

Assessing Medication Adherence with Group-Based Trajectory Modelling

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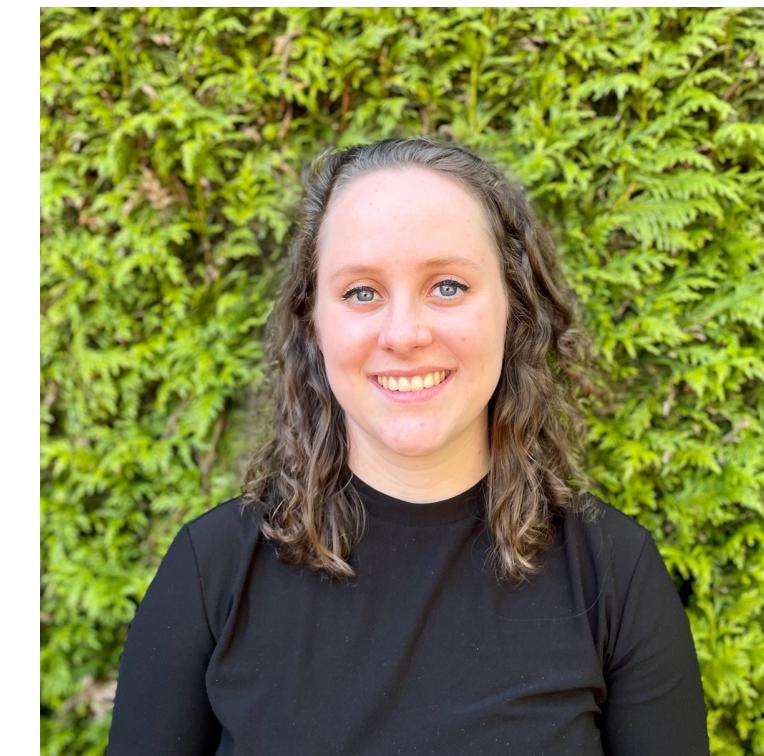
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Disclosure

- No funding was received for the research on which this workshop is based.

Speakers

**Jay JH Park****Scientific Lead****Core Clinical Sciences**jay@coreclinicalsciences.com**Rebecca Metcalfe****Senior Scientist****Core Clinical Sciences**rebecca@coreclinicalsciences.com**Heather Berringer****Statistician****Core Clinical Sciences**heather@coreclinicalsciences.com**Kristian Thorlund****Assistant Professor****McMaster University**thorluk@mcmaster.ca

Agenda

- 1. Introduction and Medication Adherence (~10 minutes, Jay)**
- 2. Key Features of Group-Based Trajectory Modelling (GBTM) (~10 minutes, Kristian)**
- 3. Technical Overview + Case Studies (~20 minutes, Heather)**
- 4. Reporting & Common Pitfalls (~10 minutes, Rebecca)**

Audience polls will be conducted throughout with the Q/A period being held the end.

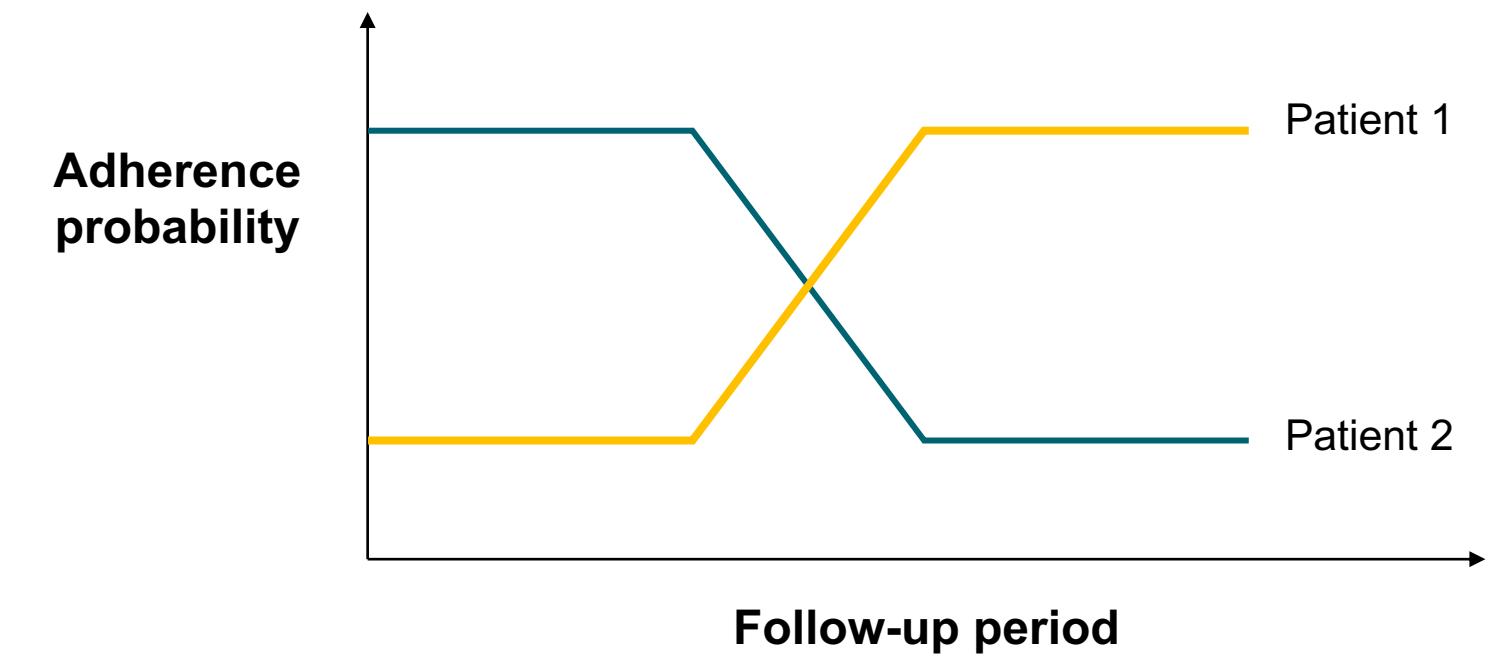
Learning Objectives

At the end of the session, participants will be able:

- Recognize the dynamic nature of adherence and challenges with current adherence measurements
- Understand the advantages and limitations of GBTM
- Describe areas for future research using GBTM in clinical trial research and real-world evidence (RWE)
- Critically appraise studies using GBTM

How Group-Based Trajectory Modelling (GBTM) Can Be Used to Study Medication Adherence

- With GBTM, we can identify groups of individuals with similar progression of outcomes over time, such as patterns of medication adherence over time
- We can enhance our understanding of medication adherence through
 - Visualization of these groups
 - Comparison of their patient characteristics
 - Comparison of their clinical outcomes
- GBTM can potentially be used to track changes to improve medication adherence and tailor adherence intervention strategies



Medication Adherence

- Patient adherence influences variability in drug response outcomes.
 - Suboptimal adherence during clinical trials may lead to underestimation of a drug's efficacy and potential for harm.
 - In the real-world, inadequate adherence is associated with poor outcomes and can increase healthcare costs.
- It is widely recognized that medication adherence is critical.
 - However, the methodology employed in most adherence studies is constrained by the how we currently measure adherence

COMMENT

Poor medication adherence in clinical trials: consequences and solutions

Alasdair Breckenridge¹, Jeffrey K. Aronson², Terrence F. Blaschke³, Dan Hartman⁴, Carl C. Peck⁵ and Bernard Vrijens⁶

Poor adherence to medicines in clinical trials can undermine the value of the trials; for example, by compromising estimates of the benefits and risks of a medicine. In this article, we highlight such consequences and also discuss approaches to tackle this problem.

Patient Preference and Adherence

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PERSPECTIVES

Understanding Processes, Outcomes, and Contexts in Medication Adherence: The Medication Adherence Context and Outcomes (MACO) Framework

Rebecca J Bartlett Ellis¹ ID, Joan E Haase¹ ID, Todd M Ruppar² ID

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Medication Adherence in Real-World: PDC

- The Pharmacy Quality Alliance (PQA) recommends the **Proportion of Days Covered (PDC)**

$$PDC = \frac{\# \text{ of fill days}}{\# \text{ of follow-up days}}$$

- We typically use a threshold of 80% to classify individuals as adherent ($\geq 80\%$) or non-adherent ($< 80\%$)

The screenshot shows the PQA website's "Adherence" page. At the top is the PQA logo, followed by a navigation bar with links to Home, About, Membership, Measures, Research, Education, and Events. Below the navigation is a section titled "Adherence" with a sub-section titled "PQA Adherence Measures". A text box explains that adherence measures examine prescription claims for specific classes of medication therapy, and that Proportion of Days Covered (PDC) is the preferred method to measure medication adherence. It notes that PQA uses this methodology for measures that assess individuals' adherence to important chronic drug therapies. Another text box below discusses Adherence measures, mentioning a standard PDC threshold of 80% and a specific threshold of 90% for the PDC: Antiretroviral Medications measure.

Adherence

PQA Adherence Measures

The adherence measures examine individuals' prescription claims for specific classes of medication therapy. Proportion of Days Covered (PDC) is the preferred method to measure medication adherence; therefore, PQA uses this methodology for measures that assess individuals' adherence to important chronic drug therapies.

Adherence measures assess the percentage of patients covered by prescription claims for the same medication (or similar medication) in the same therapeutic class, within the measurement year. The PDC threshold is the level above which the medication has a reasonable likelihood of achieving the most clinical benefit. Clinical evidence provides support for a standard PDC threshold of 80%. However, the *PDC: Antiretroviral Medications* measure requires 90% threshold.

The PQA is a non-profit, public-private partnership formed after Medicare Part D Prescription Drug Benefit's implementation. Their recommendations are widely adopted by health plans including CMS' Medicare Stars Program.

Source: PQA. Adherence. <https://www.pqaalliance.org/adherence-measures>. Accessed April 22, 2024

Challenges with Adherence Cut-Off Based on PDC

In addition to data challenges and limitations from claims data,

- The challenges with using PDC ultimately come from the fact that patterns of medication adherence are dynamic
- When we dichotomize such dynamic variable, we can lose a lot of information
 - PDC-based cut-offs can lead to a serious under-estimation of variation and patterns of medication consumption.
- The cut-off 80% (or 90% in other cases) is arbitrary. There is limited empirical justification that supports this
 - There may not be an ideal threshold that can be universally be applied across different medications and indications
- Instead of relying on PDC or other deterministic adherence measures, **longitudinal clustering approaches can be better suited to capture the dynamic nature of medication adherence**

Medication Adherence in Clinical Trials

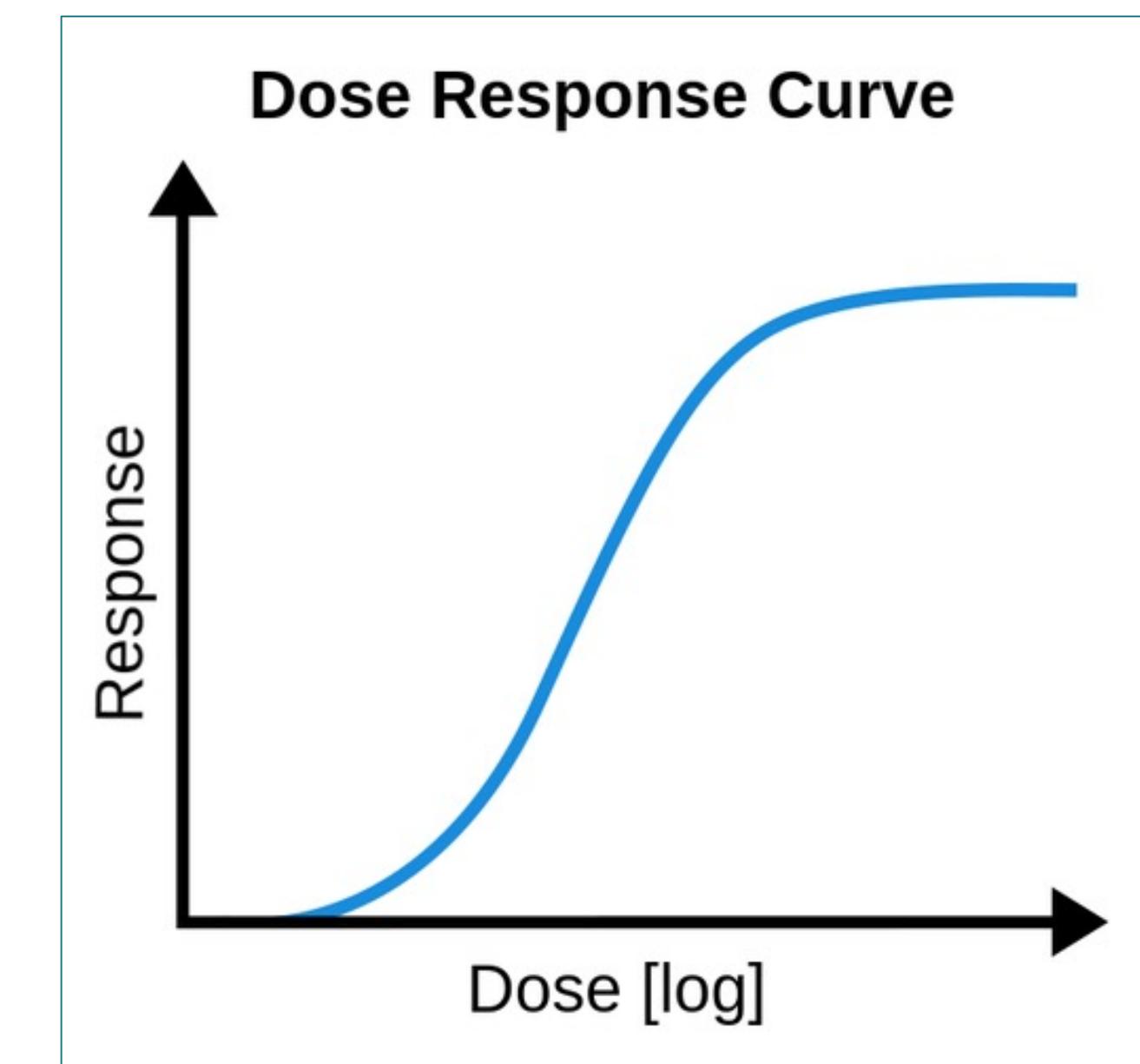
Common population definitions used for analysis in clinical trials	
Intent-to-treat (ITT) Population	<ul style="list-style-type: none">• All subjects who received at least 1 dose of study medication and had at least one post-baseline efficacy assessment performed.
Per-protocol (PP) Population	<ul style="list-style-type: none">• All subjects in the ITT population without any major protocol violations<ul style="list-style-type: none">• 80% adherence threshold commonly used to define PP population
Safety Population	<ul style="list-style-type: none">• All subjects who received at least 1 dose of study medication.

- ITT is typically the primary population for analysis of efficacy
 - PP and safety population are used to evaluate how efficacy profiles are affected by medication adherence and safety profiles of the medical product

Arbitrary Cut-Off in Clinical Trials (Again)

Regardless of the mechanism of the product,

- The drug's effects generally depend on actual dose consumed over time
- By comparing the percentage of observed adverse events on the study participants with at least 1 dose of medication, we are missing out on a lot
 - Similarly, evaluating the per-protocol level effect on arbitrary cut-off of 80% or other adherence threshold is also challenging
- ***Why not adopt a data-driven, machine-learning approach for exploratory analyses?***



Overview of Group-Based Trajectory Modelling (GBTM)

Kristian Thorlund, PhD

Introduction to GBTM

GBTM is a **finite mixture modelling** that uses **trajectory groups** to approximate unknown trajectories

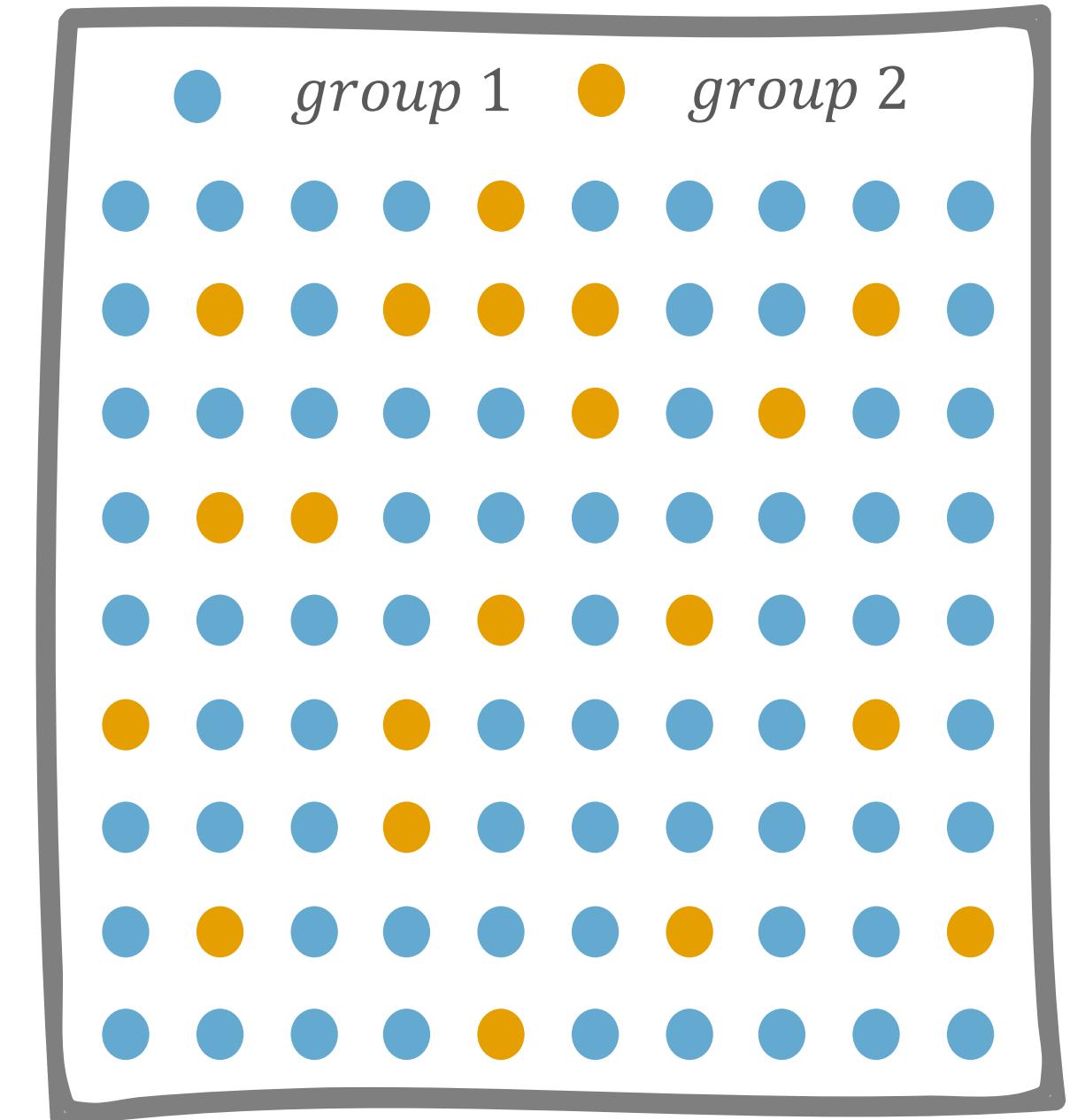
- GBTM involves grouping individuals into meaningful subjects with similar trajectories
- Let's break it down by their major concepts
 1. Trajectories
 2. Finite mixture modeling

Trajectories

- The term “**trajectory**” is used to describe progression of outcomes over time
- We can analyze trajectories of any outcomes like patterns of medication adherence using longitudinal data
- Key assumptions in GBTM as an extension of finite mixture modelling
 1. We assume there are meaningful subgroups that follow distinct trajectories
 2. These trajectories **are not identifiable (“hidden classes”) based on their individual characteristics**, such as gender and age

Visual Illustration of Distinguishable Groups

- If we have two groups that are distinguishable based on measurable characteristics, they can be analyzed separately
- If they are not distinguishable, we say our data will be composed of a mixture of the two groups
- Difficult to predict medication adherence patterns based on a set of baseline characteristic in reality



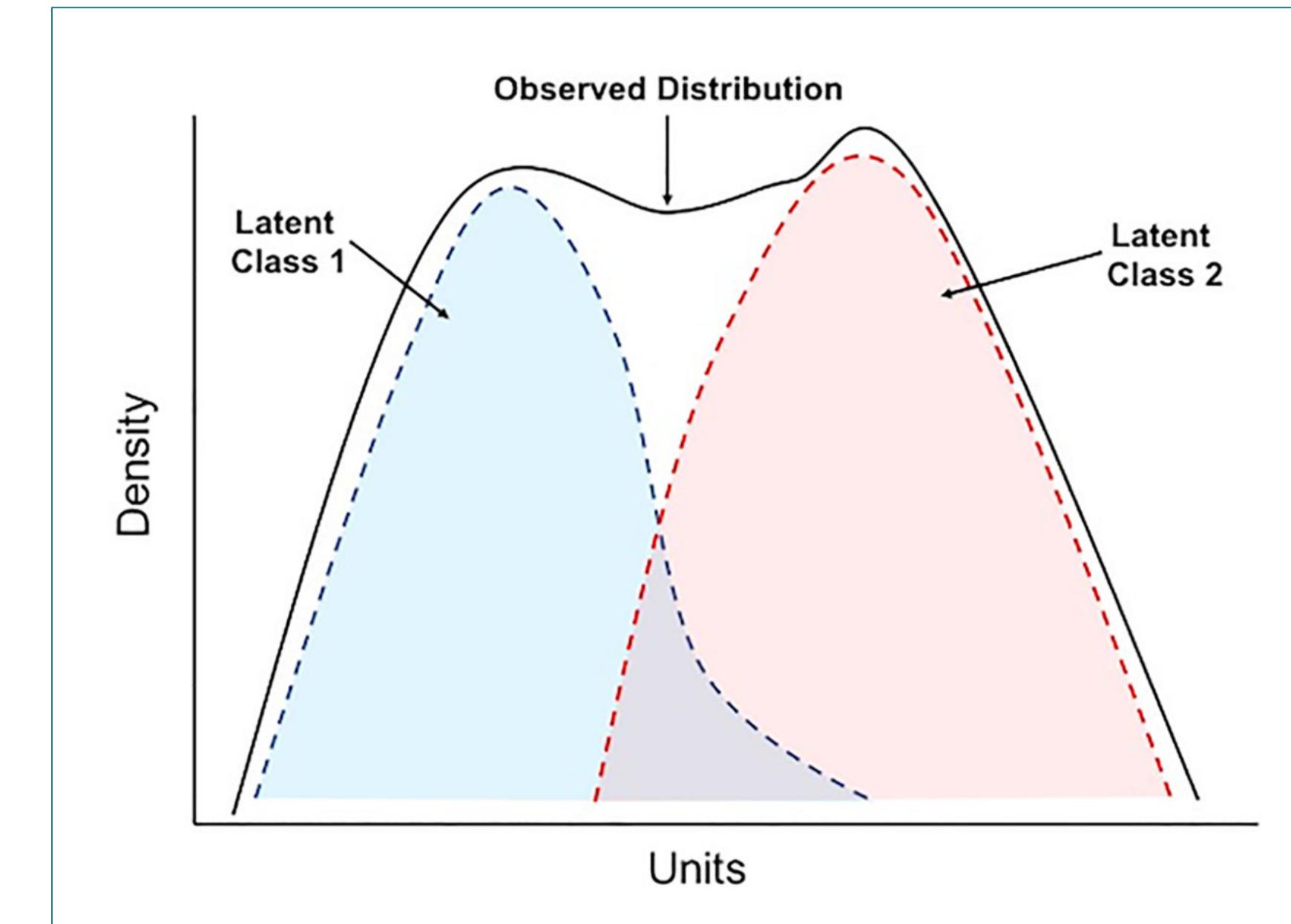
A hypothetical labels to the group

- Group 1: Male (blue)
- Group 2: Female (orange)

Source: Gao et al., 2023

Hidden Classes: Non-Distinguishable Groups

- The presence of “hidden classes” are a central assumption of GBTM, an extension of finite mixture modelling
 - These groups are not distinguishable based on a set of measured characteristics
- In this illustrative example, we have a dataset with a normal distribution (shown in black line)
 - The hidden or latent classes are shown in dotted line in blue and red



Source: Sinha P et al, 2021

Finite Mixture Modelling

- The idea behind the finite mixture modelling is that the data originates from a mixture of subpopulations (not distinguishable), and that each subpopulation follows their own distribution
- When observed variables are discrete, the finite mixture model is also referred to as latent class analysis

Common clustering analyses (e.g., K means)

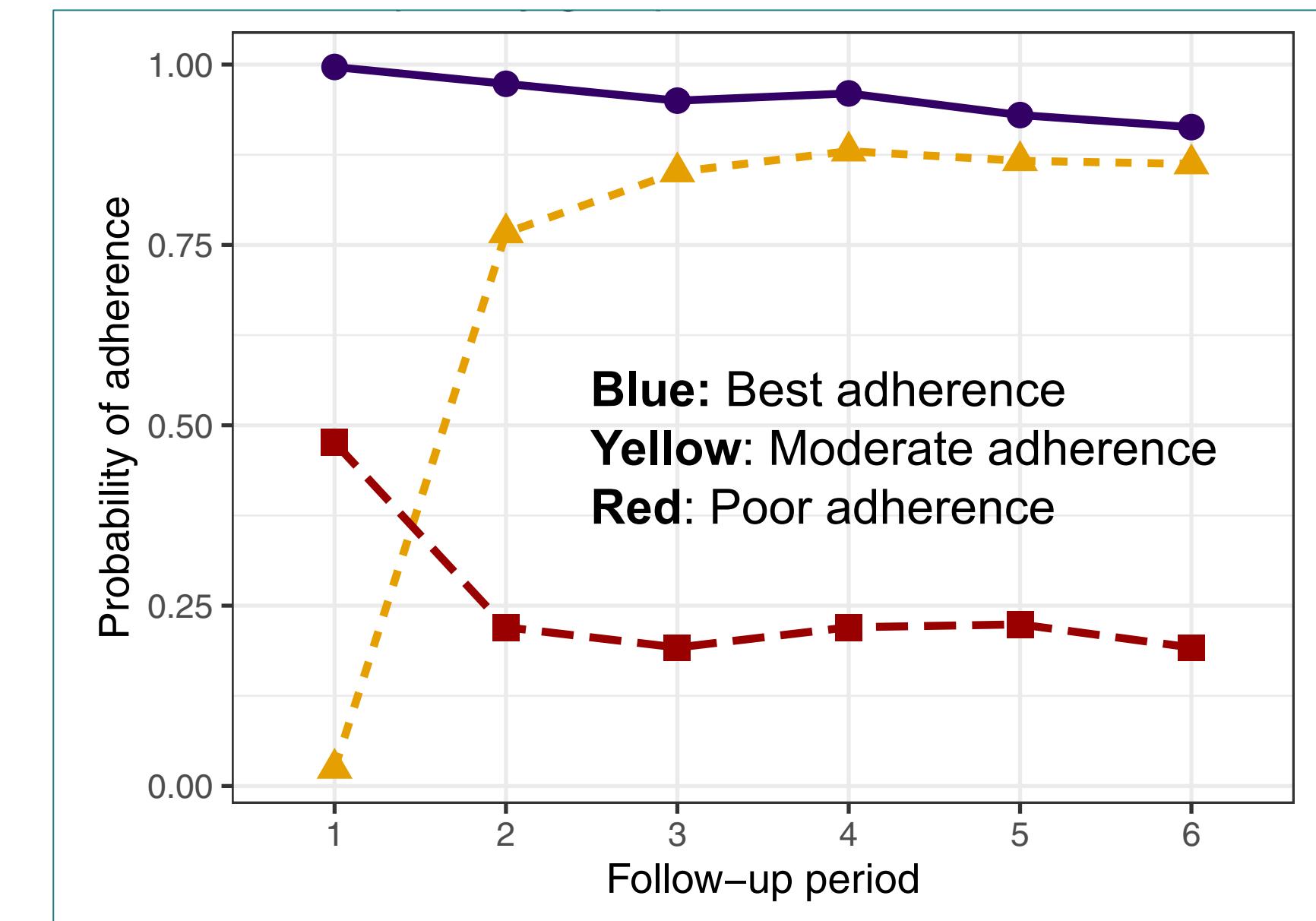
- We have hard partitioning of the data
 - Individuals do not overlap between groups

Finite mixture modelling

- We fit a statistical model that allows us to make inference
- No hard partitioning ~ we use probabilistic clustering
 - Individuals can overlap between group

Group-Based Trajectory Modelling (GBTM)

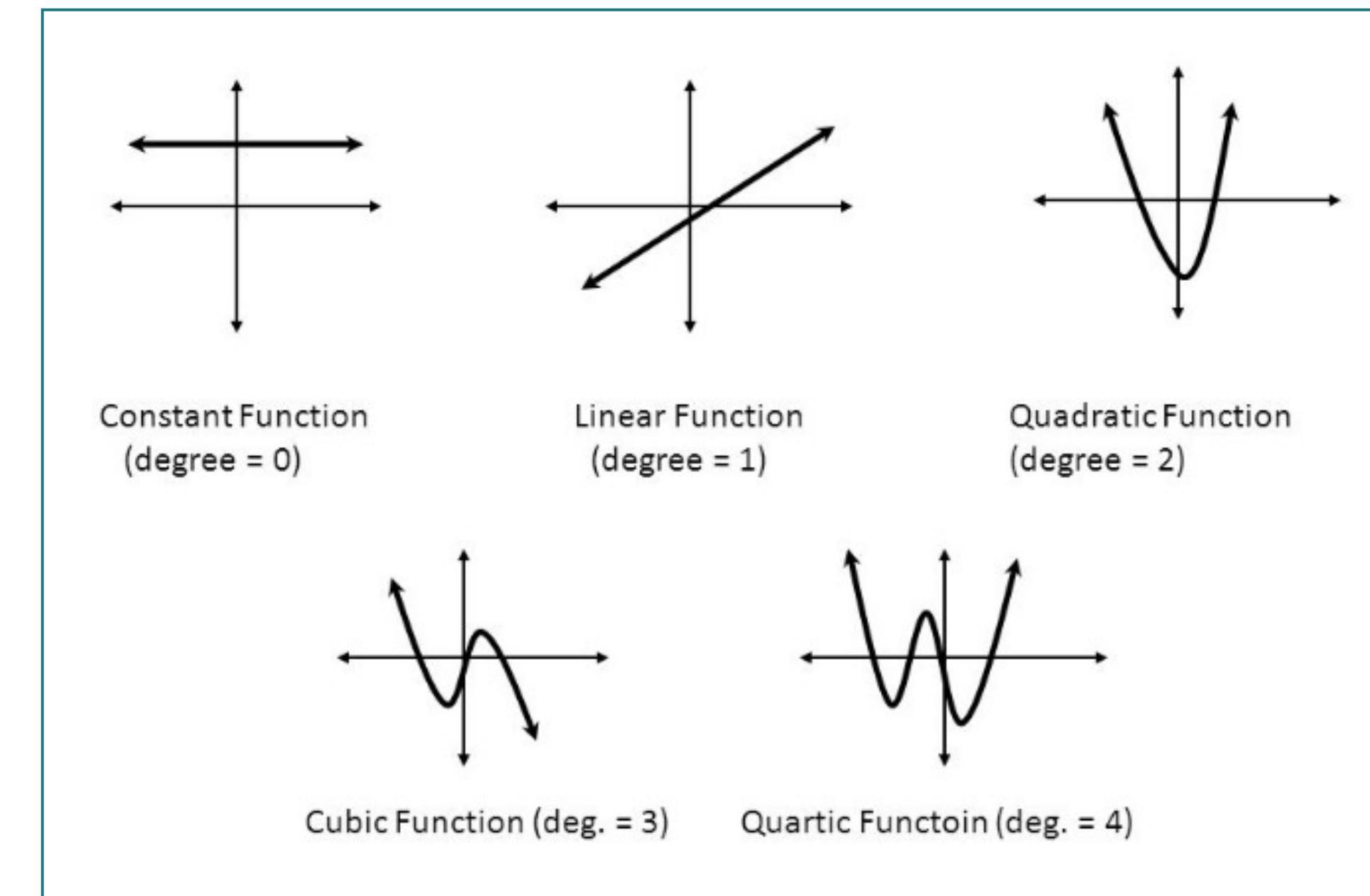
- GBTM, as a ***specialized application of finite mixture models***, provides a way to identify groups with distinct trajectories that are determined by polynomial function of time
 - GBTM allows us to analyze trajectories based on “outcomes” that are measured at different time points
- **GBTM is a valuable tool that can identify, summarize, and communicate complex patterns in longitudinal data**



Source: Diop A et al., 2024

Group-Based Trajectory Modelling (GBTM)

- When fitting GBTM, the number of groups and their polynomial function of time must be specified
 - Time can be modelled with polynomials from first-order (constant) to fourth-order (quartic)
 - *We typically would not model time based on a constant polynomial function*
- GBTM predicts the trajectory of each group and the form of each trajectory
- We estimate the probability for the individual's group membership, we then assign them to the group for which they have the highest probability



Technical Overview & Case Studies

Heather Berringer, MSc PhD(c)

General Steps to Conducting GBTM Analyses

1. Generate a plausible number of groups based on theory and literature. Refine the model to determine:
 - a. the optimal number of groups (typically between 1-7) and
 - b. the optimal shape of the trajectories
2. Run the model using R package *{flexmix}*
3. Assess how well the model fits the data
4. Investigate graphical presentations and interpretation

How do we put this into practice? We will review fundamental R code using the package *{flexmix}* and discuss two case studies.

Step-by-Step Code

```
# Initialize empty results data set
summary_table <- data.frame(Model = character(),
                             BIC = numeric())

# Running GBTM with 3 trajectories
k <- 3

# Loop over different polynomial functions
for (degree in c("Linear", "Quadratic", "Cubic")) {

  # Define the formula based on the degree
  formula <- switch(degree,
    "Linear" = RelativeDoses ~ I(WEEK),
    "Quadratic" = RelativeDoses ~ I(WEEK) + I(WEEK^2),
    "Cubic" = RelativeDoses ~ I(WEEK) + I(WEEK^2) + I(WEEK^3))

  # Fit the model
  model <- flexmix(formula ~ . | SUBJID, k = k,
                    model = FLXMRglm(formula, family = "poisson"),
                    data = DataTrajectory)

  # Calculate metrics
  bic <- BIC(model)

  # Add to summary table
  summary_table <- rbind(summary_table, data.frame(Model = paste(degree, k),
                                                BIC = bic))
}

}
```

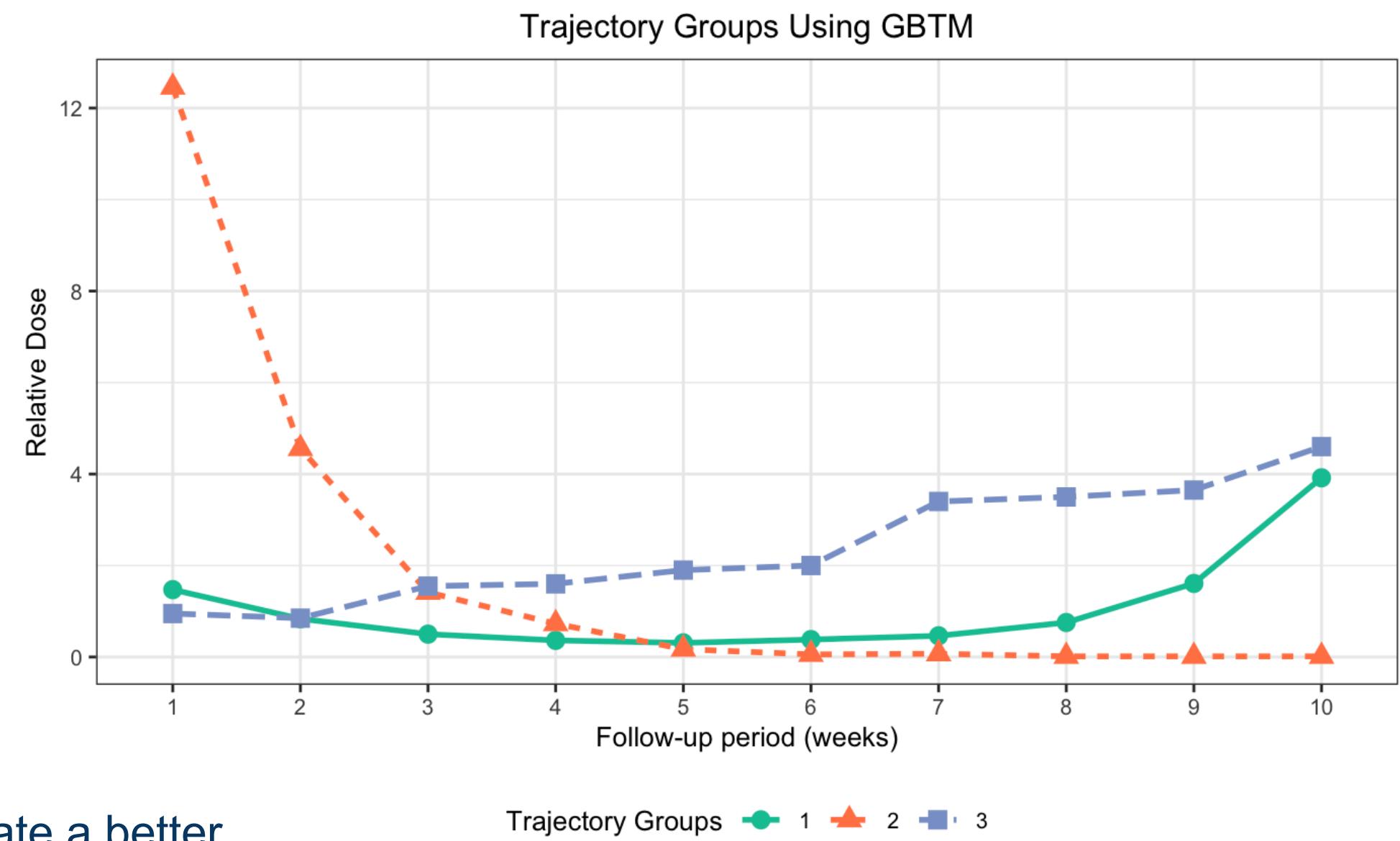
Steps

1. Initializing an empty dataset
2. Running GBTM with 3 different trajectories
3. Defining models with linear, quadratic, and cubic polynomial functions
4. Fitting the GBTM model
5. Calculating the BIC for each fitted GBTM model
6. Combining this into a data frame

Code Results

Assessment of GBTM Model Fit Based on BIC

Model	BIC	BIC Ranking
Quadratic 3	4961.165	1
Cubic 3	4981.495	2
Linear 3	5503.445	3



All else being equal, models with lower BIC value indicate a better fit

GBTM Applications to RWE and RCT

2 case studies for discussion

1. RWE case study:

- Statin prevention study based on Canadian data
- Published in Statistical Methods in Medical Research (Diop et al 2023)

2. RCT case study:

- Placebo-controlled RCT for lung cancer
- Currently being peer reviewed

MAIN PAPER

Assessing the performance of group-based trajectory modeling method to discover different patterns of medication adherence

Awa Diop^{1,2}  | Alind Gupta³ | Sabrina Mueller⁴ | Louis Dron⁵ | Ofir Harari¹  | Heather Berringer^{1,6} | Vinusha Kalatharan¹ | Jay J. H. Park^{1,7} | Miceline Mésidor^{2,8}  | Denis Talbot^{2,8}

Marginal structural models with latent class growth analysis of treatment trajectories: Statins for primary prevention among older adults

Awa Diop^{1,2} , Caroline Sirois^{2,3}, Jason Robert Guertin^{1,2,4}, Mireille E Schnitzer^{5,6} , Bernard Candas¹, Benoit Cossette⁷, Paul Poirier², James Brophy⁸ , Miceline Mésidor^{1,3} , Claudia Blais⁹ , Denis Hamel⁹, Mina Tadrous¹⁰, Lisa Lix¹¹  and Denis Talbot^{1,3} 

ORIGINAL ARTICLE

Efficacy and Safety Assessment Using Group-Based Trajectory Modelling of Dose Consumption Measured During a Randomized Clinical Trial

Awa Diop¹ | Rebecca K Metcalfe¹ | Greg Ball² | Brett L Houston^{3,4} | Ryan Zarychanski^{3,4} | Jay JH. Park^{1,5}

Statistical Methods in Medical Research
2023, Vol. 32(11) 2207–2225
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RWE Study Overview

- An RWD set from Quebec Canada
 - 52,790 individuals aged 65 or older who were on statin as a prevention of future cardiovascular diseases (CVD)

Analytical approaches:

1. Using GBTM, individuals were grouped into different trajectories based on their adherence patterns
2. We applied marginal structural modelling to account for time-varying confounding
 - Inverse probability of treatment and censoring weights estimated
3. Causal effects estimated on prevention of first CVD event

RWD from Quebec on statin and cardiovascular disease (CVD)

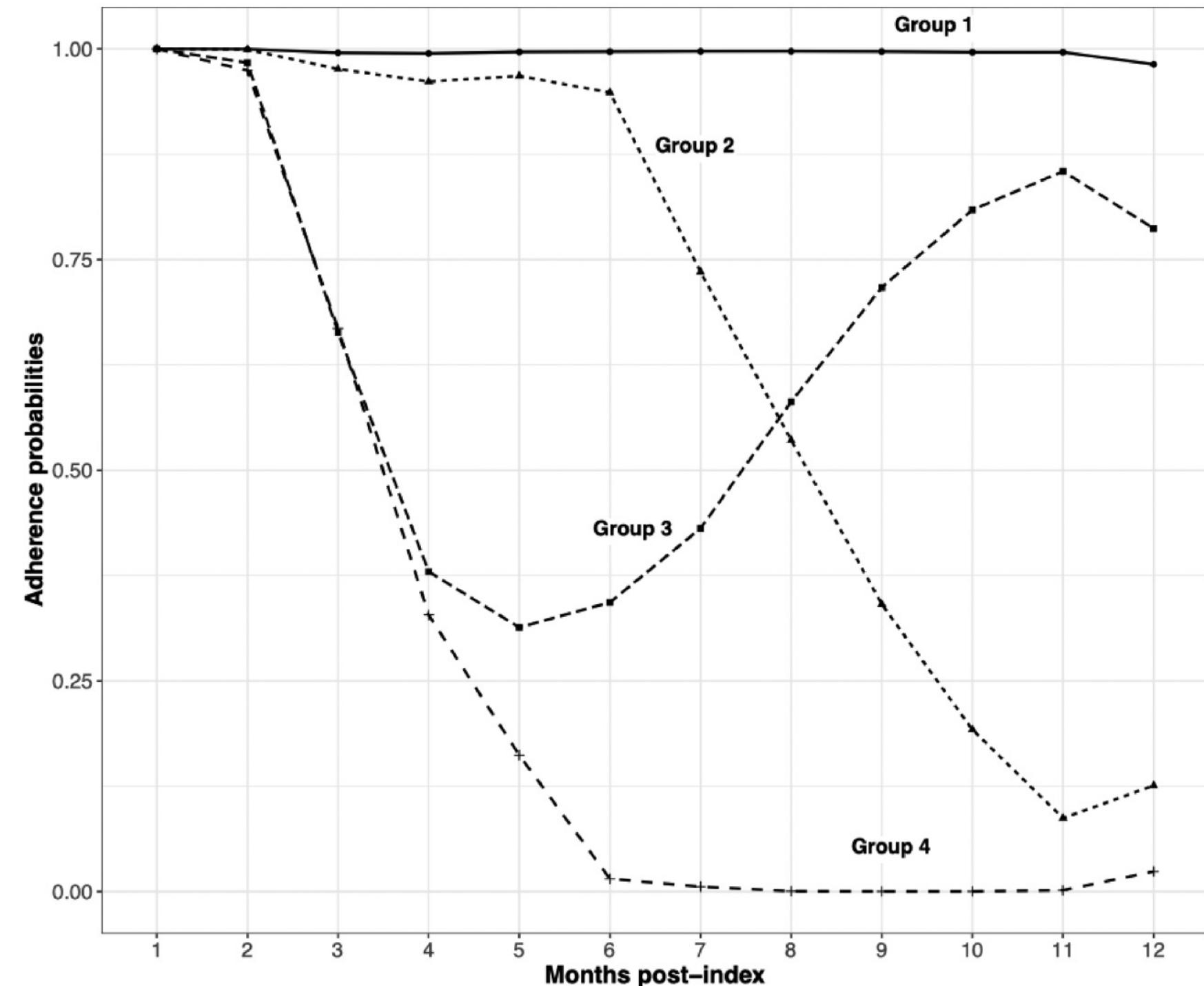
1. Application of GBTM based on statin adherence

2. Marginal structural modelling (MSM) to control for time-varying confounding

3. Causal effects of medication adherence on CVD prevention

RWD Study Overview

- Individuals were assigned to a trajectory group based on their highest conditional probability to belong to that group.
- Model fit assessed based on BIC and EIC and content expertise
 - The model with 6 trajectory groups and a quadratic polynomial form had the best fit
 - *A cubic solution with 4 trajectory groups was selected instead with stakeholder feedback*



Group 1: Nearly perfect adherence

Group 2: Steep decrease in statin use after month 6

Group 3: Drop in statin use in month 2 followed by increased use after month 5

Group 4: Lowest statin use rate; drastic drop after month 2

Characteristic	Trajectory 1 N = 40,646	Trajectory 2 N = 3801	Trajectory 3 N = 1777	Trajectory 4 N = 6566
CVD event n (%)	7596 (19)	1049 (28)	299 (17)	1669 (25)
Time to event mean (sd)	24 (15)	26 (15)	29 (13)	24 (16)
Women n (%)	21,860 (54)	2172 (57)	985 (55)	3868 (59)
Age mean (sd)	72.1 (5.5)	72.9 (6.0)	71.9 (5.1)	73.1 (6.1)
Hypertension n (%)	21,361 (53)	1919 (50)	801 (45)	3197 (49)
Chronic kidney disease n (%)	2849 (7.0)	338 (8.9)	82 (4.6)	488 (7.4)
Diabetes n (%)	7,360 (18)	716 (19)	394 (22)	1230 (19)
Comorbidity scores mean (sd)	2.06 (2.88)	2.36 (3.54)	1.43 (2.54)	2.20 (3.44)
Number of visits by a GP mean (sd)	1.18 (1.43)	1.00 (1.42)	1.25 (1.54)	1.05 (1.51)
Number of visits by a SP mean (sd)	2.9 (6.0)	2.4 (4.2)	2.9 (5.1)	2.6 (6.5)
Number of visits to an ER mean (sd)	0.30 (0.84)	0.25 (0.74)	0.32 (0.97)	0.27 (0.81)
Number of hospitalizations	0.08 (0.34)	0.06 (0.32)	0.07 (0.35)	0.06 (0.28)

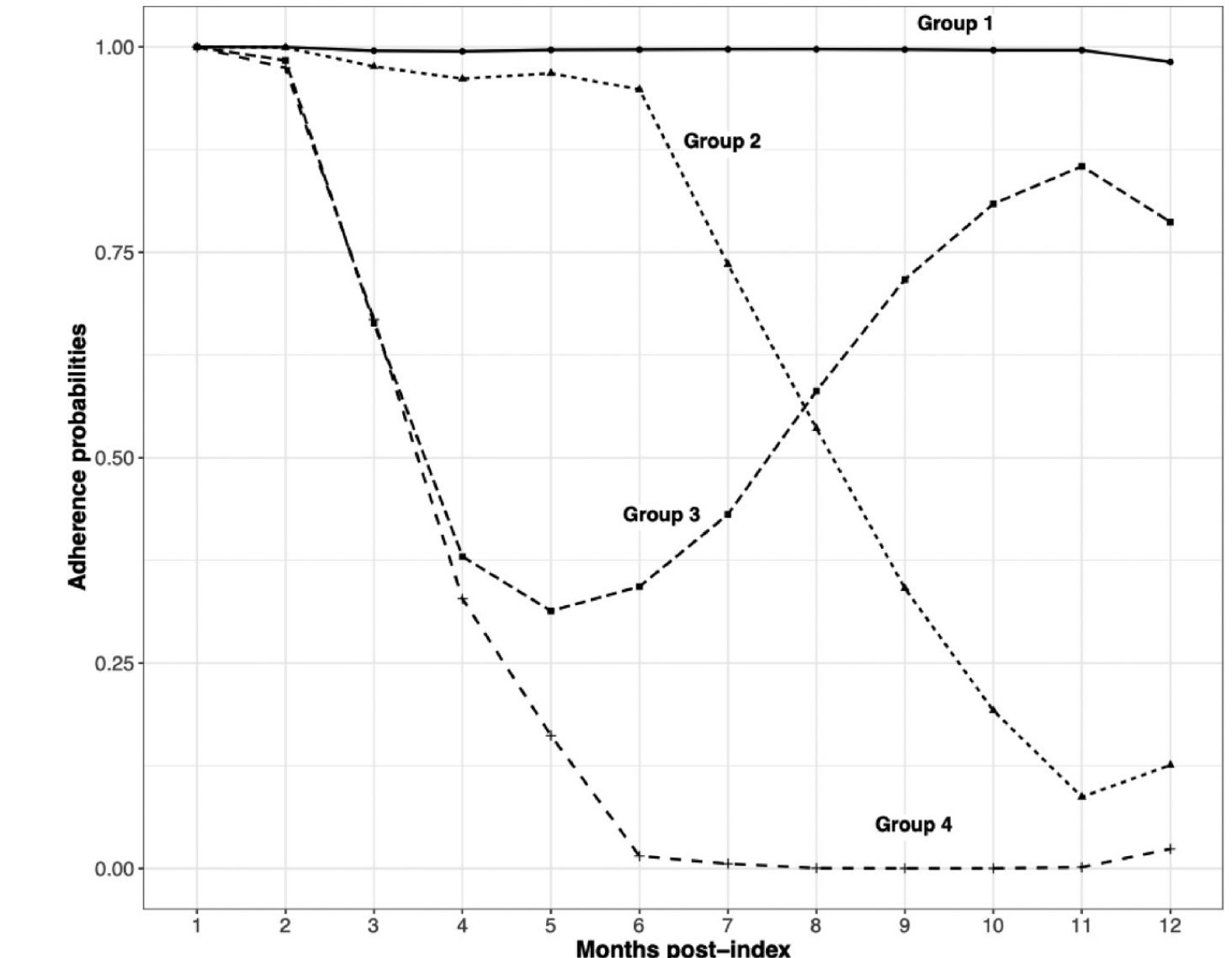
- Differential risks of CVD in different groups
- Different prevalence of hypertension, kidney disease, and co-morbidities
- To estimate the causal effects of these trajectories, we used MSM that controlled for time-varying confounding

Statin RWD Study Results

Groups	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Group 1	0.75 (0.71, 0.79)	0.70 (0.62, 0.80)
Group 2	1.04 (0.96, 1.13)	1.11 (0.91, 1.34)
Group 3	0.55 (0.49, 0.62)	0.62 (0.41, 0.73)
Group 4	Reference	Reference

Key takeaways:

- Positive comparative effects for CVD prevention seen in best adherence group (Group 1) and those that increased in use after month 5 (Group 3)
- Comparable comparative effects between Group 2 and Group 4 that had sub-optimal adherence to statin

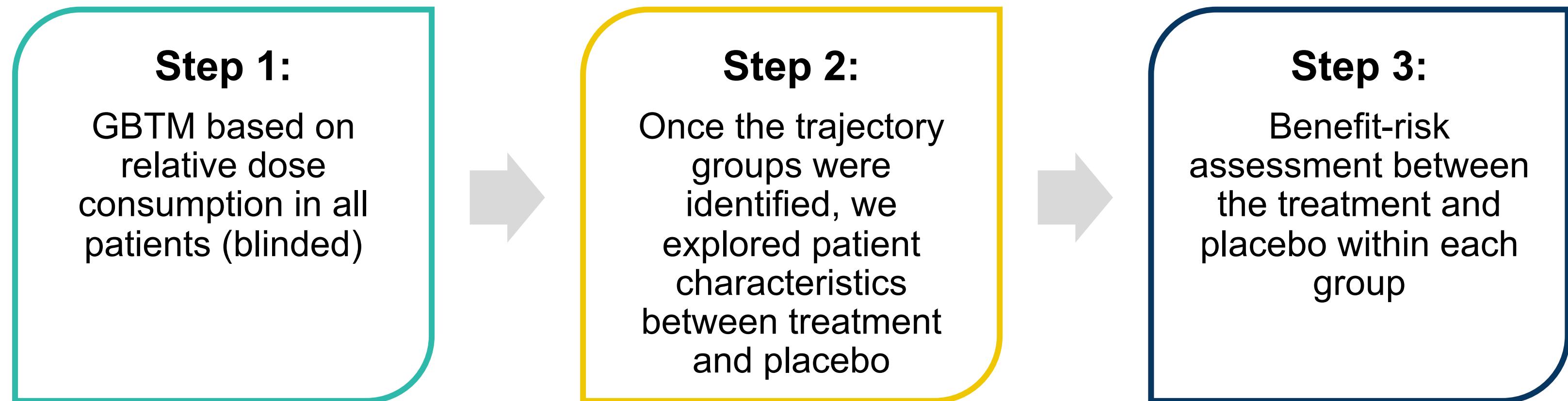


RCT Case Study Overview

- Randomized clinical trial (NCT00119613)
- Treatment administered weekly
- The relative dose to the maximum dose consumption was modelled

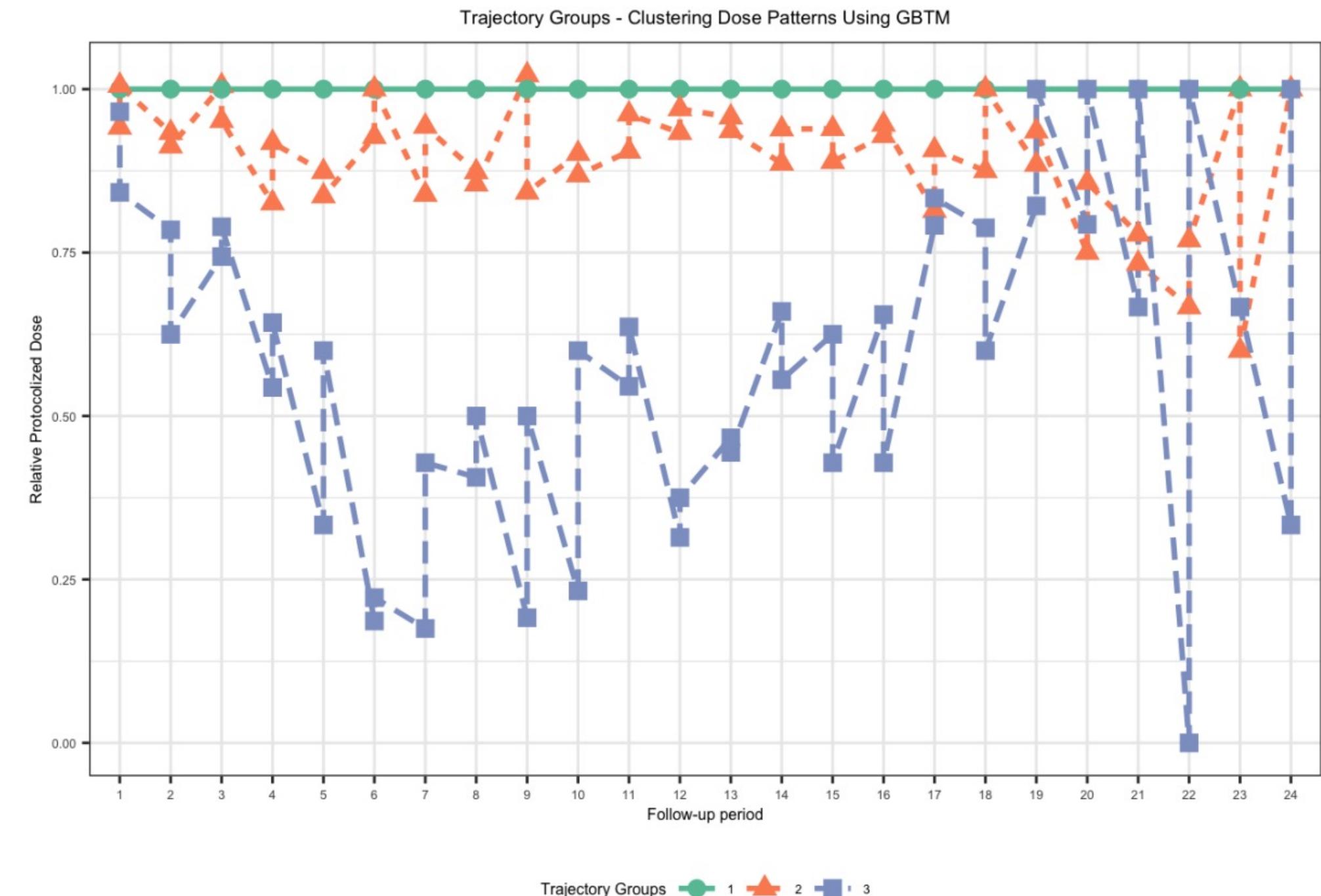
Population	6000 patients with extensive-stage small-cell lung cancer
Intervention	First-line platinum-based chemotherapy + red blood cell (RBC) stimulating agent
Comparator	First-line platinum-based chemotherapy + placebo
Outcome	hemoglobin levels and overall survival (OS)

Our Approach



Adherence Groups

- Based on their longitudinal patterns of dose consumption, we grouped all participants into three trajectory groups:
 1. Best adherence (green)
 2. Moderate adherence (orange)
 3. Poor adherence (blue)



Descriptive Statistics by Group

- A larger % of the Placebo group fell into Group 1 with the best adherence
 - Opposite trend for the Treatment group
- Group 1 had highest % of placebo-treatment patients with lower ECOG score
 - Opposite is true for the poor adherence group

Variable	Levels	Group 1: Best adherence (Total N = 248)		Group 2: Moderate adherence (Total N = 121)		Group 3: Poor adherence (Total N = 95)	
		Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Sample Size		89 (36%)	159 (64%)	63 (52%)	58 (48%)	78 (82%)	17 (18%)
Median Age		62	62	64	60	58	63
Sex	Female	34 (14%)	47 (22%)	24 (20%)	20 (17%)	26 (27%)	5 (5%)
	Male	55 (19%)	112 (45%)	39 (32%)	38 (31%)	52 (54%)	12 (13%)
Median BMI		24.5	24.6	24.5	25.5	24.1	24.1
ECOG	1	66 (27%)	131 (53%)	48 (40%)	42 (35%)	70 (74%)	10 (11%)
	2	23 (9%)	28 (11%)	15 (12%)	16 (13%)	8 (8%)	7 (7%)

Hemoglobin by Group

Variable	Group 1: Best adherence		Group 2: Moderate adherence		Group 3: Poor adherence		All groups	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Sample Size								
• N (%)*	89 (39%)	159 (68%)	63 (27%)	58 (25%)	78 (34%)	17 (7%)	230 (100%)	234 (100%)
Baseline HB								
• Mean (SD)	11.6 (1.1)	11.7 (1.0)	12.2 (1.0)	11.9 (1.0)	12.4 (1.0)	12.6 (1.1)	12.0 (1.1)	11.8 (1.1)
Δ of HB from Baseline								
• Mean (SD)	-0.95 (1.8)	-1.93 (1.7)	-1.89 (2.1)	-2.25 (2.2)	-0.69 (1.9)	-2.13 (2.5)	-1.12 (2.0)	-2.02 (1.9)
Difference in Δ of HB from Baseline	0.98 (0.52, 1.44) p < 0.001	Ref	0.36 (-0.42, 1.14) p = 0.36	Ref	1.44 (0.04, 2.85) p = 0.04	Ref	0.90 (0.54, 1.25) p < 0.001	Ref

Key takeaways:

- A significant difference for the poor adherence group but with the largest uncertainty
 - Only 17 patients in the placebo group for Group 3
- We saw convincing treatment effects in Group 1 with the best adherence

Benefit-Risk Assessment

Severe Adverse Event (Grade 3 or Greater)			
Group	Treatment	Placebo	Total
Group 1: Best adherence	74% (66/89)	57% (91/159)	63% (157/248)
Group 2: Moderate adherence	62% (39/63)	57% (33/58)	60% (72/121)
Group 3: Poor adherence	50% (39/78)	59% (10/17)	52% (49/95)
All Groups Combined	63% (144/230)	57% (134/234)	60% (278/464)

- Likely due to power issues, no differential treatment effects seen for PFS and OS (not shown here)
- In the Treatment group, we see a dose-response relationship for serious AEs with adherence
 - Highest adverse events (AE) observed in the Treatment Group with the best adherence group (Group 1 of Treated)
 - Lowest AE in the poor adherence group (Group 3 of Treated)

Reporting Guidelines, Common Misconceptions and Pitfalls

Rebecca Metcalfe, PhD

Reporting Guidelines for GBTM

- Guidelines for Reporting on Latent Trajectory Studies (**GRoLTS**) Checklist
 - 16-items that identify key considerations for GBTM and necessary details for critical appraisal of latent trajectory analyses

Teacher's Corner

The GRoLTS-Checklist: Guidelines for Reporting on Latent Trajectory Studies

Rens van de Schoot , Marit Sijbrandij, Sonja D. Winter, Sarah Depaoli & Jeroen K. Vermunt

Pages 451-467 | Published online: 11 Nov 2016

 Cite this article <https://doi.org/10.1080/10705511.2016.1247646> Full Article Figures & data References Citations Metrics Licensing Reprints & Permissions View PDF

Checklist Components

Time

Missing data & selected variables

Model building

Model selection

Transparency

TABLE 1

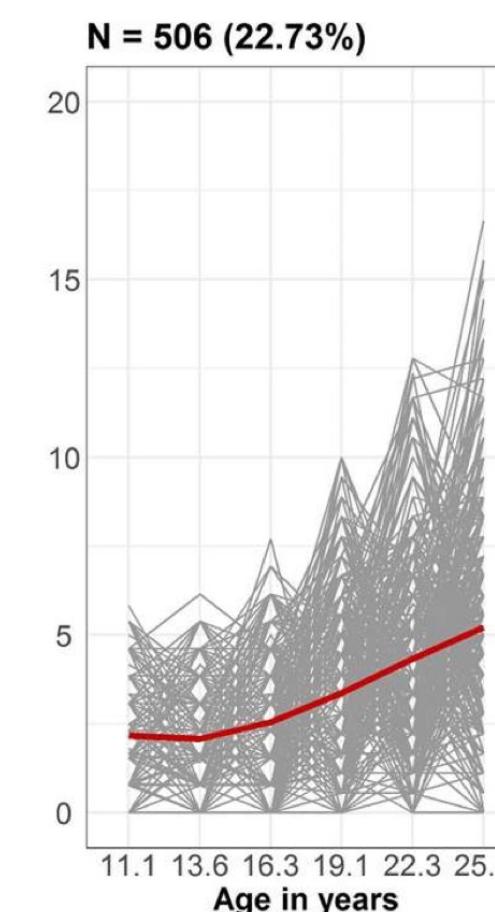
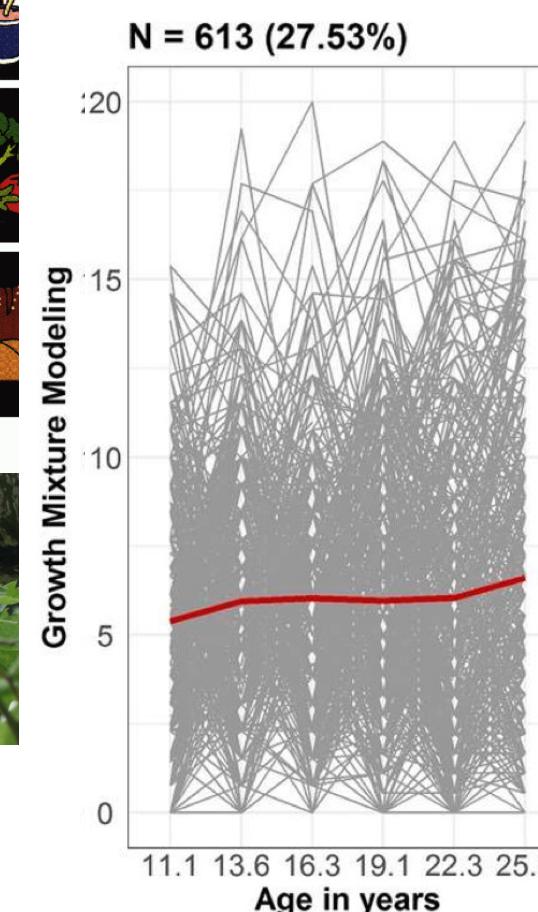
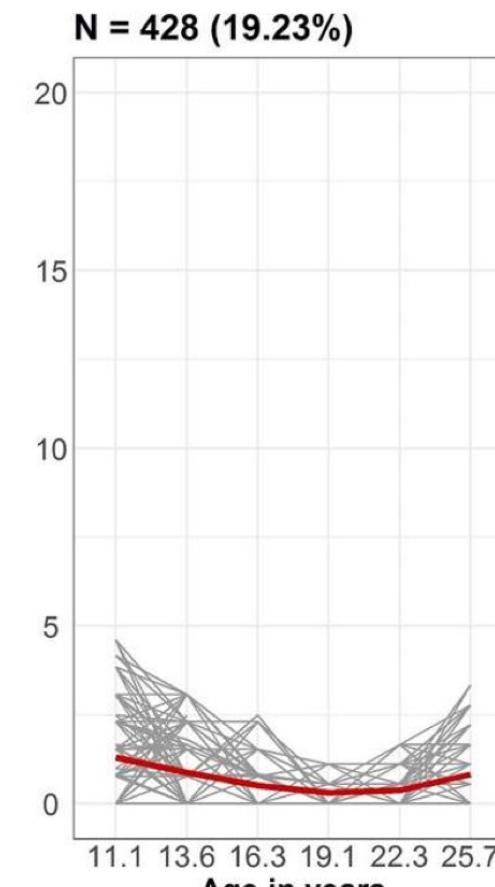
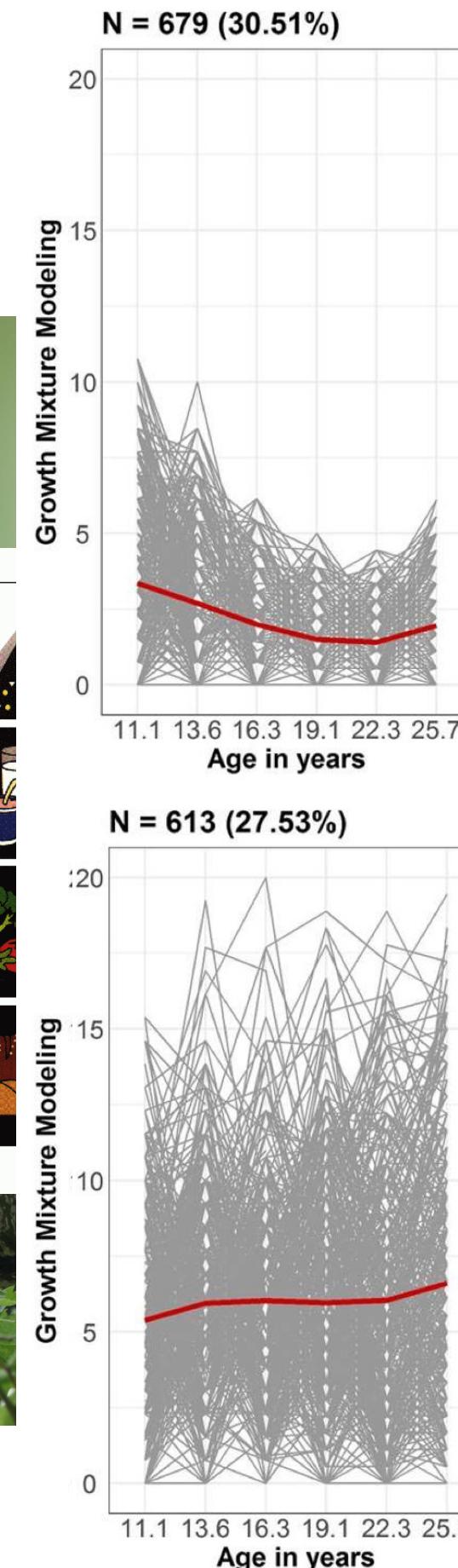
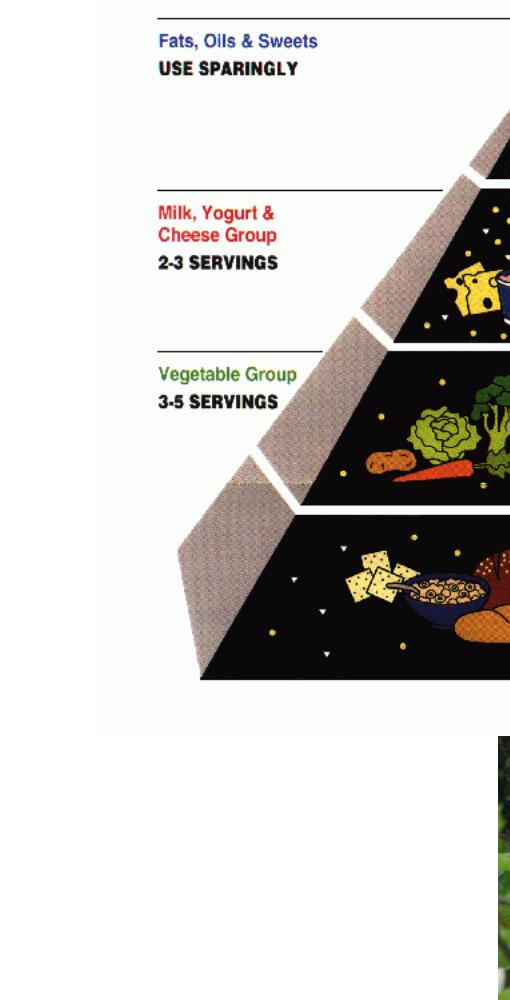
Final List of Items of the Guidelines for Reporting on Latent Trajectory Studies (GRoLTS) Checklist: Guidelines for Reporting on Latent Trajectory Studies

	<i>Checklist Item</i>	<i>Reported?</i>
1.	Is the metric of time used in the statistical model reported?	Yes/No
2.	Is information presented about the mean and variance of time within a wave?	Yes/No
3a.	Is the missing data mechanism reported?	Yes/No
3b.	Is a description provided of what variables are related to attrition/missing data?	Yes/No
3c.	Is a description provided of how missing data in the analyses were dealt with?	Yes/No
4.	Is information about the distribution of the observed variables included?	Yes/No
5.	Is the software mentioned?	Yes/No
6a.	Are alternative specifications of within-class heterogeneity considered (e.g., LGCA vs. LGMM) and clearly documented? If not, was sufficient justification provided as to eliminate certain specifications from consideration?	Yes/No
6b.	Are alternative specifications of the between-class differences in variance–covariance matrix structure considered and clearly documented? If not, was sufficient justification provided as to eliminate certain specifications from consideration?	Yes/No
7.	Are alternative shape/functional forms of the trajectories described?	Yes/No
8.	If covariates have been used, can analyses still be replicated?	Yes/No
9.	Is information reported about the number of random start values and final iterations included?	Yes/No
10.	Are the model comparison (and selection) tools described from a statistical perspective?	Yes/No
11.	Are the total number of fitted models reported, including a one-class solution?	Yes/No
12.	Are the number of cases per class reported for each model (absolute sample size, or proportion)?	Yes/No
13.	If classification of cases in a trajectory is the goal, is entropy reported?	Yes/No
14a.	Is a plot included with the estimated mean trajectories of the final solution?	Yes/No
14b.	Are plots included with the estimated mean trajectories for each model?	Yes/No
14c.	Is a plot included of the combination of estimated means of the final model and the observed individual trajectories split out for each latent class?	Yes/No
15.	Are characteristics of the final class solution numerically described (i.e., means, <i>SD/SE</i> , <i>n</i> , CI, etc.)?	Yes/No
16.	Are the syntax files available (either in the appendix, supplementary materials, or from the authors)?	Yes/No

Note. LGCA = latent class growth analysis; LGMM = latent growth mixture modeling.

Common Misconceptions

- Individuals actually belong to a trajectory group
- The number of trajectory groups is fixed and real
- Trajectories of individuals in a group follow the group-level trajectory



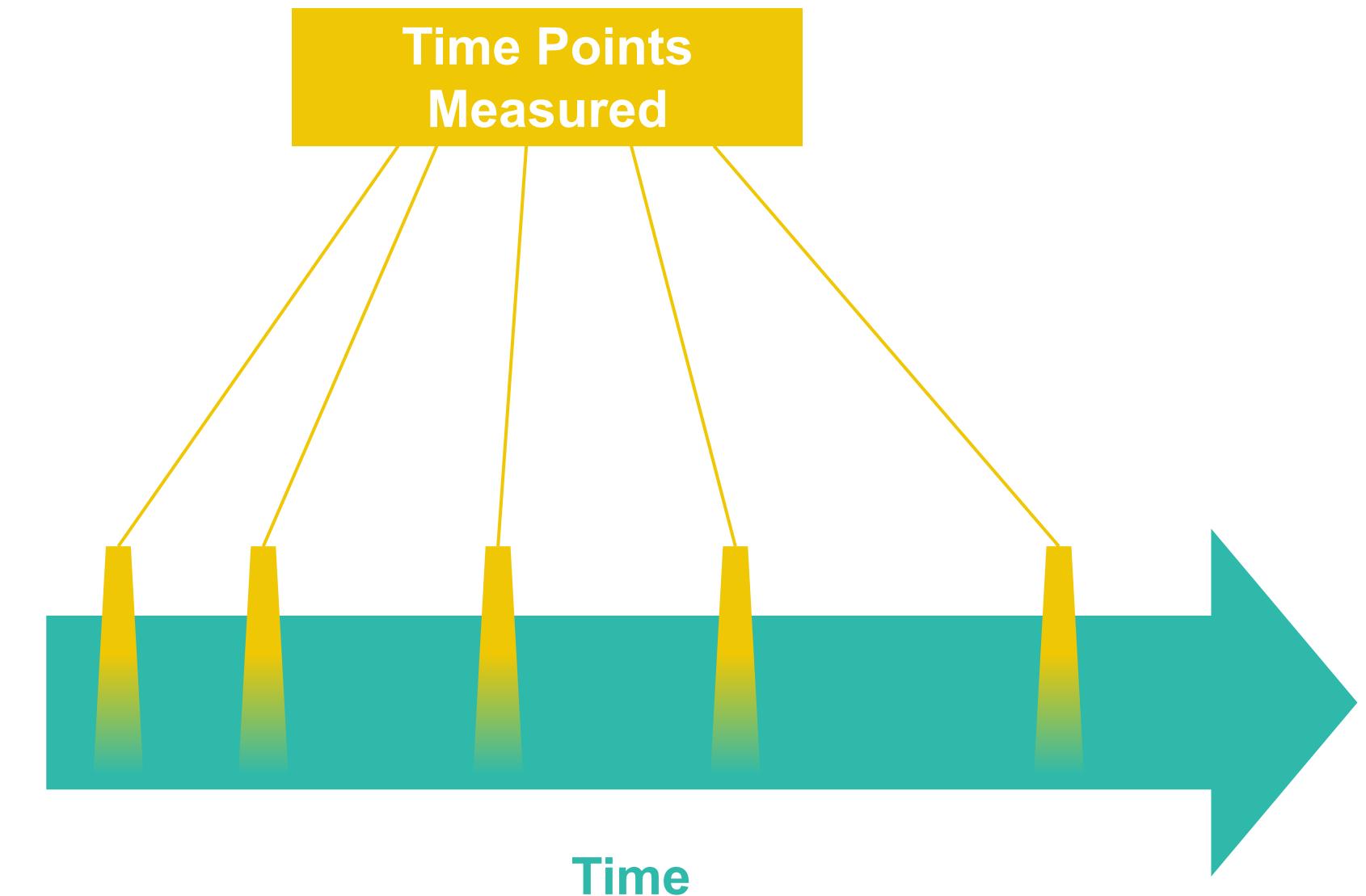
dairy



Time: The Major Pitfall

Time in GBTM

- Any observational study is only sampling some of the many possible time points that may provide a representation of a larger process
- All findings in longitudinal studies are bounded by the start and endpoints of analyses, **the selection of temporal intervals, and by the number of time points in analyses.**



Standardized vs. Unstandardized Time

- Most studies examine unstandardized time
 - i.e., aim to assess people at 1 month, 3 months and 6 months, but actual data collection falls close to those dates but not exactly on those dates
- Temptation to treat unstandardized time as standardized because it is “close enough”
- This introduces bias

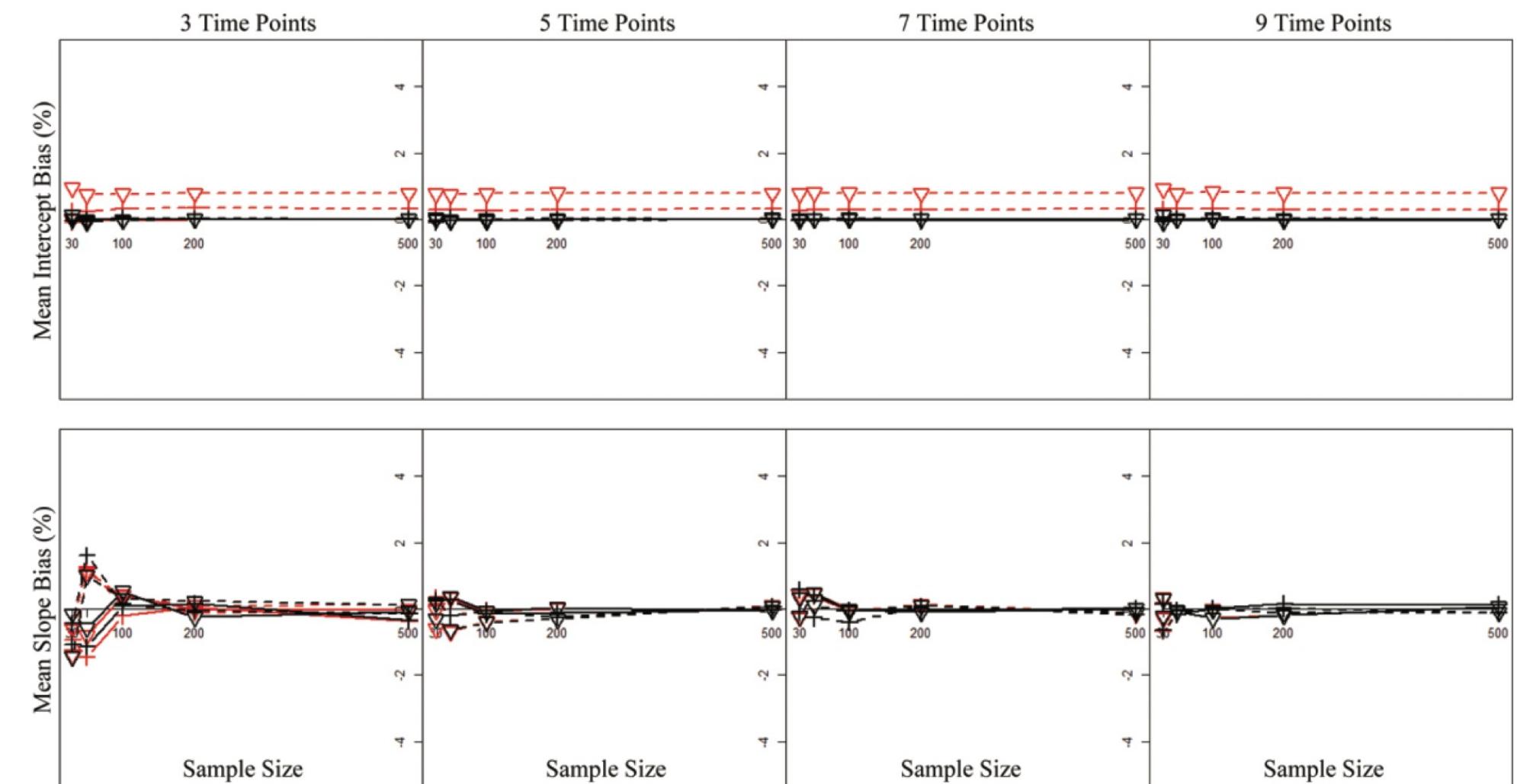
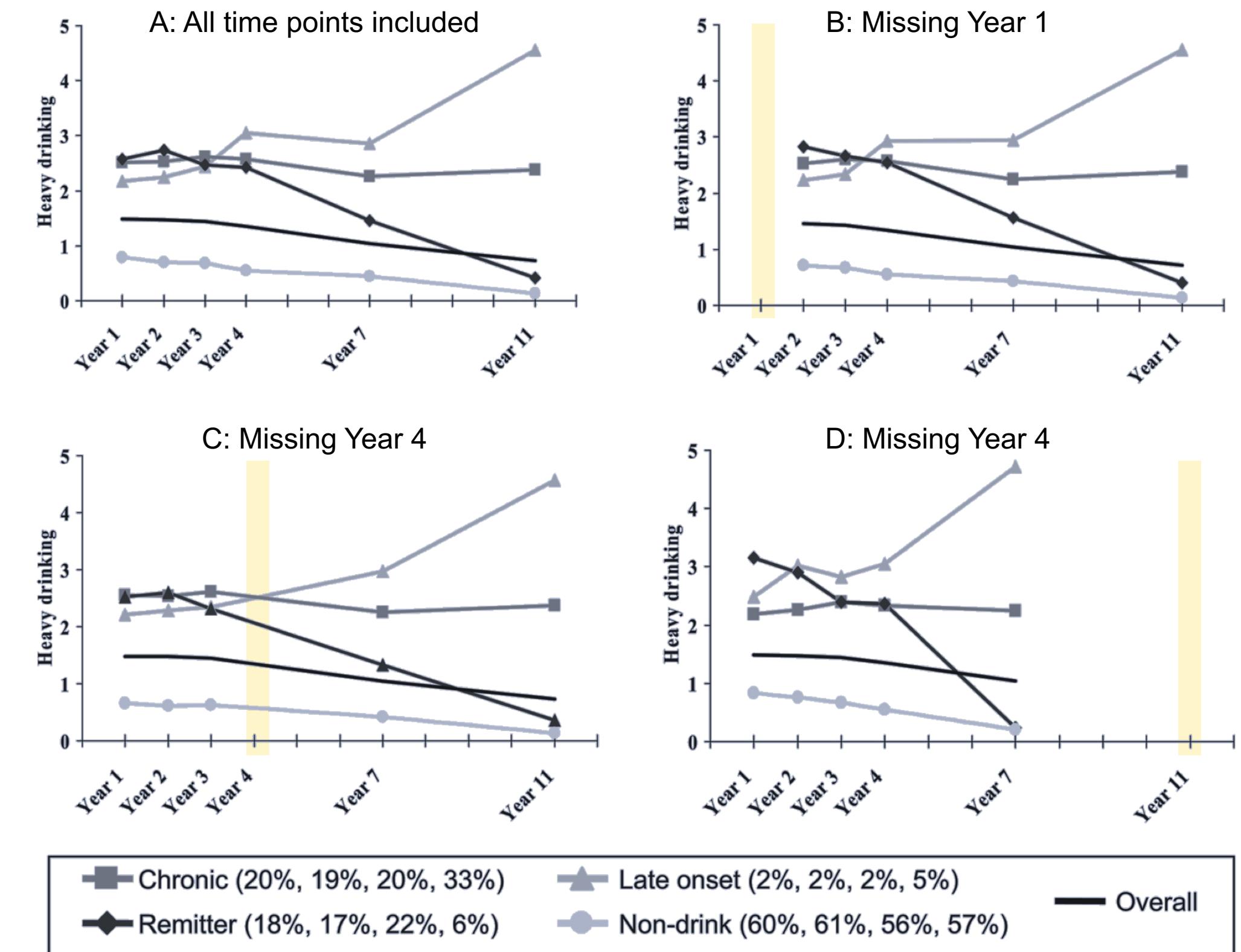


Figure 2. Mean intercept and mean slope bias (in %) as a function of sample size (x-axis), type of analysis (black line = time-structured, red line = time-unstructured), distribution of time points (solid line = not skewed, dashed line = skewed), magnitude of individual differences in time points (+ = 0.4, ▽ = 1.0), and number of time points (columns), when the slope is nonzero. (Color online only.)

Coulombe et al., 2016

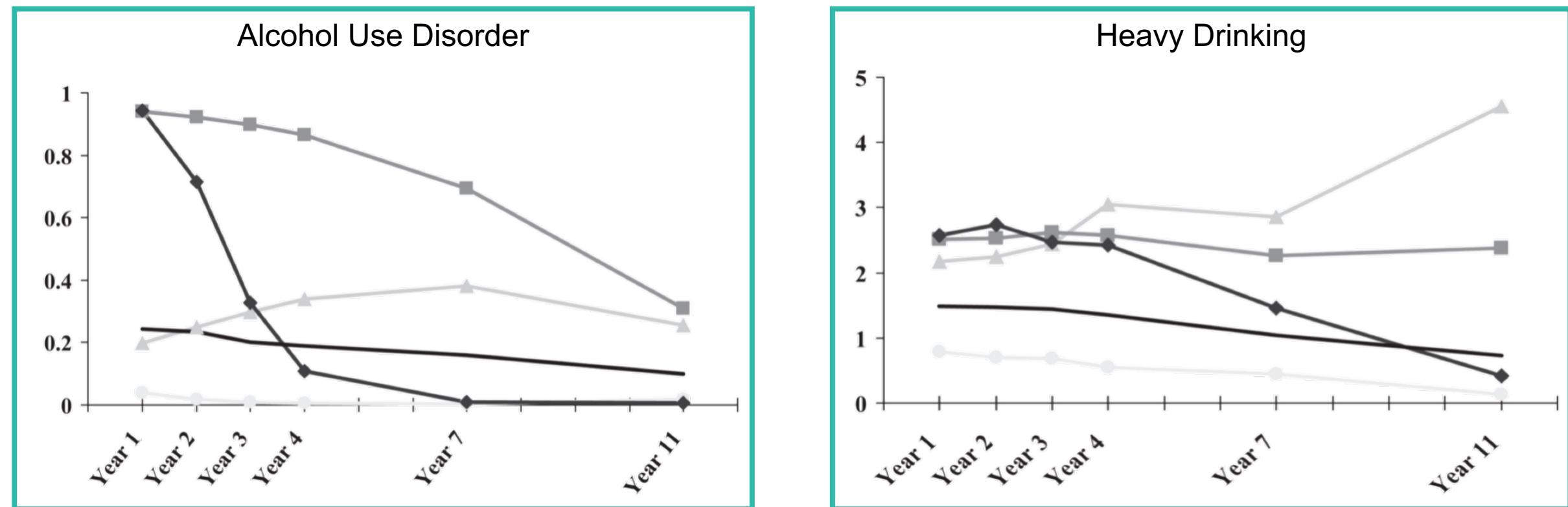
Time Points Impact Trajectories



Jackson & Sher, 2006

Additional Considerations

Outcome Selection Impacts Trajectories



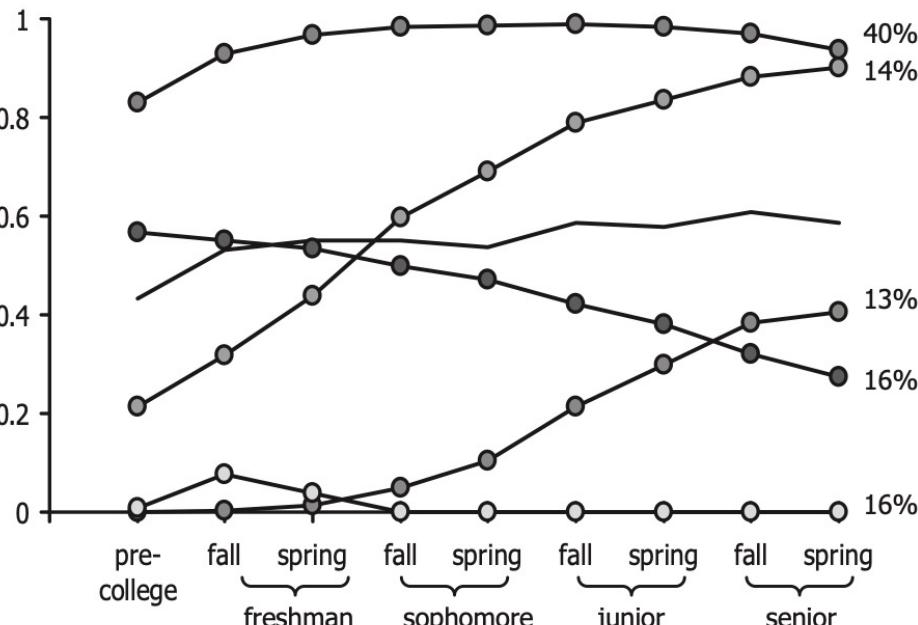
- Jackson & Sher (2006) collected two highly-related measures of problematic alcohol use from one sample across 11 years
 - Alcohol use disorder
 - Heavy drinking
- They compared trajectories identified for each measure
- Both outcomes identified 5 trajectories but the trajectory patterns differed substantially

Cut-points Impact Trajectories

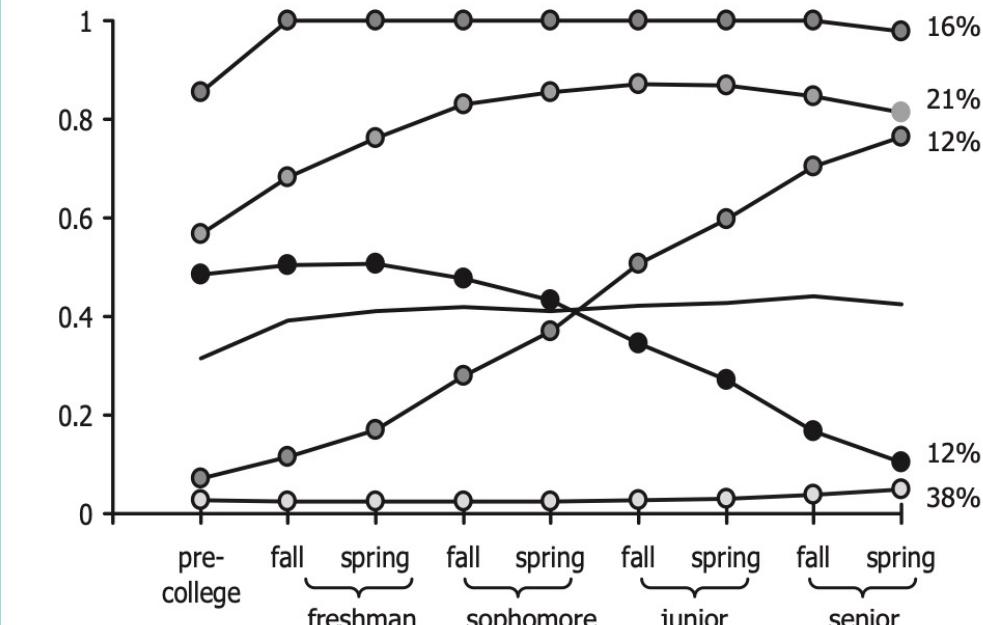
Jackson and Sher (2008) compared the impact of cut-point on identified trajectories.

They compared different definitions of problem drinking within the same data set.

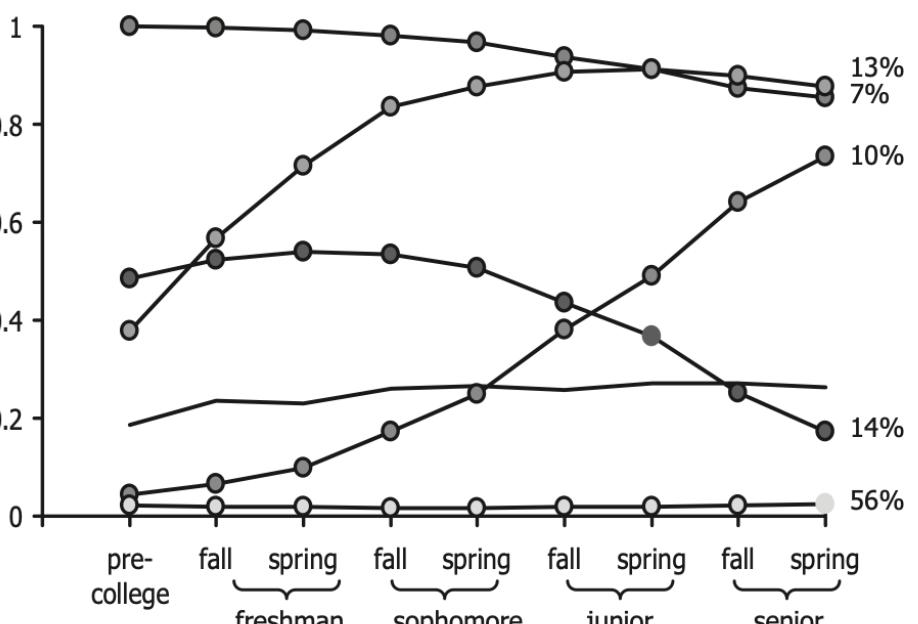
A: 5+ drinks in past 30 days



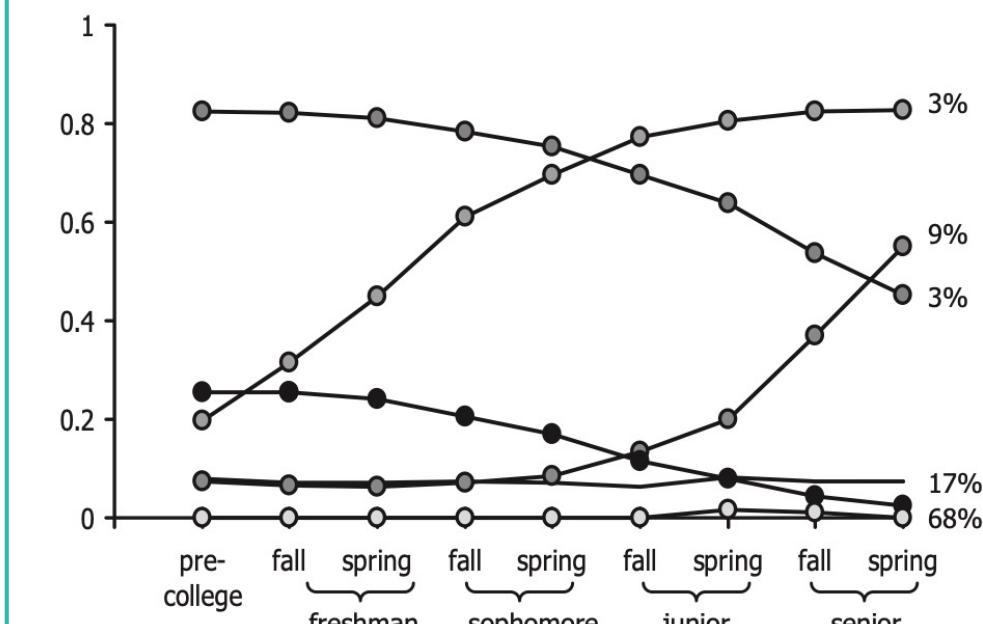
5+ drinks 2-3 times in the past 30 days



5+ drinks 1-2 times a week in the past 30 days

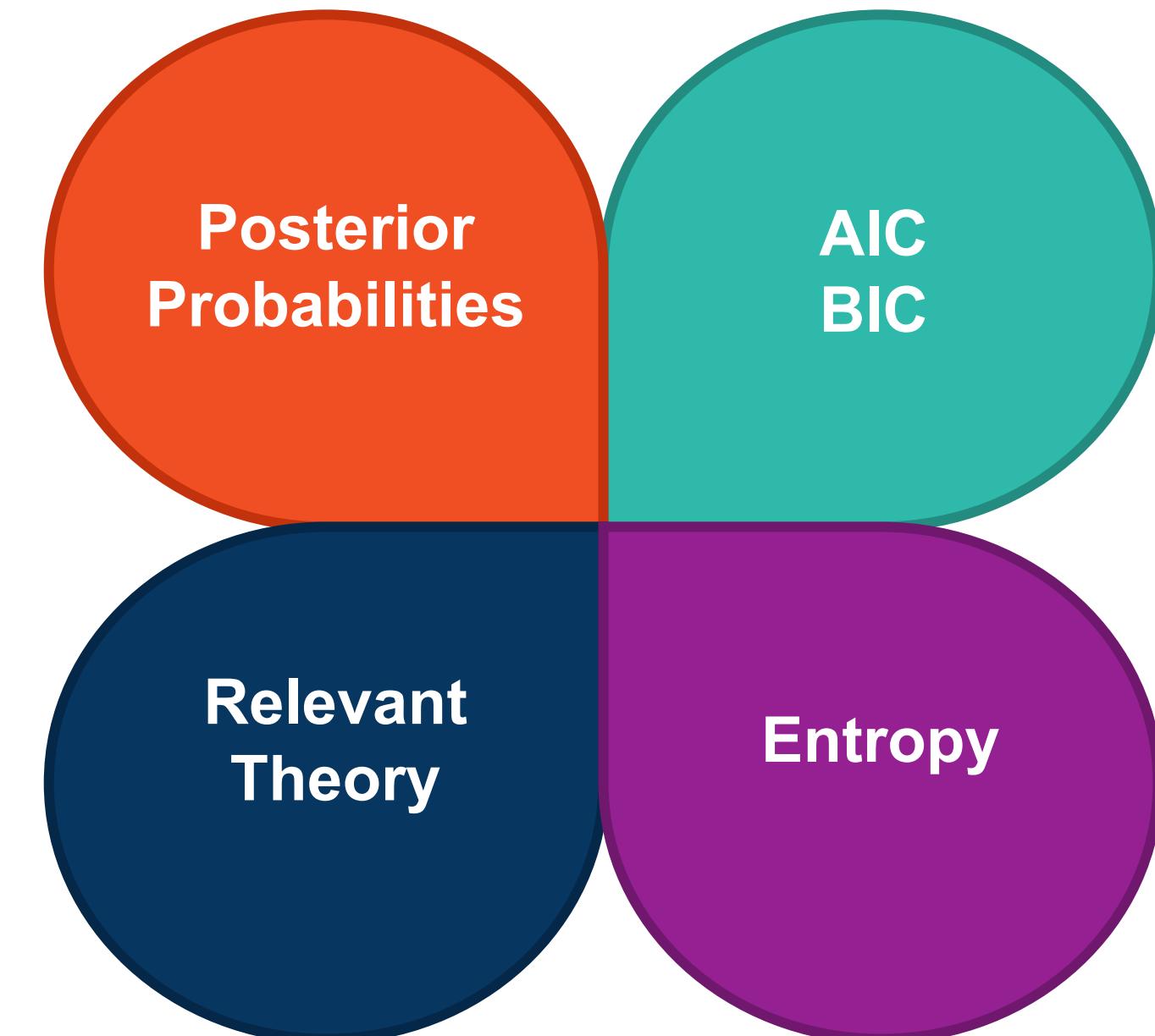


5+ drinks 3 times a week in the past 30 days



Solutions

- Consider multiple criteria in model selection
- Cross-validate your model by
 - Running the model in different but similar datasets
 - Comparing the model to what has been found in other studies
- Interpretation aids
 - Existing theory
 - Qualitative work to complement and contextualize identified trajectories



Summary and Conclusion

Summary

- Medication adherence, a key determinant of drug responses, follows dynamic patterns that are difficult to adequately capture with deterministic adherence measures, such as PDC
- GTBM is an attractive approach to examine and communicate complex patterns of medication adherence but it is very sensitive to data collection considerations
- As seen in our case studies, GTBM can be applied to study medication adherence in real-world setting and clinical trials
- Our R codes can be seen in our GitHub repo:



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Thank You!

Please reach out with any questions and comments to:

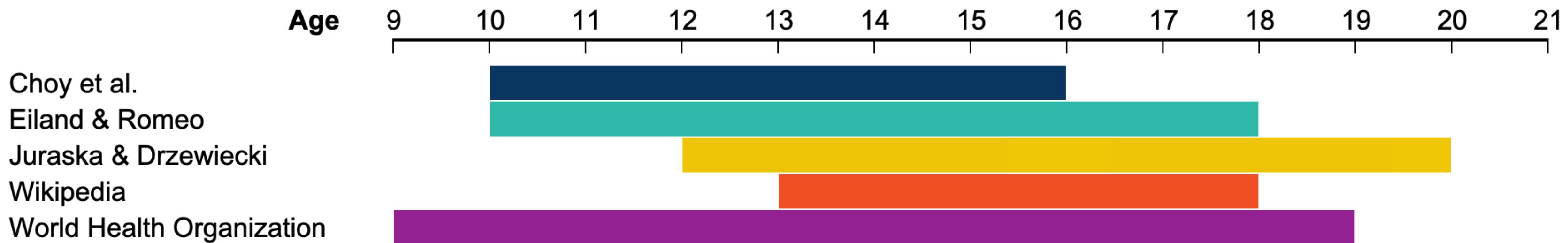
jay@coreclinicalsciences.com



Jay Park, PhD
Scientific Lead

Jingle Fallacy

When people assume that studies cover similar time periods because they use the same label (such as “adolescence”) but the studies actually measure different time spans with different time points at different intervals



GBTM Model Fit to Simulated Data

Comparison of True Groups and GBTM Groups

Groups	True Group 1	True Group 2	True Group 3
GBTM Group 1	0	0	70
GBTM Group 2	107	1	0
GBTM Group 3	3	19	0