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

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July 24, 2024

Abstract

This study investigates the broader effects of drug regulation in the United States by examining the specific case of e-cigarettes, which were unexpectedly judicially exempted from drug regulation in 2010. Our analysis shows that this exemption led to significant increases in e-cigarette innovation, as evidenced by patent applications. Leveraging differences in smoking rates across demographic groups prior to e-cigarette introduction, we find that from 2011 to 2019, e-cigarettes saved 826,000 life years, unlike nicotine replacement therapy introduced in 1984, which had no measurable effect. We demonstrate that reduced smoking is a key mechanism explaining this mortality reduction, with statistically significant mortality reductions lagging smoking reductions by approximately six years. Our calculations indicate that e-cigarettes increased social surplus by $9.5 billion annually, and we predict that social surplus will remain positive and sizable in future years.

Keywords: drug regulation, mortality, innovation, patents, e-cigarettes, smoking, nicotine replacement therapy
JEL: I12, I18, D62

Acknowledgements and Notes: Research reported in this publication was supported by the National Institute On Drug Abuse of the National Institutes of Health under Award Number R01DA045016 and by the National Cancer Institute and Food and Drug Administration Center for Tobacco Products under Award Number U54CA229974. The content is solely the responsibility of

*We appreciate helpful comments from Michael Darden, Amanda Gaulke, Joe Gitchell, Erik Nesson, Charlie Rafkin, Ljubica Ristovska, Carlywill Sloan, Brittany Street; seminar participants at Georgia State University, The University of Missouri; and conference participants at the American Society of Health Economists Conference (2024), Kansas Health Economics Conference (2024), the Workshop on the Economics of Risky Behavior (2024), the Southern Economic Association Conference (2024), and the Tobacco Online Policy Seminar (2024). We also appreciate research assistance from Guthrie Scoblic.

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the authors and does not necessarily represent the official views of the National Institutes of Health or the Food and Drug Administration.

1 Introduction

Pharmaceutical drugs significantly enhance longevity and quality of life (Lichtenberg, 1996, 2022). Market forces drive innovation in pharmaceuticals (Acemoglu and Linn, 2004; Dubois et al., 2015). The Food and Drug Administration (FDA) plays a critical role in regulating pharmaceuticals in the United States, influencing drug diffusion globally.[1] The FDA's primary role is to approve new drugs that demonstrate a positive overall risk-benefit profile in terms of safety and efficacy relative to a placebo (Lakdawalla, 2018), with some ability to consider unmet need (Chandra et al., 2024). The modern-day incarnation of the FDA first appeared in 1938, when the agency was empowered to conduct pre-market review of the safety of all new drugs before these could be brought to market. The FDA's powers were significantly expanded in 1962 by authorizing the FDA to approve efficacy of new drugs in addition to safety (Philipson and Sun, 2008), and by providing the FDA with greater control over the testing process.

FDA drug regulation is multi-faceted. It involves a lengthy, costly, and highly-uncertain drug approval process, high regulatory barriers for making even small changes to drugs after initial approval is received, and expensive post-market surveillance. In recent years, the total time it takes to bring a new pharmaceutical compound to market is approximately 15 years, which includes seven years in preparing the original application (e.g., Investigational New Drug [IND] Application) to begin human subjects testing[2] and eight years for marketing approval to be obtained after human subjects testing has started (DiMasi et al., 2016).[3] Only 11.8% of new compounds that are approved for human subjects testing are approved for marketing. The cost of firm spending on drugs is subject to significant debate (Lakdawalla, 2018), but one prominent estimate finds that firms spend on average $1.4 billion (in 2013 dollars) per approved compound (e.g., drug or vaccine), and $2.9 billion after factoring in post-approval monitoring (DiMasi et al., 2016). These costs have been growing significantly faster than the rate of inflation since the 1970s.

Current evaluations of FDA drug regulation have primarily focused on the initial drug approval process; in particular, the trade-off between safety/efficacy and speed in the FDA's evaluation of new

[1] Fifty-four percent of FDA-approved drugs were launched in the average country within ten years, versus only 19 percent of non-FDA approved drugs (Cockburn et al., 2016).

[2] This stage involves testing the properties of a potential new drug by looking at chemical evidence, animal studies, foreign experience, and use of the drug for treating other conditions (Philipson and Sun, 2008)

[3] This includes the FDA review time, which has been about 1.3 years for drugs approved between 1999 to 2005 (Chorniy et al., 2021).

drug applications.[4] One welfare evaluation leveraged shortened FDA review times for New Drug Applications mandated by the 1992 Prescription Drug User Fee Act. Authors found that the Act reduced FDA review times and increased social surplus by between $14 to $31 billion per year (or the equivalent of 140,000 to 310,000 life years saved if the statistical value of life is $100,000 per year), and had an extreme upper bound for adverse events of 56,000 life years lost, suggesting that gains of faster FDA decisions outweighed costs (Philipson et al., 2008). Several other studies have found that decreasing drug review times has no sizable effect on adverse events (Grabowski and Wang, 2008; Chandra et al., 2024), increases firm R&D expenditures (Vernon et al., 2006), increases drugs in development (Chorniy et al., 2021), and increases market entry of new drug companies (Jia et al., 2023).

These studies provide important data points for understanding how FDA drug regulation reduces innovation and welfare, but they focus on only one small aspect of the FDA drug regulation process, review times that take on average 1.3 out of 15 years from the time when application preparation starts to when marketing approval is granted (Philipson and Sun, 2008; Chorniy et al., 2021). These findings do not necessarily generalize to the earlier 13.7 years (on average), or to post-market activities. Relatively little causal research exists on FDA drug regulation outside of the drug review process. We have found only one study exploring the effect of post-market FDA drug regulation activities (Garthwaite, 2012), which estimated the effect of sudden withdrawal of drug approval on labor outcomes. Several studies explore the effect of generic drug entry (Frakes and Wasserman, 2023; Branstetter et al., 2016), but this is generally driven by patent law rather than drug regulation.

In contrast to existing evidence primarily focusing on drug review times, our current study is unique by evaluating the full effect of FDA drug regulation–from initial application preparation to post-market activities–for a single "drug," e-cigarettes, that was unexpectedly exempted from drug regulation at the end of 2010.[5] Drug exemption means that e-cigarette companies were able to bypass not just the drug review process, but the on average 15-year drug approval process entirely. Additionally, without FDA drug regulation, e-cigarette companies could also freely enter the market, modify products without approval, and bypass extensive post-market reporting requirements, quality control standards, and safety recall threats. By estimating the combined effect of all of these things,

[4]Speed in approving new drugs has the benefits of producer and consumer surplus gains accruing earlier (Philipson and Sun, 2008), but unsafe drugs and/or ineffective drugs represent welfare losses due to premature death and imperfect information.

[5]We use *drug exemption* as a shorthand way to describe the process of e-cigarettes unexpectedly escaping FDA drug regulation by a court system ruling that the FDA could not regulate e-cigarettes as drugs, which we describe in subsequent paragraphs.

our study advances the literature significantly in terms of understanding the full effect of FDA drug regulation. While e-cigarette were no longer constrained by FDA drug regulation, they did face constraints from product liability law.[6] Product liability lawsuits were regularly brought against e-cigarette companies for things like injuries from exploding e-cigarettes and for deceptive marketing practices (Berman, 2021; Willetts, 2023).

The e-cigarette drug exemption natural experiment also provides the opportunity to quasi-experimentally study the relationship between e-cigarettes and smoking. Smoking is estimated to be the largest source of preventable disease and premature death in the United States, resulting in 480,000 deaths per year (US Department of Health and Human Services, 2014),[7] which is similar to the annual death rate during the height of the COVID-19 pandemic of approximately 500,000 per year.[8] Most experts agree that e-cigarettes are safer than cigarettes, but estimates vary. Two prominent estimates of the relative risks of e-cigarettes to cigarettes are 5% (McNeill et al., 2022) and 37% (Allcott and Rafkin, 2022). A National Academies of Sciences, Engineering, and Medicine (2018) report states, "E-cigarettes contain fewer toxicants and are likely to be far less harmful than combustible tobacco cigarettes."

It is a-priori ambiguous what effect FDA drug regulation will have on social surplus, as it is unclear: 1) if drug companies will innovative more absent FDA drug regulation (but still subject to product liability law), 2) if people will trust and use "unapproved" drugs, and 3) if "unapproved" drugs are effective. Our study provides an answer to all three questions for the specific case of e-cigarettes.

E-cigarettes were first imported to the United States in August 2006.[9] Starting in September 2008, the FDA began confiscating e-cigarettes at ports of entry, and officially declared them to be an unapproved drug a few months later (Leon, 2010).[10] This declaration of e-cigarettes as a drug is

[6]Philipson and Sun (2008) discusses how product liability law may be sufficient for a safe and well-functioning drug marketplace.

[7]Darden et al. (2018) and Friedson et al. (2023) also use causal research methods to identify large effects of smoking on mortality.

[8]Throughout the paper, we refer to the act of using cigarettes as smoking and the act of using e-cigarettes as vaping. This follows colloquial use of these terms, with vaping being thought of as very different from smoking among those that use e-cigarettes.

[9]The first documented imported e-cigarette to the United States was the Ruyan v8 e-cigarette in Aug. 2006, which was produced in Hong Kong and developed by Hon Lik, a pharmacist. In assigning the product a tariff, U.S. Customs described the purpose of the product as "acting as a nicotine inhaler that has atomized smoke being forced out of the plastic mouthpiece tip" (U.S. Customs and Border Protection, 2006). Notably, these original imports were not flavored. A picture of the original e-cigarette is available in Appendix Figure B1, which can be viewed as baseline for subsequent innovation in e-cigarette space.

[10]The FDA's technical classification of e-cigarettes was they were an unapproved drug-delivery device (like a nicotine patch).

consistent with other historical examples, such as the FDA regulating a nicotine inhaler as a drug, and the FDA having successfully removed other nicotine products from the marketplace for being unapproved drugs, including a non-electronic smokeless cigarette, nicotine hand gel, lollipops, lip balm, and water (Chowdhury and Jockel, 2018). Other countries currently regulate e-cigarettes as drugs; for example, e-cigarettes are currently only available as drugs in Australia and South Africa, and can be marketed as drugs in the United Kingdom in addition to as consumer products (Global Tobacco Control, 2024).

Two e-cigarette companies took the FDA to court asking for an injunction against these e-cigarette seizures by claiming the FDA could not regulate them as a drug without authorization from Congress. The FDA had a strong legal argument, supported by Supreme Court of the United States (2000), that they could declare any nicotine product as a drug, unless the federal government had "intended" for the product to be something different than a drug by regulating them differently (for example, by taxing them).

During deliberations at the district court level, in June 2009, the Family Smoking Prevention and Tobacco Control Act (TCA) became law. This gave the FDA new authority to regulate cigarettes and smokeless tobacco. The legislation also gave the FDA power to regulate other nicotine products, like e-cigarettes and cigars, as tobacco products if the FDA first "deemed" them as tobacco products following the federal rule-making process. While Congress did not require the FDA to regulate e-cigarettes as tobacco products, e-cigarette companies argued that by creating this alternative pathway, Congress *intended* for e-cigarettes to be a tobacco product instead of a drug. In other words, the FDA's previously strong, Supreme Court-validated legal strategy became unexpectedly uncertain following the passage of this new legislation, depending on how the Courts ruled on Congressional intent.

Industry lawyers now argued that the FDA could only regulate e-cigarettes as a tobacco product. From industry perspective, being regulated as a tobacco product was far preferable to being regulated as a drug because it was expected to take the FDA years to "deem" e-cigarettes as a tobacco product, during which time e-cigarettes would be unregulated by the FDA. Additionally, even if/when the FDA "deemed" e-cigarettes to be a tobacco product, the regulatory burden of tobacco products was

much lower than the regulatory burden of drugs.[11] In contrast, FDA officials preferred to regulate e-cigarettes as drugs so that they had far broader control, including the ability to block importation.

In Jan. 2010, a district court judge sided with industry and ruled that the FDA could not regulate e-cigarettes as a drug and must do so as a tobacco product instead. In a memorandum opinion, the judge referenced the recent TCA as persuasive (Leon, 2010). This decision was unanimously validated by a three-person panel of the Washington DC Circuit Court in Dec. 2010.

Immediate effects of this ruling were that e-cigarettes were no longer seized at ports and the FDA began the lengthy process outlined by the TCA to deem e-cigarettes as a tobacco product. The FDA finalized their ability to regulate e-cigarettes as tobacco products on August 8, 2016. For almost six years, e-cigarettes were regulated as a neither a drug nor a tobacco product by the FDA.[12] Even after the FDA gained tobacco regulatory authority over e-cigarettes, actual regulation was slow in developing. For example, e-cigarette companies were only required to submit PMTAs to the FDA to sell their products four years later, in Sept. 2020, and decisions regarding these applications remain ongoing even today. Additionally, tobacco product regulation has significantly lower regulatory barriers than being regulated as a drug.[13]

To preview our results, using data from the National Vital Statistics System from 1975 to 2019, we find that e-cigarette drug exemption increased life years gained by approximately 92,000 annually from 2011-2019. Using survey data, we find between 12.7 to 17.2 million fewer annual current smoking years, suggesting 1 life year gained for every 162.5 fewer smoking years. Statistically significant reductions in mortality lagged reductions in smoking by approximately six years. We estimate that drug exemption led to approximately half of the benefit in terms of life years saved of early HIV/AIDS drugs (Philipson and Jena, 2006), and has had an equivalent effect to raising the taxes people experienced as teenagers by $1.75 (Friedman et al., 2023).

[11] New tobacco products can be approved through the Premarket Tobacco Product Application (PMTA) process, which requires that their risks be no greater than those of combustible tobacco—a much lower standard compared to proving drug safety and effectiveness. Initial cost estimates for PMTAs in 2016 were $131,643 for an e-liquid and $466,563 for an e-cigarette delivery system. However, successful applications in 2021-2022 report application costs between $5 to $8 million (Adler and Rich, 2023). While significant, these costs of successful e-cigarette applications are substantially lower than costs of successful drug compounds estimated at $1.4 billion on average (in 2013 dollars) (DiMasi et al., 2016).

[12] We are unaware of any other case where the courts prevented the FDA from regulating a new product as a drug. Medical marijuana has some interesting parallels to e-cigarettes, but key differences as well. Primarily, since marijuana is a schedule 1 controlled substance currently, it is regulated federally by the Drug Enforcement Agency (DEA). Many states have flouted the DEA's authority federally to establish and regulate medical marijuana marketplaces themselves. The DEA has largely kept a hands-off approach to these state marketplaces, but does occasionally intervene. For example, the DEA recently issued letters to Georgia pharmacies warning them that dispensing medical marijuana through the pharmacy violates federal law, even if state law allows it (Manins and Oliviero, 2023).

[13] To reduce confounding from the FDA's escalating efforts to regulate e-cigarettes as tobacco products, we end our analysis in 2019, which is the year immediately prior to PMTAs being due.

2 Background

In this section, we illustrate how innovation has been substantially faster for e-cigarettes that were exempted from FDA drug regulation than for other smoking cessation drugs that were not. The first FDA-approved smoking cessation product was a 2-mg nicotine gum in 1984 (Shiffman et al., 1997).[14] No new drug innovation occurred through the rest of the 1980s. Perhaps in response to an unmet need for smoking cessation drugs, Favor, a smokeless and vaporless cigarette in which people inhale liquid nicotine without heating, was sold in select markets between 1985 to 1987.[15] In 1987, the FDA declared Favor an unapproved drug, and removed it from the marketplace. Favor then underwent the FDA drug regulation process and the technology underlying it emerged 5 years later as an FDA-approved prescription nicotine inhaler (Advanced Tobacco Products, 2003).

Seven years after initially authorizing 2-mg nicotine gum, the FDA approved a prescription nicotine patch in 1991, a prescription nicotine inhaler in 1992, and 4-mg nicotine gum in 1993. These products were somewhat unpopular, and only between 20-30% of smokers had tried them (Shiffman et al., 1997). In 1996, the FDA approved the patch and gum for over-the-counter (OTC) sale[16] and a prescription nicotine nasal spray. In 1997, OTC nicotine inhalers became available, and a non-nicotine smoking cessation drug, Zyban (bupropion), was approved for smoking cessation. The FDA approved supplemental new drug applications for mint flavored and orange flavored nicotine gum, which were brought to market in 1999 and 2000 respectively.[17] Nicotine lozenges were first approved directly for OTC in 2002 (US Food and Drug Administration, 2013). The second non-nicotine smoking cessation drug, Chantix (varenicline), was approved in 2006.

A key takeaway on the slowness of FDA drug regulation is that 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. Further, a recent editorial laments that there has been largely non-existent innovation in FDA-approved smoking cessation drugs since 2006 (Benowitz et al., 2023). In particular, the "world's oldest smoking cessation aid" cyctisine, first brought to market in 1964 in Bulgaria (Prochaska et al., 2013), and with quit success rates exceeding single

[14] Approval came approximately four years after the start of human subjects testing in the United States in 1980 (Reuters, 1980).

[15] Tobacco industry documents reveal significant concern about this new product, with an industry survey in Austin, TX finding that 90% of smokers were aware of the product and 45% of them had tried it within its first 12 weeks (RJ Reynolds Records, 1986).

[16] While the default is for drugs to be approved for sale over-the-counter (OTC), the FDA can also approve drugs for sale by prescription only. Many drug companies request prescription-only status for their medications during the length of their patent. This approach can increase profits since health insurers are more likely to pay for drugs that require a prescription, rather than those sold over-the-counter.

[17] One study finds a review time for supplemental New Drug Applications of 10 months (Kros and Qian, 2004).

forms of NRT (Lindson et al., 2023), is not approved as a drug in the United States.[18] This situation raises concern that drugs may be over-regulated in the United States if effective smoking cessation products are not brought to market. Further, the FDA can temporarily or permanently rescind drug approval due to quality control issues or adverse events. For example, large-scale recalls of lozenges occurred in 2014 and Chantix in 2021 over quality control concerns (Frankel, 2015; Tyko, 2019) led to reported shortages of these products for smokers wanting to quit.

Regulation has been found to impede innovation in many contexts (Aghion et al., 2023). We provide quantitative evidence from Google Patents[19] of rapidly faster innovation in the e-cigarette marketplace[20] than the slow innovation that occurred for FDA regulated smoking cessation drugs. In Figure 1, we show patent applications for smoking cessation drugs not including e-cigarettes, and separately for e-cigarettes. We show these volumes separately for the United States, in which e-cigarettes were exempted from FDA drug regulation, and Australia, in which nicotine-containing e-cigarettes switched from illegal to prescription-only in 2012 (Morphett et al., 2023). There are generally low levels of annual patent applications for smoking cessation drugs (excluding e-cigarettes) in the United State (average = 10 per year from 1984-2019; high = 27) and in Australia (average = 4 per year from 1984-2019; high = 10). Similarly, e-cigarette patent applications are low in Australia, where e-cigarettes have been regulated as drugs since 2012 (Morphett et al., 2023) (average = 7 per year from 2007-2019; high = 22), but are high in the United States where e-cigarettes were exempted from FDA drug regulation (average = 142 per year from 2007-2019; high = 343). In particular, in the United States, e-cigarette patent applications averaged 2.7 per year during the short-lived phase in which e-cigarettes were imported and the FDA attempted to regulate these as drugs (2007-2009), increased to 17 in 2010 when the FDA was appealing the district court's decision that they could not regulate e-cigarettes as a drug, sharply increased to 228 per year during the phase in which

[18] One company did recently announce plans to try to bring cyctisine to market in the United States (Achieve Life Sciences, 2024).

[19] Google Patents is a search engine of filed patents. To find electronic cigarette patents, we used the following search: TAC=(("electronic nicotine delivery system") OR ("electronic cigarette") OR ("e-cigarette")) with "TAC" restricting the search to patent titles, abstracts, or claims. The search for other smoking cessation drugs was TAC=(("nicotine replacement therapy") OR ("nicotine gum") OR ("nicotine patch") OR ("nicotine lozenge") OR ("nicotine nasal spray") OR ("nicotine inhaler") OR ("cytisine") OR ("Varenicline") OR ("Bupropion")). We distinguished our searches by the "US" and "AU" patent offices, sorted by oldest and "Priority" date, and covered the timeframe of 01/01/1975 to 12/31/2023. The data was downloaded on 02/05/2024. The percentages of applications granted for US e-cigarettes, AU e-cigarettes, US smoking cessation drugs, and AU smoking cessation drugs are as follows: 27.6%, 29.9%, 24.5%, 20.5%.

[20] According to Centers for Disease Control and Prevention (2023b), innovation has been so rapid that e-cigarettes are commonly described in terms of four "generations" of evolution that affected everything from e-cigarette device types, voltage, heating temperature, battery, flavors, and nicotine formulation. We provide an example of this innovation visually by showing the original Ruyan v8 imported e-cigarette in Appendix Figure B1, and a recent example of hundreds of e-cigarette product offerings in a modern-day e-cigarette vape shop in Appendix Figure B2.

e-cigarettes were unregulated by the FDA, and remained high (at 215 per year) during the phase in which the FDA could regulate e-cigarettes as a tobacco product. This pattern of results provides evidence of drug regulation sharply restricting innovation, as e-cigarette patents sharply increased in the United States relative to Australia during the years in which e-cigarettes were not regulated as a drug.[21] This also provides evidence that while drug regulation had a large impact on innovation, tobacco regulation, at least through 2019, did not.

Finally, we use online search volume data from Google Trends to show that customer interest in e-cigarettes rapidly increased following this large increase in e-cigarette innovation.[22] For context, NRT products are widely available online, and are even sold on Amazon. Many states however ban online sales of e-cigarettes or otherwise tightly regulate them such as by requiring ID at purchase (McDonald, 2024). For these reasons, NRT product interest may be over-represented in Google Trends data.

As shown in Figure 2, e-cigarette search volume diverged from search volume for NRT and prescription pills around 2010, and peaked in 2018 with an e-cigarette search intensity index of 88.3, relative to 1.1 for NRT and 2.0 for smoking cessation prescriptions. We attribute this divergence to the ability of e-cigarettes to freely innovate whereas the other smoking cessation products were largely not able to. We further speculate that the only reason we think of e-cigarettes as "different" from these other smoking cessation products today is because of the innovation spurred by a vacuum of regulation. The originally imported Ruyan v8 e-cigarette was more similar than different to a little-used, FDA-approved nicotine inhaler. Both were unflavored, and the Ruyan v8 was sold with a nicotine concentration of 16 mg/ml versus 10 mg/ml for nicotine inhalers (versus up to 4 mg/ml for nicotine gum) (Bullen et al., 2010). One early trial found the Ruyan v8 was no more effective than the nicotine inhaler for smoking cessation (Bullen et al., 2010). If the Ruyan v8 had followed the pathway of the nicotine inhaler, and could only be changed slowly and incrementally through supplemental new drug applications, then awareness and use of e-cigarettes today may be just as low as awareness and use of nicotine inhalers today. However, because e-cigarettes were exempted

[21] We also estimate this relationship empirically in Table A1. Using a difference-in-differences (DD) regression of logged patents for e-cigarettes and other smoking cessation drugs, we find that e-cigarette applications increased in the United States in the post-drug exemption period by 276% (robust SE=31.2%) more than in Australia. Using a DDD design that includes patents for other smoking cessation drugs, we find that e-cigarette applications increased in the United States by 255% (robust SE=41.3%).

[22] Google Trends provides online search volume data for years 2004 to present. Search intensity is indexed from 0 to 100 and equals 100 in the period of greatest search volume. The e-cigarette search category contains the following searches, with search terms in quotations and search topics without quotations: e-cigarette, "electronic cigarette", "vape", Ruyan, Juul, Vuse, MarkTen, NJOY; the NRT search category contains Nicorette, Nicoderm, "nicotine gum", "nicotine patch", "nicotine lozenge"; the Prescription Pill search category contains Chantix, Varenicline, Zyban, bupropion.

from drug regulation, innovation occurred rapidly,[23] and people generally think of e-cigarettes today as a different product than other NRT products, but this would not have been an a-priori predicted outcome when e-cigarettes were first introduced.

3 Data

3.1 Mortality Data

For data on mortality, we rely on restricted access multiple-cause county-level mortality data from the National Vital Statistics System (NVSS).[24] The NVSS data is one of the most commonly used sources of public health information by epidemiologists and public health researchers, and contains the universe of mortality in the U.S. The quality of the NVSS data is considered very high given the strict standardization of death certificates and of coding procedures (Harris et al., 2021). The NVSS data is assembled from death certificates submitted each year from states and localities to the National Center for Health Statistics (NCHS), who then prepares the data for publication.

The mortality files from NVSS contain detailed geographic and demographic characteristics of the decedent, as well as information on underlying and multiple causes of death. Aside from cause of death information, we also rely on the decedent's sex, race/ethnicity, age, census region of residence, and urban status of county of residence to create our panel of demographic groups.[25] We focus our analysis on adults over the age of 30 and less than 75 years of age.[26]

We create our panel of demographic groups for every unique combination of our demographic characteristics detailed above, with some exceptions: to ensure consistency between our data, we default to the coarser categorization of demographic groups when necessary for race and for urban status. When analyzing years prior to 1990, we use 3-race categories. We do so because our source of population estimates— the Surveillance, Epidemiology, and End Results Program (SEER)—

[23]For example, the typical Juul pod is sold with a nicotine concentration of 59 mg/ml in contrast to the original Ruyan v8 of 16 mg/ml (Prochaska et al., 2022; Bullen et al., 2010), which was made possible by innovation in nicotine salt–based formulations.

[24]We also use public-use mortality files, which are identical to restricted-use files prior to 1989, from the National Bureau of Economic Research (NBER) public data repository.

[25]Our demographic dimensions consist of 2 sexes (male, female); 5 races (White non-Hispanic, Black non-Hispanic, Asian or pacific islander non-Hispanic, Native American non-Hispanic, Hispanic); 4 Census regions (Northeast, Midwest, South, West); 9 age-group bins (30-34, ..., 70-74), 2 urban status of residence (rural, urban). Urban status is defined based on 2013 and refers to whether a county lies within a core-based statistical area. This provides 720 (=2*5*4*9*2) potential demographic groups.

[26]While smoking cessation carries benefits at any age, the gains in life-expectancy for those who quit after the age of 65 are considerably smaller. Further, the rate of ever e-cigarette use among those over the age of 75 is only 2.8% from years in which BRFSS records e-cigarette use (2016-2018), and the rate of current e-cigarette use among this age group is 0.37%. For these reasons we focus attention on adults ages 30-74 in our main analyses.

only begins reporting 5-race/ethnicity population measures at the county level beginning in 1990.[27] The NVSS mortality data likewise only begins reporting Hispanic status in 1990. Urban status of residence is reported in the NVSS data without exception during our years of analysis (1975-2019), but is not consistently reported in the National Health Interview Survey (NHIS) data. We therefore use urban status as a demographic dimension in all of our analyzes except when we analyze smoking outcomes from the NHIS.[28]

We calculate mortality rates for each demographic group in our panel by dividing annual deaths for each group by that group's population, expressing rates per 100,000 population. In our main analysis, we focus on ages 30 and older in order to focus attention on the population that accounts for the vast majority of smoking-attributable causes of death; we consider younger adults later in a robustness exercise (see Figure E2). In addition to calculating total mortality rates, which we refer to as "all-cause" mortality, we also calculate smoking-attributable mortality (SAM) and cardiovascular mortality. We classify a death as smoking-attributable using the 8th, 9th, and 10th edition International Classification of Disease (ICD) codes of causes for which there is causal evidence linking smoking to mortality, following Lariscy (2019).[29]

In calculating SAM, we consider whether any line on the death certificate is smoking attributable.[30] We also examine cardiovascular mortality separately due to its uniqueness among smoking attributable causes as being immediately responsive to smoking cessation. In our panel, SAM makes up roughly 73% of all deaths, while cardiovascular mortality makes up roughly 22% of all deaths, or 31% of all smoking-attributable deaths.

[27]We use both the 1969-2020 and 1990-2020 single-year county-level population files. 3-race categories are White, Black, and Other Race. 5-race/ethnicity categories are White non-Hispanic, Black non-Hispanic, Asian or pacific islander non-Hispanic, Native American non-Hispanic, Hispanic

[28]We show that our mortality results are insensitive to dropping Census region.

[29]These include the following ICD categories (ICD-9 codes; ICD-10 codes): Lip and oral cavity cancer (140-149; C00-C14), Esophageal cancer (150; C15), Stomach cancer (151; C16), Colorectal cancer (153-154; C18-C20), Liver cancer (155; C22), Pancreatic cancer (157; C25), Laryngeal cancer (161; C32), Lung cancer (162; C33-C34), Cervical cancer (180; C53), Urinary bladder cancer (188; C67), Kidney and renal pelvis cancer (189; C64-C66), Acute myeloid leukemia (205; C92.0), Diabetes mellitus (250; E10-E14), Ischemic heart disease (410-414, 429.2; I20-I25), Other heart disease (390-398, 415-429.1, 429.3-429.9; I00-I09, I26-I51), Total stroke (430-434, 426-438; I60-I69), Artherosclerosis (440.1, 440.2; I70), Aortic aneurysm (441; I71), Other arteria diseases (442-448; I72-I78), Pneumonia, influenza, tuberculosis (010-018, 480-487; A16-A19, J10-J18), Chronic obstructive pulmonary disease (490-492, 496; J40-J44)

[30]Assigning a single cause of death to a decedent involves using only the single, underlying cause found on the death certificate. While the underlying cause arguably contains the most important information concerning how the person died, each death certificate also contains up to 20 contributing causes of death which also provide additional, useful information concerning the circumstances and context of the decedent's passing. Classifying mortality using any line on the death certificate means that we do not distinguish between whether a cause of death, such as a cardiovascular cause, was the primary condition responsible for death, or a contributing condition. Both schemes are valid approaches to classifying mortality and we argue that our approach is a more conservative approach.

Lastly, our empirical analysis spans the years 1974-1992 for NRT introduction, and 1997-2019 for e-cigarette introduction / drug exemption. This decision provides a pre-period of 10 years prior to the introduction of each drug, and 9 years either after the introduction of NRT and after e-cigarettes were exempted from FDA drug regulation in 2011. The four-years (2007-2010) between e-cigarette introduction and drug exemption are considered transition years for the e-cigarette analysis.[31]

When examining SAM in our NRT analysis, however, we begin our analysis in 1979 as this is the first year that the ICD-9 edition began, which is important for correctly identifying SAM and reducing incompatibility of mortality data across years.[32]

We end our e-cigarette analysis in 2019 to avoid the FDA's escalating efforts to regulate e-cigarettes as a tobacco product; for example, in 2020 the FDA required e-cigarette companies to submit PMTAs to obtain authorization to legally sell their products. Additionally, by ending our analysis in 2019, we also reduce potential confounding due to COVID-19.

3.2 Demographic Variation in Smoking

To measure smoking rates and intensity, we rely on cross-sectional data from the National Health Interview Survey (NHIS) and the Behavioral Risk Factor Surveillance System (BRFSS). The NHIS is a nationally representative survey that has monitored a multitude of health behaviors and outcomes since 1959, with smoking information first collected in 1970. The BRFSS is a telephone-based state-representative survey similarly tracking health behaviors and outcomes beginning in 1984. Both data sources track key smoking outcomes that are central to our analysis and in constructing our smoking share measure. The NHIS goes further back in time and tracks a more extensive range of health behaviors, but it also samples considerably fewer individuals than BRFSS and does not report outcomes in certain years. In contrast, BRFSS generally surveys a larger number of people and tracks health behaviors more consistently but contains less detailed information.

[31] As an extension to our main findings, we run analyses using alternative dates, and follow this same rule of thumb of using a 10-year pre-period and 9-year post-period.

[32] There are otherwise considerable challenges in harmonizing cause of death codes between ICD-8 and ICD-9 due to major changes in the way certain causes of death are classified. Harmonizing between ICD-9 and ICD-10, which occurs in 1999, is less disruptive because cause of death classifications are generally more consistent. ICD-8 only allows for up to 13 contributing causes of death, while ICD-9 (and ICD-10) allows up to 20 contributing causes, which may also artificially increase certain causes of death after the transition to ICD-9.

The share variable that we use in our shift-share DD model is weighted daily smoking rates from BRFSS data or NHIS data.[33] We hypothesize that people that smoke more prior to drug introduction or exemption will benefit more than people that smoke less in terms of future mortality.[34]

Because some demographic groups comprise a greater share of the population, the number of survey respondents available to construct our smoking measures and smoking share measure varies across demographic groups. If smoking rates are measured noisily in groups with few survey respondents, then we are likely introducing attenuation bias into our analysis, as our treatment variable is measured with error. In our preferred specifications, we therefore choose to require at least the 25th percentile of survey respondents used to construct our share measure for a demographic groups to be included in our analysis.[35] We feel this is a reasonable choice because it balances between gaining precision in our treatment variable while also statistical power. As a robustness exercise, we explore the sensitivity of our results when requiring at least the 50th percentile of survey respondents. For e-cigarette introduction in which we have more pre-period years of smoking information than we do for NHIS, we also explore the sensitivity of our results to using a smoking share calculated from 2002-2006. Our results are robust to these decisions.

For prescription NRT, we construct our share measure using the average daily smoking prevalence in 1983 from NHIS data. This is the most proximate year to 1984, and smoking outcomes are otherwise not available in the NHIS since 1977. BRFSS data was also not collected until 1984. For NHIS, we use 3-race categorization with urban status. While our NHIS smoking outcome panel does not include urban status because it is not consistently reported, in constructing our 1983 share measure we do incorporate urban status because it becomes intermittently available, allowing us to add an additional source of variation in our mortality analysis for prescription NRT.

[33]Following CDC definitions, these measures require that people have also smoked 100 cigarettes in their lifetime. We believe that our use of daily smoking as our share measure has two main advantages compared to using smoking over the past month as our share measure. First, there is a greater dispersion in the daily smoking prevalence than there is for current smoking prevalence, in effect meaning that groups differ from one another in their proportion of daily smokers by a greater degree than they differ from each other in their current smoking rates. In this respect, by using daily smoking as our share measure we have a richer source of identifying variation and more statistical power to identify effects on mortality or our smoking outcomes. Second, while any consumption of combustible tobacco is harmful, daily smoking is significantly more harmful and also indicative of persistent nicotine addiction. In this respect, we believe that the daily smoking rate is more conceptually aligned with "true exposure" to the exogenous entry of e-cigarettes to the U.S., because it is daily smokers who are the least able to successfully quit cold-turkey and who face the greatest risk of mortality and continued dependence on nicotine.

[34]Our share measure is unlikely to contain people that only use e-cigarettes, as e-cigarettes were not imported to the United States when this share measure is constructed, and people colloquially refer to the act of using e-cigarettes as vaping rather than smoking.

[35]For example, if the 25th percentile number of survey respondents used to construct the share variable is 50 respondents, then we exclude from our analysis demographic groups that contain at less than 50 respondents in their share variable.

It is worth noting that for consistency, we use our BRFSS share measure when analyzing smoking outcomes from BRFSS, and likewise use our NHIS share measure when analyzing NHIS outcomes. When analyzing mortality outcomes, we prefer using BRFSS due to its larger sample size, inclusion of urban status, and expanded 5-race categorization.

3.3 Descriptive Trends

In Figure 3, we show trends in mean all-cause mortality and smoking behaviors from 1976-2019 for our estimation sample, weighted by population or survey sampling weights for smoking outcomes. In Appendix Figure C1, we show similar Figures by demographic dimension. Throughout the paper, where applicable we include vertical dashed lines corresponding to drug introduction dates (1984 NRT, 2007 e-cigarette), and we denote drug exemption starting in 2011 with a vertical line as well. Both Figures 3 and C1 use 3-race categorization of demographic groups excluding urban status for consistency over time.

In Figure 3, we note the cyclical nature of mortality over time. We also note the steady downward trend in smoking rates in the population. From 1975-2019, light smokers retain a steady share of the population, ranging from 6% in the early 1990's to 4% in the late 2010's. As a reminder all of our smoking measures are out of the population, so daily smoking, cigarettes smoked, and days smoked are assigned values of zero to non-smokers and accordingly reduce these averages from those out of the current population of current smokers. Current smoking prevalence falls steadily over time alongside daily smoking prevalence, ranging from nearly 37% current smoking rates in 1976 to less than 15% in 2019. Reductions in current smoking must be explained either through reductions in the population who has ever smoked 100 cigarettes in their lives (ever smokers), or through increases in the rate of former smokers. We see that while ever smoking rates continue to fall after 2007, the rate of former smokers in the population begins rising steadily after remaining flat at 21% prior to 2009, rising to nearly 26% by 2019. Collectively, the possible acceleration in smoking rate declines and increases in the share of former smokers coinciding with e-cigarette drug exemption in 2011 provides descriptive evidence in support of e-cigarettes increasing smoking cessation.

In Figure 3, we see that average cigarettes smoked per day declines steadily over time from nearly 7 cigarettes per day in 1976 to less than 2 in 2018. Days smoked in the past month remains somewhat flat from the early 2000's through 2009 at around 3 days per month, but then begins trending downward shortly after 2010 court decisions to about 2 days in 2018.

BRFSS began collecting adult e-cigarette use information in 2016. From 2016-2018,[36] we find that 16.6% of United States adults have ever tried e-cigarettes, 3.2% currently use, and 1.4% use daily. As a share of smokers, these rates are X%, X%, and X% respectively.

4 Methods

4.1 Estimation Strategy

To estimate the causal effect of drug introduction / exemption on mortality, we use a demographic shift-share DD design, exploiting cross-sectional variation in the prevalence of cigarette smoking across demographic groups. Our empirical approach is similar in some ways to Allcott and Rafkin (2022), who used a demographic shift-share to study effects of e-cigarettes going mainstream on smoking.[37] Our strategy is itself a cousin of the "shift-share" identification strategy popularized by Bartik (1991) and discussed in Goldsmith-Pinkham et al. (2020)). Our "shift-share" relies on variation in smoking rates in years prior to drug introduction. We use a pre-period prior to drug introduction, which allows us to test for parallel pre-trends, thus bolstering the credibility of shift-share study design (Goldsmith-Pinkham et al., 2020).

In our context, we rely on cross-sectional variation in daily smoking prevalence across demographic groups, measured in pre-period years, to study the effect of drug introduction and exemption on mortality. We estimate the following reduced-form equation:

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

Above, y_{it} is the logged mortality rate of demographic group i in year t per 100,000 population. We log outcomes to better approximate the normal distribution than use levels (see Appendix Figure E1). θ_i the product of a post-period indicator (equals 1 in years post-introduction, 0 otherwise) and the daily smoking prevalence of group i in the 2 years prior to drug introduction. θ_i equals zero in the years prior to drug introduction and is equal to the (pre-period) daily smoking prevalence in the years following introduction.

Above, γ_i is a unit fixed effect which controls for time-invariant unobserved factors within groups affecting mortality or smoking.[38] This allows us to estimate within-group changes in our outcome

[36] The question was not fielded in 2019

[37] We describe differences between our work and Allcott and Rafkin (2022) in Sections 5.5

[38] Time-invariance requires that people of a given age receive the same share variable regardless of when they are interviewed.

by controlling for time-invariant unobserved heterogeneity across census regions, age, gender, race, and urban status. ϕ_t is a time fixed effect that soaks up variation in our outcome over time that is common across all groups, such as a medical invention that is equally as likely to improve survival probability across each demographic group. In our results and Figures, we multiply β by the mean of our daily smoking treatment variable so that changes in our outcome are evaluated at the mean daily smoking rate. β can therefore be interpreted as the effect of drug introduction / exemption on percent changes in mortality rates or smoking rates, evaluated at the mean daily smoking rate in the population.

4.2 Identification

To interpret β causally, it is necessary that the growth in our outcome among groups with higher smoking rates parallels the outcome trend among groups with lower smoking rates. Put differently, the growth in our outcome over time in the years prior to drug introduction cannot be correlated with the level of the daily-smoking share measure, as measured in the 2 years prior to drug introduction. This parallel trends assumption allows us to use changes in mortality among groups with lower exposure to the drug introduction shock as a counterfactual for the mortality of groups with greater exposure.

To provide evidence of parallel trends and estimate dynamic treatment effects, we conduct an event study design given by the following equation:

$$y_{it} = \sum_{k=-m}^{n} \beta_k \cdot \theta_i \cdot 1(t - T = k) + \gamma_i + \phi_t + \varepsilon_{it}. \tag{2}$$

The main difference from Equation (1) is that we replace the average treatment effect β with a series of m pre-period coefficients and n post-period coefficients, where T denotes the year of drug introduction to the U.S. market, 1984 and 2007 for prescription NRT and e-cigarettes, respectively. β_k is the effect of drug introduction on percent changes in mortality rates in the kth year relative to drug introduction evaluated at the mean daily smoking rate in the 2 years prior to that drug's introduction. We constrain period $T - 1$ to zero in order to serve as a reference period.

Equation (2) allows us to directly evaluate whether growth in mortality rates across groups that vary in their exposure to drug introduction change differently in the years prior to drug introduction. If so, in the absence of any unobserved idiosyncratic shocks correlating with baseline demographic

group smoking propensities and mortality and barring any violations of the parallel trend assumption, we can interpret β as the causal effect of the drug introduction on mortality.

We estimate both Equations (1) and (2) using ordinary least squares. Our preferred specification for our regression is unweighted, which is the equivalent of assuming each demographic group provides its own experimental laboratory, each as interesting as the other. In addition, by not weighting, we are able to exploit richer variation in our share measure for identification.[39] When examining outcomes from our survey data, we follow best practices by weighting regressions using survey sampling weights to account for inverse probability of selection into the survey.[40] We cluster standard errors at the demographic group level.

We test the sensitivity of our results to all of these assumptions in Section 5.2. Lastly, for our BRFSS outcome analyzes, we also control for the share of cellular respondents in each demographic group-year due to to a survey design change in 2011, when BRFSS began sampling cellphone respondents.

4.3 Pre-Trend Correction Procedure

We find unadjusted evidence that logged mortality was trending higher for demographic groups with higher smoking propensities prior to e-cigarette introduction. We attempt to correct for this by implementing Freyaldenhoven et al. (2019)'s pre-trend extrapolation procedure. This approach, which has been proposed and implemented in other contexts such as Goodman-Bacon (2021)[41] and Dobkin et al. (2018), relies on estimating unit-specific pre-period linear trends in the outcome variable, and then calculating an "adjusted" outcome, which is the deviation in the unadjusted outcome from the extrapolated, pre-period linear trend.

Initially, we estimate Equation (1) restricted to pre-period years and incorporate a group-specific linear trend for our sample.[42] The residuals from this regression, representing deviations from the predicted linear trend during pre-period years, are used as our "adjusted" outcome for estimating Equations (1) and (2). This adjustment helps account for any pre-existing trends, ensuring a more

[39] When weighting by population in our e-cigarette analysis, for example, the top and bottom 10% of our smoking share measure account for only 2.1% of the population, despite 14.8% of our demographic groups falling on either the top or bottom 10% of the distribution. For our NRT analysis, the top and bottom 10% of our smoking share measure account for only 0.009% of the population. The variance of our daily smoking share measure when weighting by population is roughly 1/3 that of the unweighted share measure (var= 0.43, var= 0.14)

[40] As a robustness exercise, we show our mortality results weighted by population in the year prior to drug introduction, which yields comparable results.

[41] See their online appendix

[42] This pre-period is from 1974-1983 for smoking cessation drug introduction, and from 1997-2006 for e-cigarette introduction.

accurate analysis of post-period effects. The motivation behind this is that although growth in mortality or smoking may differ across groups prior to drug introduction, deviations in our outcomes from a group's own predicted linear growth rate may indeed trend parallel across groups.

The benefit of this approach versus using group-specific linear time trends across the full time period is that we do not fit the trends using any effect of drug introduction in the post-period, which could otherwise lead to attenuation bias. In using Freyaldenhoven et al. (2019), the implied assumption is that the linear growth in a group's mortality or smoking prevalence estimated in the years prior to drug introduction is a suitable counterfactual for how that group's mortality would have continued to trend, in the absence of drug introduction. This assumption may be more reasonable for years closer to drug introduction than years further away, in that case, event study estimates for years closer to drug introduction should be interpreted as more reliable than for years further away.

We find that fitting a linear trend in the pre-period years is largely successful in removing pre-trend violations and that a linear fit generally characterizes group-specific trends in the pre-period quite well. This approach has considerable benefits over the inclusion of group-specific linear trends in our regressions because the latter can soak up meaningful variation in the post-period caused by treatment.

5 Results

We organize our results as follows: In Section 5.1, we present our main event study results of the effect of prescription NRT and e-cigarette introduction / drug exemption on mortality. In Section 5.2, we probe the sensitivity of our main results. In Section 5.3, we examine treatment effect heterogeneity by age group. In Section 5.4, we study how e-cigarette introduction / drug exemption affects smoking rates and intensity, and explore heterogeneity by categories of smoking-attributable causes of death. In Section 5.5, we contrast our approach with that of Allcott and Rafkin (2022). In Section 5.6, we discuss potential alternative explanations. In Section 5.7, we discuss our e-cigarette introduction and drug exemption results. In Section 5.8, we present the results of our social surplus analysis.

5.1 Main Findings

Figure 4 illustrates the event study results for all-cause mortality. After e-cigarette drug exemption, all-cause mortality rates decreased by 7.26% (SE=2.95%). This equates to roughly 92,000 deaths

averted each year, or put differently, a gain of 92,000 life-years each year, roughly $9.5 billion in annual consumer surplus after e-cigarette drug exemption in 2010.[43] The 2007 introduction of e-cigarettes also led to a 5.68% (SE=2.43%) reduction in mortality rates.

We find no statistically significant effect on mortality following NRT introduction in 1984. The NRT introduction coefficient is approximately 37% of the e-cigarette coefficient size, and we do not find any noticeable breaks in mortality trends following 1984. NRT introduction standard errors are also approximately equal to those of e-cigarette introduction, possibly due to fewer demographic groups with sufficient sample size using the 1983 single-year share measure (which itself is due to limited survey data availability). Further, both our estimates for e-cigarette introduction and drug exemption are statistically different from our NRT estimate (t= 14.7, t= 19.5, respectively).[44]

5.2 Robustness & Sensitivity

In Appendix Figure 5, we present a summary of our robustness estimates expressed as percent changes in mortality rates, separately for both NRT introduction and e-cigarette drug exemption. We also present event studies for these specifications in Appendix F. The figure shows that the effects we estimate for NRT introduction and e-cigarette drug exemption are insensitive to using a 5-year share measure instead of a 2-year share measure,[45] using a share measure requiring the 50th percentile of survey respondents, dropping census region and urban status as demographic dimensions and constructing our share measure using a national sample, bootstrapping standard errors by clustering at the demographic group level and using 1,000 repetitions, and lastly when we supplement our model with various fixed effect by year combinations.

We also find that the percent reduction in mortality in our weighted specification (Figure F1) is considerably larger than our preferred unweighted specification (-7.26% [SE=2.95%] unweighted, -15.10% [SE=2.45%] weighted). Both remain statistically significant at 1%. Our preferred specification generally yields more conservative estimates than the alternative specifications.

It is worth noting that our results remain remarkably stable even after controlling for various fixed effect-by-year combinations in Figure E6 (e.g., year-by-age group, year-by-race, year-by-sex, year-by-region, and year-by-urban status). This is reassuring because sources of time-varying unobserved heterogeneity, if left uncontrolled for, can bias our estimates. This kind of time-varying unobserved

[43] We discuss our welfare calculations in Section 5.8.

[44] We later show that our results are identical when we use 1996 as an alternative introduction date which corresponds with several existing medications becoming OTC and approval of new medications.

[45] We cannot produce an analogous figure for prescription NRT analysis because only a single year of 1983 is available to construct our smoking share measure from NHIS

heterogeneity includes factors that vary over time across specific demographic groups, such as for rural residents, younger individuals, or across regions, that are not already modeled with our yearly fixed effects. The results of Figure E6 indicate that our results do not change significantly when controlling for these types of changes, further bolstering our preferred specification.

For NRT introduction, results are not statistically significant but we cannot rule out economically meaningful reductions in these cases due to greater imprecision in comparison to our e-cigarette results. We can, however, rule out statistically that prescription or over-the-counter NRT introduction had an equal or greater effect on mortality as e-cigarette introduction or drug exemption.

5.3 Heterogeneity

We include a graphical summary of our heterogeneity by age-group results in Figure 6 and the corresponding event studies in Appendix H. Differences may persist due to different rates of e-cigarette take-up across demographic groups, with ever and current e-cigarette use rates from the 2016-2018 BRFSS being higher for notably higher males, Native Americans, and White non-Hispanics.

Results from 6 and Appendix H indicate that e-cigarette drug exemption reduced mortality by a larger percentage for rural residents (-17.4%, SE=6.8%) than for urban residents (-8.2%, SE=2.9%), women (-13.6%, SE=4.3%) than for men (-3.8%, SE=3.6%), and most among White non-Hispanics (-15.4%, SE=3.8%). Our pattern of results generally follow that groups with greater ever e-cigarette use rates experienced larger declines in mortality and larger shares of annual deaths averted, with the possible exception of larger estimates among women compared to men.

Figure 6 provides insight into which age groups are principally responsible for the mortality reductions we observe following e-cigarette drug exemption in 2011. We proceed to conduct separate regressions stratified by 15-year age groups, constructing our 2-year share measure using BRFSS and following our preferred specification. The results show reductions in mortality rates among ages 30-44 (-10.77%, SE=5.62%) and ages 45-59 (-9.24%, SE=5.68%), although these stratified analyses are estimated with greater imprecision. The majority of the annual deaths are generated by the 45-59 year age group, roughly 89,000 life-years gained annually after e-cigarette drug exemption in 2011. We find a positive, albeit statistically insignificant change in mortality rates among 60-74 year olds (2.02%, SE=6.76%). Plausible explanations for statistically insignificant increases in mortality for older ages could be due to a transfer of mortality from younger ages to older ages, or due to e-cigarette use rates being lower among older individuals.

In Figure E2, we examine changes in mortality among younger adults. Mortality among those younger than 30 operates as a falsification check, as we would not expect mortality from substitution away from cigarettes towards e-cigarettes to be responsive among this age group due to the smaller share of SAM. While SAM in this population is unlikely, opioid-related mortality is just as common for 30-39 year olds as for 20-29 year olds (Gomes et al., 2023), and so this exercise provides a useful check of any influence of *rising* opioid mortality on our prior estimates showing mortality reductions. In sum, we find no statistically significant effect for ages younger than 30, though the pattern of our results does not suggest a different pattern than for older adults.

We now explore in Figure I1 whether prescription NRT and e-cigarette introduction reduces smoking-attributable and cardiovascular mortality to test whether the reductions in mortality we estimate are primarily driven by reductions in deaths related to smoking.[46] We include a graphical summary of these estimates for both NRT introduction and e-cigarette drug exemption in Figure 7. We consider SAM (SAM) and cardiovascular mortality, both defined using any cause of death (underlying or contributing).

In Figure I1, we present consistent evidence that the types of mortality that fell more among groups with higher baseline smoking rates following e-cigarette introduction were precisely those causes of death most likely to be impacted by reductions in cigarette consumption. The results indicate that e-cigarette drug exemption reduced SAM by 10.66% (SE=3.58%) and cardiovascular mortality by 8.12% (SE=3.50%). These results provide further evidence of e-cigarette introduction impacting the causes of death most strongly linked to smoking.

We find no overall pattern of mortality reductions resulting from 1984 NRT introduction, although we cannot rule out large reductions due to imprecision. We can, however, for both types of SAM and heart mortality rule out the possibility that 1984 NRT reduced mortality by a greater or equal percentage amount than that of e-cigarette introduction in 2011, as evidenced by statistically significant differences between NRT and e-cigarette percent effect sizes.

5.4 Mechanisms

We now use the same empirical strategy previously described to estimate whether e-cigarette introduction / drug exemption reduces cigarette smoking, which we hypothesize is the primary

[46]According to a timeline of smoking cessation provided by Centers for Disease Control and Prevention (2023a), a person's heart rate decreases within minutes of not smoking. The risk of having a heart attack drops sharply 1 to 2 years after smoking cessation. The risk of coronary heart disease drops by half 3 to 6 years after smoking cessation. Sizable reductions in cancer risk, in contrast, do not occur until 5 to 10 years after smoking cessation and beyond, depending on the type of cancer.

channel through which e-cigarette introduction / drug exemption reduces mortality. To do this, we use the same modelling approach, and we replace our mortality outcome with various smoking outcomes. Like before when we calculated annual deaths averted, we likewise calculate annual changes in outcome magnitudes for our smoking outcomes.[47]

For smoking outcomes, we use both BRFSS survey data and NHIS survey data for smoking behaviors over the past 30 days. Advantages of the BRFSS survey data for exploring this question is that is has 496,970 respondents per year from 2000-2019, versus 29,794 respondents per year in NHIS. The BRFSS data is also state representative whereas the NHIS data is nationally representative. The NHIS data however has more granular smoking information; in particular, the number of cigarettes smoked on smoking days, that allows us to explore additional smoking outcomes.

Figure 8 shows results from BRFSS finding that e-cigarette drug exemption reduced the current smoking rate per capita by 41.0% (SE=6.4%), the daily smoking rate by 51.7% (6.8%), and the light smoking rate by 50.5% (SE=12.7%). We find evidence of immediate and sharp declines in smoking immediately following e-cigarette introduction in 2007. We calculate annual reductions of 12.7 million current smoking-years after e-cigarette drug exemption in 2011. The majority of this effect is driven by reductions in daily smoking, with daily smoking-years falling by roughly 12.1 million annually after 2007, and light smoking-years only falling by 3.9 million smoking-years annually. The annual reduction in current smoking-years (12.7 million) is less than the sum of daily and light smoking-years (12.1m + 3.9m=16.0m), which suggests that while our results are driven primarily by smoking cessation from previously everyday smokers, there is likely a reduction in smoking intensity (daily smoking to less-than-daily smoking), with our results representing the net change.

In Figure 9, we examine NHIS outcomes, which includes BRFSS outcomes plus additional outcomes on average cigarettes smoked daily and average days smoked in the past month. For consistency with our NHIS outcomes, we utilize a share measure constructed from NHIS in these regressions.

Figure 9 indicates that e-cigarette drug exemption reduced the rate of current smokers per 100,000 population by 51.6% (SE=7.8%) and daily smoking rate by 59.0% (SE=8.2%). Reassuringly, results from NHIS are comparable to the BRFSS (-51.6% vs -41.0% for current smoking rate, -59.0% vs -51.7% for daily smoking rate). Our annual estimates of smoking-years reduced are slightly

[47]We calculate i) fewer annual current smoker-years (FACSY), ii) fewer annual daily smoker-years (FADSY), iii) fewer annual light smoker-years (FALSY), iv) fewer annual packs of cigarettes smoked (FAPCS), and v) fewer annual days smoked (FADS). We describe these calculations in the footnote in Figures 8 & 9.

larger when comparing between BRFSS and NHIS (17.2m vs 12.7m for FACSY, 16.0m vs 12.1m for FADSY). We find more imprecisely estimated effects on light smoking rates in NHIS, which may be driven by non-linearities in pre-existing trends in our event study, leading to a poor fit in our linear-extrapolation procedure.

We likewise find evidence of e-cigarette drug exemption reducing smoking intensity in addition to increasing smoking cessation. Following e-cigarette drug exemption in 2011, the average daily consumption of cigarettes per capita falls by 62.0% (SE=9.4%). We calculate the fewer annual packs of cigarettes smoked (FAPCS) of around 5.7 billion packs per year after 2011. Average days smoked in the past month per capita falls by roughly 75.8% (SE=20.2%). Converting from monthly days to yearly days smoked, we estimate 4.0 billion fewer annual days smoked each year following e-cigarette drug exemption.

5.5 Comparison to Allcott and Rafkin (2022)

Our main finding is that e-cigarette introduction and drug exemption reduces smoking among adult demographic groups with higher baseline smoking rates. Allcott and Rafkin (2022) take a different approach and use the 2016-2018 e-cigarette use rate as the demographic share measure. This decision has important implications. In Appendix J, we reproduce our analysis using the same 2016-2018 e-cigarette use share measure, and do not find statistically significant evidence that demographic groups that use e-cigarettes more experience reductions in smoking or mortality.

Allcott and Rafkin (2022)'s e-cigarette use share measure has the benefit of directly measuring e-cigarette use using data from 2016-2018, whereas our approach measures groups that may disproportionately benefit from e-cigarettes (whether directly or indirectly) using 2005-2006 data from before an e-cigarette marketplace emerged. We have a moderately-strong positive correlation of 0.41 between demographic group daily smoking rates in 2005-2006 and current e-cigarette use rates in 2016-2018, so our share measure loosely tracks with theirs, though enough difference remains to meaningfully impact estimates. Their identifying assumption is that smoking trends among high versus low vaping demographic groups (as measured using 2016-2018 data) would have been parallel if not for e-cigarette introduction, whereas our identifying assumption is that smoking trends among high versus low smoking demographic groups (using 2005-2006 data) would have been parallel. One identification challenge of their approach is the potential for demographic groups to self-select into 2016-2018 e-cigarette use based on factors associated with smoking, such as perceived relative risks

of both products.[48] Our share measure is less sensitive to these self-selection concerns by using data from before an e-cigarette marketplace existed.[49] One other minor difference in our approach over theirs is that our approach allows e-cigarettes to benefit (or harm) demographic groups through spillover effects separate from direct use of e-cigarettes. For example, if one member of a cohabiting couple quits smoking with e-cigarettes, the other member is perhaps more likely to quit themselves even unaided by e-cigarettes. Our estimates incorporate such spillover effects.

Another significant difference between our studies is the use of 2013 as an alternative introduction date by the authors, which they describe as the year e-cigarettes became mainstream (e.g, they began to sizably increase in Nielsen-tracked stores).[50] However, a sizable number of people had purchased e-cigarettes from non-traditional retail stores and used these prior to 2013.[51] In contrast, we proxy e-cigarette access based on natural experiments of e-cigarette introduction in 2007 and drug exemption in 2011, with the latter being a random event that was the result of unexpected legislation and court decisions. We show in Appendix K that using a 2013 introduction date and our standard daily smoking share measure does attenuate our mortality and smoking results, though reductions in daily smoking remain statistically significant.[52] We earlier showed reductions in smoking starting as early as 2008 and mortality reductions shortly afterwards, which could cause a downward pre-trend for an event starting in 2013.[53]

5.6 Competing Explanations

Many features of our findings support a causal link between e-cigarette drug exemption and mortality reductions. For example, we find that the demographic groups that smoke more at baseline (Whites,

[48]Authors were forced to use 2016-2018 for e-cigarette use due to limited data availability. The authors attempt to mitigate self-selection concerns in different ways, such as by including demographic group-specific time trends.

[49]Our use of past values of our outcome as a share measure follows other studies, such as Alpert et al. (2018) and Callison and Pesko (2022) 's Table 6.

[50]The authors also show their results are insensitive to using 2012 as the introduction date.

[51]Tracked-stores do not include online stores, vape shops, or smaller retailers like bodegas and mall kiosks. Nationally representative surveys found that 4.7% of high school students had tried e-cigarettes by spring 2011 (Corey et al., 2013) and that 12% of U.S. adult smokers had tried e-cigarettes by 2012 (Shi et al., 2016). This suggests a sizable number of people obtained e-cigarettes from non-traditional retailers (e.g., online, vape shops) prior to 2013.

[52]In Figure E2 of Appendix K, we also examine the effect of the 1996 introduction of over-the-counter NRT on mortality, which coincided with a 152% increase in NRT sales (Shiffman et al., 1997). We do not find evidence that NRT becoming OTC reduced mortality.

[53]Two other differences that do not appear consequential: 1) There are some differences in our demographic groups. We use 9 age categories instead of 3. We also do not use education and income, since this information is not available on death certificates. 2) We use a pre-trend adjustment procedure from Freyaldenhoven et al. (2019) as recommended by Goodman-Bacon (2021) instead of using a trend fit across both the pre-period and post-periods. Goodman-Bacon (2021) warns that this can cause the model to throw out useful variation from the post-period.

rural-residing) have higher e-cigarette use rates[54] and that these same groups exhibit large reductions in mortality from e-cigarette drug exemption. Additionally, we find large effects of e-cigarette drug exemption on SAM and cardiovascular mortality, which is the type of mortality that declines soonest after smoking cessation.

As is the case with any DD model, the main threat to our identification is the potential for other concurrent changes correlated with treatment status (e.g., smoking rates at baseline) and outcomes (e.g., mortality). For several reasons, we believe that e-cigarettes are the primary explanation for the effects we observe, though we can never fully rule out the influence of competing effects. In this section we describe potential comepting explanations and rule these out as major influencers one-by-one.

Could concurrent new available of other smoking cessation products explain our findings? E-cigarette introduction in 2007 was near in timing to Chantix (varenicline) introduction in 2006 and mini-lozenge NRT introduction in 2009. This does not seem likely to drive our findings for several reasons. First, Tobacco Use Supplement of the Current Population Survey (TUS-CPS) data suggests prescription pill use and lozenge use increased only marginally between 2003 and 2010-2011 (5.7pp increase and 1.1pp increase respectively[55]) for current and recent former smokers, which is small compared to 30.2% of current/former smokers that used e-cigarettes in their most recent quit attempt in 2014-2015.[56] Second, Google Trends search volume shown in Figure 2 indicates some modest increase in prescription pill search volume in 2006 and 2008, before falling to baseline low levels comparable to NRT, which exhibited no movement in search volume during the time period. E-cigarette search volume meanwhile clearly overtakes NRT and prescription pill search volume in 2010, which is also the year that mortality began its steady decline. Third, in early 2014, GlaxoSmithKline paused production and issued a recall of Nicorette lozenges for quality reasons (Frankel, 2015), leading to a significant shortage of these drugs, and since we do not observe evidence of mortality reductions stagnating on or shortly after 2014 this suggests lozenges are incapable of explaining the reductions in mortality we document. Finally, our effects cannot be accounted for by these competing drugs (Chantix/varenicline and mini-lozenges) being more effective. A recent Cochrane review finds that e-cigarettes are at least as effective as varenicline and more effective than

[54]The correlation between our daily smoking shift share (2005-2006) and current use e-cigarette rates from 2016 to 2018 is 0.41.

[55]Based on author calculations of TUS-CPS data.

[56]The TUS-CPS is generally collected every three to four years. Smoking cessation pill and lozenge questions were not collected in 2006. E-cigarette use questions for current/former smokers was first collected in 2014-2015.

NRT for planned quit attempts (Lindson et al., 2024), and e-cigarettes meanwhile may also reduce smoking through unplanned quit attempts as well (Kasza et al., 2021).

Could concurrent improvements in medical technology affecting SAM explain our findings? We find dispersion in the types of deaths averted that is consistent with smoking cessation story affecting many types of mortality rather than a story of a single medical intervention that reduces a specific type of mortality.

Could state or nation-specific policies or economic factors drive our findings? Our identification strategy reduces the potential for state-specific policies or economic factors to influence our findings because each demographic group will be exposed to each state's policy/economic environment on some level. However, to the extent that certain demographic groups are clustered in some states but not others, this allows the potential for bias if, for example, state policy/economic condition changes occur disproportionately in states with more or less high-smoking demographic groups. Assuming that demographic imbalance across states is not a driving issue, a second source of potential bias is that any "large" policy/economic change that disproportionately affects smokers, like a national cigarette tax increase or tax increase in a large state like California, could disproportionately reduce mortality. California did not increase their cigarette taxes between 2000 to 2016. However, 2009 was an active year federally with passage of the TCA and a cigarette tax increase from $0.33 to $1.01 a pack.

For the first potential source of bias from demographic imbalance across states, we use a strategy of re-weighting the data such that each state has the weighted national prevalence of each demographic group. This matters little to our results. Second, our event studies for smoking show evidence of mortality reductions immediately after e-cigarette drug introduction in 2007 (see Figures **??** and **??**). NHIS results in Figure **??** in particular support a second level drop in smoking following drug exemption. The 2009 tax increase did not appear to have any effect. However, we cannot rule out the potential for delayed effects of the federal cigarette tax increase in particular to influence our findings.

5.7 E-cigarette Introduction, or Drug Exemption?

We find evidence that patents began increasing in the period of time after e-cigarette introduction, before drug escape, in the United States relative to Australia (see Figure 1). However, patents increased approximately 10-fold in the drug exemption period. In terms of smoking, we find evidence that approximately half of the reduction in smoking occurred in the transition period, and the

other half after e-cigarette exemption (see Figures 8, 9). This suggests that early e-cigarettes may have been effective, though subsequent innovation made them even more effective. Had the FDA won authority to regulate e-cigarettes as drugs, cleared the marketplace of e-cigarettes, and forced e-cigarette companies to start the drug approval process, we speculate that these early gains would have disappeared. As such, as believe our choice of using a pre-period before e-cigarette introduction to evaluate the effect of drug exemption is the best choice. Our e-cigarette introduction effects meanwhile are large because they include the effects of subsequent drug exemption.

It is more difficult to disentangle the effect of e-cigarette introduction and drug exemption on mortality given the lagged nature through which smoking affects mortality (see Figure 4). We find the first statistically significant reductions in smoking in 2007, and the first statistically significant reductions in mortality in 2013. This suggests approximately a six-year lag. So we acknowledge our estimates of mortality effects of e-cigarette drug exemption from 2011 to 2019 may be underestimated since some share of our findings will be capturing effects of e-cigarette introduction rather than drug exemption.

5.8 Social Surplus

From our main estimates of deaths averted in Figure 4, we calculate that e-cigarette drug exemption resulted in a gain of 826,000 life-years from 2011-2019 for adults ages 30-74, for an an average of roughly 92,000 life-years gained each year.[57]

We calculate that e-cigarette drug exemption generated $95.4 billion in social surplus from 2011-2019, roughly $85.5 billion in consumer surplus ($9.5 billion annually)[58] and $9.9 in producer

[57]E-cigarette introduction resulted in a gain of 1.19 million life-years from 2007-2019 for adults ages 30-74, roughly 72,000 life-years gained annually, on average.

[58]In calculating consumer surplus we follow Philipson and Jena (2006), calculating value of statistical life-years (VSLY) as follows: First, we take the annual deaths averted from Figure G1, which are calculated by multiplying the percent change in mortality rates by the average mortality rate, multiplied by the total population in each age group. Assuming a fairly conservative value of a statistical life-year (VSLY) of $100,000, in $2007, we multiply annual deaths averted by the VSLY for each year from 2007-2019. We then discount these values, which represent the value of statistical life-years gained by e-cigarette introduction, to the year 2007, assuming a market interest rate of 3%, and convert to $2019. We arrive at an estimate of $33.8, $82.5, and -$30.8 billion in consumer surplus generated by e-cigarette drug exemption for ages 30-44, 45-59, and 60-74, respectively, for a grand total of $85.4 billion. From 2007-2019 following e-cigarette introduction, we arrive at an estimate of $48.8, $119.1, and -$44.5 billion in consumer surplus generated by e-cigarette introduction for ages 30-44, 45-59, and 60-74, respectively, for a grand total of $123.4 billion.

surplus ($1.1 billion annually) [59]. Consumer surplus constitutes the vast majority of social surplus, at roughly 90%.[63]

For age groups 30-44, 45-59, and 60-74 (see Figure G1), we estimate that e-cigarette drug exemption generated an additional 327,000 life-years gained, 797,000 life-years gained, and 298,000 life-years lost, respectively. Of the total life-years gained across all age groups except for ages 60-74, the 45-59 age group captured roughly 71% of the total consumer surplus, followed by the 30-44 age group at 29%.[64]

Comparing our estimates to the Philipson and Jena (2006), who find that HIV/AIDS therapies introduced in the 1980's generated roughly $1.39 trillion in social surplus ($1.33 trillion in consumer surplus and $63 billion in producer surplus), we find that consumers captured a similar share of social surplus following e-cigarette drug exemption, roughly 90% compared to a share of 96% from Philipson and Jena (2006). The authors also estimate 200,000 annual life years gained of HIV/AIDS drugs for all HIV-infected individuals through 2000, whereas we estimate 826,000 from 2011-2019, suggesting that e-cigarettes have approximately half the population health benefit as early HIV/AIDS drugs.

In examining consumer surplus by cause of death, we estimate that SAM is responsible for roughly 78,000 annual deaths averted, or 85% of the total life-years gained by e-cigarettes. SAM is responsible for roughly $50.3 billion in consumer surplus after e-cigarette drug exemption in 2011.[65] Cardiovascular mortality is responsible for nearly 32,000 annual deaths averted, roughly 40% of the reduction in smoking-attributable deaths, and roughly 1/3 of all deaths averted after 2011.[66] We estimate that cardiovascular deaths averted equate to roughly $23.7 billion in consumer surplus after 2011.[67]

[59]To calculate producer surplus, we use estimates of market revenue by year from a variety of industry and government sources.[60] After discounting to 2007 and adjusting for inflation, we then assume an average variable cost of 35%.[61] Based on these calculations, we estimate a total producer surplus of $9.9 billion from 2011-2019 following e-cigarette drug exemption, or an average of $1.1 billion each year, expressed in 2019 dollars and discounted to 2007.[62]

[63]We calculate that e-cigarette introduction generated $137.7 billion in social surplus from 2007-2019, roughly $123.4 in consumer surplus ($9.5 billion annually) and $14.3 in producer surplus ($1.1 billion annually). Consumer surplus constitutes the vast majority of social surplus, at roughly 90%.

[64]For age groups 30-44, 45-59, and 60-74, (see Figure G1), we estimate that e-cigarette introduction generated an additional 343,000 life-years gained, 878,000 million life-years gained, and 287,000 life-years lost, respectively. Of the total life-years gained across all age groups except for ages 60-74, the 45-59 age group captured roughly 72% of the total consumer surplus, followed by the 30-44 age group at 28%.

[65]SAM is responsible for $72.7 billion in consumer surplus after e-cigarette introduction in 2007

[66]During our pre-period from 2000-2006, cardiovascular mortality constituted roughly 1 in 4 of all deaths, and roughly 32% of all smoking-attributable deaths. The cardiovascular share of the total mortality reduction that we estimate after 2011 is therefore roughly 1.3 times what would be expected from 2000-2006.

[67]Cardiovascular deaths averted after e-cigarette introduction in 2007 equate to roughly $34.2 billion in consumer surplus.

In order to offset the reductions in mortality from e-cigarette drug exemption we observe in our main sample of adults 30 and older, mortality rates among individuals 29 and younger would have to increase annually by 84.8%, implying that the mortality rate among young adults would need to increase to 141 deaths per 100,000, or nearly double.[68] Reassuringly, we estimate in Figure E2 a statistically insignificant reduction in mortality for those less than 30 of 9.9%. For this reason we believe that the welfare gains that we calculate are unlikely to be offset by any unintended harm to youth health or life expectancy resulting from the rise in youth vaping prior to 2019.

6 Conclusion

Our study provides evidence on the effect of FDA drug regulation by taking advantage of e-cigarettes' unprecedented and unexpected exemption from FDA drug regulation due to 2010 court decisions. Our paper makes several contributions. First, we show that e-cigarette innovation sharply increased when e-cigarettes were exempted from drug regulation. In particular, e-cigarette patent applications increased sharply in the United States between 2011-2019, compared to e-cigarette applications in Australia where e-cigarettes have been regulated as drugs, and compared to other smoking cessation drug applications in both countries that have been consistently regulated as drugs. These other smoking cessation products may have experienced greater innovation, like e-cigarettes, if not regulated as drugs by the FDA. E-cigarettes, meanwhile, experienced so much innovation that people usually do not associate them as a drug today. It is easy to forget that at their introduction point, e-cigarettes were similar in key ways to little-used FDA-approved nicotine inhalers (Bullen et al., 2010).

Our second major contribution is to identify effects on mortality of e-cigarette introduction and drug exemption. We find that e-cigarette drug exemption reduced mortality by approximately 7%. As a point of comparison Friedson et al. (2023) previously found that a $1 increase in cigarette taxes experienced between the ages of 14-17 years of age reduces later-life mortality by 4%. Our main specification finds that e-cigarette introduction increased life years saved by 71,841 annually since 2007, and by 91,784 since 2011. Further, we show evidence that the link between post-drug exemption e-cigarettes and mortality is larger for the 81.2% of any-cause mortality most directly linked to tobacco use, and 27.7% of any-cause mortality that is cardiovascular and most rapidly averted by smoking cessation (US Department of Health and Human Services and others, 2020).

[68]The mean mortality rate for individuals 29 and younger is 76 deaths per 100,000 in 2006.

We also study the effect of the 1984 introduction of the first NRT product, 2-mg nicotine gum, and find limited evidence of these products reducing mortality.

Our third major contribution is to provide evidence in two separate survey data sources of a key mechanism through which e-cigarettes reduced mortality, by reducing more-dangerous smoking along the extensive and intensive margin. In particular, we document using both NHIS and BRFSS survey data sources a 41% reduction in current smoking rates after 2011. E-cigarette introduction caused the daily smoking rate to fall by 52%, roughly 12.1 million fewer annual daily smoking-years. We also estimate a reduction in cigarettes smoked per day and the number of smoking days.

Our findings present a data point in support FDA drug deregulation. It would be useful to have further evaluation opportunities to observe if the socially beneficial effects we estimate within the smoking cessation therapeutic drug class are generalizable to effects for other therapeutic drug classes, perhaps through pilot programming that releases select drugs from drug regulation for poorly-performing therapeutic drug classes. Expanded access and right-to-try laws already allow patients with serious conditions access to unapproved experimental drugs under certain conditions (U.S. Food and Drug Administration , 2022). Our results support increasing the use of these and similar programs, and implementing new programs that allow the writ large release of under-performing therapeutic drug classes, which may turbocharge innovation and lead to the rapid development of life-saving drugs.[69] Such a law change would also have a secondary benefit of reducing the extent to which demand exists without legal supply, which could potentially create problems if underground economies emerge.[70]

How this could be done in a thoughtful way is easier said that done. One idea is to require firms developing drugs outside of the drug approval process to be insured for any potential product liability. Such an approach would effectively make the drug firm's insurer the new regulator, though possibly a faster and more flexible one. Courts would have an important role in ensuring patient safety by enforcing product liability law. The FDA could continue to use their post-market surveillance tools to, among other things, ensure these unapproved drugs are not ineffective. This alternative approach

[69]The FDA does have four accelerated drug approval processes include Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review, all aimed at expediting the approval of drugs for serious conditions. However, these programs all retain some version of the drug approval process, which may reduce benefits compared to opportunities to access drugs outside of this process.

[70]As an illustrative example, clustered regularly interspaced short palindromic repeats (CRISPR) gene-editing technology was awarded the 2020 Noble Prize in chemistry and has been heralded as technology that "may make the dream of curing inherited diseases come true" (NobelPrize.org, nd). Despite the foundation for modern-day CRISPR research being established in 2012 (Jinek et al., 2012), the FDA did not approve a CRISPR drug for human subjects trials until 2019 (Saey, 2019). During this period of time a community of biohackers formed and began to sell do-it-yourself CRISPR kits (Schultz, 2018).

to drug regulation could maintain many of the benefits of the current FDA drug approval process in terms of drug safety/effectiveness, while allowing for faster action and more innovation.

Our study also makes an important contribution to tobacco product regulation by showing that e-cigarette introduction sizably improved public health. We estimate that e-cigarette introduction and subsequent drug exemption saved 933,000 thousand life years through 2019, which translates to roughly 7 life-years gained for every 1,000 smoking-years reduced after 2007. Our results complement microsimulation modeling predicting that a hypothetical vape ban in 2019 would lead to 11 million fewer life-years over the life course for individuals age 12 and up in 2019 (Hui, 2024), and a second predicting that e-cigarettes will save nearly 40 million life-years between 2013 and 2060 (Levy et al., 2021). While the prediction that e-cigarettes will save lives is not new, our study's finding that e-cigarette ex-post did save lives is new.

FDA formally asserted regulatory authority over e-cigarettes in August 2016 by "deeming" them to be tobacco products under the TCA, and e-cigarette companies were required to submit PMTAs in Sept. 2020. For this, the companies need to show the FDA that their products are "appropriate for the protection of public health," which means that these companies need to demonstrate that the overall, population-level, net health impact of these products is positive.Our results of substantial life years saved suggest they pass this threshold easily.

Out of the 6.7 million e-cigarette applications that the FDA received by Sept. 2020, they have authorized only 34 e-cigarette product applications, all but four of them tobacco flavored, and with mostly low nicotine delivery that make them less appealing as substitutes for cigarettes. This success rate of 0.000005% is small compared to the success rate for compounds approved to enter human subjects testing of 11.8% through the drug regulatory process (Chorniy et al., 2021). If we are already concerned that drug regulation is not socially optimal, then tobacco product regulation may be even less socially optimal. At the moment many unauthorized products remain on the marketplace, but should the FDA be successful in clearing the marketplace of unauthorized products, the beneficial effects that e-cigarettes have had on mortality could evaporate. Our study joins other quasi-experimental work on the effect of e-cigarette policies on more-dangerous smoking[71] to paint a compelling and relatively consistent picture that e-cigarettes are providing important public health

[71]Eighteen studies use causal methods and variation in e-cigarette policies of taxes, minimum legal purchase age laws, advertising restrictions, and flavor bans on smoking outcomes. Of these, sixteen studies find they are substitute goods (Pesko et al., 2016; Pesko, 2023; Friedman, 2015; Dave et al., 2019b; Pesko and Currie, 2019; Chen et al., 2023; Friedman et al., 2023; Dave et al., 2019a; Tuchman, 2019; Abouk et al., 2023a,b; Pesko et al., 2020; Pesko and Warman, 2022; Cotti et al., 2022; Saffer et al., 2020; Friedman and Pesko, 2022), one study finds they are largely unrelated goods (Allcott and Rafkin, 2022), and one study finds they are complements (Abouk and Adams, 2017)

benefits; as such, they meet the public health standard of the TCA and more e-cigarette PMTA applications should be authorized.

Our results join other literature in showing how government regulation increases mortality risks (Broughel and Chambers, 2022), such as the increase in car accident deaths following the adoption of more stringent airport security in the wake of the 9/11 terrorist attack (Blalock et al., 2007) and increases in mortality due to higher energy prices and more air pollution following nuclear power shut-down following the 2011 Fukushima disaster (Neidell et al., 2021; Jarvis et al., 2022). However, these studies do not directly study costs in terms of increases in specific types of mortality against benefits in terms of reductions in other types of mortality like we do in the current study. One study that does directly study overall mortality such as the FDA's decision to reformulate OxyContin to be abuse-resistent, which the authors found led to increases in heroin deaths without decreasing opioid deaths (Alpert et al., 2018)." But this study explores the effect of replacing one set of FDA guidelines (allowing crushable Oxycotin) with another (not allowing it). In contrast, our current study examines the writ large removal of drug to outside FDA drug regulation.

One potential limitation of our study is that we observe mortality effects over thirteen years after e-cigarette introduction, instead of over the full life-course. Theoretically, e-cigarettes could reduce mortality initially, but increase it at some later point in time due to higher e-cigarette use rates among young people. As described in 5.8, offsetting the present day value of life years gained today would require an unrealistically large reversal of trends. While e-cigarettes did appear to initially create tobacco product market entry among kids, National Youth Tobacco Survey data for 2023 shows tobacco product use today that is nearly half of what it was in 2011 (See Appendix L), which does not support market entry that would eventually sizably offset life year gains. Further, Appendix L shows almost all youth that use tobacco use e-cigarettes today, which is much safer than the composition of tobacco product use in 2011. Finally, we also do not see any evidence in looking at changes in mortality for people <30 years of age to suggest the pattern of results may be different than the pattern of results for older people E2. Nevertheless, this is a limitation and future work should evaluate the effect of e-cigarettes over longer points in time.

A second limitation is we note that our BRFSS event studies suffer from some attentuation from 2011-2012 due to a change in survey design in which BRFSS began sampling cell-phones exclusively. We caveat this analysis by directing the reader to our analogous results utilizing NHIS, in which we find similar results.

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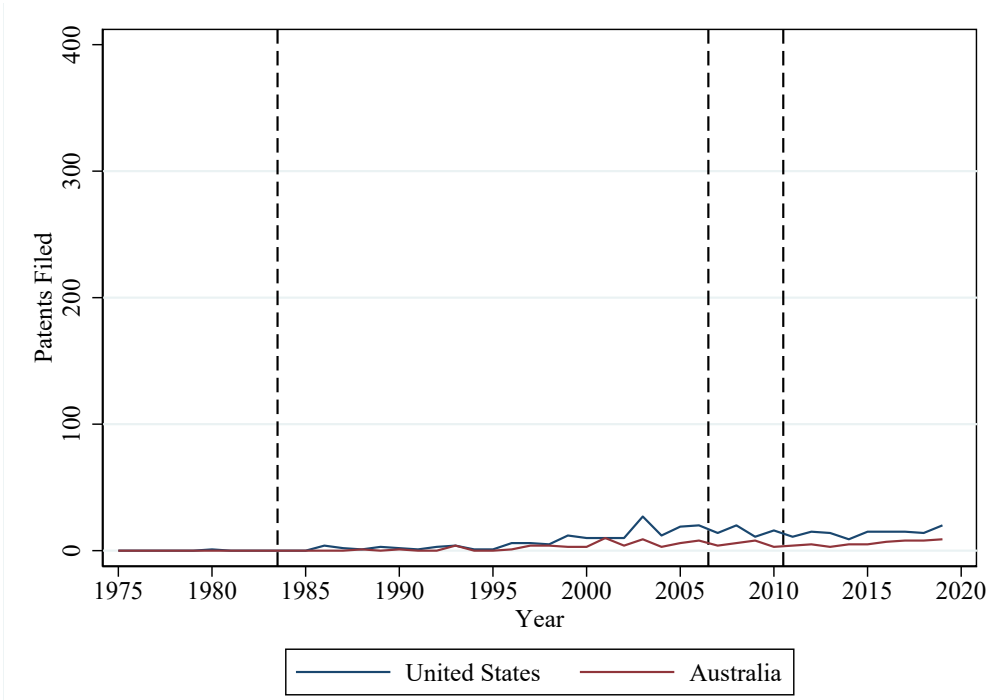
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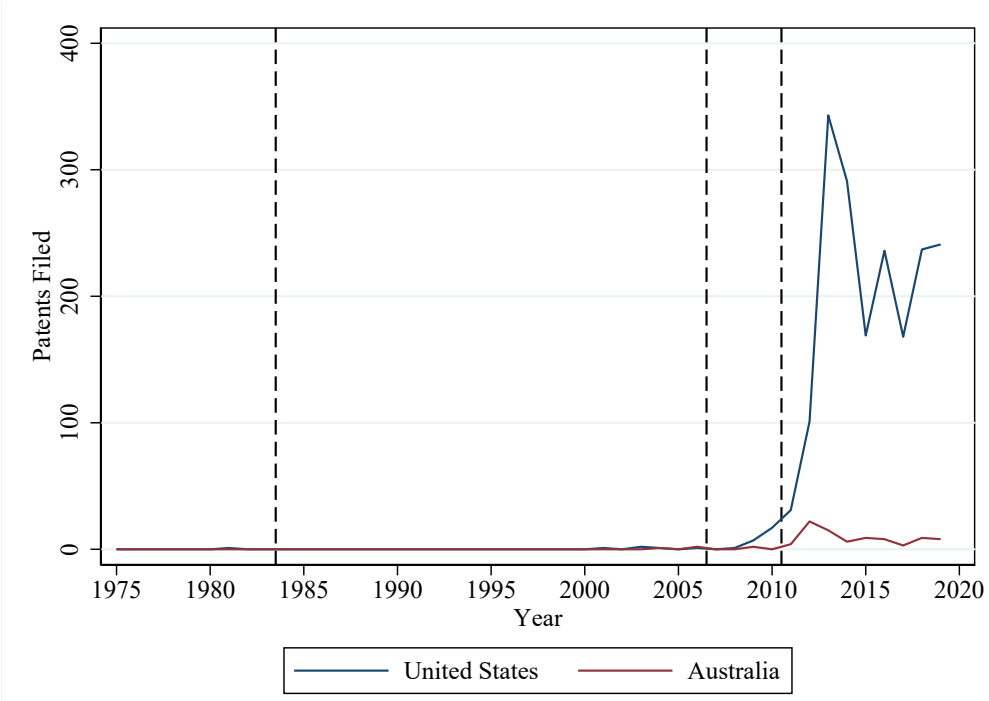
7 Tables & Figures

Figure 1: Historical Patent Applications

(a) Other Smoking Cessation Drug Patents

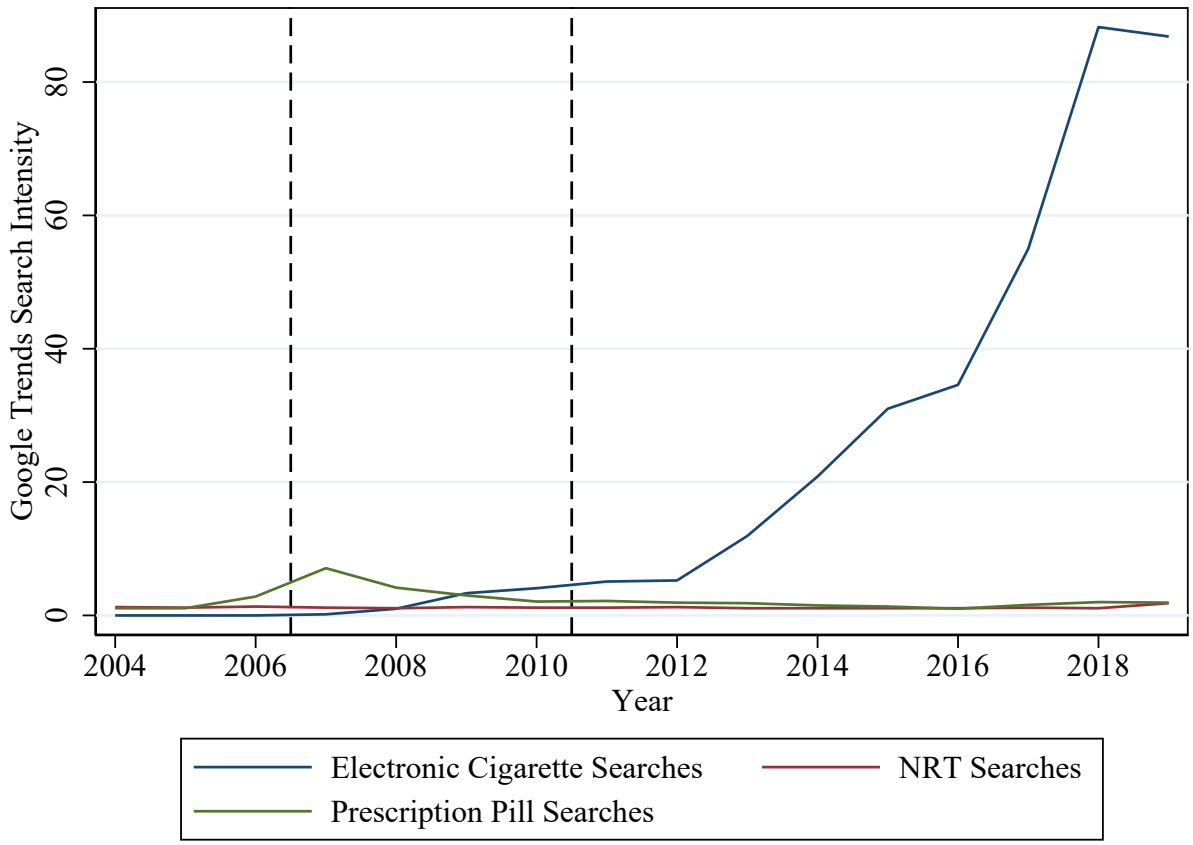


(b) E-cigarette Patents



Notes: Google Patent application intensity is shown for e-cigarettes and other smoking cessation drugs from 1975 to 2019, for both the United States and Australia.

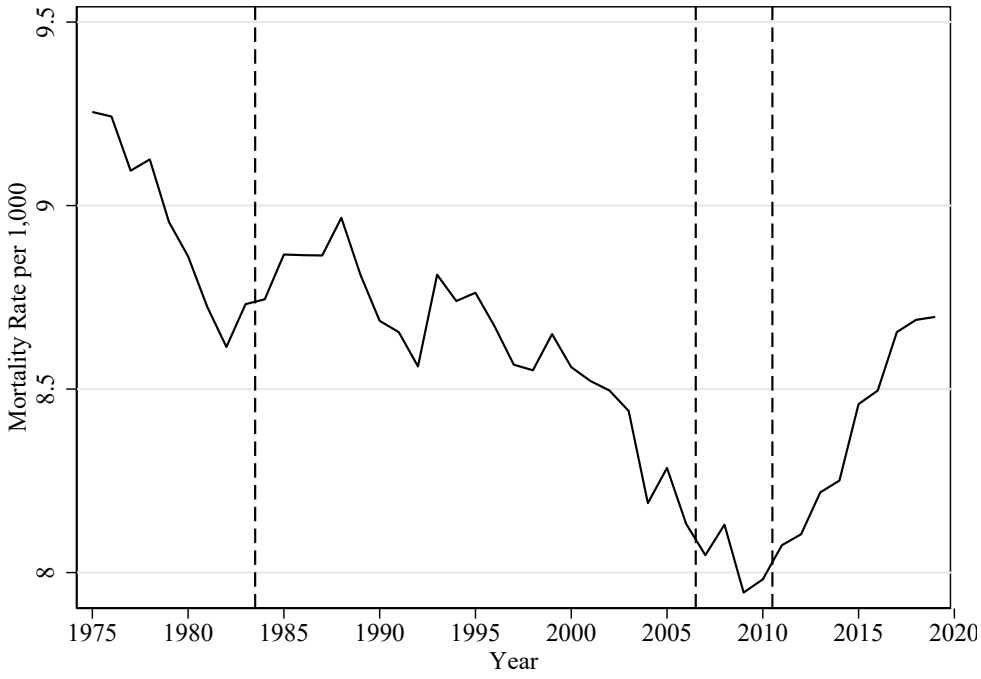
Figure 2: Smoking Cessation Drug Google Searches



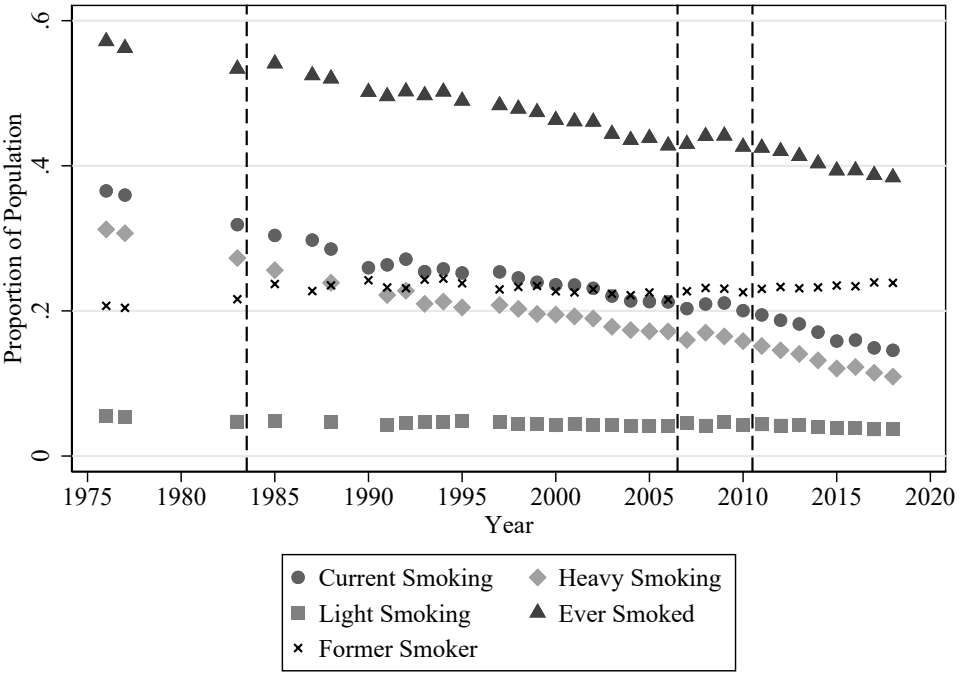
Notes: Google Trends search intensity is shown for electronic cigarette searches, NRT searches, and prescription pill searches from the earliest date available, 2004, through 2019, for the United States.

Figure 3: Trends in Mortality and Smoking

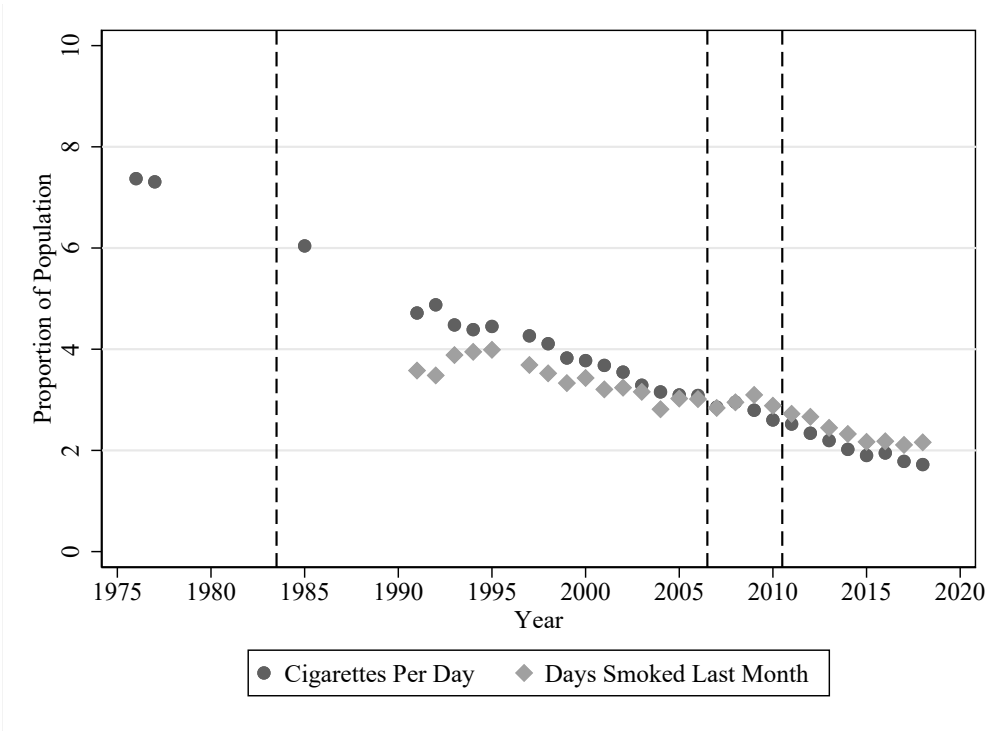
(a) Mortality



(b) Smoking Prevalence



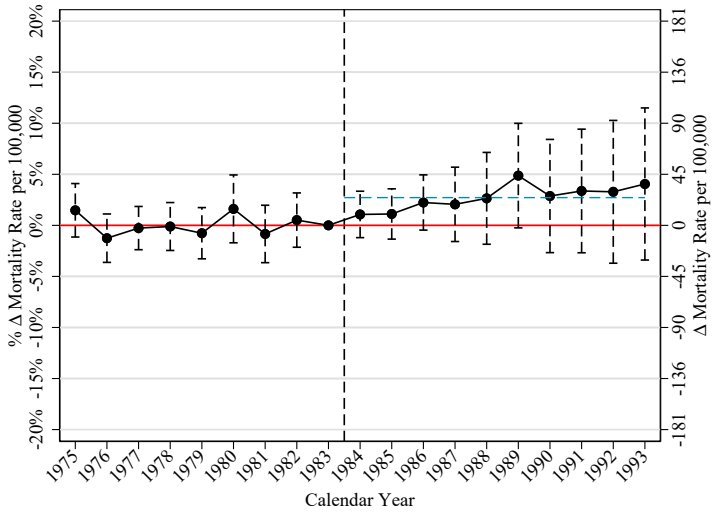
(c) Cigarette Consumption and Frequency



Mortality data is from NVSS. Smoking data is from NHIS. Population data is from SEER. Smoking variables are shown for all years available.

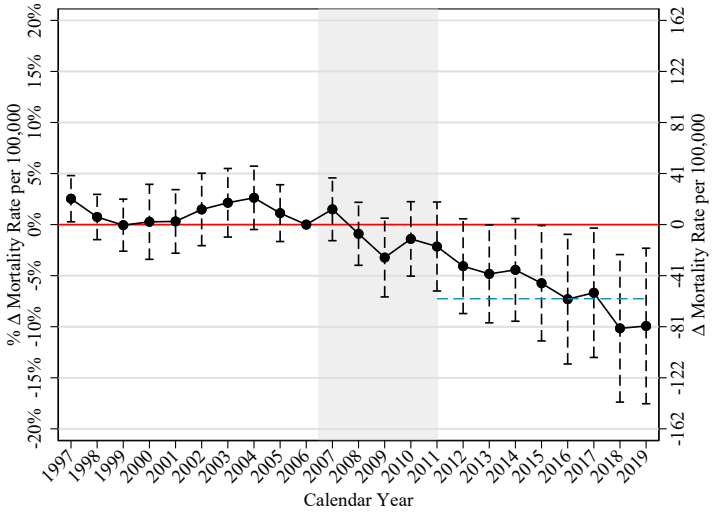
Figure 4: Event Studies for All-Cause Mortality

(a) NRT Drug Introduction



$\hat{\beta}_{Post\,1984}\,(SE) = 2.72\%\,(2.41\%)$; ADA $= -26,462$

(b) E-cigarette Drug Exemption

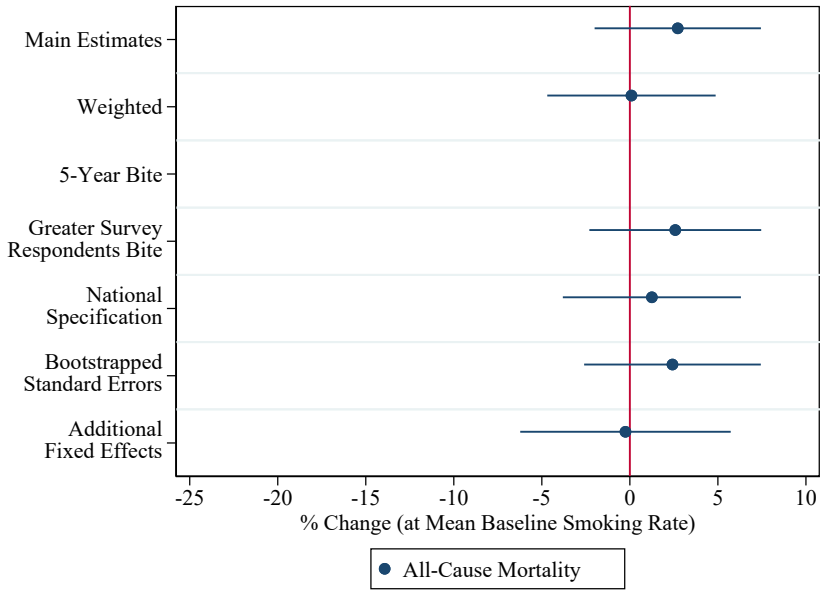


$\hat{\beta}_{Post\,2011}\,(SE) = -7.26\%^{**}\,(2.95\%)$; ADA $= 91,784$
$\hat{\beta}_{Post\,2007}\,(SE) = -5.68\%^{**}\,(2.43\%)$; ADA $= 71,841$

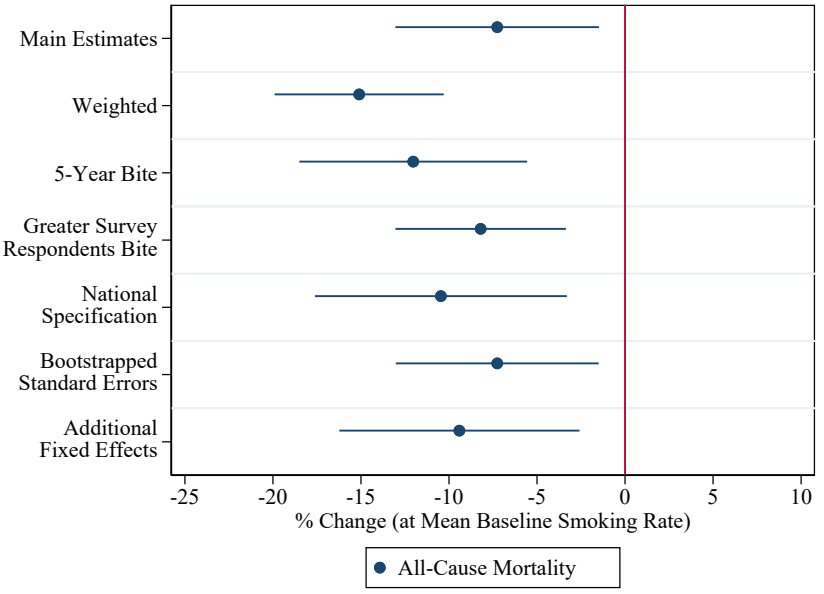
Notes: Mortality data is from the NVSS. The smoking share measures are constructed using 1983 NHIS data and 2005-2006 BRFSS data. Estimates along with 95% confidence intervals are shown. Event study leads and lags should be interpreted as the effect of drug introduction on deviations in the logged mortality rate per 100,000 from the pre-period extrapolated linear trend, evaluated at the mean level of our daily smoking share measure and relative to our base period, the year prior to drug introduction. Logged mortality rates are adjusted using the pre-trend extrapolation procedure from Freyaldenhoven et al. (2019). Regressions are conducted using ordinary least squares, control for unit and year fixed effects, with standard errors clustered at the demographic group level. Sample is restricted to ages 30-74 and demographic groups with survey respondents above the 25th percentile average count of survey respondents, yielding 200 groups for our NRT analysis and 540 groups for our e-cigarette analysis. Demographic groups are sex (male/female), 3 race categories for NRT analysis (White, Black, other) and 5 race/ethnicity categories for our e-cigarette analysis (White non-Hispanic, Black non-Hispanic, Native American non-Hispanic, Asian non-Hispanic, Hispanic), census region (Northeast, Midwest, South, West), urban status (urban/rural) for our e-cigarette analysis, and 9 5-year age groups (30-34, ..., 70-74). The mean level of our daily smoking share measure is 33.03% for our NRT analysis and 15.33% for our e-cigarette analysis. The shaded region from 2007-2010 denotes the years following E-cigarette importation to the U.S. in August 2006 but prior to the Washington D.C. Circuit Court's decision in December 2010. Annual deaths averted (ADA) are calculated by multiplying the post-period average percent change in mortality rates by the average mortality rate and the total population in our analytic sample, with positive values indicating reductions in mortality. *** p<0.01, ** p<0.05, * p<0.1

Figure 5: Summary of Main Estimates and Robustness Estimates

(a) NRT Drug Introduction



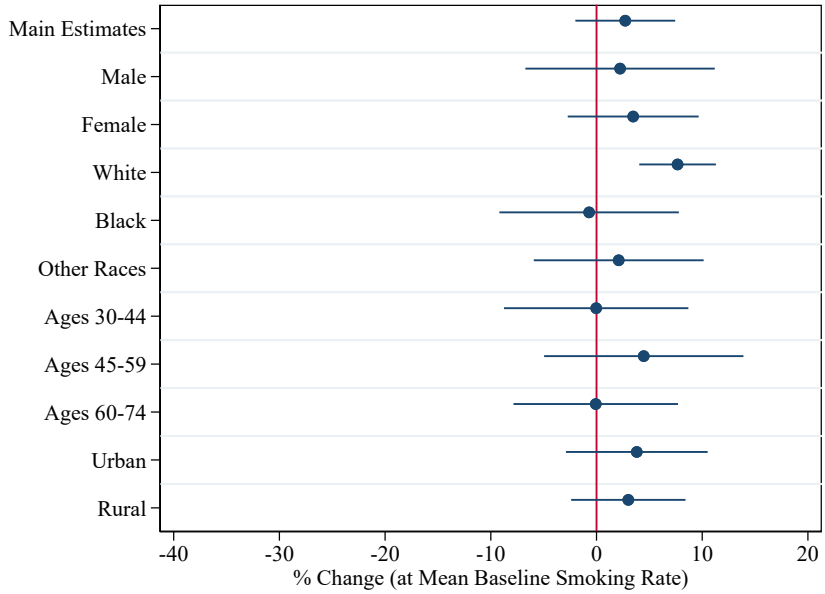
(b) E-cigarette Drug Exemption



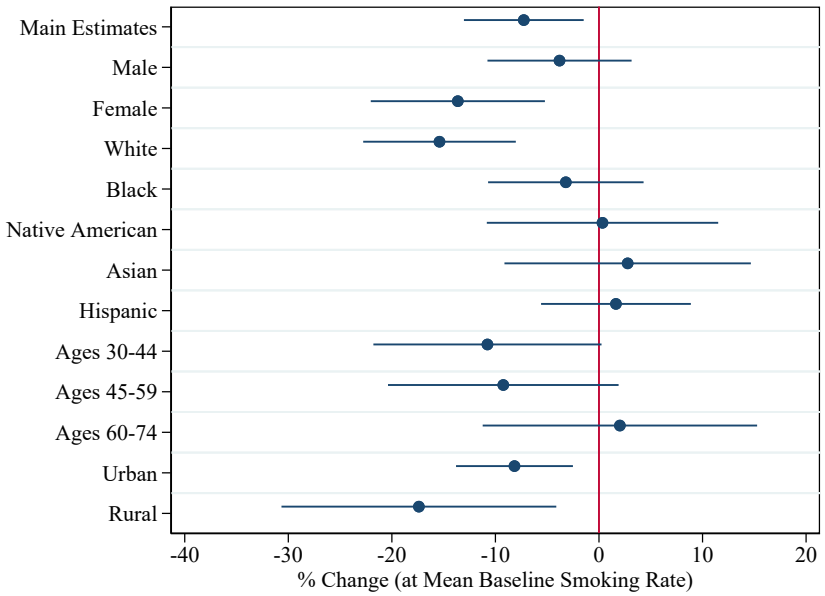
Notes: Estimates with 95% confidence intervals are shown for our main sample. Estimates come from Figures 4, F1, E2, E3, E4, and E5.

Figure 6: Summary of Main Estimates by Demographics

(a) NRT Drug Introduction



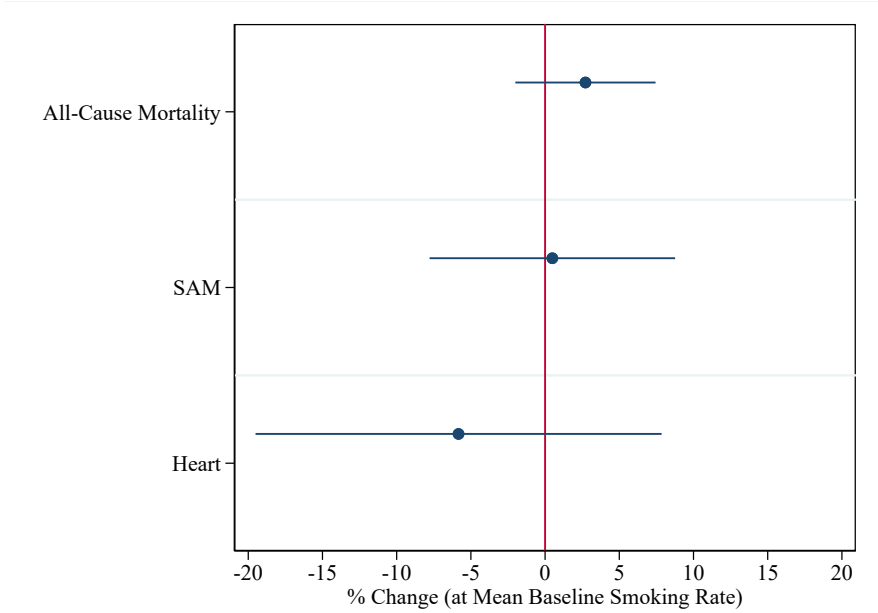
(b) E-cigarette Drug Exemption



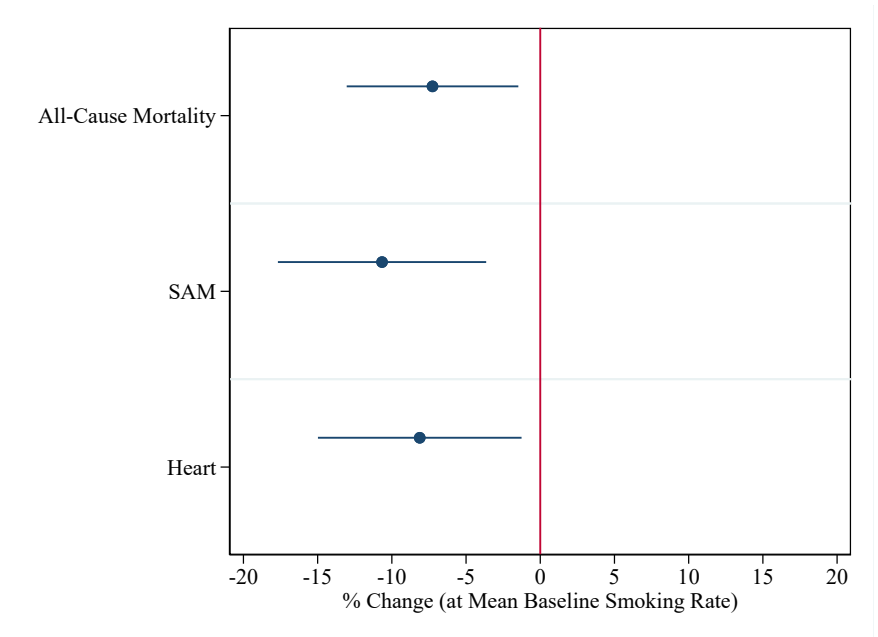
Notes: Estimates with 95% confidence intervals are shown for our main sample. Estimates come from Figures 4, G1, E2, H1, E2, and E3. The mean population-weighted daily smoking share measure is 13.7% (Main Estimates), 15.0% (Male), 12.6% (Female), 14.6% (White), 14.7% (Black), 6.0% (Native American), 22.5% (Asian American), 9.7% (Hispanic), 15.5% (Ages 30-44), 16.5% (Ages 45-59), 10.5% (Ages 60-74), 13.1% (Urban), and 17.3% (Rural).

Figure 7: Summary of Main Estimates by Cause of Death

(a) NRT Drug Introduction



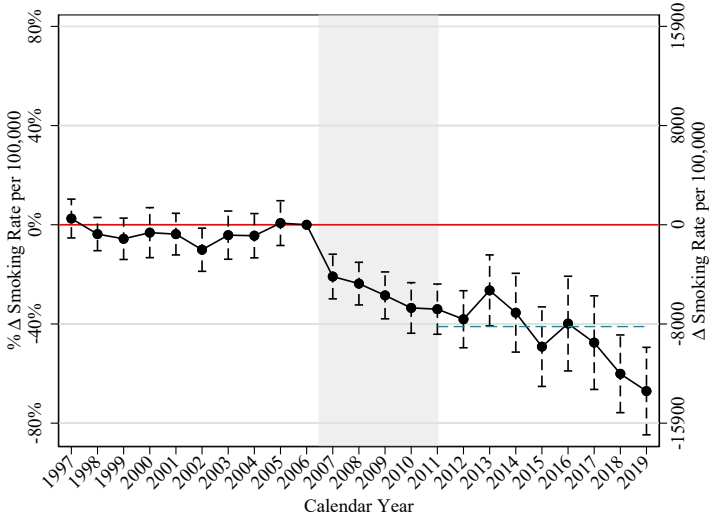
(b) E-cigarette Drug Exemption



Notes: Estimates with 95% confidence intervals are shown for our main sample. Estimates come from Figures 4 and I1.

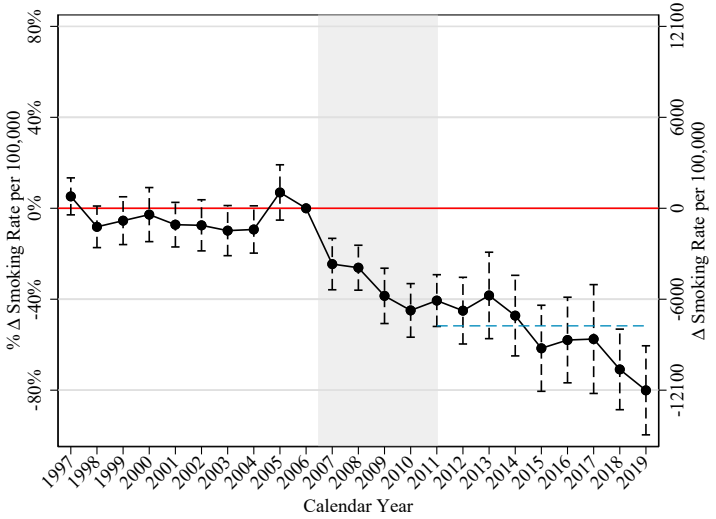
Figure 8: Event Studies for Smoking Outcomes (BRFSS)

(a) Current Smoking Rate, E-cigarette Exemption



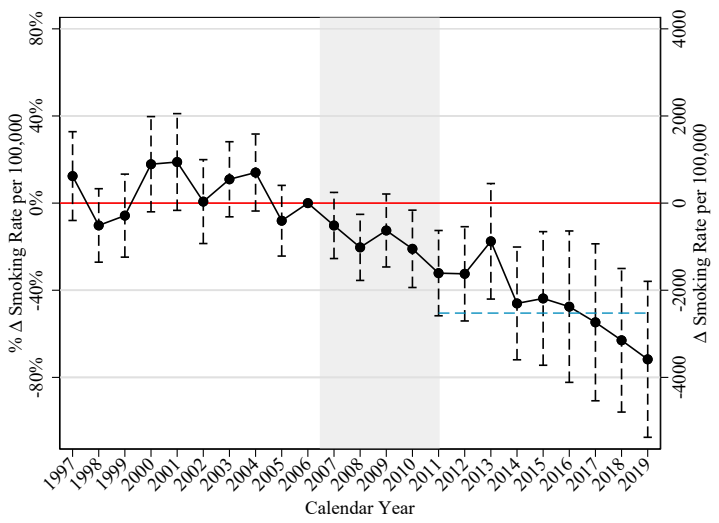
$\hat{\beta}_{Post\,2011}\,(SE) = -41.04\%^{***}\,(6.38\%)$; FACSY = 12.7m
$\hat{\beta}_{Post\,2007}\,(SE) = -35.58\%^{***}\,(5.37\%)$; FACSY = 11.1m

(b) Daily Smoking Rate, E-cigarette Exemption



$\hat{\beta}_{Post\,2011}\,(SE) = -51.70\%^{***}\,(6.83\%)$; FADSY = 12.1m
$\hat{\beta}_{Post\,2007}\,(SE) = -44.84\%^{***}\,(5.68\%)$; FADSY = 10.5m

(c) Light Smoking Rate, E-cigarette Exemption

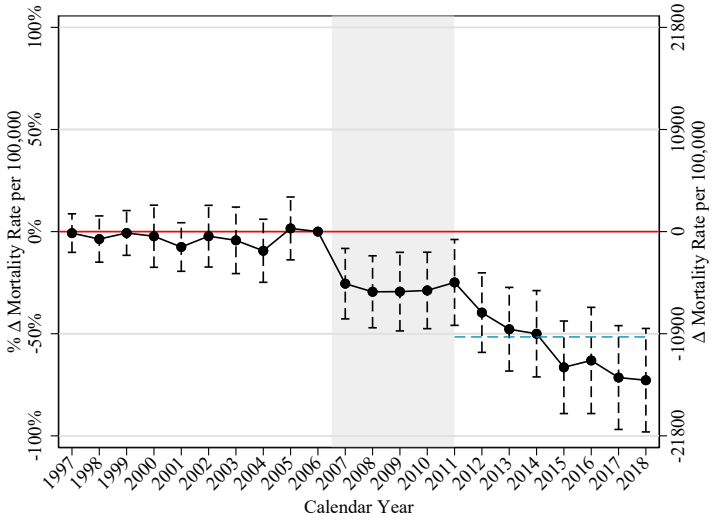


$\hat{\beta}_{Post\,2011}\,(SE) = -50.48\%^{***}\,(12.73\%)$; FALSY = 3.9m
$\hat{\beta}_{Post\,2007}\,(SE) = -41.17\%^{***}\,(10.38\%)$; FALSY = 3.2m

Notes: Smoking outcomes are from BRFSS. The smoking share measure is constructed using 2005-2006 BRFSS data. Estimates along with 95% confidence intervals are shown. Event study leads and lags should be interpreted as the effect of drug introduction on deviations in the logged smoking rate per 100,000 from the pre-period extrapolated linear trend, evaluated at the mean level of our daily smoking share measure and relative to our base period, the year prior to drug introduction. Logged smoking rates are adjusted using the pre-trend extrapolation procedure from Freyaldenhoven et al. (2019). Regressions are weighted by BRFSS survey weights, control for unit and year fixed effects, conducted using ordinary least squares, with standard errors clustered at the demographic group level. Sample is restricted to ages 30-74 and demographic groups with survey respondents above the 25th percentile average count of survey respondents, yielding 540 groups. Demographic groups are sex (male/female), 5 race/ethnicity categories for our e-cigarette analysis (White non-Hispanic, Black non-Hispanic, Native American non-Hispanic, Asian non-Hispanic, Hispanic), census region (Northeast, Midwest, South, West), urban status (urban/rural), and 11 5-year age groups (30-34, ..., 80+). The mean weighted level of our daily smoking share measure is 15.13%. The shaded region from 2007-2010 denotes the years following E-cigarette importation to the U.S. in August 2006 but prior to the Washington D.C. Circuit Court's decision in December 2010. Fewer annual 'current smoker-years' (FACSY), fewer annual 'daily smoker-years' (FADSY), and fewer annual 'light smoker-years' (FALSY) are calculated by multiplying the post-period average percent change in the outcome by the average outcome and the total population in our analytic sample. *** $p<0.01$, ** $p<0.05$, * $p<0.1$

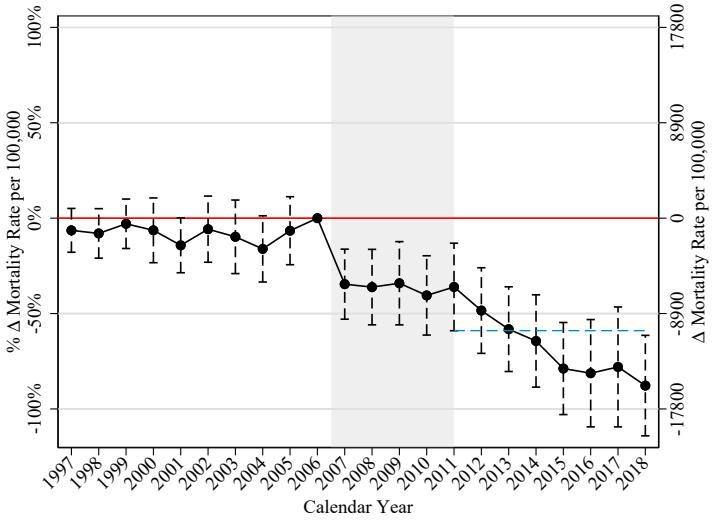
Figure 9: Event Studies for Smoking Outcomes (NHIS)

(a) Current Smoking Rate, E-cigarette Exemption



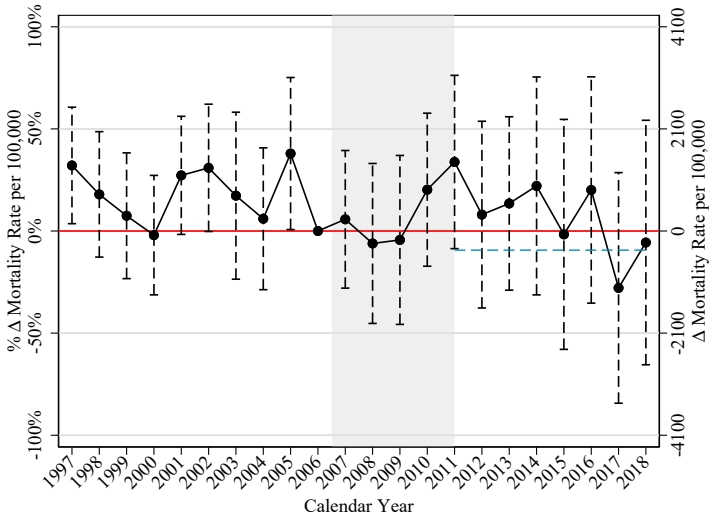
$\hat{\beta}_{Post\,2011}\,(SE) = -51.56\%^{***}\,(7.80\%)$; FACSY = 17.2m
$\hat{\beta}_{Post\,2007}\,(SE) = -42.85\%^{***}\,(6.51\%)$; FACSY = 14.3m

(b) Daily Smoking Rate, E-cigarette Exemption



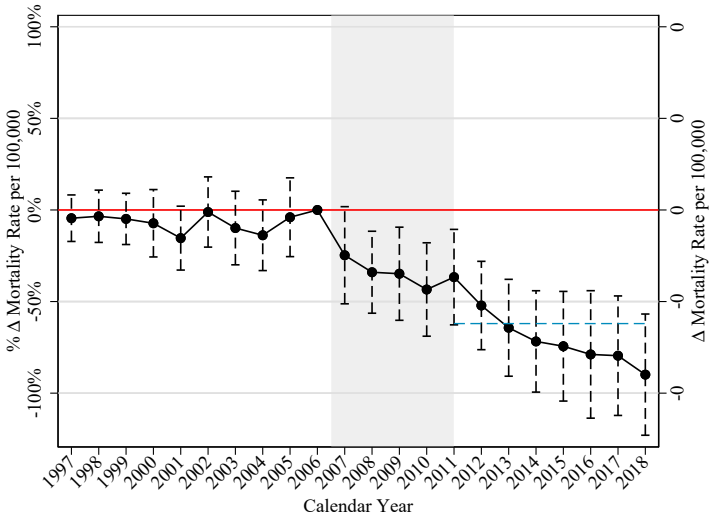
$\hat{\beta}_{Post\,2011}\,(SE) = -58.96\%^{***}\,(8.15\%)$; FADSY = 16.0m
$\hat{\beta}_{Post\,2007}\,(SE) = -48.95\%^{***}\,(6.71\%)$; FADSY = 13.3m

(c) Light Smoking Rate, E-cigarette Exemption



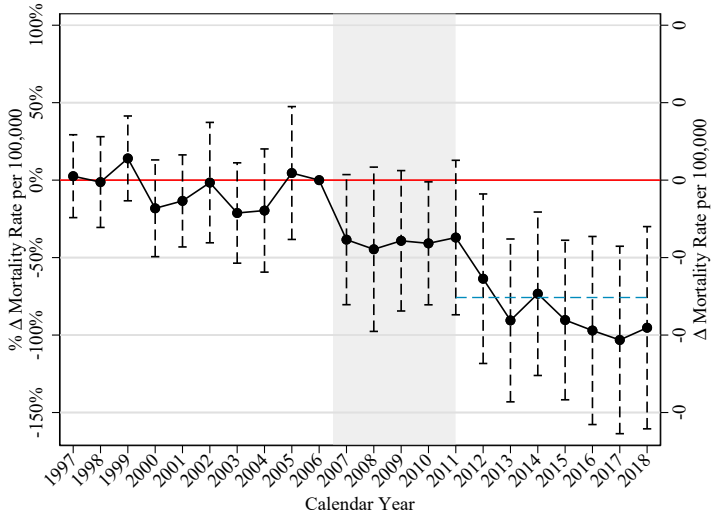
$\hat{\beta}_{Post\,2011}\,(SE) = -9.36\%\,(21.58\%)$; FALSY = 0.57m
$\hat{\beta}_{Post\,2007}\,(SE) = -10.80\%\,(18.61\%)$; FALSY = 0.66m

(d) Average Daily Cigarettes per Capita, E-cigarette Exemption



$\hat{\beta}_{Post\,2011}\,(SE) = -62.01\%^{***}\,(9.37\%)$; FAPCS = 5.7b
$\hat{\beta}_{Post\,2007}\,(SE) = -50.64\%^{***}\,(7.74\%)$; FAPCS = 4.7b

(e) Average Days Smoked Last Month per Capita, E-cigarette Exemption



$\hat{\beta}_{Post\,2011}\,(SE) = -75.75\%^{***}\,(20.19\%)$; FADS = 4.0b
$\hat{\beta}_{Post\,2007}\,(SE) = -62.42\%^{***}\,(17.15\%)$; FADS = 3.3b

Notes: Smoking outcomes are from NHIS. The smoking share measures are constructed using 2005-2006 NHIS data. Estimates along with 95% confidence intervals are shown. Event study leads and lags should be interpreted as the effect of drug introduction on deviations in the logged outcome from the pre-period extrapolated linear trend, evaluated at the mean level of our daily smoking share measure and relative to our base period, the year prior to drug introduction. Logged outcomes are adjusted using the pre-trend extrapolation procedure from Freyaldenhoven et al. (2019). Figures (a)-(c) express logged outcomes as rates per 100,000 population. Figure (d)-(e) express logged outcomes as rates per capita. Regressions are weighted by NHIS survey weights, control for unit and year fixed effects, conducted using ordinary least squares, with standard errors clustered at the demographic group level. Sample is restricted to ages 30-74 and demographic groups with survey respondents above the 25th percentile average count of survey respondents, yielding 190 groups. Demographic groups are sex (male/female), 3 race categories (White, Black, other), census region (Northeast, Midwest, South, West), and 9 5-year age groups (30-34, ..., 70-74). The mean population-weighted level of our daily smoking share measure is 17.84%. The shaded region from 2007-2010 denotes the years following E-cigarette importation to the U.S. in August 2006 but prior to the Washington D.C. Circuit Court's decision in December 2010. Fewer annual 'current smoker-years' (FACSY), fewer annual 'daily smoker-years' (FADSY), fewer annual 'light smoker-years' (FALSY), fewer annual 'packs of cigarettes smoked' (FAPCS), and fewer annual 'days smoked' (FADS) are calculated by multiplying the post-period average percent change in the outcome by the average population-weighted outcome and the total population in our analytic sample. Fewer annual 'packs of cigarettes smoked' (FAPCS) is multiplied by 365 to convert from daily consumption to annual consumption. Fewer annual 'days smoked' (FADS) is multiplied by 12 to convert from days smoked in past month to days smoked in past year. *** $p<0.01$, ** $p<0.05$, * $p<0.1$

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Appendix A Analysis of Patent Applications

Table A1: Effect of E-cigarette Drug Exemption on Logged Patent Applications

	Pre-2011	Post-2011	Time-Difference
E-cigarettes:			
United States:	0.265	5.145	4.880***
	(0.105)	(0.241)	(0.255)
Australia:	0.080	2.205	2.125***
	(0.046)	(0.179)	(0.179)
		Differences-	2.755***
		in-Differences:	(0.312)
	Pre-2011	Post-2011	Time-Difference
Other Smoking Cessation Drugs:			
United States:	1.392	2.704	1.313***
	(0.190)	(0.069)	(0.203)
Australia:	0.796	1.905	1.109***
	(0.148)	(0.102)	(0.179)
		Differences-	0.203
		in-Differences:	(0.270)
		DDD Estimator:	2.552***
			(0.413)

Notes: Differences-in-differences estimates (DID) and triple-differences (DDD) estimates with robust standard errors shown for log(patent applications + 1) from 1975-2019, with the post-period beginning after FDA drug exemption in 2011. DID estimates show before-and-after differences in patent applications between the United States and Australia by drug type. DDD estimate is the difference between the DID estimate for the E-cigarette and the DID estimate for other smoking cessation drugs.

Appendix B Background Figures on E-cigarette Innovation

Figure B1: Ruyan V8 E-cigarette



Notes: This is a promotional image of the first e-cigarette imported to the United States, the Ruyan v8 e-cigarette, in August 2006. It was advertised with a nicotine concentration of 16 mg/ml (Bullen et al., 2010) and were not flavored. If e-cigarettes had been consistently regulated as drugs, they are unlikely to look much different today. Source: https://bit.ly/4a3udWE.

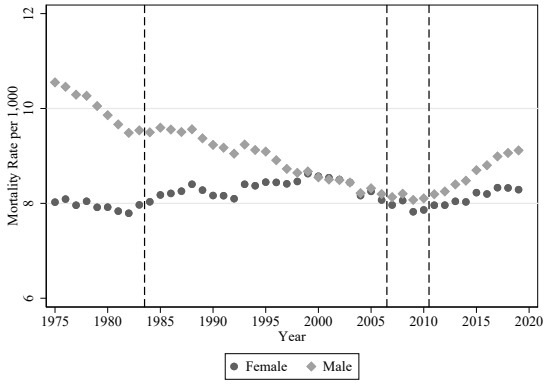
Figure B2: E-cigarette Vape Shop



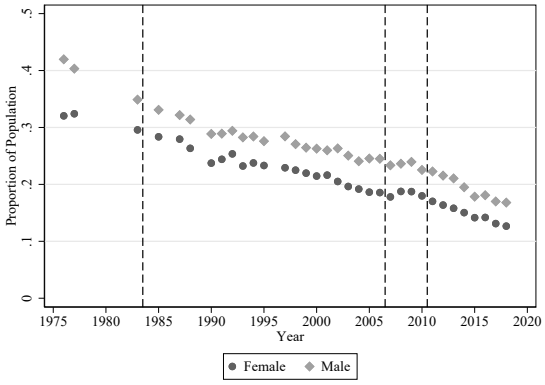
Notes: This image of a modern-day vape shop provides an illustration of the rapid innovation in the e-cigarette marketplace made possible by the judicial exemption of e-cigarettes from drug regulation. Source: https://bit.ly/3x0XH8Z.

Appendix C Descriptive Figures

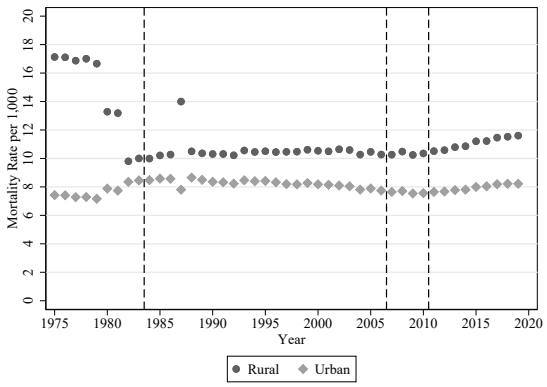
(g) All-Cause Mortality, Sex



(h) Current Smoking Prevalence, Sex



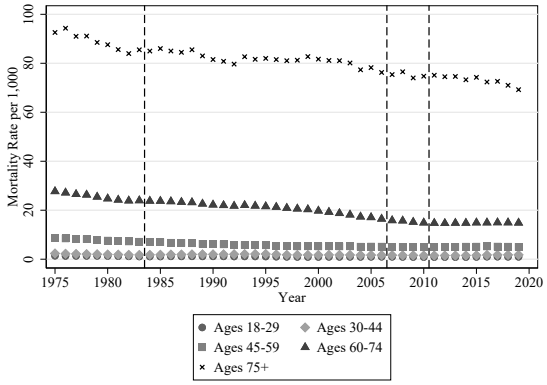
(i) All-Cause Mortality, Urban Status



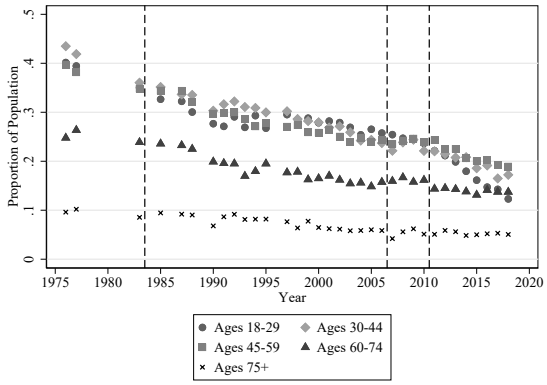
Notes: Mortality data is from NVSS. Smoking data is from NHIS. Population data is from SEER. Mean mortality rates per 1,000 population are shown using 3 race categories. Mean smoking prevalences are shown using 3 race categories without urban status. Smoking prevalences are weighted NHIS survey weights. Smoking prevalences are unavailable from NHIS in some earlier years. Demogrpahic groups are sex (male/female), 3 race categories (White, Black, other), census region (Northeast, Midwest, South, West), urban status (urban/rural) only for mortality figures, and 9 5-year age groups (30-34, . . . , 70-74).

Figure C1: Trends in Mortality by Demographic Category

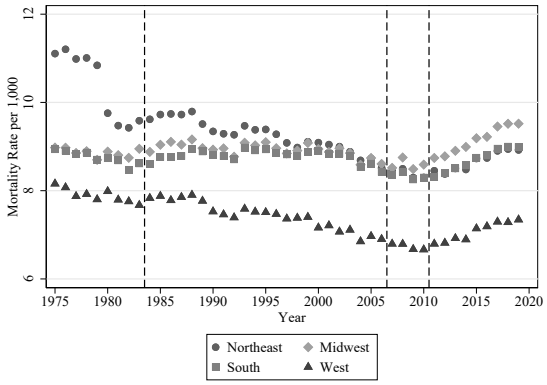
(a) All-Cause Mortality, Age



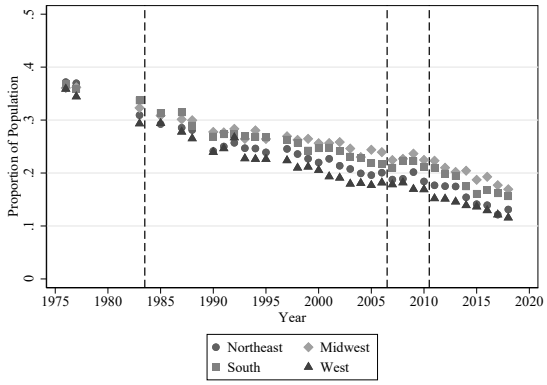
(b) Current Smoking Prevalence, Age



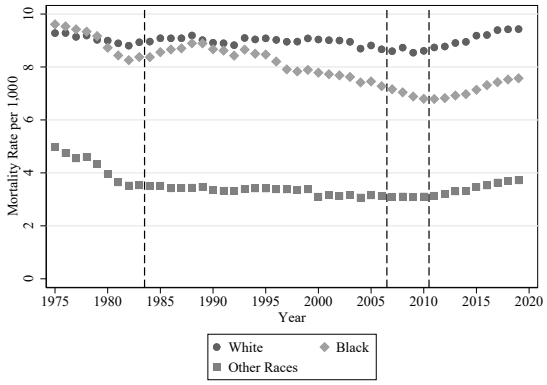
(c) All-Cause Mortality, Census Region



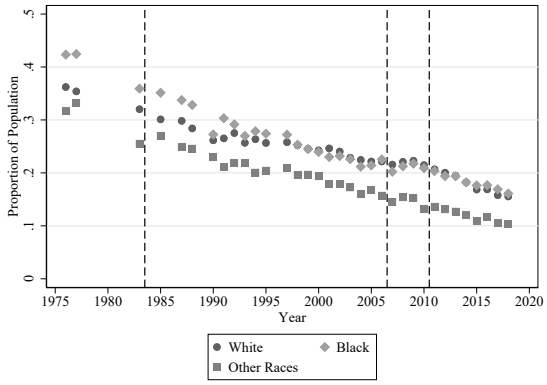
(d) Current Smoking Prevalence, Census Region



(e) All-Cause Mortality, Race



(f) Current Smoking Prevalence, Race



Appendix D Data Appendix

D.1 Smoking Outcomes

We use BRFSS data from 1990-2019 and NHIS data from 1975-2019.[D1] We construct two main outcomes from NHIS and BRFSS related to smoking prevalence: current smoking and daily smoking.[D2] We follow convention by defining current smokers as those individuals who have smoked at least 100 cigarettes in their lifetime (ever smokers) and who currently smoke at least some days in the past month. Heavy or daily smoking is similarly defined as a current smoker who reports smoking everyday in the past month and at least 100 cigarettes in their lifetime.[D3] We also calculate the proportion of former smokers (ever smokers who do not currently smoke), light smokers (current smokers who currently smoke less than everyday), and never smokers (those who have never smoked at least 100 cigarettes in their life). Like with mortality, when analyzing smoking prevalence outcomes we express as rates— e.g. daily smokers per 100,000 population.

We calculate two additional measures of smoking intensity: average cigarettes per day smoked (in past month) and average days smoked in the past month. Both of these variables are administered in NHIS and BRFSS but only NHIS consistently reports these measures through 2019, albeit with some gaps in earlier years. We express these intensity outcomes as rates per capita— e.g. average cigarettes smoked per capita, average days smoked in past month per capita.[D4]

We collapse our four annual smoking measures to the demographic group-level using survey sampling weights.[D5] When pooling outcomes over multiple years, we account for varying sample sizes in each survey wave by weighting each demographic group's sampling weight by the share of total survey respondents in that group surveyed in that particular year.

From NHIS, current and daily smoking is available from 1976-1977, 1983, 1985, 1987-1988, 1990-1995, and 1997-2018. Cigarettes smoked per day is available from 1976-1977, 1985, 1991-1995, and 1997-2018. Days smoked in the past month is available from 1991-1995, and from 1997-2018. For BRFSS, current and daily smoking is available during our entire analysis window from 199-2019.

[D1] IPUMS provides harmonized NHIS data at https://nhis.ipums.org/nhis/. BRFSS data is available starting in 1984 but only a handful of states participated prior to 1990.

[D2] Throughout the paper we use the terms cigarette smoking and smoking interchangeably.

[D3] Prior to 1996 in BRFSS, smoking frequency is not asked but average cigarettes smoked per day is asked. For years prior to 1996, we follow best practice and define heavy smokers as those who report smoking an average of at least 1 pack per day in the past month.

[D4] All of our smoking variables are out of the total group's population: i.e. both the smoking and non-smoking population. Former smokers and never smokers therefore contain values of zero. We use demographic group-specific population to generate rates, i.e. *adjusted* rates, not total U.S. population.

[D5] For NHIS, we weight by $perweight$. For BRFSS, we weight by $_finalwt$.

Cigarettes smoked per day and days smoked in the past month are only intermittently available in later years of BRFSS.

For 2007 e-cigarette introduction, the average current smoking rate from 2000-2006 is 18.8% (SE=8.9%) and the average daily smoking rate is 13.3% (SE=7.5%), both from BRFSS. For 1984 NRT introduction, the average current smoking rate from 1975-1983 where available is 33.1% (SE=11.8%) and the average daily smoking rate is 28.9% (SE=11.3%), both from NHIS. The average number of cigarettes smoked per day during this same period is 7.4 (SE=3.4) cigarettes per day.

We proceed to construct our NHIS panel and BRFSS panel consisting of our key outcomes of smoking prevalence, consumption, and frequency for each demographic group from 1975-2019 for all years in which those outcomes are measured. For NHIS, our demographic groups use 3-race categories excluding urban status from 1975-2019, yielding 216 unique demographic groups.[D6] For BRFSS, our demographic groups use 5-race categories with urban status from 1990-2019, consisting of 720 unique demographic groups.

D.2 Additional Information on Share Measure

For e-cigarette introduction in 2007, we construct a 2-year daily smoking share measure from the years 2005-2006 and a 5-year daily smoking share measure from the years 2002-2006. We use the 2-year share measure in our preferred analysis because we believe it is a more precise measure of a demographic group's exposure to the 2007 introduction shock than a group's smoking rates in the past 5 years. We conduct a sensitivity test using the 5-year share measure for e-cigarette introduction and find similar results to using our 2-year share measure. We calculate a share measure for NHIS data and separately for BRFSS data, using 3-race categories without urban status for our NHIS e-cigarette share measure and 5-race with urban status for our BRFSS e-cigarette share measure. We weight using BRFSS and NHIS sampling weights.

We also construct share measures for our two alternative introduction dates of 1996 for over-the-counter NRT and 2013 for e-cigarette introduction. We construct our share measure in the same manner as with prescription NRT and e-cigarettes using NHIS and separately for BRFSS data for 2-years and 5-years prior to these alternative dates, using the 2-year share measure as our preferred analysis as before.

[D6] Urban status is not consistently available in NHIS in all years, particularly after 2000. NHIS only begins using 5-race categories in the 1990's.

For 1984 NRT introduction, the mean daily smoking rate in our 1-year 1983 NHIS share measure analytic sample is 33.0% (SE=8.3%).[D7] The average number of respondents used to construct our 1-year share measure is 83. The average smoking rate from 1976-1983 in years available is 36.5% (SE=8.3%), the associated daily smoking rate over this same period is 32% (SE=8.5%), and the average all-cause mortality rate over this same period is 1,417 deaths per 100,000 population. The average number of cigarettes smoked from 1975-1983 is 8.3 (SE=2.8) The analytic sample contains 200 demographic groups from 1974-1993.

For 2007 e-cigarette introduction, the mean daily smoking rate of our 2-year BRFSS share measure is 15.3%.[D8] The average number of respondents used to construct our 2-year share measure is 421. The average smoking rate from 2000-2006 is 19.4%, the corresponding daily smoking rate is 15.1%, and the average all-cause mortality rate from 2000-2006 is 1,401 deaths per 100,000 population. The analytic sample contains 540 demographic groups from 1997-2019. Of the demographic categories used in constructing our share measure, age and race explain the most variation in smoking rates.[D9]

E-cigarette use questions are available in BRFSS survey data in 2016-2018, and we use these to explore if the 2-year BRFSS share measure corresponds with higher e-cigarette use rates. We find a moderately-strong positive correlation. For example, rates of ever/current/daily e-cigarette use were 7%/1.3%/0.7% for people in the bottom tercile of the 2-year BRFSS daily smoking share measure, 6%/3.1%/1.2% for people in the middle tercile, and 24.5%/5.1%/2.2% for people in the top tercile.[D10]

[D7] For NRT introduction, the mean daily smoking prevalence in 1983, the year we use in constructing our NHIS share measure, is rural White men ages 35-39 who reside in the northern census region, at 41.13%. The group with the lowest daily smoking rate over this same period is rural White men ages 75-79 who reside in the western census region.

[D8] For e-cigarette introduction in 2007, the group with the highest daily smoking rate from 2005-2006 at 29.24% is rural White males ages 30-34 who reside in the Northern census region. The group with the lowest daily smoking rate at 4.59% from 2005-2006 is urban White women ages 75-79 who live in the midwest census region. The mean daily smoking prevalence from 2000-2006 is 16.18% with a standard deviation of 7.38%.

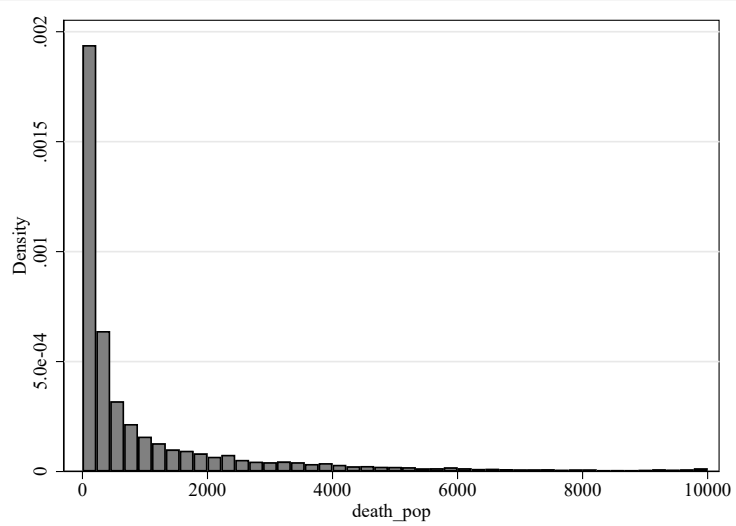
[D9] A cross-sectional regression of our 2005-2006 smoking share measure on demographic group indicators yields an adjusted R-squared of 53.3%. When removing demographic dimensions one-by-one and assessing the loss of R-squared, removing age as a dimension reduces adjusted R-squared by 22.8%, followed by race, which when removed reduces our adjusted R-squared by 17.7%. Removing urban status, sex, and region, and reduces the model's adjusted R-squared by 3.4%, 3.1%, and 1.9%, respectively.

[D10] The correlation between our daily smoking share measure (2005-2006) and current use e-cigarette rates after 2016 is 0.41.

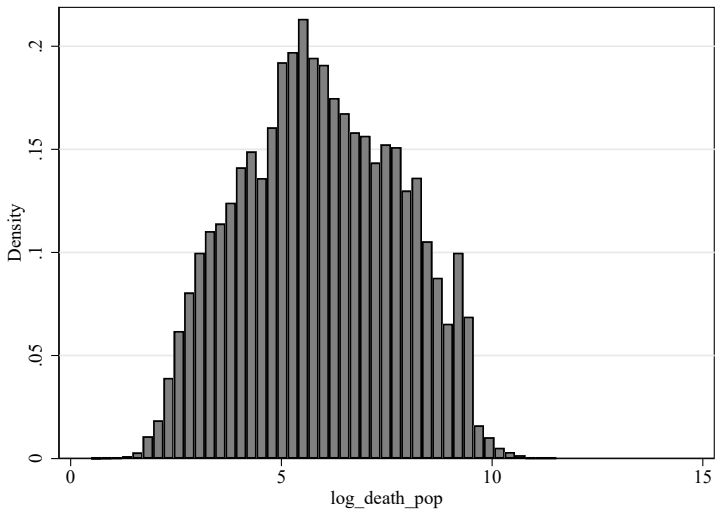
Appendix E Functional Form

Figure E1: Distribution of All-Cause Mortality Rates

(a) Rates in Levels



(b) Rates in Logs

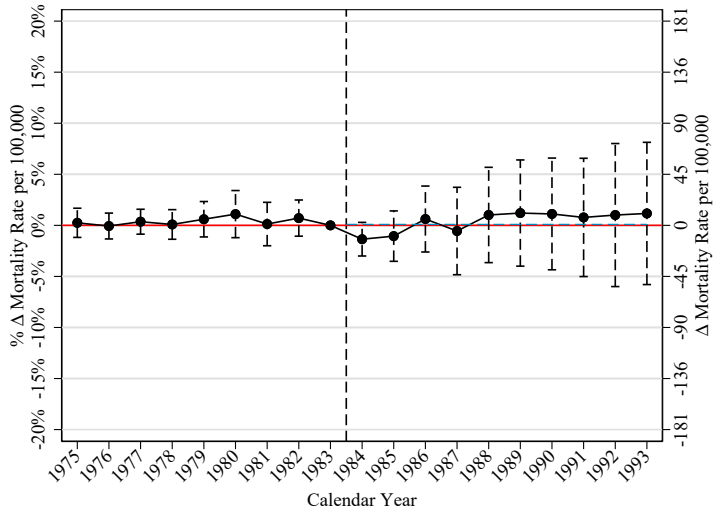


Notes: Mortality data is from NVSS. Data is shown for years 1975-2019.

Appendix F Robustness & Sensitivity

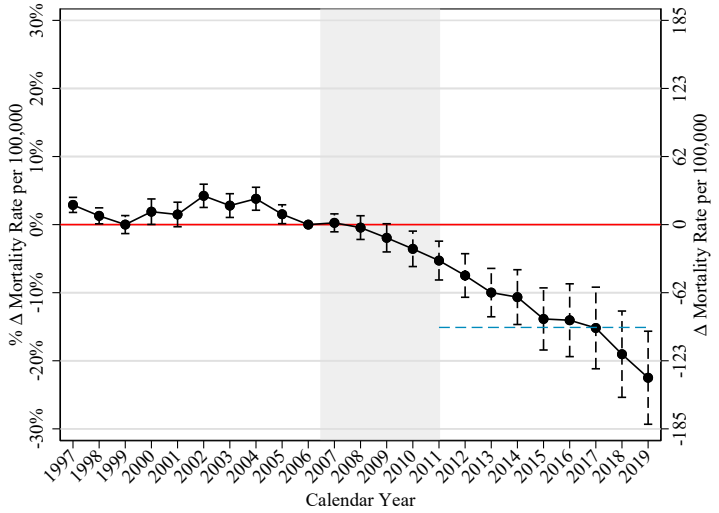
Figure F1: Event Studies for All-Cause Mortality, Weighted

(a) NRT Drug Introduction



$\hat{\beta}_{Post\,1984}\,(SE) = 0.09\%\,(2.44\%)$; ADA$= -866$

(b) E-cigarette Drug Exemption

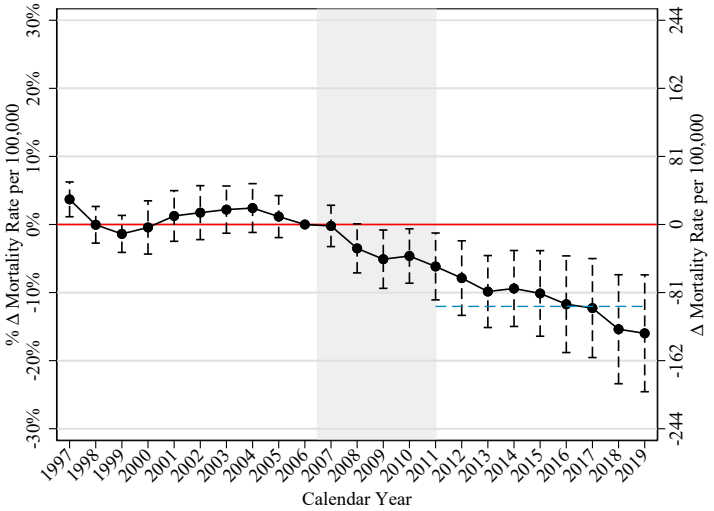


$\hat{\beta}_{Post\,2011}\,(SE) = -15.10\%^{***}\,(2.45\%)$; ADA $= 145,268$
$\hat{\beta}_{Post\,2007}\,(SE) = -11.51\%^{***}\,(1.93\%)$; ADA $= 102,674$

Notes: Mortality data is from the NVSS. The smoking share measures are constructed using 1983 NHIS data and 2005-2006 BRFSS data. Estimates along with 95% confidence intervals are shown. Event study leads and lags should be interpreted as the effect of drug introduction on deviations in the logged mortality rate per 100,000 from the pre-period extrapolated linear trend, evaluated at the mean level of our daily smoking share measure and relative to our base period, the year prior to drug introduction. Logged mortality rates are adjusted using the pre-trend extrapolation procedure from Freyaldenhoven et al. (2019). Regressions are conducted using ordinary least squares, weighted by population in the year prior to drug introduction, control for unit and year fixed effects, with standard errors clustered at the demographic group level. Sample is restricted to ages 30-74 and demographic groups with survey respondents above the 25th percentile average count of survey respondents, yielding 200 groups for our NRT analysis and 540 groups for our e-cigarette analysis. Demographic groups are sex (male/female), 3 race categories for NRT analysis (White, Black, other) and 5 race/ethnicity categories for our e-cigarette analysis (White non-Hispanic, Black non-Hispanic, Native American non-Hispanic, Asian non-Hispanic, Hispanic), census region (Northeast, Midwest, South, West), urban status (urban/rural) for our e-cigarette analysis, and 9 5-year age groups (30-34, . . . , 70-74). The mean population-weighted level of our daily smoking share measure is 33.11% for our NRT analysis and 14.85% for our e-cigarette analysis. The shaded region from 2007-2010 denotes the years following E-cigarette importation to the U.S. in August 2006 but prior to the Washington D.C. Circuit Court's decision in December 2010. Annual deaths averted (ADA) are calculated by multiplying the post-period average percent change in mortality rates by the average population-weighted mortality rate and the total population in our analytic sample, with positive values indicating reductions in mortality. *** p<0.01, ** p<0.05, * p<0.1

Figure E2: Event Studies for All-Cause Mortality, 5 Year Share Measure

(a) E-cigarette Drug Exemption

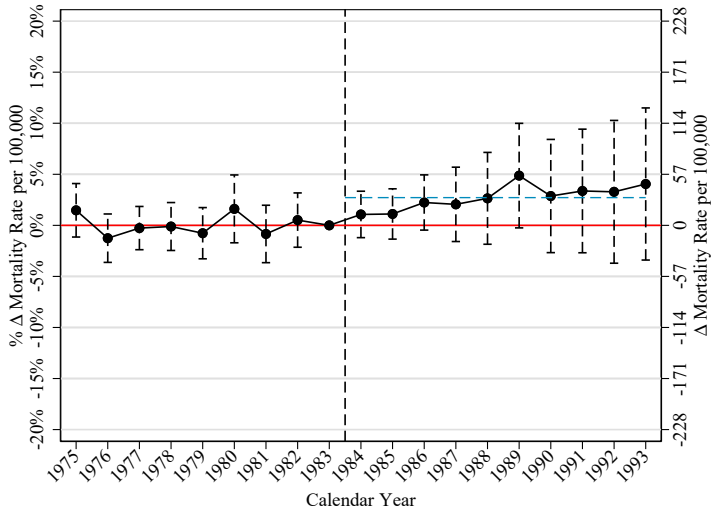


$\hat{\beta}_{Post\,2011}\,(SE) = -12.03\%^{***}\,(3.30\%)$; ADA $= 152,440$
$\hat{\beta}_{Post\,2007}\,(SE) = -9.70\%^{***}\,(2.74\%)$; ADA $= 122,789$

Notes: Mortality data is from the NVSS. The smoking share measures are constructed using 2005-2006 BRFSS data. Estimates along with 95% confidence intervals are shown. Event study leads and lags should be interpreted as the effect of drug introduction on deviations in the logged mortality rate per 100,000 from the pre-period extrapolated linear trend, evaluated at the mean level of our daily smoking share measure and relative to our base period, the year prior to drug introduction. Logged mortality rates are adjusted using the pre-trend extrapolation procedure from Freyaldenhoven et al. (2019). Regressions are conducted using ordinary least squares, control for unit and year fixed effects, with standard errors clustered at the demographic group level. Sample is restricted to ages 30-74 and demographic groups with survey respondents above the 25th percentile average count of survey respondents, yielding 542 groups. Demographic groups are sex (male/female), 5 race/ethnicity categories (White non-Hispanic, Black non-Hispanic, Native American non-Hispanic, Asian non-Hispanic, Hispanic), census region (Northeast, Midwest, South, West), urban status (urban/rural), and 9 5-year age groups (30-34, ..., 70-74). The mean level of our daily smoking share measure is 15.88%. The shaded region from 2007-2010 denotes the years following E-cigarette importation to the U.S. in August 2006 but prior to the Washington D.C. Circuit Court's decision in December 2010. Annual deaths averted (ADA) are calculated by multiplying the post-period average percent change in mortality rates by the average mortality rate and the total population in our analytic sample, with positive values indicating reductions in mortality. *** p<0.01, ** p<0.05, * p<0.1

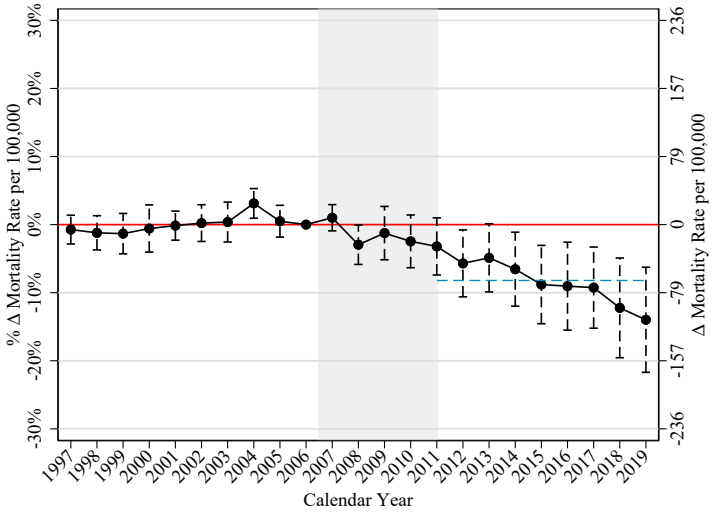
Figure E3: Event Studies for All-Cause Mortality, Greater Share Measure Cell Size

(a) NRT Drug Introduction



$\hat{\beta}_{Post\,1984}\,(SE) = 2.58\%\,(2.49\%)$; ADA $= -33,301$

(b) E-cigarette Drug Exemption

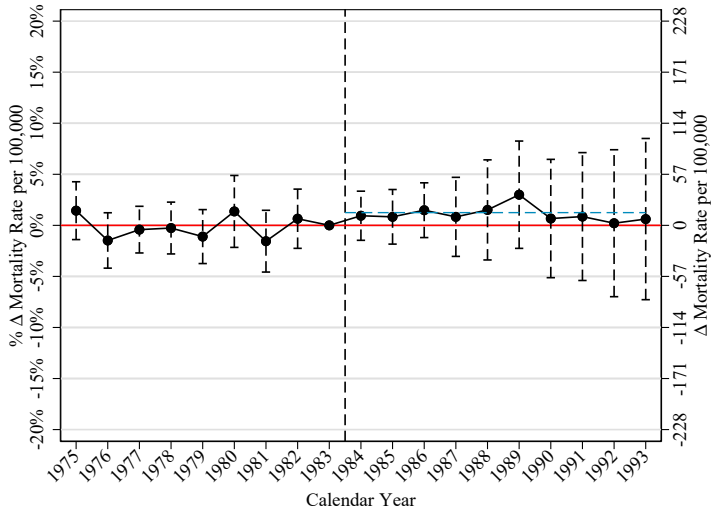


$\hat{\beta}_{Post\,2011}\,(SE) = -8.20\%^{***}\,(2.47\%)$; ADA $= 96,844$
$\hat{\beta}_{Post\,2007}\,(SE) = -6.12\%^{***}\,(2.47\%)$; ADA $= 72,262$

Notes: Mortality data is from the NVSS. The smoking share measures are constructed using 1983 NHIS data and 2005-2006 BRFSS data. Estimates along with 95% confidence intervals are shown. Event study leads and lags should be interpreted as the effect of drug introduction on deviations in the logged mortality rate per 100,000 from the pre-period extrapolated linear trend, evaluated at the mean level of our daily smoking share measure and relative to our base period, the year prior to drug introduction. Logged mortality rates are adjusted using the pre-trend extrapolation procedure from Freyaldenhoven et al. (2019). Regressions are conducted using ordinary least squares, control for unit and year fixed effects, with standard errors clustered at the demographic group level. Sample is restricted to ages 30-74 and demographic groups with survey respondents above the 50th percentile average count of survey respondents, yielding 140 groups for our NRT analysis and 343 groups for our e-cigarette analysis. Demographic groups are sex (male/female), 3 race categories for NRT analysis (White, Black, other) and 5 race/ethnicity categories for our e-cigarette analysis (White non-Hispanic, Black non-Hispanic, Native American non-Hispanic, Asian non-Hispanic, Hispanic), census region (Northeast, Midwest, South, West), urban status (urban/rural) for our e-cigarette analysis, and 9 5-year age groups (30-34, ..., 70-74). The mean level of our daily smoking share measure is 33.03% for our NRT analysis and 14.17% for our e-cigarette analysis. The shaded region from 2007-2010 denotes the years following E-cigarette importation to the U.S. in August 2006 but prior to the Washington D.C. Circuit Court's decision in December 2010. Annual deaths averted (ADA) are calculated by multiplying the post-period average percent change in mortality rates by the average mortality rate and the total population in our analytic sample, with positive values indicating reductions in mortality. *** p<0.01, ** p<0.05, * p<0.1

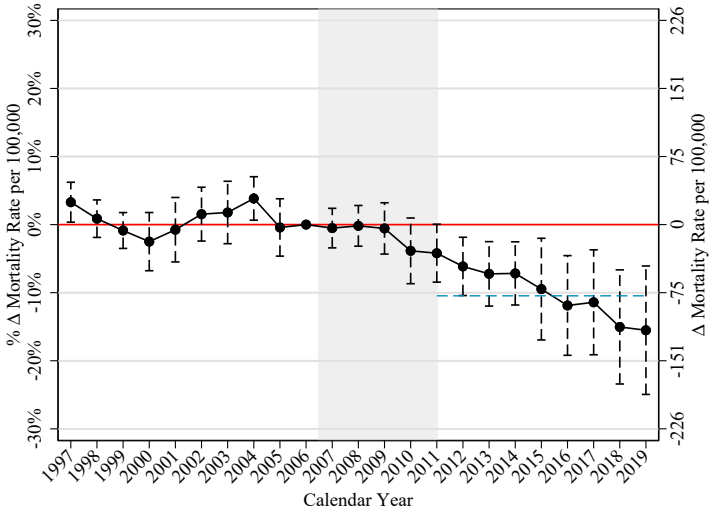
Figure E4: Event Studies for All-Cause Mortality, National

(a) NRT Drug Introduction



$\hat{\beta}_{Post\,1984}\,(SE) = 1.25\%\,(2.58\%)$; ADA $= -15,280$

(b) E-cigarette Drug Exemption

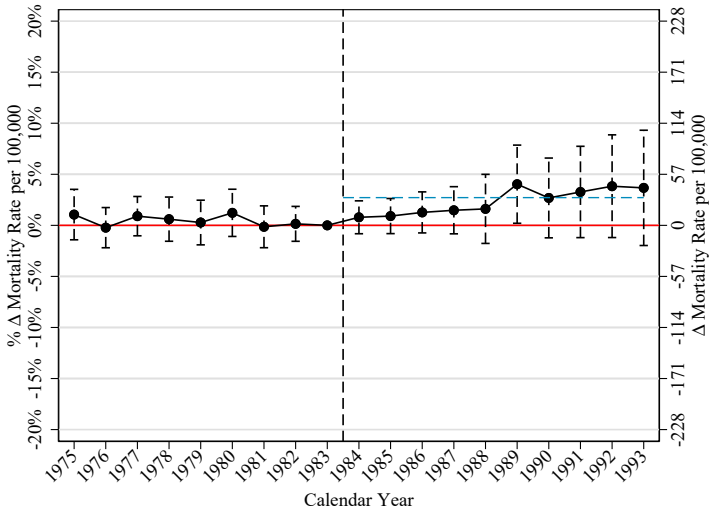


$\hat{\beta}_{Post\,2011}\,(SE) = -10.46\%^{***}\,(3.65\%)$; ADA $= 119,915$
$\hat{\beta}_{Post\,2007}\,(SE) = -7.84\%^{***}\,(2.87\%)$; ADA $= 89,914$

Notes: Mortality data is from the NVSS. The smoking share measures are constructed using 1983 NHIS data and 2005-2006 BRFSS data. Estimates along with 95% confidence intervals are shown. Event study leads and lags should be interpreted as the effect of drug introduction on deviations in the logged mortality rate per 100,000 from the pre-period extrapolated linear trend, evaluated at the mean level of our daily smoking share measure and relative to our base period, the year prior to drug introduction. Logged mortality rates are adjusted using the pre-trend extrapolation procedure from Freyaldenhoven et al. (2019). Regressions are conducted using ordinary least squares, control for unit and year fixed effects, with standard errors clustered at the demographic group level. Sample is restricted to ages 30-74 and demographic groups with survey respondents above the 25th percentile average count of survey respondents, yielding 50 groups for our NRT analysis and 67 groups for our e-cigarette analysis. Demographic groups are sex (male/female), 3 race categories for NRT analysis (White, Black, other) and 5 race/ethnicity categories for our e-cigarette analysis (White non-Hispanic, Black non-Hispanic, Native American non-Hispanic, Asian non-Hispanic, Hispanic), and 9 5-year age groups (30-34, ..., 70-74). The mean level of our daily smoking share measure is 27.89% for our NRT analysis and 13.63% for our e-cigarette analysis. The shaded region from 2007-2010 denotes the years following E-cigarette importation to the U.S. in August 2006 but prior to the Washington D.C. Circuit Court's decision in December 2010. Annual deaths averted (ADA) are calculated by multiplying the post-period average percent change in mortality rates by the average mortality rate and the total population in our analytic sample, with positive values indicating reductions in mortality. *** p<0.01, ** p<0.05, * p<0.1

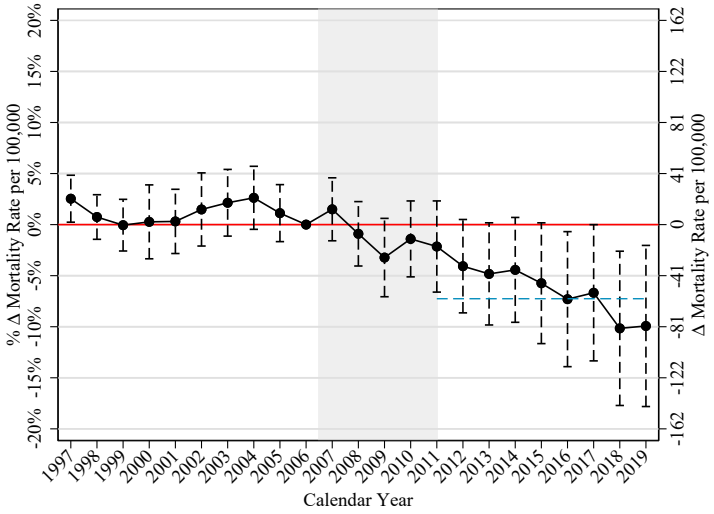
Figure E5: Event Studies for All-Cause Mortality, Bootstrapped Standard Errors

(a) NRT Drug Introduction



$\hat{\beta}_{Post\,1984}\,(SE) = 2.42\%\,(2.56\%)$; ADA $= -25,789$

(b) E-cigarette Drug Exemption

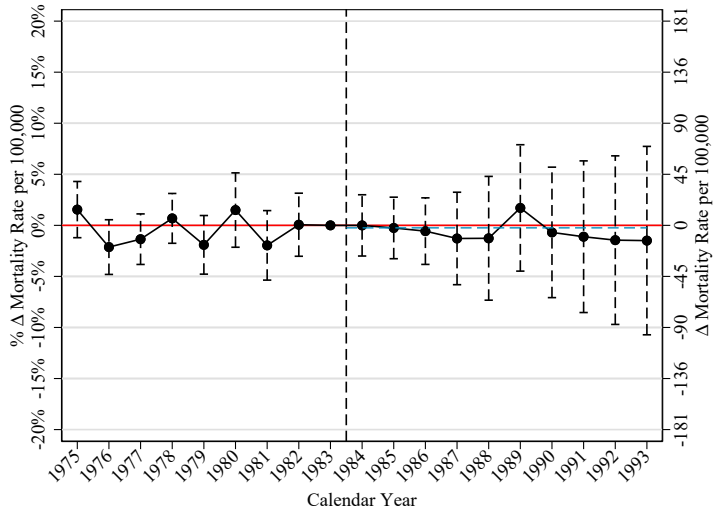


$\hat{\beta}_{Post\,2011}\,(SE) = -7.26\%^{**}\,(2.94\%)$; ADA $= 91,784$
$\hat{\beta}_{Post\,2007}\,(SE) = -5.68\%^{**}\,(2.45\%)$; ADA $= 71,841$

Notes: Mortality data is from the NVSS. The smoking share measures are constructed using 1983 NHIS data and 2005-2006 BRFSS data. Estimates along with 95% confidence intervals are shown. Event study leads and lags should be interpreted as the effect of drug introduction on deviations in the logged mortality rate per 100,000 from the pre-period extrapolated linear trend, evaluated at the mean level of our daily smoking share measure and relative to our base period, the year prior to drug introduction. Logged mortality rates are adjusted using the pre-trend extrapolation procedure from Freyaldenhoven et al. (2019). Regressions are conducted using ordinary least squares, control for unit and year fixed effects, with standard errors clustered at the demographic group level bootstrapped with 1,000 replications. Sample is restricted to ages 30-74 and demographic groups with survey respondents above the 25th percentile average count of survey respondents, yielding 176 groups for our NRT analysis and 540 groups for our e-cigarette analysis. Demographic groups are sex (male/female), 3 race categories for NRT analysis (White, Black, other) and 5 race/ethnicity categories for our e-cigarette analysis (White non-Hispanic, Black non-Hispanic, Native American non-Hispanic, Asian non-Hispanic, Hispanic), census region (Northeast, Midwest, South, West), urban status (urban/rural) for our e-cigarette analysis, and 9 5-year age groups (30-34, ..., 70-74). The mean level of our daily smoking share measure is 33.03% for our NRT analysis and 15.33% for our e-cigarette analysis. The shaded region from 2007-2010 denotes the years following E-cigarette importation to the U.S. in August 2006 but prior to the Washington D.C. Circuit Court's decision in December 2010. Annual deaths averted (ADA) are calculated by multiplying the post-period average percent change in mortality rates by the average mortality rate and the total population in our analytic sample, with positive values indicating reductions in mortality. *** p<0.01, ** p<0.05, * p<0.1

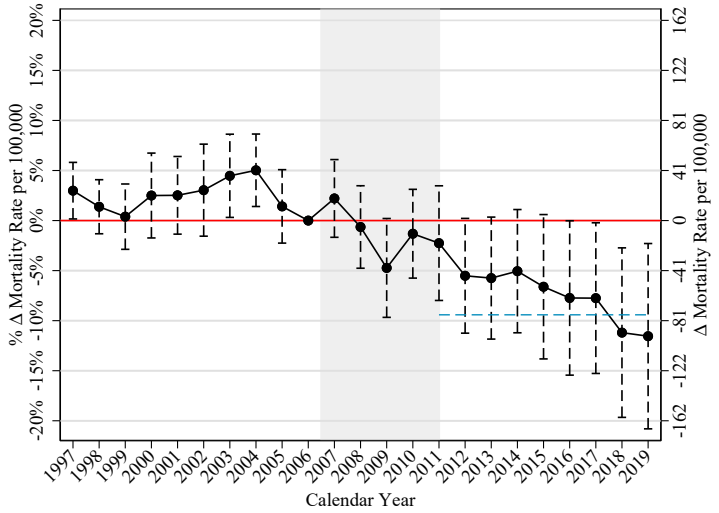
Figure E6: Event Studies for All-Cause Mortality, Additional Fixed Effects

(a) NRT Drug Introduction



$\hat{\beta}_{Post\,1984}\,(SE) = -0.25\%\,(3.05\%)$; ADA $= 2,387$

(b) E-cigarette Drug Exemption



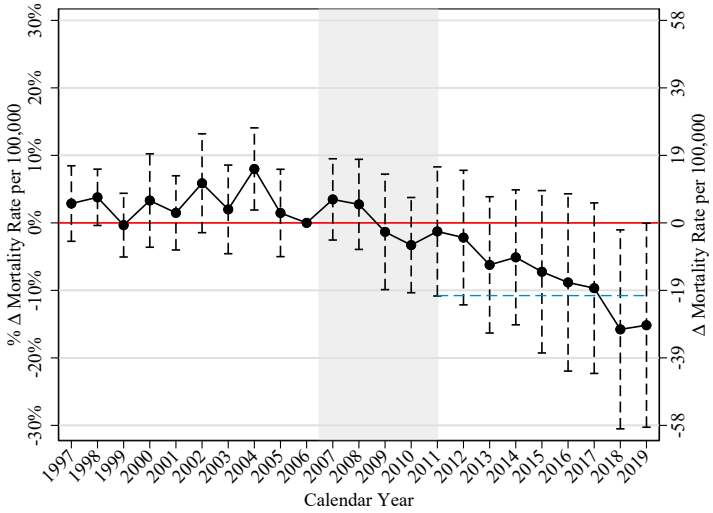
$\hat{\beta}_{Post\,2011}\,(SE) = -9.41\%^{***}\,(3.48\%)$; ADA $= 119,039$
$\hat{\beta}_{Post\,2007}\,(SE) = -7.60\%^{***}\,(2.86\%)$; ADA $= 96,061$

Notes: Mortality data is from the NVSS. The smoking share measures are constructed using 1983 NHIS data and 2005-2006 BRFSS data. Estimates along with 95% confidence intervals are shown. Event study leads and lags should be interpreted as the effect of drug introduction on deviations in the logged mortality rate per 100,000 from the pre-period extrapolated linear trend, evaluated at the mean level of our daily smoking share measure and relative to our base period, the year prior to drug introduction. Logged mortality rates are adjusted using the pre-trend extrapolation procedure from Freyaldenhoven et al. (2019). Regressions are conducted using ordinary least squares, control for unit and year-by-age, sex, race, region, and urban status fixed effects, with standard errors clustered at the demographic group level. Sample is restricted to ages 30-74 and demographic groups with survey respondents above the 25th percentile average count of survey respondents, yielding 200 groups for our NRT analysis and 540 groups for our e-cigarette analysis. Demographic groups are sex (male/female), 3 race categories for NRT analysis (White, Black, other) and 5 race/ethnicity categories for our e-cigarette analysis (White non-Hispanic, Black non-Hispanic, Native American non-Hispanic, Asian non-Hispanic, Hispanic), census region (Northeast, Midwest, South, West), urban status (urban/rural) for our e-cigarette analysis, and 9 5-year age groups (30-34, . . . , 70-74). The mean level of our daily smoking share measure is 33.03% for our NRT analysis and 15.33% for our e-cigarette analysis. The shaded region from 2007-2010 denotes the years following E-cigarette importation to the U.S. in August 2006 but prior to the Washington D.C. Circuit Court's decision in December 2010. Annual deaths averted (ADA) are calculated by multiplying the post-period average percent change in mortality rates by the average mortality rate and the total population in our analytic sample, with positive values indicating reductions in mortality. *** p<0.01, ** p<0.05, * p<0.1

Appendix G Heterogeneity By Age Group

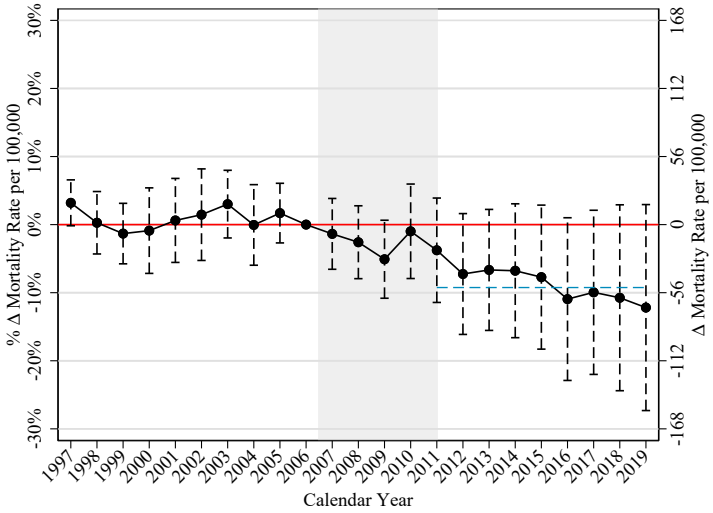
Figure G1: Event Studies for All-Cause Mortality by Age Group

(a) E-cigarette Drug Exemption, Ages 30-44



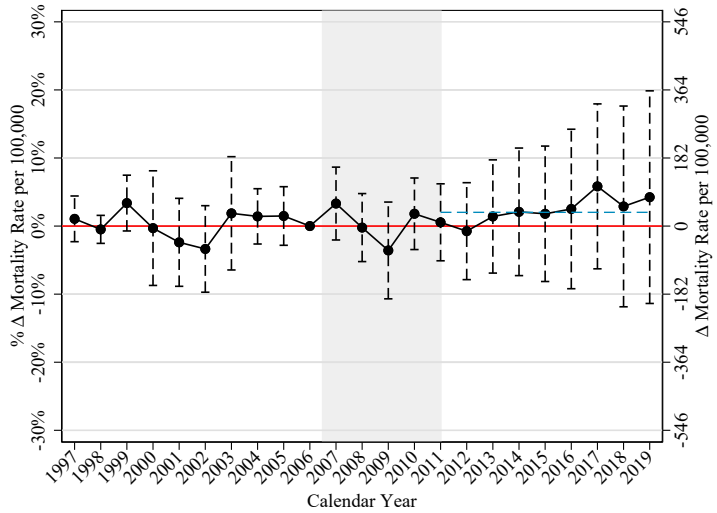
$\hat{\beta}_{Post\,2011}\,(SE) = -10.77\%^{*}\,(5.62\%)$; ADA $= 36,320$
$\hat{\beta}_{Post\,2007}\,(SE) = -8.23\%^{*}\,(4.69\%)$; ADA $= 26,365$

(b) E-cigarette Drug Exemption, Ages 45-59



$\hat{\beta}_{Post\,2011}\,(SE) = -9.24\%^{*}\,(5.68\%)$; ADA $= 88,594$
$\hat{\beta}_{Post\,2007}\,(SE) = -7.42\%^{*}\,(4.61\%)$; ADA $= 67564$

(c) E-cigarette Drug Exemption, Ages 60-74

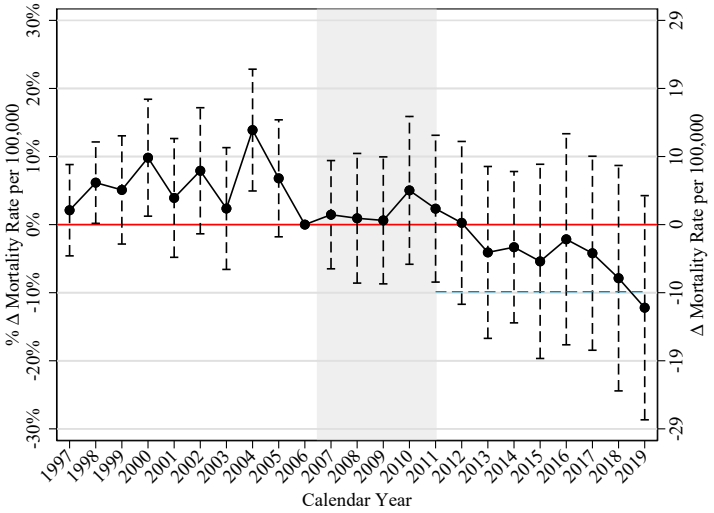


$\hat{\beta}_{Post\,2011}\,(SE) = 2.02\%\,(6.76\%)$; ADA $= -33,130$
$\hat{\beta}_{Post\,2007}\,(SE) = 1.42\%\,(5.54\%)$; ADA $= -22,088$

Notes: Mortality data is from the NVSS. The smoking share measures are constructed using 1983 NHIS data and 2005-2006 BRFSS data. Estimates along with 95% confidence intervals are shown. Event study leads and lags should be interpreted as the effect of drug introduction on deviations in the logged mortality rate per 100,000 from the pre-period extrapolated linear trend, evaluated at the mean level of our daily smoking share measure and relative to our base period, the year prior to drug introduction. Logged mortality rates are adjusted using the pre-trend extrapolation procedure from Freyaldenhoven et al. (2019). Regressions are conducted using ordinary least squares, control for unit and year fixed effects, with standard errors clustered at the demographic group level. Sample is restricted to ages 30-74 and demographic groups with survey respondents above the 25th percentile average count of survey respondents and stratified by 15-year age ranges, yielding 191, 186, and 163 groups for Figures (a)-(c), respectively. Demographic groups are sex (male/female), 3 race categories for NRT analysis (White, Black, other) and 5 race/ethnicity categories for our e-cigarette analysis (White non-Hispanic, Black non-Hispanic, Native American non-Hispanic, Asian non-Hispanic, Hispanic), census region (Northeast, Midwest, South, West), urban status (urban/rural) for our e-cigarette analysis, and 9 5-year age groups (30-34, . . . , 70-74). The mean level of our daily smoking share measure is 15.7%, 18.4%, and 11.4% for Figures (a)-(c), respectively. The shaded region from 2007-2010 denotes the years following E-cigarette importation to the U.S. in August 2006 but prior to the Washington D.C. Circuit Court's decision in December 2010. Annual deaths averted (ADA) are calculated by multiplying the post-period average percent change in mortality rates by the average mortality rate and the total population in our analytic sample, with positive values indicating reductions in mortality. *** $p<0.01$, ** $p<0.05$, * $p<0.1$

Figure E2: Event Studies for Youth, All-Cause Mortality

(a) E-cigarette Drug Exemption, Ages <30



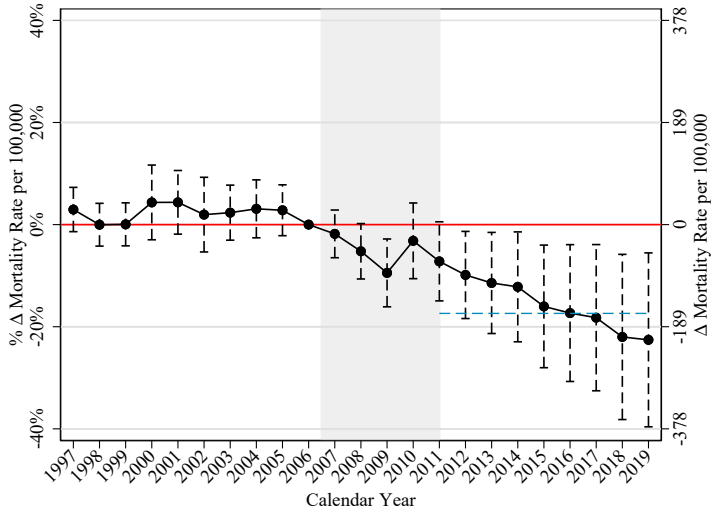
$\hat{\beta}_{Post\,2011}\,(SE) = -9.85\%\,(6.55\%)$; ADA $= 11,548$
$\hat{\beta}_{Post\,2007}\,(SE) = -8.00\%\,(5.59\%)$; ADA $= 9,361$

Notes: Mortality data is from the NVSS. The smoking share measures are constructed using 1983 NHIS data and 2005-2006 BRFSS data. Estimates along with 95% confidence intervals are shown. Event study leads and lags should be interpreted as the effect of drug introduction on deviations in the logged mortality rate per 100,000 from the pre-period extrapolated linear trend, evaluated at the mean level of our daily smoking share measure and relative to our base period, the year prior to drug introduction. Logged mortality rates are adjusted using the pre-trend extrapolation procedure from Freyaldenhoven et al. (2019). Regressions are conducted using ordinary least squares, control for unit and year fixed effects, with standard errors clustered at the demographic group level. Sample is restricted to ages 29 and younger and demographic groups with survey respondents above the 25th percentile average count of survey respondents, yielding 386 groups. Demographic groups are sex (male/female), 5 race/ethnicity categories for our e-cigarette analysis (White non-Hispanic, Black non-Hispanic, Native American non-Hispanic, Asian non-Hispanic, Hispanic), census region (Northeast, Midwest, South, West), urban status (urban/rural), and 6 age groups (0-2, 3-7, 8-12, 13-17, 18-24, 15-29). The mean level of our daily smoking share measure is 18.15%. The shaded region from 2007-2010 denotes the years following E-cigarette importation to the U.S. in August 2006 but prior to the Washington D.C. Circuit Court's decision in December 2010. Annual deaths averted (ADA) are calculated by multiplying the post-period average percent change in mortality rates by the average mortality rate and the total population in our analytic sample, with positive values indicating reductions in mortality. *** p<0.01, ** p<0.05, * p<0.1

Appendix H Heterogeneity By Demographics

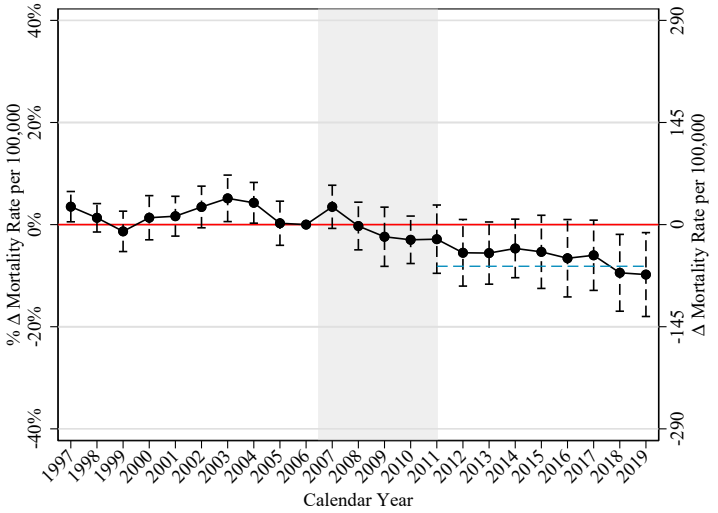
Figure H1: Event Studies for All-Cause Mortality by Urban Status

(a) E-cigarette Drug Exemption, Rural



$\hat{\beta}_{Post\,2011}\,(SE) = -17.39\%^{**}\,(6.77\%)$; ADA $= 60,781$
$\hat{\beta}_{Post\,2007}\,(SE) = -14.23\%^{**}\,(5.57\%)$; ADA $= 46,963$

(b) E-cigarette Drug Exemption, Urban

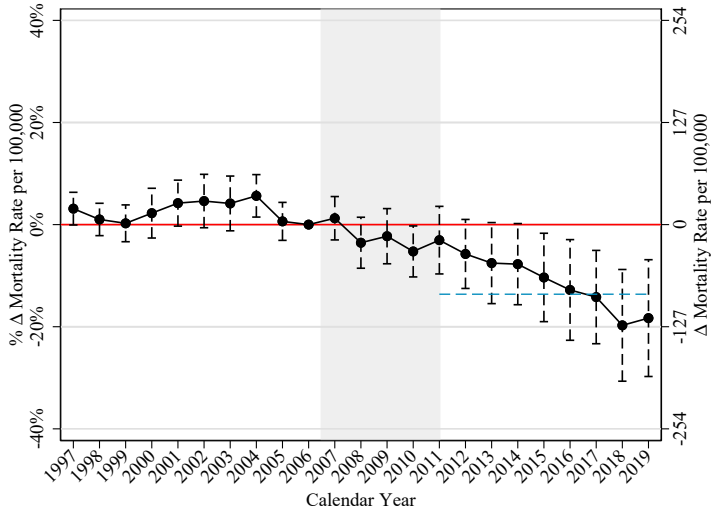


$\hat{\beta}_{Post\,2011}\,(SE) = -8.16\%^{***}\,(2.88\%)$; ADA $= 31,003$
$\hat{\beta}_{Post\,2007}\,(SE) = -6.43\%^{***}\,(2.33\%)$; ADA $= 24,877$

Notes: Mortality data is from the NVSS. The smoking share measures are constructed using 1983 NHIS data and 2005-2006 BRFSS data. Estimates along with 95% confidence intervals are shown. Event study leads and lags should be interpreted as the effect of drug introduction on deviations in the logged mortality rate per 100,000 from the pre-period extrapolated linear trend, evaluated at the mean level of our daily smoking share measure and relative to our base period, the year prior to drug introduction. Logged mortality rates are adjusted using the pre-trend extrapolation procedure from Freyaldenhoven et al. (2019). Regressions are conducted using ordinary least squares, control for unit and year fixed effects, with standard errors clustered at the demographic group level. Sample is restricted to ages 30-74 and demographic groups with survey respondents above the 25th percentile average count of survey respondents and stratified by urban status, yielding 211 and 329 groups for Figures (a)-(b), respectively. Demographic groups are sex (male/female), 5 race/ethnicity categories for our e-cigarette analysis (White non-Hispanic, Black non-Hispanic, Native American non-Hispanic, Asian non-Hispanic, Hispanic), census region (Northeast, Midwest, South, West), urban status (urban/rural), and 9 5-year age groups (30-34, ..., 70-74). The mean level of our daily smoking share measure is 18.5% and 13.3% for Figures (a)-(b), respectively. The shaded region from 2007-2010 denotes the years following E-cigarette importation to the U.S. in August 2006 but prior to the Washington D.C. Circuit Court's decision in December 2010. Annual deaths averted (ADA) are calculated by multiplying the post-period average percent change in mortality rates by the average mortality rate and the total population in our analytic sample, with positive values indicating reductions in mortality. *** p<0.01, ** p<0.05, * p<0.1

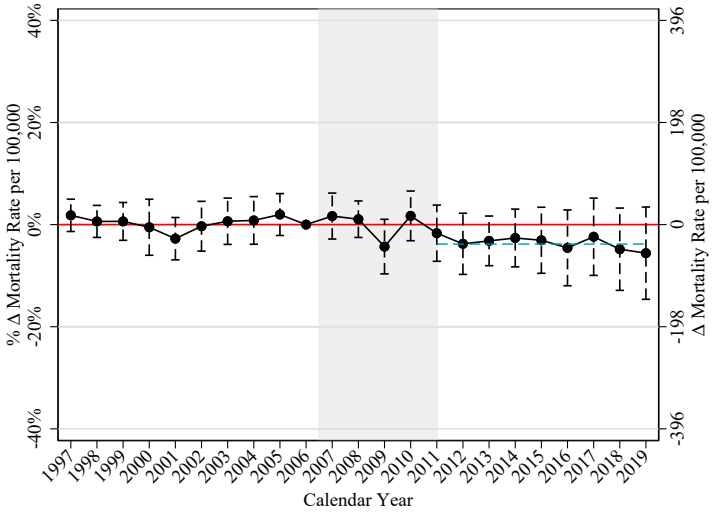
Figure E2: Event Studies for All-Cause Mortality by Sex

(a) E-cigarette Drug Exemption, Female



$\hat{\beta}_{Post\,2011}\,(SE) = -13.63\%^{***}\,(4.29\%)$; ADA $= 64,840$
$\hat{\beta}_{Post\,2007}\,(SE) = -11.00\%^{***}\,(3.50\%)$; ADA $= 52,544$

(b) E-cigarette Drug Exemption, Male

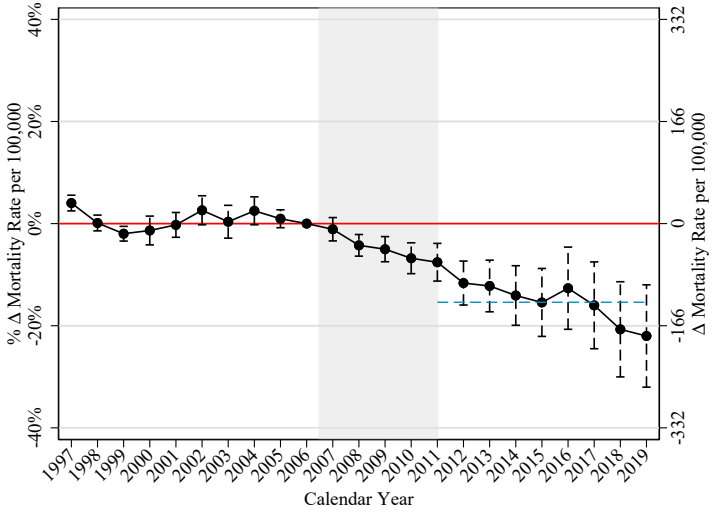


$\hat{\beta}_{Post\,2011}\,(SE) = -3.81\%\,(3.55\%)$; ADA $= 26,944$
$\hat{\beta}_{Post\,2007}\,(SE) = -2.72\%\,(2.94\%)$; ADA $= 19,297$

Notes: Mortality data is from the NVSS. The smoking share measures are constructed using 1983 NHIS data and 2005-2006 BRFSS data. Estimates along with 95% confidence intervals are shown. Event study leads and lags should be interpreted as the effect of drug introduction on deviations in the logged mortality rate per 100,000 from the pre-period extrapolated linear trend, evaluated at the mean level of our daily smoking share measure and relative to our base period, the year prior to drug introduction. Logged mortality rates are adjusted using the pre-trend extrapolation procedure from Freyaldenhoven et al. (2019). Regressions are conducted using ordinary least squares, control for unit and year fixed effects, with standard errors clustered at the demographic group level. Sample is restricted to ages 30-74 and demographic groups with survey respondents above the 25th percentile average count of survey respondents and stratified by sex, yielding 274 and 266 groups for Figures (a)-(b), respectively. Demographic groups are sex (male/female), 5 race/ethnicity categories (White non-Hispanic, Black non-Hispanic, Native American non-Hispanic, Asian non-Hispanic, Hispanic), census region (Northeast, Midwest, South, West), urban status (urban/rural), and 9 5-year age groups (30-34, ..., 70-74). The mean level of our daily smoking share measure is 13.5% and 17.2% for Figures (a)-(b), respectively. The shaded region from 2007-2010 denotes the years following E-cigarette importation to the U.S. in August 2006 but prior to the Washington D.C. Circuit Court's decision in December 2010. Annual deaths averted (ADA) are calculated by multiplying the post-period average percent change in mortality rates by the average mortality rate and the total population in our analytic sample, with positive values indicating reductions in mortality. *** p<0.01, ** p<0.05, * p<0.1

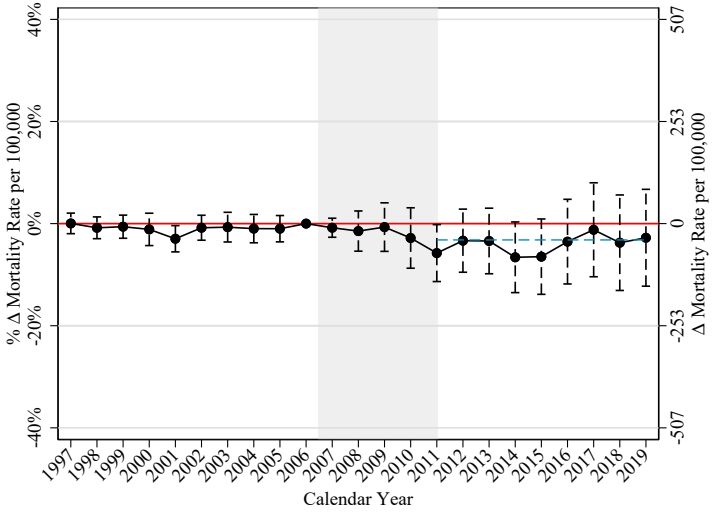
Figure E3: Event Studies for All-Cause Mortality by Race

(a) E-cigarette Drug Exemption, White non-Hispanic



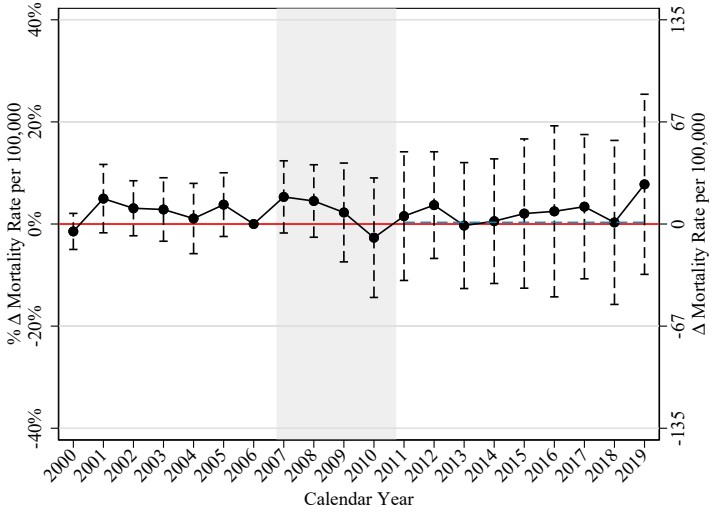
$\hat{\beta}_{Post\,2011}\,(SE) = -15.40\%^{***}\,(3.76\%)$; ADA $= 88,593$
$\hat{\beta}_{Post\,2007}\,(SE) = -12.20\%^{***}\,(2.99\%)$; ADA $= 69,753$

(b) E-cigarette Drug Exemption, Black non-Hispanic



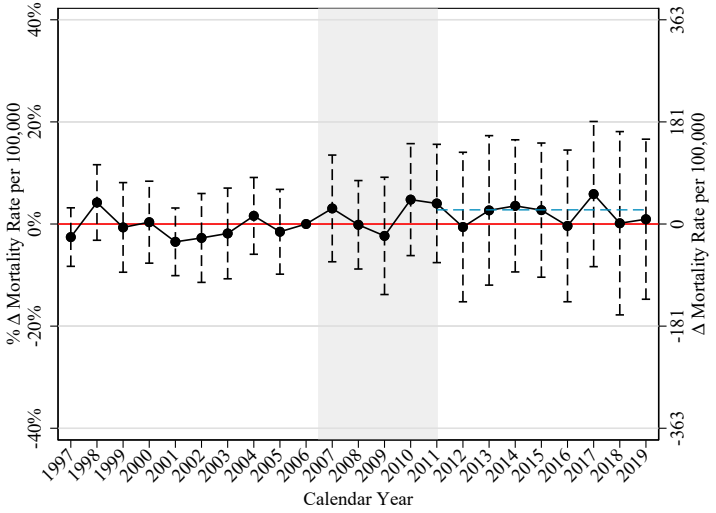
$\hat{\beta}_{Post\,2011}\,(SE) = -3.20\%\,(3.83\%)$; ADA $= 4,522$
$\hat{\beta}_{Post\,2007}\,(SE) = 2.38\%\,(3.16\%)$; ADA $= 3,349$

(c) E-cigarette Drug Exemption, Native American non-Hispanic



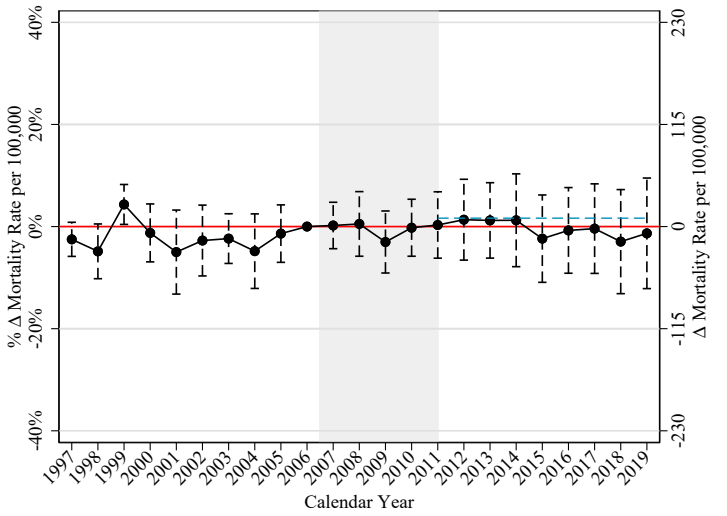
$\hat{\beta}_{Post\,2011}\,(SE) = 0.34\%\,(5.70\%)$; ADA $= -52$
$\hat{\beta}_{Post\,2007}\,(SE) = 0.33\%\,(4.83\%)$; ADA $= -50$

(d) E-cigarette Drug Exemption, Asian non-Hispanic



$\hat{\beta}_{Post\,2011}\,(SE) = 2.77\%\,(6.07\%)$; ADA $= -175$
$\hat{\beta}_{Post\,2007}\,(SE) = 2.54\%\,(5.08\%)$; ADA $= -159$

(e) E-cigarette Drug Exemption, Hispanic



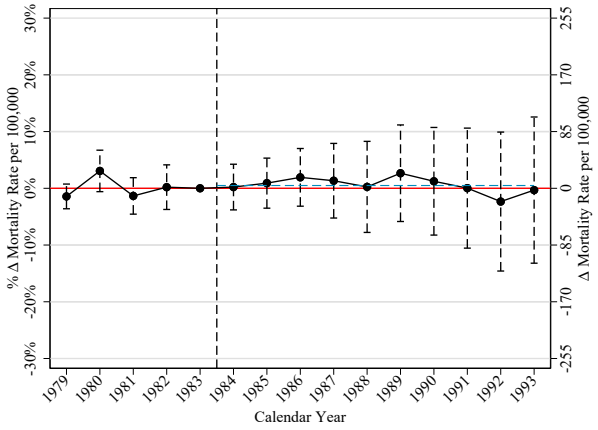
$\hat{\beta}_{Post\,2011}\,(SE) = 1.64\%\,(3.69\%)$; ADA $= -1,104$
$\hat{\beta}_{Post\,2007}\,(SE) = 1.58\%\,(3.12\%)$; ADA $= -1,052$

Notes: Mortality data is from the NVSS. The smoking share measures are constructed using 1983 NHIS data and 2005-2006 BRFSS data. Estimates along with 95% confidence intervals are shown. Event study leads and lags should be interpreted as the effect of drug introduction on deviations in the logged mortality rate per 100,000 from the pre-period extrapolated linear trend, evaluated at the mean level of our daily smoking share measure and relative to our base period, the year prior to drug introduction. Logged mortality rates are adjusted using the pre-trend extrapolation procedure from Freyaldenhoven et al. (2019). Regressions are conducted using ordinary least squares, control for unit and year fixed effects, with standard errors clustered at the demographic group level. Sample is restricted to ages 30-74 and demographic groups with survey respondents above the 25th percentile average count of survey respondents and stratified by race, yielding 144, 90, 74, 111, and 121 groups for Figures (a)-(e), respectively. Demographic groups are sex (male/female), 5 race/ethnicity categories (White non-Hispanic, Black non-Hispanic, Native American non-Hispanic, Asian non-Hispanic, Hispanic), census region (Northeast, Midwest, South, West), urban status (urban/rural), and 9 5-year age groups (30-34, ..., 70-74). The mean level of our daily smoking share measure is 16.0%, 15.0%, 8.0%, 23.6%, and 11.7% for Figures (a)-(e), respectively. The shaded region from 2007-2010 denotes the years following E-cigarette importation to the U.S. in August 2006 but prior to the Washington D.C. Circuit Court's decision in December 2010. Annual deaths averted (ADA) are calculated by multiplying the post-period average percent change in mortality rates by the average mortality rate and the total population in our analytic sample, with positive values indicating reductions in mortality. Figure (c) begins in 2000 due to a change in race/ethnicity coding by NVSS in 2000. *** p<0.01, ** p<0.05, * p<0.1

Appendix I Heterogeneity By Causes of Death

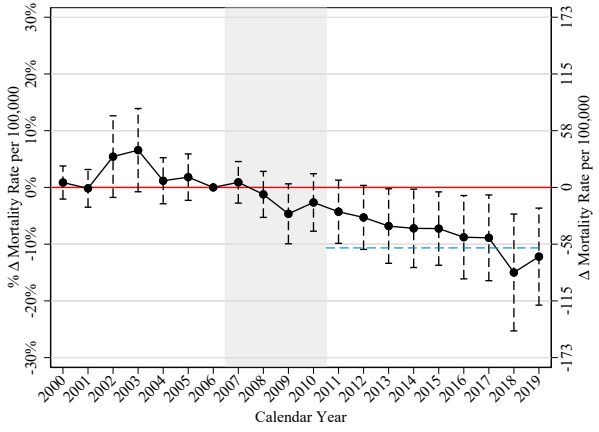
Figure I1: Additional Causes of Death Event Studies

(a) NRT Introduction, SAM



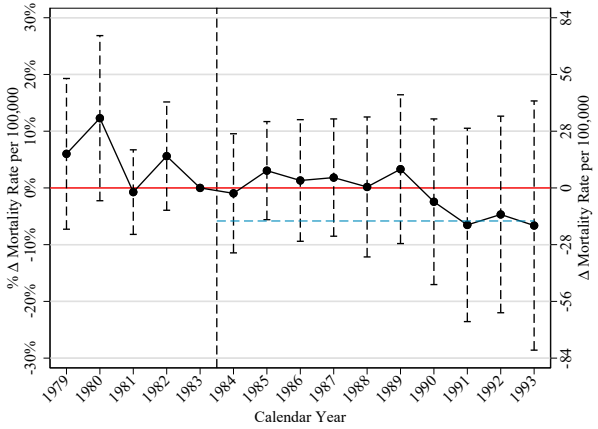
$\hat{\beta}_{Post\,1984}\,(SE) = 0.49\%\,(4.22\%)$; ADA $= -4,514$

(b) E-cigarette Drug Exemption, SAM



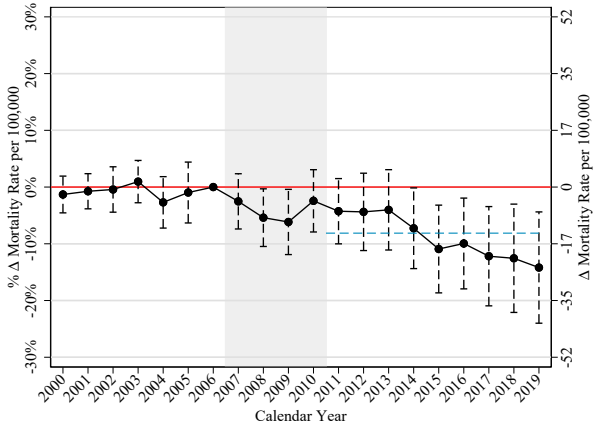
$\hat{\beta}_{Post\,2011}\,(SE) = -10.66\%^{***}\,(3.58\%)$; ADA $= 77,811$
$\hat{\beta}_{Post\,2007}\,(SE) = -8.66\%^{***}\,(3.00\%)$; ADA $= 61,689$

(c) NRT Introduction, Heart



$\hat{\beta}_{Post\,1984}\,(SE) = -5.83\%\,(6.98\%)$; ADA $= 17,456$

(d) E-cigarette Drug Exemption, Heart



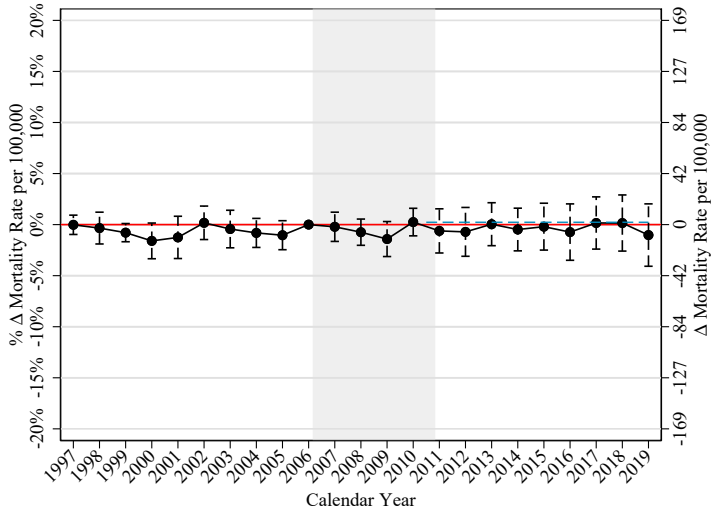
$\hat{\beta}_{Post\,2011}\,(SE) = -8.12\%^{**}\,(3.50\%)$; ADA $= 31,501$
$\hat{\beta}_{Post\,2007}\,(SE) = -6.69\%^{**}\,(2.93\%)$; ADA $= 25,285$

Notes: Mortality data is from the NVSS. The smoking share measures are constructed using 1983 NHIS data and 2005-2006 BRFSS data. Estimates along with 95% confidence intervals are shown. Event study leads and lags should be interpreted as the effect of drug introduction on deviations in the logged mortality rate per 100,000 from the pre-period extrapolated linear trend, evaluated at the mean level of our daily smoking share measure and relative to our base period, the year prior to drug introduction. Logged mortality rates are adjusted using the pre-trend extrapolation procedure from Freyaldenhoven et al. (2019). Regressions are conducted using ordinary least squares, control for unit and year fixed effects, with standard errors clustered at the demographic group level. Sample is restricted to ages 30-74 and demographic groups with survey respondents above the 25th percentile average count of survey respondents, yielding 200 groups for our NRT analysis and 540 groups for our e-cigarette analysis. Demographic groups are sex (male/female), 3 race categories for NRT analysis (White, Black, other) and 5 race/ethnicity categories for our e-cigarette analysis (White non-Hispanic, Black non-Hispanic, Native American non-Hispanic, Asian non-Hispanic, Hispanic), census region (Northeast, Midwest, South, West), urban status (urban/rural) for our e-cigarette analysis, and 9 5-year age groups (30-34, . . . , 70-74). The mean level of our daily smoking share measure is 33.03% for our NRT analysis and 15.33% for our e-cigarette analysis. The shaded region from 2007-2010 denotes the years following E-cigarette importation to the U.S. in August 2006 but prior to the Washington D.C. Circuit Court's decision in December 2010. Annual deaths averted (ADA) are calculated by multiplying the post-period average percent change in mortality rates by the average mortality rate and the total population in our analytic sample, with positive values indicating reductions in mortality. *** $p<0.01$, ** $p<0.05$, * $p<0.1$

Appendix J Alternative Vaping Share Measure

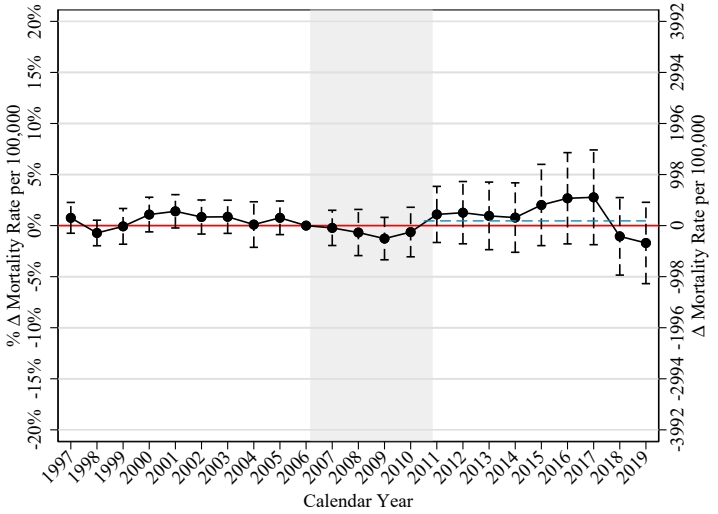
Figure J1: Event Studies Using E-cigarette Using Daily Vaping Share Measure

(a) All-Cause Mortality



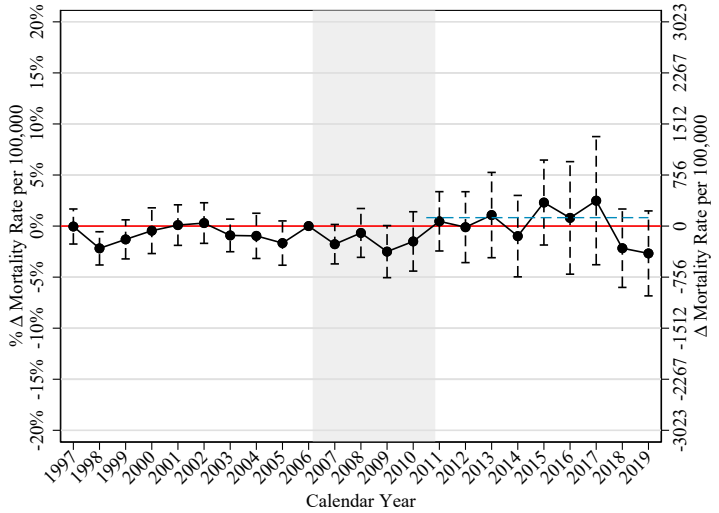
$\hat{\beta}_{Post\,2011}\,(SE) = 0.23\%\,(1.23\%)$; ADA $= -2,951$
$\hat{\beta}_{Post\,2007}\,(SE) = 0.18\%\,(1.01\%)$; ADA $= -2,358$

(b) Current Smoking Rate (BRFSS)



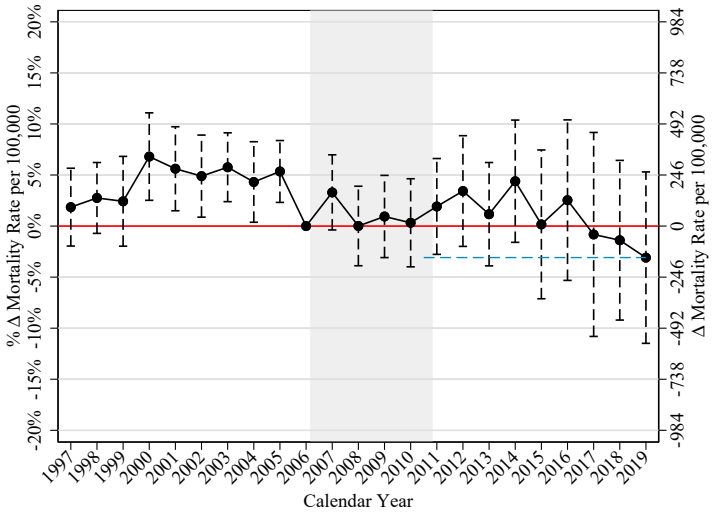
$\hat{\beta}_{Post\,2011}\,(SE) = 0.46\%\,(1.59\%)$; FACSY $= -138,676$
$\hat{\beta}_{Post\,2007}\,(SE) = -0.05\%\,(1.33\%)$; FACSY $= 16,368$

(c) Daily Smoking Rate (BRFSS)



$\hat{\beta}_{Post\,2011}\,(SE) = 0.83\%\,(1.82\%)$; FADSY $= -188,037$
$\hat{\beta}_{Post\,2007}\,(SE) = 0.29\%\,(1.51\%)$; FADSY $= -66,243$

(d) Light Smoking Rate (BRFSS)



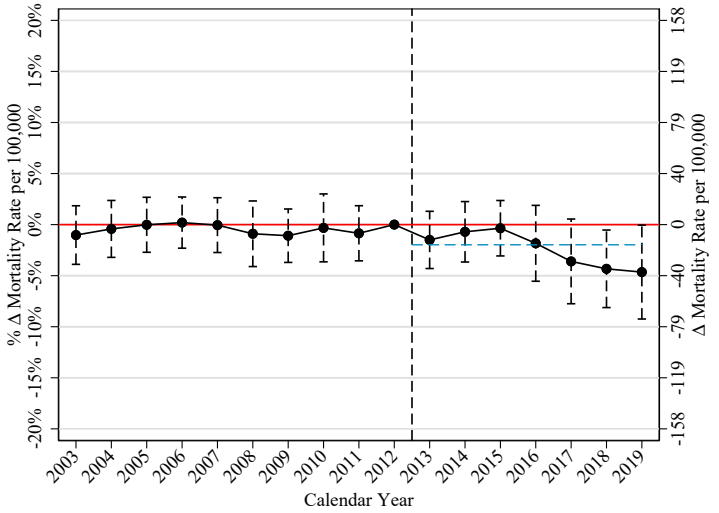
$\hat{\beta}_{Post\,2011}\,(SE) = -3.08\%\,(2.86\%)$; FALSY $= 227,927$
$\hat{\beta}_{Post\,2007}\,(SE) = -3.01\%\,(2.40\%)$; FALSY $= 222,545$

Notes: Mortality data is from the NVSS. The daily vaping share measure is constructed 2016-2018 BRFSS data. Estimates along with 95% confidence intervals are shown. Event study leads and lags should be interpreted as the effect of drug introduction on deviations in the logged mortality rate per 100,000 from the pre-period extrapolated linear trend, evaluated at the mean level of our daily vaping share measure and relative to our base period, the year prior to drug introduction. Logged mortality rates are adjusted using the pre-trend extrapolation procedure from Freyaldenhoven et al. (2019). Regressions are conducted using ordinary least squares, control for unit and year fixed effects, with standard errors clustered at the demographic group level. Figures (b)-(d) are weighted using BRFSS survey weights. Sample is restricted to ages 30-74 and demographic groups with survey respondents above the 25th percentile average count of survey respondents, yielding 452 groups for Figures (a)-(d). Demographic groups are sex (male/female), 5 race/ethnicity categories (White non-Hispanic, Black non-Hispanic, Native American non-Hispanic, Asian non-Hispanic, Hispanic), census region (Northeast, Midwest, South, West), urban status (urban/rural), and 9 5-year age groups (30-34, ..., 70-74). The mean level of our daily vaping share measure is 1.08%. The shaded region from 2007-2010 denotes the years following E-cigarette importation to the U.S. in August 2006 but prior to the Washington D.C. Circuit Court's decision in December 2010. Annual deaths averted (ADA) are calculated by multiplying the post-period average percent change in mortality rates by the average mortality rate and the total population in our analytic sample, with positive values indicating reductions in mortality. Fewer annual 'current smoker-years' (FACSY) and fewer annual 'daily smoker-years' (FADSY) are calculated by multiplying the post-period average percent change in the outcome by the average outcome and the total population in our analytic sample. *** $p<0.01$, ** $p<0.05$, * $p<0.1$

Appendix K Alternative Introduction Dates

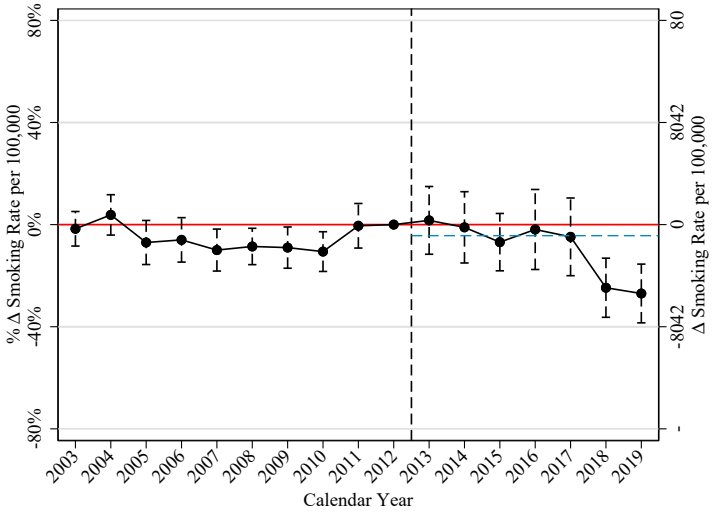
Figure K1: Event Studies for 2013 Alternative Introduction Date

(a) All-Cause Mortality



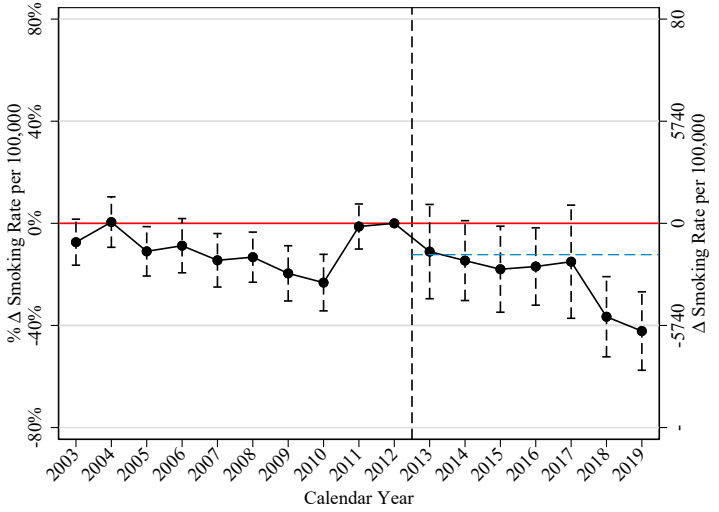
$\hat{\beta}_{Post\,2013}\,(SE) = -2.00\%\,(1.30\%)$; ADA $= 24,412$

(b) Current Smoking Rate (BRFSS)



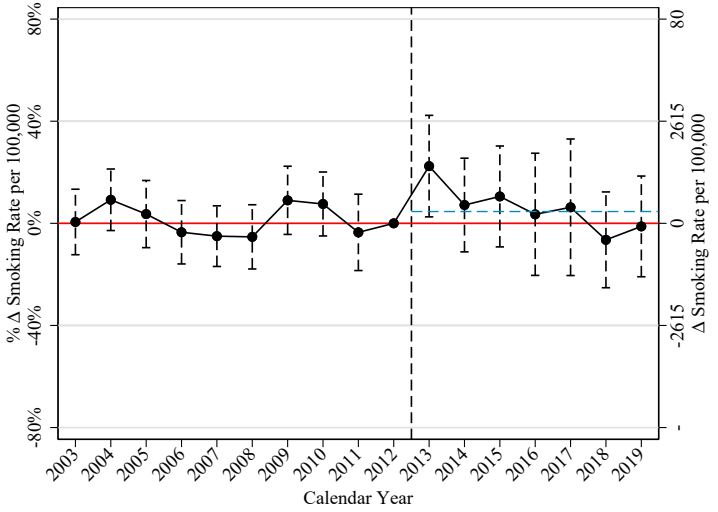
$\hat{\beta}_{Post\,2013}\,(SE) = -4.33\%\,(3.85\%)$; FACSY $= 1.5m$

(c) Daily Smoking Rate (BRFSS)



$\hat{\beta}_{Post\,2013}\,(SE) = -12.26\%^{**}\,(4.98\%)$; FADSY $= 2.9m$

(d) Light Smoking Rate (BRFSS)

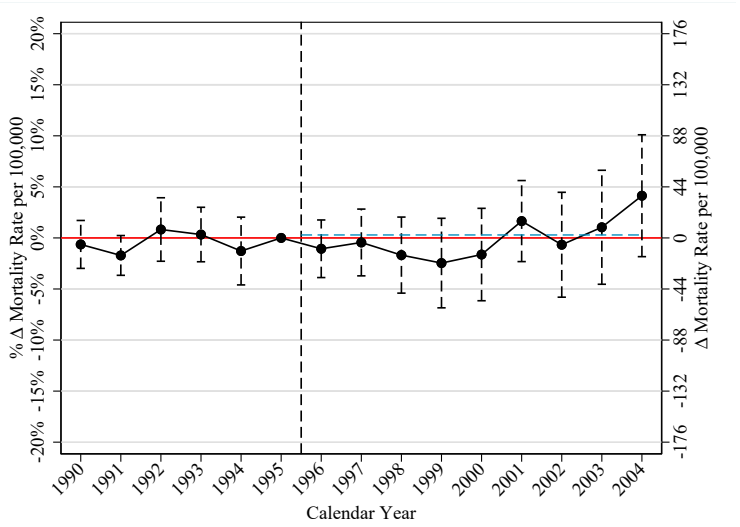


$\hat{\beta}_{Post\,2013}\,(SE) = 4.62\%\,(7.05\%)$; FALSY $= -0.5m$

Notes: Mortality data is from the NVSS. Smoking outcomes are from BRFSS. The smoking share measure is constructed using 2011-2012 BRFSS data. Estimates along with 95% confidence intervals are shown. Event study leads and lags should be interpreted as the effect of drug introduction on deviations in the logged mortality rate per 100,000 from the pre-period extrapolated linear trend, evaluated at the mean level of our daily smoking share measure and relative to our base period, the year prior to drug introduction. Logged mortality rates are adjusted using the pre-trend extrapolation procedure from Freyaldenhoven et al. (2019). Regressions are weighted by BRFSS survey weights, conducted using ordinary least squares, control for unit and year fixed effects, with standard errors clustered at the demographic group level. Sample is restricted to ages 30-74 and demographic groups with survey respondents above the 25th percentile average count of survey respondents, yielding 430 groups for Figure (a) and 549 groups for Figures (b)-(d). Demographic groups are sex (male/female), 5 race/ethnicity categories for our e-cigarette analysis (White non-Hispanic, Black non-Hispanic, Native American non-Hispanic, Asian non-Hispanic, Hispanic), census region (Northeast, Midwest, South, West), urban status (urban/rural), and 9 5-year age groups (30-34, . . . , 70-74). The mean level of our daily smoking share measure is 12.1% for Figure (a) and 14.6% for Figures (b)-(d). Annual deaths averted (ADA) are calculated by multiplying the post-period average percent change in mortality rates by the average mortality rate and the total population in our analytic sample, with positive values indicating reductions in mortality. Fewer annual 'current smoker-years' (FACSY), fewer annual 'daily smoker-years' (FADSY), and fewer annual 'light smoker-years' (FALSY) are calculated by multiplying the post-period average percent change in the outcome by the average outcome and the total population in our analytic sample. *** $p<0.01$, ** $p<0.05$, * $p<0.1$

Figure E2: Event Studies for All-Cause Mortality, 1996 OTC NRT Introduction Date

(a) 1996 OTC NRT Introduction

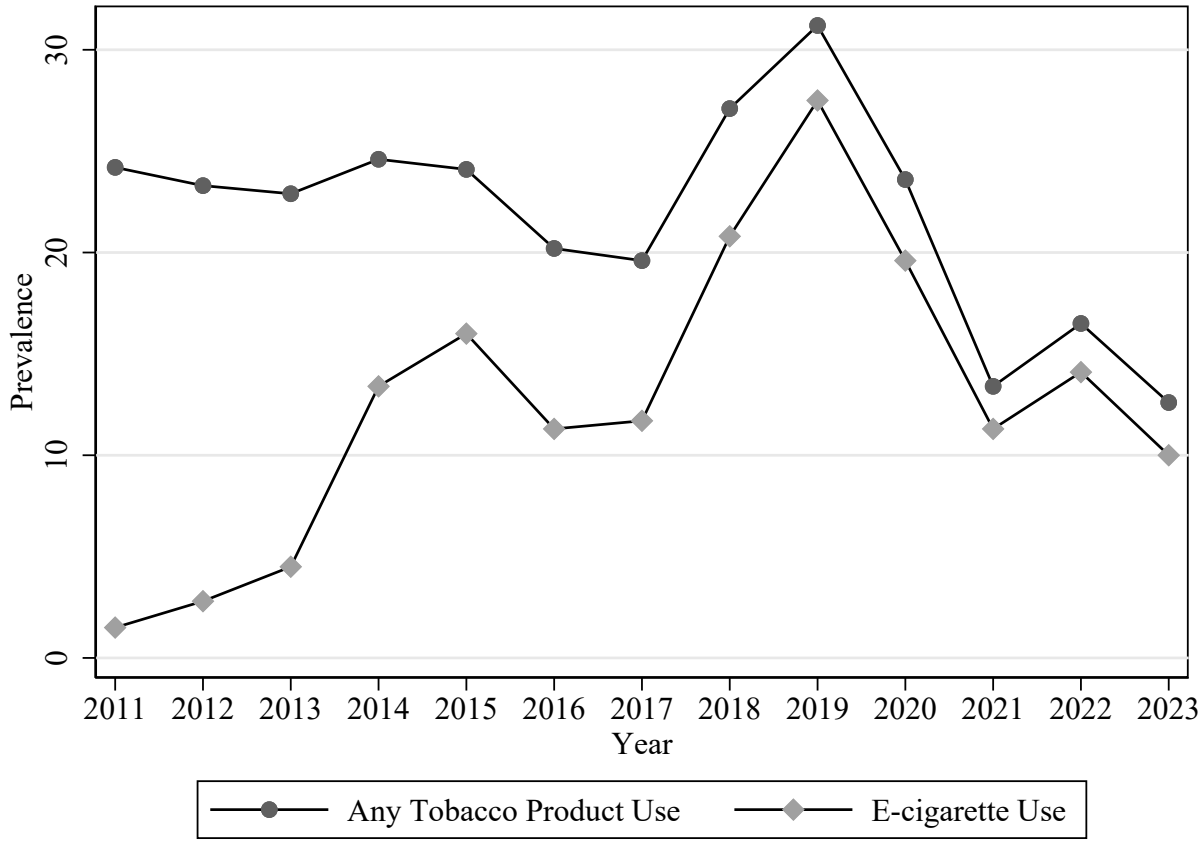


$\hat{\beta}_{Post\,1996}\,(SE) = 0.29\%\,(1.91\%)$; ADA $= -3,418$

Notes: Mortality data is from the NVSS. The smoking share measure is constructed using 1994-1995 BRFSS data. Estimates along with 95% confidence intervals are shown. Event study leads and lags should be interpreted as the effect of drug introduction on deviations in the logged mortality rate per 100,000 from the pre-period extrapolated linear trend, evaluated at the mean level of our daily smoking share measure and relative to our base period, the year prior to drug introduction. Logged mortality rates are adjusted using the pre-trend extrapolation procedure from Freyaldenhoven et al. (2019). Regressions are conducted using ordinary least squares, control for unit and year fixed effects, with standard errors clustered at the demographic group level. Sample is restricted to ages 30-74 and demographic groups with survey respondents above the 25th percentile average count of survey respondents, yielding 430 groups. Demographic groups are sex (male/female), 5 race/ethnicity categories for our e-cigarette analysis (White non-Hispanic, Black non-Hispanic, Native American non-Hispanic, Asian non-Hispanic, Hispanic), census region (Northeast, Midwest, South, West), urban status (urban/rural), and 9 5-year age groups (30-34, ..., 70-74). The mean level of our daily smoking share measure is 12.1%. Annual deaths averted (ADA) are calculated by multiplying the post-period average percent change in mortality rates by the average mortality rate and the total population in our analytic sample, with positive values indicating reductions in mortality. *** p<0.01, ** p<0.05, * p<0.1

Appendix L Youth Trends in Nicotine Consumption

Figure L1: Trends in High School Student Current (Past 30-Day) Tobacco Product Use



Notes: Data from the National Youth Tobacco Survey, as described in a variety of reports (Gentzke, 2019, 2020, 2022; Park-Lee, 2022; Birdsey, 2023).

Appendix References

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Freyaldenhoven, S., Hansen, C., and Shapiro, J. M. (2019). Pre-event trends in the panel event-study design. *American Economic Review*, 109(9):3307–38.

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