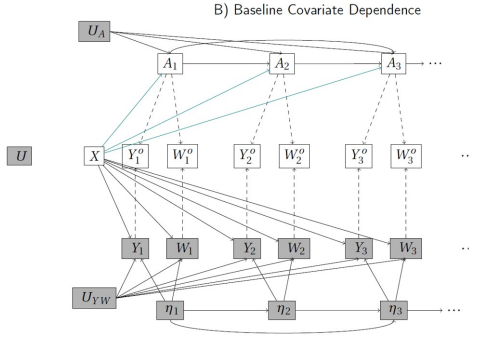
Past Observed Outcome/Covariate (Auxiliary and Baseline) Dependence



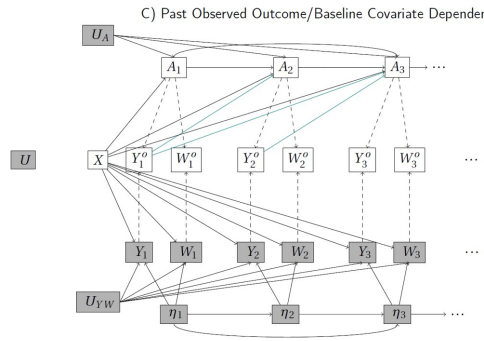
A) Independence



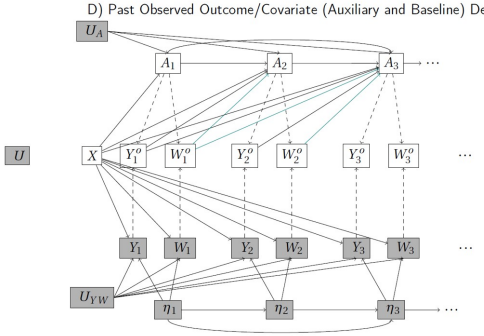
B) Baseline Covariate Dependence



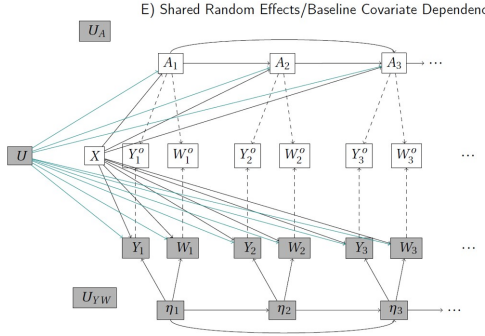
C) Past Observed Outcome/Baseline Covariate Dependence



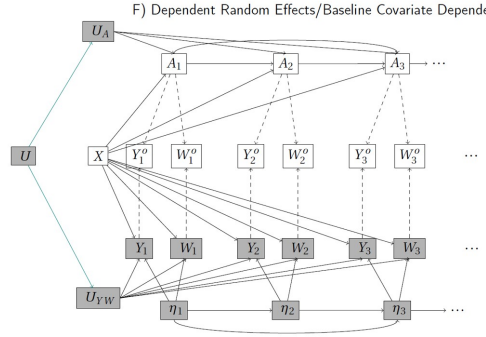
D) Past Observed Outcome/Covariate (Auxiliary and Baseline) Dependence



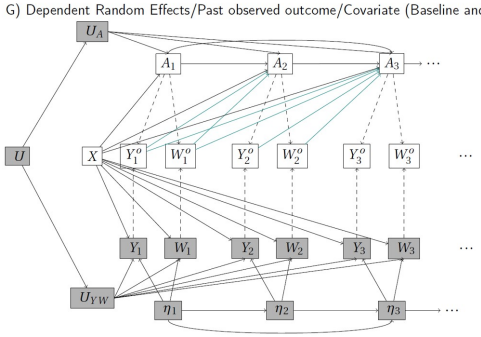
E) Shared Random Effects/Baseline Covariate Dependence



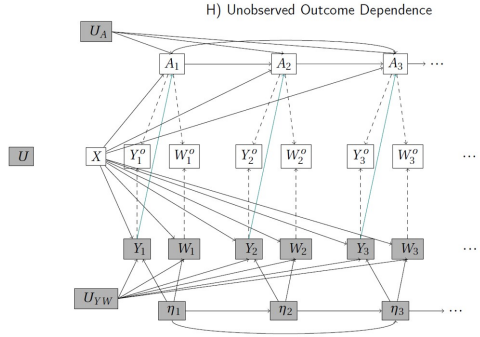
F) Dependent Random Effects/Baseline Covariate Dependence



G) Dependent Random Effects/Past observed outcome/Covariate (Baseline and Auxiliary) Dependence



H) Unobserved Outcome Dependence



A Note on Testing

- In general, cannot determine which DAG is appropriate through testing
- *Some* of the assumptions in our DAGs are testable *subject* to modelling assumptions
- For example, suppose we are willing to assume
  - DAG C) (past outcome dependence) holds
  - a proportional intensity model holds
- Then we can test whether a simpler DAG (A or B) holds
- Even so, remember "absence of evidence is not evidence of absence"

Modelling the Assessment Intensity

Modelling the assessment process can assist in deciding which DAG(s) are plausible for our data.

- Assessment times form a recurrent event process
- Can use an Andersen-Gill model
- May need to add time to censoring

To depict dependencies using DAGs we discretized time and had assessment indicators A_j

For the purposes of modelling we shall work in continuous time and use standard counting process notation

Assessment Times as Recurrent Events

Let $N(t)$ denote the number of assessments by time t, i.e.

$$N(t) = \sum_{j=1}^{\infty} I(T_j \leq t)$$

Standard approaches to recurrent event analyses can then be used.

It is also helpful to define

- $A(t)$: indicator of assessment at time t; $A(0) = 1$
- $A[t, t + \epsilon)$:indicator of assessment in the time window $[t, t + \epsilon)$

For an arbitrary set of random variables $\mathcal{S}(t)$, let

$$\lambda(t; \mathcal{S}(t)) = \lim_{\epsilon \downarrow 0} \frac{P\big(A[t, t+\epsilon) = 1 \mid \mathcal{S}(t)\big)}{\epsilon}$$

Suppose we are willing to assume a specific form of AAR:

$$\lambda(t; X, Z(t)) = \lambda_0(t) \exp(X\gamma_1 + Z(t)\gamma_2)$$

where $Z(t)$ is known at all times t and is predictable, i.e. known prior to time t.

- If $\gamma_2 = 0$ then ACAR-X holds
- If $\gamma_2 = 0$ & $\gamma_1 = 0$ then ACAR holds

We can use the Andersen-Gill estimates of γ_1 & γ_2 with robust standard errors:

- `coxph` in `R`
- use `cluster(id)` to get robust standard errors

Frailty Models

We may also wish to consider random-effect-dependent assessment schemes.

- Let U_A be a latent (unobserved) variable.
- We consider models of the form

$$\lambda(t; X, Z(t), U_A) = U_A \lambda_0(t) \exp(X\gamma_1 + Z(t)\gamma_2),$$

where for identifiability we assume $E(U_A \mid X, Z(s) : s \in \{0, \tau\}) = 1$.
You can fit frailty models in R:

- `coxph` with `frailty(id)` assumes Gamma frailties
- `coxme` assumes log-Normal frailties

Practical Note: Include Time-to-Censoring in your Data

- Timeline for a single patient
- Filled dots: assessment times
- Open dot: censoring time
- Likelihood must capture
  - Assessment times
  - Periods where there was no assessment

$\rightarrow$ Add censoring time to your dataset

id	time	event
1	0	1
1	4	1
1	6	1
2	2	0
2	3	1
3	1	0
3	3	1
3	5	1
3	6	1
3	7	1

id	time	event
1	0	1
1	4	1
1	6	1
1	8	0
2	2	0
2	3	1
2	8	0
3	1	0
3	3	1
3	5	1
3	6	1
3	7	1
3	8	0

Assessment Process in STAR*D

Begin by assuming assessment intensity

- may depend on past observed outcomes & baseline covariates
- does not depend on current value of the outcome given the observed history
- follows a proportional intensity model
- may depend on a multiplicative time-invariant frailty

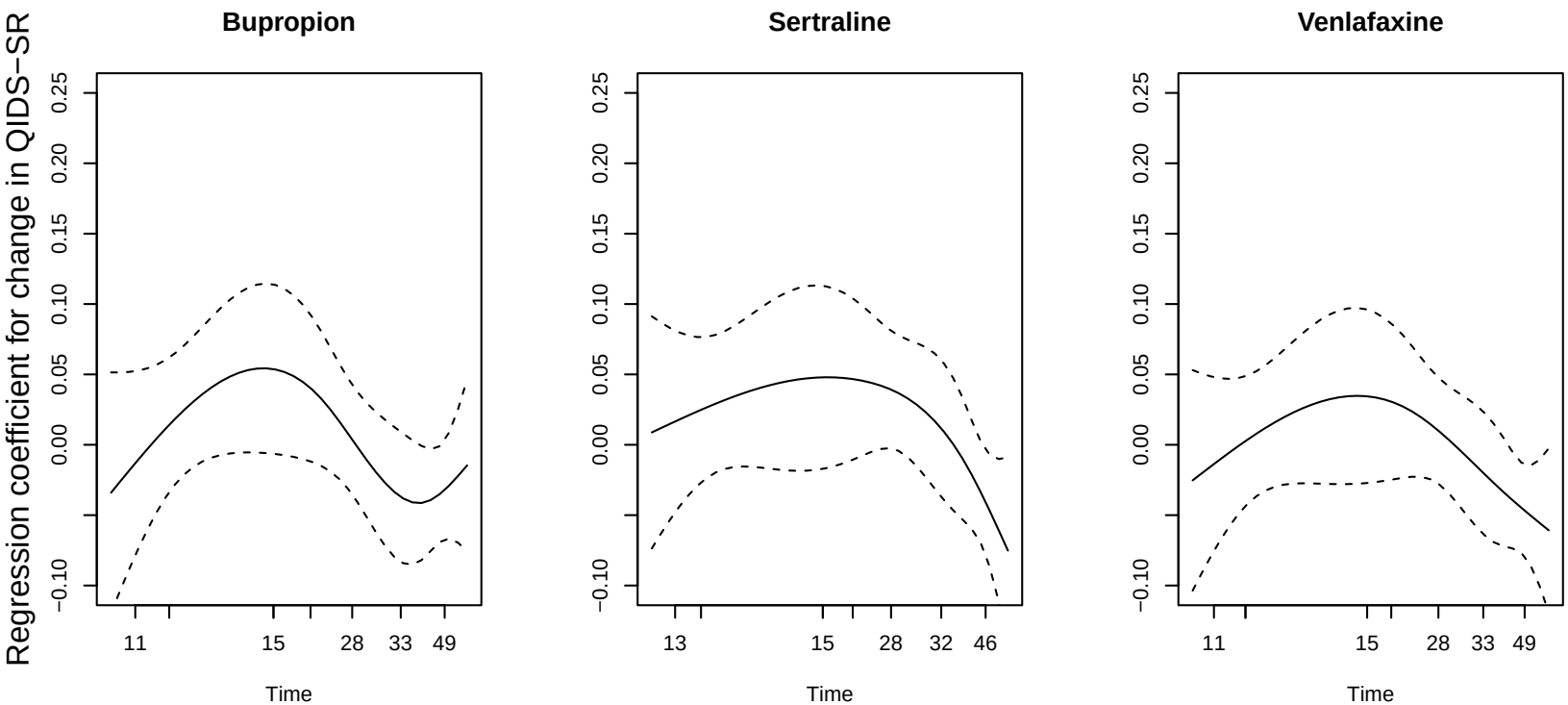
Assessment Process in STAR*D: Intensity Model

Covariate	Bupropion	Sertraline	Venlafaxine
Male	1.08 (0.91-1.27)	1.16 (0.99-1.36)	1.02 (0.88-1.20)
Age (years)	1.04 (0.96-1.12)	1.03 (0.96-1.11)	1.07 (0.99-1.15)
Medical/Psychiatric Leave	1.20 (0.92-1.56)	0.86 (0.63-1.17)	1.08 (0.82-1.44)
QIDS-SR at baseline	1.00 (0.98-1.01)	1.01 (0.99-1.02)	0.99 (0.97-1.01)
Δ QIDS-SR	1.01 (0.98-1.03)	1.04 (1.01-1.06)	1.01 (0.98-1.03)
Δ QIDS-SR $\times(\frac{(days-15)}{7})^2/100$	0.93 (0.84-1.02)	0.83 (0.76-0.92)	0.89 (0.83-0.96)

Table: Intensity rate ratios (95% Confidence Intervals) for predictors of assessment intensity in Level 2 of the STAR*D data.
Δ QIDS-SR = QIDS-SR at last visit − QIDS-SR at baseline.

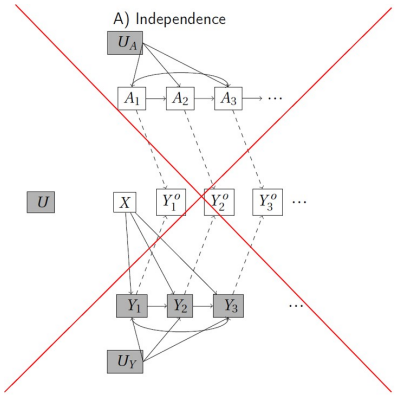
Intensity models fitted with `coxph` in `R`

Assessment Process in STAR*D: Time-varying HRs

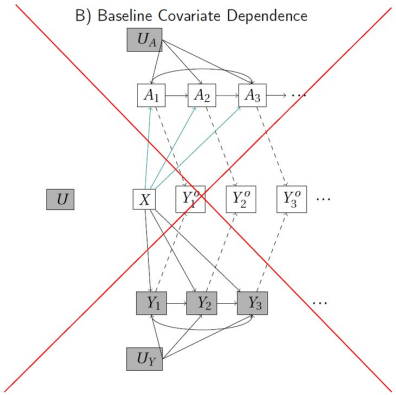


Assessment Process in STAR*D

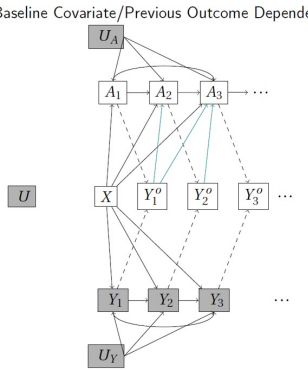
A) Independence



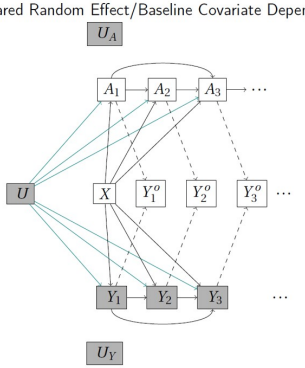
B) Baseline Covariate Dependence



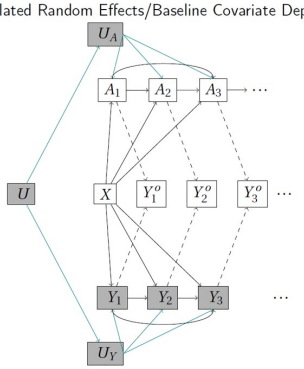
C) Baseline Covariate/Previous Outcome Dependence



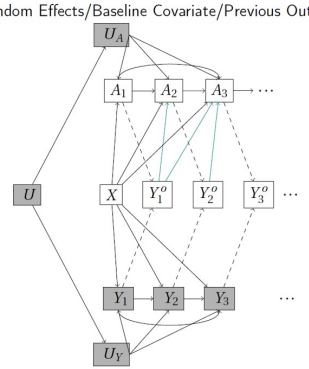
D) Shared Random Effect/Baseline Covariate Dependence



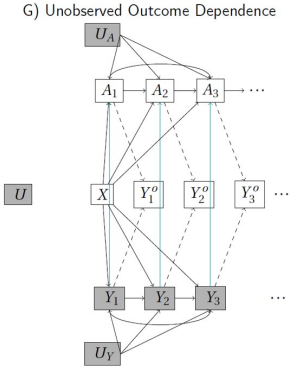
E) Correlated Random Effects/Baseline Covariate Dependence



F) Correlated Random Effects/Baseline Covariate/Previous Outcome Dependence



G) Unobserved Outcome Dependence

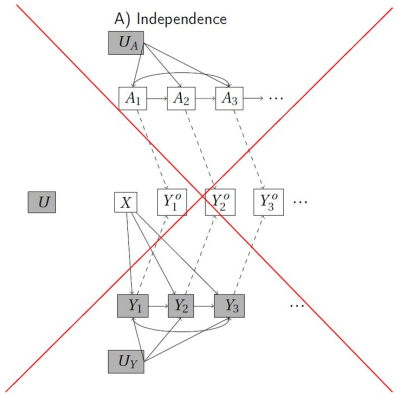


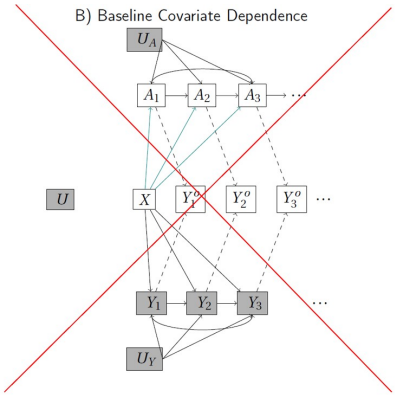
Frailty Models in STAR*D

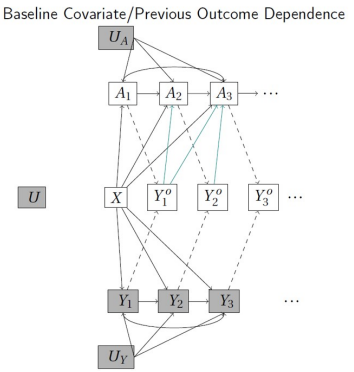
- Re-fit the model with a log-Normal frailty
- Estimated frailty SDs: 0.009 Bupropion & Sertraline groups; 0.004 for Venlafaxine
- Variance of frailty is tiny
- We do not need to worry about random-effect dependent assessment times

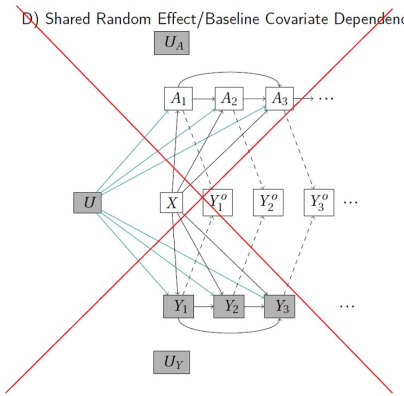
Frailty models fitted with `coxme` in `R`.

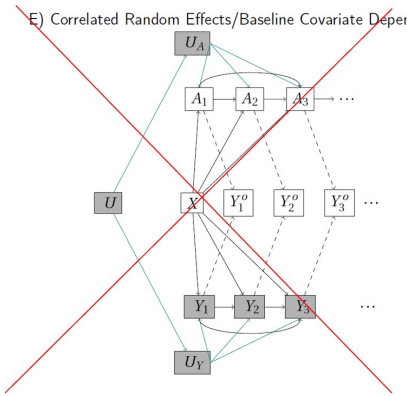
Assessment Process in STAR*D

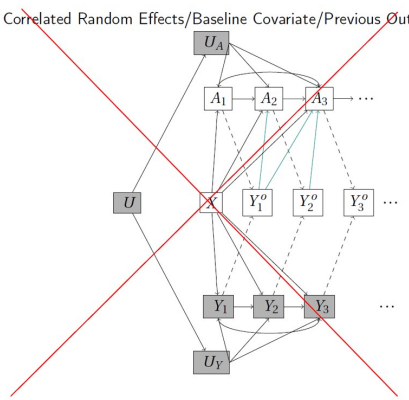


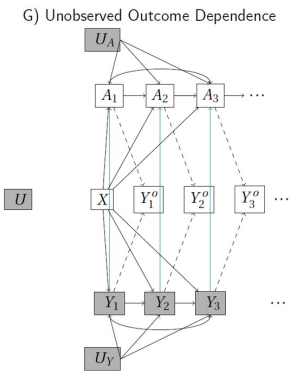










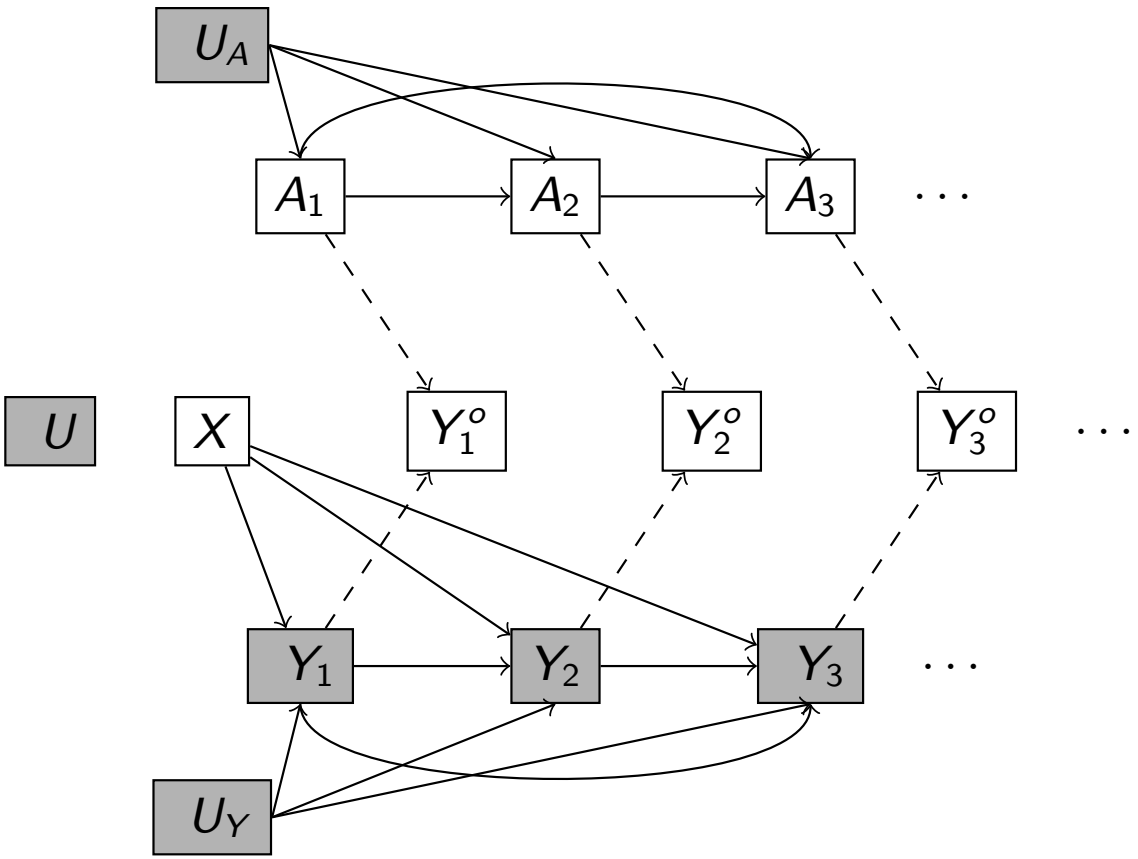


Why Does Assessment Mechanism Matter?

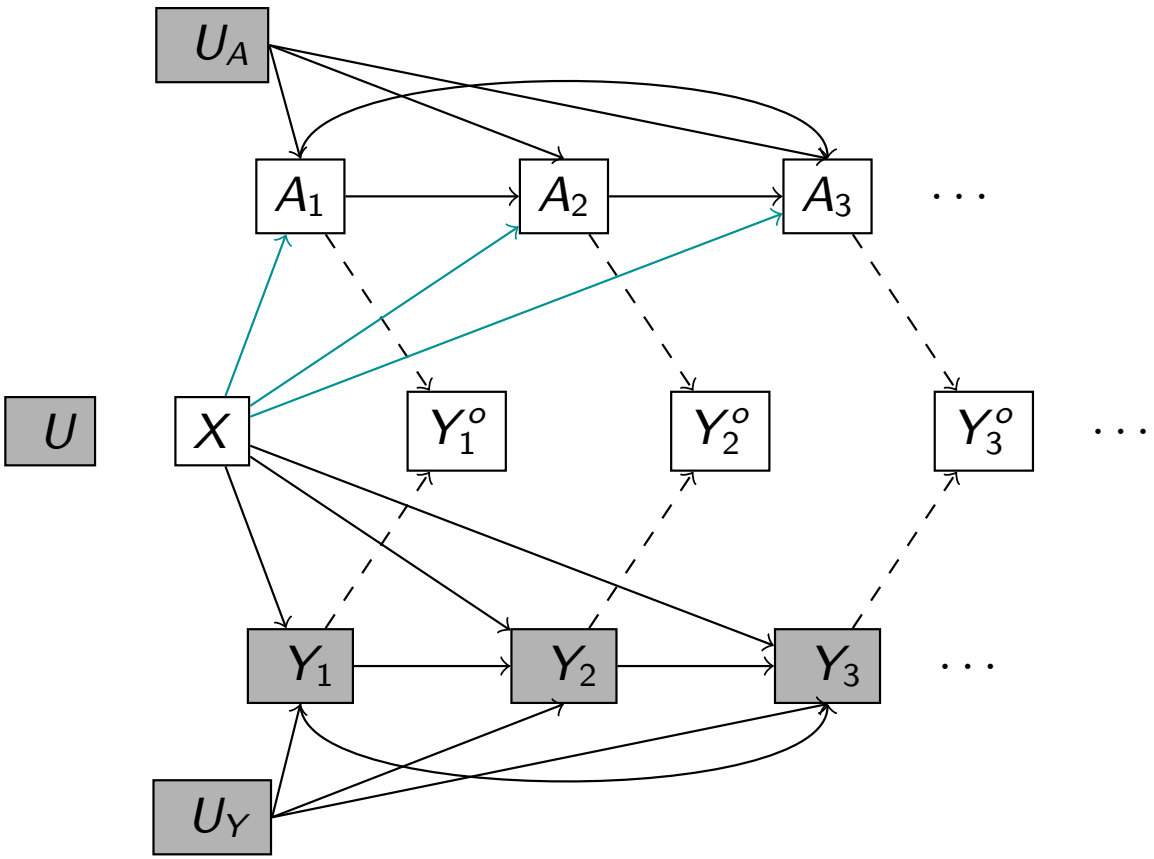
- GEEs are valid under ACAR and ACAR-X
- *Inverse intensity weighted* GEEs are valid under AAR
- Sensitivity analysis is required for ANAR

Part 1: Appendix

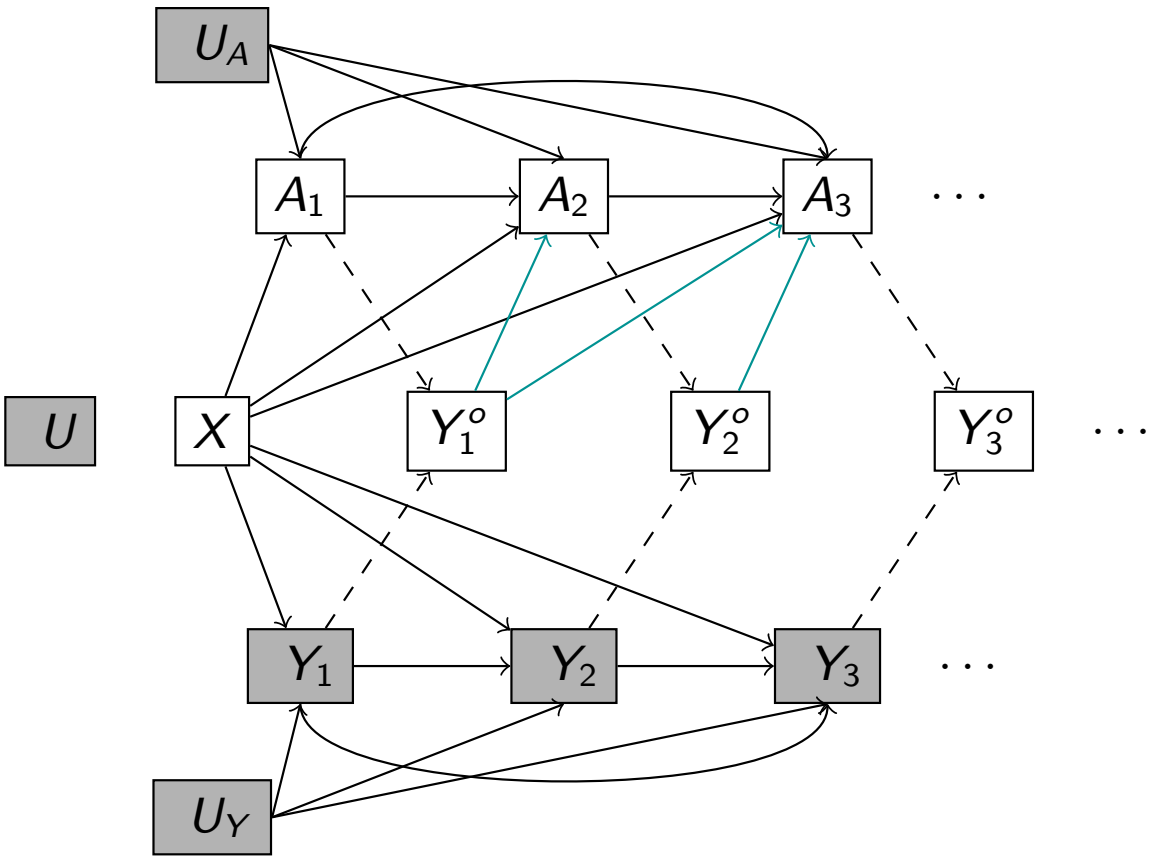
DAGs (no auxiliaries): (A) Independence



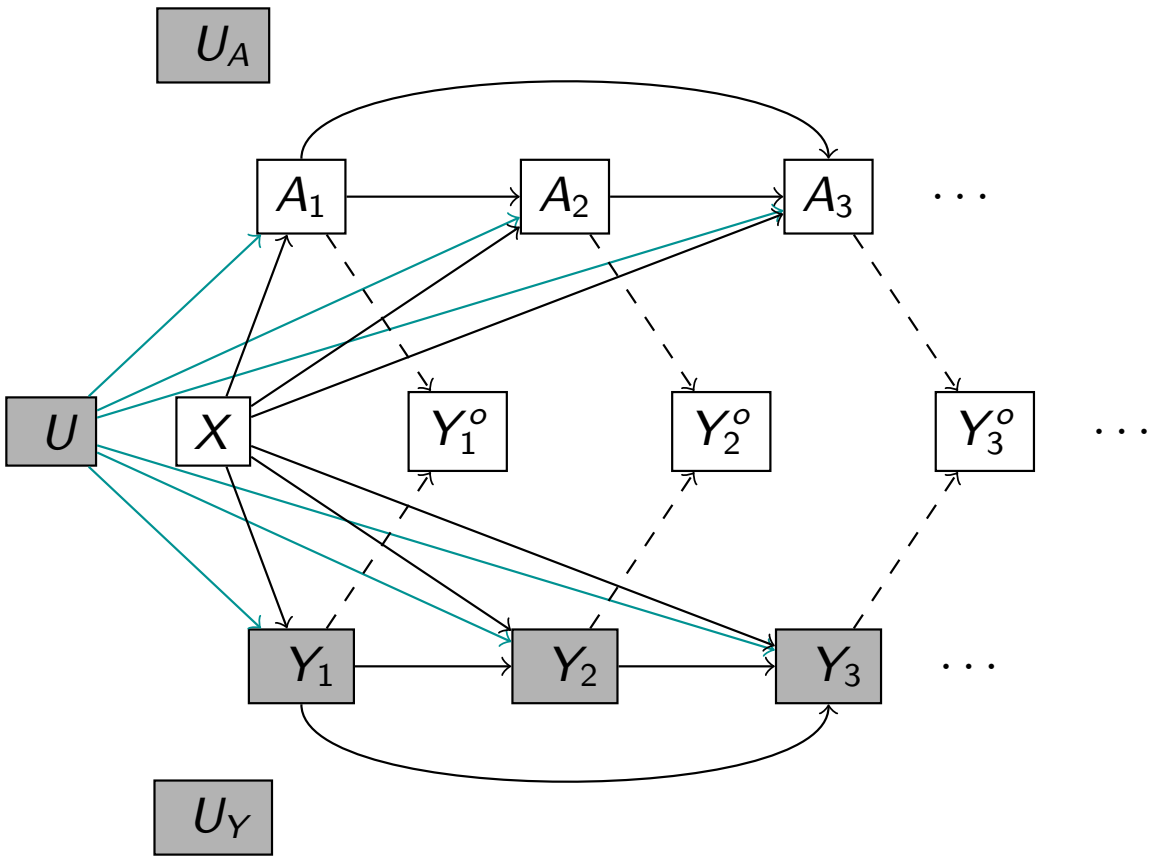
DAGs (no auxiliaries): (B) Baseline covariate dependence



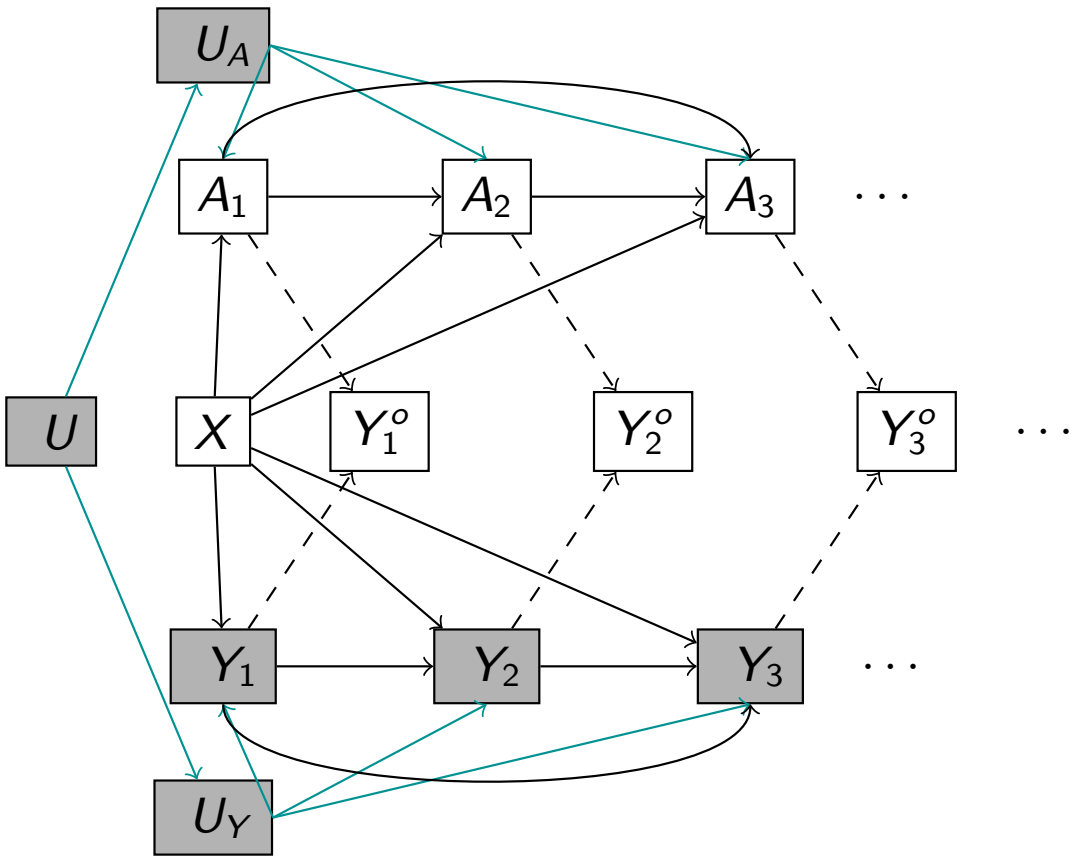
DAGs (no auxiliaries): (C) Past outcome dependence



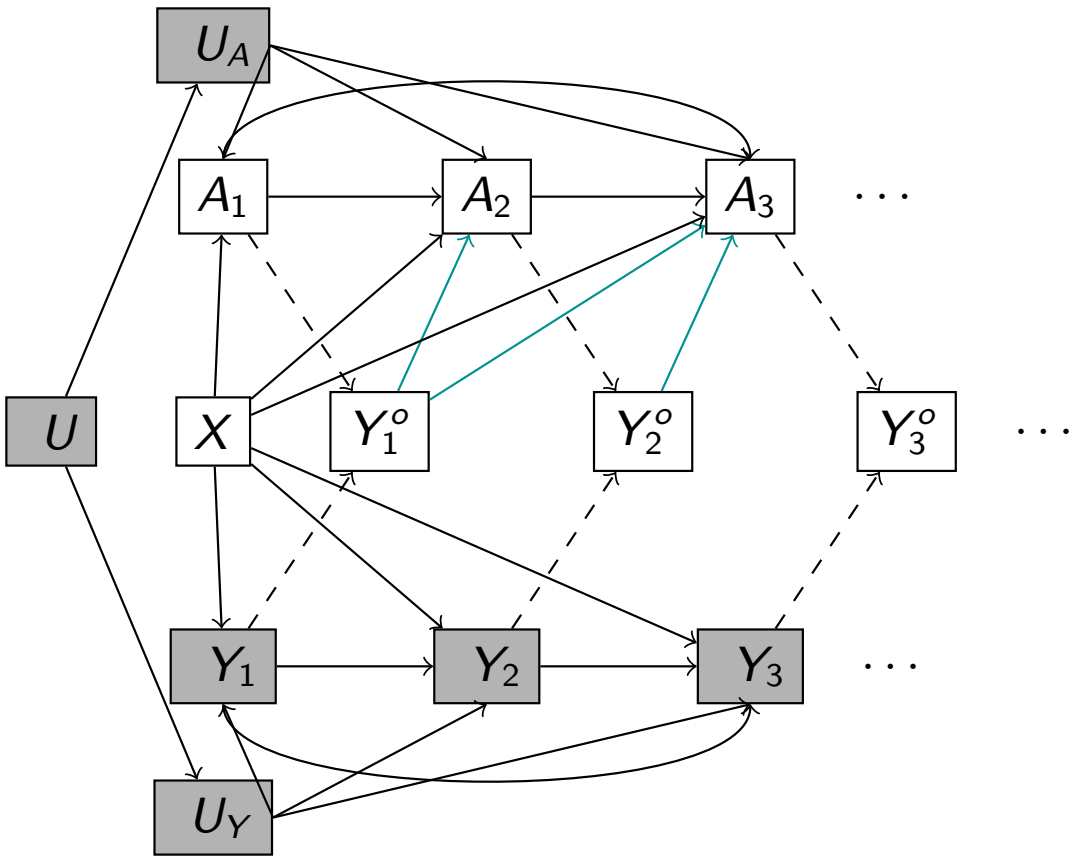
DAGs (no auxiliaries): (D) Random effect/baseline covariate dependence



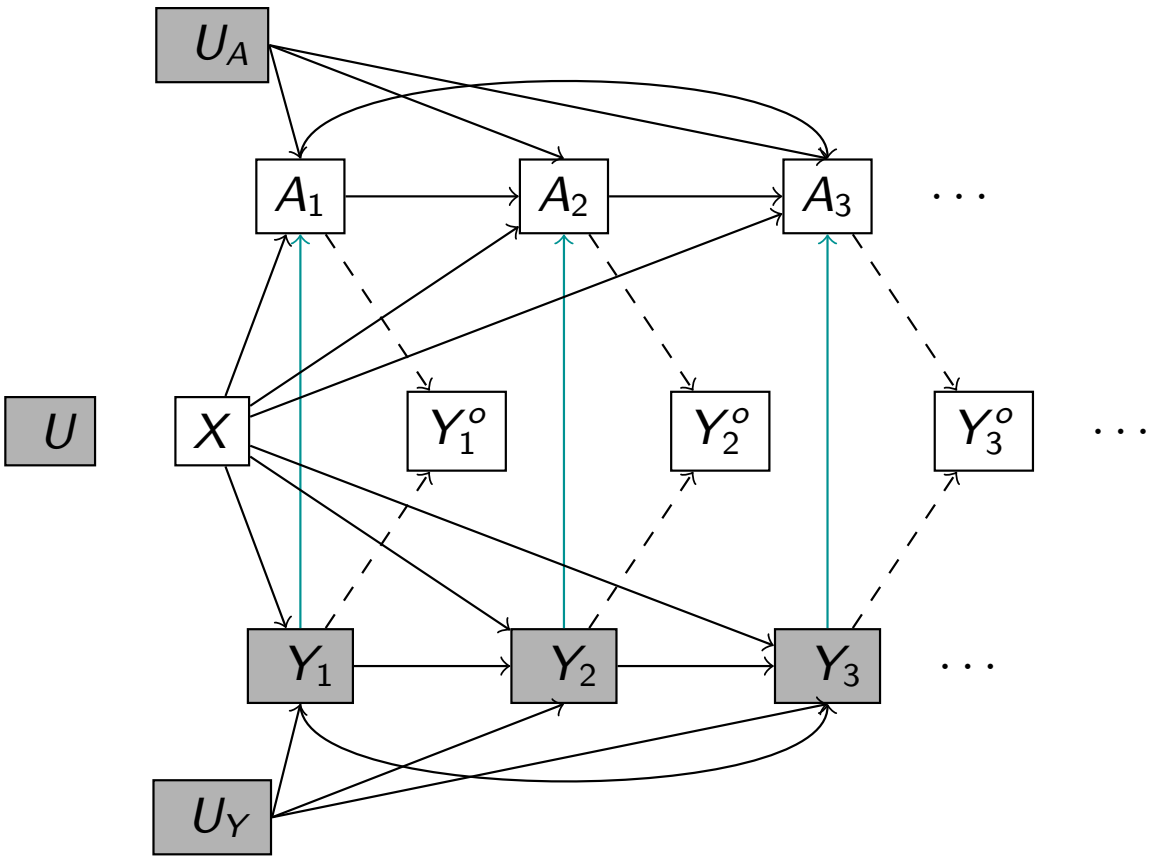
DAGs (no auxiliaries): (E) Correlated random effect & baseline covariate dependence



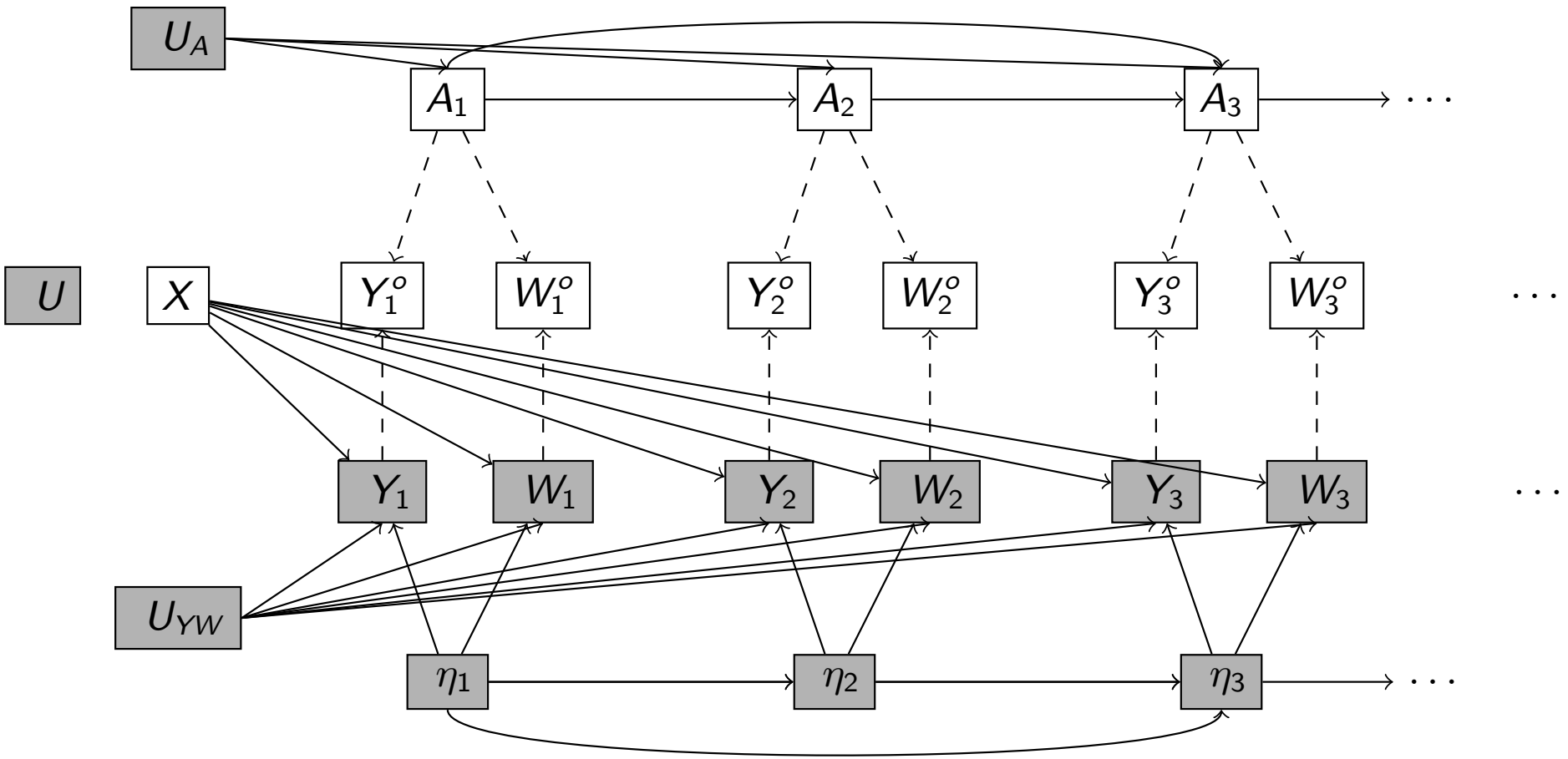
DAGs (no auxiliaries): (F) Correlated Random Effects/Baseline Covariate/Previous Outcome Dependence



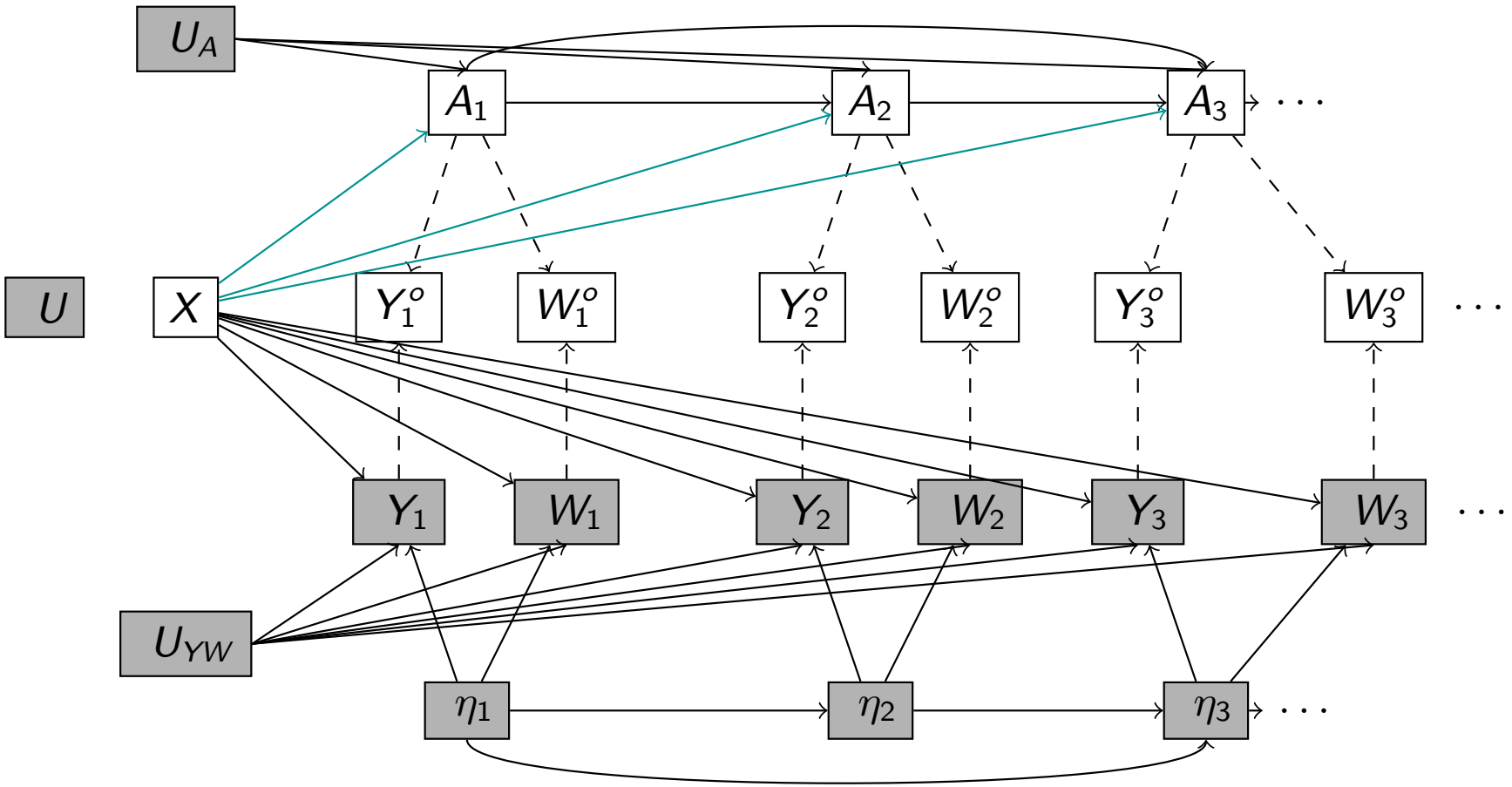
DAGs (no auxiliaries): (G) Unobserved Outcome Dependence



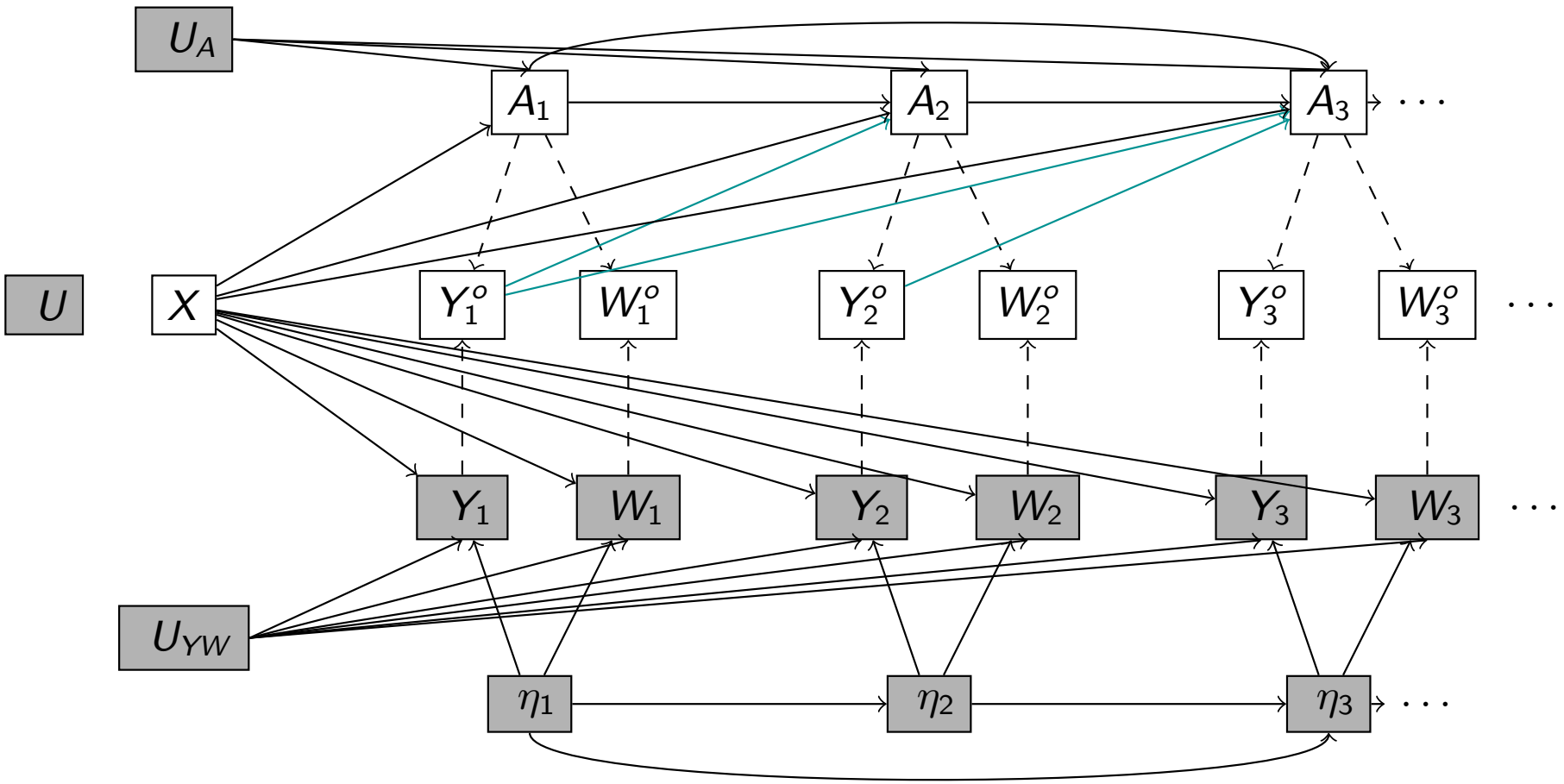
DAGs (with auxiliaries): (A) Independence



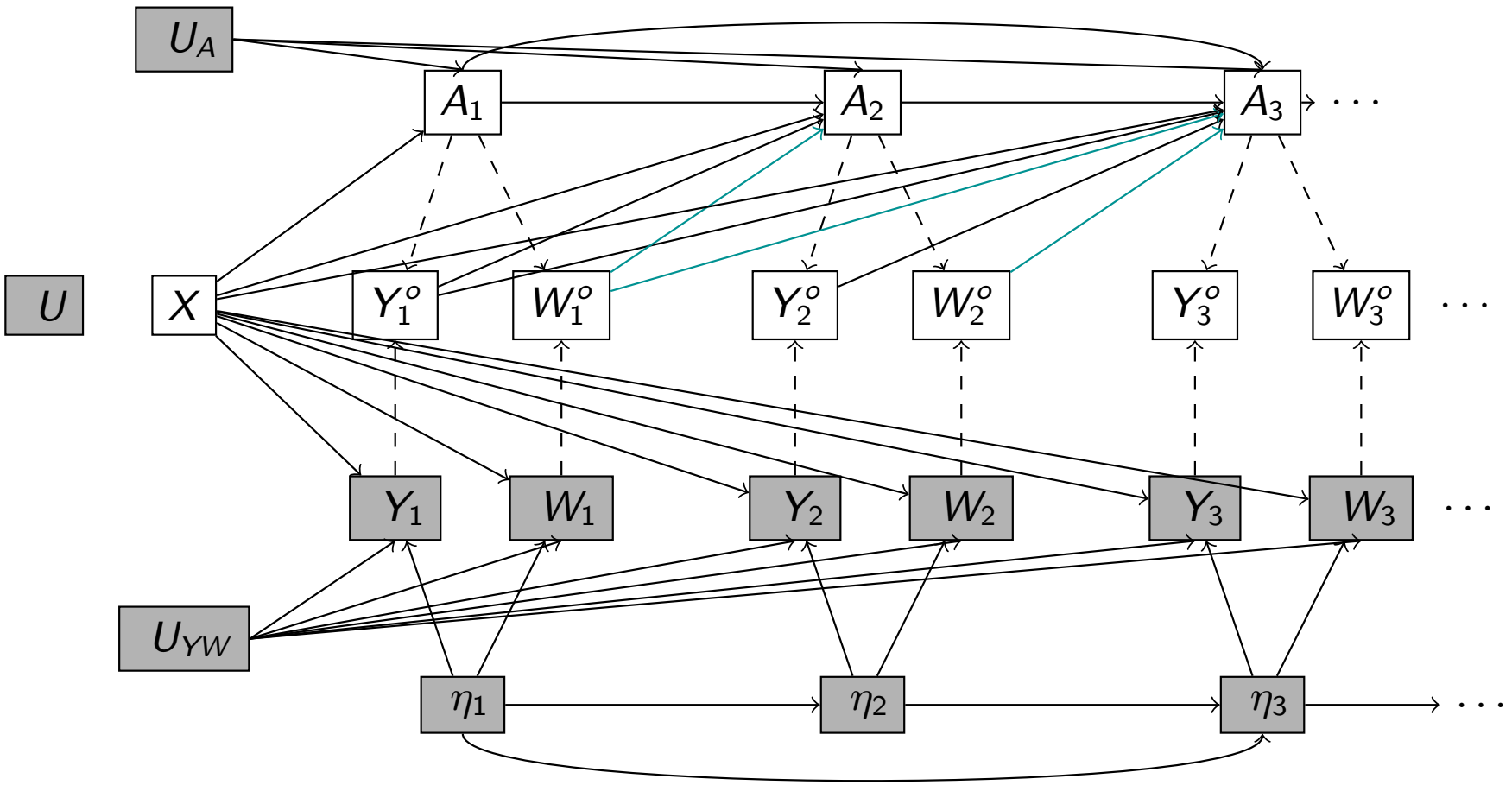
DAGs (with auxiliaries): (B) Baseline Covariate Dependence



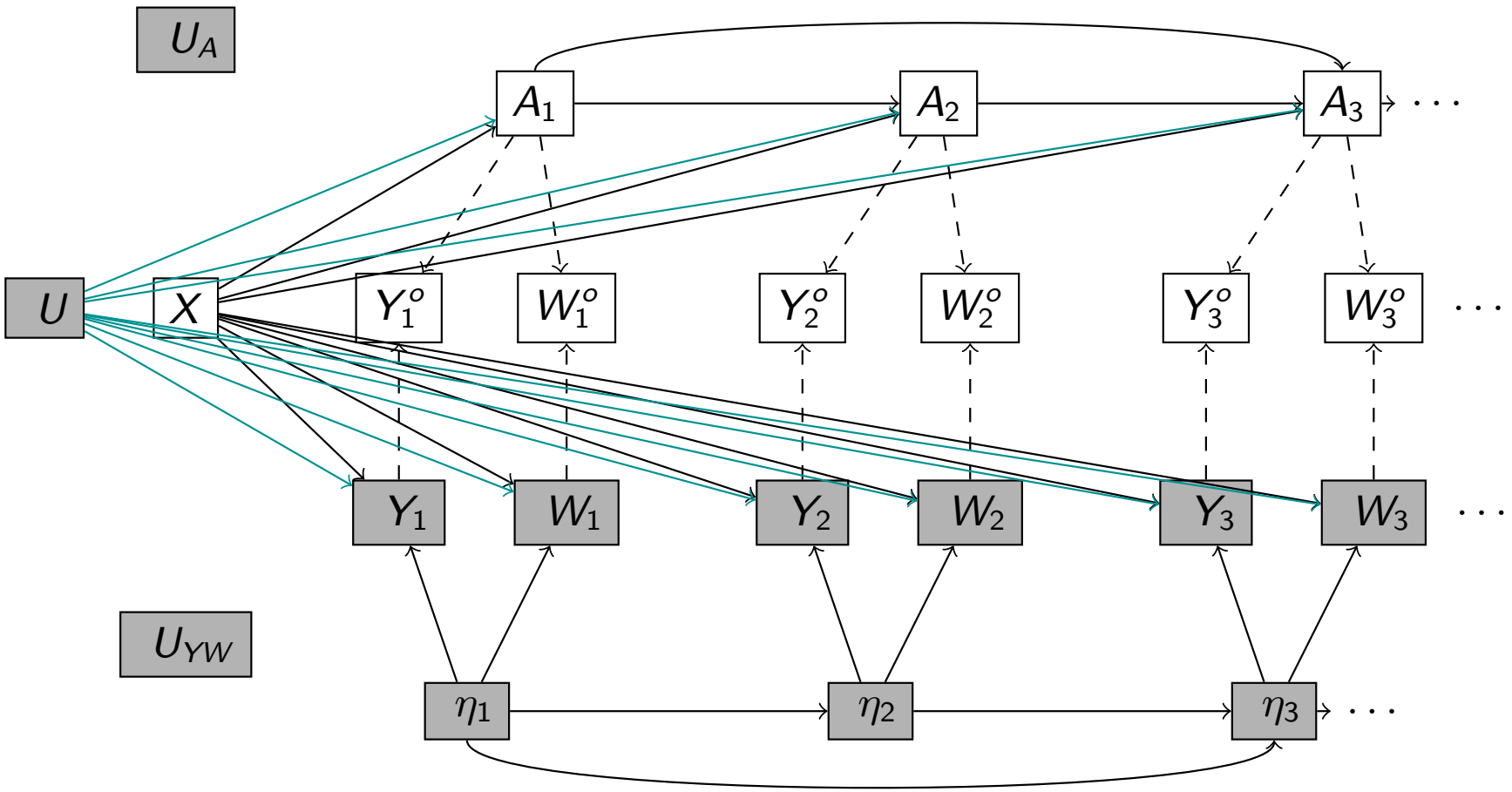
DAGs (with auxiliaries): (C) Past Observed Outcome/Baseline Covariate Dependence



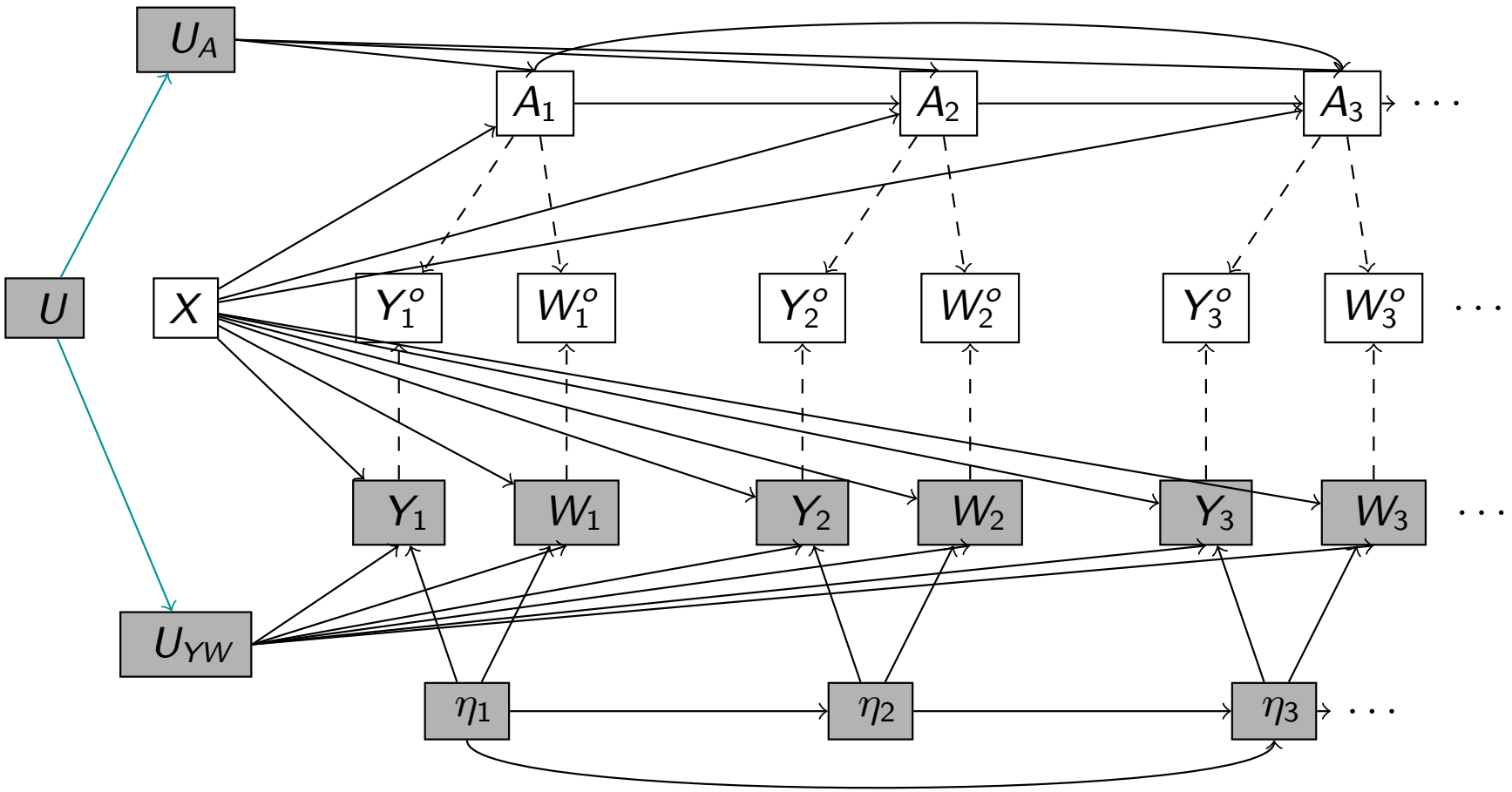
DAGs (with auxiliaries): (D) Past Observed Outcome/Covariate (Auxiliary and Baseline) Dependence



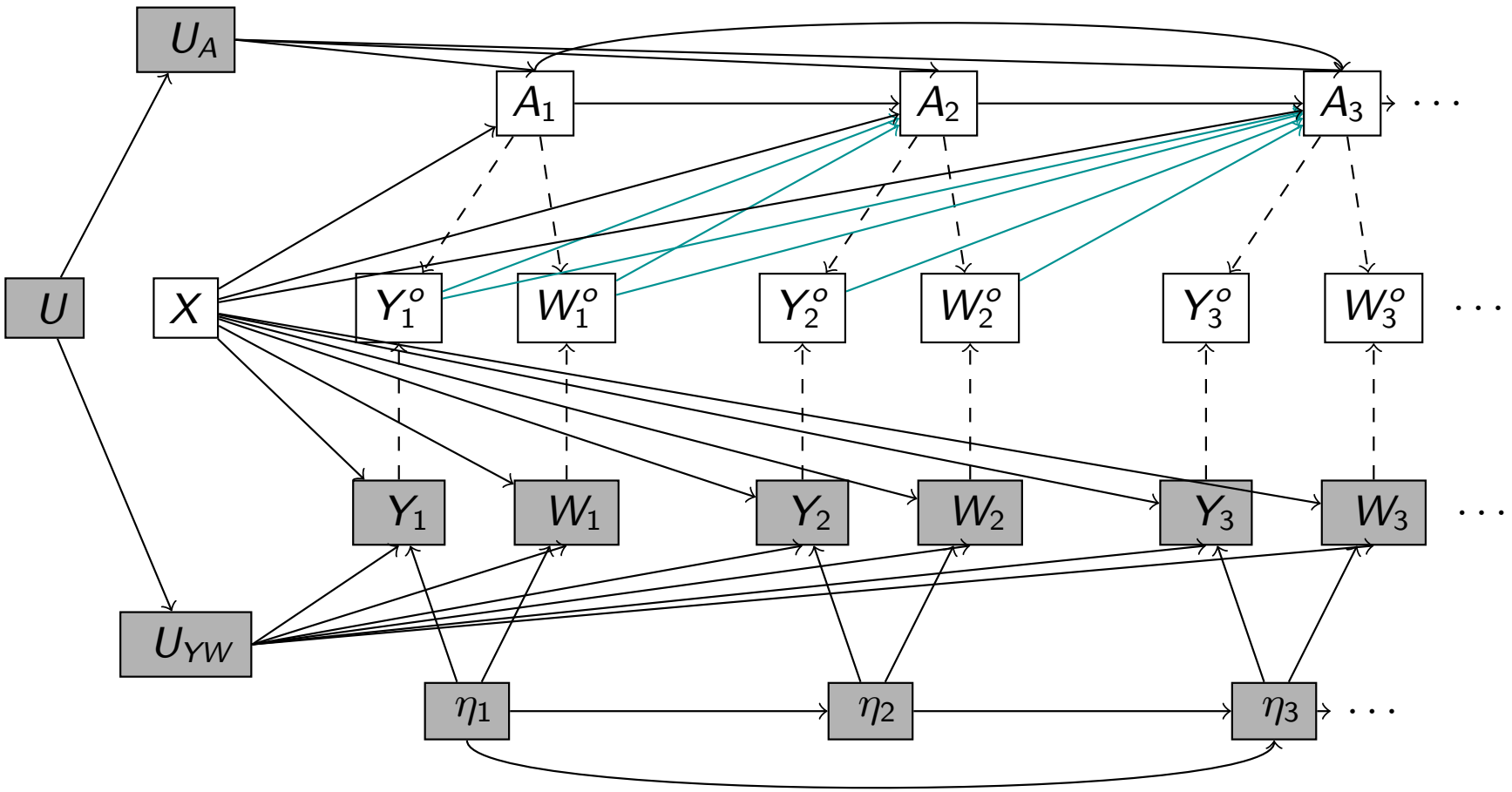
DAGs (with auxiliaries): (E) Shared Random Effects/Baseline Covariate Dependence



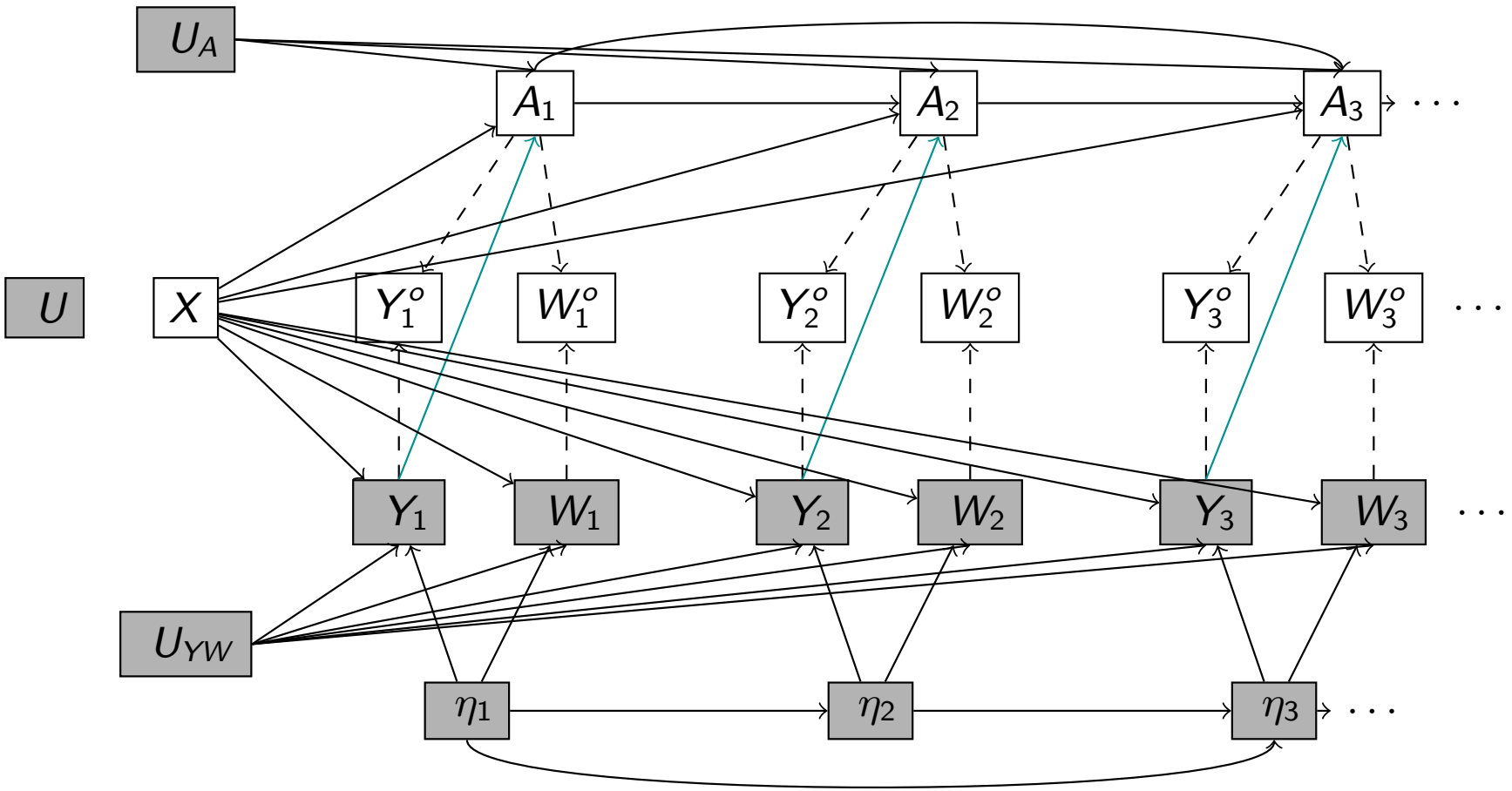
DAGs (with auxiliaries): (F) Dependent Random Effects/Baseline Covariate Dependence



DAGs (with auxiliaries): (G) Dependent Random Effects/Past observed outcome/Covariate (Baseline and Auxiliary) Dependence



DAGs (with auxiliaries): (H) Unobserved Outcome Dependence



Part 2. Analysis

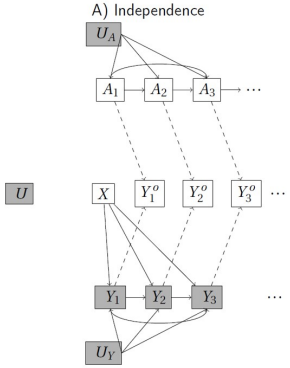
Analyses: Learning Objectives

By the end of this module, you should be able to

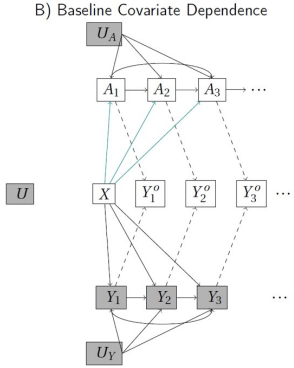
- Articulate the circumstances under which GEEs can be used for irregular assessment times
- Explain how and when IIW-GEEs work
- Identify some semi-parametric joint models
- Formulate a fully parametric joint model

Recap: First Determine Your Assessment Process

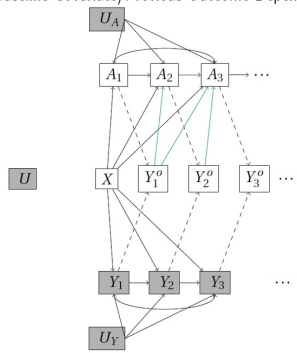
A) Independence



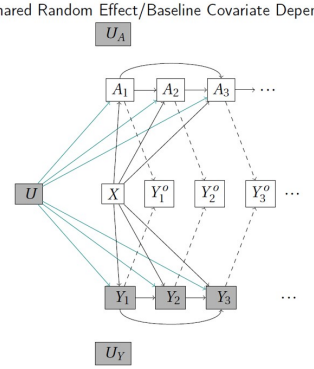
B) Baseline Covariate Dependence



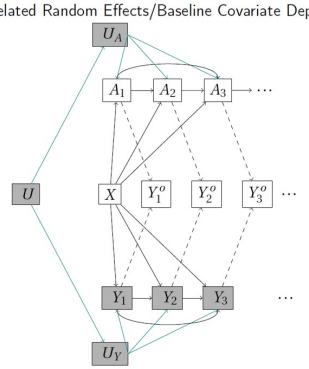
C) Baseline Covariate/Previous Outcome Dependence



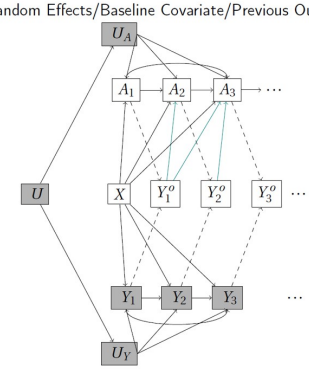
D) Shared Random Effect/Baseline Covariate Dependence



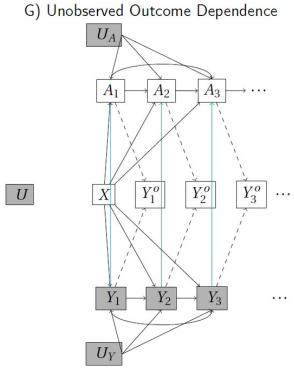
E) Correlated Random Effects/Baseline Covariate Dependence



F) Correlated Random Effects/Baseline Covariate/Previous Outcome Dependence



G) Unobserved Outcome Dependence



Then Choose an Analytic Approach

- GEEs
- (Generalized) linear mixed models
- IIW-GEEs
- Multple Outputation
- Semi-parametric joint models
- Fully parametric joint models

To choose a model, we need to understand what assumptions they make about the assessment process

Recap: Why do GEEs Work for Regular Visits?

Suppose we have regular visits & want to fit

$$\mu(X;\beta) = E(Y_j \mid X) = s(X\beta)$$

for some function s.

GEEs are asymptotically unbiased because the pseudo-score function is mean zero.

$$\begin{aligned} E\left(\frac{\partial\mu(X;\beta)}{\partial\beta}V^{-1}(Y-\mu(X;\beta))\right) &= E\left(E(\frac{\partial\mu(X;\beta)}{\partial\beta}V^{-1}(Y-\mu(X;\beta)) \mid X)\right) \\ &= E\left(\frac{\partial\mu(X;\beta)}{\partial\beta}V^{-1}E((Y-\mu(X;\beta)) \mid X)\right) \\ &= 0, \end{aligned}$$

where $Y = (Y_1, \ldots, Y_N)'$ and V is the assumed working variance matrix.
Is the pseudo-score function still mean zero when assessment times are irregular?

GEEs for Irregular Visits

When assessment times are irregular, it is helpful to re-express the standard GEE pseudo-score function, where each subject contributes

$$\sum_j \frac{\partial \mu(X;\beta)}{\partial \beta}\big(Y(T_j) - \mu(X;\beta)\big) = 0$$

in continuous time

$$\int_0^\tau \frac{\partial \mu(X;\beta)}{\partial \beta}\big(Y(t) - \mu(X;\beta)\big)\, dN(t) = 0,$$

where for simplicity we have used an independent working correlation

When Can You Use a GEE for Irregular Assessment Times?

Is this pseudo-score function zero mean?

$$
\begin{aligned}
& E\left(\int_0^\tau \frac{\partial \mu(X;\beta)}{\partial \beta}(Y(t)-\mu(X;\beta))dN(t)\right) \\
&= E\left(\int_0^\tau E\Big(\frac{\partial \mu(X;\beta)}{\partial \beta}(Y(t)-\mu(X;\beta))dN(t) \mid X\Big)\right) \\
&= E\left(\int_0^\tau \frac{\partial \mu(X;\beta)}{\partial \beta} E\big((Y(t)-\mu(X;\beta))dN(t) \mid X\big)\right) \\
&= 0 \quad \text{if } Y(t) \perp\!\!\!\perp dN(t) \mid X \\
&\neq 0 \quad \text{if } Y(t) \not\perp\!\!\!\perp dN(t) \mid X(t)
\end{aligned}
$$

That is, GEEs remain unbiased under ACAR and ACAR-X, but will in general be biased under AAR or ANAR

Inverse Intensity Weighted GEEs (IIW-GEEs)

- Under AAR, we can weight the GEE equations
- Suppose $\exists\, Z(t) \in \bar{O}(t)$ such that $Y(t) \perp\!\!\!\perp dN(t) \mid Z(t)$
- Weight the integrand in the GEE equations by $\frac{1}{\lambda(t;Z(t))}$
- Similar concept to survey weighting
- Observations that have low chance of occurring are under-represented in the data and receive greater weight
- Each subject now contributes

$$\int_0^\tau \frac{\partial \mu(X;\beta)}{\partial \beta} \frac{(Y(t) - \mu(X;\beta))}{\lambda(t;Z(t))} dN(t)$$

Why are IIW-GEEs Asymptotically Unbiased Under AAR?

$$E\left(\int_0^\tau \frac{\partial\mu(X;\beta)}{\partial\beta}\frac{(Y(t)-\mu(X;\beta))}{\lambda(t;Z(t))}dN(t)\right)$$

$$= E\left(\int_0^\tau E\Big(\frac{\partial\mu(X;\beta)}{\partial\beta}\frac{(Y(t)-\mu(X(t);\beta))}{\lambda(t;Z(t))}dN(t)\mid X,Z(t),Y(t)\Big)\right)$$

$$= E\left(\int_0^\tau \frac{\partial\mu(X;\beta)}{\partial\beta}\frac{(Y(t)-\mu(X(t);\beta))}{\lambda(t;Z(t))}E\big(dN(t)\mid X,Z(t),Y(t)\big)\right)$$

We have conditional independence of $dN(t)$ and $Y(t)$ given $Z(t)$ and so

$$E(dN(t)\mid X,Z(t),Y(t)) = \lambda(t;Z(t))dt$$

Why are IIW-GEEs Asymptotically Unbiased under AAR?

$$
\begin{aligned}
& E\left(\int_0^\tau \frac{\partial \mu(X;\beta)}{\partial \beta}\frac{(Y(t)-\mu(X;\beta))}{\lambda(t;Z(t))}dN(t)\right) \\
&= E\left(\int_0^\tau E\Big(\frac{\partial \mu(X;\beta)}{\partial \beta}\frac{(Y(t)-\mu(X(t);\beta))}{\lambda(t;Z(t))}dN(t)\mid X, Z(t), Y(t)\Big)\right) \\
&= E\left(\int_0^\tau \frac{\partial \mu(X;\beta)}{\partial \beta}\frac{(Y(t)-\mu(X;\beta))}{\cancel{\lambda(t;Z(t))}}\cancel{E\big(dN(t)\mid X, Z(t), Y(t)\big)}\right) \\
&= 0
\end{aligned}
$$

IIW-GEEs: Practical Notes (1)

We can stabilize the weights by any non-stochastic function s(t) and maintain the zero-mean property

$$E\left(\int_0^\tau \frac{\partial\mu(X;\beta)}{\partial\beta}\frac{(Y(t)-\mu(X;\beta))}{\lambda(t;Z(t))}s(t)dN(t)\right)$$

- Suppose $\lambda(t;Z(t)) = \lambda_0(t)\exp(Z(t)\gamma)$
- Set $s(t) = \lambda_0(t) \rightarrow$ weight observation at time t by $\exp(-Z(t)\gamma)$
- No need to estimate the baseline hazard

IIW-GEEs: Practical Notes (2)

- Fit the proportional intensity model (e.g. `coxph`)
- Derive the linear predictors $Z(t)\gamma$ (e.g. `predict(model,type="lp")`
- Add the weights $\exp(-Z(t)\gamma)$ to your dataset
- Fit the weighted GEE (e.g. `geeglm(...,weights=...)`)
- *Important:* You must using working independence if you are using `geeglm`

Heteroscedasticity vs. Sampling Weights in GEEs

- D is a diagonal matrix of weights with jj entry $\exp(-Z(T_j)\gamma)$
- Let V be the working variance matrix
- Heteroscedasticity weights: Replace V with $D^{-1/2}VD^{-1/2}$
- Sampling weights: Replace V with VD^{-1} $\leftarrow$ these are the weights we want
- The two are the same when V is the identity matrix.

Fitting IIW-GEEs in Practice

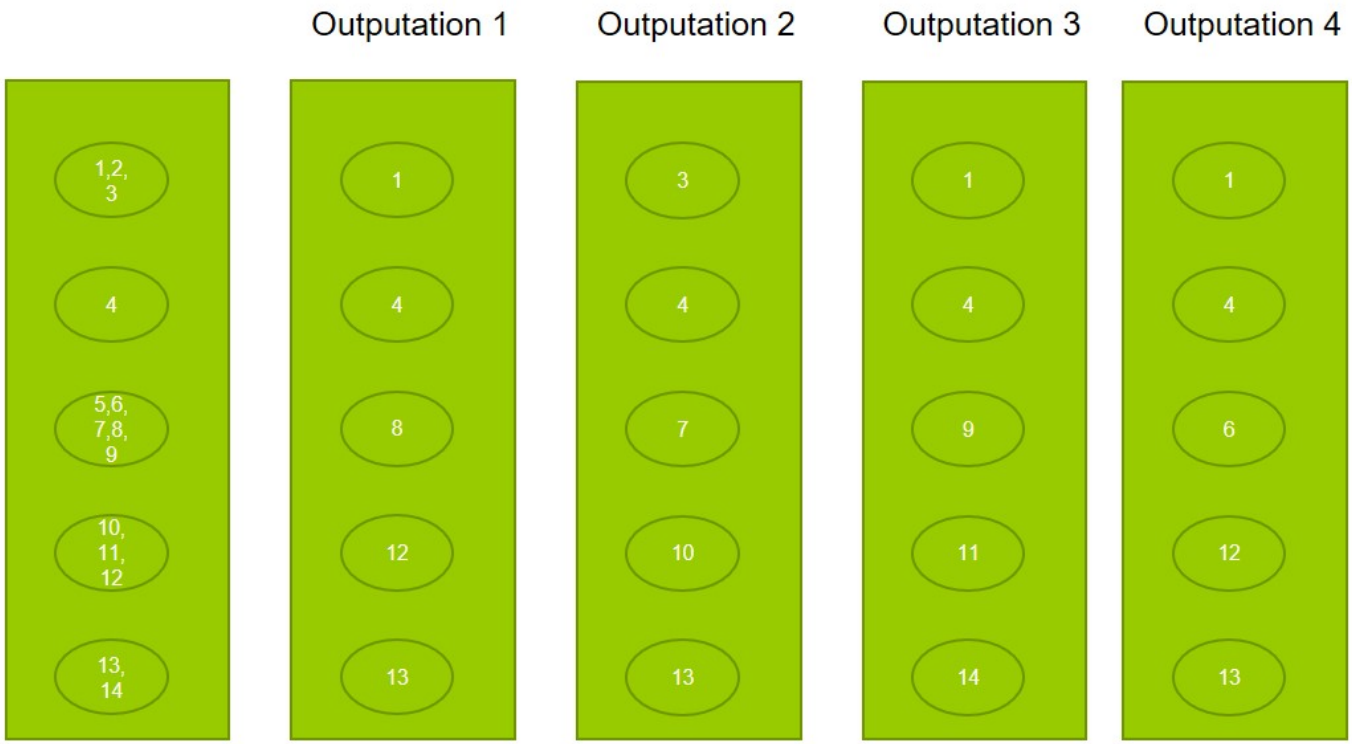
SAS: PHREG and PROC GENMOD

R:

- coxph and `geeglm, or`
- `iiwgee` in the `IrregLong` package will
  - Create lagged versions of time-dependent covariates
  - Add rows for the interval between the last assessment time and censoring
  - Fit the IIW-GEE

Multiple Outputation

- Designed to study cases where cluster size is informative
  - Pups in a litter
  - Maternal predictors of pup outcomes
  - Size of the litter is itself predictive of pup outcomes
- Proposal: Randomly select one pup from each litter
  - Equal representation across litters
  - Can analyse using standard methods
- Repeat the random selection so as to use all the data
- Take means across outputations



Mean of regression coefficients over outputations
Variance: Within - Between

Multiple Outputation: Adaptation to Irregular Observation

- Select observations with probability inversely proportional to visit intensity
- Resulting thinned dataset has independent visit and outcome processes
- Asymptotically equivalent to inverse-weighted GEE
  $\rightarrow$ useful when you cannot weight
- Implementation: Manually, or using `mo` in `R` package `IrregLong`

Random Effect-Induced ANAR: Semi-Parametric Joint Models

Method	Outcome mean model conditional on random effects	Intensity model conditional on outcomes and random effects
Liang (2009)	$\beta_0(t) + X\beta + X_R U_Y$	$U_A \lambda_0(t) \exp(X_N \gamma)$
Sun (2012)	$\beta_0(t; U_Y) + X\beta$	$\lambda_0(t; U_A) \exp(X\gamma)$
Sun (2011)	$U\beta_0(t) \exp(X\beta)$	$U\lambda_0(t) \exp(X\gamma)$
Song (2012)	$\beta_0(t) + X\beta + U_Y$	$U_A \lambda_0(t) \exp(X\gamma)$

Table: Comparison of semi-parametric joint modelling approaches: outcome and visit intensity models. X_F, X_R, and X_N are subvectors of the vector of baseline covariates X

Semi-Parametric Joint Models

The Liang model:

$$E(Y(t) \mid X_F, X_R, U_Y) = \beta_0(t) + X_F\beta + X_R(t)U_Y$$
$$\lambda(t) = U_A\lambda_0(t)\exp(X_N\gamma),$$

$\beta_0(t)$ non-parametric intercept
$EU_Y \mid U_A) = \theta(U_A - 1)$ for some θ

- Can set up zero-mean estimating equations (Liang, 2009)
- Implementation: `Liang` in `IrregLong` package

Fully Parametric Joint Models

Random effects capture dependence between outcomes & assessment times

Ryu et al (2007) use

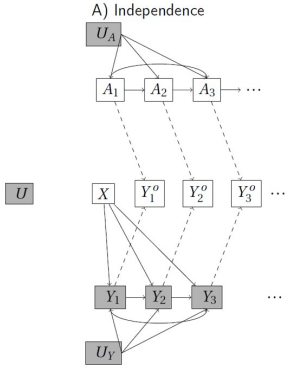
$$Y(t) = \mu_0(t) + X\beta + U + \epsilon(t)$$
$$\lambda(t; \bar{O}(t), U) = \lambda_0(t) \exp(U\alpha + X\gamma_1 + Y(T_{N(t^-)})\gamma_2)$$
where $\epsilon_i(t) \perp\!\!\!\perp \epsilon(s) \forall t \neq s$ & $\epsilon(t) \sim N(0, \sigma^2)$
$U \sim N(0, \sigma_u^2)$
$\mu_0(t)$ & $\lambda_0(t)$ are parametric functions of time

Gasparini et al (2020) use

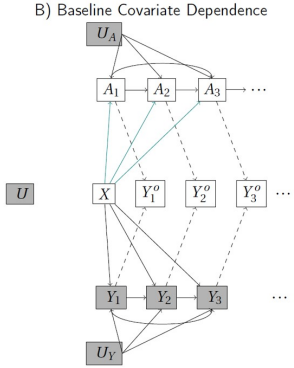
$$Y(t) = \mu_0(t) + X\beta + U + \epsilon(t)$$
$$\lambda^{gap}(s; X, U) = \lambda_0^{gap}(s) \exp(U\alpha + X\gamma)$$
where λ^{gap} is the intensity for the gaps $S_j = T_j - T_{j-1}$

When to use which method?

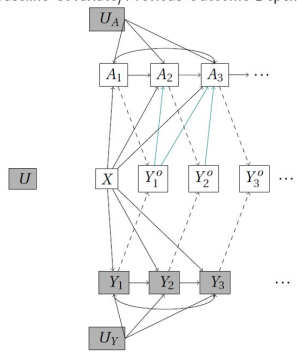
A) Independence



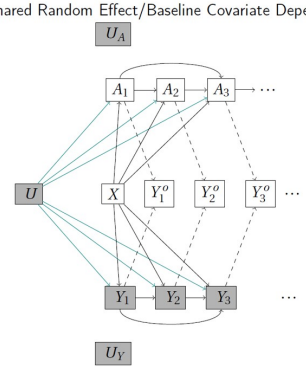
B) Baseline Covariate Dependence



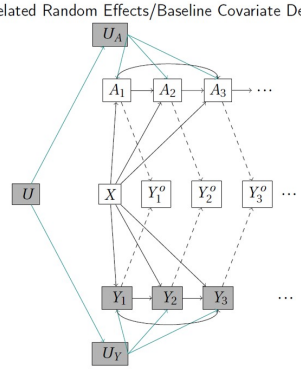
C) Baseline Covariate/Previous Outcome Dependence



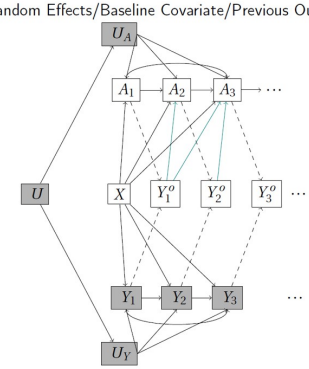
D) Shared Random Effect/Baseline Covariate Dependence



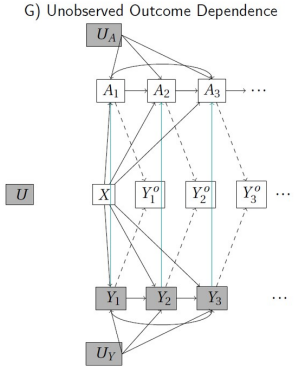
E) Correlated Random Effects/Baseline Covariate Dependence



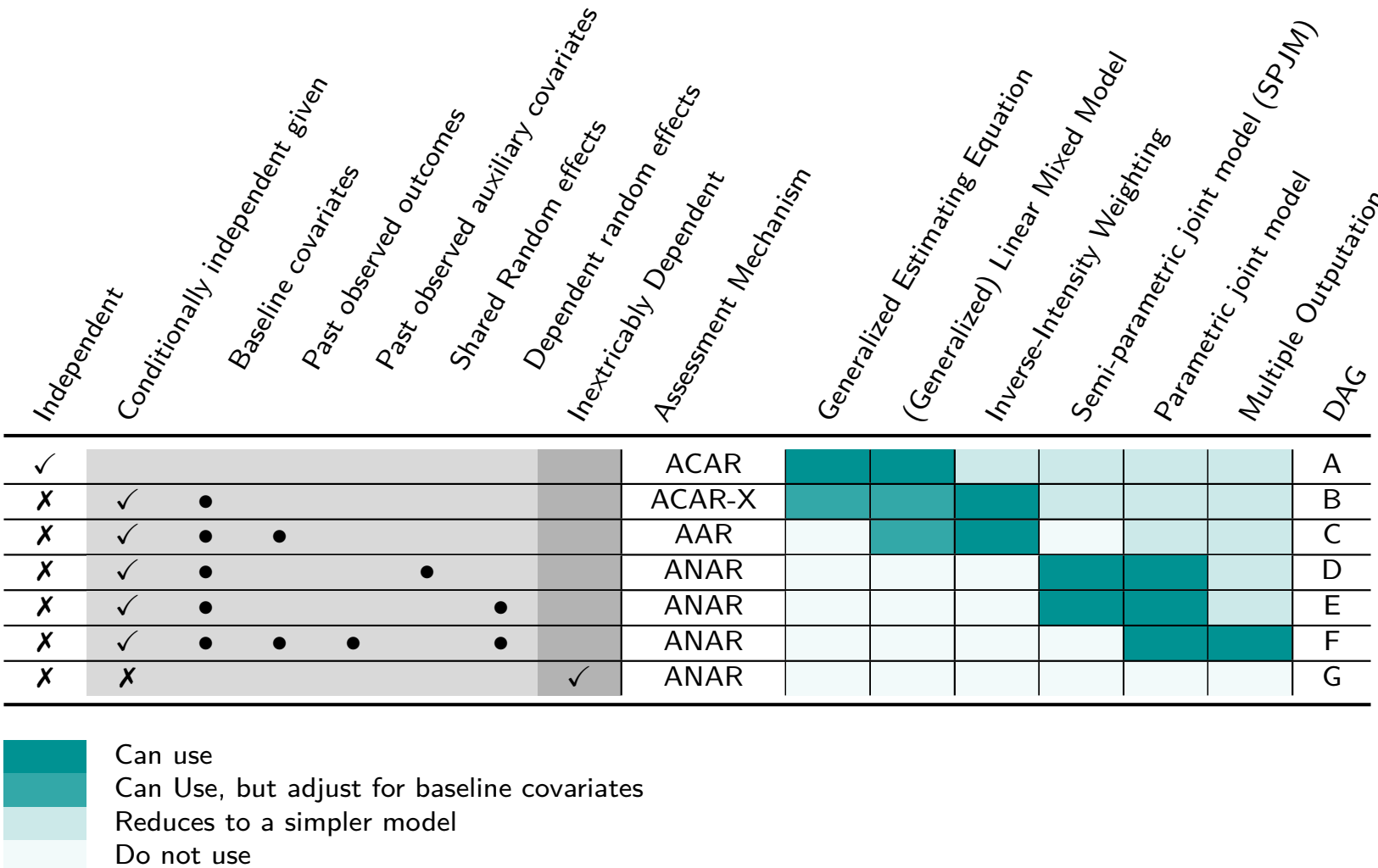
F) Correlated Random Effects/Baseline Covariate/Previous Outcome Dependence



G) Unobserved Outcome Dependence

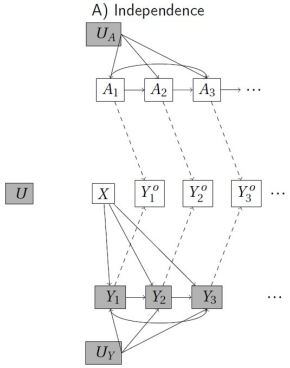


When to Use Which Method? (No Auxiliaries)

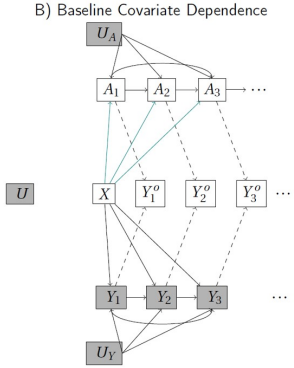


When to Use Which Method? (No Auxiliaries)

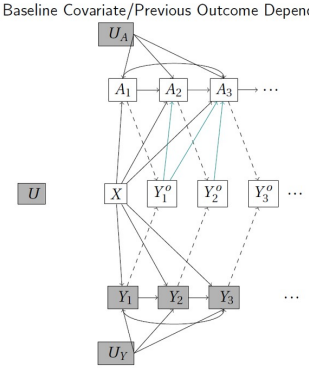
A) Independence



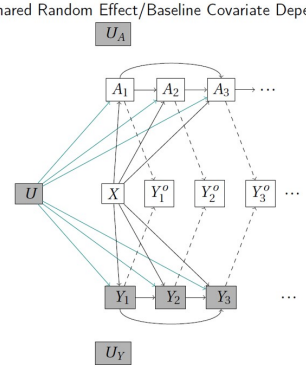
B) Baseline Covariate Dependence



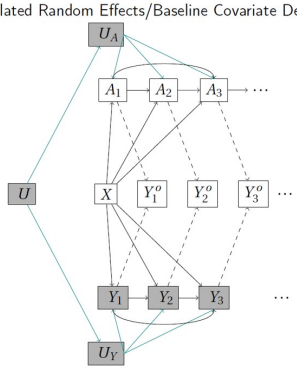
C) Baseline Covariate/Previous Outcome Dependence



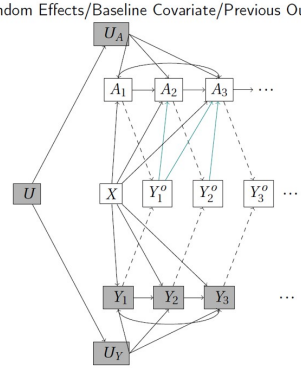
D) Shared Random Effect/Baseline Covariate Dependence



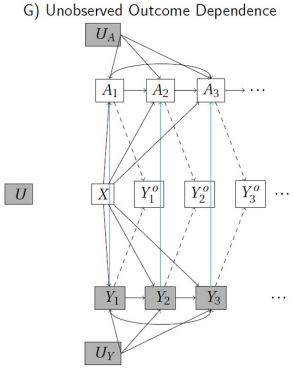
E) Correlated Random Effects/Baseline Covariate Dependence



F) Correlated Random Effects/Baseline Covariate/Previous Outcome Dependence



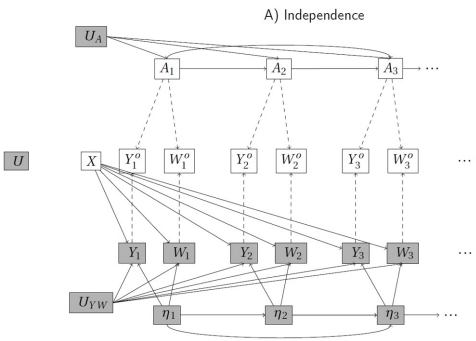
G) Unobserved Outcome Dependence

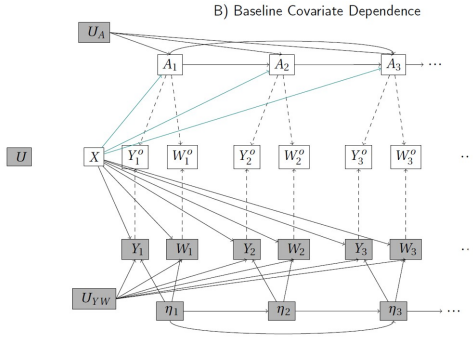


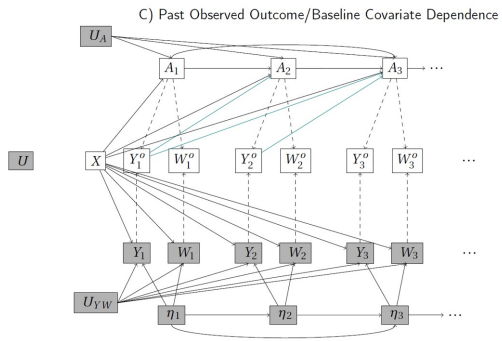
	Independent	Conditionally independent given	Baseline covariates	Past observed outcomes	Past observed auxiliary covariates	Shared Random effects	Dependent random effects	Inextricably Dependent	Assessment Mechanism		Generalized Estimating Equation	(Generalized) Linear Mixed Model	Inverse-Intensity Weighting	Semi-parametric joint model (SPJM)	Parametric joint model	Multiple Outputation + SPJM	DAG
	✓									ACAR							A
	✗	✓	•							ACAR-X							B
	✗	✓	•	•						AAR							C
	✗	✓	•			•				ANAR							D
	✗	✓	•				•			ANAR							E
	✗	✓	•	•	•		•			ANAR							F
	✗	✗							✓	ANAR							G

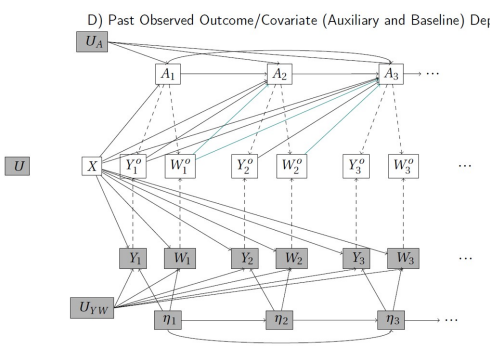
Can use
Can Use, but adjust for baseline covariates
Reduces to a simpler model
Do not use

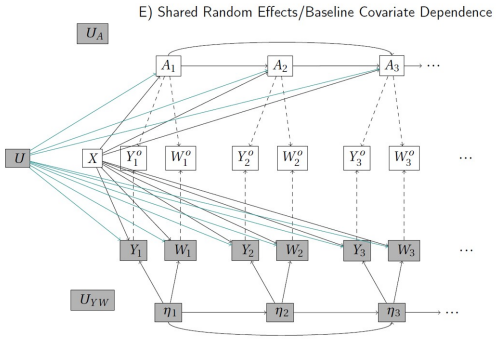
When to Use Which Method? (With Auxiliaries)

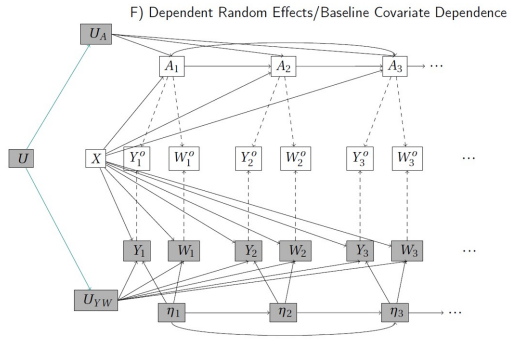


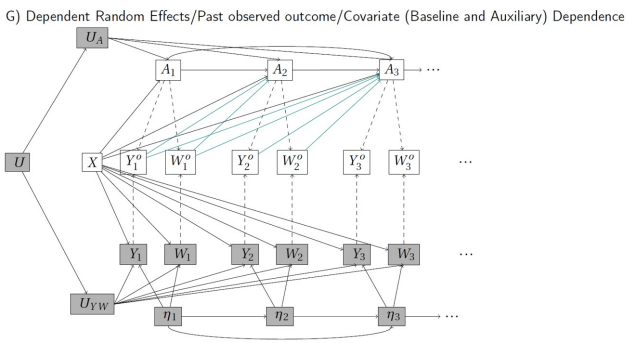


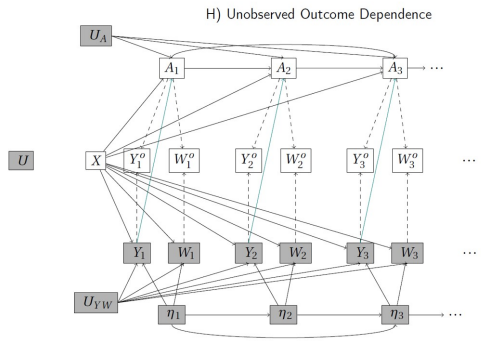


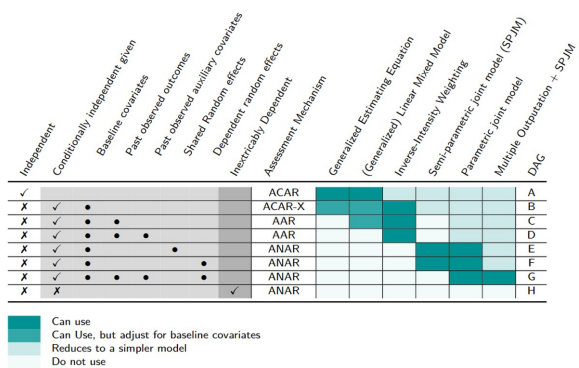




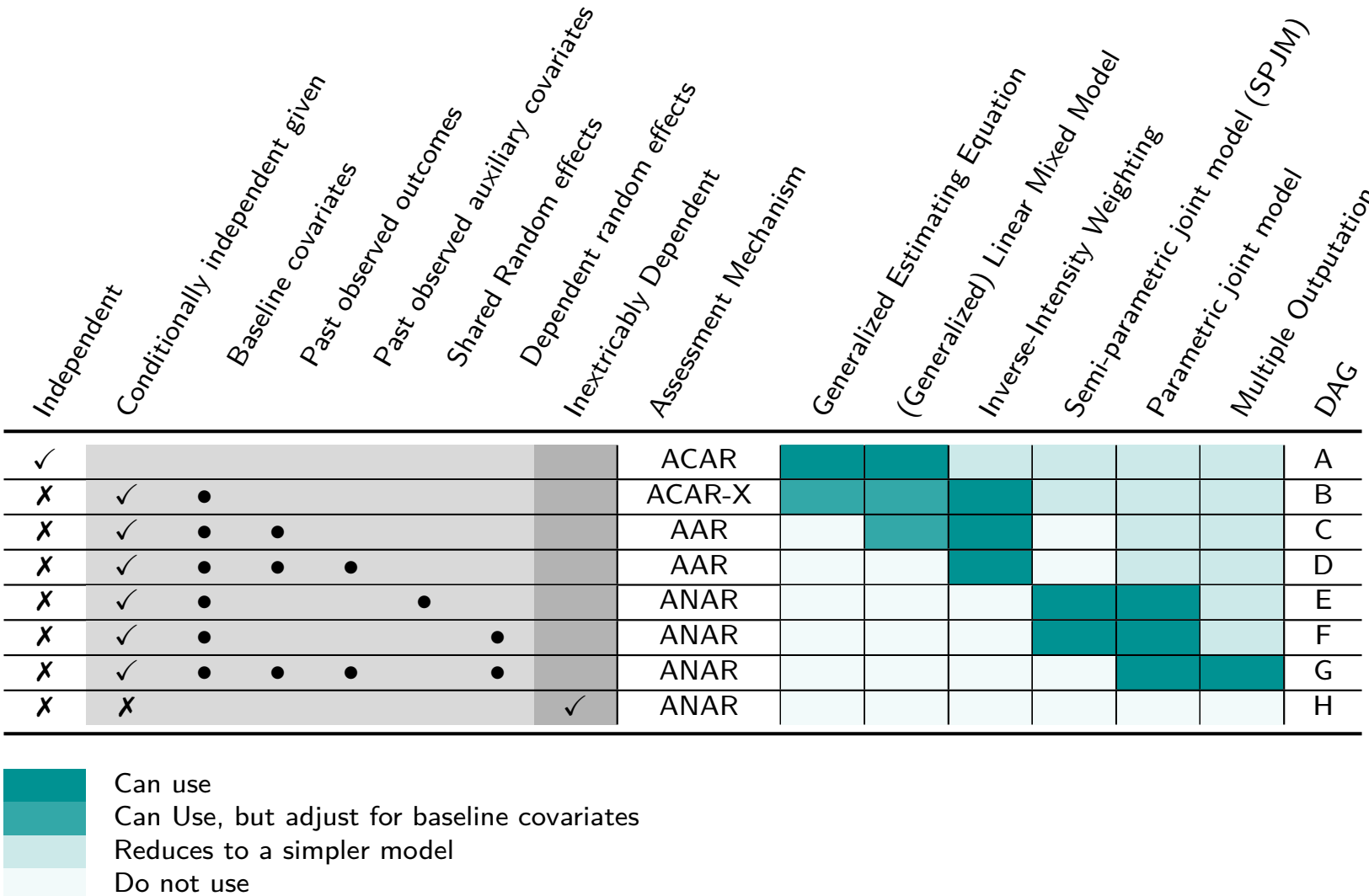




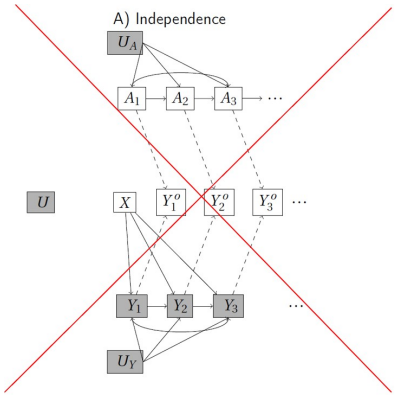


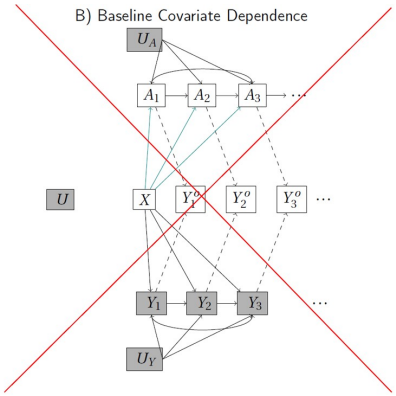


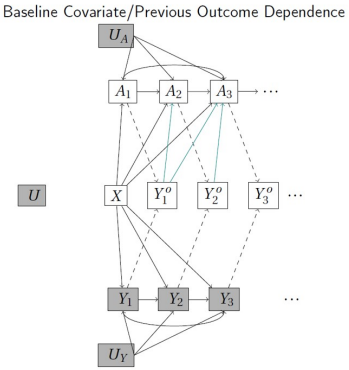
When to Use Which Method? (With Auxiliaries)

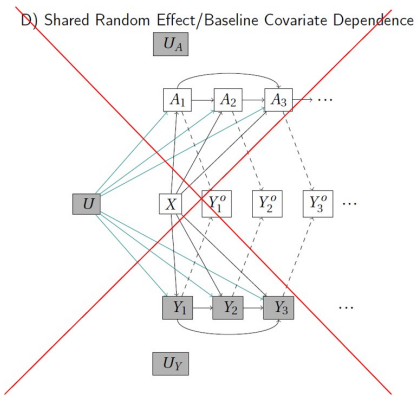


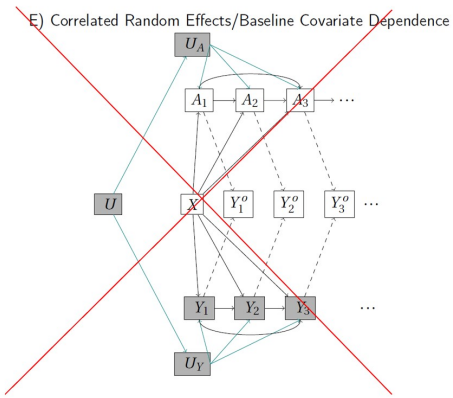
STAR*D Analysis: Which Model?

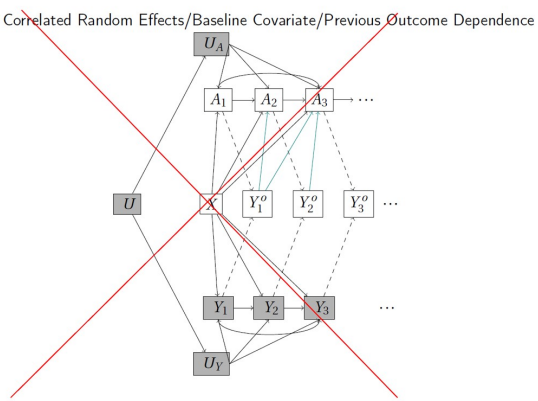


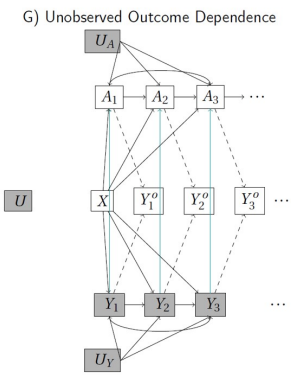


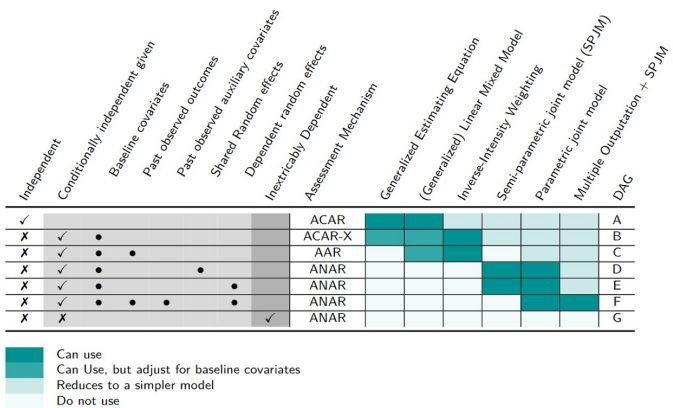










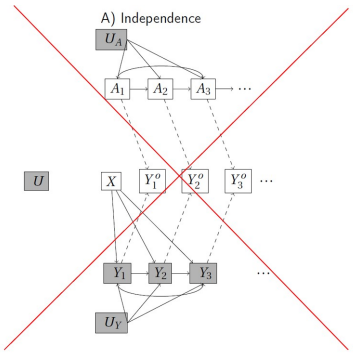


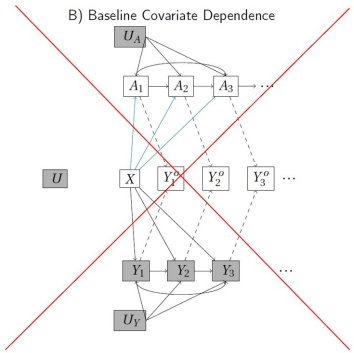
STAR*D Analysis

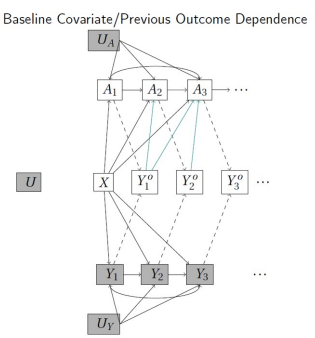
Method	Buproprion	Sertraline	Venlafaxine	S-B	V-B	V-S
Intercepts						
Binned GEE	3.22 (1.47)	3.34 (1.48)	2.10 (1.37)	0.12 (2.08)	-1.12 (2.01)	-1.24 (2.02)
GEE	0.65 (1.08)	1.82 (0.96)	0.82 (0.89)	1.17 (1.44)	0.17 (1.40)	-1.00 (1.31)
IIW-GEE	0.00 (1.13)	0.96 (0.97)	-0.23 (0.96)	0.96 (1.49)	-0.23 (1.48)	-1.19 (1.37)
MO	-0.02 (1.11)	0.97 (0.97)	-0.24 (1.00)	0.99 (1.48)	-0.22 (1.50)	-1.21 (1.39)
Mixed model	1.07 (0.85)	1.65 (0.83)	0.13 (0.86)	0.58 (1.19)	-0.94 (1.21)	-1.53 (1.19)
Slopes for logarithm of days in level						
Binned GEE	-1.63 (0.43)	-1.71 (0.42)	-1.39 (0.39)	-0.08 (0.61)	0.24 (0.59)	0.32 (0.58)
GEE	-0.98 (0.34)	-1.37 (0.29)	-1.10 (0.27)	-0.39 (0.44)	-0.12 (0.44)	0.27 (0.39)
IIW-GEE	-0.75 (0.36)	-1.09 (0.29)	-0.78 (0.29)	-0.34 (0.46)	-0.03 (0.46)	0.31 (0.41)
MO	-0.74(0.36)	-1.10 (0.29)	-0.78(0.30)	-0.35 (0.46)	-0.03 (0.47)	0.32 (0.42)
Mixed model	-1.07 (0.26)	-1.28 (0.25)	-0.84 (0.25)	-0.21 (0.36)	0.24 (0.36)	0.45 (0.35)

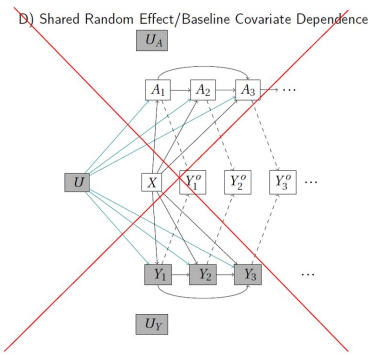
Table: Estimated regression coefficients (standard error) for change in QIDS-SR.
S-B = Sertraline-Bupropion,
V-B = Venlafaxine-Bupropion,
V-S = Venlafaxine-Sertraline

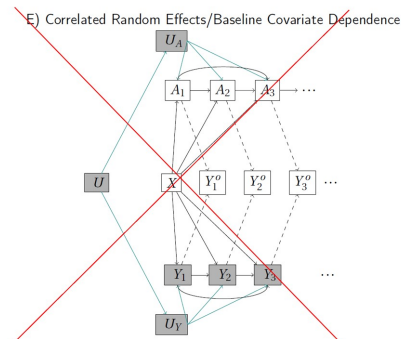
Methods for Sensitivity Analysis are Needed

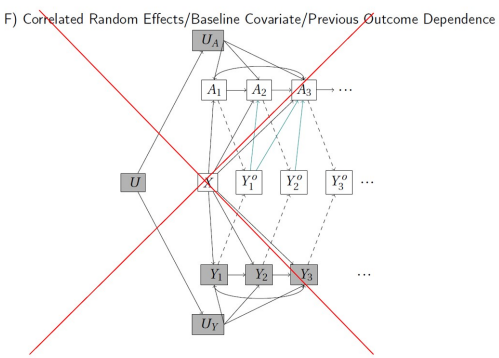


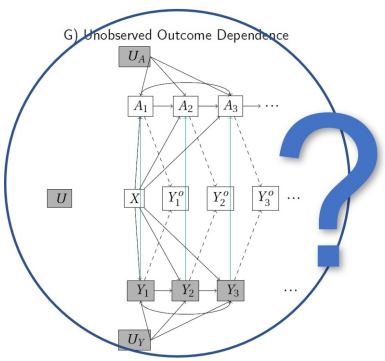


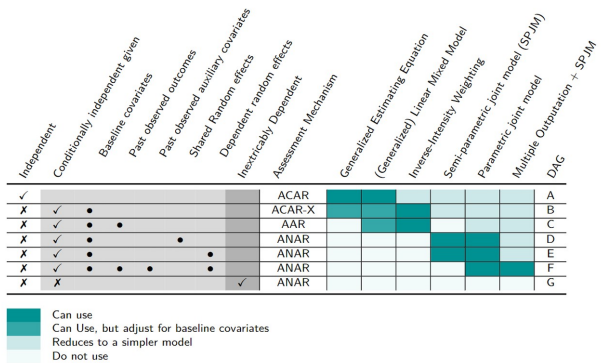












Part 2 Appendix: Reference Material

Andersen-Gill Code Example

For your reference: code for fitting the Andersen-Gill model

```
datacox <-
addcensoredrows(data=data,maxfu=maxfu,tinvarcols=c("subjectkey","sex.x","qs0.s","qs0.c","leave","publica"
,"medicaid","privins","famim","married","livesalone","hs","student1","work","volunteer","decisions","enjo
y3","txassign","interview_age.x"),id=id,time=time,event=event)

datacox <-
lagfn(datacox,lagvars=c("dayslevel2","qstot.x","qstot.y"),id="subjectkey",time="dayslevel2",lagfirst=NA)

m.tt.bup <- coxph(Surv(dayslevel2.lag,dayslevel2,obs)~
                    sex.x + interview_age.x + leave + qs0.s  + qs.s.change
          + tt(qs.s.change)  + cluster(subjectkey),
          data=datacox[datacox$dayslevel2>0,],subset=txassign=="BUP",
            tt = function(x, t, ...){
               x*(((t-15)^2)/49)/100
             })
summary(m.tt.bup)

m.tt.ser <- coxph(Surv(dayslevel2.lag,dayslevel2,obs)~
                    sex.x + interview_age.x + leave + qs0.s  + qs.s.change
          + tt(qs.s.change)  + cluster(subjectkey),
          data=datacox[datacox$dayslevel2>0,],subset=txassign=="SER",
            tt = function(x, t, ...){
               x*(((t-15)^2)/49)/100
             })
summary(m.tt.ser)

m.tt.ven <- coxph(Surv(dayslevel2.lag,dayslevel2,obs)~
                    sex.x + interview_age.x + leave + qs0.s  + qs.s.change
          + tt(qs.s.change)  + cluster(subjectkey),
          data=datacox[datacox$dayslevel2>0,],subset=txassign=="VEN",
            tt = function(x, t, ...){
               x*(((t-15)^2)/49)/100
             })
summary(m.tt.ven)
```

Frailty Code Example

```
mcoxme.bup <- coxme(Surv(dayslevel2.lag,dayslevel2,obs)~
                 interview_age.x + sex.x + leave + qs0.s + I(qs0.c-qs0.s) + qs.s.change +
                 I(qs.c.change-qs.s.change) + (1|subjectkey),
                 data=datacox[datacox$dayslevel2>0,],
                 subset=txassign=="BUP")
summary(mcoxme.bup)
mcoxme.ser <- coxme(Surv(dayslevel2.lag,dayslevel2,obs)~
                  interview_age.x + sex.x + leave + qs0.s + I(qs0.c-qs0.s) + qs.s.change +
                  I(qs.c.change-qs.s.change) + (1|subjectkey),
                    data=datacox[datacox$dayslevel2>0,],
                    subset=txassign=="SER")
summary(mcoxme.ser)
mcoxme.ven <- coxme(Surv(dayslevel2.lag,dayslevel2,obs)~
                interview_age.x + sex.x + leave + qs0.s + I(qs0.c-qs0.s) + qs.s.change +
                 I(qs.c.change-qs.s.change) + (1|subjectkey),
                data=datacox[datacox$dayslevel2>0,],
                    subset=txassign=="VEN")
summary(mcoxme.ven)
```

IIW-GEE Code Example

```
mgeew.bup <- geeglm(qstot.x-qs0.s~log(dayslevel2)
, id=src_subject_id.x,data=datacox, subset=txassign=="BUP", weights=weight.stab);
mgeew.ser <- geeglm(qstot.x-qs0.s~log(dayslevel2)
, id=src_subject_id.x,data=datacox, subset=txassign=="SER", weights=weight.stab);
mgeew.ven <- geeglm(qstot.x-qs0.s~log(dayslevel2)
, id=src_subject_id.x,data=datacox, subset=txassign=="VEN", weights=weight.stab);
```

Part 3. Sensitivity Analysis

Introduction

- As with trials with missing data, untestable assumptions are needed.
- Assessing how inferences would change under departures from these assumptions is crucial.
- Develop a sensitivity analysis methodology for estimating the treatment-specific mean outcome at fixed times after randomization.
- The methodology is anchored around the *assessment at random* (AAR) assumption.

Notation

- τ: end of follow-up,
- $[a, b]$: inferential time period
- $L := \{Y(t) : 0 \leq t \leq \tau\}$: outcome process
- $\{N(t) : a \leq t \leq \tau\}$: assessment time process
  - $A(t)$: indicator of assessment at time t; $A(0) = 1$
  - $A[t, t + \epsilon)$:indicator of assessment in the time window $[t, t + \epsilon)$
- $O := \{N(t) : a \leq t \leq \tau\} \cup \{Y(t) : A(t) = 1, 0 \leq t \leq \tau\}$: observed data
- $\bar{O}(t)$: observed data up to, but not including, time t; we refer to this as the *observed past*.

Conditional Intensity Functions

Conditional on observed past:

$$\lambda(t, \bar{O}(t)) := \lim_{\epsilon \to 0^+} \left\{ P\Big(A[t, t+\epsilon) = 1 | \bar{O}(t)\Big)/\epsilon \right\}$$

Conditional on observed past and L:

$$\rho(t, \bar{O}(t), L) := \lim_{\epsilon \to 0^+} \left\{ P\Big(A[t, t+\epsilon) = 1 | \bar{O}(t), L\Big)/\epsilon \right\}$$

Assessment at Random (AAR) Assumption

$$\underbrace{dF(y(t)|A(t)=0,\bar{O}(t))}_{\text{Subgroup 0 Distribution}} = \underbrace{dF(y(t)|A(t)=1,\bar{O}(t))}_{\text{Subgroup 1 Distribution}}$$

- Subgroups 0 and 1 share the same observed past up to time $t-$
- Differ with respect to assessment at time t
- AAR is not testable

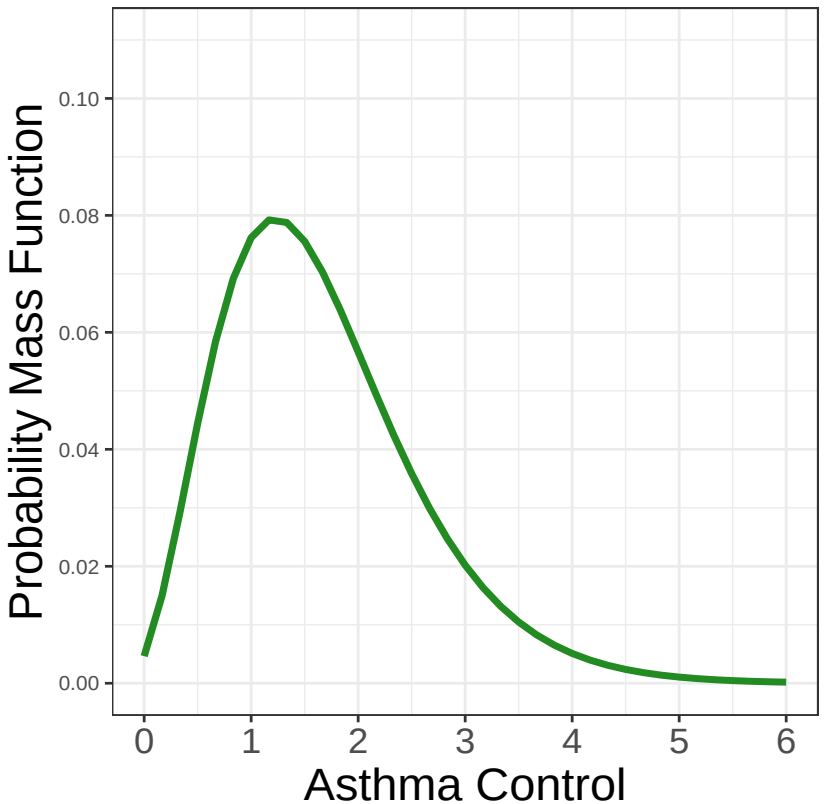
Assessment Not at Random (ANAR) Assumptions

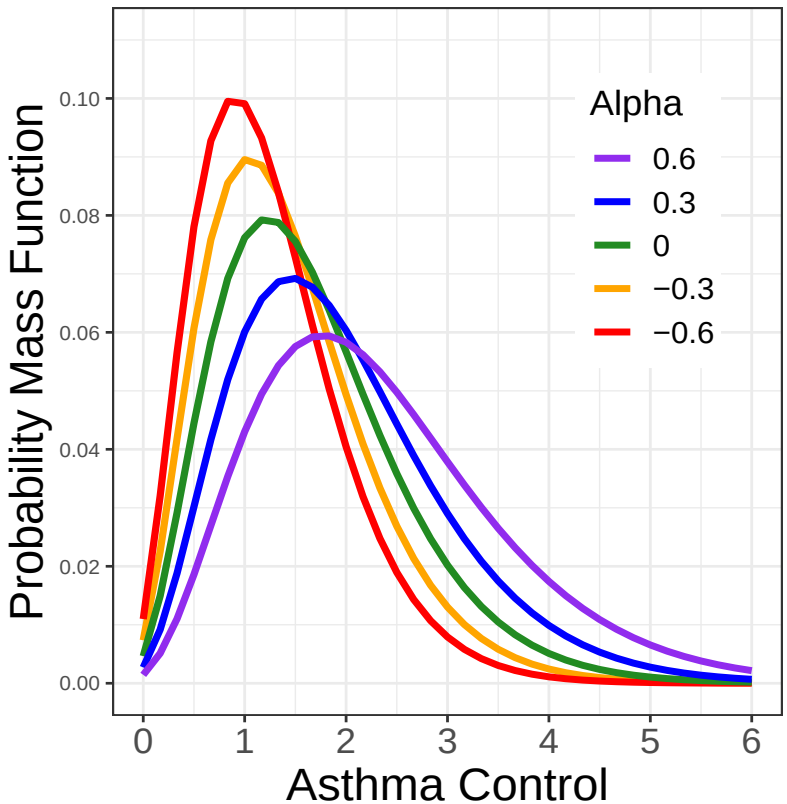
$$\underbrace{dF\left(y(t)|A(t)=0,\bar{O}(t)\right)}_{\text{Subgroup 0 distribution}}$$

$$= \underbrace{dF\left(y(t)|A(t)=1,\bar{O}(t)\right)}_{\text{Subgroup 1 distribution}} \underbrace{\frac{\exp\{\alpha y(t)\}}{E[\exp\{\alpha Y(t)\}|A(t)=1,\bar{O}(t)]}}_{\text{tilting factor}}$$

- $\alpha = 0$ corresponds to AAR
- α governs deviations from AAR; not identifiable
- α is varied in a sensitivity analysis
- Rotnitzky, Scharfstein, Su, and Robins (2001); Birmingham, Rotnitzky, and Fitzmaurice (2003); Vansteelandt, Rotnitzky, and Robins (2007) ....

Class of Assessment Not at Random (ANAR) Assumptions





Additional Assumptions

$$\begin{aligned}\rho(t, \bar{O}(t), L) &:= \lim_{\epsilon \to 0^+} \frac{P\Big(A[t, t+\epsilon) = 1 | \bar{O}(t), L\Big)}{\epsilon} \\ &= \lim_{\epsilon \to 0^+} \frac{P\Big(A[t, t+\epsilon) = 1 | \bar{O}(t), Y(t)\Big)}{\epsilon} \\ &=: \rho(t, \bar{O}(t), Y(t)).\end{aligned}$$

With this additional assumption, we have:

$$\rho(t, Y(t), \bar{O}(t)) = \lambda(t, \bar{O}(t)) \frac{E\Big[\exp\{\alpha Y(t)\} | A(t) = 1, \bar{O}(t)\Big]}{\exp\{\alpha Y(t)\}}.$$

$$\frac{\rho(t, Y(t)+1, \bar{O}(t))}{\rho(t, Y(t), \bar{O}(t))} = \exp\{-\alpha\}$$

Additional Assumptions

$$E[Y(t)] = s\big(\beta' B(t)\big), \quad a \leq t \leq b$$

- $B(t)$ be a specified spline basis with dimension p
- $\beta \in \mathbb{R}^p$
- $s(\ )$ be a specified invertible link function.

Identification

$$E[Y(t)] = \int_w \int_{y(t)} \frac{y(t)\exp\{\alpha y(t)\}}{E[\exp\{\alpha Y(t)\}|A(t)=1, \bar{O}(t)=w]} \\ dF(y(t)|A(t)=1, \bar{O}(t)=w)dF(w).$$

$$\beta = \int_{t=a}^{b} V^{-1} B(t) s^{-1}\Big(E[Y(t)]\Big)\, dt,$$

where $V := \int_{t=a}^{b} B(t)B(t)'dt$.

Influence Function

Theorem

Let $V(\beta) := \int_{t=a}^{b} \left\{ \left(\frac{\partial}{\partial \beta} s\left(\beta' B(t)\right) \right) \left(\frac{\partial}{\partial \beta'} s\left(\beta' B(t)\right) \right) \right\} dt$, *and let* $W(t;\beta) := V(\beta)^{-1} \frac{\partial}{\partial \beta} s\left(\beta^t B(t)\right)$. *Then an influence function for* β *is given by:*

$$\varphi(O;P) =$$

$$\int_{t=a}^{b} W(t;\beta) \left\{ \frac{Y(t) - E\left[Y(t)|\bar{O}(t)\right]}{\rho(t,\bar{O}(t),Y(t))} \right\} dN(t) +$$

$$\int_{a}^{b} W(t;\beta) \left(E\left[Y(t)|\bar{O}(t)\right] - s(\beta^t B(t)) \right) dt.$$

Influence Function

Corollary

When $s(\ )$ is the identity link, an influence function for β is $\varphi(O;P) = m(O;P) - \beta$, where $m(O;P) :=$

$$\int_{t=a}^{b} \left\{ V^{-1} B(t) \frac{\left(Y(t) - E\left[Y(t)|\bar{O}(t)\right]\right)}{\rho(t, Y(t), \bar{O}(t))} \right\} dN(t) +$$

$$\int_{t=a}^{b} \left\{ V^{-1} B(t) E\left[Y(t)|\bar{O}(t)\right] \right\} dt$$

and $V := \int_{t=a}^{b} B(t)B(t)'dt$.

$\rho(t, \bar{O}(t), Y(t))$ and $E\Big[Y(t)|\bar{O}(t)\Big]$

$$\begin{aligned}\rho(t, \bar{O}(t), Y(t)) =& \lambda(t, \bar{O}(t)) \exp\{-\alpha Y(t)\} \times \\ & E\Big[\exp\{\alpha Y(t)\} \ |A(t) = 1, \bar{O}(t)\Big]\end{aligned}$$

$$E\Big[Y(t)|\bar{O}(t)\Big] = \frac{E\Big[Y(t) \exp\{\alpha Y(t)\} \ |A(t) = 1, \bar{O}(t)\Big]}{E\Big[\exp\{\alpha Y(t)\} \ |A(t) = 1, \bar{O}(t)\Big]}$$

.

Models

- $\lambda(t, \bar{O}(t))$ (stratified Andersen-Gill model)
- $dF(y(t)|A(t) = 1, \bar{O}(t))$

Estimation

$$\hat{\beta} = \frac{1}{n}\sum_{i=1}^{n}\left\{\sum_{t_k \in S_i} V^{-1}B(t_k)\frac{\left(Y_i(t_k) - \hat{E}\left[Y(t_k)|\bar{O}(t_k)_i\right]\right)}{\hat{\rho}(t_k, \bar{O}(t_k)_i, Y_i(t_k))} + \int_{t=a}^{b} V^{-1}B(t)\hat{E}\left[Y(t)|\bar{O}(t)_i\right]dt\right\},$$

where S_i denotes the set of participant i's assessment times that occur in the interval $[a, b]$.

Asymptotics

- We establish conditions for $\sqrt{n}$-asymptotics for β.
- Estimators for $\lambda(t, \bar{O}(t))$ and $dF(y(t)|A(t) = 1, \bar{O}(t))$ can converge at slower than $\sqrt{n}$-rates, but not slower than $n^{1/4}$.

Under these conditions,

$$\sqrt{n}(\hat{\beta} - \beta) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \varphi(O_i; P) + o_P(1)$$

Selection of Sensitivity Analysis Parameters

- Domain expertise should decide on a range of α values.
- Explored in the context of sensitivity analysis for unmeasured confounding in observational studies.
- Cinelli and Hazlett (2020)
  - “perhaps [the] most fundamental obstacle to the use of sensitivity analysis is the difficulty in connecting the formal results to the researcher’s substantive understanding about the object under study"
  - “bounding procedure we should use depends on which . . . quantities the investigator prefers and can most soundly reason about in their own research."

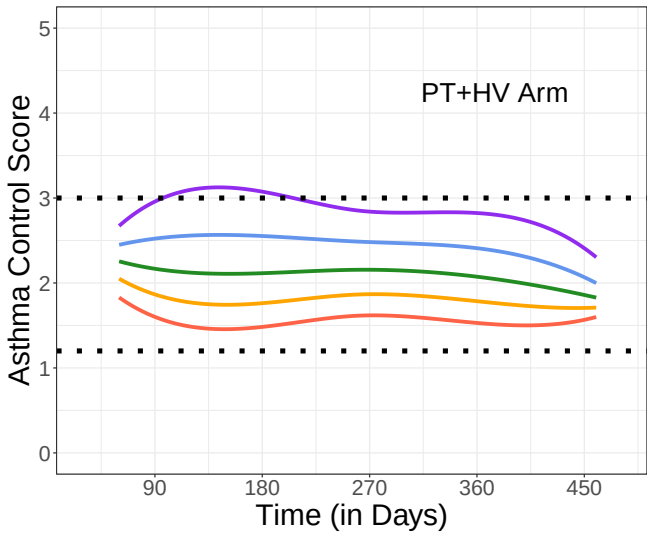
Selection of Sensitivity Analysis Parameters

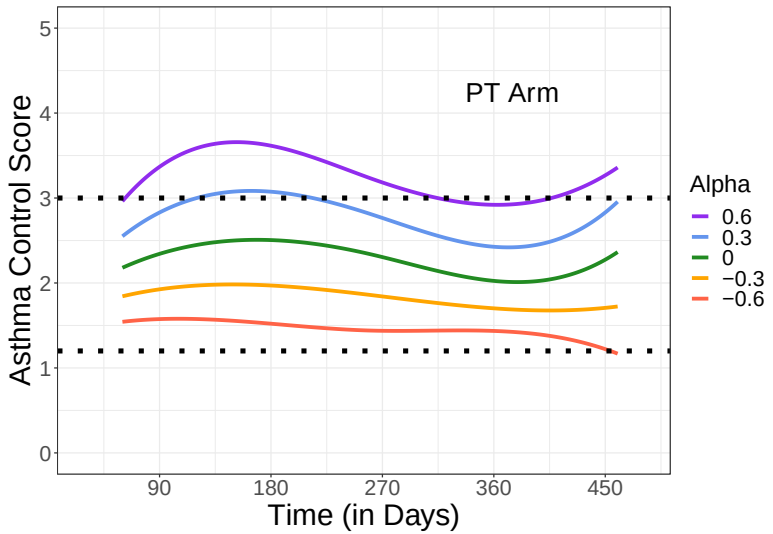
- Cinelli and Hazlett (2020), Franks *et al.* (2020), Veitch and Zaveri (2020) have proposed ways for using the strength of the impact of a key covariate or group of covariates X_j given the remaining covariates X_{-j} to obtain a bound on the strength of unmeasured confounders, and hence obtain bounds for the sensitivity parameters.
- This may not adapt well to our setting: the impact of any group of variables in the observed past on assessment at time t may actually be weaker than the impact of $Y(t)$ on assessment at time t (after adjusting for the remaining variables in the observed past).

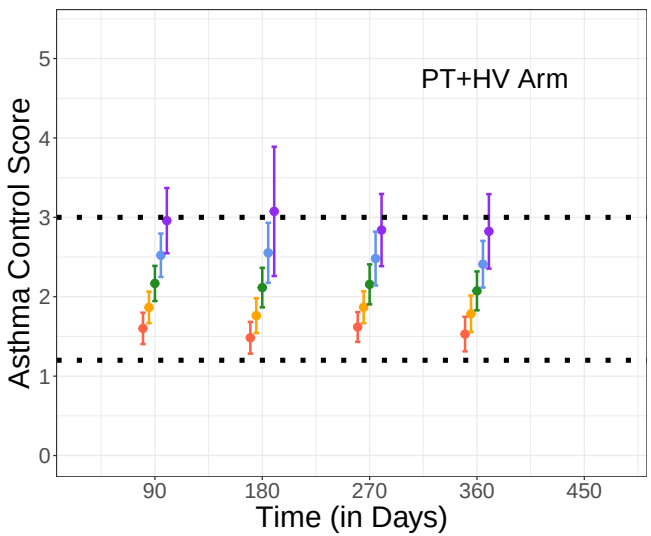
Selection of Sensitivity Analysis Parameters

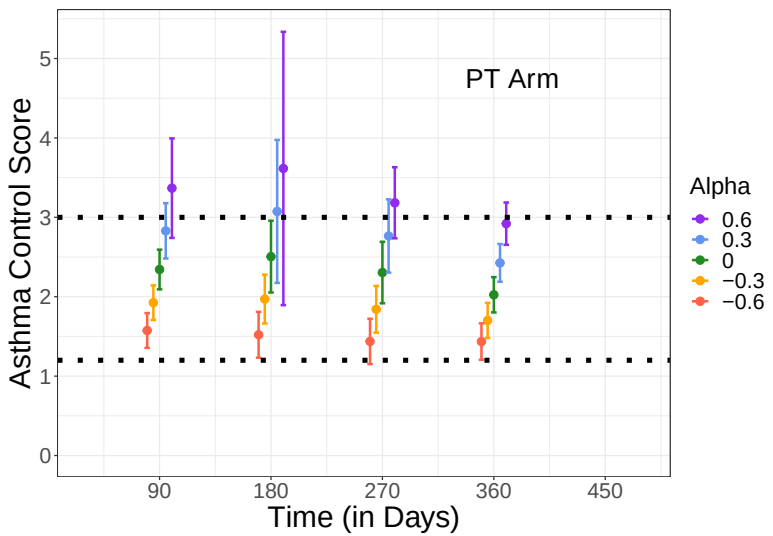
- Instead, we query domain experts for extreme values μ_{min} and μ_{max} such that, in their judgment, a mean outcome $E[Y(t)]$ outside of the bounds (μ_{min}, μ_{max}) at any time t would be implausible.
- We then treat any α under which $E[Y(t)]$ falls outside of (μ_{min}, μ_{max}) for some t as implausible and exclude such values from our sensitivity analysis. We do this separately for each treatment arm.
- This approach is aligned with Cinelli and Hazlett (2020)'s recommendation, as it is based on the treatment arm-specific mean outcome, a quantity about which subject matter experts can provide direct guidance.

Analysis of ARC study

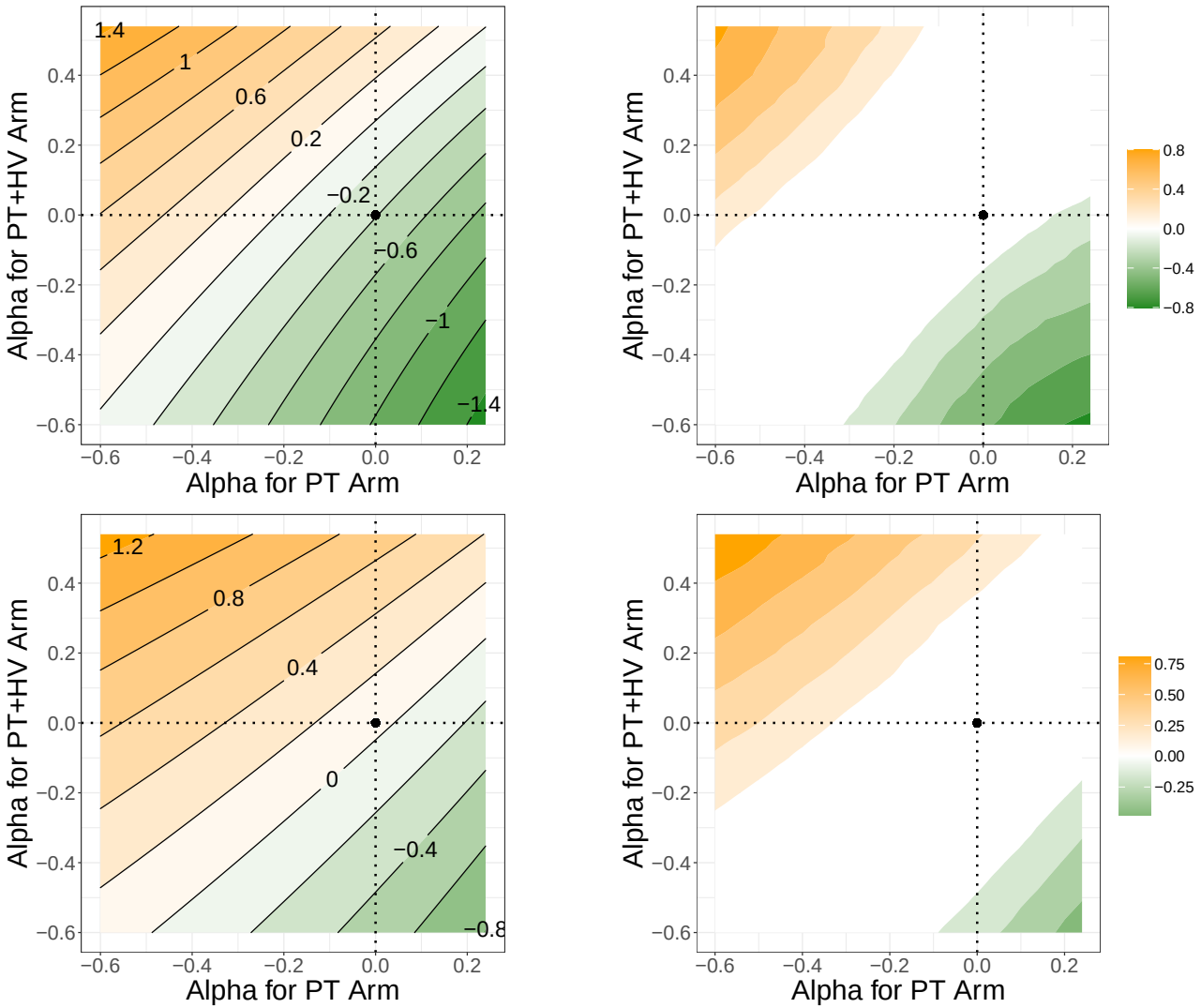








Analysis of ARC study



Discussion

- Irregularity of assessment times is largely ignored in applied work.
- Visit windows are typically created and data are analyzed using missing data methods.
- There is no need to create artificial visit windows.
- Methods have been developed for analyzing trials with irregular and potentially informative assessment times.
- Like missing data methods, they rely on untestable assumptions and therefore sensitivity analysis is important.