Applying Group-Based Trajectory Modeling in Health Outcomes Research

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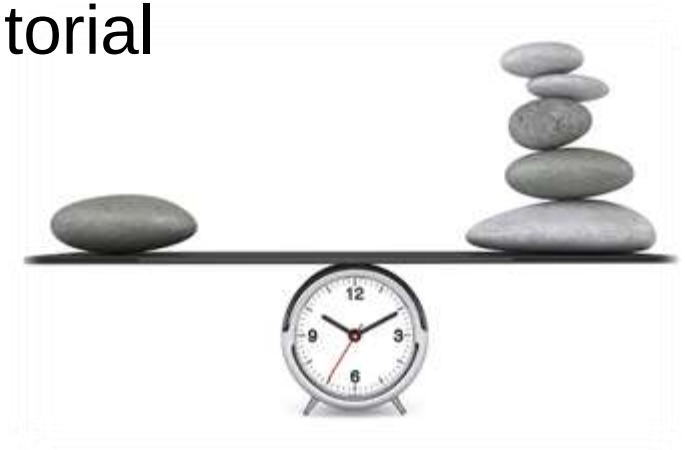
- PhRMA Foundation Research Starter Award
- No conflict of interests

Learning Objectives

- Overview the concept, capacities, and applications of group-based trajectory models (GBTM)
- Describe the key framework of conducting group-based trajectory models
- Understand the basic functions of group-based trajectory models using Stata
- Discuss the extensions and challenges of using GBTM

Disclaimer

- Learning everything about GBTM (even introduction-level) is too much for a 2-hour workshop
- Focus on concepts, applications and basic STATA tutorial
- Examples and emphasized focus on health and pharmaceutical outcomes related topics
- Omission is necessary in order to focus on the most important topics



Outline

- I. Overview of basic GBTM concepts
- II. Applications in health and pharmaceutical outcomes research
- III. Basic GBTM Methods with STATA tutorials
- IV. Extensions and challenges of using GBTM

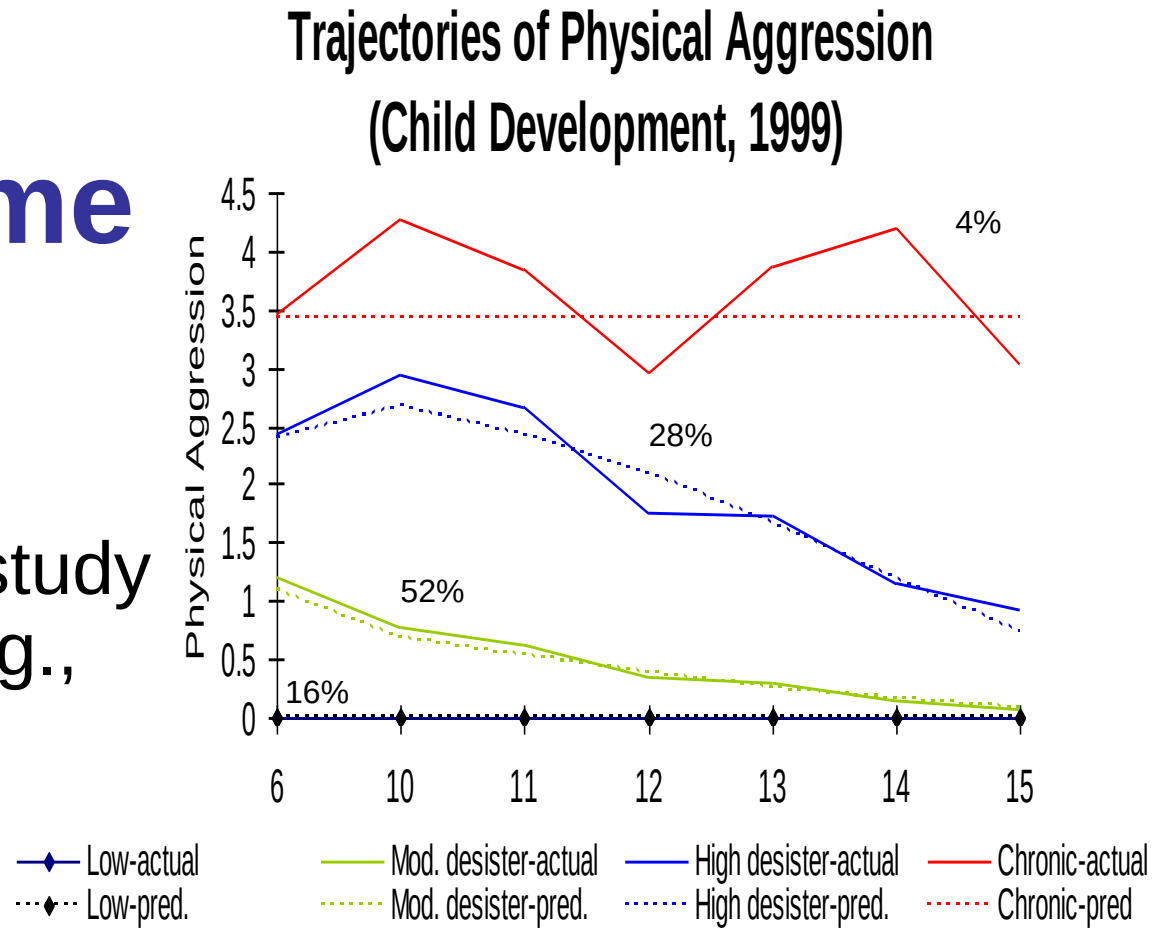
At this point, you probably have many questions….

- How do you select the number of groups/trajectories? How do you evaluate model adequacy?
- How do you profile or describe group members?
- Can you add time-invariant covariates to the trajectory itself?
- Can you add time-varying covariates to the trajectory itself?
- Can you describe two or more behaviors/outcomes at the same time?
- What are differences between different methods to develop trajectory groups?

What is a trajectory?

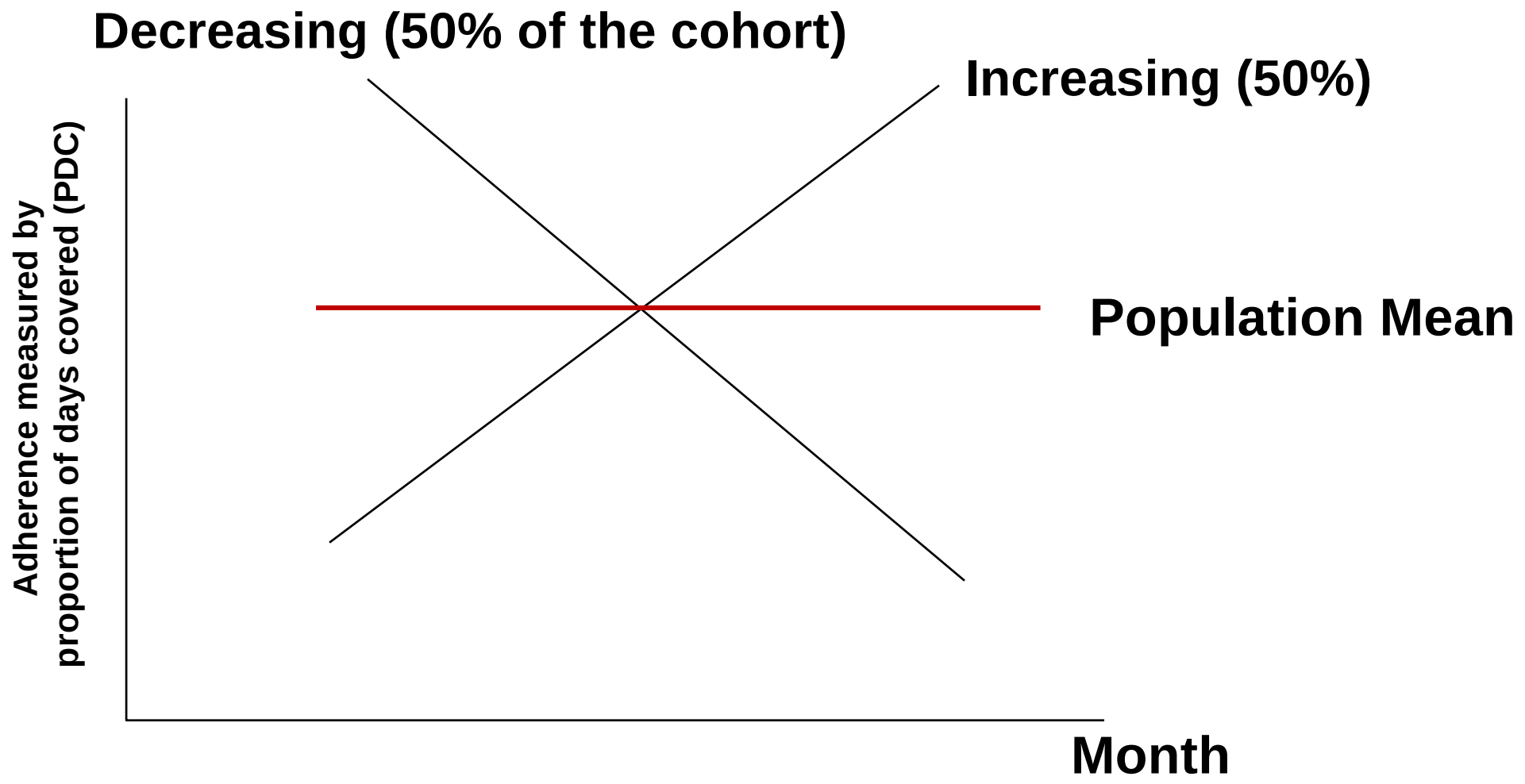
A trajectory is "the evolution of an outcome over age or time."

- GBTM was originally developed to study criminology and social behaviors (e.g., Montreal data in Nagin's textbook)



Nagin. 2005. Group-Based Modeling of Development, Harvard University Press

An example where population-based average analysis fails



Motivations for using GBTM

- Test taxonomic theories
- Identify distinct development or behavioral paths from complex longitudinal data
- Provide more person-centered methods of analysis
- Summarize data with more transparency and visualized outputs

Nagin. 2005. Group-Based Modeling of Development, Harvard University Press

Important capabilities of GBTM

- **Account for the dynamic outcome change over time**
  - Medication utilization pattern changes can result from clinician's decision, patient non-adherence, payer restrictions
- **Identify differential patterns of individual change**
  - Poorly identified by single annual adherence measure
- **Characterize subgroups more likely to follow certain trajectories**
  - Rather than arbitrarily assume or assign individuals to certain groups
  - Capable to estimate the proportion of the population following each trajectory
- **Use groups to approximate an unknown distribution**
  - Non-parametric or semi-parametric assumptions to allow flexibility

1. Nagin DS. Group-Based Modeling of Development. Harvard University Press; 2005
2. Franklin JM. Med Care. 2013; 51:789-96 3. Modi AC. JAMA 2011;305:1669-76

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Example 1

ADDICTION

SSA SOCIETY FOR THE STUDY OF ADDICTION

RESEARCH REPORT

doi:10.1111/add.13270

Association between Trajectories of Buprenorphine Treatment and Emergency Department and In-patient Utilization

Wei-Hsuan Lo-Ciganic[1,2], Walid F. Gellad[2,3,4], Adam J. Gordon[2,3,4], Gerald Cochran[2,5], Michael A. Zemaitis[2,6], Terri Cathers[7], David Kelley[7] & Julie M. Donohue[2,8]

More details, see Lo-Ciganic et al. Addiction 2016; 111(5):892-902.

Rationale, Scientific Question & Methods

Rationale

- Little is known about current treatment patterns of buprenorphine for opioid use disorder.

Question

- Is there a specific trajectory of buprenorphine use associated with adverse clinical outcomes?

Methods

- A retrospective cohort study using 2007-2011 Pennsylvania Medicaid claims data

10,945 beneficiaries aged 18-64, non-dual eligible for Medicare who initiated buprenorphine fills

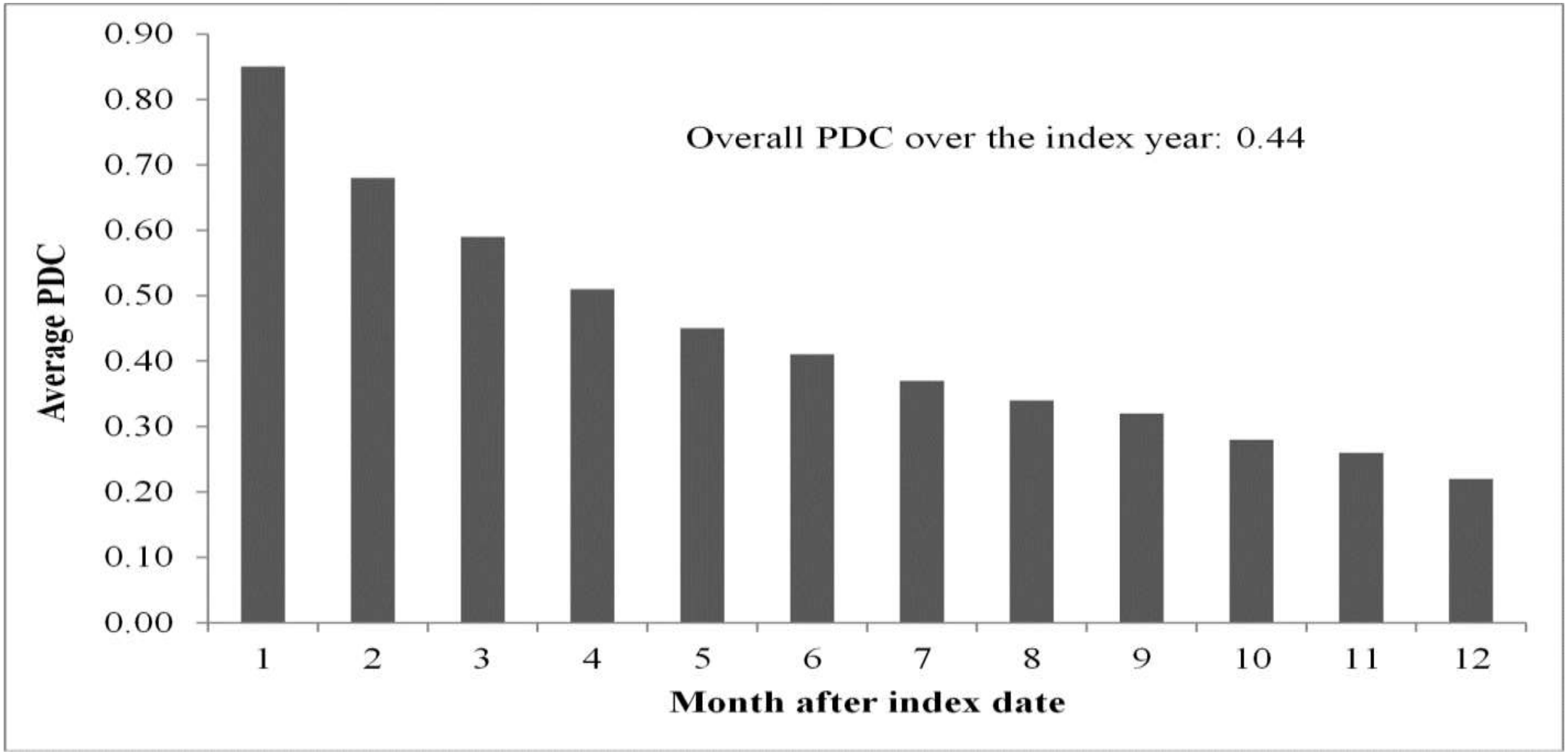
Exposure: (1) calculated interval-based **monthly proportion of days covered (PDC) of buprenorphine** for 1 year, and (2) used GBTM to identify buprenorphine trajectories

Outcomes: (1) time to first all-cause hospitalization, and (2) time to first emergency department visit

Multivariable Cox proportional hazard models, adjusting for sociodemographics, health status and provider-level factors

Lo-Ciganic et al. Addiction 2016; 111(5):892-902.

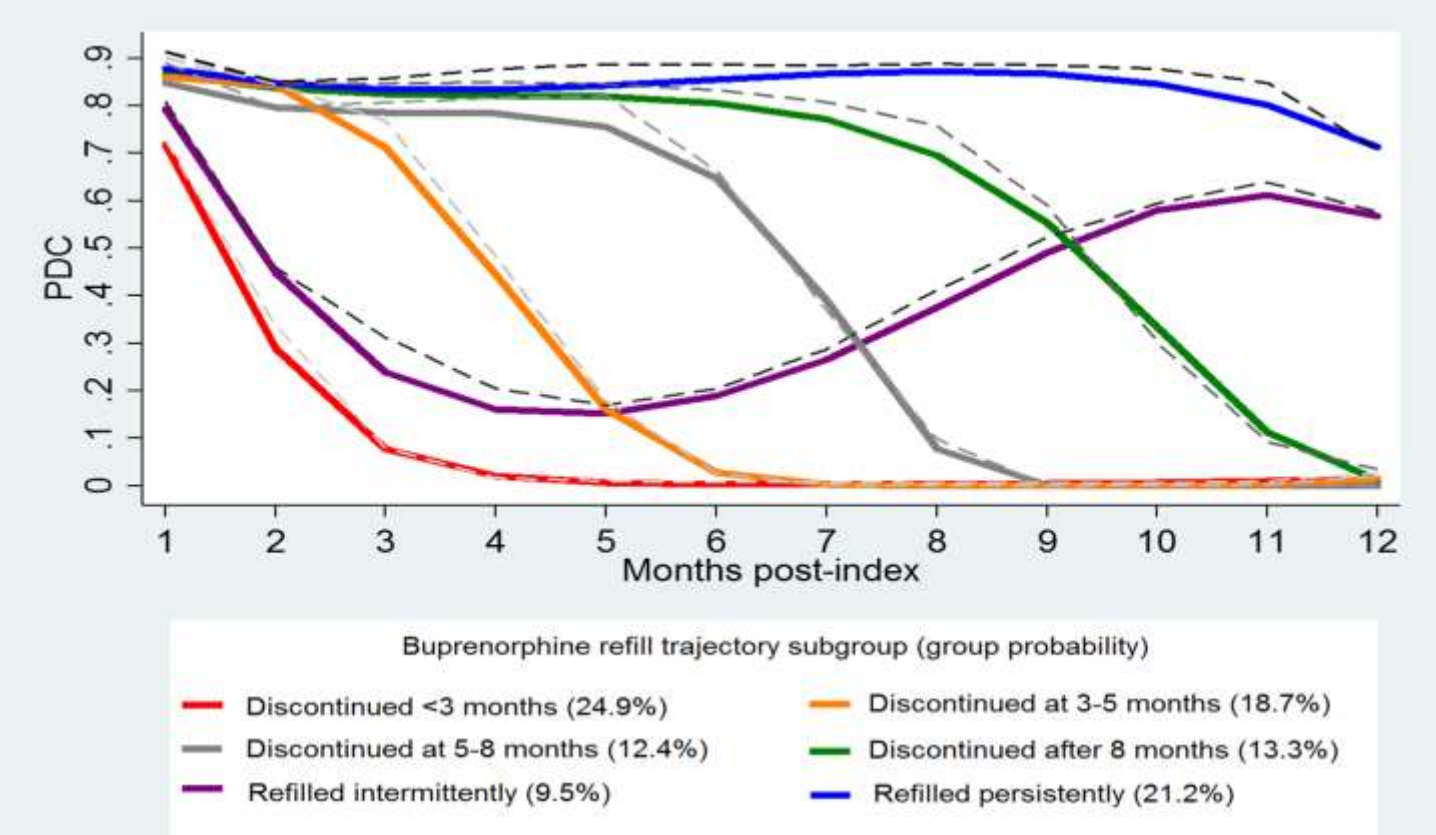
Overall PDC among Enrollees with Buprenorphine Prescriptions



Lo-Ciganic et al. Addiction 2016; 111(5):892-902.

Example 1

Association between Trajectories of Buprenorphine Treatment and Emergency Department and inpatient Utilization



All cause hospitalization: compared to those who discontinued at 3-5 months

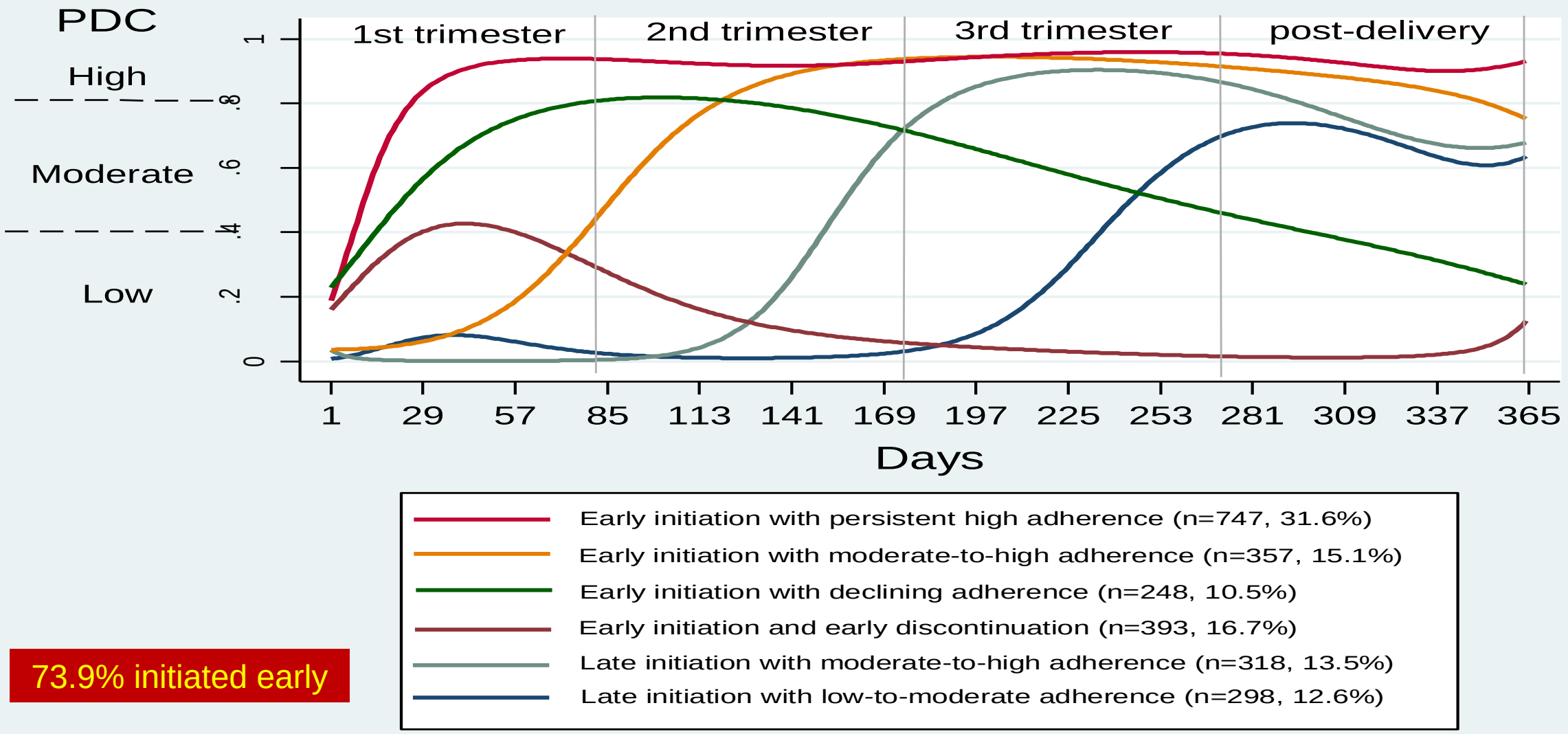
- **Refilled persistently: 20% lower risk (HR=0.80, 95% CI: 0.68-0.94)**

ED visits: compared to those who discontinued at 3-5 months

- **Refilled persistently: 15% lower risk (HR=0.85, 95% CI: 0.77-0.94)**
- **Refilled intermittently: 21% higher risk (HR=1.21, 95% CI: 1.07-1.36)**

More details, see Lo-Ciganic et al. Addiction 2016; 111(5):892-902.

Example 2 Buprenorphine Trajectories among Pregnant Women with Opioid User Disorder

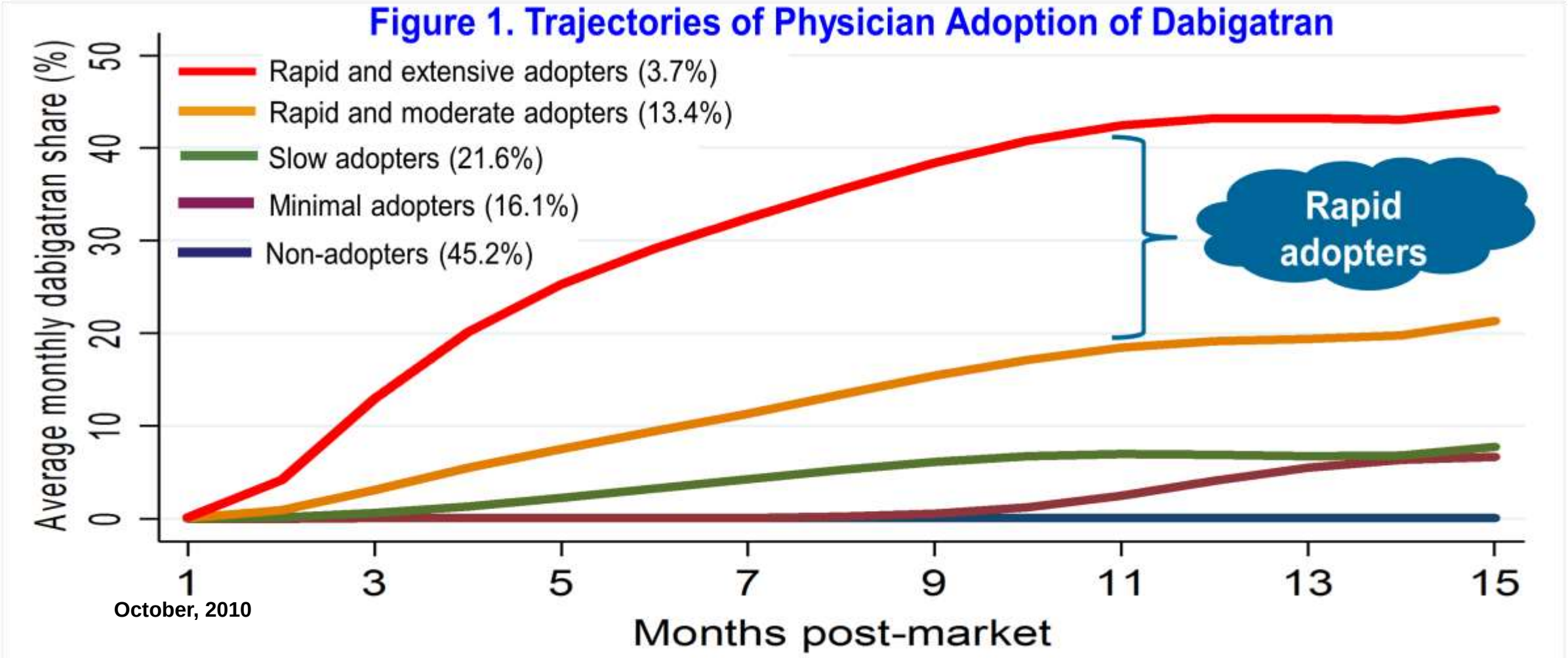


73.9% initiated early

Example 3

Who were the Early Adopters of Dabigatan? An Application of Group-based Trajectory Models

Lo-Ciganic et al. Med Care. 2016 Jul;54(7):725-32.



Example 4

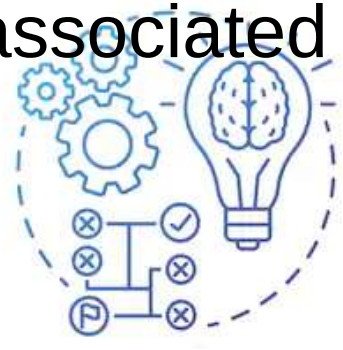
More details, see ICPE 2020 September 14 oral presentation (manuscript submitted)

Rationale and Scientific Question

➢Rationale:

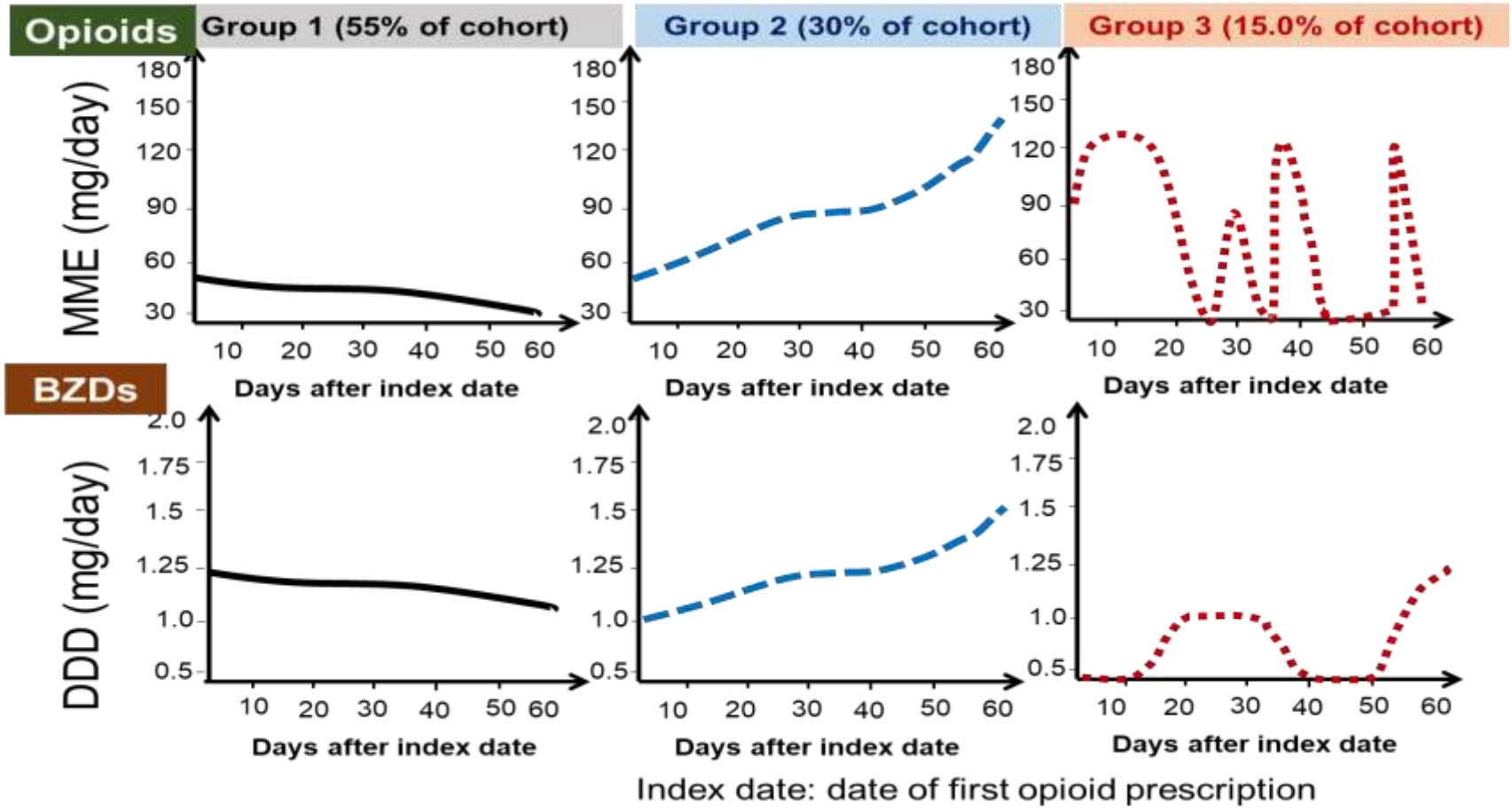
- Concurrent opioid and benzodiazepine (OPI-BZD) use continues to rise despite clinical guidelines and US FDA black box warnings opposing such use.
- Compared with younger adults, older adults have a greater prevalence of anxiety, insomnia and pain, and are 3 times more likely to be prescribed OPIs and BZDs
- The definitions of concurrent use vary substantially in the literature and have focused on arbitrary thresholds of duration (e.g., ≥1 day overlap) or dose alone.
- Little is known about OPI-BZD dose and duration patterns most associated with OPI overdose risk.

➢**Question:** What distinct dosing profiles of OPI-BZD use are associated with higher opioid overdose risk in Medicare?



Group-based Multi-Trajectory Models

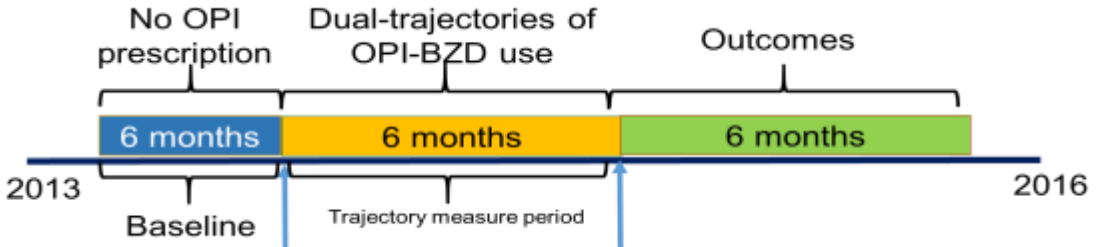
- Advantage of group-based multi-trajectory models
  - Capture dynamic OPI and BZD dose changes simultaneously over time



1. Nagin DS et al. Stat Methods Med Res 2018;27:2015–23;
2. Zhou L et al. Addiction. 2020 Jul 10. doi: 10.1111/add.15189.

Methods: study design and cohort

- **A retrospective cohort study using a 5% national sample of Medicare claims data (2013-2016)**



Censored: (1) switch to Advantage plan, (2) death, or (3) without outcome within 6 months following the 6-month trajectory period.

- **Study cohort: 37,818** met the following inclusion/exclusion criteria
  - Had ≥1 prescription fill for non-injectable, non-buprenorphine (for opioid use disorder) OPI or BZD
  - Excluded:
    - ❑ Had a cancer diagnosis, were in hospice care or enrolled in Medicare Advantage plans
    - ❑ Did not have continuous enrollment 6 months prior to and after initiating OPIs
    - ❑ Had opioid or benzodiazepine overdose 6 months prior to and after initiating OPIs
    - ❑ Used only BZDs
    - ❑ Filled only 1 OPI or BZD prescription, or with <15 days of OPI or BZD supply during the 6-month trajectory measurement period (Pharmacy Quality Alliance criteria)

Methods: Statistical Analysis

➢ Among 37,818 eligible Medicare beneficiaries

Step 1: Calculate average daily **morphine milligram equivalent (MME) for OPIs** and **diazepam milligram equivalent (DME) for BZDs** in the 6 months after initiating OPIs

Step 2: Identify distinct OPI-BZD dose and duration trajectories using **group-based multi-trajectory model**

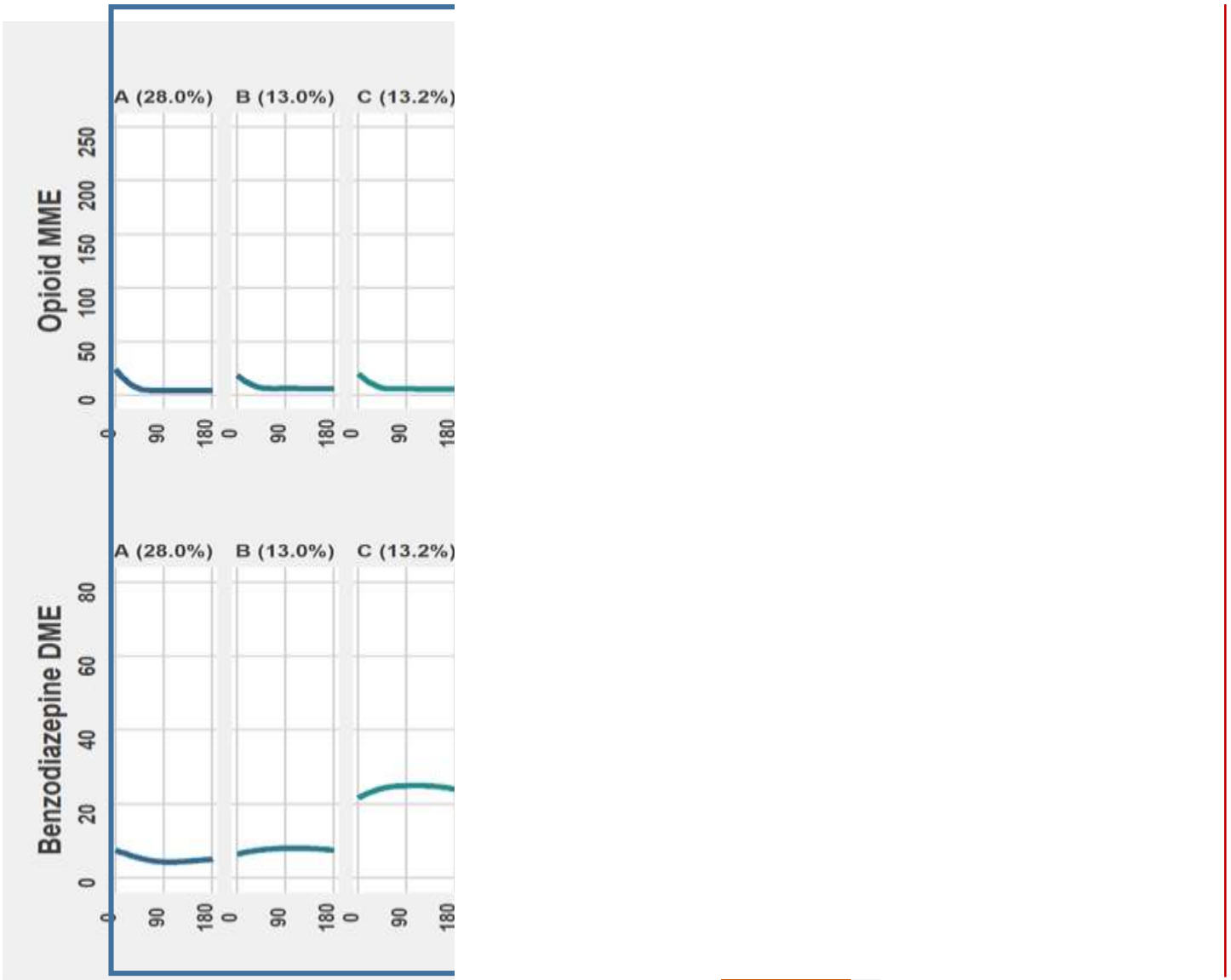
Step 3: Calculate stabilized inverse probability of treatment weights (IPTW) for each beneficiary (*excluded extreme IPTW >10 [n=123])

Step 4: For each trajectory, estimate adjusted hazard ratios (HRs) of time to first OPI overdose episode within the 6 months following the 6-month trajectory measurement period using **IPTW multivariable Cox model**

(1) Austin PC. Multivariate Behav Res. 2011;46:399-424; (2) Faraone SV. P T. 2018;33:700-103, 710-711

Results: 9 OPI-BZD Trajectory Groups

Very-low-dose OPI (<25 MME)



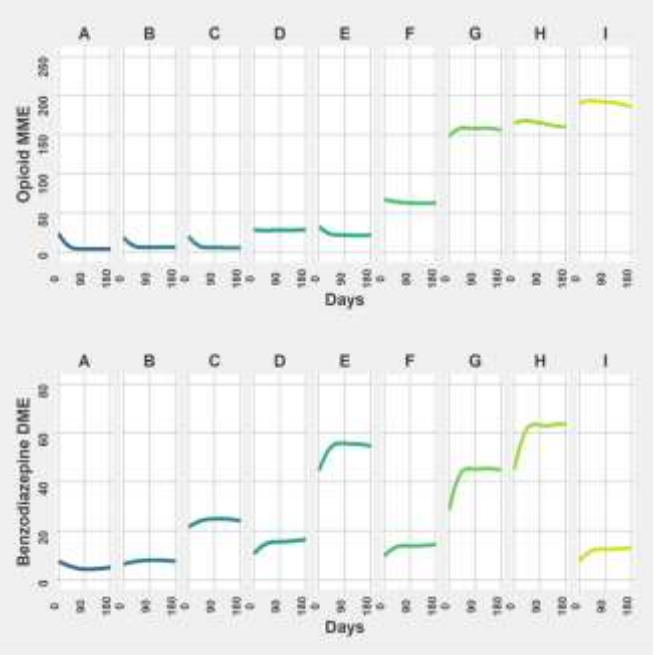
Group	N	Labeling*
A	10,561	Very-low-dose OPI-BZD users with slowly decreasing BZD use (<25 MME, <10 DME)
B	4,900	Very-low-dose OPI-BZD users with consistent BZD use (<25 MME, <10 DME)
C	4,992	Very-low-dose OPI (<25 MME) and medium-dose BZD (21-40 DME)

*Dose level in group labeling:

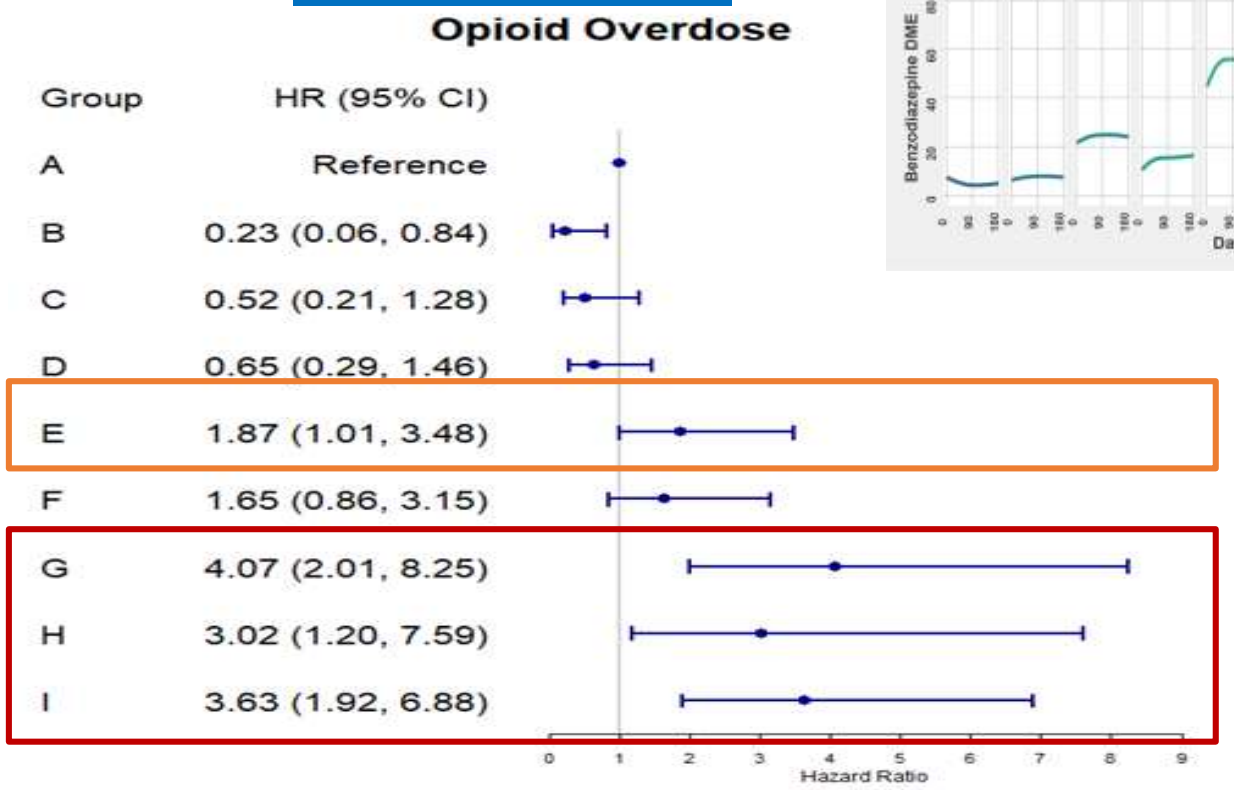
- Opioids: very low (<25 MME), low (25-50), moderate (51-90), high (91-150 MME), and very high (>150 MME).
- BZD dose level in diazepam equivalent milligram (DME): very low (<10 DME), low (10-20 DME), moderate (21-40 DME), high (41-60 DME), and very high (>60 DME).

Results: Dual Trajectories of OPI-BZD Use and Opioid Overdose Risk

Group	% of the cohort	OPI overdose N (% of the trajectory)	Crude incidence (per 10,000 person mos)
A	28.0	8 (0.08)	1.3
B	13.0	2 (0.04)	0.7
C	13.2	7 (0.14)	2.3
D	13.5	12 (0.24)	3.9
E	**10.3**	**20 (0.51)**	**8.6**
F	10.4	20 (0.51)	8.5
G	**3.6**	**16 (1.18)**	**19.6**
H	**2.5**	**11 (1.16)**	**19.2**
I	**5.5**	**22 (1.06)**	**17.6**



IPTW-adjusted HRs



Groups E, and G to I accounted for 21.9% of the cohort and captured ~60% of opioid overdoses

Conclusions

- **9 distinct OPI-BZD trajectories were identified during the 6 months following opioid initiation among Medicare fee-for-service beneficiaries**

- **OPI overdose risks varied substantially across OPI-BZD trajectories**
  - Very-high-dose opioid use (MME >150) or high-dose benzodiazepine use (DME>40, even in the presence of low-dose opioid use) had a 2 to 4 times increased opioid overdose risk
  - 21% of the cohort were in the high-risk trajectories: captured ~60% of OPI overdoses

- Clinicians should avoid prescribing OPIs and BZDs concurrently whenever possible. When co-prescribing is necessary, clinicians should:
  - Discuss safety concerns with patients
  - Limit dosage and duration to the minimum required
  - Monitor closely with prescription drug monitoring program (PDMP)

Limitations

- Claim-based analyses have limited clinical and socio-behavior information such as **pain severity**
  - **E-value ranged 3.6 to 6.7** for high-risk trajectory groups

- Unable to link to death certificate data and thus could not distinguish fatal from non-fatal overdoses

- Limited generalizability to other populations (e.g., Medicaid)

- Unable to evaluate the impact of US FDA black box warning released in August 2016

1. Kim HM. BMC Health Serv Res. 2012;12:18; 2. Rowe C. Acad Emerg Med. 2017:24(4):475-483.

Example 5

Dual-Trajectories of Opioid and Gabapentinoid Use and Risk of Subsequent Drug Overdose among Medicare Beneficiaries in the US

ADDICTION SSA SOCIETY FOR THE STUDY OF ADDICTION

RESEARCH REPORT

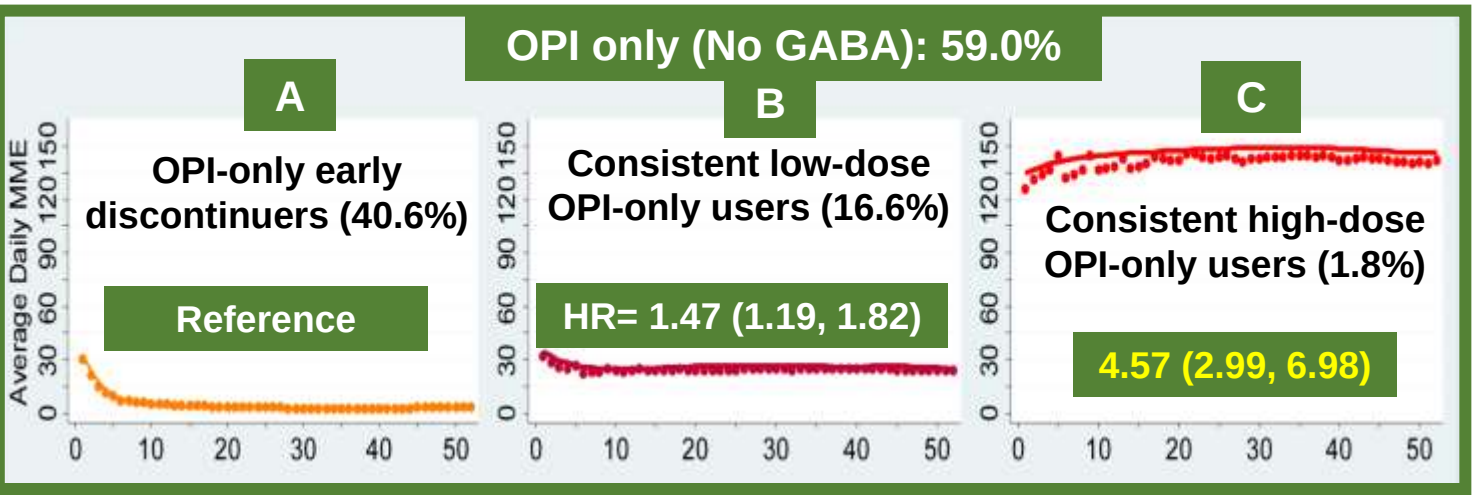
doi:10.1111/add.15189

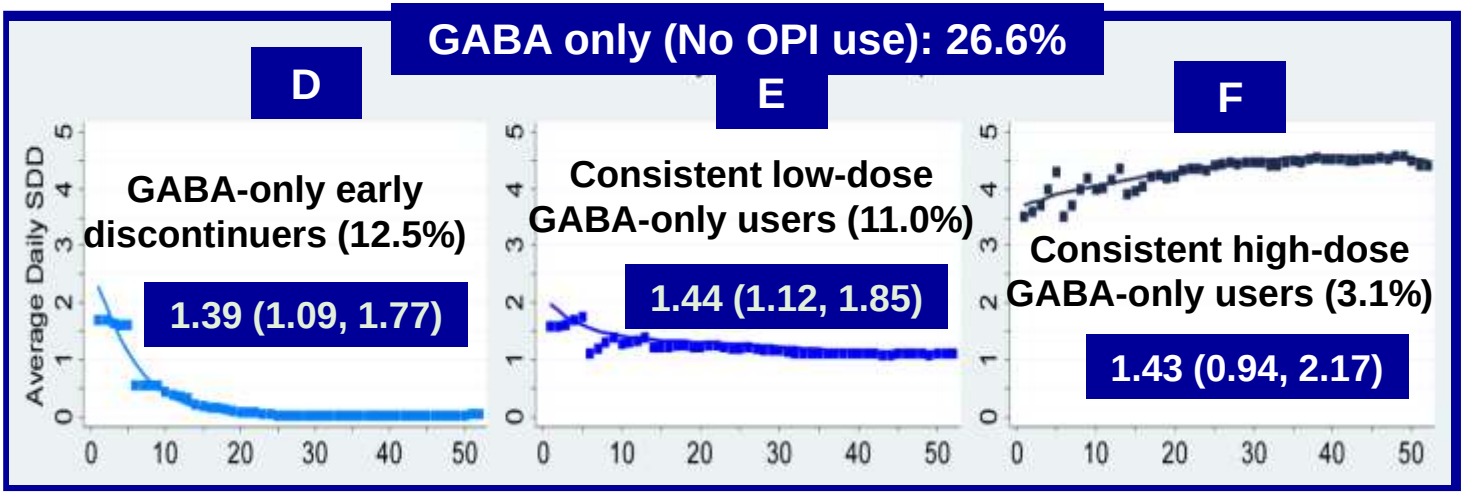
Dual-trajectories of opioid and gabapentinoid use and risk of subsequent drug overdose among Medicare beneficiaries in the United States: a retrospective cohort study

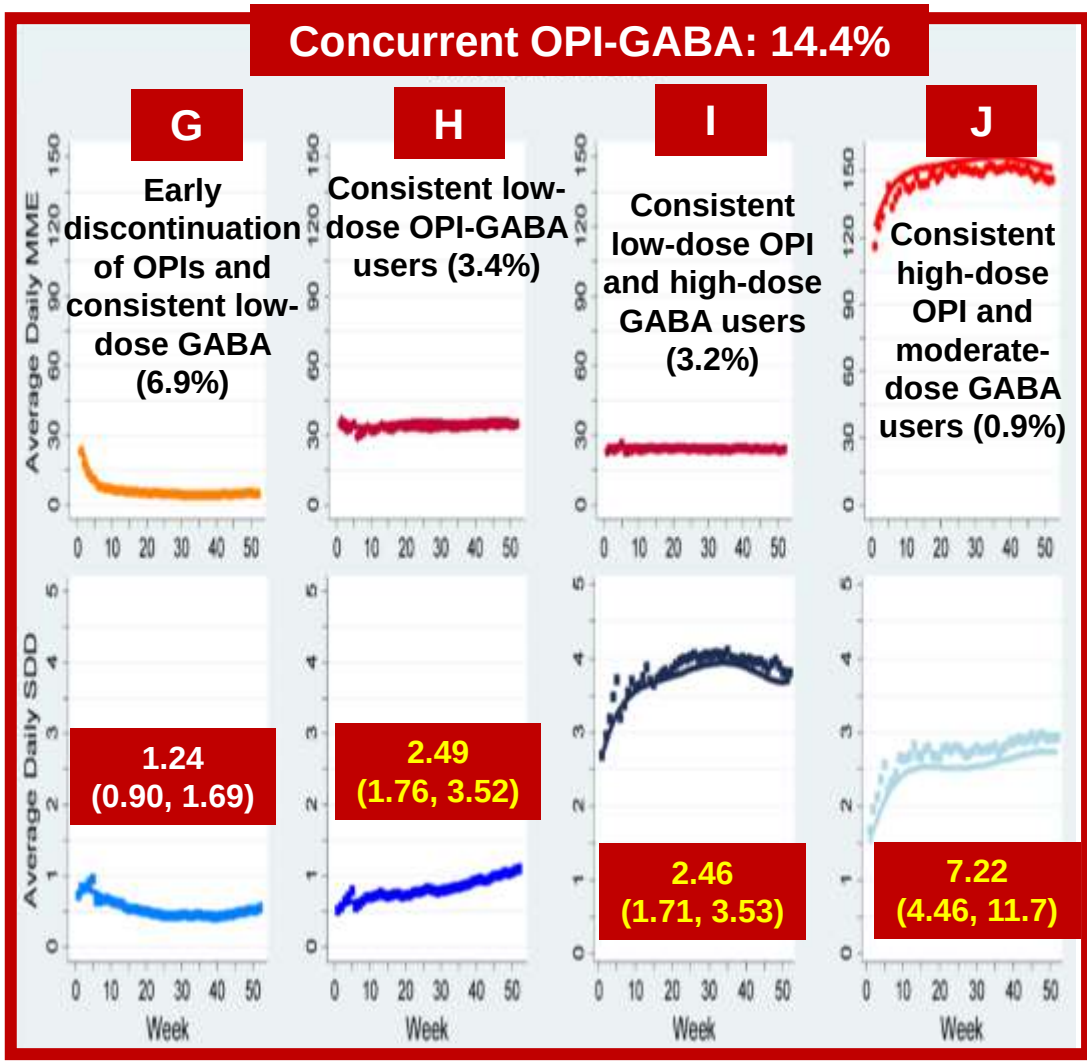
Lili Zhou[1], Sandipan Bhattacharjee[1], C. Kent Kwoh[2,3], Patrick J. Tighe[4], Gary M. Reisfield[5], Daniel C. Malone[6], Marion Slack[1], Debbie L. Wilson[7], Ching-Yuan Chang[7,8] & Wei-Hsuan Lo-Ciganic[7,8]

More details, see Addiction 2020 Jul 10.
doi: 10.1111/add.15189. Online ahead of print..

Key Results & Main Conclusions







- Subsequent overdose risk varied substantially by different OPI-GABA trajectories
- High-dose OPI-only users and all consistent OPI-GABA users were associated with more than doubled drug overdose risk.

Example 6

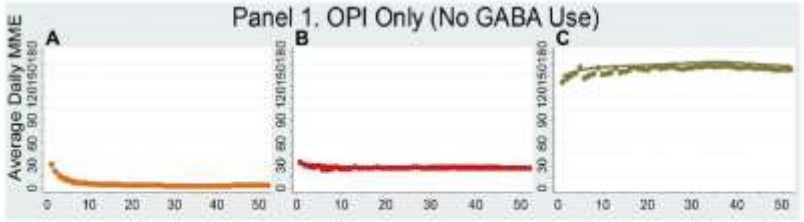
Dual-Trajectories of Opioid and Gabapentinoid Use and **Health Expenditures** among Medicare Beneficiaries in the US

Association Between Dual Trajectories of Opioid and Gabapentinoid Use and Healthcare Expenditures Among US Medicare Beneficiaries

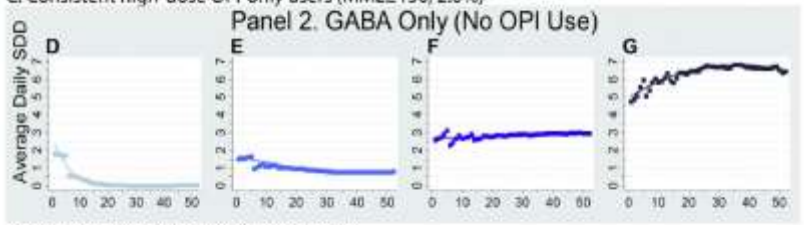
Lili Zhou, PhD, Sandipan Bhattacharjee, PhD, C. Kent Kwoh, MD, Daniel C. Malone, PhD, Patrick J. Tighe, MD, Gary M. Reisfield, MD, Marion Slack, PhD, Debbie L. Wilson, PhD, Wei-Hsuan Lo-Ciganic, PhD

More details, see Value in Health 2021 (in press)

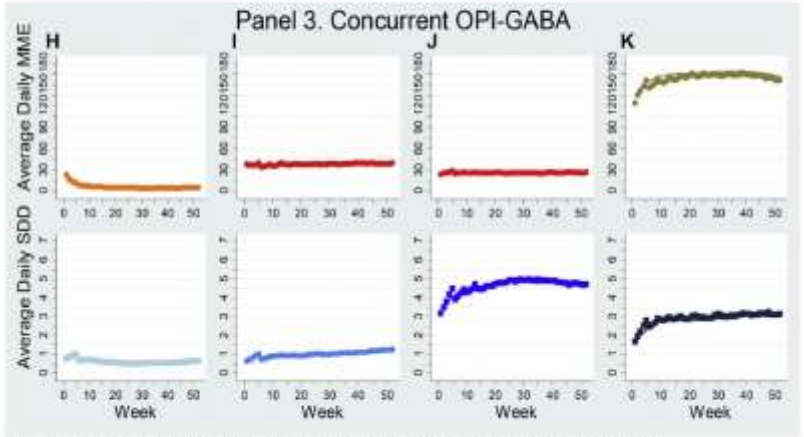
Key Results & Main Conclusions



A: OPI-only early discontinuers (39.3%)
B: Consistent low-dose OPI-only users (MME≤30; 16.4%)
C: Consistent high-dose OPI-only users (MME≥150; 2.0%)



D: GABA-only early discontinuers (11.9%)
E: Consistent low-dose GABA-only users (SDD<2; 9.5%)
F: Consistent moderate-dose GABA-only users (2<SDD≤3; 4.8%)
G: Consistent high-dose GABA-only users (SDD>5; 1.1%)



H: Early discontinuation of OPIs and consistent low-dose GABA users (SDD≤1; 7.4%)
I: Consistent low-dose OPI-GABA users (MME<40 and SDD<1.5; 3.8%)
J: Consistent low-dose OPI and high-dose GABA users (MME<30 and SDD≥3; 2.8%)
K: Consistent high-dose OPI and moderate-dose GABA users (MME>120 and 1.5<SDD≤3; 1.0%)

Group	Mean total annual concurrent direct medical costs (95% CI)	Cost ratio (95% CI)
A	$13,830 ($13,643-$14,019)	Reference
B	**$15,721 ($15,395-$16,055)**	**1.14 (1.11-1.17)**
C	**$22,908 ($21,421-$24,497)**	**1.66 (1.55-1.77)**
D	$10,607 ($10,345-$10,876)	0.77 (0.75-0.79)
E	$12,397 ($12,053-$12,751)	0.89 (0.87-0.92)
F	$11,713 ($11,254-$12,191)	0.85 (0.81-0.88)
G	$13,659 ($12,574-$14,838)	0.99 (0.91-1.07)
H	**$18,309 ($17,743-$18,893)**	**1.32 (1.28-1.37)**
I	**$22,869 ($21,841-$23,946)**	**1.65 (1.58-1.73)**
J	**$20,281 ($19,211-$21,411)**	**1.47 (1.39-1.55)**
K	**$28,464 ($25,910-$31,271)**	**2.06 (1.87-2.26)**

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GBTM specifications: maximum likelihood estimation

$$P(Y_i) = \sum_j \pi_j(X_i) P^j(Y_i)$$

Y_i: longitudinal patterns of outcomes

j: group or trajectory j

π_j: probability of membership in group j

X_i: covariates

$P^j(Y_i)$: probability of Y_i given membership in group j

$$\pi_j(X_i) = \frac{e^{X_i\theta_j}}{\sum e^{X_i\theta_j}}$$

Joint probability or likelihood: $\prod_{i=1}^{N} P(Y_i)$

Nagin. 2005. Group-Based Modeling of Development, Harvard University Press

Types of Outcome Data in GBTM

$$P(Y_i) = \sum_j \pi_j (X_i) P^j (Y_i)$$

Y_i: longitudinal patterns of outcomes

Outcome Data Type	Example	Distribution/model used in GBTM
Continuous data	Medication adherence measured by proportion of days covered (PDC), psychometric scale	**Censored normal model or beta-distributed model**
Count data	Number of readmission, number of times in jail	**Poisson-based model (e.g., zero-inflated Poisson [ZIP])**
Binary data	PDC >80% (yes vs. no)	**Logit-based model**

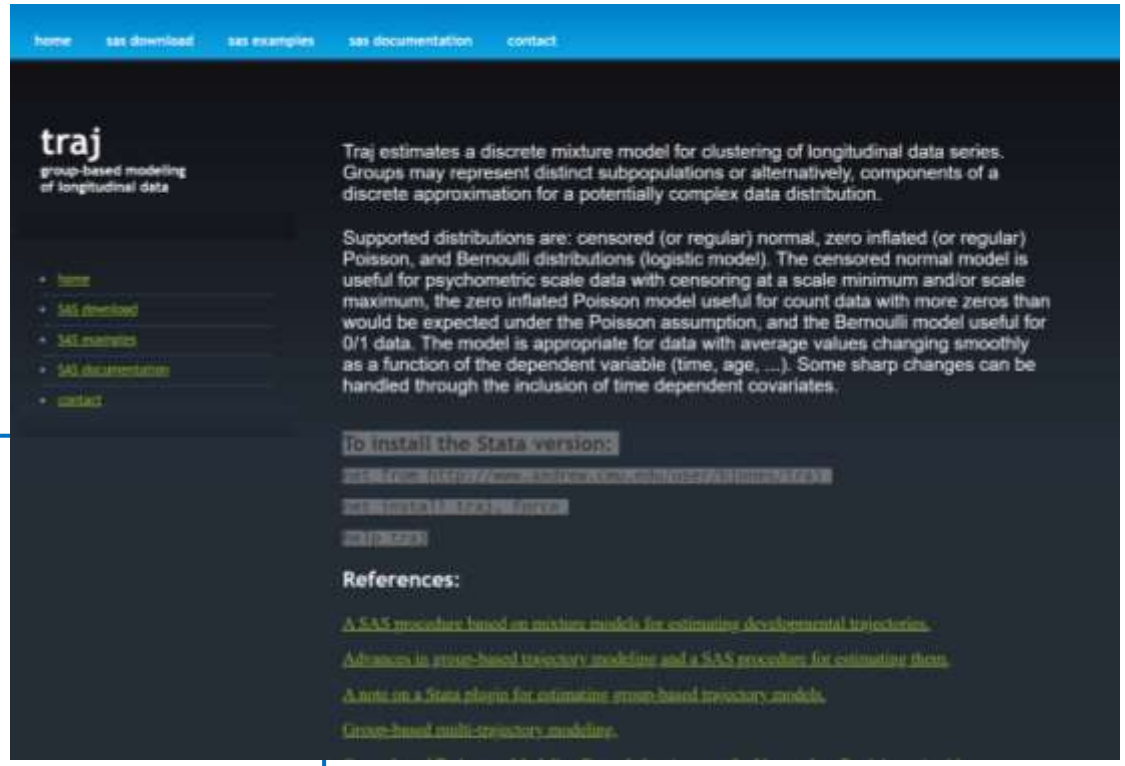
Software for GBTM

- Free and easy to use: SAS and STATA-based procedure
  - Available for download at https://www.andrew.cmu.edu/user/bjones/
- Provide confidence intervals on trajectory estimates
- Accommodate missing data
- Can handle sample weights (e.g., for panel data)
- Allow for irregular time spacing of measurement
- Accommodate over-lapping cohort designs

Traj in STATA

- https://www.andrew.cmu.edu/user/bjones/
- **To install the Stata version:**

  net from http://www.andrew.cmu.edu/user/bjones/traj
  net install traj, force
  help traj



Examples

1. Censored normal (cnorm) model
2. Variability (sigma) by group option - cnorm model
3. Zero-inflated Poisson (zip) model
4. Logistic (logit) model
5. Providing start values
6. Including time-stable covariates (risk) associated with group membership
7. Obtaining group membership probabilities from a model with risk variables
8. Including covariates (tcov), specified at each time point, associated with group trajectory means
9. Parametric bootstrap sampling for model parameters e.g. group size confidence intervals
10. Wald hypothesis tests of the traj model parameters (like SAS %trajtest)
11. Distal outcome model
12. Distal outcome model with bootstrap CI for individual outcome predictions
13. Joint trajectory model
14. Multi-trajectory model
15. Dropout modeling
16. Exposure time / sample weights

Traj: basic syntax

traj [if], var(varlist) indep(varlist) model(modeltype) order(numlist) [additional options]

options	Description
Trajectory Variables	
var(*varlist***)**	dependent variables, measured at different times or ages
indep(*varlist***)**	independent variables i.e. when the dependant variables were measured
Model	
model(*modeltype***)**	**beta**, **cnorm** (censored normal), **logit** (Bernoulli), **zip** (zero-inflated Poisson) - probability distribution for the dependent variables
order(*numlist***)**	**0=intercept, 1=linear, 2=quadratic, 3=cubic** - polynomial type for each group trajectory
min(#)	(cnorm, defaults to 0) minimum value for the censored normal model
max(#)	(required for cnorm) maximum value for the censored normal model
sigmabygroup	(cnorm) fit group specific sigma parameters
iorder(*numlist***)**	optional polynomial type (0=intercept, 1=linear, 2=quadratic, 3=cubic) for the zero-inflation of each group
exposure(*varlist***)**	optional exposure variables for the zero-inflated Poisson model
weight(*varname***)**	optional sampling weight variable
Time-Stable Covariates for Group Membership	
risk(*varlist***)**	covariates for the probability of group membership
refgroup(#)	controls the reference group (default = 1) when the risk option is used
Time-Varying Covariates Influencing Trajectory Paths	
tcov(*varlist***)**	time-varying covariates for each group trajectory
plottcov(*matrix***)**	optional values for plotting trajectories with time-varying covariates
Dropout Model	
dropout(*numlist***)**	include logistic model of dropout probability per wave with 0 = constant rate, 1 = depends on the previous response, 2 = depends on the two previous responses, for each group
dcov(*varlist***)**	optional lagged time-varying covariates for the dropout model
obsmar(*varname***)**	optional binary variable to mark which observations are to be included in the dropout model and those to be treated as missing at random. This variable = 1 for observations to be treated as data MAR (include completers) and = 0 for observations to be used for the modeled dropout
Distal Outcome Model	
outcome(*varname***)**	a distal variable to be regressed on the probability of group membership
omodel(*modeltype***)**	probability distribution for the outcome variable: **normal**, **logit**, **mlogit**, or **poisson**
ocov(*varlist***)**	optional covariates for the outcome model
Joint Trajectory Model	
The joint trajectory model uses the options shown above with a '2' suffix to specify the second model e.g. **model2(***modeltype***)** etc. See the joint trajectory example.	
Multi-Trajectory Model	
multrisk(*varlist***)**	covariates for the probability of multi-trajectory group membership
multgroups(#)	the number of multi-trajectory groups for the multi-trajectory model (2 to 6). The multi-trajectory model uses the options shown above with a '2', '3', etc. (up to 6) suffix to specify the additional models. See the multi-trajectory example.
Other	
start(*matrix***)**	parameter start values to override default start values
detail	shows start values, minimization iterations, and ending values for monitoring model fitting progress. The ending values can be useful as start values for future traj models.
ci	parametric bootstrap confidence intervals of individual distal outcome and probability of group memberships.
reps	number of bootstrap replications (default = 1000).
scoreci	confidence intervals of individual distal outcome and probability of group memberships using the method of Sison and Glaz (1995).

Basic Data Layout for GBTM

Var(varlist): longitudinal outcome patterns of interest (dependent variable in GBTM)

Indep(varlist): age or time when dependent variables were measured

Patient_ID	PDC_1	PDC_2	PDC_3…	PDC_12	Time_1	Time_2…	Time_12
001	1.00	0.90	0.75	0.55	1	2	12
002	0.85	0.75	0.55	0.40	1	2	12
003	0.50	0.35	0.25	0.55	1	2	12
004	0.35	0.55	0.65	0.75	1	2	12
005	0.75	0.55	0.65	0.75	1	2	12
006	0.77	0.80	0.82	0.85	1	2	12
007	1.00	0	0.50	0.75	1	2	12
….	….	…	…	…	…	…	…

GBTM: Censored normal (Tobit) model

Time polynomial order in GBTM: liner $= time^1$; quadratic $= time^2$; cubic $= time^3$; quartic $= time^4$; quintic $= time^5$

➢ **Censored normal model:** $y_{it}^{*j} = \beta_0^j + \beta_1^j \times age_{it} + \beta_2^j \times age_{it}^2 + \beta_3^j \times age_{it}^3 + \varepsilon$

j: group/number of groups

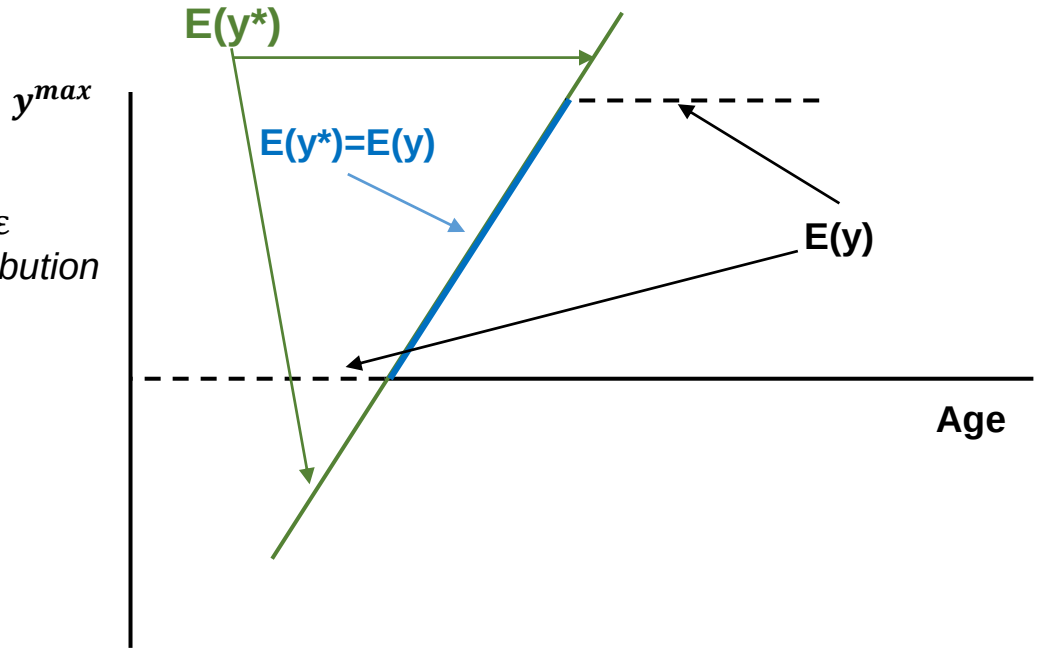
For example: $y^* = \beta_0 + \beta_1 \times age + \varepsilon$

Definition of censored normal distribution

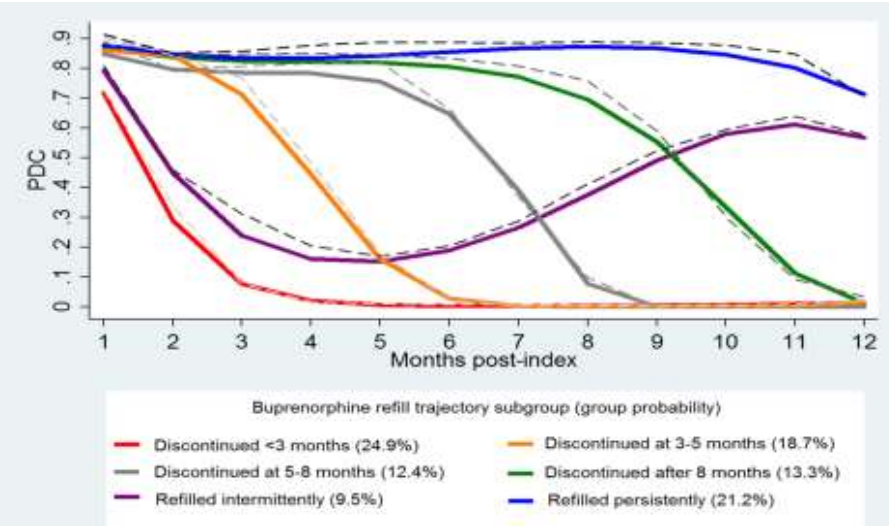
$y = 0 \quad if \quad y^* \leq 0$

$y = y^* \quad if \quad 0 < y \leq y^{max}$

$y^* = y^{max} \quad if \quad y^* > y^{max}$



Buprenorphine Refill Trajectories



Addiction 2016; 111(5):892-902

STATA: Censored normal model example

- Montreal data: The data consist of annual assessments on 1,037 boys at age 6 (spring 1984) and **ages 10 through 15** on an **oppositional behavior scale (ranges from 0 to 10)** gathered in low socioeconomic areas of Montreal, Canada. See Tremblay et al. (1987) for details. Scores of zero are frequent and the scores decrease in frequency as the score increases. Hence, the censored normal distribution is sensible for modeling the data. The following commands fit a 3-group model to the opposition data and provide a graph of the results.

STATA Syntax

```
use http://www.andrew.cmu.edu/user/bjones/traj/data/montreal_sim.dta, clear
traj, var(qcp*op) indep(age*) model(cnorm) min(0) max(10) order(1 3 2)
trajplot, xtitle(Age) ytitle(Opposition) xlabel(6(1)15) ylabel(0(1)6)
 list _traj_Group - _traj_ProbG3 if _n < 3, ab(12)
 matrix list e(plot1), format(%9.2f) noheader
```


Adapted from Jones BL and Nagin DS. A Stata Plugin for Estimating Group-based Trajectory Models (https://ssrc.indiana.edu/doc/wimdocs/2013-03-29_nagin_trajectory_stata-plugin-info.pdf)

STATA: Censored normal model output (Example 1)

```
==== traj stata plugin ====  Jones BL  Nagin DS,  build: May 17 2020

1037 observations read.
1037 observations used in the trajectory model.

                      Maximum Likelihood Estimates
                      Model: Censored Normal (cnorm)

                                          Standard       T for H0:
 Group    Parameter          Estimate        Error     Parameter=0    Prob > |T|

 1        Intercept           1.00232      0.35105           2.855        0.0043
          Linear             -0.19098      0.03065          -6.232        0.0000

 2        Intercept         -13.84777      4.09008          -3.386        0.0007
          Linear              4.95268      1.30802           3.786        0.0002
          Quadratic          -0.45532      0.12967          -3.511        0.0004
          Cubic               0.01261      0.00407           3.094        0.0020

 3        Intercept          -1.61607      0.97421          -1.659        0.0972
          Linear              1.45292      0.19585           7.418        0.0000
          Quadratic          -0.07251      0.00939          -7.721        0.0000

          Sigma               2.61114      0.03276          79.709        0.0000

  Group membership
1         (%)                30.84358      2.48526          12.411        0.0000
2         (%)                46.12672      2.40002          19.219        0.0000
3         (%)                23.02970      1.82029          12.652        0.0000

 BIC=-11908.18 (N=6231)  BIC=-11897.42 (N=1037)  AIC=-11867.75  ll= -11855.75
```

```
.     /* Shows the assigned group and probabilties of group membership */
.     list _traj_Group - _traj_ProbG3 if _n < 3, ab(12)
```

	_traj_Group	_traj_ProbG1	_traj_ProbG2	_traj_ProbG3
1.	1	.984025	.015975	1.36e-08
2.	2	.0507331	.9485434	.0007235

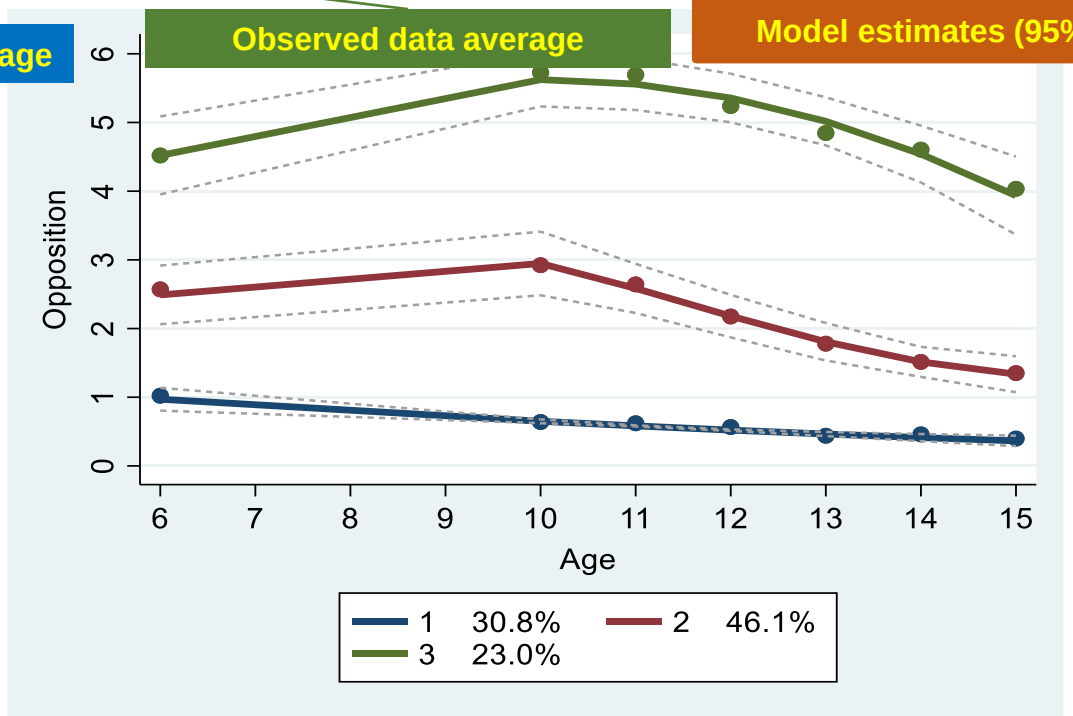
```
.
.     /* trajT = x-axis, Avg# = data averages, Est# = model estimates */
.     matrix list e(plot1), format(%9.2f) noheader
```

	trajT	Avg1	Avg2	Avg3	Est1	Est2	Est3	L951	U951	L952	U952	L953	U953
r1	6.00	1.02	2.57	4.52	0.97	2.49	4.52	0.81	1.14	2.06	2.92	3.95	5.09
r2	10.00	0.64	2.92	5.73	0.65	2.95	5.62	0.62	0.68	2.48	3.41	5.23	6.01
r3	11.00	0.62	2.64	5.70	0.58	2.58	5.56	0.58	0.59	2.23	2.94	5.18	5.94
r4	12.00	0.57	2.18	5.24	0.52	2.18	5.36	0.51	0.53	1.87	2.49	5.00	5.71
r5	13.00	0.44	1.78	4.85	0.46	1.81	5.02	0.43	0.49	1.53	2.08	4.67	5.37
r6	14.00	0.46	1.51	4.60	0.41	1.51	4.54	0.36	0.46	1.30	1.73	4.13	4.95
r7	15.00	0.40	1.35	4.03	0.36	1.34	3.94	0.29	0.44	1.07	1.60	3.37	4.50

Time/age

Observed data average

Model estimates (95%CI)



GBTM: Poisson-based model

Time polynomial order in GBTM: liner $= time^1$; quadratic $= time^2$; cubic $= time^3$; quartic $= time^4$; quintic $= time^5$

- **Basic Poisson−based model:** $\log(\lambda_{it}^j) = \beta_0^j + \beta_1^j \times age_{it} + \beta_2^j \times age_{it}^2 + \beta_3^j \times age_{it}^3$

λ: mean value (e.g., event rate)

- **Zero − inflated Posisson Model: using when there are a lot of 0s in Poisson model**

$$p(x) = \begin{cases} 0 \; with \; probability \; \rho \\ Poisson(\lambda) \; with \; probability \; 1-\rho \end{cases}$$

$$ln(\lambda) = \beta_0 + \beta_1 \times age + \beta_2 \times age^2 + \beta_3 \times age^3$$

$$\rho = \frac{e^{\alpha_0 + \alpha_1 \times age + \alpha_2 \times age^2 + \alpha_3 \times age^3}}{1 + e^{\alpha_0 + \alpha_1 \times age + \alpha_2 \times age^2 + \alpha_3 \times age^3}}$$

STATA: ZIP model example (Example 3)

- The data are **the annual number of criminal offense convictions** for 411 subjects from a prospective longitudinal survey conducted in a working-class section of London (Farrington and West, 1990). The annual criminal offense convictions were recorded for boys from **age 10 through age 30**. The Poisson model is appropriate here; however, more zeros are present than would be expected in the purely Poisson model, so we will use the ZIP model. The following commands fit a 3-group model to the data and provide a graph of the results.

STATA Syntax

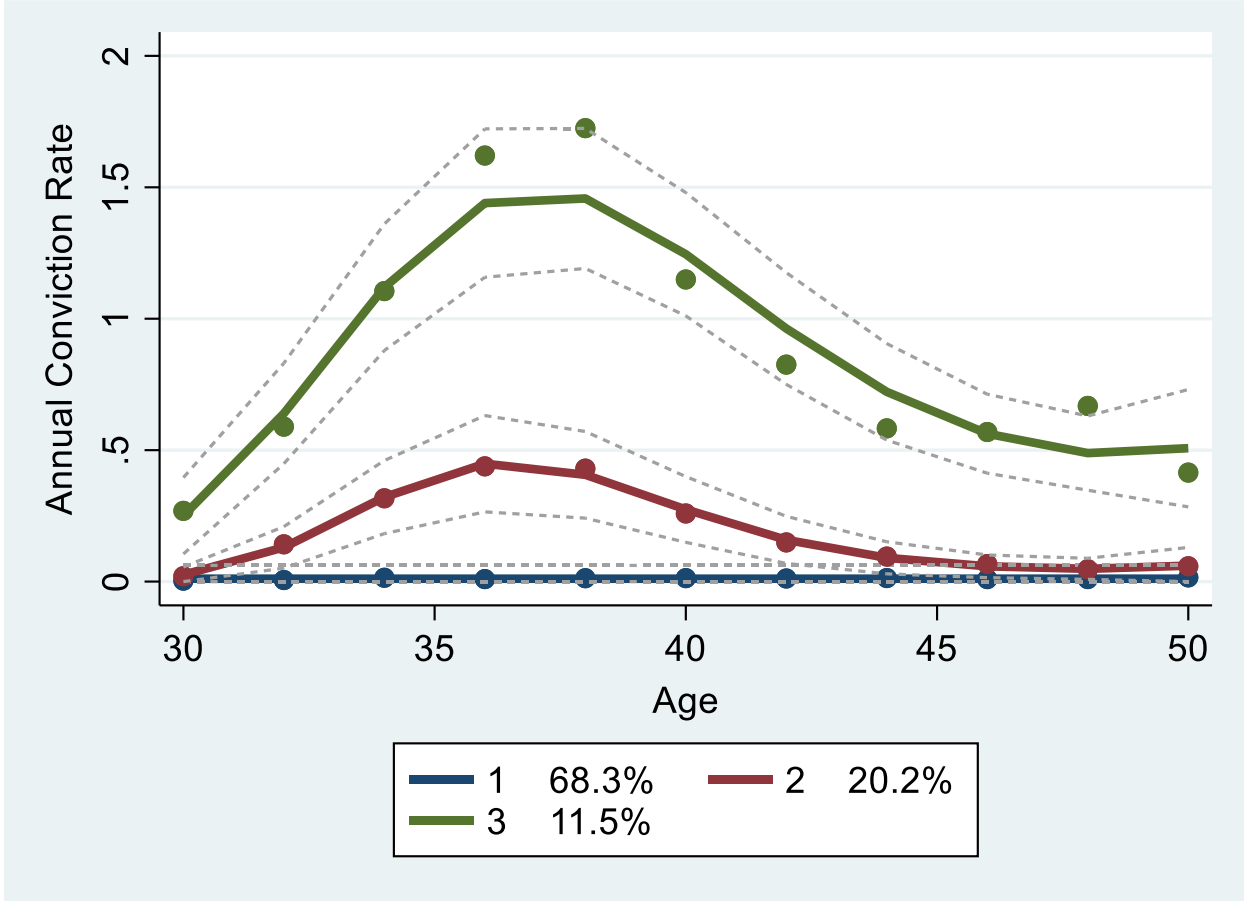
```
use http://www.andrew.cmu.edu/user/bjones/traj/data/anag1.dta, clear
traj, var(y*) indep(t*) model(zip) order(0 3 3) iorder(0 -1 0)
 /* t1-t11 were scaled from -1 to 1 that may work with the default start values, but no guarantee sometimes */
 /* The following Stata commands return the x-axis to the original time scale.*/
mat P = e(plot1)
svmat P, names(col)
replace trajT = 10 * trajT + 40
trajplot, xtitle(Age) ytitle(Annual Conviction Rate) plotvars(trajT-U953) ci
  drop trajT - U953
 /* Assigned group and probabilities of group membership */
  list _traj_Group - _traj_ProbG3 if _n > 400, ab(12)
```


Adapted from Jones BL and Nagin DS. A Stata Plugin for Estimating Group-based Trajectory Models (https://ssrc.indiana.edu/doc/wimdocs/2013-03-29_nagin_trajectory_stata-plugin-info.pdf)

STATA: ZIP model output (Example 3)

```
403 observations read.
6 had no trajectory data.
397 observations used in the trajectory model.

                      Maximum Likelihood Estimates
                      Model: Zero Inflated Poisson (zip)

                                                Standard       T for H0:
Group    Parameter          Estimate              Error     Parameter=0    Prob > |T|

1        Intercept          -1.41663            0.84311          -1.680        0.0930

2        Intercept          -1.29319            0.23242          -5.564        0.0000
         Linear             -2.46477            0.55400          -4.449        0.0000
         Quadratic          -1.93476            0.40930          -4.727        0.0000
         Cubic               2.88839            0.78760           3.667        0.0002

3        Intercept           0.61512            0.09540           6.448        0.0000
         Linear             -1.09516            0.24499          -4.470        0.0000
         Quadratic          -1.25101            0.19201          -6.515        0.0000
         Cubic               1.44852            0.35736           4.053        0.0001

1        Alpha0              3.05252            0.76850           3.972        0.0001


3        Alpha0             -0.72287            0.22094          -3.272        0.0011


 Group membership
1        (%)                68.26470            4.48078          15.235        0.0000
2        (%)                20.19498            3.94145           5.124        0.0000
3        (%)                11.54033            2.22091           5.196        0.0000

BIC= -1491.66 (N=4367)  BIC= -1476.07 (N=397)  AIC= -1450.17  ll=  -1437.17
```

_traj_Group	_traj_ProbG1	_traj_ProbG2	_traj_ProbG3
2	.0006211	.9855553	.0138236
1	.8807653	.1148225	.0044122
3	2.79e-12	.0000938	.9999062



GBTM: Logistic (logit) model

$$p(y=1) = \frac{e^{\beta_0+\beta_1\times age+\beta_2\times age^2+\beta_3\times age^3}}{1+e^{\beta_0+\beta_1\times age+\beta_2\times age^2+\beta_3\times age^3}}$$

$$where \begin{cases} y=1 \ if \ yes \\ y=0 \ if \ no \end{cases}$$

STATA: Logistic (logit) model example (Example 4)

- It is common in research on criminal careers to analyze the **absence or presence of offenses (i.e. a dichotomous prevalence measure).** The ZIP analysis is repeated for a derived criminal offense prevalence measure using a logistic model (i.e., periods in which 1 or more convictions are reported are coded as “1” and periods with no convictions are coded as “0”). The following commands fit a three-group model to the prevalence measure data and graph the results.

STATA Syntax

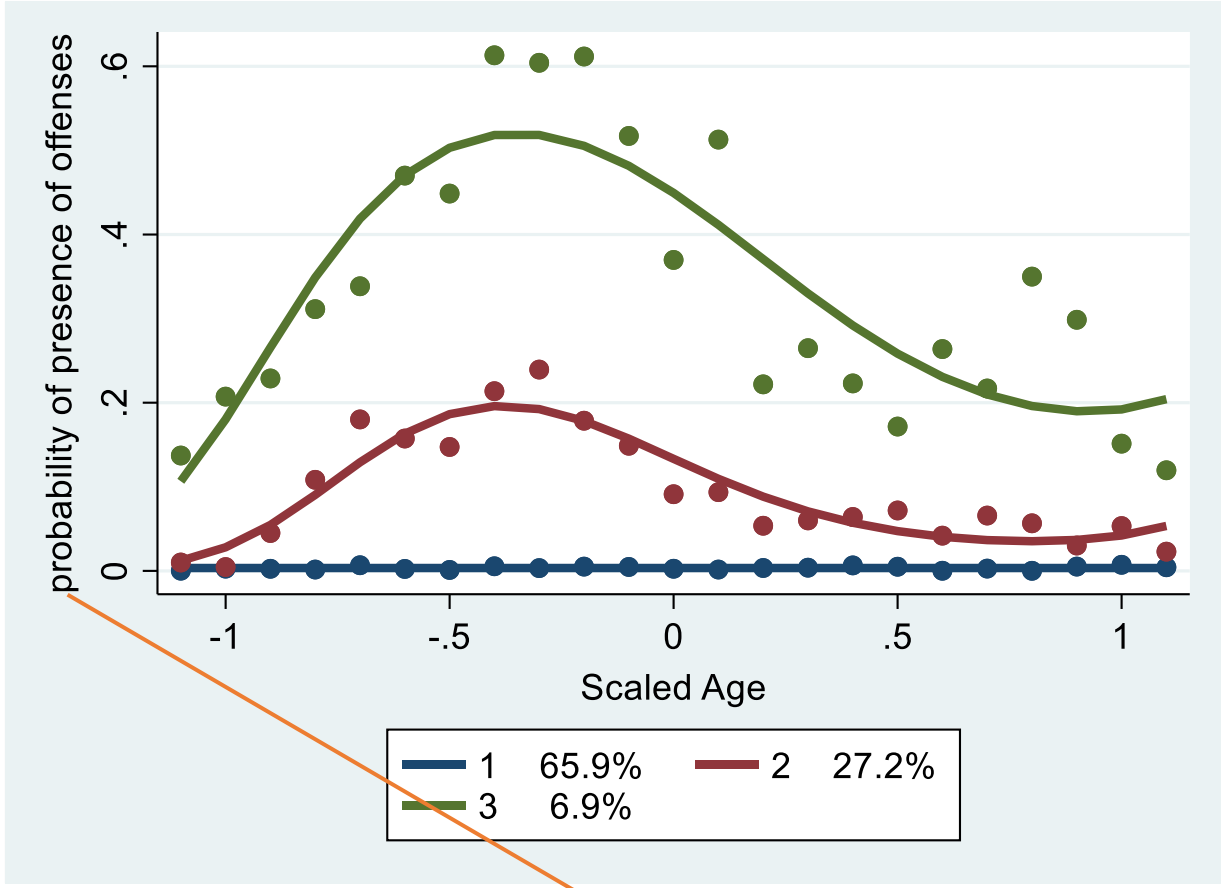
```
use http://www.andrew.cmu.edu/user/bjones/traj/data/cambrdge.dta, clear
traj, var(p1-p23) indep(tt1-tt23) model(logit) order(0 3 3)
trajplot, xtitle(Scaled Age) ytitle(probability of presence of offenses)
/* Assigned group and probabilties of group membership */
 list _traj_Group - _traj_ProbG3 if _n > 400, ab(12)
```


Adapted from Jones BL and Nagin DS. A Stata Plugin for Estimating Group-based Trajectory Models (https://ssrc.indiana.edu/doc/wimdocs/2013-03-29_nagin_trajectory_stata-plugin-info.pdf)

STATA: Logit model output (Example 4)

```
403 observations read.
403 observations used in the trajectory model.

                      Maximum Likelihood Estimates
                      Model: Logistic (logit)

                                          Standard       T for H0:
 Group    Parameter        Estimate         Error      Parameter=0    Prob > |T|

 1        Intercept        -5.66365       0.46767          -12.110       0.0000

 2        Intercept        -1.87264       0.21567           -8.683       0.0000
          Linear           -2.10869       0.38115           -5.533       0.0000
          Quadratic        -1.46178       0.24860           -5.880       0.0000
          Cubic             2.31942       0.46977            4.937       0.0000

 3        Intercept        -0.20271       0.20155           -1.006       0.3146
          Linear           -1.43570       0.40751           -3.523       0.0004
          Quadratic        -1.27310       0.25513           -4.990       0.0000
          Cubic             1.47440       0.47338            3.115       0.0018


  Group membership
 1        (%)              65.85275       4.18013           15.754       0.0000
 2        (%)              27.23881       3.66010            7.442       0.0000
 3        (%)               6.90843       2.16292            3.194       0.0014

 BIC= -1532.06 (N=9269)  BIC= -1514.81 (N=403)  AIC= -1492.82  ll=  -1481.82

.
.      trajplot, xtitle(Scaled Age) ytitle(probability of presence of offenses)

.
.      /* Assigned group and probabilties of group membership */
.      list _traj_Group - _traj_ProbG3 if _n > 400, ab(12)
```

	_traj_Group	_traj_ProbG1	_traj_ProbG2	_traj_ProbG3
401.	2	.000158	.9843408	.0155012
402.	1	.7270437	.2726521	.0003042
403.	3	5.52e-20	.0000444	.9999557



The logistic model gives the log-odds of response. The log-odds is converted to the probability of response.

GBTM: Beta-distribution based trajectory

- An alternative to the normal distribution for modeling continuous longitudinal data that are poorly fit by the normal distribution even with censoring.
- Primary advantage: the flexibility of the shape of the density function
- Disadvantage: the data under study must be transformable to a 0–1 scale.

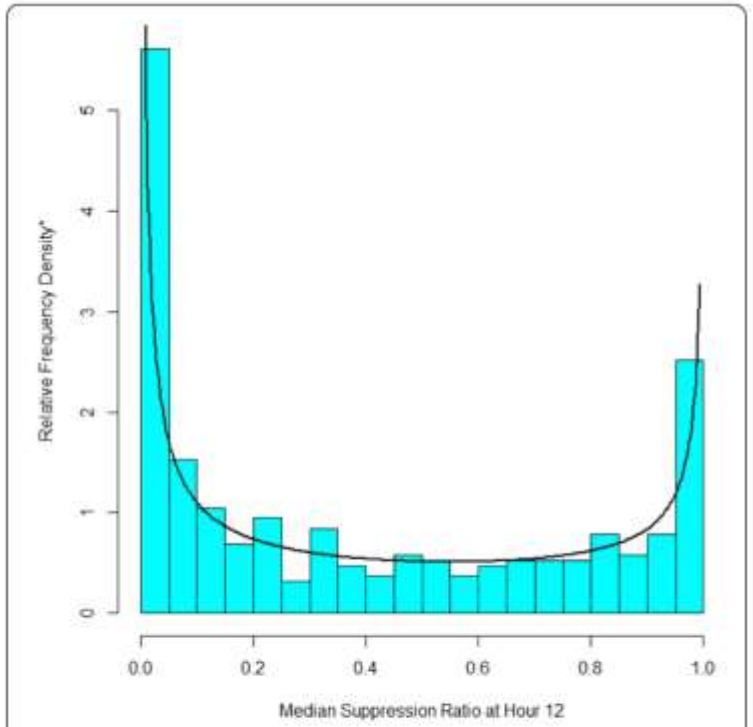


Fig. 1 The Distribution of Hour 12 Suppression Ratio Data with the Best Fitting Beta Distribution. *The sum of the heights of the relative frequency density bars multiplied by their width sum to 1.0 so as to conform the with estimated beta density

Elmer J et al. BMC Med Res Method. 2018; 18:152

Posterior Probability of Group Membership (PPGM)

$$PPGM = AvePP_j = \hat{p}(group\ j|data_i) = \frac{\hat{p}(data_i|group\ j)\hat{\pi}_j}{\sum_j \hat{p}(data_i|group\ j)\hat{\pi}_j}$$

$\hat{p}(data_i|group\ j)$: probability of your data, given group membership

$\hat{\pi}_j$: probability of being in group j

- Maximum probability group assignment rule: **Bayes' rule**
  - Used to assign individual to group j in which they have the largest posterior probability

- **Other uses of PPGM: one of the most important values/features in GBTM**
  - Diagnostics for model fit (i.e., PPGM >0.7)
  - Match people with comparable developmental histories (e.g., used with propensity score)
  - Compute weighted averages that account for group membership uncertainty
  - Can be further used as serial measured to examine how quickly you can correctly estimate which trajectory an individual will ultimately follow

Nagin. 2005. Group-Based Modeling of Development, Harvard University Press

Outline

- I. Overview of basic GBTM concepts
- II. Applications in health and pharmaceutical outcomes research
- III. Basic GBTM Methods with STATA tutorials
- **IV. Extensions and challenges of using GBTM**

At this point, you probably have many questions….

- How do you select the number of groups/trajectories? How do you evaluate model adequacy?
- How do you profile or describe group members?
- Can you add time-invariant covariates to the trajectory itself?
- Can you add time-varying covariates to the trajectory itself?
- Can you describe two or more behaviors/outcomes at the same time?
- What are differences between different methods to develop trajectory groups?

Select GBTM final model & model evaluation

- "Forward" classifying approach (i.e., adding one extra group at a time)
- A combination of BIC and Nagin's criteria
  - BIC: larger is better (i.e., BIC more towards to right direction of x-axis is better!)

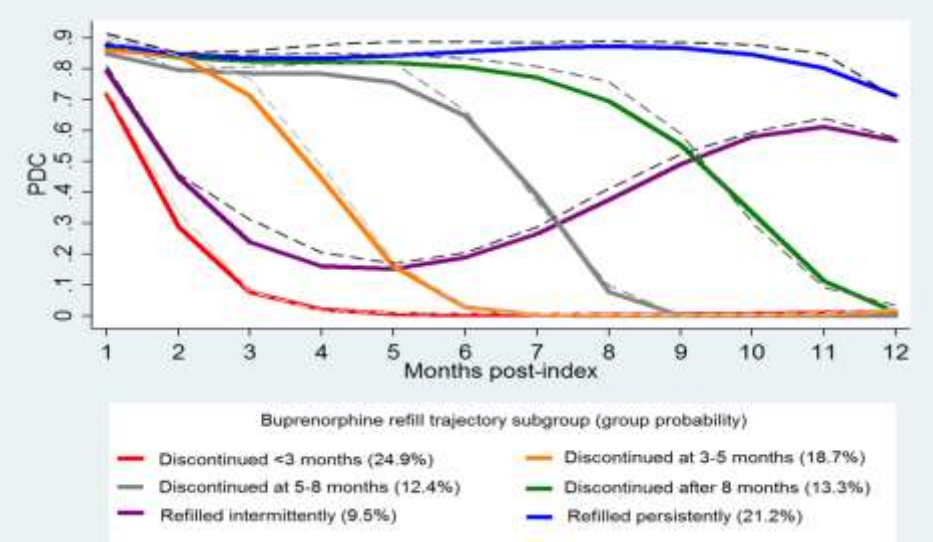
$$BIC = \log(L) - 0.5 \times \log(n) * k$$

$$(where\ L: \log\ likelihood, n: sample\ size, k: number\ of\ parameters)$$

  - Nagin's criteria
    - ❑ Average posterior probability of assignment ($PPGM\ or\ AvePP_j$) for all J groups >0.7
    - ❑ Odds of correct classification (OCC_j) ≥ 0.5, where $OCC_j = \frac{AvePP_j / 1-AvePP_j}{\hat{\pi}_j / 1-\hat{\pi}_j}$
    - ❑ Model estimate ($\hat{\pi}_j$) close to proportion of sample assigned to j ($\frac{N_j}{N}$)
    - ❑ Confidence intervals for $\hat{\pi}_j$ reasonably narrow
- Challenge: BIC keeps improving when number of groups increases, especially using large data→ usually we cannot only rely on BIC

Nagin. 2005. Group-Based Modeling of Development, Harvard University Press

Model selection example



Appendix Table 1. Bayesian Information Criterion (BIC) Values and Predicted Group Proportions for Group-Based Trajectory Models for 2-, 3-, 4-, 5-, 6-, and 7-Group Trajectory Solutions

		Predicted Group Proportions						
No. of Groups	BIC[a]	Group1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
2	-102214.5	54.8%	45.2%	-	-	-	-	
3	-94942.81	40.2%	24.9%	34.9%	-	-	-	
4	-91482.74	37.8%	9.4%	23.4%	29.3%	-	-	
5	-87557.36	29.3%	9.3%	20.8%	16.6%	23.9%	-	
6	-86246.70	9.5%	24.9%	12.3%	13.3%	18.7%	21.2%	
7	-89498.81	14.2%	13.8%	14.3%	14.3%	14.3%	14.3%	14.8%

Abbreviation: **BIC**: Bayesian information criterion

[a] This value is based on the model likelihood with a penalty for the number of model parameters. It is not directly interprAppendix Table, but the higher value here indicates better model fit.

Appendix Table 2. Final 6-Group Group-Based Trajectory Model for Buprenorphine Refill Patterns

Group (Pattern)	Estimated (95% Confidence Interval)	t	P Value
Discontinued <3 months			
Intercept	1.75 (1.70, 1.80)	72.06	<0.0001
Month	-1.00 (-1.04, -0.96)	-46.58	<0.0001
Month^2	0.11 (0.10, 0.12)	25.70	<0.0001
Month^3	-0.0037 (-0.0041, -0.0032)	-16.01	<0.0001
Discontinued at 3-5 months			
Intercept	0.91 (0.85, 0.98)	26.46	<0.0001
Month	0.41 (0.35, 0.47)	12.98	<0.0001
Month^2	-0.18 (-0.19, -0.16)	-24.26	<0.0001
Month^3	0.011 (0.010, 0.012)	26.48	<0.0001
Discontinued at 5-8 months			
Intercept	1.42 (1.34, 1.51)	32.85	<0.0001
Month	-0.41 (-0.49, -0.33)	-10.29	<0.0001
Month^2	0.13 (0.11, 0.15)	12.37	<0.0001
Month^3	-0.013 (-0.014, -0.011)	-16.77	<0.0001
Discontinued after 8 months			
Intercept	1.31 (1.25, 1.37)	42.93	<0.0001
Month	-0.18 (-0.22, -0.14)	-8.55	<0.0001
Month^2	0.045 (0.037, 0.053)	11.13	<0.0001
Month^3	-0.0037 (-0.0042, -0.0033)	-17.17	<0.0001
Refilled intermittently			
Intercept	1.84 (1.78, 1.90)	55.91	<0.0001
Month	-0.99 (-1.03, -0.94)	-42.94	<0.0001
Month^2	0.15 (0.14, 0.16)	37.37	<0.0001
Month^3	-0.0064 (-0.0068, -0.0060)	-31.77	<0.0001
Refilled persistently			
Intercept	1.36 (1.31, 1.40)	61.55	<0.0001
Month	-0.18 (-0.21, -0.15)	-12.59	<0.0001
Month^2	0.037 (0.032, 0.042)	14.69	<0.0001
Month^3	-0.0021 (-0.0024, -0.0019)	-16.61	<0.0001

Appendix Table 3. Nagin's Diagnostic Criteria for Group-Based Trajectory Model

Group	Model Estimate of Group Probability (95% CI)[a]	Proportion Classified in Group[b]	Average Posterior Probability[c]	Odds Correct Classification[d]
Discontinued at 1-3 months	0.249 (0.239, 0.259)	0.249	0.94	47.33
Discontinued at 3-5 months	0.187 (0.177, 0.197)	0.188	0.90	38.98
Discontinued at 5-8 months	0.123 (0.116, 0.131)	0.126	0.91	70.43
Discontinued after 8 months	0.133 (0.125, 0.141)	0.130	0.92	77.14
Refilled intermittently	0.095 (0.089, 0.101)	0.095	0.93	126.67
Refilled persistently	0.212 (0.204, 0.221)	0.214	0.96	88.40

[a] 95% confidence intervals (CIs), based on parametric bootstrap method, should be reasonably narrow.

[b] Proportion classified in group is based on the maximum posterior probability rule. The values of the proportion classified in the group should be similar to the model estimates of group probabilities in the second column.

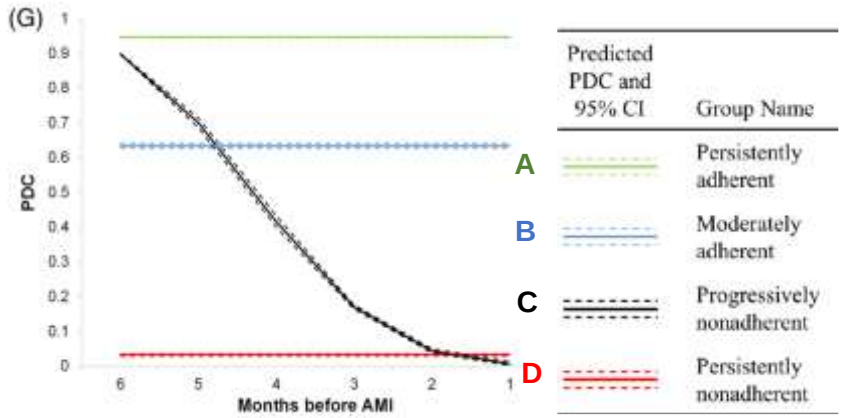
[c] Average posterior probability is obtained by averaging the posterior probabilities for a given group for all individuals placed in this group by the maximum posterior probability rule. Acceptable values for this criterion are 0.7 or greater for all groups.

[d] Acceptable values of the odds correct classification are 5.0 or greater for all groups.

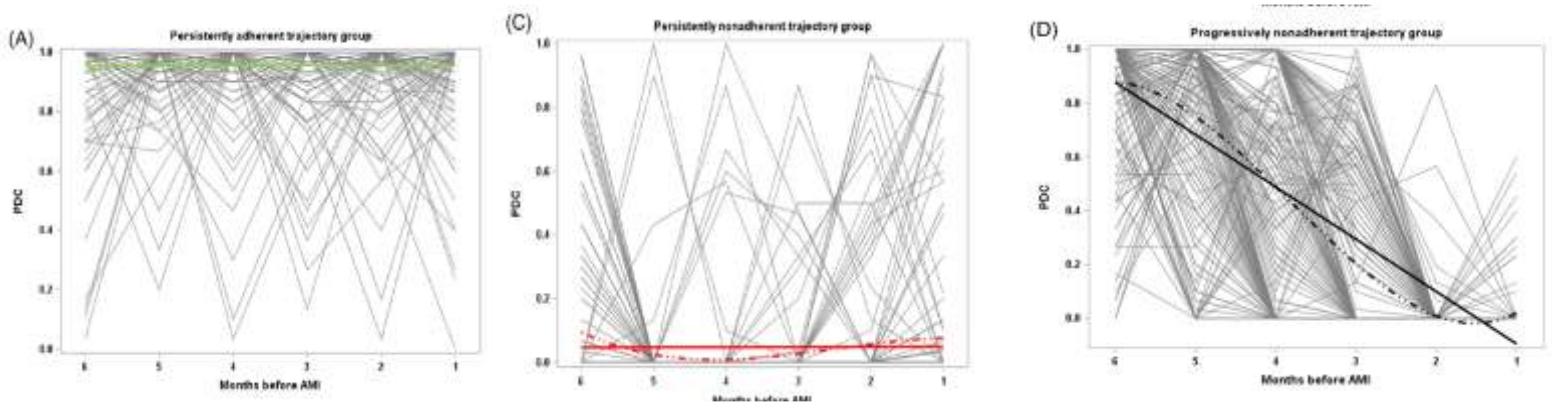
Lo-Ciganic et al. Addiction 2016; 111(5):892-902.

Implications of "Trajectory Groups" & "Group Membership"

- Sample size and length of follow-up period influence the number of groups
- Goal: identify approximation of unique patterns, not the true number of groups
- **Subjective decisions sometimes are necessary to identify a final trajectory model → transparency and disclosure of the decision are needed**
- Group membership is a convenient statistical fiction, not a state of being
  - Individuals are not necessary following the exact group-level trajectory
  - **Spaghetti plots** can provide additional diagnostic information about model fitness and homogeneity by identifying through visual inspection



Random samples of 200 individuals



Hickson RP et al. Pharmacoepidemiol Drug Saf 2020;29:357-362

Other recommended steps in model selection

- Decide optimal order of groups for the “base specification” (e.g., all cubic, 1 linear and other cubics)
  - Use BIC if possible
  - Stop when the prominent features of data appear (by consulting clinicians or experts)
- Refine the trajectories order for the optimal number of group

- Require minimum % of the cohort assigned to each trajectory group (e.g., 1%, 2.5%, 5%) based on intervention needs

- When evaluating an association between trajectories and outcomes, minimum number of outcomes occurred in each trajectory may be required to stabilize the modeling (e.g., ≥2 cases)

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- Can you add time-varying covariates to the trajectory itself?
- Can you describe two or more behaviors/outcomes at the same time?
- What are differences between different methods to develop trajectory groups?

Profile Group Characteristics

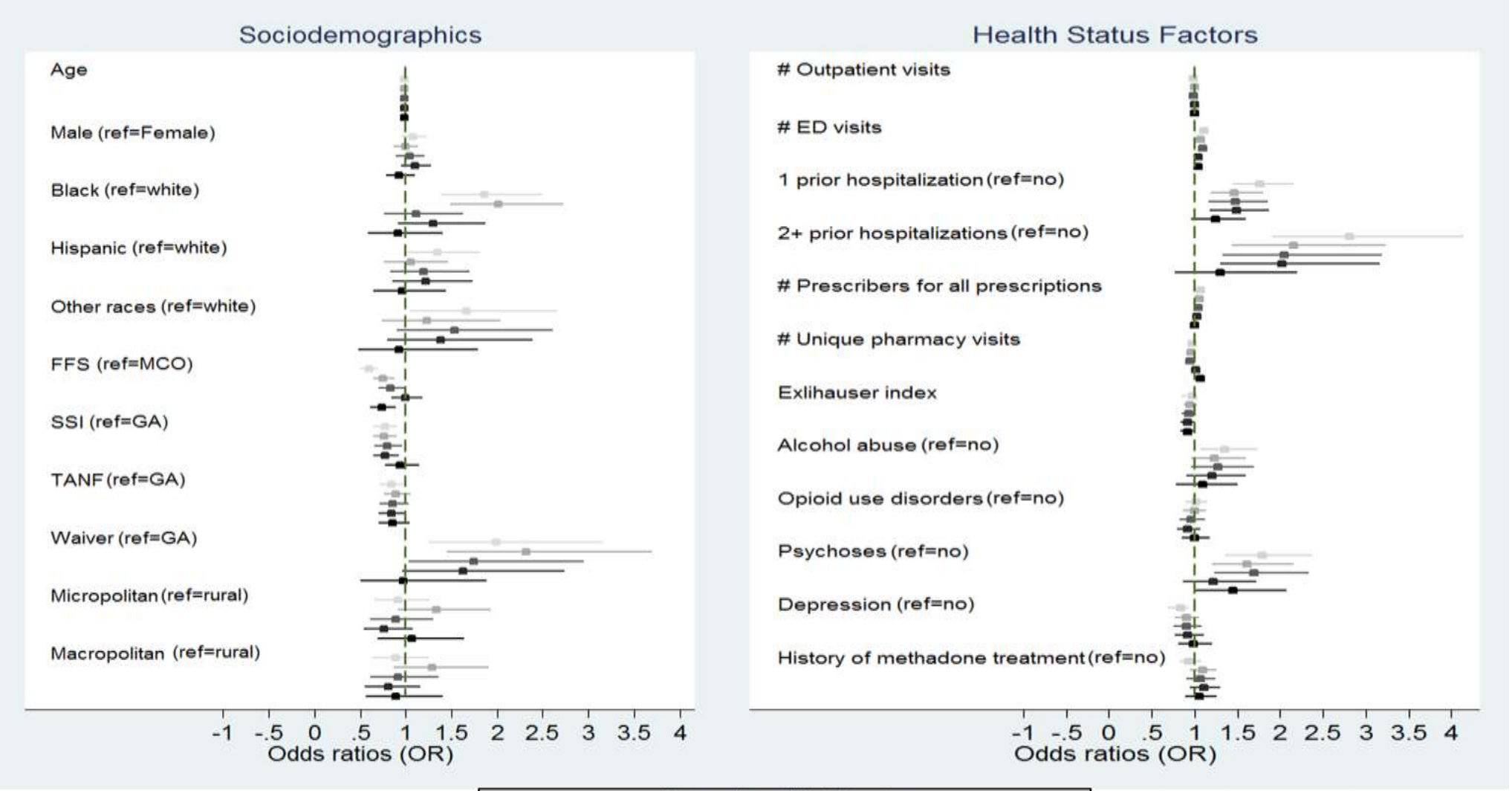
➢Conduct descriptive statistics by trajectory group

Table 1 Characteristics of Pennsylvania Medicaid enrollees with buprenorphine prescriptions and by trajectory group.

Characteristics[a]	*All cohort (n = 10 945)*	*Discontinued at 1–3 months (n = 2722)*	*Discontinued at 3–5 months (n = 2053)*	*Discontinued at 5–8 months (n = 1374)*	*Discontinued after 8 months (n = 1420)*	*Refilled intermittently (n = 1039)*	*Refilled persistently (n = 2337)*
Socio-demographics							
Age, mean (SD)***	32.8 (9.3)	32.2 (9.2)	32.7 (9.4)	32.7 (9.4)	32.8 (9.2)	32.7 (9.2)	33.7 (9.1)
Female sex, *n* (%)	6379 (58.3)	1556 (57.2)	1218 (59.3)	789 (57.4)	813 (57.3)	629 (60.5)	1374 (58.8)
Race, *n* (%)***							
White	9784 (89.4)	2370 (87.1)	1809 (88.1)	1232 (89.7)	1279 (90.1)	953 (91.7)	2141 (91.6)
Black	508 (4.7)	155 (5.7)	128 (6.2)	55 (4.0)	56 (3.9)	34 (3.3)	80 (3.4)
Hispanic	464 (4.2)	136 (5.0)	82 (4.0)	60 (4.4)	60 (4.2)	39 (3.8)	87 (3.7)
Others	189 (1.7)	61 (2.2)	34 (1.7)	27 (1.9)	25 (1.8)	13 (1.2)	29 (1.3)
Managed care health plan, *n* (%)***	7783 (71.1)	2075 (76.2)	1492 (72.7)	965 (70.2)	944 (66.5)	766 (73.7)	1541 (65.9)
Type of medical assistance eligibility, *n* (%)[§]							
GA	3248 (29.7)	846 (31.1)	618 (30.1)	424 (30.9)	441 (31.1)	301 (29.0)	618 (26.4)
SSI	3219 (29.4)	749 (27.5)	569 (27.7)	397 (28.9)	409 (28.8)	328 (31.6)	767 (32.8)
TANF	4229 (38.7)	1053 (38.7)	802 (39.1)	521 (37.9)	536 (37.7)	395 (38.0)	922 (39.5)
Waiver	249 (2.3)	74 (2.7)	64 (3.1)	32 (2.3)	34 (2.4)	15 (1.4)	30 (1.3)
Resided county, *n* (%)***							
Rural	387 (3.5)	89 (3.3)	50 (2.4)	53 (3.9)	68 (4.8)	32 (3.1)	95 (4.1)
Micropolitan	1539 (14.1)	345 (12.7)	277 (13.5)	199 (14.5)	227 (16.0)	124 (11.9)	367 (15.7)
Metropolitan	9019 (82.4)	2288 (84.1)	1726 (84.1)	1122 (81.7)	1125 (79.2)	883 (85.0)	1875 (80.2)
Health-status							
Elixhauser comorbidity index (exclude drug abuse diagnoses, range 0–30), mean (SD)	1.1 (1.4)	1.06 (1.38)	1.11 (1.38)	1.06 (1.41)	1.02 (1.30)	1.01 (1.30)	1.00 (1.28)
Opioid use disorder diagnosis, *n* (%)	7371 (67.4)	1856 (68.2)	1397 (68.1)	927 (67.5)	953 (67.1)	701 (67.5)	1537 (65.8)

Lo-Ciganic et al. Addiction 2016; 111(5):892-902.

Using multi-nominal logistic regression



Lo-Ciganic et al. Addiction 2016; 111(5):892-902.

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Statistically link group membership to individual characteristics

- Move beyond univariate contrasts
- Group identification is probabilistic, not certain
- Use of multinomial logit model to create a multivariate probabilistic linkage

$$\pi_j(X_i) = \frac{e^{X_i\theta_j}}{\sum e^{X_i\theta_j}}$$

X_i: covariate at baseline

Nagin. 2005. Group-Based Modeling of Development (Chapter 6), Harvard University Press

Including time-invariant covariates in estimating group membership (Examples 6 & 7)

STATA Syntax

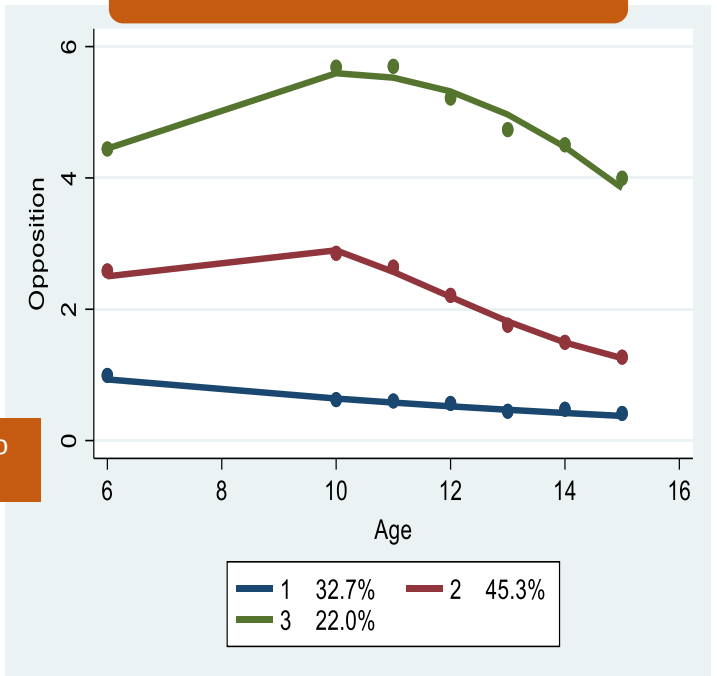
```
use http://www.andrew.cmu.edu/user/bjones/traj/data/montreal_sim.dta, clear
traj, var(qcp*op) indep(age*) model(cnorm) min(0) max(10) order(1 3 2)
risk(scolmer scolper)
trajplot, xtitle(Age) ytitle(Opposition)
```

Note: scolmer(mother's schooling); scolper (father's schooling)

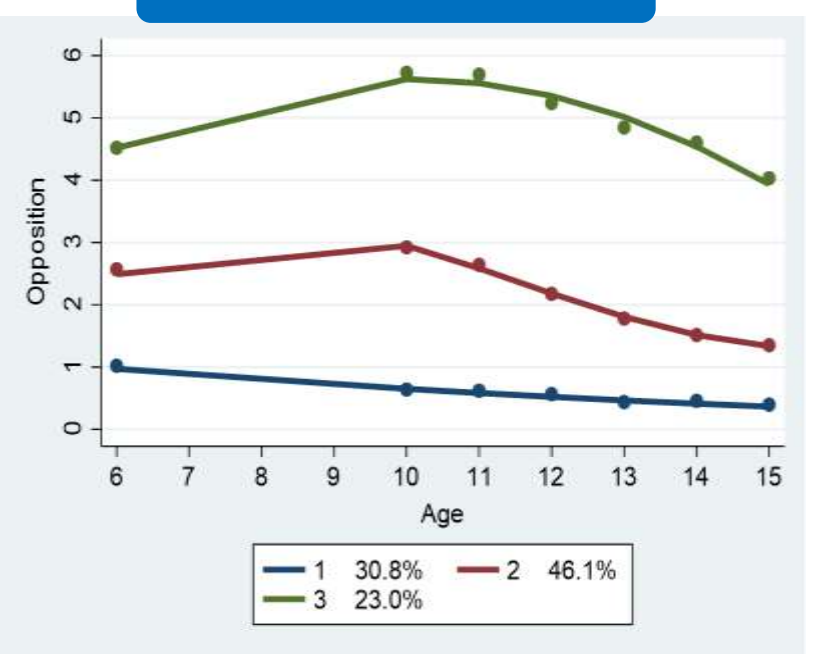
```
1037 observations read.
103 excluded by if condition or by missing values in risk variables.
934 observations used in the trajectory model.

                    Maximum Likelihood Estimates
                    Model: Censored Normal (cnorm)

                                        Standard       T for H0:
Group   Parameter        Estimate          Error     Parameter=0   Prob > |T|

1       Intercept         0.84560        0.35474           2.384       0.0172
        Linear           -0.17547        0.03054          -5.745       0.0000

2       Intercept       -11.09778        4.27423          -2.596       0.0094
        Linear            4.06464        1.36724           2.973       0.0030
        Quadratic        -0.36582        0.13554          -2.699       0.0070
        Cubic             0.00974        0.00426           2.286       0.0223

3       Intercept        -1.91440        1.02478          -1.868       0.0618
        Linear            1.50566        0.20591           7.312       0.0000
        Quadratic        -0.07512        0.00986          -7.621       0.0000

        Sigma             2.58639        0.03404          75.987       0.0000

 Group membership

1       Baseline         (0.00000)

2       Constant          1.38129        0.41387           3.337       0.0009
        scolmer          -0.04285        0.03898          -1.099       0.2717
        scolper          -0.05367        0.03128          -1.716       0.0862

3       Constant          2.43032        0.46885           5.184       0.0000
        scolmer          -0.11164        0.04285          -2.605       0.0092
        scolper          -0.16086        0.03807          -4.225       0.0000

BIC=-10802.78 (N=5726)  BIC=-10788.27 (N=934)  AIC=-10749.55  ll= -10733.55
```

Log-odds estimates (can exponentiate it to get odds ratio)

Include covariates



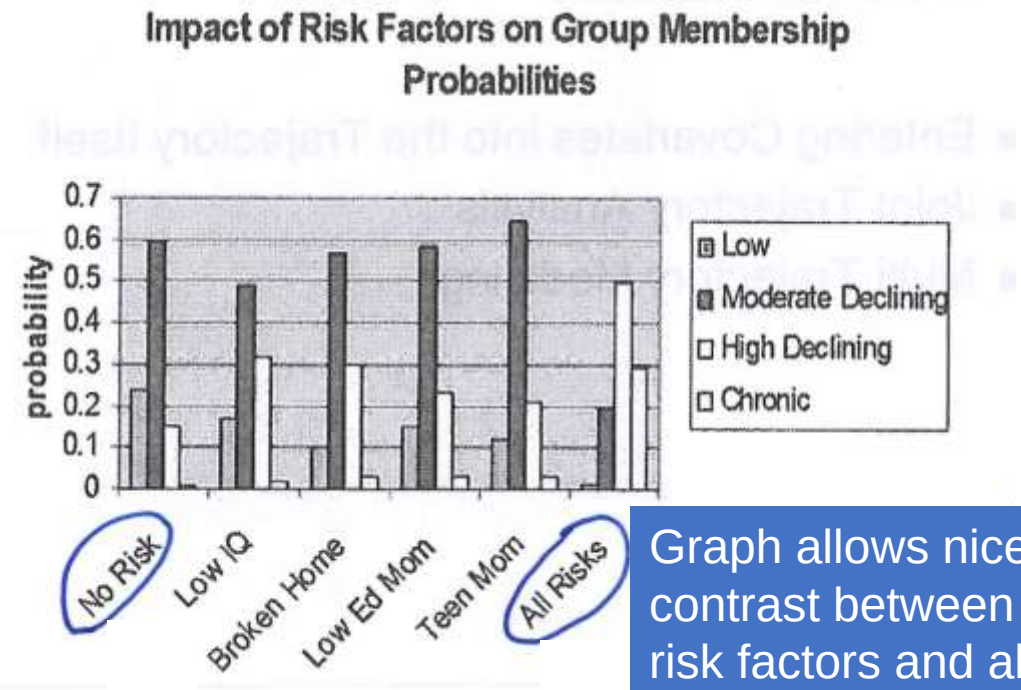
No covariates



Adapted from Jones BL and Nagin DS. A Stata Plugin for Estimating Group-based Trajectory Models (https://ssrc.indiana.edu/doc/wimdocs/2013-03-29_nagin_trajectory_stata-plugin-info.pdf)

Effect of individual covariates on probability of trajectory group membership

- Covariates or risk factors on physical aggression: broken home at age 5, low IQ, low maternal education, mother began childbearing as a teenager



Graph allows nice contrast between no risk factors and all risk factors

Nagin. 2005. Group-Based Modeling of Development, Harvard University Press

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Including time-varying covariates in estimating group membership (Example 8)

STATA Syntax (the effect of gang membership on violent delinquency)

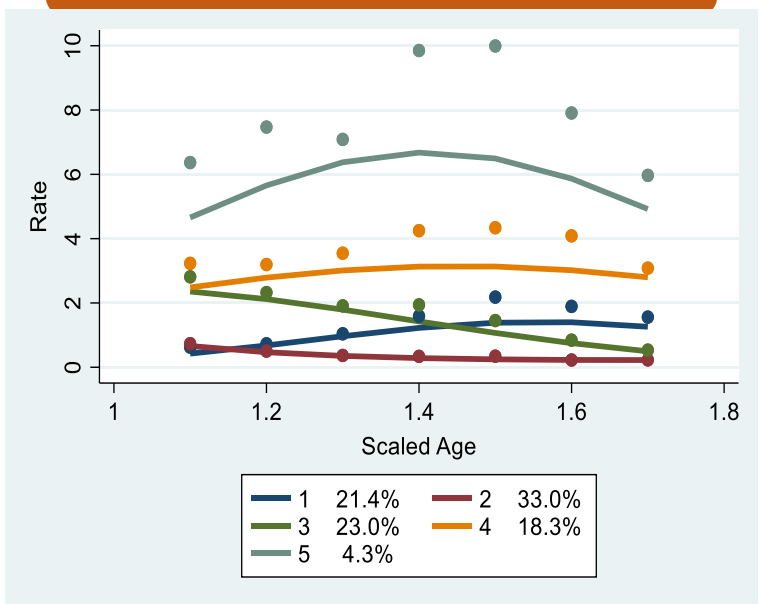
```
use http://www.andrew.cmu.edu/user/bjones/traj/data/gang_data_sim.dta, clear
matrix tc1 = 0, 0, 0, 0, 0, 0, 0
matrix tc2 = 0, 0, 0, 1, 1, 1, 1
traj, var(bat*) indep(t*) model(zip) order(2 2 2 2 2) tcov(gang*) plottcov(tc1)
trajplot, xtitle(Scaled Age) ytitle(Rate)
traj, var(bat*) indep(t*) model(zip) order(2 2 2 2 2) tcov(gang*) plottcov(tc2)
trajplot, xtitle(Scaled Age) ytitle(Rate)
```

plottcov: using a specified set of values for time-varying covariates to calculate the trajectory for each group

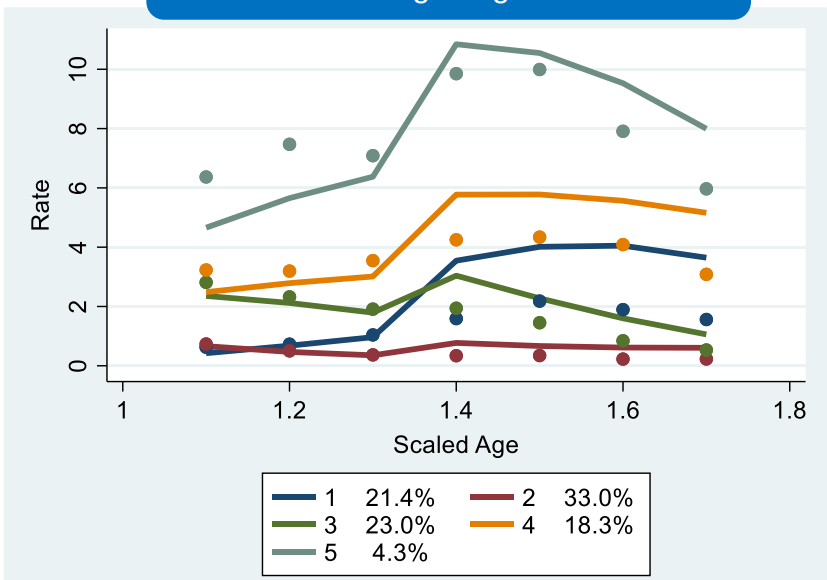
Group	Parameter	Estimate	Standard Error	T for H0: Parameter=0	Prob > |T|
1	Intercept	-13.55766	2.13701	-6.344	0.0000
	Linear	17.84557	2.98115	5.986	0.0000
	Quadratic	-5.72618	1.03068	-5.556	0.0000
	gang89	1.06276	0.07251	14.657	0.0000
2	Intercept	7.82507	2.56823	3.047	0.0023
	Linear	-11.16548	3.78599	-2.949	0.0032
	Quadratic	3.34247	1.36953	2.441	0.0147
	gang89	0.99655	0.12505	7.969	0.0000
3	Intercept	-2.03971	1.83689	-1.110	0.2669
	Linear	6.01567	2.71625	2.215	0.0268
	Quadratic	-3.07499	0.98124	-3.134	0.0017
	gang89	0.75663	0.06906	10.956	0.0000
4	Intercept	-2.88225	1.22741	-2.348	0.0189
	Linear	5.54916	1.76641	3.141	0.0017
	Quadratic	-1.91078	0.62615	-3.052	0.0023
	gang89	0.61176	0.04155	14.723	0.0000
5	Intercept	-5.46934	1.66370	-3.287	0.0010
	Linear	10.43342	2.39771	4.351	0.0000
	Quadratic	-3.69331	0.85512	-4.319	0.0000
	gang89	0.48505	0.06131	7.912	0.0000
Group membership					
1	(%)	21.43402	2.32631	9.214	0.0000
2	(%)	32.95471	2.52515	13.051	0.0000
3	(%)	23.02751	2.41169	9.548	0.0000
4	(%)	18.31497	1.80843	10.128	0.0000
5	(%)	4.26880	0.86775	4.919	0.0000

BIC= -9869.98 (N=5962) BIC= -9847.41 (N=909) AIC= -9789.67 ll= -9765.67

Predicted trajectories for **not in a gang** from age 11 to 17



Predicted trajectories for joining a gang starting at age 14



Adapted from Jones BL and Nagin DS. A Stata Plugin for Estimating Group-based Trajectory Models (https://ssrc.indiana.edu/doc/wimdocs/2013-03-29_nagin_trajectory_stata-plugin-info.pdf)

Using Wald tests to examine differential time-varying factor effects by trajectory group (Example 8)

STATA Syntax (the effect of gang membership on violent delinquency)

```
/* List the parameter estimates to verify the names for testnl */
matrix list e(b), format(%8.3f)
testnl        _b[gang89G1]=_b[gang89G5]
testnl        _b[gang89G4]=_b[gang89G5]
```

```
.     matrix list e(b), format(%8.3f)

e(b)[1,24]
     interc1   linear1   quadra1  gang89G1   interc2   linear2   quadra2  gang89G2   interc3   linear3   quadra3  gang89G3   interc4
y1   -13.558    17.846    -5.726     1.063     7.825   -11.165     3.342     0.997    -2.040     6.016    -3.075     0.757    -2.882

     linear4   quadra4  gang89G4   interc5   linear5   quadra5  gang89G5    theta2    theta3    theta4    theta5
y1     5.549    -1.911     0.612    -5.469    10.433    -3.693     0.485     0.430     0.072    -0.157    -1.614

.          testnl  _b[gang89G1]=_b[gang89G5]

  (1)  _b[gang89G1] = _b[gang89G5]

           chi2(1) =       37.22
         Prob > chi2 =      0.0000

.
end of do-file

. do "C:\Users\wlociganic\AppData\Local\Temp\STD1b6c_000000.tmp"

.          testnl  _b[gang89G4]=_b[gang89G5]

  (1)  _b[gang89G4] = _b[gang89G5]

           chi2(1) =        2.99
         Prob > chi2 =      0.0836
```

The coefficient estimates of gang effect differ for groups 1 and 5 (p<0.0001)

The coefficient estimates of gang effect differ for groups 1 and 4 (p=0.0836)

Adapted from Jones BL and Nagin DS. A Stata Plugin for Estimating Group-based Trajectory Models (https://ssrc.indiana.edu/doc/wimdocs/2013-03-29_nagin_trajectory_stata-plugin-info.pdf)

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Joint GBTM (Conditional Probability)

- Design to analyze the trajectory of two distinct but related outcomes

- To analyze connections between the developmental trajectories of two outcomes that are evolving contemporaneously (e.g., depression and alcohol use) or that evolve over different time periods (e.g., prosocial behavior in childhood and school achievement in adolescence)

- Key outputs:
  - Trajectory groups for both measurement series
  - The probability of membership in each identified trajectory
  - **Conditional probabilities** linking membership across trajectory groups of the two respective behaviors.

Adapted from Jones BL and Nagin DS. A Stata Plugin for Estimating Group-based Trajectory Models (https://ssrc.indiana.edu/doc/wimdocs/2013-03-29_nagin_trajectory_stata-plugin-info.pdf)

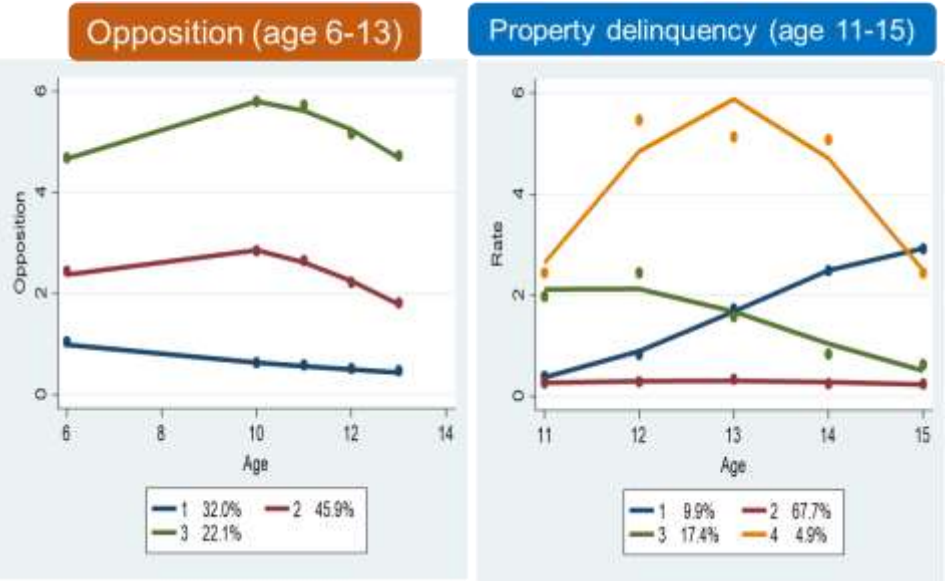
Stata: Joint GBTM (Example 13)

- Montreal data: the linkage of opposition behaviors from age 6 to 13 with property delinquency from ages 11 to 15.

STATA Syntax

```
use http://www.andrew.cmu.edu/user/bjones/traj/data/montreal_sim.dta, clear
traj, var(qcp84op qcp88op qcp89op qcp90op qcp91op) indep(age1-age5) model(cnorm)
max(10) order(1 2 2) var2(qas91det qas92det qas93det qas94det qas95det) indep2(age3-
age7) model2(zip) order2(2 2 2 2)
trajplot, ytitle(Opposition) xtitle(Age)
trajplot, model(2) ytitle(Rate) xtitle(Age)
```

Linkage of the second behavior to the first one.




```
1037 observations read.
111 had no trajectory data in one or more models.
926 observations used in the trajectory model.

                                Maximum Likelihood Estimates

Model 1: Censored Normal (cnorm)

                                                 Standard       T for H0:
 Group    Parameter          Estimate             Error     Parameter=0    Prob > |T|

 1        Intercept           1.16474           0.42020           2.772        0.0056
          Linear             -0.20897           0.04067          -5.138        0.0000

 2        Intercept          -4.05910           1.21540          -3.340        0.0008
          Linear              1.54350           0.28069           5.499        0.0000
          Quadratic          -0.08723           0.01492          -5.846        0.0000

 3        Intercept          -3.10754           1.66309          -1.869        0.0617
          Linear              1.88769           0.37550           5.027        0.0000
          Quadratic          -0.09922           0.02004          -4.951        0.0000

          Sigma               2.58442           0.03869          66.791        0.0000

  Group membership
 1        (%)                31.98140           2.84491          11.242        0.0000
 2        (%)                45.87196           2.67176          17.169        0.0000
 3        (%)                22.14664           2.22598           9.949        0.0000

Model 2: Zero Inflated Poisson (zip)

 1        Intercept         -26.00646           9.25612          -2.810        0.0050
          Linear              3.56733           1.36971           2.604        0.0092
          Quadratic          -0.11746           0.05029          -2.336        0.0195

 2        Intercept          -9.40269           4.17323          -2.253        0.0243
          Linear              1.29761           0.64879           2.000        0.0455
          Quadratic          -0.05117           0.02501          -2.046        0.0408

 3        Intercept         -15.18443           4.93818          -3.075        0.0021
          Linear              2.77275           0.79982           3.467        0.0005
          Quadratic          -0.12038           0.03216          -3.744        0.0002

 4        Intercept         -33.08770           4.27629          -7.737        0.0000
          Linear              5.37717           0.66146           8.129        0.0000
          Quadratic          -0.20736           0.02543          -8.154        0.0000
```


Adapted from Jones BL and Nagin DS. A Stata Plugin for Estimating Group-based Trajectory Models (https://ssrc.indiana.edu/doc/wimdocs/2013-03-29_nagin_trajectory_stata-plugin-info.pdf)

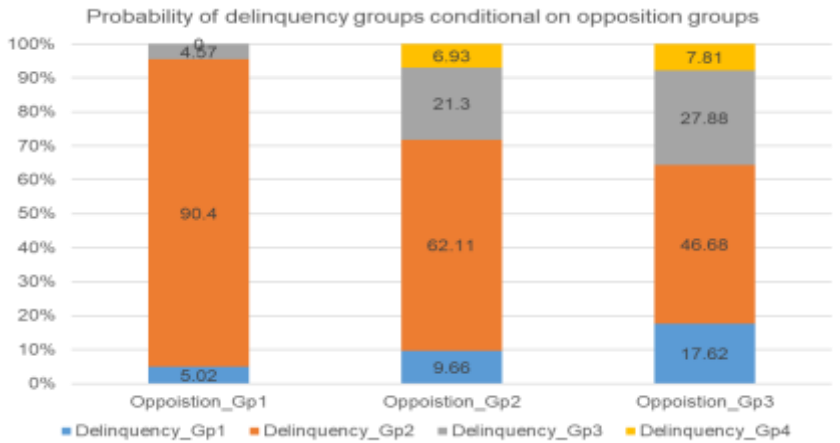
State: Joint GBTM (Example 13, continued)

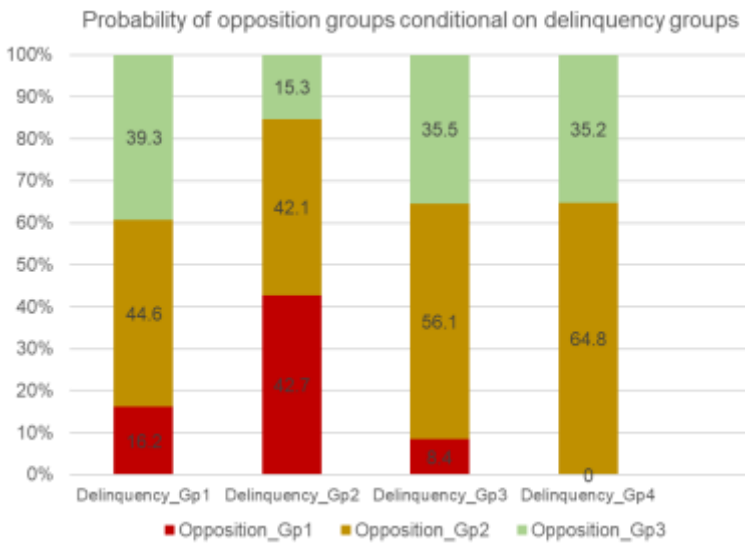
```
Group membership (model 2 group | model 1 group)

1|1     (%)              5.02072      1.86656         2.690       0.0072
2|1     (%)             90.40582      2.75608        32.802       0.0000
3|1     (%)              4.57346      2.42051         1.889       0.0589
4|1     (%)              0.00000      0.00089         0.001       0.9989
1|2     (%)              9.65663      2.35961         4.092       0.0000
2|2     (%)             62.11232      3.52639        17.614       0.0000
3|2     (%)             21.30089      3.15883         6.743       0.0000
4|2     (%)              6.93015      1.52323         4.550       0.0000
1|3     (%)             17.62210      4.71857         3.735       0.0002
2|3     (%)             46.68406      4.67178         9.993       0.0000
3|3     (%)             27.87968      5.30155         5.259       0.0000
4|3     (%)              7.81416      2.56922         3.041       0.0024
```

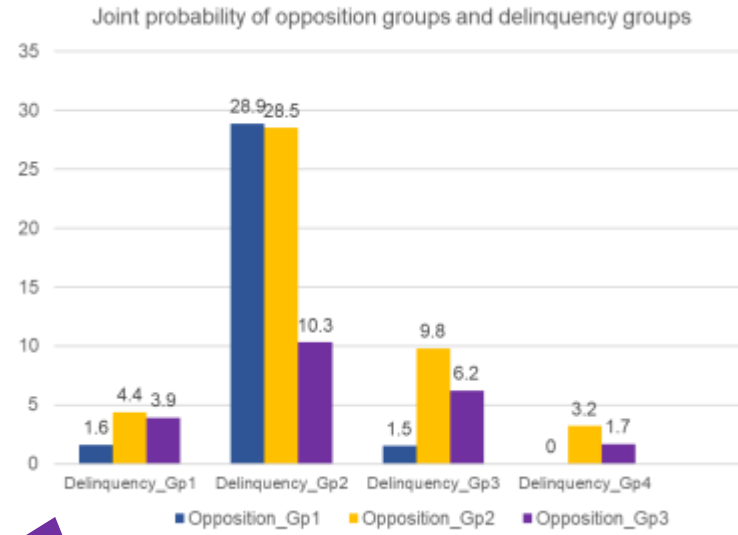
```
Group membership (model 1 group | model 2 group)

1|1    (16.2%)
2|1    (44.6%)
3|1    (39.3%)
1|2    (42.7%)
2|2    (42.1%)
3|2    (15.3%)
1|3    ( 8.4%)
2|3    (56.1%)
3|3    (35.5%)
1|4    ( 0.0%)
2|4    (64.8%)
3|4    (35.2%)
```

```
Group membership (model 1 group and model 2 group)

1 1    ( 1.6%)
2 1    ( 4.4%)
3 1    ( 3.9%)
1 2    (28.9%)
2 2    (28.5%)
3 2    (10.3%)
1 3    ( 1.5%)
2 3    ( 9.8%)
3 3    ( 6.2%)
1 4    ( 0.0%)
2 4    ( 3.2%)
3 4    ( 1.7%)
```

```
Group membership (model 2 group)

1 ( 9.9%)
2 (67.7%)
3 (17.4%)
4 ( 4.9%)
BIC=-13612.04 (N=8872)  BIC=-13575.89 (N=926)  AIC=-13498.59  ll= -13466.59
```







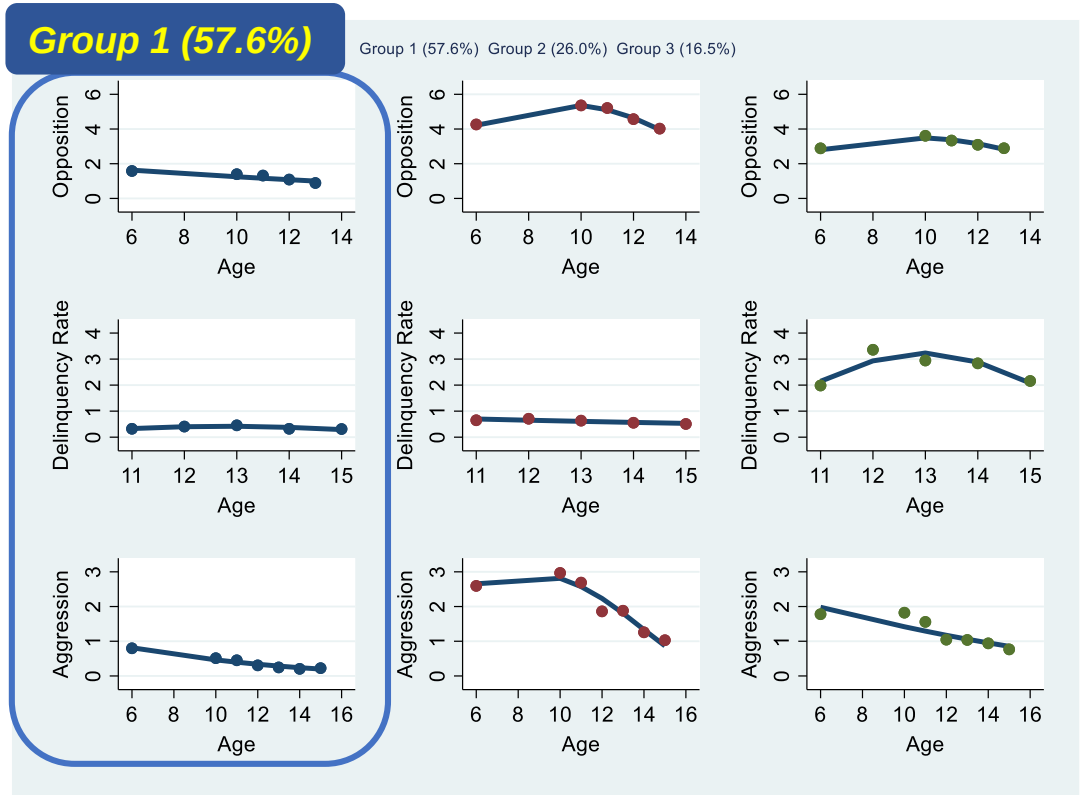
Adapted from Jones BL and Nagin DS. A Stata Plugin for Estimating Group-based Trajectory Models (https://ssrc.indiana.edu/doc/wimdocs/2013-03-29_nagin_trajectory_stata-plugin-info.pdf)

Stata: Multi-trajectory modeling (Example 14)

- Montreal data: opposition behaviors from age 6 to 13, property delinquency from ages 11 to 15, and aggression from age 6 to 16

STATA Syntax

```
use http://www.andrew.cmu.edu/user/bjones/traj/data/montreal_sim.dta, clear
traj, multgroups(3) var1(qcp84op-qcp91op) indep1(age1-age5) model1(cnorm) max1(10) order1(1 2 2) var2(qas*det)
indep2(age3-age7) model2(zip) order2(2 1 2) var3(qcp*bat) indep3(age*) model3(cnorm) max3(6) order3(1 2 1)
multtrajplot, xtitle(Age) ytitle1(Opposition) ytitle2(Rate) ytitle3(Aggression) ylabel1(0(2)6) ylabel2(0(1)4) ylabel3(0(1)3)
```



Maximum Likelihood Estimates
Model: Censored Normal (cnorm)

Group	Parameter	Estimate	Standard Error	T for H0: Parameter=0	Prob > |T|
1	Intercept	1.89454	0.27078	6.997	0.0000
	Linear	-0.16393	0.02576	-6.365	0.0000
2	Intercept	-4.69104	1.49713	-3.133	0.0017
	Linear	2.17218	0.33965	6.395	0.0000
	Quadratic	-0.11641	0.01816	-6.411	0.0000
3	Intercept	-2.62020	1.91519	-1.368	0.1713
	Linear	1.25196	0.43270	2.893	0.0038
	Quadratic	-0.06562	0.02311	-2.840	0.0045
	Sigma	2.79749	0.04031	69.395	0.0000

Maximum Likelihood Estimates
Model: Zero Inflated Poisson (zip)

Group	Parameter	Estimate	Standard Error	T for H0: Parameter=0	Prob > |T|
1	Intercept	-13.09851	3.71311	-3.528	0.0004
	Linear	1.91301	0.57907	3.304	0.0010
	Quadratic	-0.07478	0.02238	-3.341	0.0008
2	Intercept	0.40663	0.45454	0.895	0.3710
	Linear	-0.06939	0.03458	-2.007	0.0448
3	Intercept	-16.67314	2.58595	-6.448	0.0000
	Linear	2.75359	0.40141	6.860	0.0000
	Quadratic	-0.10621	0.01546	-6.871	0.0000

Maximum Likelihood Estimates
Model: Censored Normal (cnorm)

Group	Parameter	Estimate	Standard Error	T for H0: Parameter=0	Prob > |T|
1	Intercept	1.11025	0.21865	5.078	0.0000
	Linear	-0.23407	0.01906	-12.280	0.0000
2	Intercept	-1.98752	0.86319	-2.303	0.0213
	Linear	1.18337	0.17354	6.819	0.0000
	Quadratic	-0.07083	0.00831	-8.522	0.0000
3	Intercept	2.91652	0.38085	7.658	0.0000
	Linear	-0.20810	0.03228	-6.447	0.0000
	Sigma	2.39838	0.04016	59.726	0.0000
Group membership					
1	(%)	57.55564	1.85684	30.997	0.0000
2	(%)	25.95763	1.75031	14.830	0.0000
3	(%)	16.48673	1.41183	11.678	0.0000

BIC=-21566.96 (N=15098) BIC=-21529.27 (N=926) AIC=-21464.05 ll= -21437.05

Nagin DS et al. Stat Methods Med Res. 2018;27:2015–2023.

At this point, you probably have many questions….

- How do you select the number of groups/trajectories? How do you evaluate model adequacy?
- How do you profile or describe group members?
- Can you add time-invariant covariates to the trajectory itself?
- Can you add time-varying covariates to the trajectory itself?
- Can you describe two or more behaviors/outcomes at the same time?
- What are differences between different methods to develop trajectory groups?

Comparisons of Different Methods to Develop Trajectory Groups

Methods	Descriptions
K-mean clustering	1. Simpler and faster (less computational time) 2. Longitudinal nature of the data is ignored
'Two-step'' approach (i.e., mixed modeling + K-means clustering)	1. Does not ignore the longitudinal nature of the data
Latent class analysis (LCA)	1. Structural equation modeling (SEM)-based using latent variable (finite mixture modeling) 2. Accommodate inter-individual variability (between-subjects) and intraindividual (within-subjects) patterns of change over time 3. Assumption: data consist of ≥1 trajectory groups 4. Have relative objective criteria (i.e., model fit indicators, e.g., BIC)
Latent class growth analysis (LCGA)	1. Same as (1) to (4) in LCA **2. Assumption: there is no within class variation (i.e., no random effects)** **3. GBTM is a LCGA (GBTM approximates an unknown distribution of individual differences with group)** 4. Software: SAS, STATA
Latent class growth mixture modeling (LCGMM)	1. Same as (1) to (4) in LCA **2. Assumption: there can be within class variation (including normally-distributed random effects; may cause computation difficulties)** 3. Usually has less groups identified than LCA 4. Software: M-plus

1. Twish J et al. J Clin Epidemiol 2012; 65:1078-1087; 2. Advances in Life Course Research 43 (2020) 100323;

Comparisons of Different Methods to Develop Trajectory Groups

- Generally, all classification methods revealed comparable trajectories
  - GBTM, LCGA, and LCGMM seem to be preferable above the more simple methods (e.g., k-means clustering), all classification methods should be applied with great caution.
  - The optimal solution for LCA and LCGA contained more classes compared with LCGMM
  - LCGMM may increase computational times.

Table 3
Features of popular software for longitudinal FMM (as at May 2019) (*Only those mentioned in Section 3 in this paper are reported).

Software	SAS	Stata	Mplus	R	Latent GOLD
Relevant package/ procedure	Proc Traj	Traj, GLLAMM	TYPE = MIXTURE	LCMM, OpenMX, flexMix, mclust, mixtools	FM Regression
Model types	GBTM	Traj: GBTM, GLLAMM: GMM, LCGA	GMM, LCGA, GBTM	GMM, LCGA, GBTM	GMM, LCGA, GBTM
Outcome types and link function					
Continuous	Censored normal	Censored normal/ beta	Normal/ censored normal	Normal/ censored normal	Multivariate/ censored/ truncated normal
Categorical (ordinal and nominal)	✗	Traj: ✗ GLLAMM: Multinomial logit	Multinomial logit	Multinomial logit	Multinomial logit
Binary	Logit	Probit/ logit	Probit/ logit	Probit/ logit	Probit/ logit
Count	Poisson, Zero inflated Poisson	Zero inflated Poisson	Poisson, Zero inflated Poisson, Negative binomial	Poisson	Truncated/ overdispersed Poisson, truncated/ overdispersed binomial, Zero inflated Poisson, Negative binomial
Trajectory specification					
Random effects	Censored normal only	Traj: ✗ GLLAMM: ✓	✓	✓	✓
Covariance structure of random effects (D matrix)	Censored normal: Equal between classes	Traj: No random effects GLLAMM: Covariance structure may be specified by user	Covariance structure may be specified by user	Covariance structure may be specified by user	Covariance structure may be specified by user
R matrix	Fixed to be the same across classes and time	Traj: Fixed to be the same across classes and time GLLAMM: Structure may be specified by user	Structure may be specified by user	Structure may be specified by user	Structure may be specified by user
Allows for first-order autoregressive term in R	✗	Traj: ✗ GLLAMM: ✓	✓	Package dependent LCMM, OpenMX: ✓	✓
Fit criteria and test statistics					
Fit and test statistics*	AIC, APPA, BIC, log-likelihood, Wald test	AIC, BIC, log-likelihood	AIC, APPA, aLMR, BIC, BLRT, MVK, MVS, ssBIC, VLMR, Wald test	AIC, APPA, BIC, BLRT, CAIC, CVE, ssBIC	AIC, BIC, BLRT, CAIC, CLC, ICL-BIC, ssBIC

1. Twish J et al. J Clin Epidemiol 2012; 65:1078-1087; 2. Advances in Life Course Research 43 (2020) 100323;

At this point, you probably have many questions….

- How do you select the number of groups/trajectories? How do you evaluate model adequacy?
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- Can you add time-varying covariates to the trajectory itself?
- Can you describe two or more behaviors/outcomes at the same time?

Summary of GBTM

- Identify and visualize groups following similar dynamic changes in medication utilization or other measures over time
- Transparency and disclosure of the decision for final model section are needed
- Equivalent or better prediction performance
- Different trajectories may have different characteristic profiles
- May better inform and guide target interventions and clinical management

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- **University of Kentucky**: Chris Delcher

Thank you!

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