Medicine: Mind the Gap

Time-varying effect modeling to study developmental and dynamic processes

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PENNSTATE 1855
The Methodology Center
advancing methods, improving health

Outline

1. Background
2. Study I: Nicotine addiction
   - Recovery is dynamic
3. Study II: E-cigarette use
   - A developmental perspective
4. Next steps

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1. **Background**
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Human behavior as it relates to health is dynamic

Orientation is relevant for understanding

- Behavioral change – across age, time
- Changes in process – across age, time
- Differential intervention effects – across age, time

A motivating example

We know that negative affect and craving to smoke are tightly linked among addicted smokers. What does recovery look like?

TVEM can address questions such as:

Is negative affect differentially associated with craving at various points in the smoking cessation process?

How does a smoking cessation intervention affect that link over time?

A thought exercise

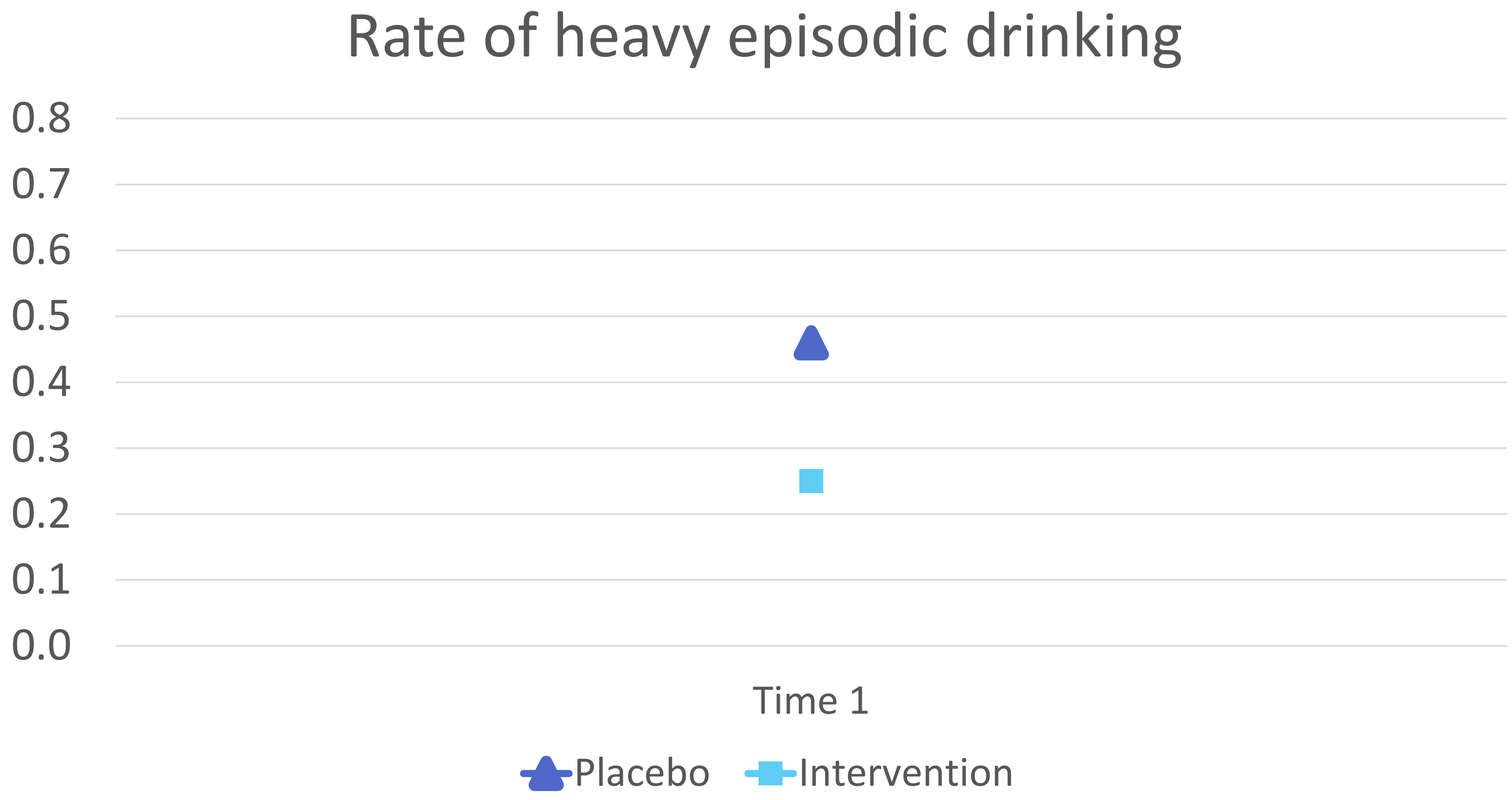
Suppose an intervention was conducted to reduce alcohol abuse

2-arm RCT

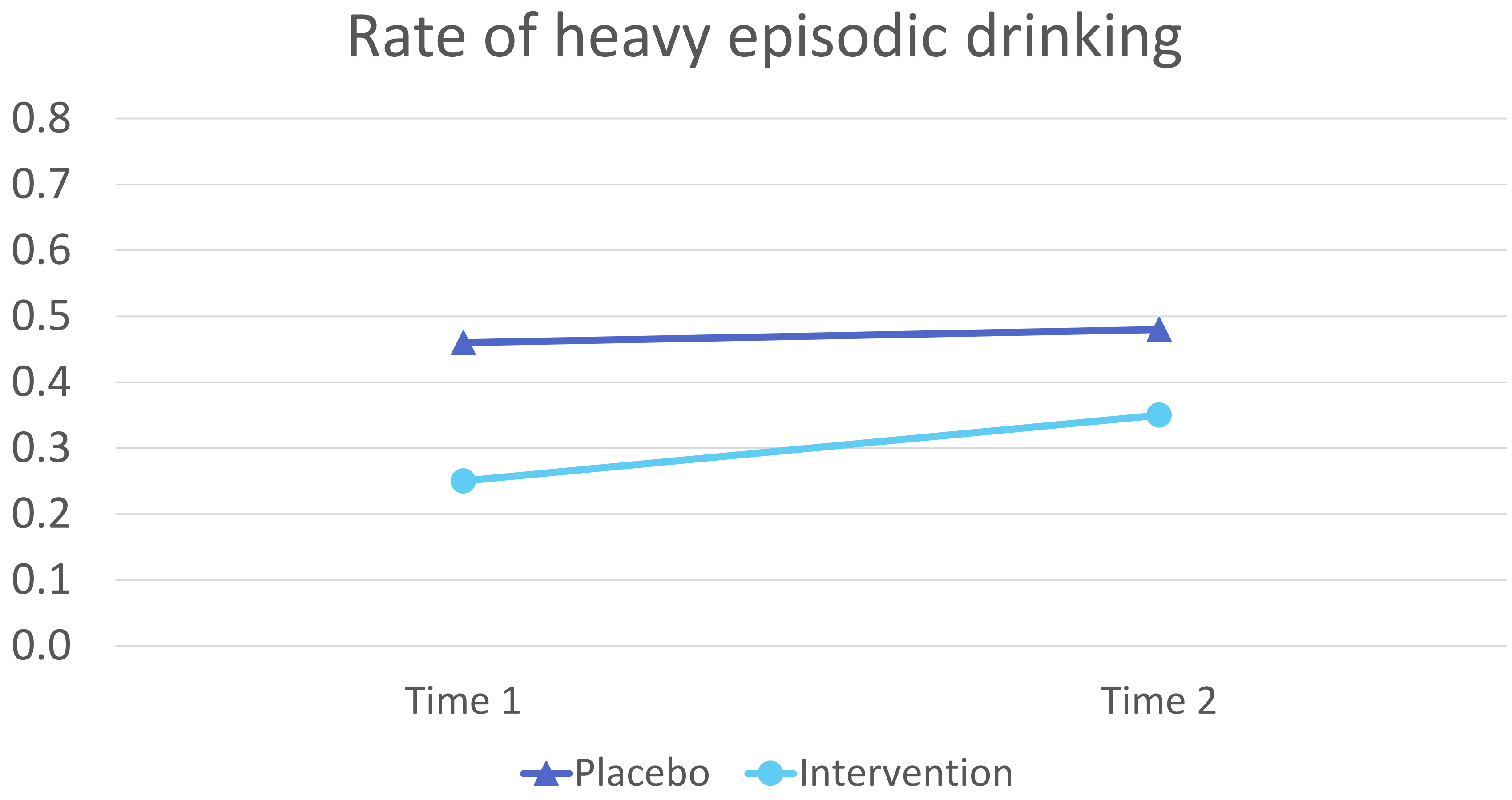
Post-baseline measurement

- One time point
- Two time points
- Multiple time points (moving window)

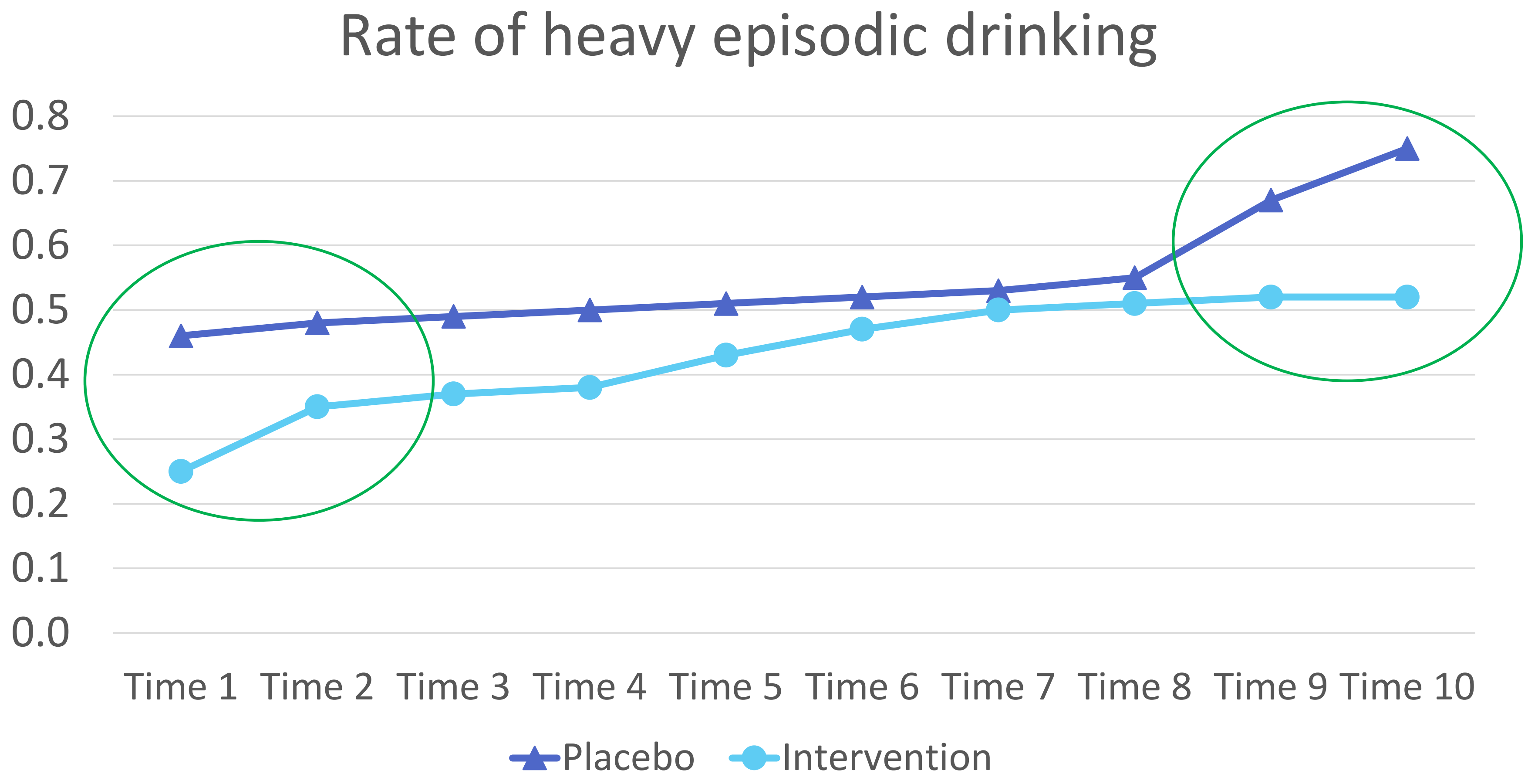
Effect of intervention: One time



Effect of intervention: Two times



Effect of intervention: Multiple times



TVEM: Direct extension of regression

P50-DA039838: Center for Complex Data to Knowledge (CD2K) in Drug Abuse and HIV Behavioral Science

Why collect longitudinal data?

- capture temporal changes in an outcome and time-varying covariates

Natural to expect that the associations between covariates and outcome may change over time

TVEM is designed to evaluate whether and how associations change over time

TVEM: Direct extension of regression

Regression coefficients express associations between variables

Traditional regression predicting outcome (*Y*) from covariate (*X*)

$$Y = \beta_0 + \beta_1 X + e$$

TVEM allows coefficients to be <u>dynamic</u>

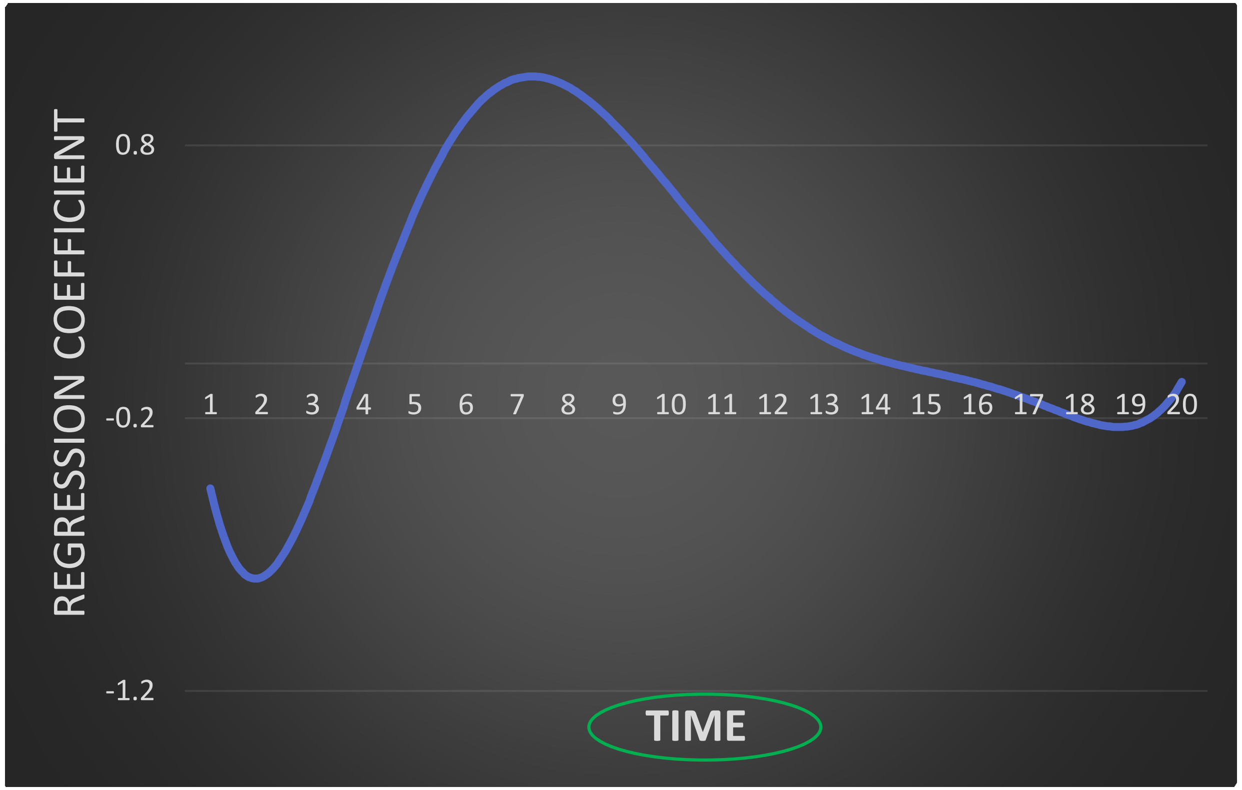
$$Y = \beta_0(\boldsymbol{t}) + \beta_1(\boldsymbol{t}) X + e$$

Coefficient functions are estimated

TVEM estimates regression coefficients as flexible function of continuous time

- Intercept
- Slopes

Use figure to interpret a "coefficient function"



Brief history of TVEM

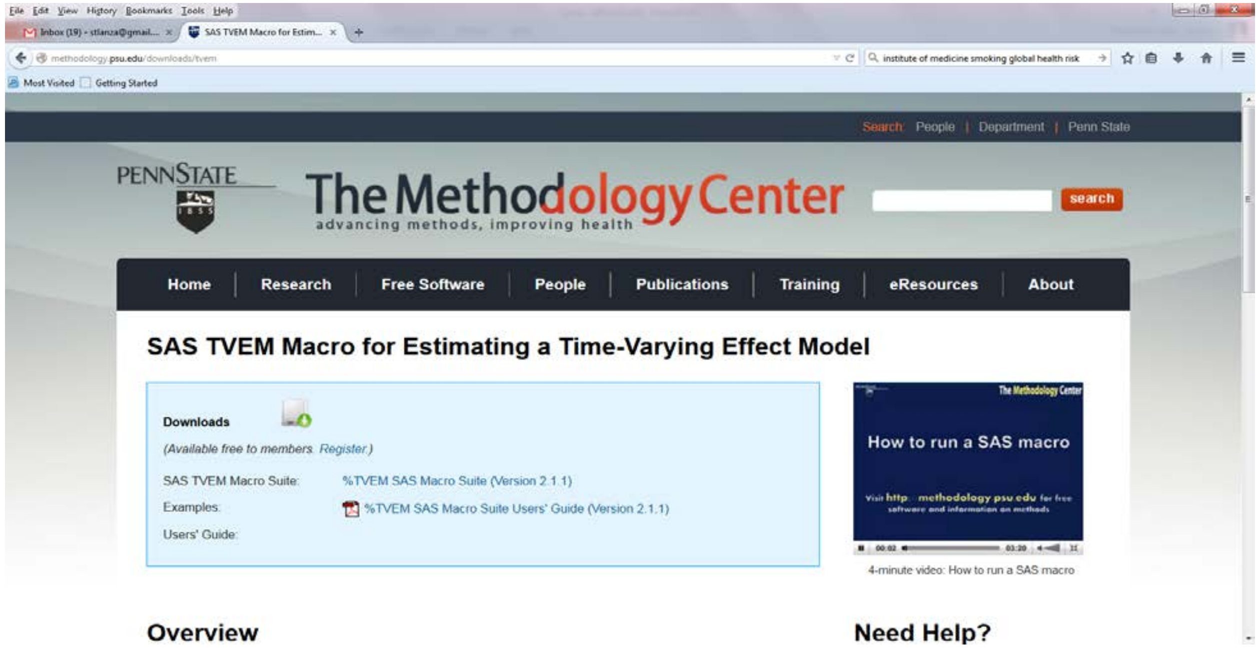
1990's

- Functional regression analysis introduced in statistical literature (Hastie & Tibshirani, 1993; Hoover et al., 1998)

2010

- SAS software released

(under direction of Runze Li)



Brief history of TVEM

2012

- Demonstration paper – *Prevention Science*
- Pre-conference workshop – Society for Research on Nicotine and Tobacco
- NCI R01 – Smoking cessation dynamics

2013

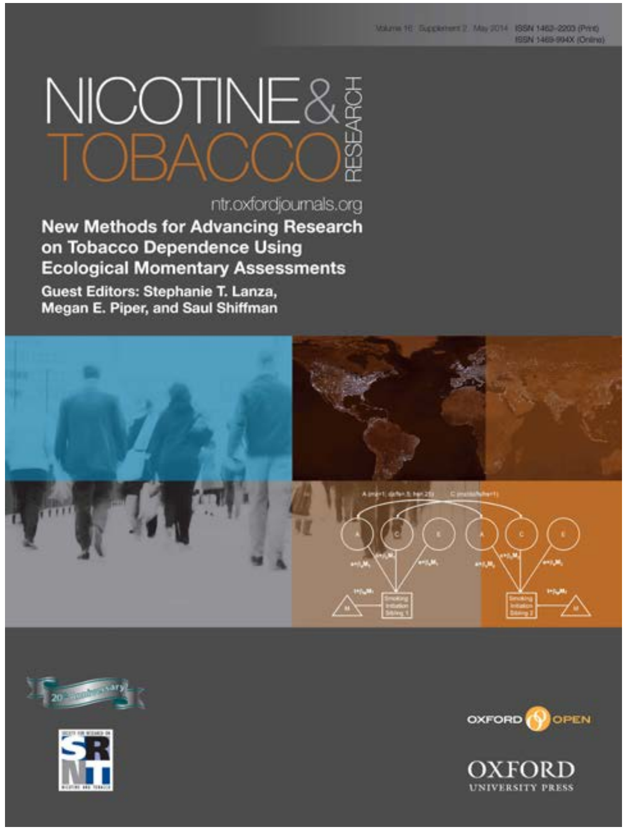
- Pre-conference workshop – Society for Prevention Research
- NCI, OBSSR funds supplemental issue of *Nicotine and Tobacco Research*
- Application paper – *Drug and Alcohol Dependence*

Brief history of TVEM

2014

- Supplemental issue published

  (Lanza, Piper, & Shiffman, Eds.)
- **Other researchers picking up TVEM**



2015

- Summer Institute on Innovative Methods
- Pre-conference workshop – Society for Ambulatory Assessments
- Software extended: random effects
- NIDA R01 – Epidemiology of substance use

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Nicotine addiction

Tobacco use is leading cause of preventable death globally

95% cessation attempts end in relapse; withdrawal symptoms primary reason

Improved understanding of withdrawal symptoms and how treatments alleviate them could:

- Lead to new treatments
- Inform tailored treatments (to people, to time)

Nicotine addiction

Overall goal:

To apply innovative methods to existing data from an RCT to gain knowledge that can inform next generation of smoking interventions

R01-CA168676: Advancing Tobacco Research by Integrating Systems Science and Mixture Models

Wisconsin Smokers' Health Study

1504 daily smokers enrolled in smoking cessation RCT

- Funded by P50-CA84724

Placebo group

- Counseling only

Treatment group

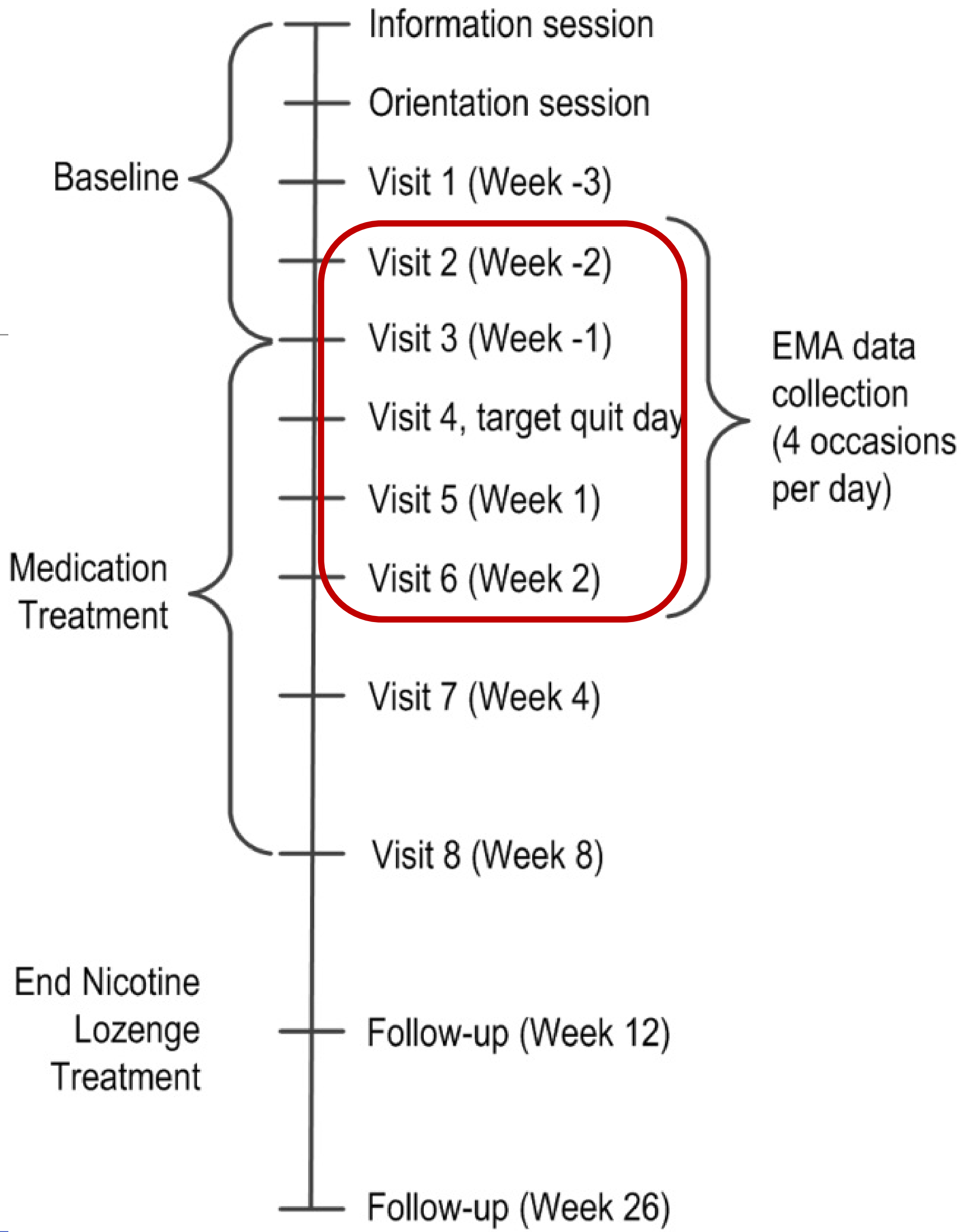
- Five combinations of Bupropion, lozenge, patch

Real-time assessment of dynamic phenomena (withdrawal symptoms, mood, behavior)

Study design

EMA: 4 assessments per day

- Upon waking
- 2 random times
- At bedtime



Time-varying effects of smoking intervention

Goal 1: Study the underlying dynamics of craving during cessation attempt

Goal 2: Estimate effect of intervention on decoupling craving from its key drivers (e.g., negative affect)

From Lanza et al. (2014) *Nicotine and Tobacco Research*

Measures

Outcome: **Craving** during first two weeks of quit attempt

- Intensively assessed via EMA

Predictors:

- **Baseline nicotine dependence** (not time-varying, but *effect* can be!)
- **Negative affect** (time-varying)

Moderator: **Intervention group**

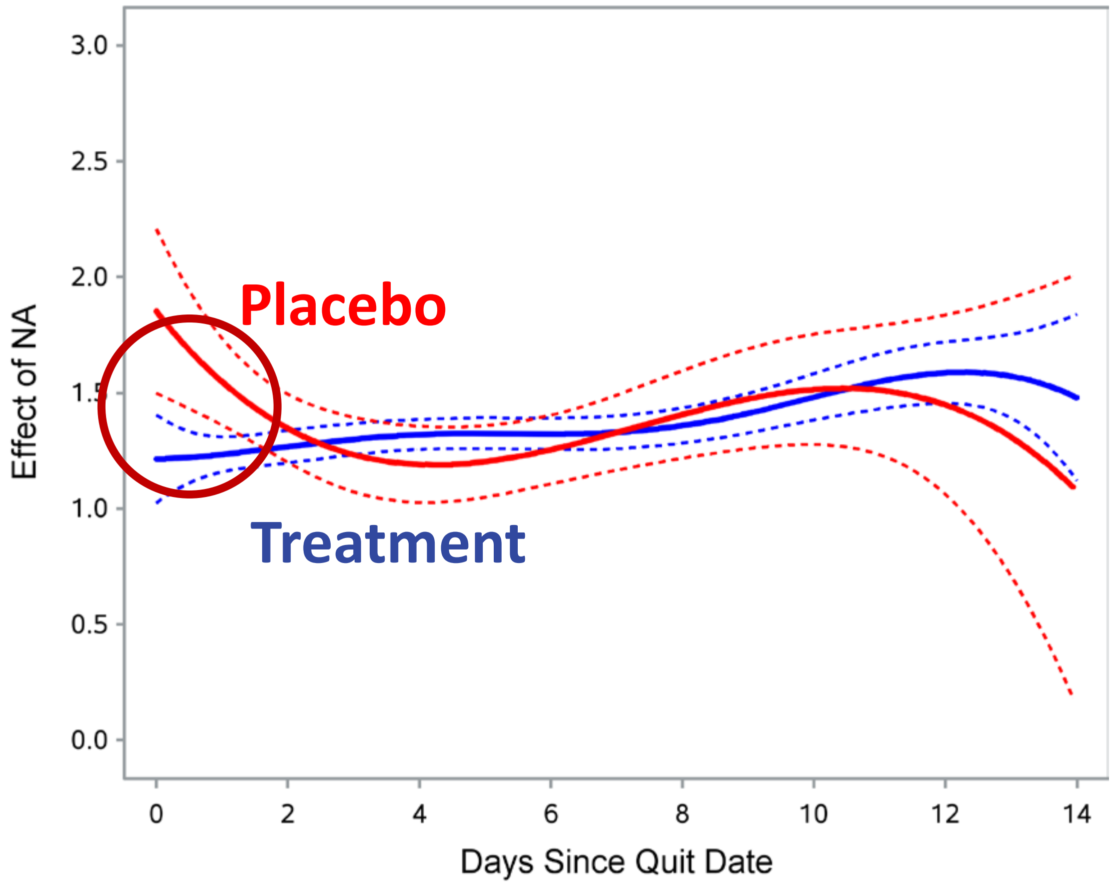
Specify model

Within each intervention group, what varies with time?

- Mean craving (intercept function)
- Negative affect
- Effect of negative affect (slope function)
- Effect of baseline dependence (slope function)

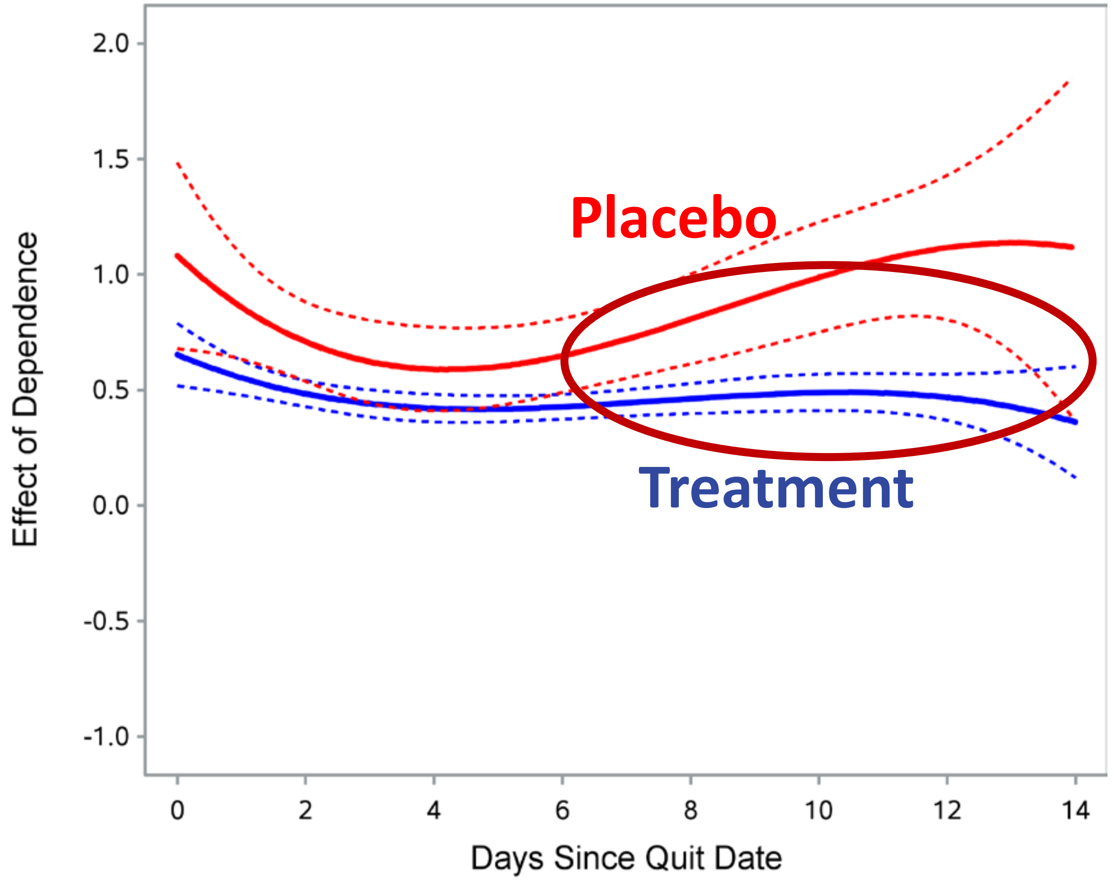
$$CRAVING_{it} = \beta_0(t) + \beta_1(t)AFFECT_{it} + \beta_2(t)DEP_i + \epsilon_{it}$$

Effect on craving: Negative affect



Lanza et al. (2014) Nicotine and Tobacco Research

Effect on craving: Baseline dependence



Lanza et al. (2014) Nicotine and Tobacco Research

Implications for smoking cessation

Think differently about intervention effects

With time, intervention changes the relationship between baseline dependence and craving

Intervention diffuses role of negative affect– a key driver of craving – early in quit attempt

Broader implications

Effects of static “baseline” variables can change over time

Effect of treatment in standard RCT may be time-varying

- Model intervention processes we posit

Could inform tailoring of treatment to **individuals** and to **time** (adaptive intervention designs)

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NIDA R01

Overall goal:

To apply TVEM to existing national data to study etiology of substance use, co-use, comorbidity with mental health problems, and health disparities

R01-DA039854: Age-Varying Effects in the Epidemiology of Drug Abuse

E-cigarette use among adolescents

Developed as "reduced harm product" thus often considered safe alternative to traditional cigarettes *(Cobb et al., 2010)*

Inhalation-activated devices; heat produced which turns solution (nicotine, other additives) into vapor

- Eliminates combustion/smoke, but long-term effects of use inconclusive *(Chapman & Wu, 2014; Cobb et al., 2010; Pepper & Brewer, 2014, Williams & Talbot, 2011)*

Rate of adolescent use rising rapidly

- Lack of FDA regulations
- Gateway to traditional cigarettes?

National Youth Tobacco Study

Cross-sectional data from 2014

CDC to assess “tobacco-related beliefs, attitudes, behaviors, and exposure to pro- and anti-tobacco influences”

22,007 US middle- and high-school students

- ages 11-19 (mean 14.5)
- 49% female
- 29% Hispanic, 48% NH White, 17% NH Black

Etiology of traditional and e-cigarette use

Goal 1: Estimate disparities in rates of use across adolescence for sex and race/ethnicity population subgroups

Goal 2: Estimate rate of use of <u>both</u> products as continuous function of age

From Lanza et al. (under review)

Measures

Current traditional cigarette smoking

- Coded 1 if use in past 30 days, 0 otherwise (6.4% yes)

Current e-cigarette smoking

- Coded 1 if use in past 30 days, 0 otherwise (9.2% yes)

Age (to nearest year)

Sex, Race/ethnicity (moderators)

Specify model (logistic TVEM)

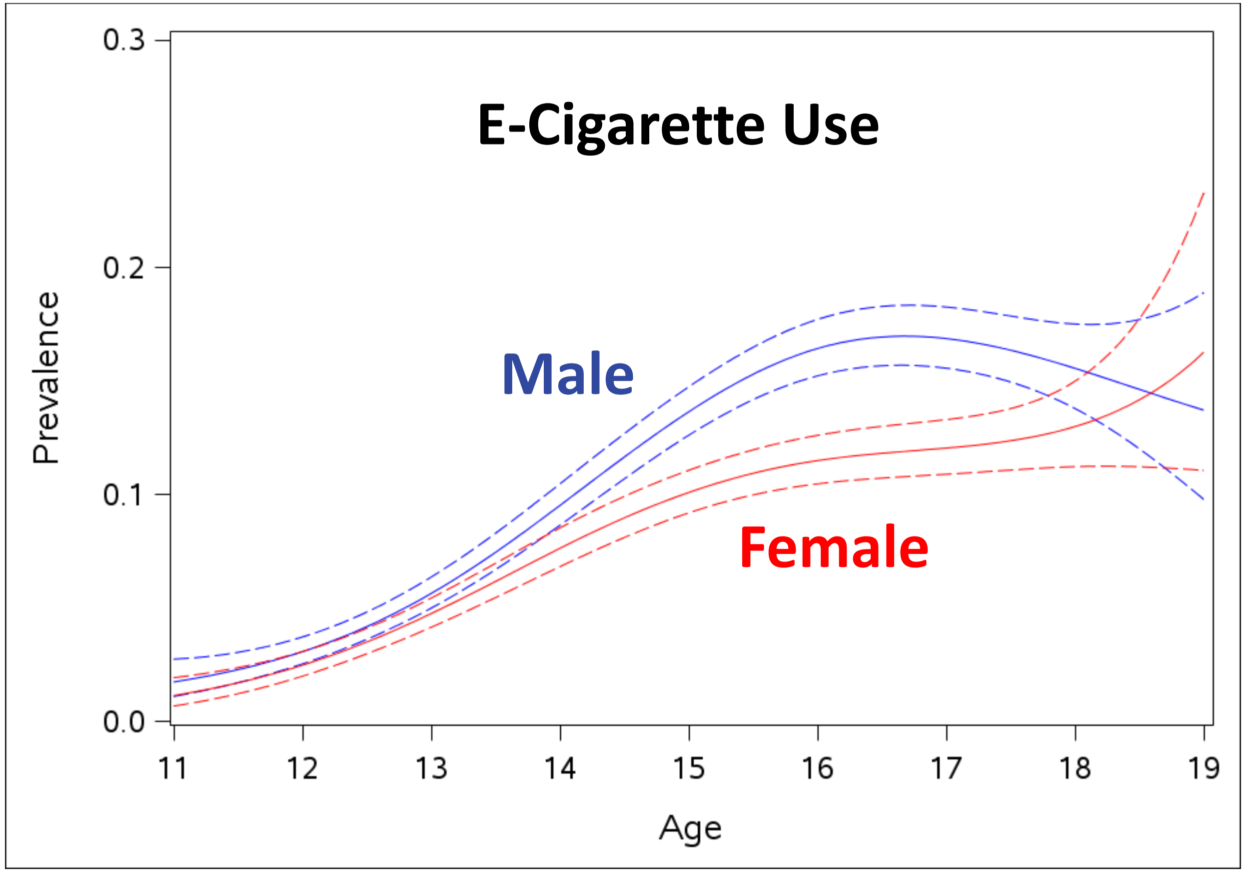
What varies with age?

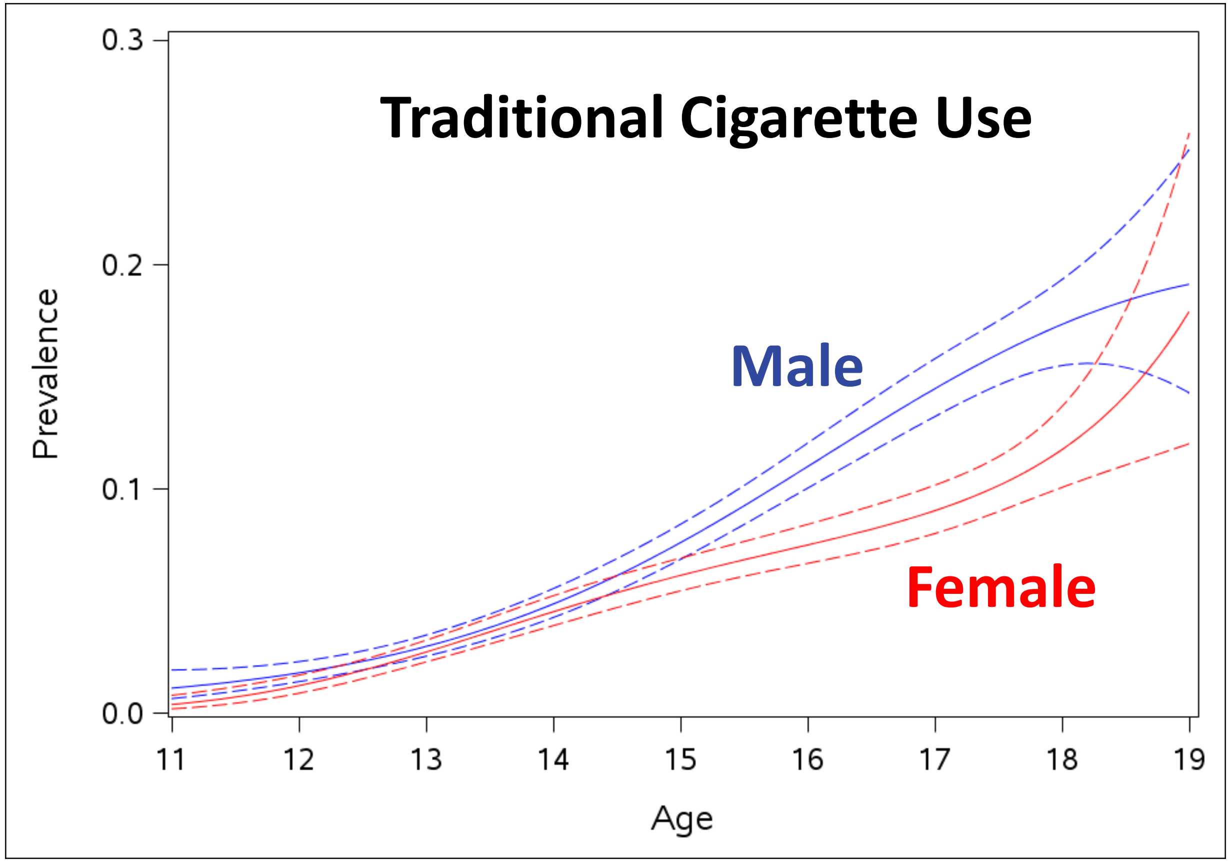
- Probability of cig use
- Probability of e-cig use
- Effects of sex, race/ethnicity
- Effect of cig on e-cig (age-varying odds ratio)

$$ln\left(\frac{p(CIG_i)}{1-p(CIG_i)}\right) = \beta_0(age) + \beta_1(age)SEX_i$$

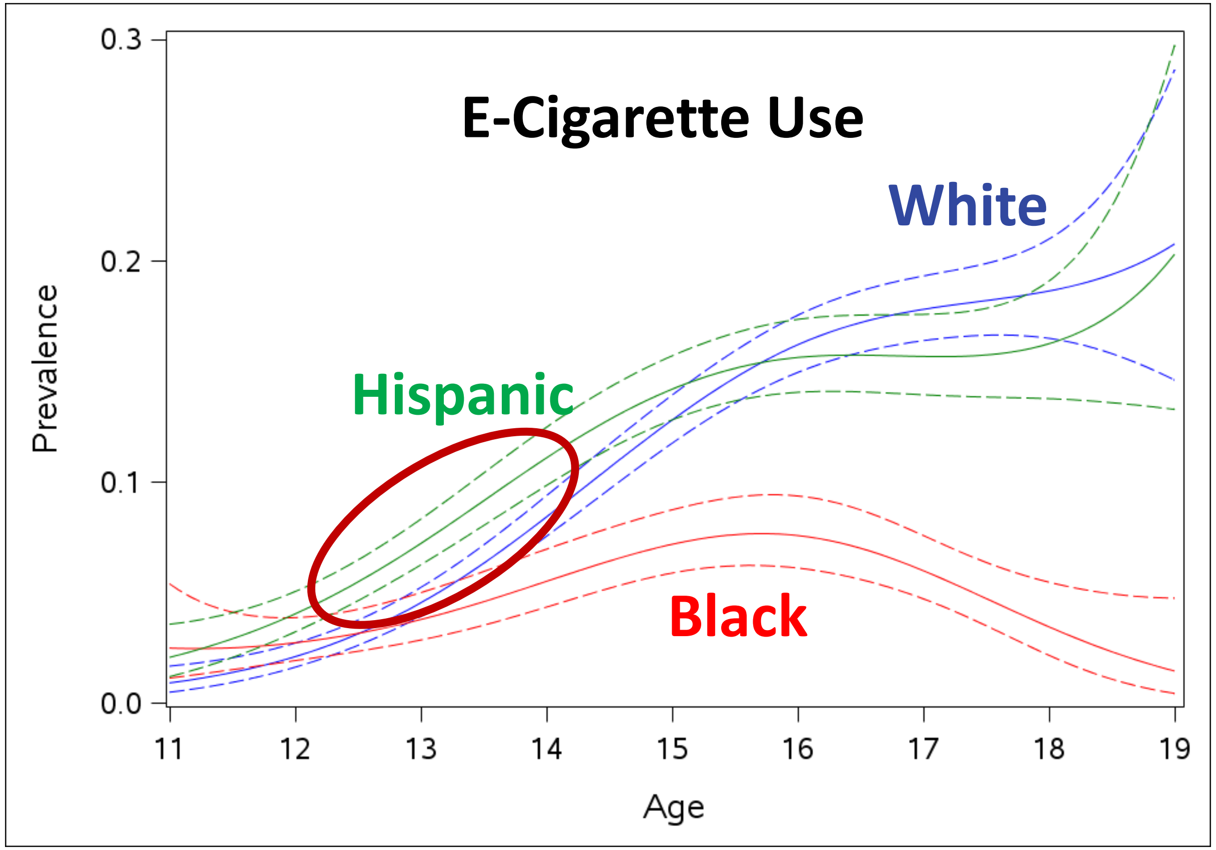
$$ln\left(\frac{p(E\_CIG_i)}{1-p(E\_CIG_i)}\right) = \beta_0(age) + \beta_1(age)CIG_i$$

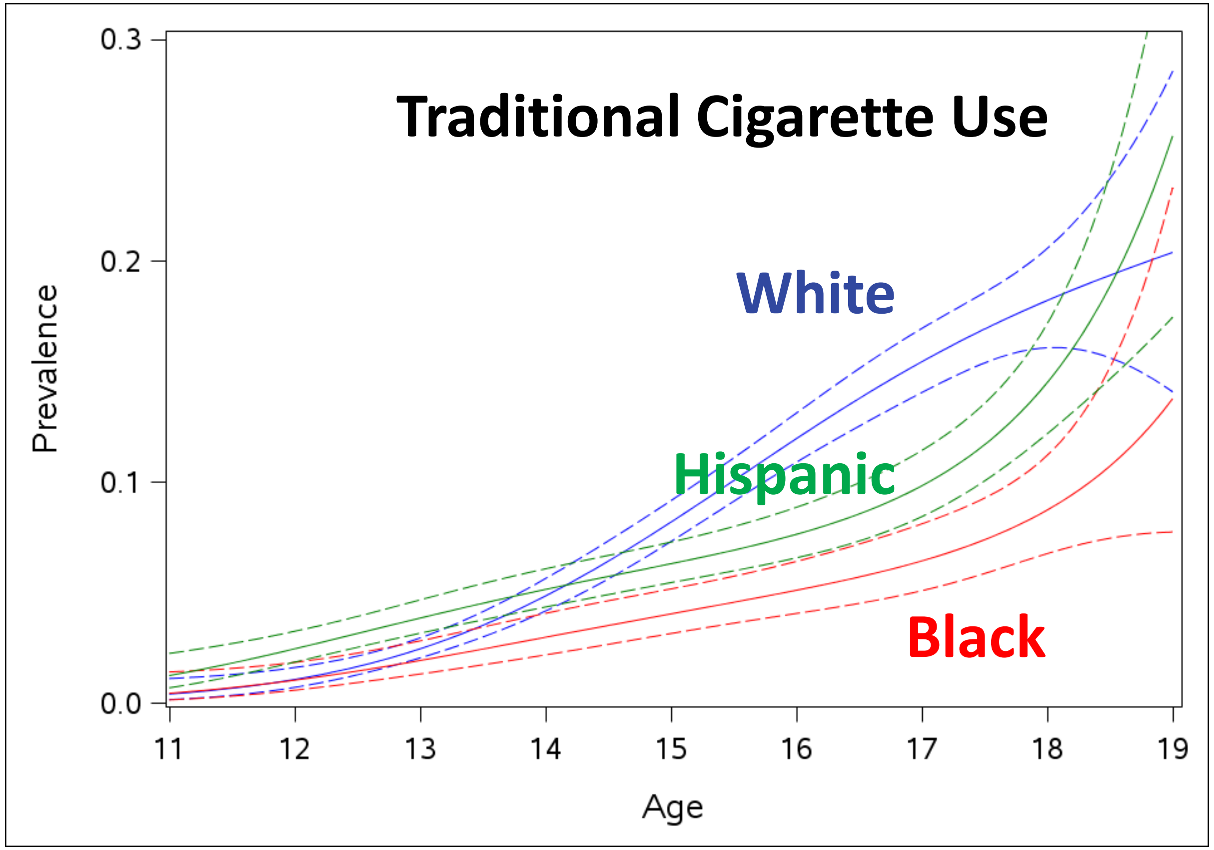
E-cigarette and traditional cigarette use: Sex differences (ages 11-19)



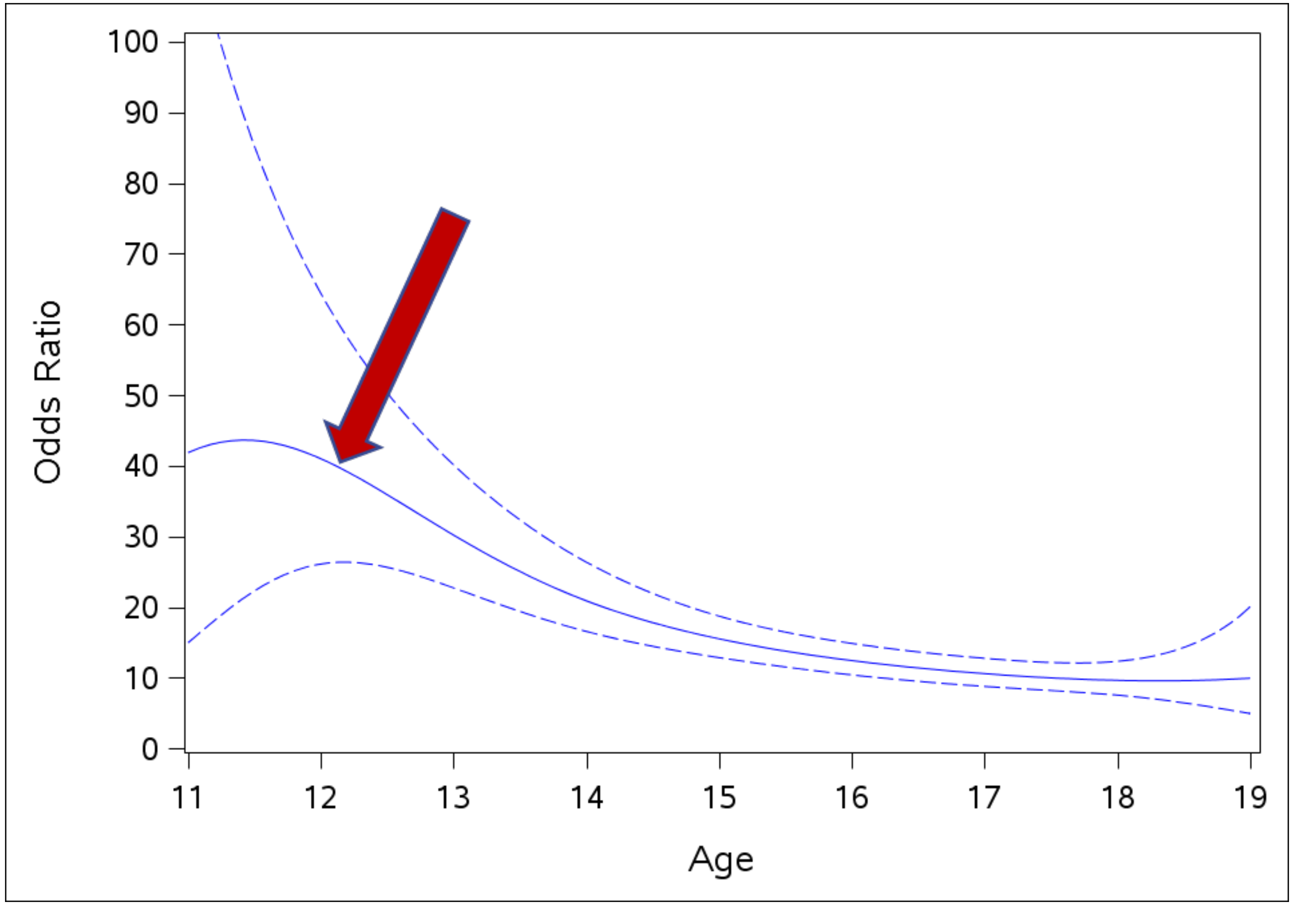


E-cigarette and traditional cigarette use: Race/ethnicity differences (ages 11-19)





Use of both products
(odds ratio, ages 11-19)



Among those age 12, adolescents using e-cigarettes are >40 times as likely to use traditional cigarettes compared to those not using e-cigarettes

Implications for policy and prevention

Identification of key ages of risk can inform targeted, age-appropriate intervention

Traditional and e-cigarette use go hand in hand, particularly in very early adolescence

Early use of e-cigarettes significantly more likely among Hispanic youth, suggesting greater risk for future nicotine dependence

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New information contained in contemporary data sources

Intensive longitudinal data (ILD)
- EMA, wearable devices

Electronic medical records (EMR)

Genetic data

Big data, complex data = big opportunity

Adaptive interventions, Mobile interventions, Precision medicine
- Stress, mood, context, health behaviors

TVEM can unlock new knowledge from existing data

Complex processes unfolding with time

Dynamic effects of interventions

Developmental associations

Associations across historical time

Complex link between age-of-onset and later outcomes




John Dziak
Runze Li
Michael Russell
Sara Vasilenko

KEY TVEM COLLABORATORS

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The Science of Drug Abuse & Addiction

P50-DA010075, P50-DA039838, R01-DA039854

NATIONAL CANCER INSTITUTE

R01-CA168676

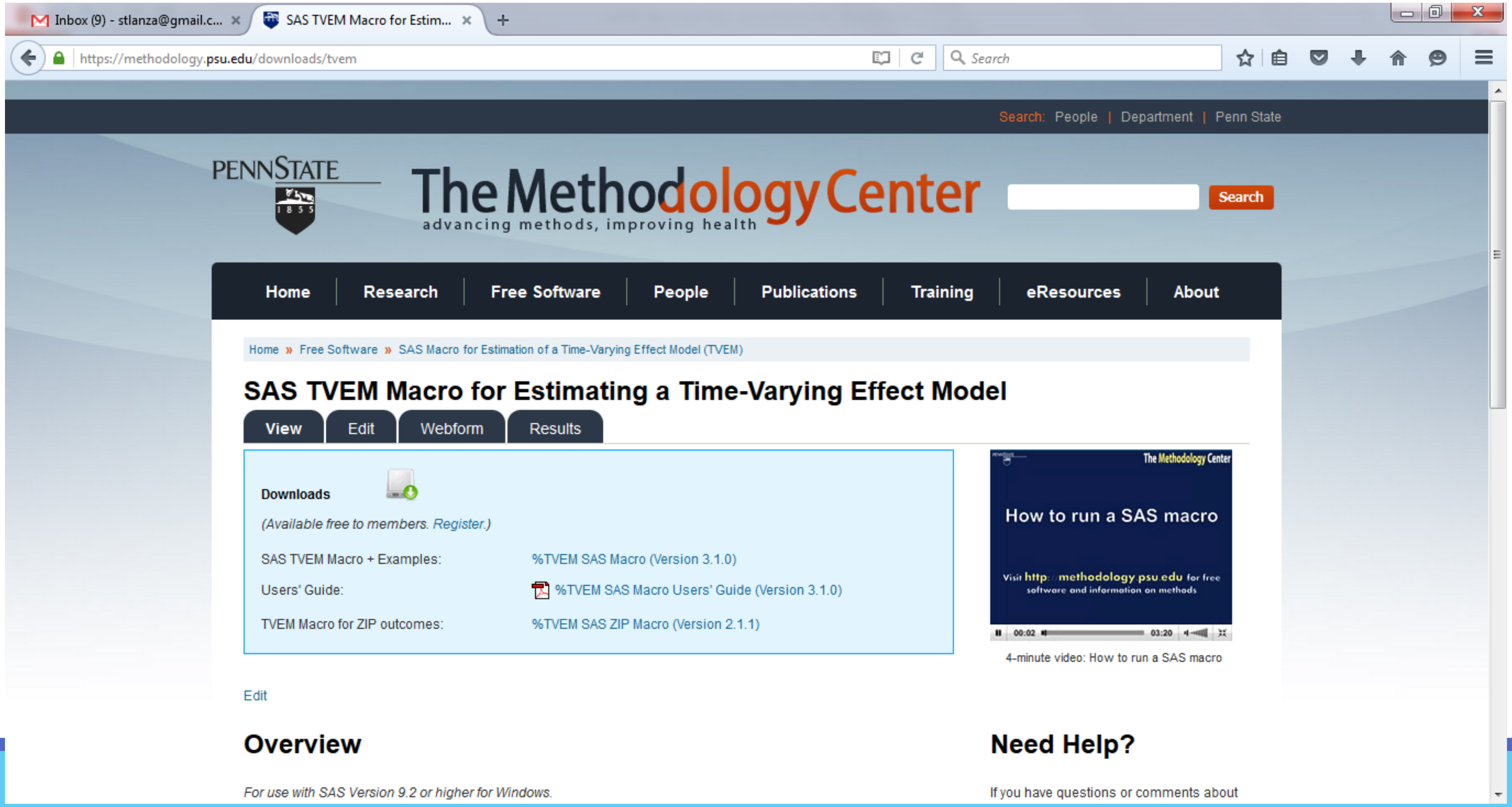
THANK YOU!

EXTRA SLIDES

Getting started with TVEM

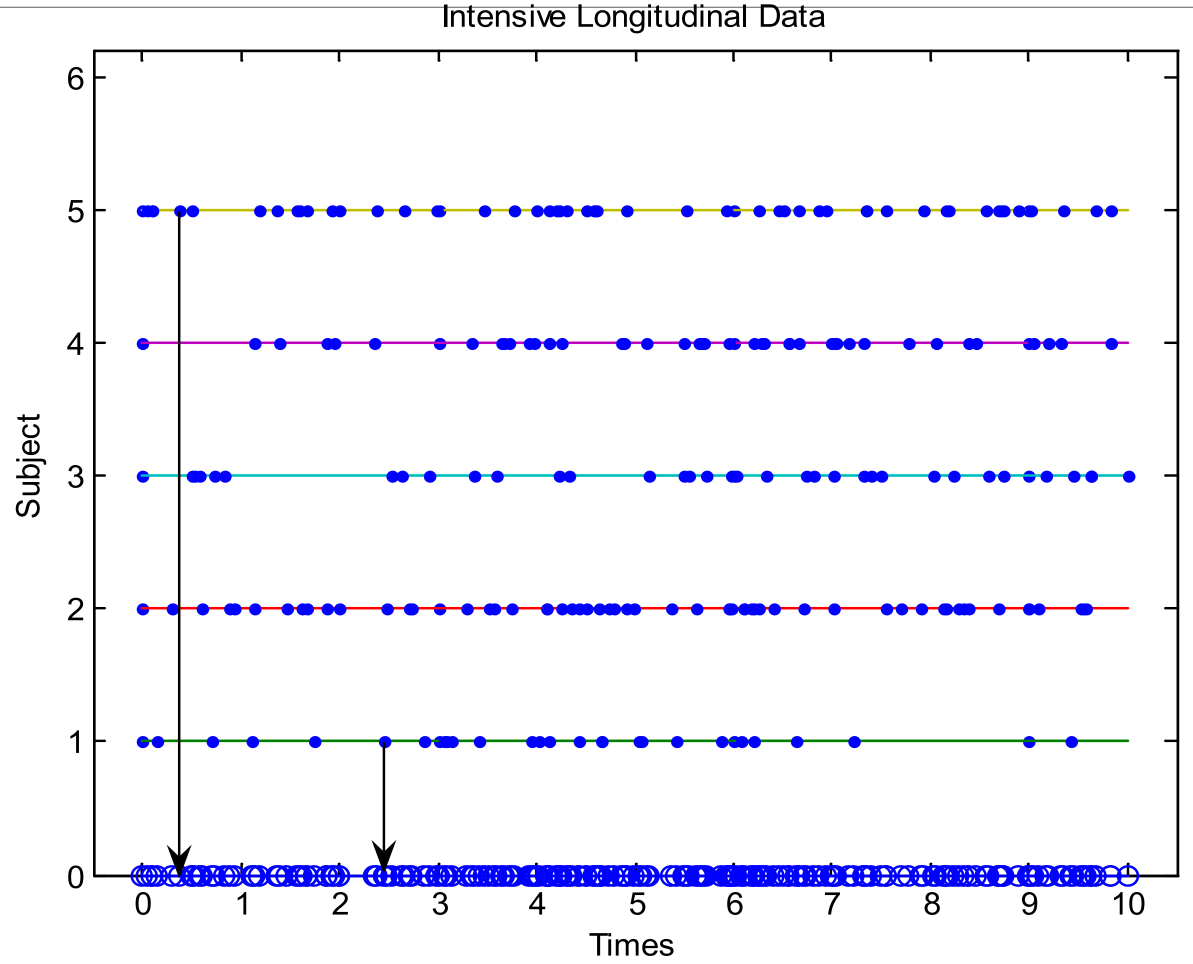
TVEM is freely available

Download SAS macro and user's guide at **methodology.psu.edu**



Data requirements for TVEM

Data requirements (intensive longitudinal data)



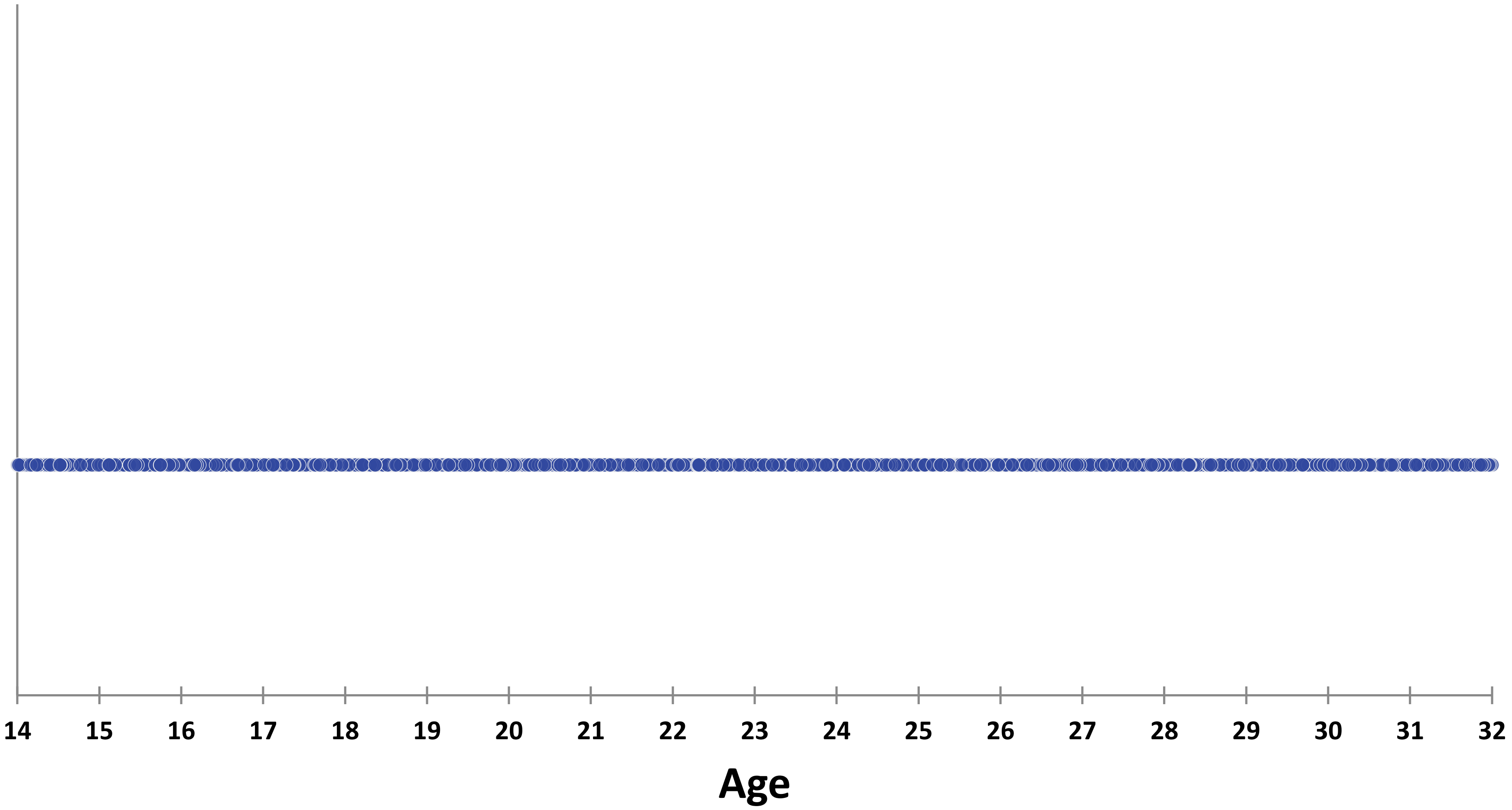
Data requirements (cross-sectional and panel studies)

Only one or a few waves, but many ages sampled

Example: The National Longitudinal Study of Adolescent to Adult Health (Add Health)

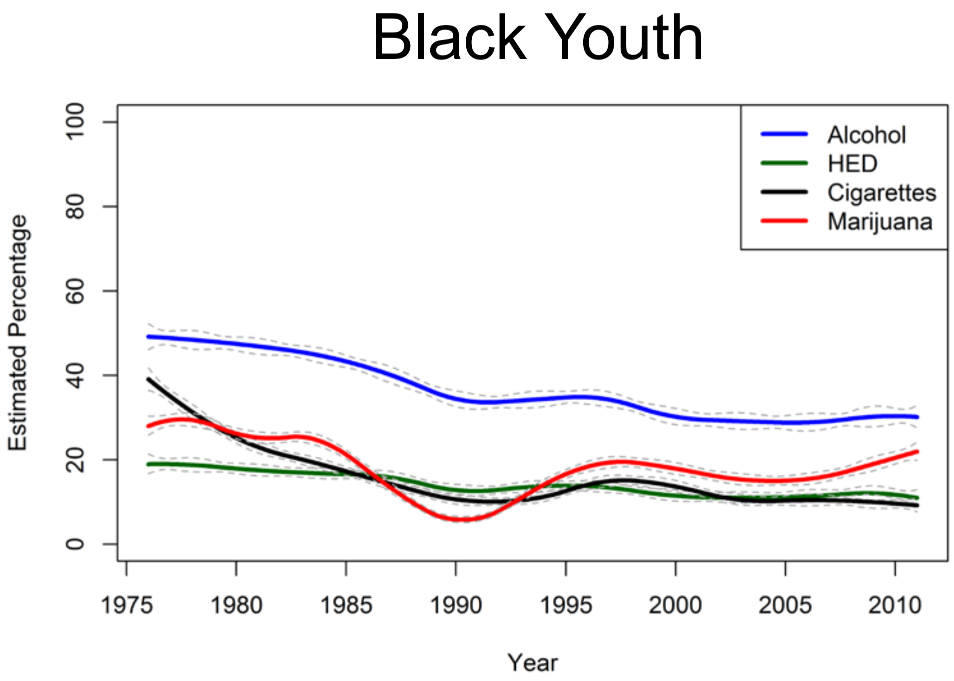
- Nationally representative sample
- **4 waves** of data collected from 1996-2008
- **N~12,000** (core sample)
- **34,562 person-times (spans ages 12-32)**

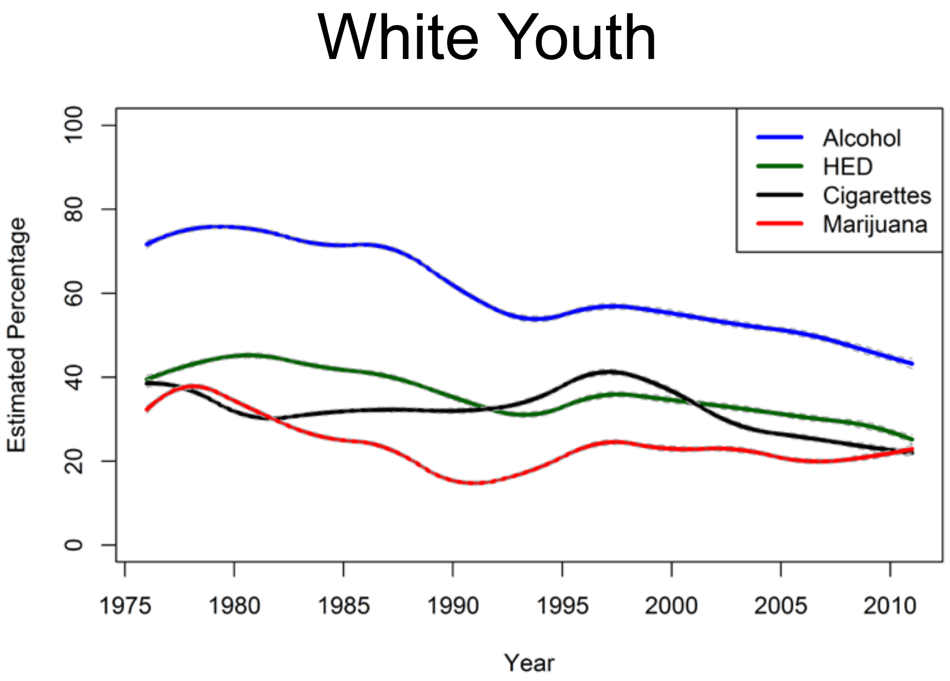
Add Health: Coverage across age



TVEM to examine change over historical time

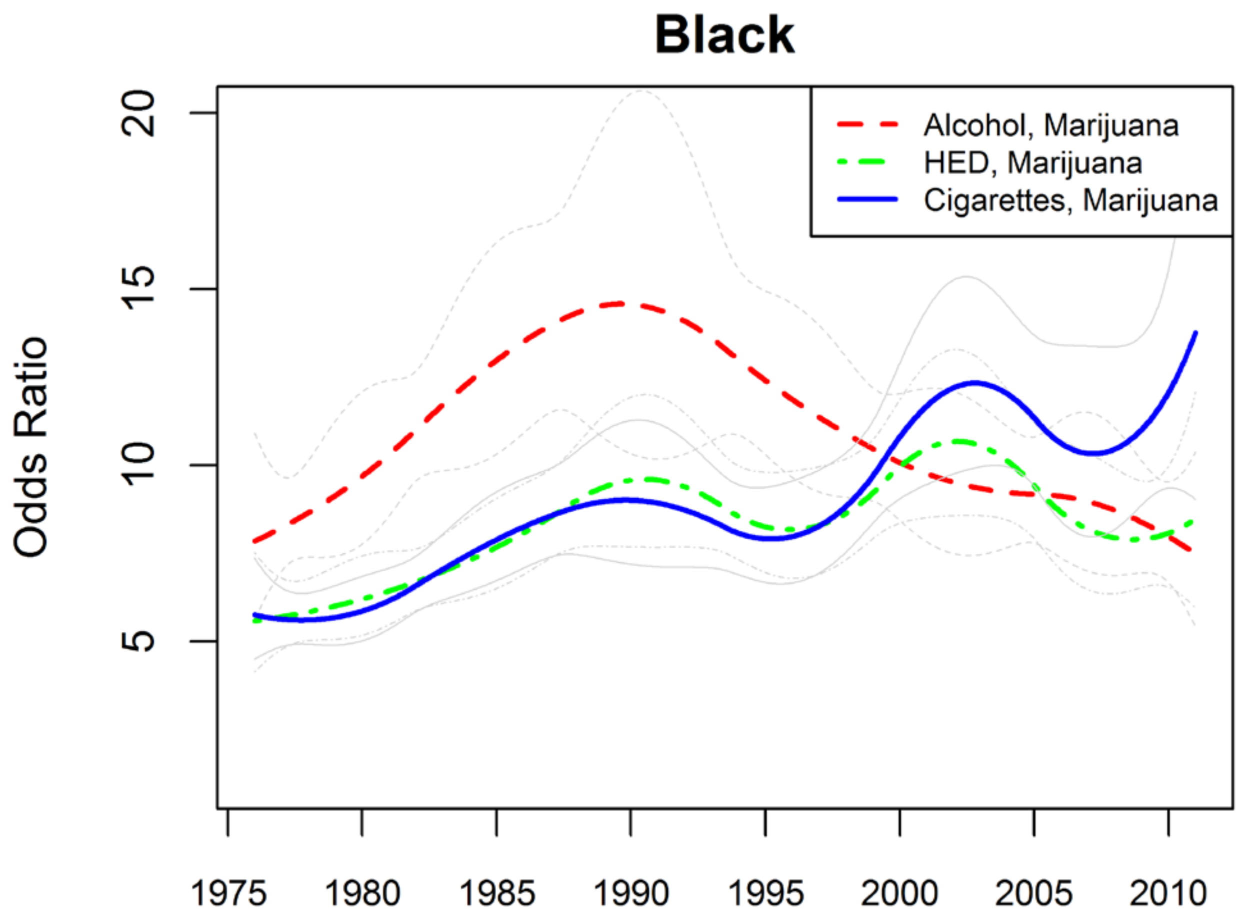
Rates of use over time: By race





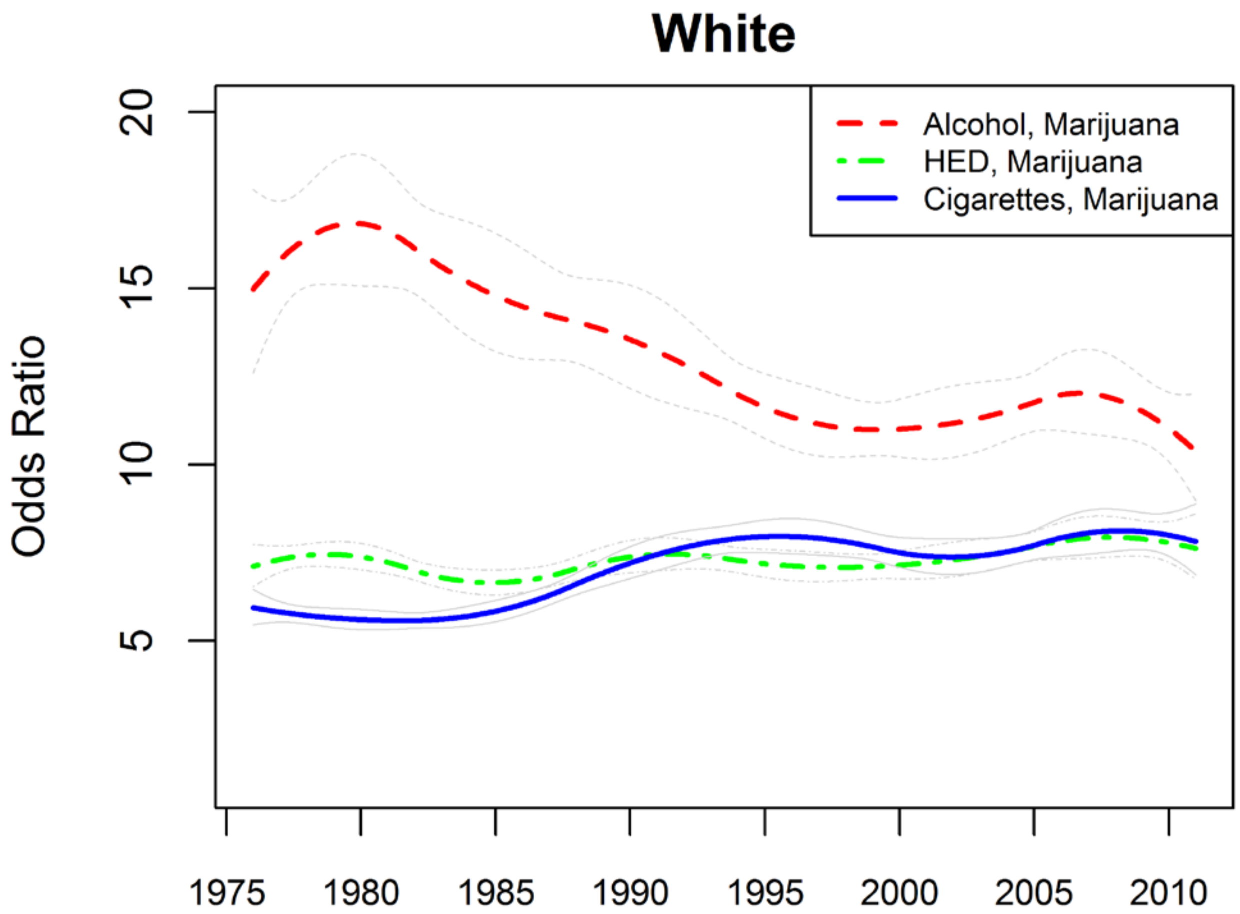
Lanza et al. (2015)
Journal of Adolescent Health

Rates of co-use over time: Black youth



Lanza et al. (2015)
Journal of Adolescent Health

Rates of co-use over time: White youth



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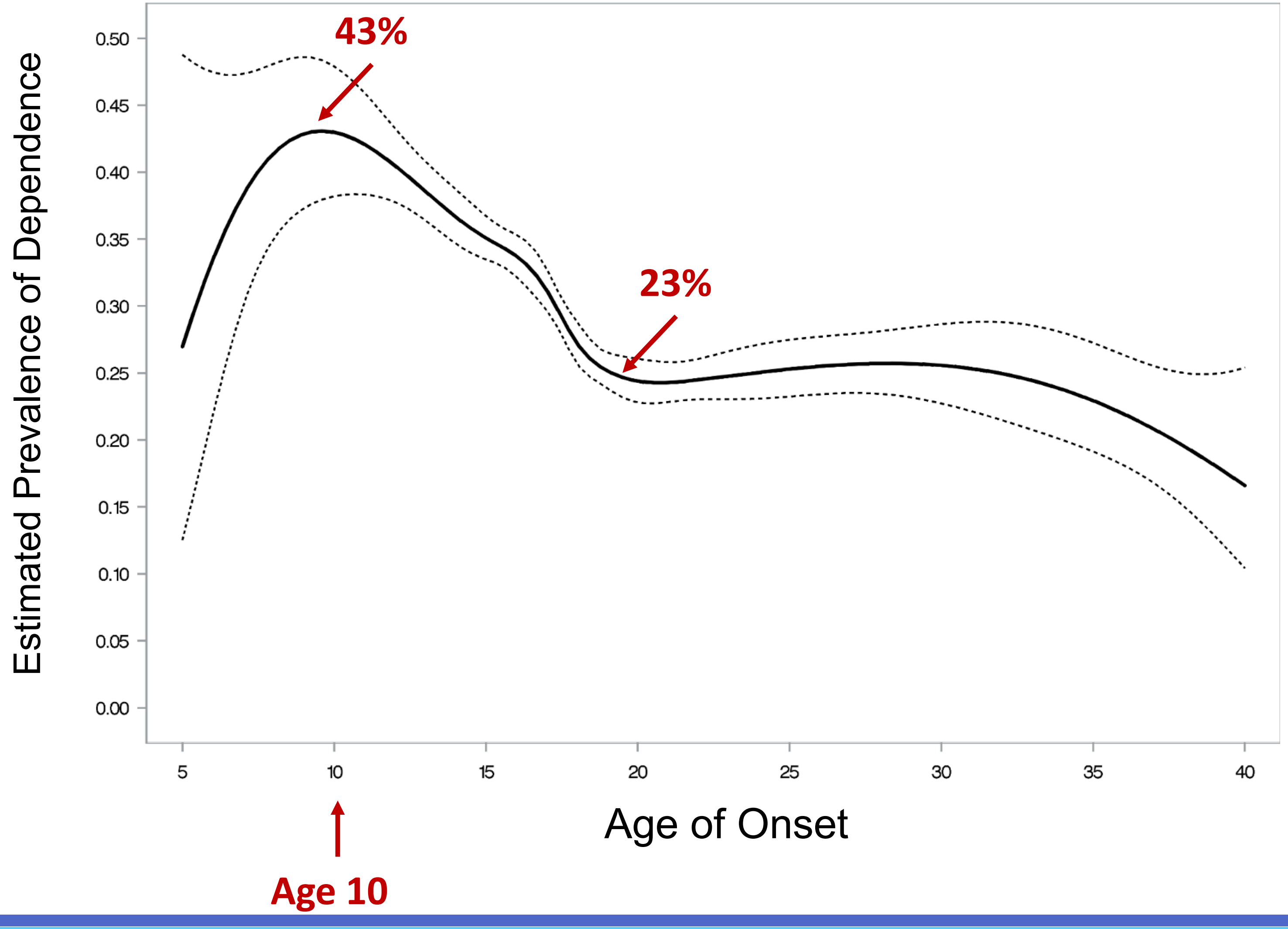
Journal of Adolescent Health

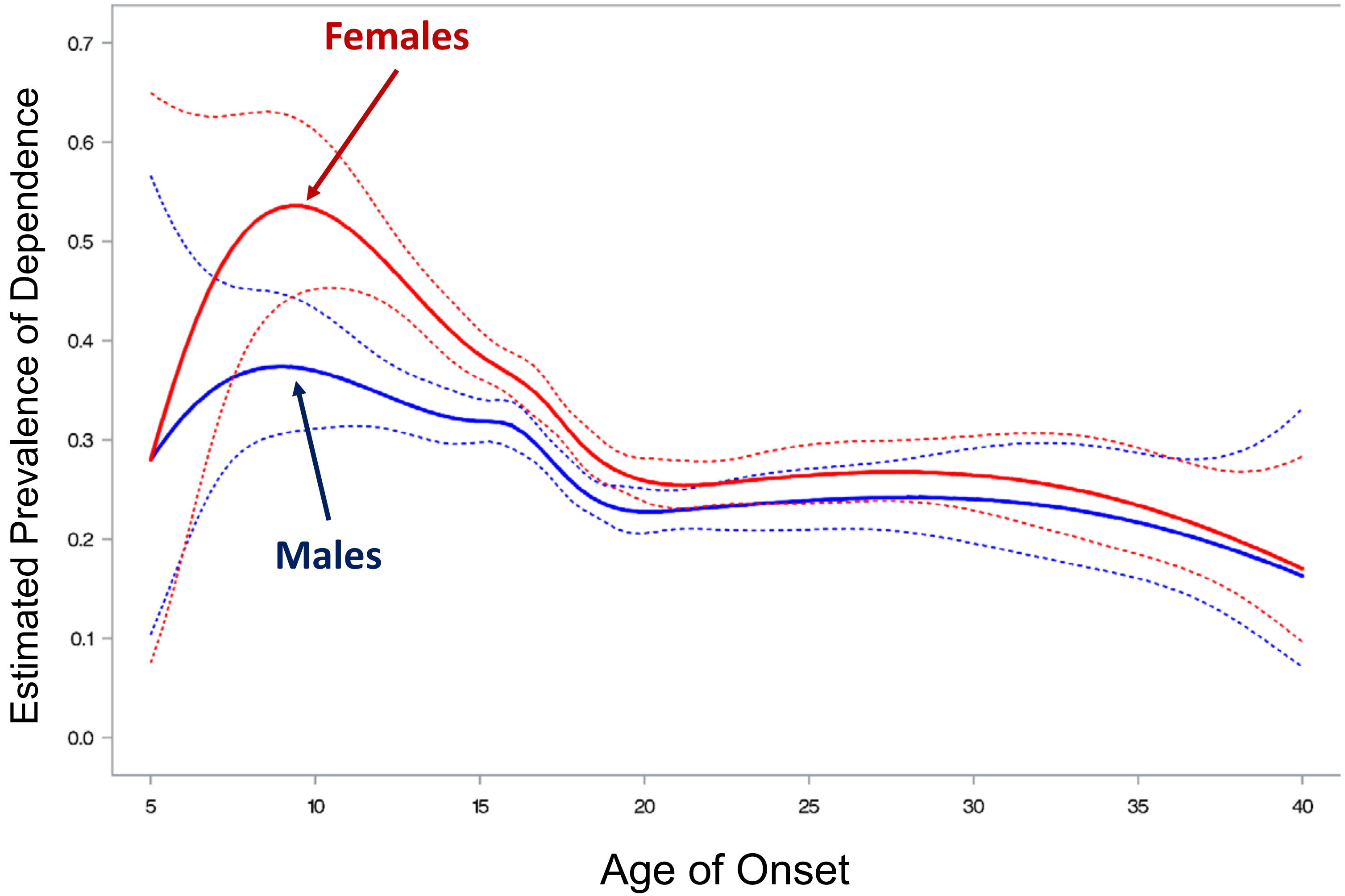
TVEM to understand age-of-onset

Rate of dependence as function of age of onset



Lanza & Vasilenko (2015)
Journal of Adolescent Health

Rate of dependence as function of age of onset: By sex



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