Pharmaceutical Drug Regulation and Mortality: The Peculiar Case of E-cigarettes

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The FDA

- The Food and Drug Administration (FDA) is tasked with regulating pharmaceutical drugs in the U.S. and approving new drugs
- FDA drug regulation involves a lengthy, costly, and high-uncertain drug approval process; expensive post-market surveillance; and high regulatory barriers for making even small changes after initial approval is received,
  - Average time to bring new pharmaceutical compound to market is 15 years, 7 of which is spent on preparing original application
  - Firm spending on approved compound averages $2.9 billion, including post-approval monitoring (DeMasi et al., 2016)
- Only 11.8% of new compounds approved for human subjects are approved for marketing

FDA Approval Process

- FDA drug regulation represents a trade-off between safety/efficacy and speed
- Social welfare could accrue earlier with fast approval, but at the risk of welfare losses from unsafe/ineffective compounds
- Studies have found that decreasing drug review times
  - has no effect on adverse events (Grabowski & Wang, 2008)
  - increases firm R&D expenditures (Vernon et al., 2006),
  - increases drugs in development (Chorniy et a., 2021)
  - increases market entry (Jia et al., 2023)
- The 1992 Prescription Drug User Fee Act, which reduced FDA review times, increased social surplus by \$14-\$31 billion per year (Philipson et al., 2008)
  - Upper bound of life-years lost is 56,000, suggesting that faster decisions outweighed costs

Our Paper

- Most research estimates effect of FDA drug review times, just one aspect of FDA drug regulation, on social welfare, adverse events, innovation, etc
- **Big Picture Question**: How does FDA drug regulation *writ-large* impact consumer welfare and mortality?
- In this paper, we evaluate a single "drug", *e-cigarettes*, that unexpectedly "escaped' FDA drug regulation in 2009 due to change in federal law.
- **Research Question** How did e-cigarettes impact mortality and social welfare, compared to nicotine replacement therapy (NRT)?
- Studying the effect of e-cigarettes on mortality, and comparing these effets to NRT, provides a 'glimpse' into a modern-day world without FDA drug regulation

Background

- In 8/2006, the Ruyan v8 e-cigarette began being imported into the U.S.
- In 3/2009, the FDA declared e-cigarettes to be unapproved drug and began seizing them at ports of entry
- Two e-cigarette companies subsequently took the FDA to court challenging their declaration that e-cigarettes were a drug and seeking an injunction against seizures
- The FDA's policy at the time was that they could declare any tobacco product as a "drug", unless the federal gov't *indirectly* declared the product as a "tobacco product" through legislation

Ruyan V8

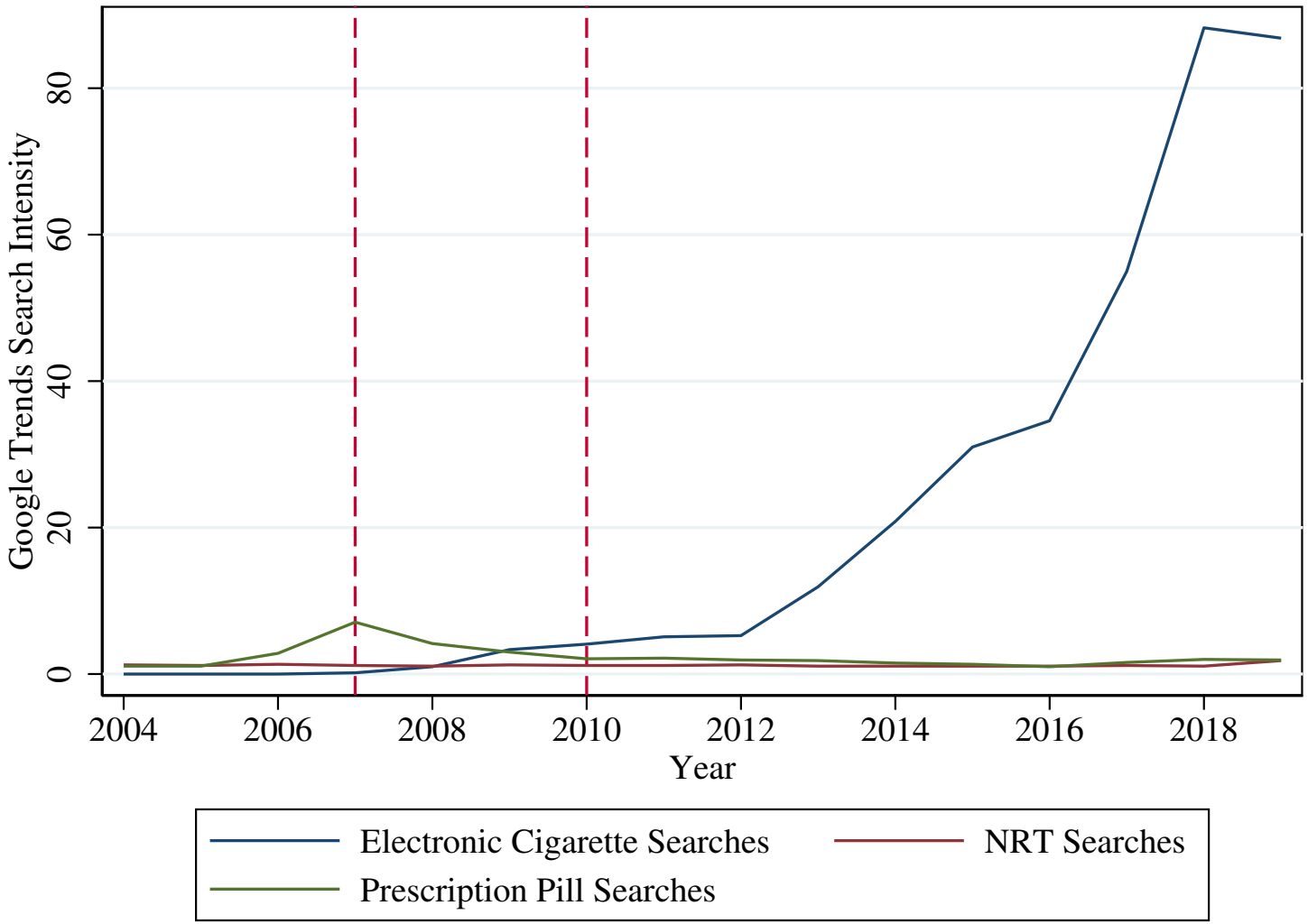
Background

- In 6/2009, the Family Smoking Prevention and Tobacco Act (TCA) was signed into law
- The TCA gave the FDA new authority to regulate existing tobacco products, like cigarettes, and a pathway to regulate new products if the FDA "deemed" them as tobacco products through the federal rule-making process.
- An unintended effect of the TCA, however, was that it diminished the FDA's legal argument that e-cigarettes were a drug, since Congress now legislated that even new tobacco products can be regulated as tobacco products.
- In 1/2010, a district court judge sided with industry, ruling that the FDA must regulate e-cigarettes as a tobacco product, not a "drug"

Post-TCA

- The FDA began the process of deeming e-cigarettes as tobacco products, which was finalized in 8/2016.
- As a consequence e-cigarettes were entirely unregulated federally for 7 years after TCA (10 years after importation in 2006), but were still subject to product liability law.
- E-cigarette companies avoided drug approval process, could innovate without regulator approval, could enter without regulatory barriers, and avoided potential product safety recalls.
- In this unregulated marketplace, e-cigarette sales exploded: Gen 1: Disposables; Gen 2: "Vape pens" with refillable cartridges, tanks, and rechargable batteries; Gen 3: "Tanks" and "mods" with more customization; Gen 4: "Pods", nicotine salts, more flavors

Nicotine Drug Searches



NRT

- In contrast to e-cigarettes, consider slow evolution of other smoking cessation medications:
- In 1984, 2mg NRT gum first marketed.
- 4 mg gum in 1993; Over-the-Counter (OTC) gum in 1996; mint and orange flavored gum in 1999 and 2000.
- It took 9 years before nicotine gum could be sold with a higher nicotine strength, 12 years before it could be sold OTC, and 15 years before nicotine gum could be sold with a flavor
- Cyctisine, a highly effectice smoking cessation drug available elsewhere, not approved as a drug in the U.S.

"Paper in One Slide"

- **Big Picture Question**: What are the public health benefits, or harms, from FDA drug deregulation?
- **Research Question**: How do e-cigarettes and over-the-counter NRT impact mortality for high-smoking demographics relative to low-smoking demographics?
- **Data**: NVSS restricted-use mortality data, BRFSS
- **Identifying Variation**: Cross-sectional variation in smoking prevalence prior to drug introduction
- **Estimation Strategy**: Bite-style differences-in-differences
- **Results**: E-cigarettes saved roughly 1.7 million life-years from 2007-2019, or $13.3 billion in annual consumer surplus.
- E-cigarettes reduced smoking. No detected effect from NRT on mortality or smoking.

BRFSS

- We use data from BRFSS from 1989-2020 to construct smoking bite
- Construct our bite variable using 2 years prior to drug introduction (1996, 2007). Calculate daily smoking prevalence by group. Use BRFSS sample weights.
- Mean daily smoking rate prior to e-cigarettes is 12.0% (16.7% for NRT). Avg. of 1,220 (575) respondents used to construct e-cigarette bite (NRT bite).
  - Highest daily smoking rate (ENDS intro) is 33.6%: 40-44 years old, American Indian, female, rural, South
  - Lowest daily smoking rate (ENDS intro) is 0.16%: 70-74 years old, Asian/Pacific Islander, female, rural, West
- Require at least 100 respondents to calculate prevalence. Daily smoking prevalence is preferred bite.

NVSS

- Restricted-use death records from NVSS from 1989-2020. Contains detailed information from death certificates in U.S.
- Create panel of all-cause and cause-specific mortality rates by demographic group from 1989-2019
- Smoking-attributable ICD codes from Lariscy (2019). Include prostate and breast cancer due to causal evidence linking smoking to these causes (Lariscy, 2019).
- Panel consists of annual mortality rates for 960 groups from 1989-2019. 28,800 group-year observations

BRFSS

- We also examine current and daily smoking prevalence as outcomes at the yearly level.
- Calculate same as before with bite variable: estimate mean smoking prevalence by group using BRFSS sampling weights
- Drop census region as a demographic dimension to increase cell sizes.
- Merge current and daily smoking prevalence onto our mortality panel.

Reduced-Form Estimation

- We estimate a bite-style DID model given below (Bartik, 1991; Allcott & Rafkin, 2022)

$$y_{it} = \alpha + \beta \cdot \theta_i + \gamma_i + \phi_t + \varepsilon_{it}. \tag{1}$$

- y_{it}: mortality per 100,000 for group i in year t
- θ_i: daily smoking prevalence of group i in 2 years prior to drug introduction
- γ_i: county fixed effects
- ϕ_t: year fixed effects
- ε: error term, cluster at demographic group level
- Note: Estimate through OLS, weight by population.

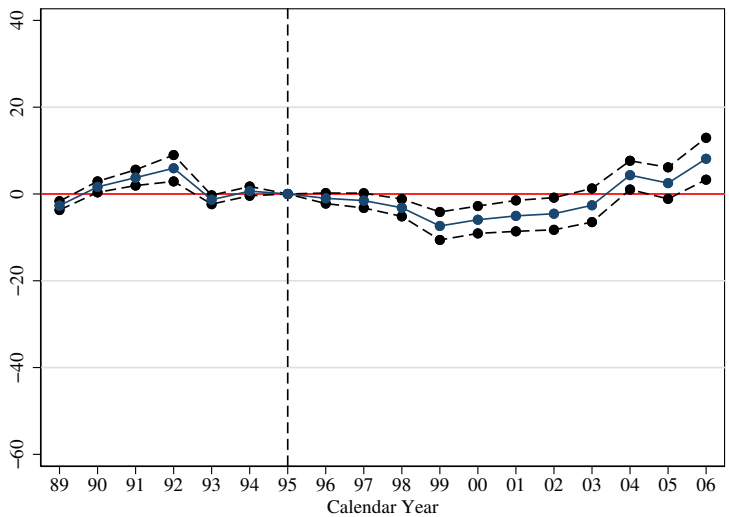
Pre-Trend Correction Procedure

- **Identifying Assumption**: Prior to drug introduction, mortality among high-smoking groups trends parallel to that of low-smoking groups.
- Challenge is that parallel trend assumption rarely holds
  - i.e. mortality for higher-smoking groups tends to increase relative to lower smoking groups, prior to drug introduction.
- To ensure parallel trends, use Andrew Goodman-Bacon (2021) pre-trend correction:
  - 1. For each demographic group, regress y_{it} on linear trend using pre-period years
  - 2. Take residuals from regression above, call 'adjusted' outcome
  - 3. Use adjusted outcome in Equation (1) and event studies
- This procedure effectively transforms mortality from levels to deviations in mortality from the pre-period linear trend, extrapolated into the post period.

Mortality Event Studies

Figure: All-Cause Mortality Event Studies

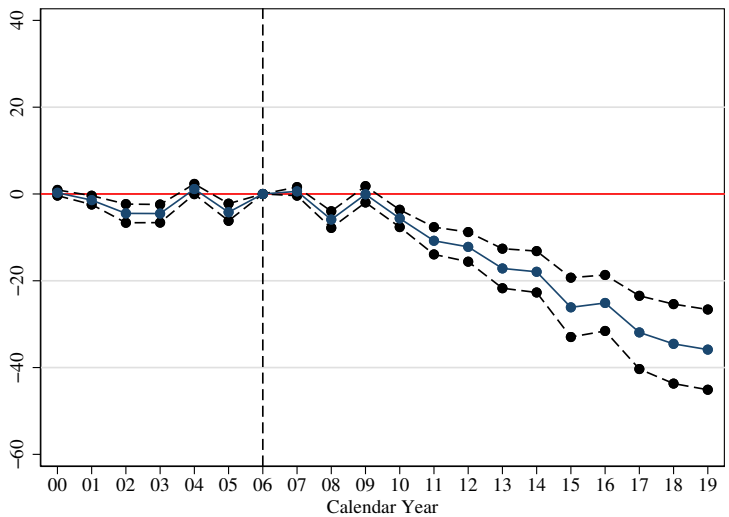
(a) NRT Introduction



$\beta\,(SE) = -2.60\,(1.46), \bar{y}_{pre} = 1,311$

Implied % Change $= -0.20\%$

(b) E-cigarette Introduction



$\beta\,(SE) = -15.47\,(1.98), \bar{y}_{pre} = 1,352$

Implied % Change $= -1.07\%$

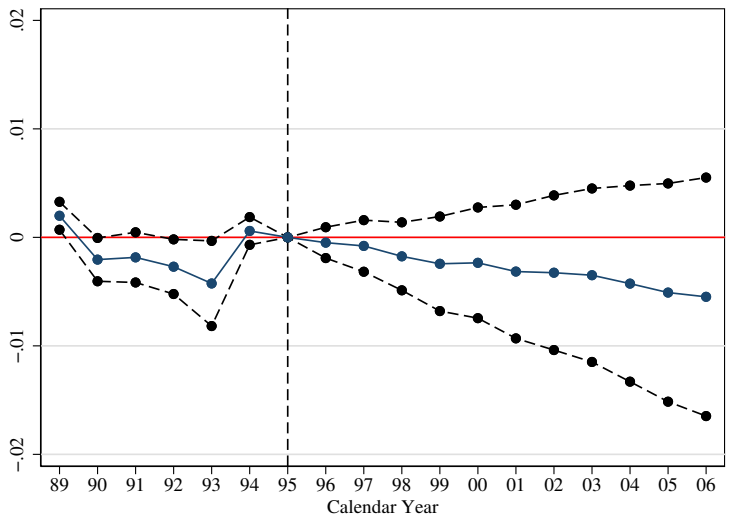
Mortality Event Studies

- **Takeaways:** Mortality rates after 2007 fell by 1.07% (relative to pre-2007 trend) for every 1pp difference in daily smoking from 2005-2006. No significant effects from OTC NRT.
- Now let's look at how drug introduction impacted smoking prevalence...

Smoking Event Studies

Figure: OTC NRT Introduction and Smoking Prevalence

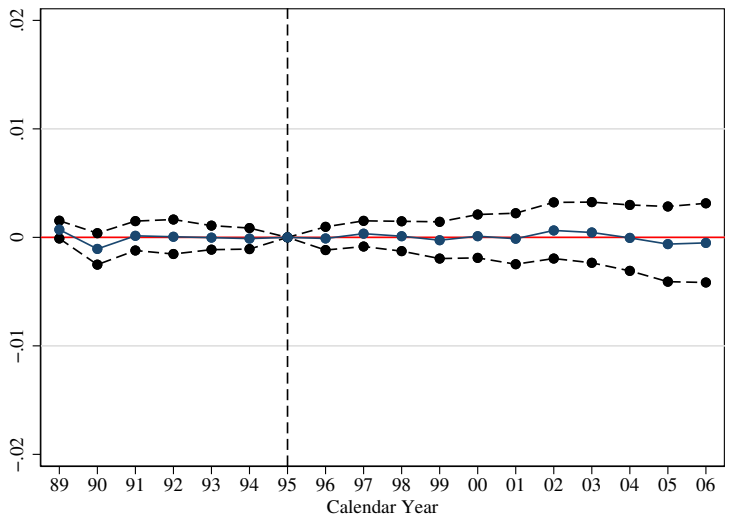
(a) Current Smoking



$\beta\,(SE) = 0.0006\,(0.0008), \bar{y}_{pre} = 0.43$

Implied % Change $= 0.14\%$

(b) Heavy Smoking



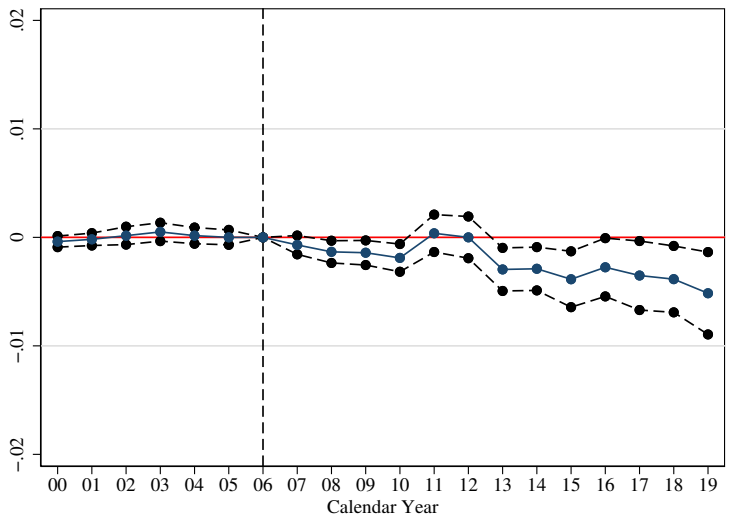
$\beta\,(SE) = 0.0002\,(0.0006), \bar{y}_{pre} = 0.21$

Implied % Change $= 0.11\%$

Smoking Event Studies

Figure: E-cigarette Introduction and Smoking Prevalence

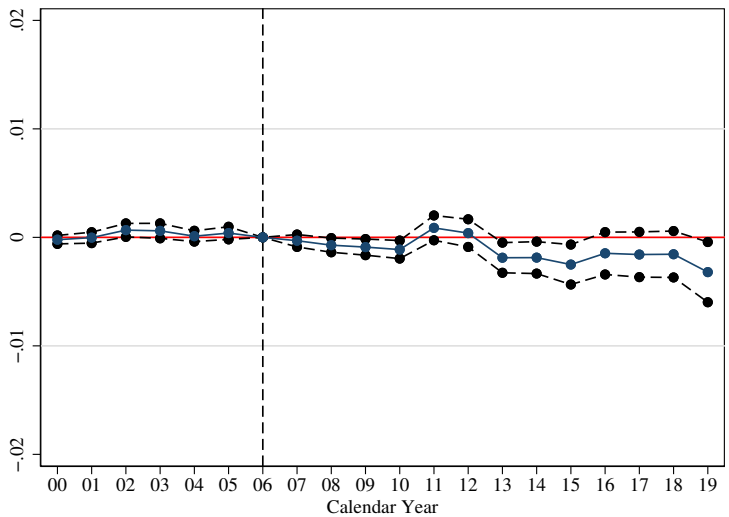
(a) Current Smoking



$\beta\,(SE) = -0.0023\,(0.0009), \bar{y}_{pre} = 0.19$

Implied % Change $= -1.21\%$

(b) Heavy Smoking



$\beta\,(SE) = -0.0014\,(0.0007), \bar{y}_{pre} = 0.15$

Implied % Change $= -0.93\%$

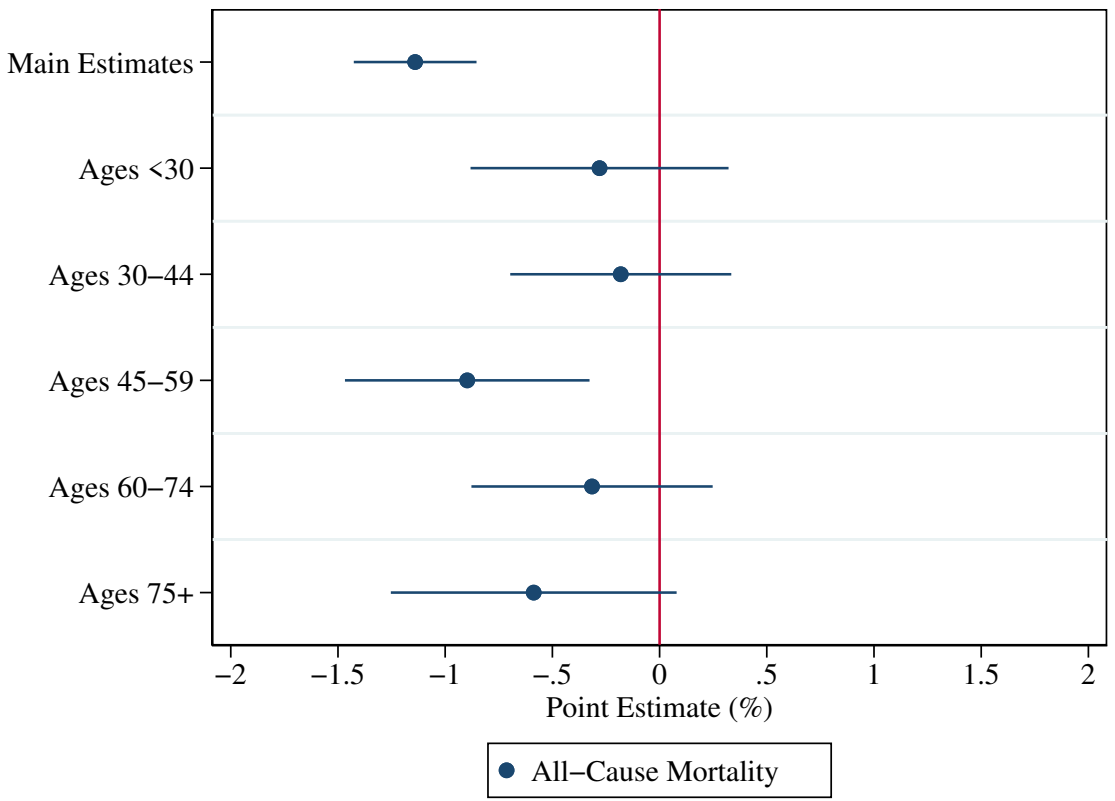
Smoking Event Studies

- **Takeaways** Current smoking rates fell by 1.21% (relative to pre-2007 trend in smoking) for every 1pp difference in daily smoking pre-e-cigarette introduction.
- Daily smoking rates fell by 0.93% (relative to pre-2007 trend) for every 1pp difference in daily smoking pre-e-cigarette introduction.
- No significant effects from OTC NRT introduction.

Mortality Results by Age

Figure: Summary of Main Estimates and Age-Heterogeneity Estimates

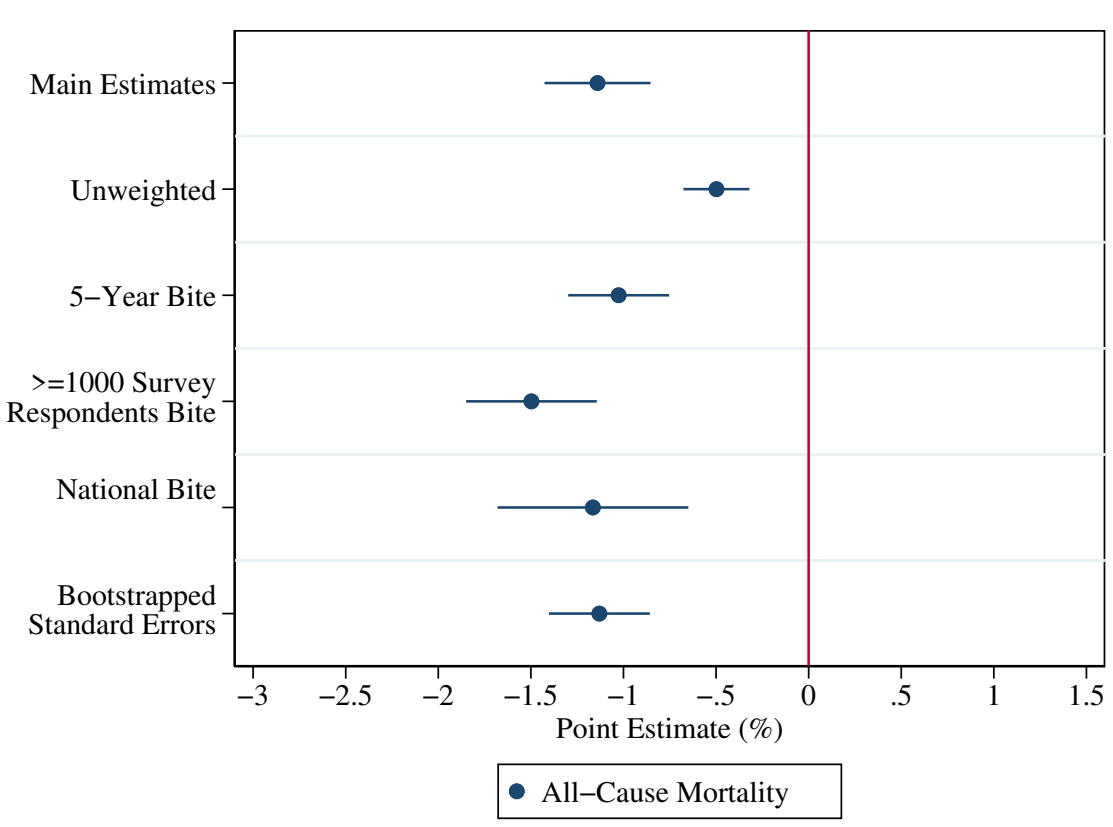
(a) E-cigarette Introduction



Mortality Results by Specification

Figure: Summary of Main Estimates and Robustness Estimates

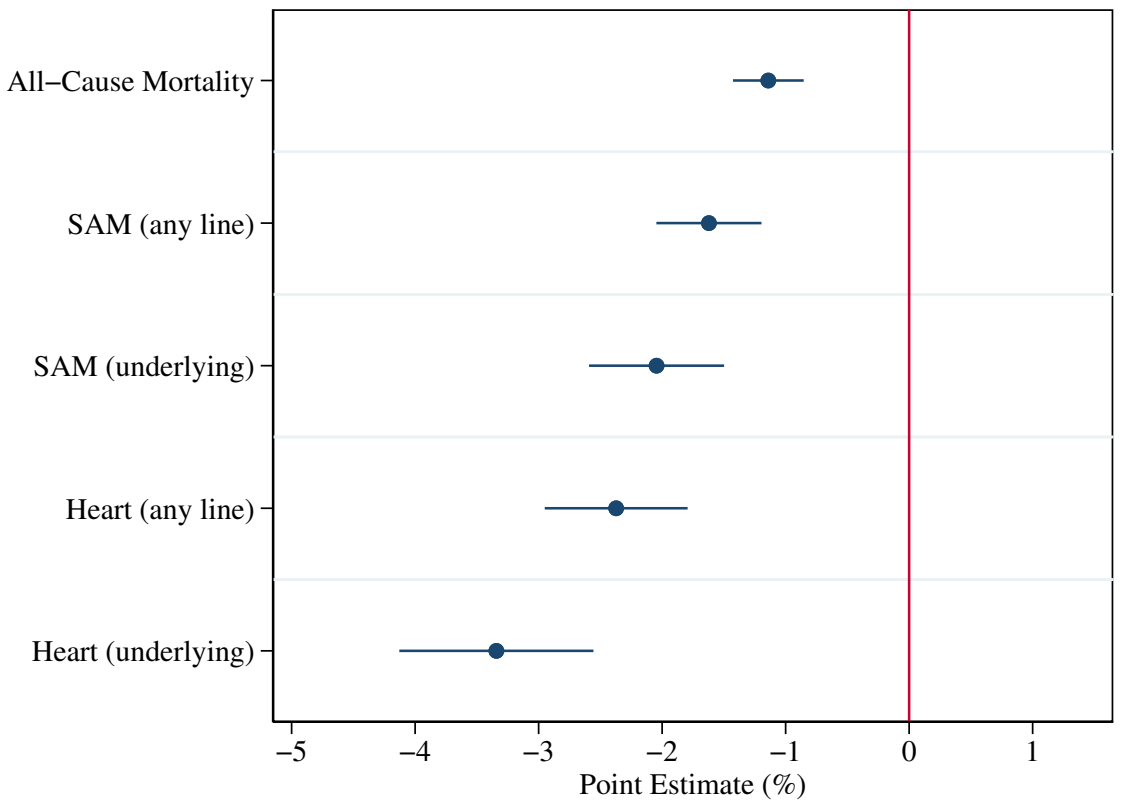
(a) E-cigarette Introduction



Results by Cause of Death

Figure: Summary of Main Estimates by Cause of Death

(a) E-cigarette Introduction



Consumer Surplus

- We calculate consumer surplus as follows:
- 1. Take annual ATT's post-2007 by age group, multiply by mean pop-weighted daily smoking prevalence in that age group (2005-2006).
- 2. We've now converted our estimates into implied changes in mortality evaluated at the mean daily smoking rate. Multiply by population to convert from mortality rate to mortality reductions.
- 3. Smoking cessation should increase life expectancy by 9, 6, 4, and 2.85 years for those 35-44, 45-54, 55-64, and 65+, respectively (Philipson & Jena, 2006; Taylor et al., 2002). Multiply deaths averted from step 2. by expected gain in life-years.

Consumer Surplus

- 4. Discount gain in life-years from step 3. by 50% to account for mix of smoking reduction and smoking cessation from our results. Discount by 50% again to account for Darden (2018) finding that life years lost from smoking are roughly half of CDC estimates.
- 5. We now have a total of roughly 165k life-years gained annually from e-cigarettes, or 2.2 million from 2007-2019.
- 6. Multiply life-years gained by VSLY ($100,000 per life-year), discount to 2007 using 3% market interest rate, convert to 2019 dollars.
- **Takeaways** Total of $173 billion in consumer surplus from 2007-2019, or $13.3 annually.

Conclusion

- FDA drug regulation can unintentionally reduce innovation and diminish social welfare
- This study examines how e-cigarettes, a drug which unexpectedly managed to "escape" FDA drug regulation, impacted mortality, compared to NRT.
- Our results indicate that e-cigarettes saved **1.66 million life years** and generated $173 billion in consumer surplus from 2007-2019.
- This suggests that FDA drug regulation may be too restrictive, and deregulation could lead to public health gains.
- Our study also suggests if the FDA Center for Tobacco Products is successful in clearing the e-cigarette marketplace of all but 23 authorized e-cigarette products, this is likely to offset mortality reduction gains that e-cigarettes are otherwise providing.