Disentangling the gateway hypothesis: does e-cigarette use cause subsequent smoking in adolescents?

THE E-CIGARETTE SUMMIT

Science, Regulation & Public Health

The Royal Society • London • November 15th, 2018

Lion Shahab, PhD

University College London

@LionShahab

Background


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Science
E-cigarettes act as gateway to smoking for teens, scientists warn
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Vaping may desensitise youngsters to the dangers of smoking, say sc


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E-cigarette use 'can start children smoking for real by tempting them to try nicotine' claims new study
Research has shown that three-quarters of teenagers who puff on e-cigs also smoke cigarettes
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E-cigarettes are seen by Welsh ministers as a 'gateway' to tobacco smoking
Three times as many children have tried e-cigarettes as have smoked tobacco, according to official figures.
It has reinforced concerns that using the devices could become a "gateway" to smoking cigarettes.
The study found 6% of 10 to 11-year-olds in Wales said they had used e-cigarettes.
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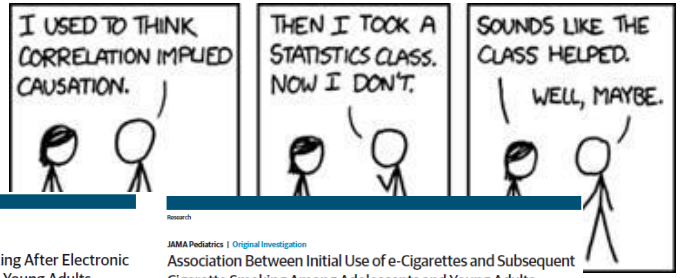
Background

A priori considerations

1) Extant literature



E-cigarette Use and Subsequent Smoking Frequency Among Adolescents

Jessica L. Barrington-Trimis, PhD,* Grace Kong, PhD,† Adam M. Leventhal, PhD,* Feifei Liu, MS,* Margaret Mayer, MPH,* Tess Boley Cruz, PhD,* Sunshita Krishnan-Sarin, PhD,* Rob McConnell, MD*

abstract

BACKGROUND AND OBJECTIVES: Electronic cigarette (e-cigarette) use is associated with cigarette initiation among adolescents. However, it is unclear whether e-cigarette use is associated with more frequent cigarette use after initiation. Also, the extent to which cigarette or dual cigarette and e-cigarette users transition to exclusive e-cigarette use or to the nonuse of either product is not yet known.

METHODS: Data were pooled from 3 prospective cohort studies in California and Connecticut (baseline: 2013–2014; follow-up: 2014–2016; $N = 6258$). Polytomous regression models were used to evaluate the association of baseline e-cigarette use (never or ever) with cigarette use frequency at follow-up (experimental: initiation but no past-30-day use; infrequent: 1–2 of the past 30 days; frequent: 3–5 or more of the past 30 days). Polytomous regression models were also used to evaluate transitions between baseline ever or past-30-day single or dual product use and past-30-day single or dual product use at follow-up.

RESULTS: Among baseline never smokers, e-cigarette users had greater odds of subsequent experimental (odds ratio [OR] = 4.58; 95% confidence interval [CI]: 3.56–5.88), infrequent (OR = 4.27; 95% CI: 2.75–6.62) or frequent (OR = 3.51; 95% CI: 1.97–6.24) cigarette use; the 3 OR estimates were not significantly different. Baseline past-30-day exclusive cigarette use was associated with higher odds at follow-up of exclusive cigarette or dual product use than of exclusive e-cigarette use.

CONCLUSIONS: Tobacco control policy to reduce adolescent use of both e-cigarettes and cigarettes is needed to prevent progression to more frequent tobacco use patterns and reduce combustible cigarette use (with or without concurrent e-cigarette use) to lessen the adverse public health impact of e-cigarettes.

*Department of Preventive Medicine, University of Southern California, Los Angeles, California; and †Department of Psychiatry, School of Medicine, Yale University, New Haven, Connecticut

Dr Barrington-Trimis formulated the research question, interpreted the results, wrote and edited the manuscript, and is the guarantor; Ms Liu and Ms Mayer contributed to formulating the research question, conducted the analyses, interpreted the results, and edited the manuscript; Drs Kong and Cruz contributed to formulating the research question, the interpretation of results, and the editing of the manuscript; Drs Leventhal, Krishnan-Sarin, and McConnell designed the study (each cohort), collected data, contributed to formulating the research question and the interpretation of the results, and critically reviewed the manuscript; and all authors approved the final version for publication.

WHAT'S KNOWN ON THIS SUBJECT: Electronic cigarette (e-cigarette) use is associated with cigarette initiation. However, it is unclear whether e-cigarette use is associated with more frequent cigarette use after initiation or whether adolescent cigarette or dual product users transition to exclusive e-cigarette use or nonuse.

WHAT THIS STUDY ADDS: Adolescent e-cigarette users appear to follow similar trajectories of cigarette smoking frequency as nonusers. Exclusive cigarette or dual product users are more likely to continue using cigarettes than to transition away from smoking to exclusive e-cigarette use or to nonuse.

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Research

Original Investigation

Association of Electronic Cigarette Use With Initiation of Combustible Tobacco Product Smoking in Early Adolescence

Adam M. Leventhal, PhD; David R. Strong, PhD; Matthew G. Kirkpatrick, PhD; Jennifer B. Unger, PhD; Steve Sussman, PhD; Nathaniel R. Riggs; Matthew D. Stone, BA; Rubin Khoddam, MA; Jonathan M. Samet, MD, MS; Janet Audrain-McGovern, PhD

IMPORTANCE Exposure to nicotine in electronic cigarettes (e-cigarettes) is becoming increasingly common among adolescents who report never having smoked combustible tobacco.

OBJECTIVE To evaluate whether e-cigarette use among 14-year-old adolescents who have never tried combustible tobacco is associated with risk of initiating use of 3 combustible tobacco products (ie, cigarettes, cigars, and hookah).

DESIGN, SETTING, AND PARTICIPANTS Longitudinal repeated assessment of a school-based cohort at baseline (fall 2013, 9th grade, mean age = 14.1 years) and at a 6-month follow-up (spring 2014, 9th grade) and a 12-month follow-up (fall 2014, 10th grade). Ten public high schools in Los Angeles, California, were recruited through convenience sampling. Participants were students who reported never using combustible tobacco at baseline and completed follow-up assessments at 6 or 12 months (N = 2530). At each time point, students completed self-report surveys during in-classroom data collections.

EXPOSURE Student self-report of whether he or she ever used e-cigarettes (yes or no) at baseline.

MAIN OUTCOMES AND MEASURES Six- and 12-month follow-up reports on use of any of the following tobacco products within the prior 6 months: (1) any combustible tobacco product (yes or no); (2) combustible cigarettes (yes or no), (3) cigars (yes or no); (4) hookah (yes or no); and (5) number of combustible tobacco products (range: 0-3).

RESULTS Past 6-month use of any combustible tobacco product was more frequent in baseline e-cigarette ever users (n = 222) than never users (n = 2308) at the 6-month follow-up (30.7% vs 8.1%, respectively; difference between groups in prevalence rates, 22.7% [95% CI, 16.4%-28.9%]) and at the 12-month follow-up (25.2% vs 9.3%, respectively; difference between groups, 15.9% [95% CI, 10.0%-21.8%]). Baseline e-cigarette use was associated with greater likelihood of use of any combustible tobacco product averaged across the 2 follow-up periods in the unadjusted analyses (odds ratio [OR], 4.27 [95% CI, 3.19-5.71]) and in the analyses adjusted for sociodemographic, environmental, and intrapersonal risk factors for smoking (OR, 2.73 [95% CI, 2.00-3.73]). Product-specific analyses showed that baseline e-cigarette use was positively associated with combustible cigarette (OR, 2.65 [95% CI, 1.73-4.05]), cigar (OR, 4.85 [95% CI, 3.38-6.96]), and hookah (OR, 3.25 [95% CI, 2.29-4.62]) use and with the number of different combustible products used (OR, 4.26 [95% CI, 3.16-5.74]) averaged across the 2 follow-up periods.

CONCLUSIONS AND RELEVANCE Among high school students in Los Angeles, those w ever used e-cigarettes at baseline compared with nonusers were more likely to repo initiation of combustible tobacco use over the next year. Further research is needed understand whether this association may be causal.

Viewpoint page 663 and Editorial page 673

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Author Affiliations: Department of Preventive Medicine, University of Southern California, Keck School of Medicine, Los Angeles (Leventhal, Kirkpatrick, Unger, Sussman, Stone, Khoddam, Samet). Department of Psychology, University of Southern California, Los Angeles (Leventhal, Sussman, Khoddam). Department of Family Medicine and Public Health, University of California-San Diego School of Medicine, La Jolla (Strong). School of Social Work, University of Southern California, Los Angeles (Sussman). Department of Human Development and Family Studies, Colorado State University, Fort Collins (Riggs). Department of Psychiatry, University of Pennsylvania, Perelman School of Medicine, Philadelphia (Audrain-McGovern).

Corresponding Author: Adam M. Leventhal, PhD, University of Southern California, Keck School of Medicine, 2250 Alcazar St, CSC 271, Los Angeles, CA [redacted] (adam.leventhal@usc.edu).

JAMA. 2015;314(7):700-707. doi:10.1001/jama.2015.8950

Research

Original Investigation

Progression to Traditional Cigarette Smoking After Electronic Cigarette Use Among US Adolescents and Young Adults

Brian A. Primack, MD, PhD; Samir Soneji, PhD; Michael Stoolmiller, PhD; Michael J. Fine, MD, MSc; James D. Sargent, MD

IMPORTANCE Electronic cigarettes (e-cigarettes) may help smokers reduce the use of traditional combustible cigarettes. However, adolescents and young adults who have never smoked traditional cigarettes are now using e-cigarettes, and these individuals may be at risk for subsequent progression to traditional cigarette smoking.

OBJECTIVE To determine whether baseline use of e-cigarettes among nonsmoking and nonsusceptible adolescents and young adults is associated with subsequent progression along an established trajectory to traditional cigarette smoking.

DESIGN, SETTING, AND PARTICIPANTS In this longitudinal cohort study, a national US sample of 694 participants aged 16 to 26 years who were never cigarette smokers and were attitudinally nonsusceptible to smoking cigarettes completed baseline surveys from October 1, 2012, to May 1, 2014, regarding smoking in 2012-2013. They were reassessed 1 year later. Analysis was conducted from July 1, 2014, to March 1, 2015. Multinomial logistic regression was used to assess the independent association between baseline e-cigarette use and cigarette smoking, controlling for sex, age, race/ethnicity, maternal educational level, sensation-seeking tendency, parental cigarette smoking, and cigarette smoking among friends. Sensitivity analyses were performed, with varying approaches to missing data and recanting.

EXPOSURES Use of e-cigarettes at baseline.

MAIN OUTCOMES AND MEASURES Progression to cigarette smoking, defined using 3 specific states along a trajectory: nonsusceptible nonsmokers, susceptible nonsmokers, and smokers. Individuals who could not rule out smoking in the future were defined as susceptible.

RESULTS Among the 694 respondents, 374 (53.9%) were female and 531 (76.5%) were non-Hispanic white. At baseline, 16 participants (2.3%) used e-cigarettes. Over the 1-year follow-up, 11 of 16 e-cigarette users and 128 of 678 of those who had not used e-cigarettes (18.9%) progressed toward cigarette smoking. In the primary fully adjusted models, baseline e-cigarette use was independently associated with progression to smoking (adjusted odds ratio [AOR], 8.3; 95% CI, 1.2-58.6) and to susceptibility among nonsmokers (AOR, 8.5; 95% CI, 1.3-57.2). Sensitivity analyses showed consistent results in the level of significance and slightly larger magnitude of AORs.

CONCLUSIONS AND RELEVANCE In this national sample of US adolescents and young adults, use of e-cigarettes at baseline was associated with progression to traditional cigarette smoking. These findings support regulations to limit [redacted] ease the appeal of [redacted] to adolescents and young adults.

Editorial page 993

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Brian A. Primack, MD, PhD, Division of General Internal Medicine, Department of Medicine, University of Pittsburgh School of Medicine, 230 McKee Pl, Ste 600, Pittsburgh, PA 15213.

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Research

JAMA Pediatrics | Original Investigation

Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults
A Systematic Review and Meta-analysis

Samir Soneji, PhD; Jessica L. Barrington-Trimis, PhD; Thomas A. Wills, PhD; Adam M. Leventhal, PhD; Jennifer B. Unger, PhD; Laura A. Gibson, PhD; JaeWon Yang, BA; Brian A. Primack, MD, PhD; Judy A. Andrews, PhD; Richard A. Miech, PhD; Tory R. Spindle, MS; Danielle M. Dick, PhD; Thomas Eissenberg, PhD; Robert C. Hornik, PhD; Rui Dang, PhD; James D. Sargent, MD

IMPORTANCE The public health implications of e-cigarettes depend, in part, on whether e-cigarette use affects the risk of cigarette smoking.

OBJECTIVE To perform a systematic review and meta-analysis of longitudinal studies that assessed initial use of e-cigarettes and subsequent cigarette smoking.

DATA SOURCES PubMed, EMBASE, Cochrane Library, Web of Science, the 2016 Society for Research on Nicotine and Tobacco 22nd Annual Meeting abstracts, the 2016 Society of Behavioral Medicine 37th Annual Meeting & Scientific Sessions abstracts, and the 2016 National Institutes of Health Tobacco Regulatory Science Program Conference were searched between February 7 and February 17, 2017. The search included indexed terms and text words to capture concepts associated with e-cigarettes and traditional cigarettes in articles published from database inception to the date of the search.

STUDY SELECTION Longitudinal studies reporting odds ratios for cigarette smoking initiation associated with ever use of e-cigarettes or past 30-day cigarette smoking associated with past 30-day e-cigarette use. Searches yielded 6959 unique studies, of which 9 met inclusion criteria (comprising 17 389 adolescents and young adults).

DATA EXTRACTION AND SYNTHESIS Study quality and risk of bias were assessed using the Newcastle-Ottawa Scale and the Risk of Bias in Non-randomized Studies of Interventions tool, respectively. Data and estimates were pooled using random-effects meta-analysis.

MAIN OUTCOMES AND MEASURES Among baseline never cigarette smokers, cigarette smoking initiation between baseline and follow-up. Among baseline non-past 30-day cigarette smokers who were past 30-day e-cigarette users, past 30-day cigarette smoking at follow-up.

RESULTS Among 17 389 adolescents and young adults, the ages ranged between 14 and 30 years at baseline, and 56.0% were female. The pooled probabilities of cigarette smoking initiation were 23.2% for baseline ever e-cigarette users and 7.2% for baseline never e-cigarette users. The pooled probabilities of past 30-day cigarette smoking at follow-up were 21.5% for baseline past 30-day e-cigarette users and 4.6% for baseline non-past 30-day e-cigarette users. Adjusting for known demographic, psychosocial, and behavioral risk factors for cigarette smoking, the pooled odds ratio for subsequent cigarette smoking initiation was 3.50 (95% CI, 2.38-5.16) for ever vs never e-cigarette users, and the pooled odds ratio for past 30-day cigarette smoking at follow-up was 4.28 (95% CI, 2.52-7.27) for past 30-day e-cigarette vs non-past-30-day e-cigarette users at baseline. A moderate level of heterogeneity was observed among studies ($I^2 = 56\%$).

CONCLUSIONS AND RELEVANCE e-Cigarette use was associated with greater risk for subsequent cigarette smoking initiation and past 30-day cigarette smoking. Strong e-cigarette regulation could potentially curb use among youth and possibly limit the future population-level burden of cigarette smoking.

Journal Club Slides and Supplemental content

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Samir Soneji, [redacted]

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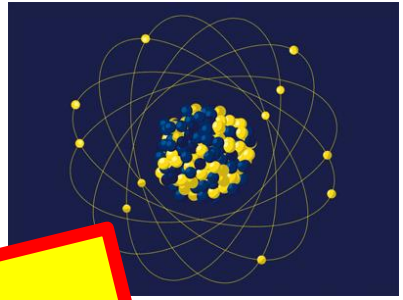
How to solve a problem like ~~Maria~~ The Gateway?



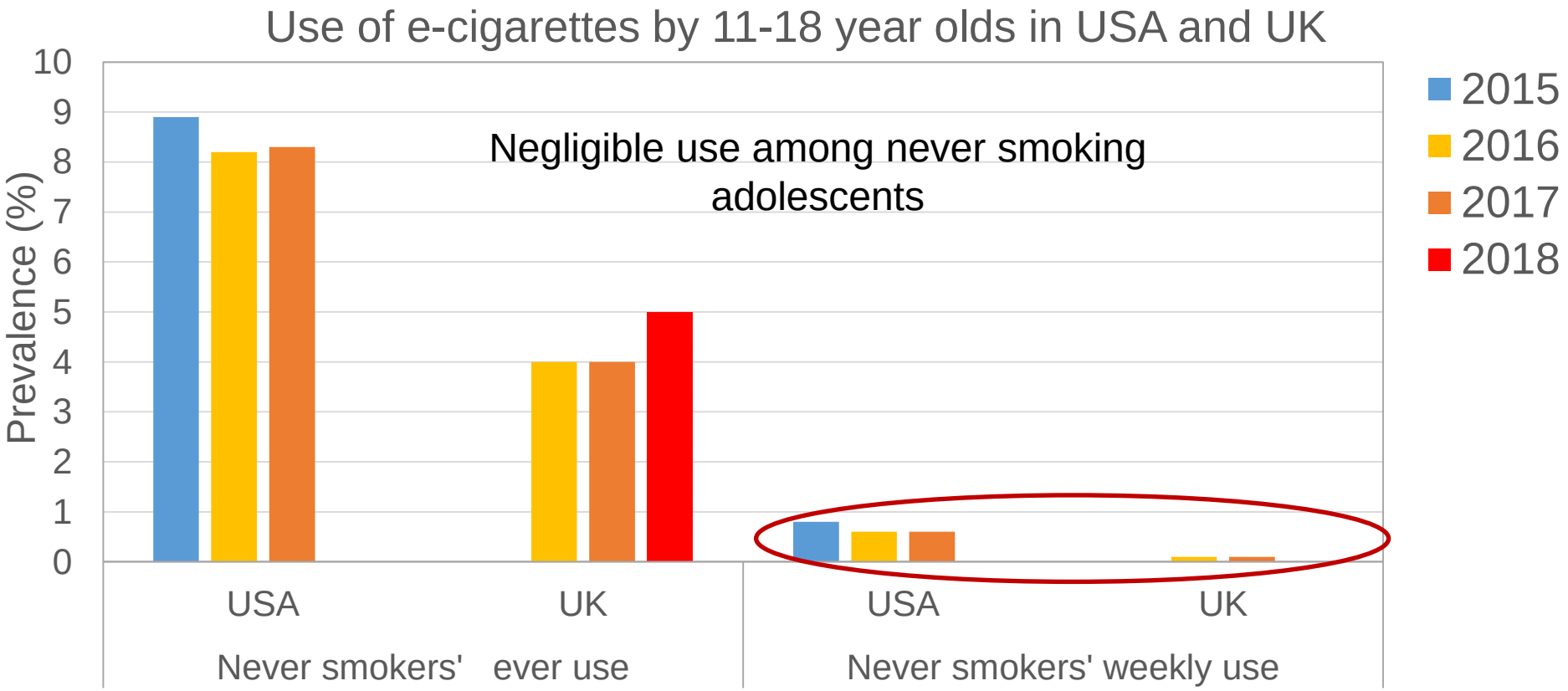
- Best way to assess causality is via an RCT
  - But impractical, unethical and provides net effect only
- Direct observation is not possible
  - Need to infer likely association using different m aches
- Will present three ways to determ
  concerned about "the c

Fourth way: instrumental variable analysis (e.g. MR) – but need good genetic instrument (might be forthcoming)

1) Face Vali
   e among *never* smoking adolescents?
   g rates changed among adolescents since the advent of EC?
2) ed analytical techniques (inferential statistics)
   a. Individual level: case-control design (using synthetic (PSM) and real-world controls)
   b. Population level: quasi-experimental and time-series design
3) Forecasting techniques (theoretical computer modelling)
   a. Micro-simulation (agent-based) modelling to assess likely future impact/effect magnitude/ parameter estimates

1) Face Validity

a. Regular EC use among never smoking adolescents

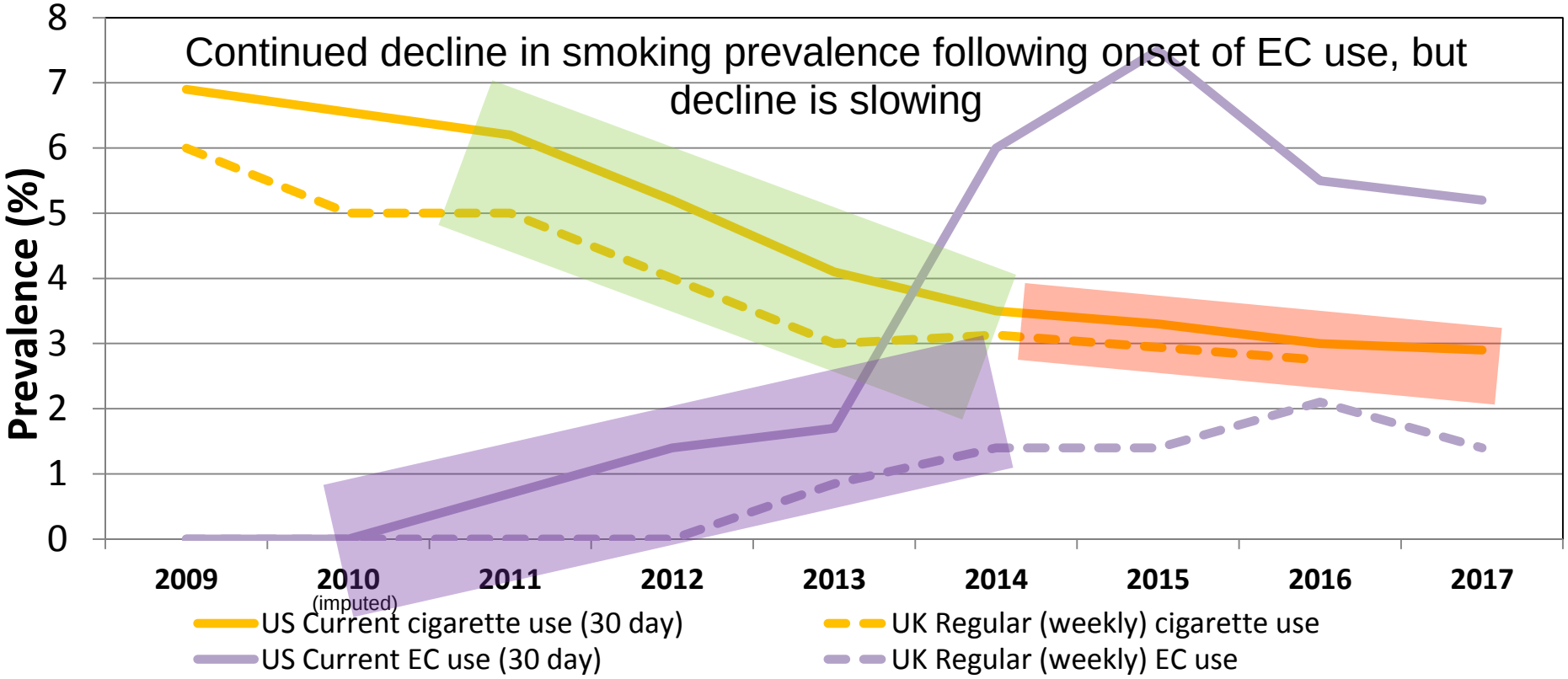


Data sources: National Youth Tobacco Survey; ASH Survey

1) Face Validity

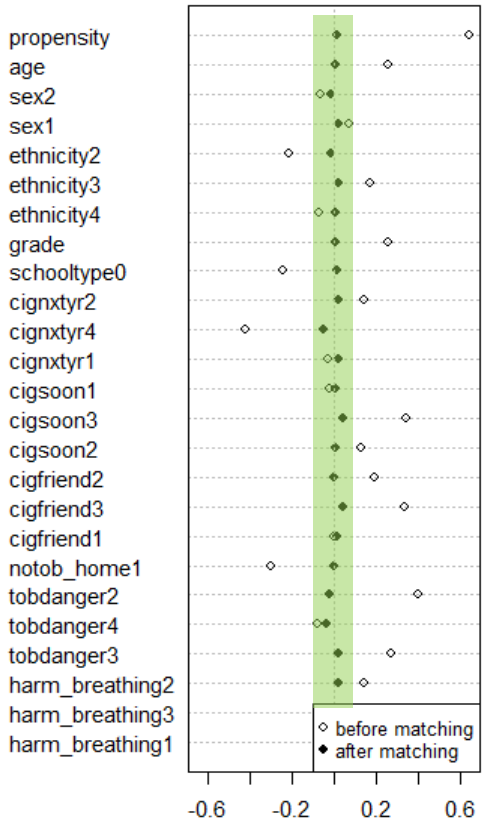
b. Change in cigarette smoking and EC prevalence in adolescents

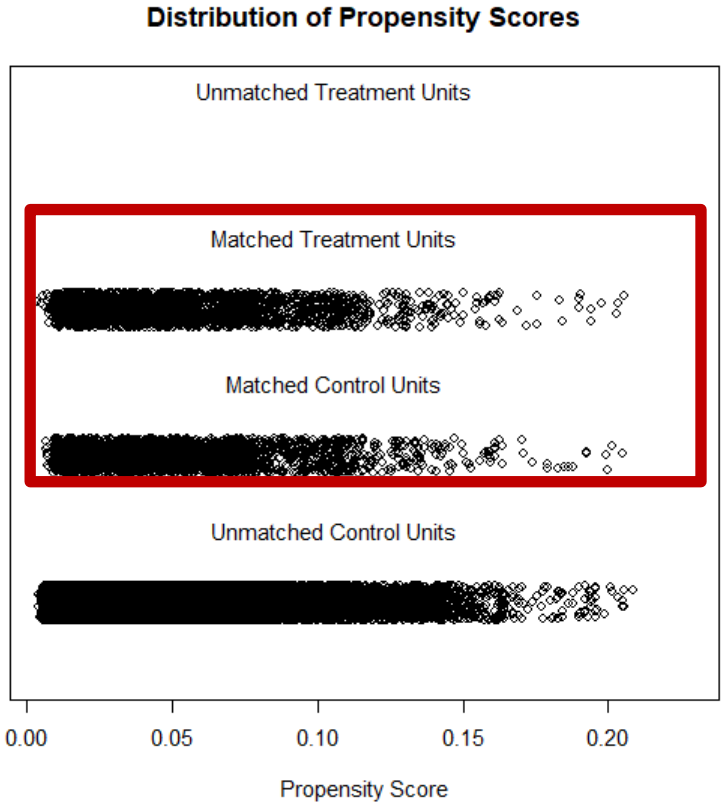
Base: Total Population (all 11-15 year olds)

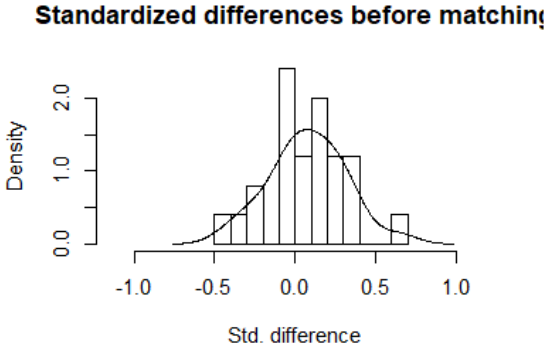


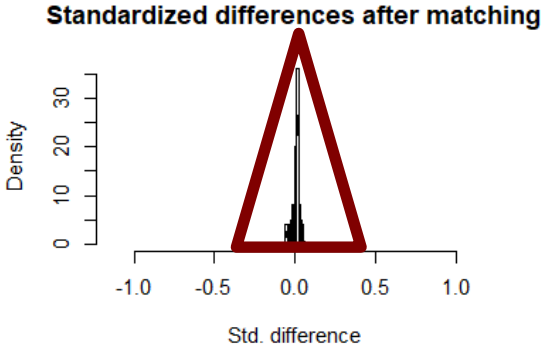
Data sources: National Youth Tobacco Survey; Smoking Drinking and Drug Use among Young People, Eastwood et al, 2015

2) Advanced Analytical Techniques







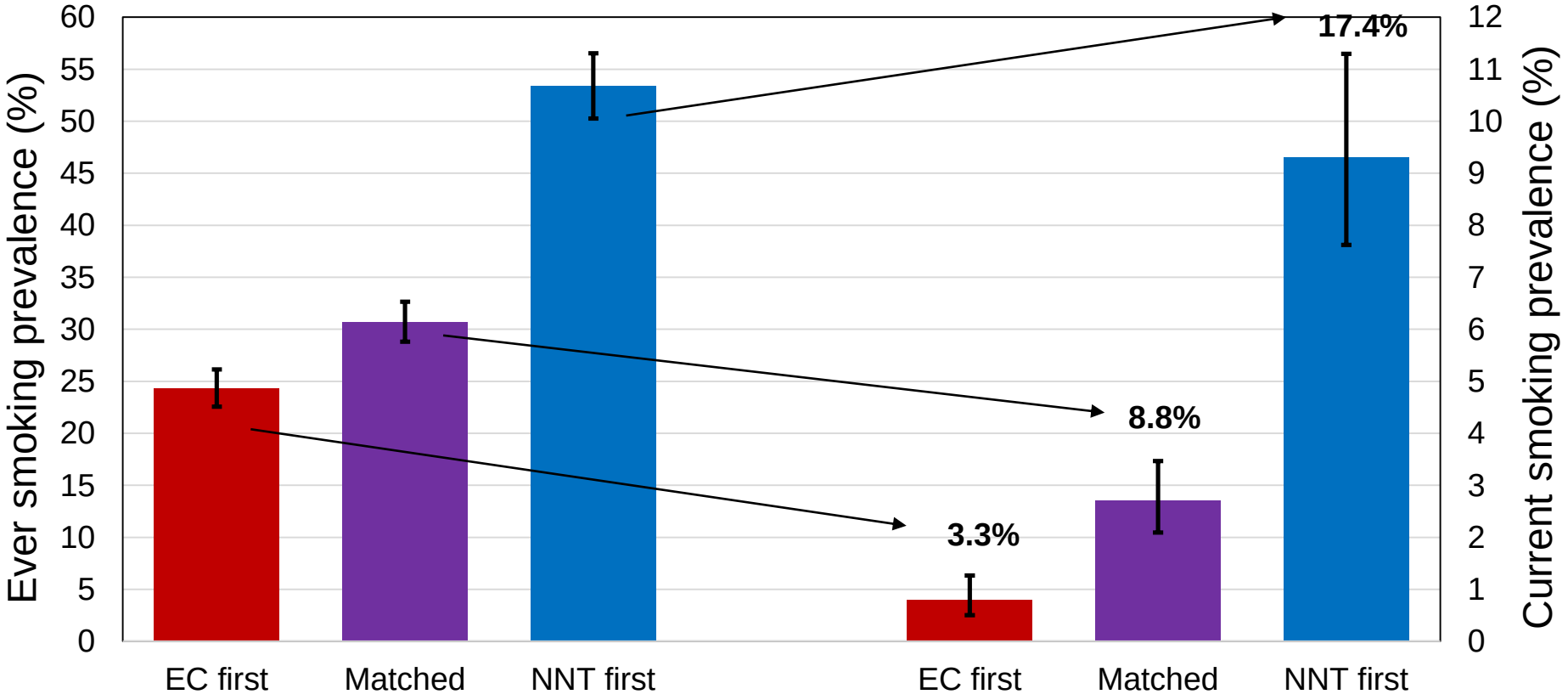


rettes and past 30-

noking

2) Advanced Analytical Techniques

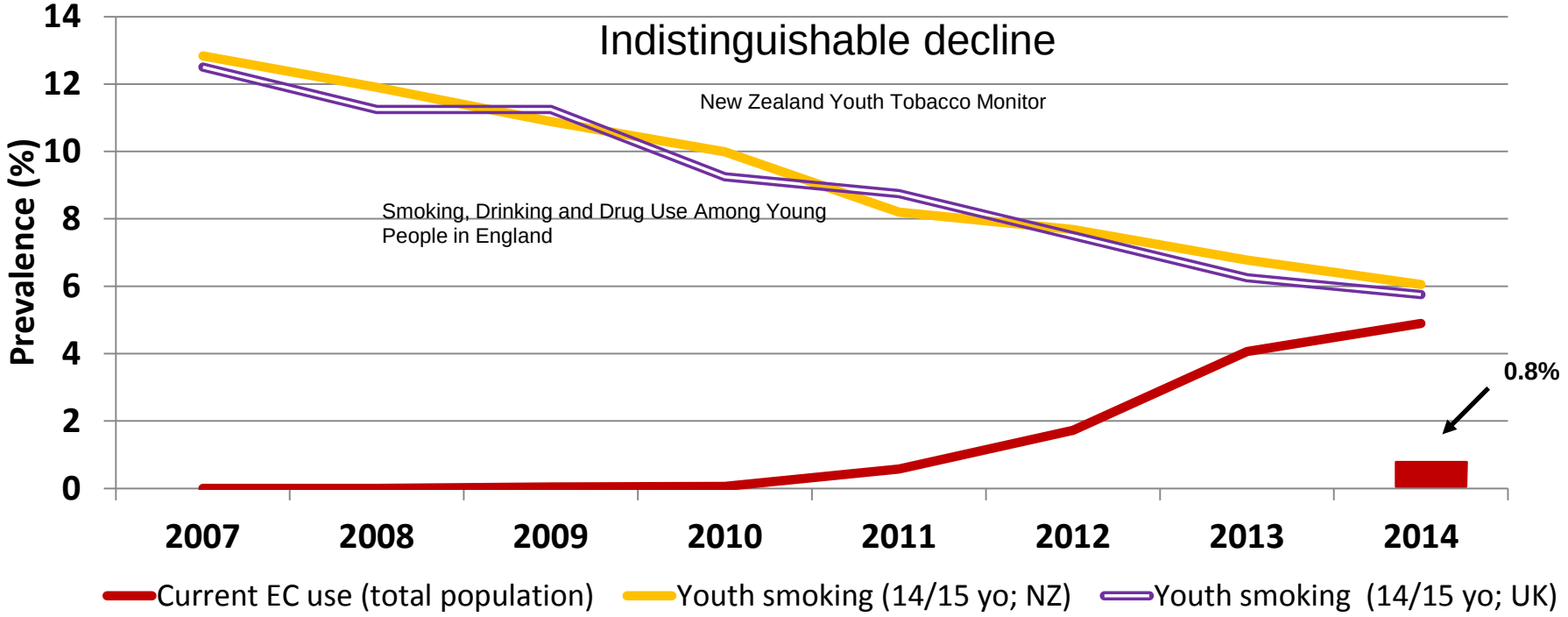
a) Individual level: case control design



2) Advanced Analytical Techniques

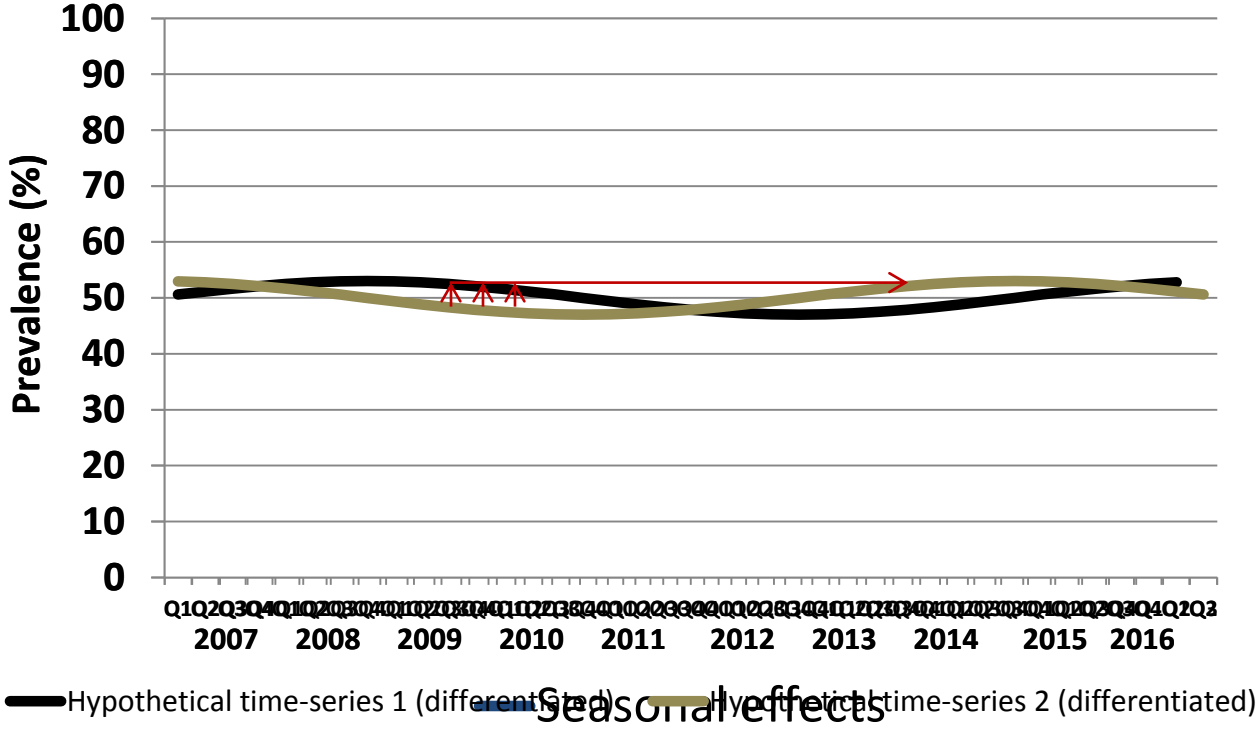
b) Population level: quasi-experimental

- Natural variation in legislation
  - Comparatively lax regulation of EC in UK as consumer product (prior to EU TPD)
  - New Zealand much stricter; use of nicotine in EC banned until 2018



2) Advanced Analytical Techniques

b) Population level: time-series

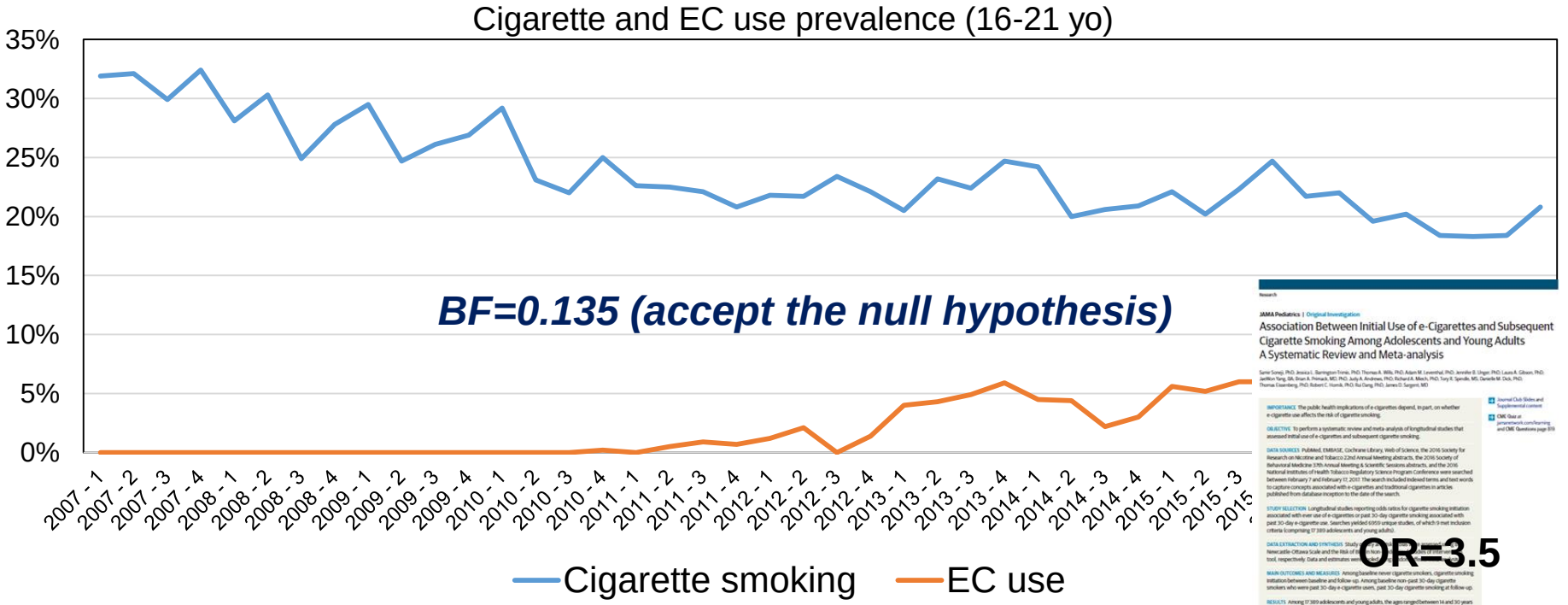


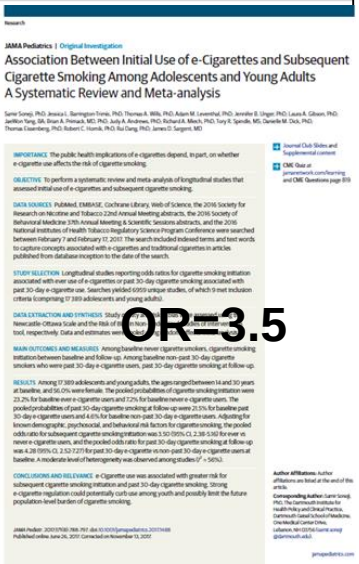
Seasonal effects

- **ARIMAX**: **A**uto**R**egressive (to model earlier scores, *q*), **I**ntegrated (to capture trends, *d*), **M**oving **A**verage (to model random noise, *p*) with e**X**ogenous input (to model impact of one on another time-series)
  - If seasonality is present, also need to have seasonal *q*, *d*, *p*

2) Advanced Analytical Techniques

b) Population level: time-series

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Samir Soneji, PhD, The Dartmouth Institute for Health Policy and Clinical Practice, Dartmouth-Geisel School of Medicine, One Medical Center Drive, Lebanon, NH 03756 (samir.soneji@dartmouth.edu).

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OR=3.5

- No evidence of an association
  - β=-0.015 95%CI -0.342 to 0.312; **p=0.929**

3) Forecasting

a) Micro-simulation

- Uses individual agents (act independently or interact with other agents) to simulate macro events (bottom up)
  - Set of rules that governs behaviour probabilistically

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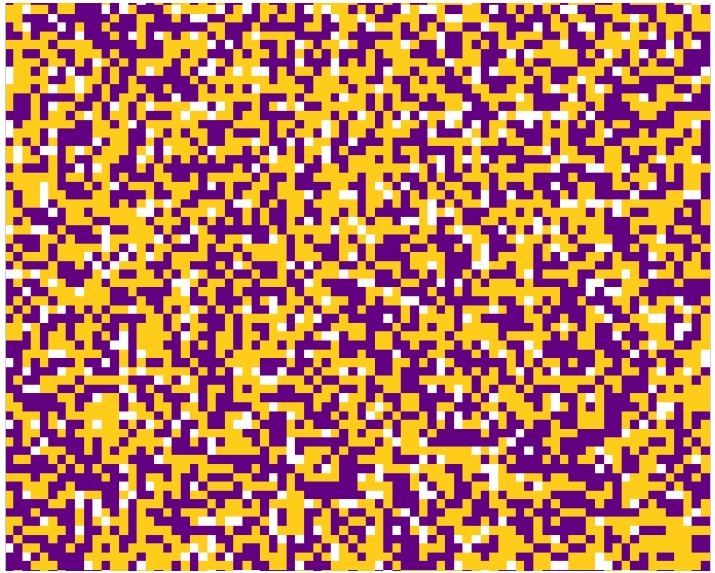
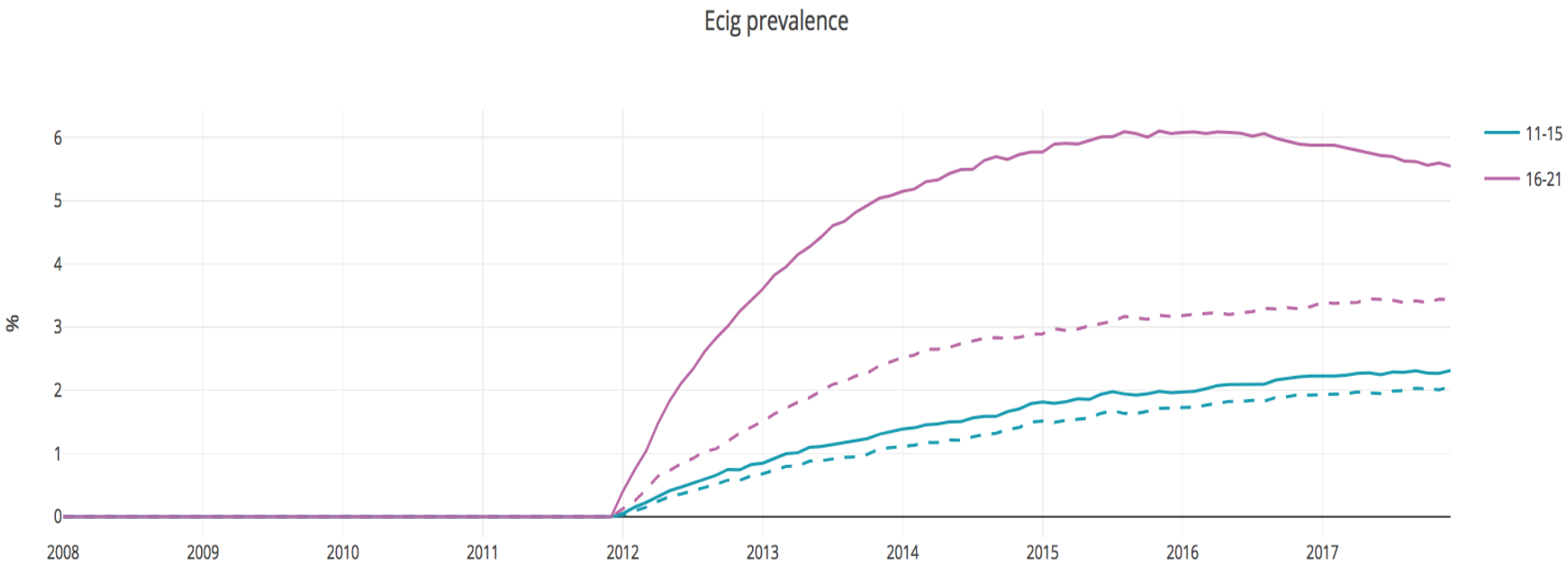


3) Forecasting

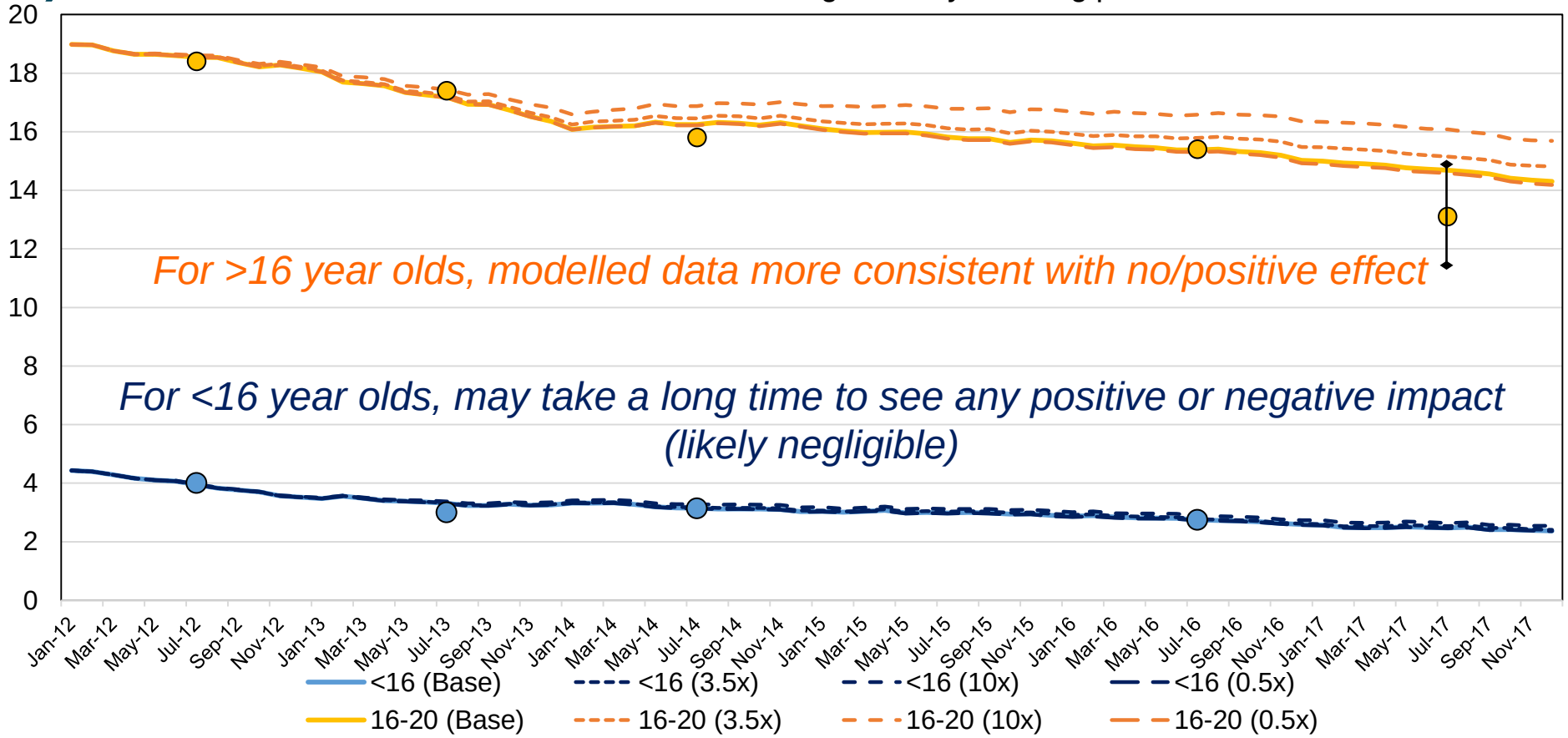
Smoking prevalence | Ecig prevalence | Smoking uptake | Ecig uptake



3) Forecasting

b) Micro-simulation

Modelled and actual regular/daily smoking prevalence



Data sources: Smoking Drinking and Drug Use among Young People; Smoking Toolkit Study

Conclusions

1) Epidemiological and modelled data suggest impact, if any, of EC use on adolescent cigarette smoking prevalence i ble
2) Time-series analysis and micro-simu tulated effects based on longitudi al impact that EC
3) C gest a potentially protective e cents who might have smoked

On balance of probabilities, panic about EC acting as a significant gateway to smoking in youth is not warranted based on current best evidence

However, continued need to monitor data and cross-validate results

"I tried to warn him - garbage in, garbage out."

Acknowledgements

- Emma Beard
- Jamie Brown
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