Public Health Implications of Vaping in The US: The Smoking and Vaping Simulation Model

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Abstract

**Background:** Nicotine vaping products (NVPs) are increasingly popular worldwide. They may provide public health benefits if used as a substitute for smoking, but may create public health harms if used as a gateway to smoking or to discourage smoking cessation. This paper presents the Smoking and Vaping Model (SAVM), a user-friendly model which estimates the public health implications of NVPs in the US.

**Methods:** SAVM adopts a cohort-approach. We derive public health implications by comparing smoking- and NVP-attributable deaths and life-year lost under a No-NVP and an NVP Scenario. The No-NVP Scenario projects current, former and never smoking rates via smoking initiation and cessation rates, with their respective mortality rates. The NVP Scenario allows for smoking- and NVP-specific mortality rates, switching from cigarette to NVP use, separate NVP and smoking initiation rates, and separate NVP and smoking cessation rates. After validating the model against recent US survey data, we present the base model with extensive sensitivity analyses.

**Results:** The SAVM projects that under current patterns of US NVP use and substitution, NVP use will translate into 1.8 million premature smoking- and vaping-attributable deaths avoided and 38.9 million life-years gained between 2013 and 2060. When the NVP relative risk is set to 5%, the results are sensitive to the level of switching and smoking cessation rates and to a lesser extent smoking initiation rates. When the NVP relative risk is raised to 40%, the public health gains in terms of averted deaths and LYL are reduced by 42% in the base case, and the results become much more sensitive to variations in the base case parameters.

**Discussion:** Policymakers, researchers and other public health stakeholders can apply the SAVM to estimate the potential public health impact of NVPs in their country or region using their own data sources. In developing new simulation models involving NVPs, it will be important to conduct extensive sensitivity analysis and continually update and validate with new data.

**Conclusion:** The SAVM indicates potential benefits of NVP use. However, given the uncertainty surrounding model parameters, extensive sensitivity analysis becomes particularly important.

Background

Smoking prevalence has markedly declined in the US over the past 50 years (Holford et al. 2014b, U.S. Department of Health and Human Services 2014). During that time, cigarette taxes were substantially increased, and smoke-free air policies, media campaigns, youth access policies and smoking cessation treatments were implemented (U.S. Department of Health and Human Services 2014). These policies have been shown to be effective (Levy et al. 2018b), and can explain much of the reduction in smoking prevalence (Holford et al. 2014b, Levy et al. 2016, U.S. Department of Health and Human Services 2014, Warner 2014, Warner et al. 2014). Despite this progress, the harms from cigarette smoking remain unacceptably high (U.S. Department of Health and Human Services 2014). More than 480,000 Americans die each year due to smoking, and two-thirds of long-term smokers die prematurely of a smoking-
attributable disease (Carter et al. 2015, Jha et al. 2013, Thun, Lopez and Hartge 2013). To drastically reduce the harms of smoking on population health, innovative approaches are needed.

The rising use of nicotine vaping products (NVPs), also known as e-cigarettes or electronic nicotine delivery systems (ENDS), has been a source of both promise and controversy (Levy et al. 2017). NVPs, especially later generation models, have been shown to more efficiently deliver nicotine (DeVito and Krishnan-Sarin 2018, Farsalinos et al. 2014, Glasser et al. 2016, Wagener et al. 2016, Yingst et al. 2019) and have sensorimotor effects and throat irritation similar to smoking (Etter 2016, Goldenson et al. 2016, Hajek et al. 2018, Voos et al. 2019), thus potentially serving as a substitute for cigarettes. NVPs are increasingly being used by smokers to quit (Caraballo et al. 2017, Filippidis et al. 2017, Giovenco and Delnevo 2018), and recent studies indicate their effectiveness (Bullen et al. 2013, Hajek et al. 2019, Levy et al. 2018c, Zhu et al. 2017). If smokers switch entirely to NVPs, the health benefits could be substantial since NVPs deliver only a fraction of the toxicants delivered by smoking (Goniewicz et al. 2014, Goniewicz et al. 2017, Hecht et al. 2014, Ratajczak et al. 2018, Royal College of Physicians 2016, Shahab et al. 2017a, Shahab et al. 2017b). However, there is also concern about increased use of these products by youth (Cullen et al. 2019) and their potential to increase youth cigarette smoking (Soneji et al. 2017, Watkins, Glantz and Chaffee 2018), inhibit smoking cessation (Miller, Smith and Goniewicz 2020, National Academy of Sciences 2018), and promote relapse (Azagba et al. 2020, Dai and Leventhal 2019).

The US Food and Drug Administration has the authority to regulate NVPs (Federal Register 2014) and must now consider “the risks and benefits of the tobacco product to the population as a whole” (U.S. Food and Drug Administration 2020). In their review of NVPs, the agency evaluates the toxicity of the product and its effect on the uptake and cessation of existing tobacco products from a public health perspective. The impact of NVP use (“vaping”) on population health will depend on its use in relation to cigarette use (“smoking”) (Levy et al. 2017). As a reduced risk alternative, vaping would improve public health when used by those who would have otherwise initiated smoking or by those who would not have otherwise quit smoking. Vaping would worsen public health when used by those who would not have otherwise initiated NVPs or smoking (i.e., as a gateway to smoking) or if used by those who would have otherwise quit smoking. The ability to accurately predict these impacts will depend on the ability to incorporate transitions between NVPs and smoking, but knowledge of the relevant transitions is often lacking.

While many models have been developed that incorporate NVPs (Bachand, Sulsky and Curtin 2018, Cherng et al. 2016, Cobb et al. 2015, Hill and Camacho 2017, Kalkhoran and Glantz 2015, Mendez and Warner 2020, Poland and Teischinger 2017, Soneji et al. 2018, Warner and Mendez 2019, Weitkunat et al. 2015), these models are often geared towards specific applications, lack the flexibility to be easily applied to other settings, require substantial efforts to understand, require data that is not generally available and have not been validated against real-world data. Because NVP model parameters are subject to considerable uncertainty, it is also important that sensitivity analysis can be easily conducted.

We present the Smoking and Vaping Model (SAVM), which aims to bridge these gaps. This user-friendly model is based on an earlier model (Levy et al. 2018a), but provides greater flexibility by incorporating a
wider range of initiation, cessation and switching parameters and can easily be adapted to other
countries, states, or local areas. The SAVM differs from previous work in four ways. First, the SAVM
adopts a cohort-based approach, thereby incorporating any dependence of NVP use patterns on the
availability of NVPs and current policies in effect at a particular age and year (e.g., adolescents who
initiated e-cigarette use prior to 2013 had less exposure to NVPs than adolescents who initiated after
2013). Second, the model has a simplified structure and is available in Excel, making it transparent and
more easily adapted and applied. Third, the model is validated against recent national survey data.
Finally, the model is developed to conduct comprehensive sensitivity analyses of the NVP parameters.
This study presents the model and demonstrates its application to the US.

Methods

The public health impact of NVP use among smokers and non-smokers is estimated by comparing two
scenarios: a) the No-NVP Scenario which projects future cigarette use and associated mortality outcomes
for each birth cohort in the absence of NVPs, and b) the NVP Scenario which incorporates NVP use
patterns into each cohort’s cigarette use trajectory. To simplify the model and ensure that health
outcomes reflect regular (i.e. stable) use patterns over time (Jha et al. 2013), we focus on the regular
(rather than experimental) use of NVPs and cigarettes and the transitions between those uses.

The No-NVP Scenario

The SAVM begins with separate cohorts of males and females by individual age. Within each cohort, the
population evolves with age. The No-NVP Scenario projects the prevalence of current and former smokers
over time using age- and gender-specific initiation and cessation rates for each cohort that were
previously developed using an age-period-cohort statistical smoking model (Holford et al. 2014a, Holford,
Levy and Meza 2016, Jeon et al. 2018, Tam et al. 2018). The initiation and cessation rates are projected
forward based on data from the US National Health Interview Survey (NHIS) through the year 2013,
before NVPs were in more widespread use (Levy et al. 2019c) and thus reflects smoking patterns in the
absence of NVPs. The transitions are shown in Figure 1.a.

Individuals are born as never users, which in the context of the No-NVP model is just never smokers. For a
given cohort, never users at age a and year t includes surviving never users in the previous year (age a-1,
year t-1) who did not initiate smoking, where surviving never users are modeled as never users at age a-1
in year t-1 multiplied by (1- mortality rate of never users_{a-1,t-1}). Smoking initiation among never users can
occur through age 40, and reflects the transition to becoming an established current smoker, defined as
having smoked at least 100 cigarettes during one’s lifetime and currently smoking every day or some
days. Smokers at age a and year t include surviving never users at age a-1 and year t-1 who initiated
smoking and surviving smokers (using current smoker mortality rates) who did not quit since the previous
year (age a-1, year t-1). Smoking cessation among current smokers reflects the permanent transition to
becoming a former smoker and requires that the smoker quit at least two year; this avoids the need to
model relapse and reflects the underlying inputs used for this and other tobacco models (Holford et al.
2014b, Holford, Levy and Meza 2016, Tam et al. 2018). Former smokers include surviving former smokers (based on age- and former smoker-specific mortality rates) and surviving smokers who quit smoking for at least two years.

**The NVP Scenario**

Starting from the same initial current, former and never smoking prevalence as in the No-NVP Scenario, the NVP Scenario is expanded to include current and former NVP use. The transitions are shown in Figure 1.b.

Because SAVM focuses on measures of regular use, the NVP Scenario does not explicitly model individual youth transitions directly from short-term vaping to regular smoking. Any such transitions are however incorporated indirectly through a smoking initiation multiplier reflecting the net effect of vaping on smoking initiation rates. Similarly, the NVP Scenario does not explicitly model short-term NVP use leading to quitting both cigarettes and NVPs, but is indirectly incorporated through a smoking cessation multiplier reflecting the net effect of vaping on smoking cessation rates. In addition, the NVP Scenario does not distinguish dual cigarette and NVP users from exclusive smokers, because dual users have generally been found to either remain dual users or soon transition to either exclusive cigarette or exclusive NVP use (Azagba, Shan and Latham 2019, Borland et al. 2019, Coleman et al. 2018, Robertson et al. 2019, Stanton et al. 2020, Taylor et al. 2020) and the health risks of dual users are similar to those of exclusive smokers (Goniewicz et al. 2017, Shahab et al. 2017a, Shahab et al. 2017b). However, transitions from dual use to exclusive NVP use or neither cigarette nor NVP use are reflected in the switching and smoking cessation parameters.

Never users include surviving never users from the previous age and year who do not initiate into regular smoking or NVP use. The model directly relates the NVP Scenario to the No-NVP Scenario through separate linear multipliers applied to the smoking initiation rate in the No-NVP Scenario. Using a linear multiplier assures that NVP and smoking initiation follows the same age patterns for smoking initiation as in the No-NVP case, e.g., smoking initiation mostly occurs before age 21 and is minimal after age 30. NVP initiation is similarly tied to smoking initiation in the No-NVP Scenario, whereby a multiplier value less than (or greater than) 100% implies that NVP initiation rates are less than (or greater than) smoking initiation rates in the No-NVP Scenario.

In the NVP Scenario, smokers become former smokers in one of two ways: 1) they may switch to regular exclusive NVP use, or 2) they may quit both regular smoking and regular NVP use (e.g., dual users would quit both) and thereby become former smokers. In the latter case, the smoker may temporarily use NVPs but quit both smoking and vaping. The overall reduction in smokers in the NVP Scenario is the reduction in smokers from switching and complete cessation, and this sum may be less (e.g. harm reduction) or more (harm increasing ) than the number of smokers in the No-NVP Scenario. Smokers age a in year t include surviving smokers at age a-1 and year t-1 who did not switch to exclusive vaping and who did not quit smoking, and surviving never users at age a-1 and year t-1 who initiated smoking.
Similar to the initiation process, smoking and vaping cessation are modelled as separate linear multipliers of smoking cessation in the No-NVP Scenario, so that smoking cessation follows the same age pattern in the No-NVP Scenario and tends to increase with age. Since studies to date do not indicate different age patterns, the smoking and vaping initiation and cessation multipliers are simply modeled as independent of age. In addition, these multipliers are assumed to remain constant over time, so that smoking and vaping initiation and cessation in the NVP Scenario follow the same temporal patterns as in the No-NVP Scenario.

Former smokers who either switch to or quit smoking before age 35 are distinguished from those who quit or switch at age 35 or above. Those who quit smoking (by switching to NVPs or cessation) before age 35 are classified the same as never smokers who vape rather than as former smokers, because mortality risks of smoking are minimal when quitting before age 35 (Jha et al. 2013). Those who quit at age 35 or above maintain the former smoker status and its resulting mortality risks. Thus former smokers include surviving former smokers, surviving smokers (age $\geq 35$) who quit smoking and do not vape, surviving smokers who switched to vaping (age $\geq 35$) and surviving former smokers who at one point regularly vaped but quit vaping.

Exclusive NVP users include surviving never users who initiate vaping, surviving vapers who do not quit, and those switching to vaping from surviving current smokers before age 35. Similar to smokers, those who quit smoking before age 35 are treated the same as never smokers who vape rather than former smokers. Since former smokers using NVPs may quit vaping, former smokers using NVPs includes surviving former smokers using NVPs who do not quit vaping and smokers who switch to vaping (after age 35).

A detailed discussion of the parameters and equations used in both scenarios can be found in the Supplement 1.

**Public Health Outcomes**

The SAVM considers two public health outcomes: 1) Smoking- and vaping-attributable deaths, and 2) smoking- and vaping-attributable life-years lost (LYLs). Both are based on the excess risks of smoking or vaping and the number of current and former smokers and vapers.

In the No-NVP Scenario, smoking-attributable deaths (SADs) by age and gender for current smokers are calculated by applying the excess risks of current smokers relative to never smokers (current smoker mortality rate $a,t - never smoker mortality rate a,t$) to the smoking population and for former smokers are calculated by applying the excess risks of former smokers relative to never smokers (former smoker mortality rate $a,t - never smoker mortality rate a,t$) to the former smoker population. SADs for current and former smokers are summed over all ages in a particular year to obtain total SADs in that year. LYLs are estimated as the number of premature deaths multiplied by the remaining life expectancy of a never smoker at age $a$ in year $t$. The sum over all ages in a particular year obtains the LYLs in that year.
In the NVP Scenario, current and former smoker SADs are calculated in the same manner in the No-NVP Scenario as above except using their respective current and former smoker population sizes from the NVP scenario. For current and former exclusive NVP users, attributable deaths are a product of the number of NVP users and the excess risks of smoking adjusted by NVP relative risk, denoted by Risk\textsubscript{NVP}, i.e., Risk\textsubscript{NVP}(current smoker mortality rate\textsubscript{a,t} – never smoker mortality rate\textsubscript{a,t}) for current users and Risk\textsubscript{NVP}(former smoker mortality rate\textsubscript{a,t} – never smoker mortality rate\textsubscript{a,t}) for former users. As a special case in the NVP Scenario, the mortality rate of NVP users who previously smoked is determined by the mortality rate of former smokers plus the portion of excess NVP risk of current relative to former smokers. Smoking and vaping-attributable deaths (SVADs) for former smokers who currently use NVPs is measured as a product of the number of former smokers who currently use NVPs and the excess mortality risk of these users to never smokers, calculated as (former smoker using NVPs mortality rate\textsubscript{a,t} – never smoker mortality rate\textsubscript{a,t}). Total attributable deaths are calculated by summing SVADs over all ages in each year. LYLs in the NVP Scenario at each age are calculated as the product of SVADs and life-years remaining of never smokers. Summing over all ages in a particular year obtains the total LYLs in that year.

The public health impact of NVP use each year is evaluated as the difference in attributable deaths between the No-NVP and NVP Scenarios, and similarly for LYLs.

**Data and Parameter Specification**

In SAVM, the analysis of current, former and never smoking and vaping is in terms of their prevalence. These prevalence rates are translated into population numbers using actual and projected US population size estimates (Centers for Disease Control and Prevention 2019a). While the model itself does not explicitly incorporate projected births, mortality and immigration, the CDC projections incorporate projected births, mortality and immigration.

A detailed description of model parameters is provided in Table 1.

**The No-NVP Scenario**

The initial level of current, former and never smoking prevalence, the smoking initiation and cessation rates used to project these future prevalence rates, mortality rates by smoking status, and the life expectancy of never smokers used in the No-NVP model were previously developed (Holford et al. 2014a, Holford et al. 2014b, Holford, Levy and Meza 2016, Rosenberg et al. 2012) available on the National Cancer Institute: Cancer Intervention and Surveillance Modeling Network (CISNET) website (CISNET 2016). These measures apply data only through 2013 to incorporate trends prior to the time when NVPs became more widely used.

**The NVP Scenario**
The NVP Scenario requires six input parameters: NVP mortality risks, NVP switching rate, smoking initiation, vaping initiation, smoking cessation, and vaping cessation.

The NVP relative risk multiplier, Risk$_{NVP}$, represents the relative risk of death associated with current NVP use as a percentage of the excess mortality risk experienced by current or former smokers as defined above. NVP relative mortality risk is designated at 5% of cigarette excess risks based on a multi-criteria decision analysis (Nutt et al. 2016) and a Public Health England review (McNeill et al. March 2020). Since others have suggested higher risks (de Groot et al. 2018, Nelluri et al. 2016, Tegin et al. 2018, Unger and Unger 2018), an NVP relative risk multiplier of 40% is also considered.

The NVP switching rate is the annual rate at which current smokers switch from smoking to NVP use, leading to a direct reduction in smoking prevalence. Baseline male (female) NVP yearly switching rates are based on weighted data by age group that we generated from the 2013/2014, 2014/2015, 2015/2016, and 2016/2017 Population Assessment of Tobacco and Health (PATH) surveys (U.S. Food and Drug Administration, National Institutes of Health and Abuse. 2019) averaged over years, as described in Supplement 2. These are: 8% (5%) age 10-17; 4.0% (2.5%) for ages 18-24, 2.5% (2.0%) for ages 25-34, 2.5% (1.6%) for age 35-44, 1.3% (1.4%) for ages 45-54, 1.2% (1.4%) for ages 55-64, and 0.6% (1.0%) for ages 65. We also consider switching rates that are 50% lower and 100% higher than the baseline estimates. These rates are initially assumed constant over time (i.e., 0% decay), but we also consider a 10% decay (i.e., annual rate of decline) to reflect the possibility of reduced innovation in NVPs over time and the tendency for those who are most amenable to switching to or quitting NVPs to have already switched, leaving a population less amenable to switching and quitting. However, because innovation in NVP design may increase their substitutability for cigarettes and potentially increase switching, we also consider an annual 5% increase rate for the first five years (2018-2022).

Since the smoking initiation in the NVP Scenario is measured relative to smoking initiation in the No-NVP Scenario, the smoking initiation multiplier is greater than 100% if NVP use increases net smoking initiation beyond the rate at which individuals would have otherwise initiated smoking in the absence of NVPs (i.e., gateway in > gateway out), and is less than 100% if those who would have initiated smoking tend to transition to exclusive NVP use instead of smoking (i.e., gateway out > gateway in). Based on the more rapid downward trend in US youth and young adult smoking as NVP use increased in recent years (Levy et al. 2019b), the age- and year-invariant baseline smoking initiation multiplier is initially set at 75%, i.e. a 25% net decrease in smoking initiation due to vaping. A range of 25% to 125% is also considered.

The NVP initiation rate multiplier reflects the youth and young adult initiation of NVP use relative to smoking initiation rates in the No-NVP Scenario. If less than 100%, NVP initiation rates are lower than smoking initiation rates in the No-NVP Scenario. i.e., fewer individuals become regular NVP users than who would have become smokers in the No-NVP Scenario. Reflecting the increased US youth and young adults regular NVP users in recent years (Cullen et al. 2019, Hammond et al. 2019, Levy, Yuan and Li 2017, Miech et al. 2019b, Miech et al. 2019c), the age- and year-invariant baseline NVP initiation multiplier is initially set at 50%. Sensitivity analysis is conducted over the range of 25% to 75%.
Since smoking cessation in the NVP Scenario is measured relative to smoking cessation in the No-NVP Scenario, the smoking cessation multiplier is greater than 100% if smoking cessation rates are higher in the NVP Scenario than in the No-NVP Scenario, e.g., if the availability of NVPs leads to increased smoking cessation. A parameter less than 100% implies that smokers are less likely to quit smoking in the NVP Scenario compared to the No-NVP Scenario, e.g., NVP use leads to dual use (continued smoking) rather than complete cessation among smokers. The baseline smoking cessation rate multiplier is initially set at 100%, with sensitivity analysis at 50% and 150%.

The NVP cessation multiplier is greater than 100% if NVP cessation rates are higher than smoking cessation rates in the No-NVP Scenario, e.g., NVPs are less addictive than cigarettes. The parameter is less than 100% if NVP cessation rates are lower than smoking cessation rates in the No-NVP Scenario. The baseline NVP cessation multiplier is set at 100%, with sensitivity analysis at 50% and 150%.

**Model Validation and Analysis**

The model estimates the NVP effects over time for the prevalence of current and former smokers, current and former NVP users, and former smokers using NVPs, and for smoking-attributable and NVP-attributable deaths and LYLs. The model was first validated over the years 2013 to 2018 by comparing model predictions of current smoking prevalence to current smoking prevalence rates from the NHIS (Centers for Disease Control and Prevention 2019b). We focus on relative reductions over the period 2013-2018, because levels of model predictions in the initial year 2013 differ from those in the NHIS.

We also validated NVP use. Although NVP use was already occurring in 2013, the model itself begins with no NVP use that year and is adjusted to reach the 2018 levels (Levy et al. 2019b). Consequently, we validated NVP use prevalence against NHIS estimates for 2018, the latest year for which data was available rather than rely on prior trend data. We defined NVP users as those who used NVPs at least 10 of the past 30 days to reflect more regular use (Amato, Boyle and Levy 2016, Levy et al. 2019c).

Upon validating the model, we consider how NVP use affects smoking prevalence, smoking-attributable and NVP-attributable deaths and LYLs. We conduct sensitivity analyses for the NVP transition and risk parameters over the plausible ranges specified above focusing on their impact on premature attributable deaths and LYLs.

**Results**

**Validation of Smoking Prevalence**

Using the initial (best estimate) input parameter estimates, the SAVM predictions are validated against smoking prevalence from NHIS data for 2013-2018 as shown in Table 2. For ages 18 and above, SAVM projects that male (female) smoking prevalence fell from 21.4% (15.9%) in 2013 to 16.7% (12.6%) in 2018, while NHIS shows a decline from 20.3% (15.4%) in 2013 to 15.8% (12.0%) in 2018. NHIS shows a
22.2% (22.1%) relative reduction between 2013 and 2018 compared to a 22.2% (20.7%) relative reduction in SAVM.

The SAVM and NHIS smoking prevalence for males ages 18 and above is shown in Figure 2.a. (including NHIS estimates with 95% confidence intervals) with male SAVM prevalence rates scaled by the ratio of survey estimate to the SAVM level in 2013, e.g. NHIS 20.3%/ SAVM 21.4% = 94.9%). Female prevalence rates are shown in Figure 2.b., with female SAVM prevalence scaled by 96.9%.

By age group, SAVM projects that male (female) prevalence for ages 18-24 fell by 33.0% (33.7%) in relative terms between 2013 and 2018 compared to 60.8% (52.6%) from NHIS over the same time period. For ages 25-44, SAVM projects a relative decline of 21.0% (17.6%) compared to 17.2% (16.6%) from NHIS. For ages 45-64, SAVM projects a relative decline of 19.9% (18.1%) compared to 15.2% (20.9%) from NHIS. For ages 65 and above, SAVM projects a relative decline of 16.6% (20.3%) compared to 6.3% (4.0%) from NHIS.

Thus, while predicting smoking prevalence well for the adult population, SAVM tends to under-predict relative reductions in smoking prevalence at younger ages and over-predict relative reduction at older ages. While SAVM estimates for 2018 are often outside the NHIS confidence intervals, upon scaling all years by the initial year (2013) from SAVM relative to the initial year in NHIS for comparability, the SAVM 2018 estimates are generally within the NHIS confidence intervals, with the exceptions of the 18-24 age group for males and the 65 and above age group for females.

Validation of NVP Prevalence

The SAVM predictions for exclusive NVP use are validated against the overall NVP prevalence from NHIS for 2018 as shown in Table 3. For ages 18 and above, SAVM projects a 2018 NVP prevalence of 3.0% compared to 3.1% (95% CI:2.7%-3.5%) from NHIS for males, and 1.8% compared to 1.5% (95% CI:1.3%-1.8%) for females. By age group for males, the SAVM projection against NHIS (with confidence intervals) for 2018 are 7.5% vs 6.8% (95% CI:4.8%-8.8%) for ages 18-24, 4.2% vs. 4.7% (95% CI:3.8%-5.6%) for ages 25-44, 1.4% vs. 1.5% (95% CI:1.0%-1.9%) for ages 45-64, and 0.5% vs. 0.6% (95% CI:0.3%-0.9%) for ages 65 and above. For females, SAVM projections vs. NHIS estimates are 4.9% vs. 3.1% (95% CI:1.8%-4.5%) for ages 18-24, 2.4% vs. 1.9% (95% CI:1.4%-2.3%) for ages 25-44, 1.0% vs. 1.3% (95% CI:1.0%-1.7%) for ages 45-64, and 0.4% vs. 0.5% (95% CI:0.3%-0.7%) for ages 65 and above. SAVM predictions fell within the 95% confidence intervals estimated from NHIS data for overall and by age groups, except for females ages 18-24 and 25-44.

Public Health Impact Under the Baseline NVP and No-NVP Scenario

Table 4 presents US smoking and NVP use prevalence, deaths, and LYLs for males and females ages 18-99 over the modeling period 2013-2060 for all existing and new birth cohorts. We focus on prevalence estimates for the year 2023 as an indication of short-term projection and for 2060 as an example long-term projections. We first apply the baseline parameters: Risk_{NVP} =5% that of smoking, with multipliers
for smoking initiation = 75%, NVP initiation =50%, smoking cessation =100%, NVP cessation =100%, and with switching rates remaining constant over time.

In the No-NVP Scenario, smoking prevalence for ages 18 and above is 21.4% in 2013 declining to 17.4% in 2023, and 12.2% in 2060 for males, 15.9% in 2013 declining to 12.7% in 2023, and 8.7% in 2060 for females. Cumulative (2013-2060) SADs are 12.6 million for males and 5.0 million for females, while cumulative LYLs are 141.5 million for males and 54.1 million for females.

In the NVP Scenario, male (female) smoking prevalence declines to 12.9% (10.1%) in 2023 and then declines to 4.5% (4.1%) in 2060. Exclusive NVP users include those who initiated NVP use from never users (de novo) at all ages and those who switched to NVP use from smoking before age 35. Male (female) exclusive NVP use increases from 0% (0%) in 2013 to 3.8% (2.2%) in 2023, and to 8.8% (5.5%) in 2060. The prevalence of former smokers using NVPs (those switching from smoking to vaping after age 35) increases from 0% (0%) in 2013 to 1.5% (1.0%) in 2023, then increases to 1.6% (1.0%) in 2060. Compared with females, greater reduction in smoking and increase in NVP use in males is due to higher levels of switching to NVPs at younger ages among males. SVADs and LYLs cumulate to 11.3 million and 112.8 million during 2013-2060 for males and to 4.5 million and 43.9 million for females.

Under the NVP Scenario, approximately 1.8 million (1.3 million males, 0.5 million females) SVADs are averted, a 10.4% relative reduction compared to the No-NVP Scenario, and 38.9 million (28.7 million males, 10.1 million females) LYLs are averted, a 19.9% relative reduction.

**Sensitivity to NVP Transition Parameters**

Sensitivity analyses are shown in Table 5 for smoking-attributable and vaping-attributable deaths (SVADs) and in Table 6 for life-years lost (LYLs). While holding the NVP relative risk multiplier (Risk\textsubscript{NVP}) constant at 5% (columns 2 and 3 in both tables), we examine the individual impact of variations in transition rates on SVADs and LYLs averted relative to the initial levels in the NVP Scenario. Each of five transition multipliers were varied for 1) NVP switching, 2) smoking initiation, 3) NVP initiation, 4) smoking cessation, and 5) NVP cessation.

If the baseline NVP switching rate parameter is reduced by 50% with 0% annual decay, NVP replacement of smoking is less in the NVP Scenario. Compared to the baseline NVP Scenario, averted SVADs decline in relative terms by 39% from 1.8 million to 1.1 million; averted LYLs decline by 37% from 38.9 million to 24.6 million. A doubling of the NVP switching rates from their initial levels yields a 50% relative increase in averted SVADs to 2.8 million and a 47% relative increase in averted LYLs to 57 million. Using the initial NVP switching rates but with a 10% decay rate reduces averted SVADs by 40% to 1.1 million and reduces averted LYLs by 38% to 24.0 million. Using the initial NVP switching rates but with a 5% annual increase rate in the first five years (2018-2022) increases averted SVADs by 11.0% to 2.0 million and increases averted LYLs by 10% to 42.9 million.
Increasing the smoking initiation multiplier from its baseline level primarily increases youth and young adult use at first, leading to more SVADs and LYLs later in life. An increase from 75% to 125% reduces averted SVADs by 5% and averted LYLs by 7.6%, and a reduction from 75% to 25%, increases averted SVADs by 6% and averted LYLs by 8%. Increasing or decreasing the NVP initiation multiplier yields a smaller relative change in averted SVADs and LYLs. Increasing the NVP initiation multiplier from 50% to 75% yields a relative reduction of 0.1% in averted SVADs and of 0.1% in averted LYLs. A reduction in the NVP initiation multiplier to 25% increases averted SVADs and averted LYLs by 0.2% or less.

Compared to changes in the initiation parameters, changes in cessation multipliers lead to a more immediate impact on SVADs, since cessation generally occurs later in life when mortality risk is highest. Increasing the smoking cessation multiplier from 100% to 150% of cessation in the No-NVP Scenario yields a 59% relative increase to 2.9 million averted SVADs and a 42% relative increase to 55.3 million averted LYLs. Reducing the smoking cessation multiplier from 100% to 50% yields a 100% relative reduction to 224 averted SVADs and a 64.6% relative reduction to 13.8 million averted LYLs. Comparable change in the NVP cessation multipliers yields less change. Increasing the NVP cessation multiplier from 100% to 150%, averted SVADs increased by 1.7% and LYLs increased by 1.4%. Reducing the NVP cessation multiplier to 50%, averted SVADs and LYLs decline by 2.8% and 2.1%, respectively.

Since the NVP risk is substantially lower than the smoking risk in the above analyses, the relative changes in averted SVADs and LYLs by varying the NVP initiation or cessation multipliers are less than the relative changes by varying the smoking initiation or cessation multipliers within comparable ranges.

**Sensitivity to NVP Relative Risks**

Tables 5 and 6 also provide estimates of averted SVADs and LYLs with an NVP relative risk multiplier (Risk\(_{NVP}\)) of 40% (columns 4 and 5) under the different NVP transition parameter ranges. With all other parameters at their baseline levels in the NVP Scenario, averted SVADs decrease in relative terms by 42% from 1.8 million with 5% NVP risks to 1.1 million with 40% NVP risks, and averted LYLs decrease by 42% from 38.9 million to 22.6 million.

By setting Risk\(_{NVP}\) at 40%, reducing the NVP switching rates by 50% yields a 39% relative reduction in averted LYLs, while increasing the NVP switching rates by 100% (from 100% to 200%) yields a 49% relative increase. Annually reducing the switching rates by 10% yields a 41% relative reduction in averted LYLs, while annually increasing the switching rates by 5% only in the first five years (2018-2022) yields a 11% relative increase in averted LYLs. Reducing the smoking initiation multiplier from 75% to 25% yields a 21% relative increase in LYLs, while an increase to 125% yields a 19% relative reduction compared to baseline. Reducing the NVP initiation multiplier from 50% to 25% yields 6% additional averted LYLs, while an increase to 75% yields 6% fewer averted LYLs. Reducing the smoking cessation multiplier from 100% to 50% yields 122% fewer averted LYLs, while an increase to 150% yields 81% additional averted LYLs. Reducing the NVP cessation rate multiplier from 100% to 50% yields 28% fewer averted LYLs, while increasing to 150% yields 19% additional averted LYLs.
Table 5 and 6 (last row) also provide the change in SVADs and LYL with Risk_{NVP} at 40% compared to Risk_{NVP} = 5%. In all cases, the public health benefits in terms of averted SVADs and averted LYLs are reduced, with relative reductions of at least 35% associated with the NVP initiation and cessation rates as well as the smoking initiation and cessation rates. Thus, increasing NVP risks leads to greater sensitivity of LYLs to changes in switching, NVP initiation, and NVP cessation parameters.

Discussion

The SAVM is the first simulation model incorporating vaping that was subjected to validation. SAVM projections of US smoking prevalence were generally close to estimates from 2013-2018 NHIS, except at younger ages where the relative reductions in smoking prevalence from surveys were greater than those predicted by the model. NVP use projections from SAVM were generally consistent with those of the 2018 NHIS.

While not discussed above, we also conducted validations of smoking prevalence against two other major national surveys: the Tobacco Use Supplement to the Current Population Survey (TUS-CPS) and the National Survey on Drug Use and Health (NSDUH) (See Supplement 3). The relative reductions in SAVM estimates were generally closer to 18-24 year old estimates from these two surveys than to NHIS estimates, but they performed slightly less well overall. However, the prevalence estimates from TUS-CPS and NSDUH differ substantially from those of the NHIS both in terms of levels and trends over 2013-2018, which is consistent with previous studies (Levy et al. 2019c, Ryan, Trosclair and Gfroerer 2012). Thus, validation results may depend on the survey used to validate the model.

Using our baseline estimates of NVP relative mortality risks, switching rates, smoking and NVP initiation rates, and smoking and NVP cessation rates, the SAVM projects that NVP use in the population will translate to 1.8 million premature smoking-attributable and vaping-attributable deaths avoided and 38.9 million life years gained from 2013-2060. However, these estimates are based on a specific set of parameters, and should be carefully considered in the context of sensitivity analyses which show the influence of each parameter on public health outcomes. While the validation results increase confidence in the model, predictions for the future depend on the stability of its underlying transition behaviors and are subject to much greater uncertainty when considering longer time horizons.

The NVP relative risk relative to smoking was initially set to 5% (McNeill et al. March 2020, Nutt et al. 2016), but when increased to 40%, the associated public health gains were substantially reduced. This finding is particularly important in light of the uncertainty and controversy surrounding the relative risks of NVP use compared to smoking (Eissenberg et al. 2020). In addition, with the NVP relative risk at 5%, public health gains were more sensitive to the level of switching and smoking cessation rates and to a lesser extent smoking or NVP initiation rates. However, with NVP relative risks raised to 40%, public health impacts became much more sensitive to all parameters except for the NVP initiation rate.
Our analysis is subject to limitations. While our No-NVP Scenario is based on trends informed by data through 2013, future trends are subject to uncertainty and depend on tobacco control policies and other environmental changes that would have occurred if NVPs had not come onto the US market. In general, the NVP relative risk, switching, initiation, and cessation parameters applied in the NVP Scenario are also subject to considerable uncertainty. Compared to smoking, NVPs are new products with less empirical evidence on their long-term health effects and usage/transition patterns (Fairchild, Bayer and Lee 2019, Green, Bayer and Fairchild 2016). In addition, patterns of future NVP use are difficult to predict. NVP use is still relatively new and use patterns can be expected to change as a result of the “disruptive” nature of the product (Abrams 2014, Levy et al. 2019d). Future NVP use will depend on product innovations and industry structure (Levy et al. 2019a, Levy et al. 2020a, Levy et al. 2020b) and regulations surrounding NVP content, marketing and use (Levy et al. 2017). In particular, NVP risks may be reduced with prudent FDA regulations that ban or limit the presence of known toxicants in e-liquids. In addition, public health benefits can be amplified with stronger policies directed at reducing smoking initiation and increasing smoking cessation.

Limitations to the model were identified in the 2013-2018 validation. In particular, the model underestimates the reduction in smoking among 18-24 year olds observed in the NHIS, thereby overestimating future smoking prevalence. Because the No-NVP Scenario is based on age, period, and cohort effects through 2013, before NVPs became more widespread, some divergence is expected: more young adult smokers may be switching to NVP use or not initiating smoking than our model captures. Our sensitivity analyses indicated that public health impacts were particularly sensitive to the rate of switching from smoking to NVPs by 18-24 year olds and smoking initiation in the NVP Scenario. In particular, downward trends in youth and young adult smoking have increased since 2017, when vaping devices such as JUUL became more widely used (Chu et al. 2018, Jackler and Ramamurthi 2019, McKeganey and Russell 2019, Vallone et al. 2018). The 2019 Monitoring the Future survey (Meza, Jimenez-Mendoza and Levy 2020) indicates past 30 day smoking rates as low as 5.8% and daily smoking rates as low as 2%. Recent studies (Al Rifai et al. 2020, Creamer et al. 2019, Levy et al. 2019c, Mirbolouk et al. 2018, Vallone et al. 2020) also indicate that NVP use among US young adult smokers may be higher than indicated by our NVP initiation rates.

The validation of NVP use is sensitive to how regular NVP use is defined. Unlike for cigarette smoking where regular use is generally defined in terms of having smoked at least 100 cigarettes lifetime, there is no accepted measure of regular NVP use. While we defined regular use by 10+ days in the last month, we also considered 1+ day and 20+ days measures based on PATH in 2013-2017. The 20+ days measure yielded levels similar to our 10+ days measure of NVP use, while the 1+ day measure yielded much higher estimates. Still, there is currently considerable uncertainty about NVP initiation, especially regarding initiation into more regular use (Hammond et al. 2019, Miech et al. 2019a, Miech et al. 2019b, Miech et al. 2019c). Although youth NVP rates increased substantially in 2019 (Gentzke et al. 2020, Wang et al. 2019), they fell in 2020 (Gentzke et al. 2020), highlighting the challenges inherent in predicting future NVP use, even in the short-term. Nevertheless, like earlier simulation results (Cherng et al. 2016, National
Academy of Sciences 2018, Warner and Mendez 2019), public health impacts were found to be relatively insensitive to the NVP initiation parameter.

Our NVP cessation multiplier baseline value of 100% implies that cessation from both smoking and NVPs is at the identical rate that of smoking cessation in the No-NVP Scenario. This transition implicitly include cessation from both smoking and vaping. While this complete cessation from smoking may increase with the availability of NVPs, some smokers may instead switch to NVPs. In our model, the public health impact regarding smoking depends on the number who quit smoking through both complete cessation and switching in the NVP Scenario compares to the number of smokers who would otherwise quit in the absence of NVPs (the No-NVP Scenario). In addition, some recent evidence indicates that NVPs may be less addictive than smoking (Bold et al. 2018, Liu et al. 2017, Martinez et al. 2019, Morean, Krishnan-Sarin and O’Malley 2018, Strong et al. 2017), implying a value greater than 100% and that those smokers switching to vaping may be more likely to quit vaping in future years than smokers in the No-NVP Scenario.

The NVP Scenario in SAVM applies simplifying assumptions so that the model is user-friendly. A never smoker who experiments with NVPs and does not transition to smoking is considered a non-user. Because transitions to and from dual use are often particularly unstable (Azagba, Shan and Latham 2019, Borland et al. 2019, Coleman et al. 2018, Robertson et al. 2019), we have chosen not to distinguish dual from exclusive cigarette use in the NVP Scenario. In addition, consistent with previous CISNET models (Holford et al. 2014a, Holford et al. 2014b, Holford, Levy and Meza 2016), SAVM does not consider relapse, with transitions to former smokers or former NVP users treated as permanent. Except for the switching parameter, we have assumed that the NVP relative risk and other transition parameters are age and time invariant to simplify the analysis. However, other key parameters, such as the smoking cessation and initiation parameters could shift over time. Intertemporal and age patterns will depend on technological advances in NVPs and regulatory policies. It will be important to update key parameters to reflect new evidence as it becomes available.

Finally, although other categories of nicotine delivery products are available on the market, including cigars, smokeless tobacco, and heated tobacco products (Czoli et al. 2020), we only consider two categories of products, cigarettes and NVPs, to keep the model tractable. As a substitute for NVPs, heated tobacco products in particular may affect NVP as well as cigarette use.

While subject to limitations, the SAVM model can be easily modified. The model is developed in Excel both for transparency and to ensure its accessibility to non-technical audiences. More experienced users can modify the model’s underlying assumptions and structure as described in the SAVM User Guide, thereby providing the user flexibility. The model and an accompanying User Guide are available at http://savm.yuanzhe.io.

The SAVM can also be easily applied to other contexts and policy scenarios. The requisite data on smoking prevalence and population by age and gender are generally available by state and for most countries. Further, the model can be used to consider the impact of different policies by comparing the
NVP Scenario under current conditions to a scenario with user-specified policy parameters. However, the results will depend on the user’s knowledge of the impact of the policy both on cigarette and NVP use and any age- or cohort-related variations in these parameters, so that sensitivity analysis is strongly encouraged.

In conclusion, the SAVM was developed as a user-friendly tool to examine the potential public health impact of NVP use on smoking behaviors and to show how public health outcomes vary across different assumptions related to NVP health risks and the initiation and cessation of NVP use and smoking. Using readily available data, SAVM can be applied by policymakers, researchers and other stakeholders in other countries to help understand the role of NVPs vis-à-vis smoking and the impact that those products have on public health.

**Abbreviations**

NVP=nicotine vaping product, SAVM = Smoking and Vaping Model. SADs = smoking-attributable deaths, LYLs = life years lost.

**Declarations**

**Ethics approval and consent to participate:**

All original data are publicly available.

**Consent for publication:**

All authors have approved the manuscript for submission.

**Competing interests:**

We have no conflicts of interests.

**Notes**

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Authors' contributions:

DTL wrote the original draft. ZY and YL did the initial modeling and helped write the original methods section. All authors contributed to the development of the model and have contributed to the writing of the paper.

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References

1. Abrams, D. B. 2014. "Promise and Peril of E-Cigarettes: Can Disruptive Technology Make Cigarettes Obsolete?". JAMA 311(2):135-6. doi: 10.1001/jama.2013.285347.

2. Al Rifai, M., A. T. Merchant, V. Nambi, X. Jia, M. Gulati, J. Valero-Elizondo, K. Nasir, C. M. Ballantyne and S. S. Virani. 2020. "Temporar
t Trends in E-Cigarette Use among U.S. Adults: Behavioral Risk Factor Surveillance System, 2016 to 2018." Am J Med. doi: 10.1016/j.amjmed.2019.12.020.

3. Amato, M. S., R. G. Boyle and D. Levy. 2016. "How to Define E-Cigarette Prevalence? Finding Clues in the Use Frequency Distribution." Tob Control 25(e1):e24-9. doi: 10.1136/tobaccocontrol-2015-052236.

4. Azagba, S., L. Shan and K. Latham. 2019. "Adolescent Dual Use Classification and Its Association with Nicotine Dependence and Quit Intentions." J Adolesc Health 65(2):195-201. doi: 10.1016/j.jadohealth.2019.04.009.

5. Azagba, S., F. Qeadan, L. Shan, K. Latham and M. Wolfson. 2020. "E-Cigarette Use and Transition in Adult Smoking Frequency: A Longitudinal Study." Am J Prev Med 59(3):367-76. doi: 10.1016/j.amepre.2020.02.024.

6. Bachand, A. M., S. I. Sulsky and G. M. Curtin. 2018. "Assessing the Likelihood and Magnitude of a Population Health Benefit Following the Market Introduction of a Modified-Risk Tobacco Product: Enhancements to the Dynamic Population Modeler, Dpm(+1)." Risk Anal 38(1):151-62. doi: 10.1111/risa.12819.

7. Bold, K. W., S. Sussman, S. S. O'Malley, R. Grana, J. Foulds, H. Fishbein and S. Krishnan-Sarin. 2018. "Measuring E-Cigarette Dependence: Initial Guidance." Addict Behav 79:213-18. doi: 10.1016/j.addbeh.2017.11.015.

8. Borland, R., K. Murray, S. Gravely, G. T. Fong, M. E. Thompson, A. McNeill, R. J. O'Connor, M. L. Goniewicz, H. H. Yong, D. T. Levy, B. W. Heckman and K. M. Cummings. 2019. "A New Classification
System for Describing Concurrent Use of Nicotine Vaping Products Alongside Cigarettes (So-Called 'Dual Use'): Findings from the Itc-4 Country Smoking and Vaping Wave 1 Survey." *Addiction.* doi: 10.1111/add.14570.

9. Bullen, C., C. Howe, M. Laugesen, H. McRobbie, V. Parag, J. Williman and N. Walker. 2013. "Electronic Cigarettes for Smoking Cessation: A Randomised Controlled Trial." *Lancet* 382(9905):1629-37. doi: 10.1016/S0140-6736(13)61842-5.

10. Caraballo, R. S., P. R. Shafer, D. Patel, K. C. Davis and T. A. McAfee. 2017. "Quit Methods Used by US Adult Cigarette Smokers, 2014-2016." *Prev Chronic Dis* 14:E32. doi: 10.5888/pcd14.160600.

11. Carter, B. D., C. C. Abnet, D. Feskanich, N. D. Freedman, P. Hartge, C. E. Lewis, J. K. Ockene, R. L. Prentice, F. E. Speizer, M. J. Thun and E. J. Jacobs. 2015. "Smoking and Mortality—Beyond Established Causes." *N Engl J Med* 372(7):631-40. doi: 10.1056/NEJMsa1407211.

12. Centers for Disease Control and Prevention. 2019a, "Us Population and Mortality Data". Retrieved November 1, 2019.

13. Centers for Disease Control and Prevention. . 2019b. "National Health Interview Survey." Vol. 2019.

14. Cherng, S. T., J. Tam, P. J. Christine and R. Meza. 2016. "Modeling the Effects of E-Cigarettes on Smoking Behavior: Implications for Future Adult Smoking Prevalence." *Epidemiology* 27(6):819-26. doi: 10.1097/EDE.0000000000000497.

15. Chu, K. H., J. B. Colditz, B. A. Primack, A. Shensa, J. P. Allem, E. Miller, J. B. Unger and T. B. Cruz. 2018. "Juul: Spreading Online and Offline." *J Adolesc Health* 63(5):582-86. doi: 10.1016/j.jadohealth.2018.08.002.

16. 2016, "Smoking Histories". Retrieved December 20, 2019 (https://resources.cisnet.cancer.gov/projects/).

17. Cobb, C. O., A. C. Villanti, A. L. Graham, J. L. Pearson, A. M. Glasser, J. M. Rath, C. A. Stanton, D. T. Levy, D. B. Abrams and R. 2015. "Markov Modeling to Estimate the Population Impact of Emerging Tobacco Products: A Proof-of-Concept Study." *Tobacco Regulatory Science* 1(2):129-41.

18. Coleman, B., B. Rostron, S. E. Johnson, A. Persoskie, J. Pearson, C. Stanton, K. Choi, G. Anic, M. L. Goniewicz, K. M. Cummings, K. A. Kasza, M. L. Silveira, C. Delnevo, R. Niaura, D. B. Abrams, H. L. Kimmel, N. Borek, W. M. Compton and A. Hyland. 2018. "Transitions in Electronic Cigarette Use among Adults in the Population Assessment of Tobacco and Health (Path) Study, Waves 1 and 2 (2013-2015)." *Tob Control.* doi: 10.1136/tobaccocontrol-2017-054174.

19. Creamer, M. R., T. W. Wang, S. Babb, K. A. Cullen, H. Day, G. Willis, A. Jamal and L. Neff. 2019. "Tobacco Product Use and Cessation Indicators among Adults - United States, 2018." *MMWR Morb Mortal Wkly Rep* 68(45):1013-19. doi: 10.15585/mmwr.mm6845a2.

20. Cullen, K. A., A. S. Gentzk, M. D. Sawdey, J. T. Chang, G. M. Anic, T. W. Wang, M. R. Creamer, A. Jamal, B. K. Ambrose and B. A. King. 2019. "E-Cigarette Use among Youth in the United States, 2019." *JAMA.* doi: 10.1001/jama.2019.18387.

21. Czoli, C. D., C. M. White, J. L. Reid, O. Connor RJ and D. Hammond. 2020. "Awareness and Interest in Iqos Heated Tobacco Products among Youth in Canada, England and the USA." *Tob Control* 29(1):89-
95. doi: 10.1136/tobaccocontrol-2018-054654.

22. Dai, H. and A. M. Leventhal. 2019. "Association of Electronic Cigarette Vaping and Subsequent Smoking Relapse among Former Smokers." Drug Alcohol Depend 199:10-17. doi: 10.1016/j.drugalcdep.2019.01.043.

23. de Groot, P. M., C. C. Wu, B. W. Carter and R. F. Munden. 2018. "The Epidemiology of Lung Cancer." Transl Lung Cancer Res 7(3):220-33. doi: 10.21037/tlcr.2018.05.06.

24. DeVito, E. E. and S. Krishnan-Sarin. 2018. "E-Cigarettes: Impact of E-Liquid Components and Device Characteristics on Nicotine Exposure." Curr Neuropharmacol 16(4):438-59. doi: 10.2174/1570159X15666171016164430.

25. Eissenberg, T., A. Bhatnagar, S. Chapman, S. E. Jordt, A. Shihadeh and E. K. Soule. 2020. "Invalidity of an Oft-Cited Estimate of the Relative Harms of Electronic Cigarettes." Am J Public Health 110(2):161-62. doi: 10.2105/AJPH.2019.305424.

26. Etter, J. F. 2016. "Throat Hit in Users of the Electronic Cigarette: An Exploratory Study." Psychol Addict Behav 30(1):93-100. doi: 10.1037/adb0000137.

27. Fairchild, A. L., R. Bayer and J. S. Lee. 2019. "The E-Cigarette Debate: What Counts as Evidence?". Am J Public Health 109(7):1000-06. doi: 10.2105/AJPH.2019.305107.

28. Farsalinos, K. E., A. Spyrou, K. Tsimopoulou, C. Stefopoulos, G. Romagna and V. Voudris. 2014. "Nicotine Absorption from Electronic Cigarette Use: Comparison between First and New-Generation Devices." Sci Rep 4:4133. doi: 10.1038/srep04133.

29. Federal Register. . 2014, " Deeming Tobacco Products to Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Regulations on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products". (https://www.federalregister.gov/articles/2014/04/25/2014-09491/deeming-tobacco-products-to-be-subject-to-the-federal-food-drug-and-cosmetic-act-as-amended-by-the#h-39).

30. Filippidis, F. T., A. A. Laverty, V. Gerovasili and C. I. Vardavas. 2017. "Two-Year Trends and Predictors of E-Cigarette Use in 27 European Union Member States." Tob Control 26(1):98-104. doi: 10.1136/tobaccocontrol-2015-052771.

31. Gentzke, A. S., T. W. Wang, A. Jamal, E. Park-Lee, C. Ren, K. A. Cullen and L. Neff. 2020. "Tobacco Product Use among Middle and High School Students - United States, 2020." MMWR Morb Mortal Wkly Rep 69(50):1881-88. doi: 10.15585/mmwr.mm6950a1.

32. Giovenco, D. P. and C. D. DelNer. 2018. "Prevalence of Population Smoking Cessation by Electronic Cigarette Use Status in a National Sample of Recent Smokers." Addict Behav 76:129-34. doi: 10.1016/j.addbeh.2017.08.002.

33. Glasser, A. M., L. Collins, J. L. Pearson, H. Abudayyeh, R. S. Niaura, D. B. Abrams and A. C. Villanti. 2016. "Overview of Electronic Nicotine Delivery Systems: A Systematic Review." Am J Prev Med. doi: 10.1016/j.amepre.2016.10.036.

34. Goldenson, N. I., M. G. Kirkpatrick, J. L. Barrington-Trimis, R. D. Pang, J. F. McBeth, M. A. Pentz, J. M. Samet and A. M. Leventhal. 2016. "Effects of Sweet Flavorings and Nicotine on the Appeal and
Sensory Properties of E-Cigarettes among Young Adult Vapers: Application of a Novel Methodology. "Drug Alcohol Depend" 168:176-80. doi: 10.1016/j.drugalcdep.2016.09.014.

35. Goniewicz, M. L., J. Knysak, M. Gawron, L. Kosmider, A. Sobczak, J. Kurek, A. Prokopowicz, M. Jablonska-Czapla, C. Rosik-Dulewska, C. Havel, P. Jacob, 3rd and N. Benowitz. 2014. "Levels of Selected Carcinogens and Toxicants in Vapour from Electronic Cigarettes." Tob Control 23(2):133-9. doi: 10.1136/tobaccocontrol-2012-050859.

36. Goniewicz, M. L., M. Gawron, D. M. Smith, M. Peng, P. Jacob, 3rd and N. L. Benowitz. 2017. "Exposure to Nicotine and Selected Toxicants in Cigarette Smokers Who Switched to Electronic Cigarettes: A Longitudinal within-Subjects Observational Study." Nicotine Tob Res 19(2):160-67. doi: 10.1093/ntr/ntw160.

37. Green, S. H., R. Bayer and A. L. Fairchild. 2016. "Evidence, Policy, and E-Cigarettes." N Engl J Med 375(5):e6. doi: 10.1056/NEJMc1606395.

38. Hajek, P., D. Przulj, A. Phillips-Waller, R. Anderson and H. McRobbie. 2018. "Initial Ratings of Different Types of E-Cigarettes and Relationships between Product Appeal and Nicotine Delivery." Psychopharmacology (Berl) 235(4):1083-92. doi: 10.1007/s00213-017-4826-z.

39. Hajek, P., A. Phillips-Waller, D. Przulj, F. Pesola, K. Myers Smith, N. Bisal, J. Li, S. Parrott, P. Sasieni, L. Dawkins, L. Ross, M. Goniewicz, Q. Wu and H. J. McRobbie. 2019. "A Randomized Trial of E-Cigarettes Versus Nicotine-Replacement Therapy." N Engl J Med 380(7):629-37. doi: 10.1056/NEJMoa1808779.

40. Hammond, D., J. L. Reid, V. L. Rynard, G. T. Fong, K. M. Cummings, A. McNeill, S. Hitchman, J. F. Thrasher, M. L. Goniewicz, M. Bansal-Travers, R. O’Connor, D. Levy, R. Borland and C. M. White. 2019. "Prevalence of Vaping and Smoking among Adolescents in Canada, England, and the United States: Repeat National Cross Sectional Surveys." BMJ 365:l2219. doi: 10.1136/bmj.l2219.

41. Hecht, S. S., S. G. Carmella, D. Kotandeniya, M. E. Pillsbury, M. Chen, B. W. Ransom, R. I. Vogel, E. Thompson, S. E. Murphy and D. K. Hatsukami. 2014. "Evaluation of Toxicant and Carcinogen Metabolites in the Urine of E-Cigarette Users Versus Cigarette Smokers." Nicotine Tob Res. doi: 10.1093/ntr/ntu218.

42. Hill, A. and O. M. Camacho. 2017. "A System Dynamics Modelling Approach to Assess the Impact of Launching a New Nicotine Product on Population Health Outcomes." Regul Toxicol Pharmacol 86:265-78. doi: 10.1016/j.yrtph.2017.03.012.

43. Holford, T. R., D. T. Levy, L. A. McKay, L. Clarke, B. Racine, R. Meza, S. Land, J. Jeon and E. J. Feuer. 2014a. "Patterns of Birth Cohort-Specific Smoking Histories, 1965-2009." Am J Prev Med 46(2):e31-7. doi: 10.1016/j.amepre.2013.10.022.

44. Holford, T. R., R. Meza, K. E. Warner, C. Meernik, J. Jeon, S. H. Moolgavkar and D. T. Levy. 2014b. "Tobacco Control and the Reduction in Smoking-Related Premature Deaths in the United States, 1964-2012." JAMA 311(2):164-71. doi: 10.1001/jama.2013.285112.

45. Holford, T. R., D. T. Levy and R. Meza. 2016. "Comparison of Smoking History Patterns among African American and White Cohorts in the United States Born 1890 to 1990." Nicotine Tob Res 18
46. Jackler, R. K. and D. Ramamurthi. 2019. "Nicotine Arms Race: Juul and the High-Nicotine Product Market." *Tob Control*. doi: 10.1136/tobaccocontrol-2018-054796.

47. Jeon, J., T. R. Holford, D. T. Levy, E. J. Feuer, P. Cao, J. Tam, L. Clarke, J. Clarke, C. Y. Kong and R. Meza. 2018. "Smoking and Lung Cancer Mortality in the United States from 2015 to 2065: A Comparative Modeling Approach." *Ann Intern Med* 169(10):684-93. doi: 10.7326/M18-1250.

48. Jha, P., C. Ramasundarahettige, V. Landsman, B. Rostron, M. Thun, R. N. Anderson, T. McAfee and R. Peto. 2013. "21st-Century Hazards of Smoking and Benefits of Cessation in the United States." *N Engl J Med* 368(4):341-50. doi: 10.1056/NEJMsa1211128.

49. Kalkhoran, S. and S. A. Glantz. 2015. "Modeling the Health Effects of Expanding E-Cigarette Sales in the United States and United Kingdom: A Monte Carlo Analysis." *JAMA Intern Med* 175(10):1671-80. doi: 10.1001/jamainternmed.2015.4209.

50. Levy, D. T., R. Meza, Y. Zhang and T. R. Holford. 2016. "Gauging the Effect of U.S. Tobacco Control Policies from 1965 through 2014 Using Simsmoke." *Am J Prev Med* 50(4):535-42. doi: 10.1016/j.amepre.2015.10.001.

51. Levy, D. T., K. M. Cummings, A. C. Villanti, R. Niaura, D. B. Abrams, G. T. Fong and R. Borland. 2017. "A Framework for Evaluating the Public Health Impact of E-Cigarettes and Other Vaporized Nicotine Products." *Addiction* 112(1):8-17. doi: 10.1111/add.13394.

52. Levy, D. T., Z. Yuan and Y. Li. 2017. "The Prevalence and Characteristics of E-Cigarette Users in the U.S." *Int J Environ Res Public Health* 14(10). doi: 10.3390/ijerph14101200.

53. Levy, D. T., R. Borland, E. N. Lindblom, M. L. Goniewicz, R. Meza, T. R. Holford, Z. Yuan, Y. Luo, R. J. O’Connor, R. Niaura and D. B. Abrams. 2018a. "Potential Deaths Averted in USA by Replacing Cigarettes with E-Cigarettes." *Tob Control* 27(1):18-25. doi: 10.1136/tobaccocontrol-2017-053759.

54. Levy, D. T., J. Tam, C. Kuo, G. T. Fong and F. Chaloupka. 2018b. "The Impact of Implementing Tobacco Control Policies: The 2017 Tobacco Control Policy Scorecard." *J Public Health Manag Pract* 24(5):448-57. doi: 10.1097/PHH.0000000000000780.

55. Levy, D. T., Z. Yuan, Y. Luo and D. B. Abrams. 2018c. "The Relationship of E-Cigarette Use to Cigarette Quit Attempts and Cessation: Insights from a Large, Nationally Representative U.S. Survey." *Nicotine Tob Res* 20(8):931-39. doi: 10.1093/ntr/ntx166.

56. Levy, D. T., E. N. Lindblom, D. T. Sweanor, F. Chaloupka, R. J. O’Connor, C. Shang, T. Palley, G. T. Fong, K. M. Cummings, M. L. Goniewicz and R. Borland. 2019a. "An Economic Analysis of the Pre-Deeming Us Market for Nicotine Vaping Products." *Tob Regul Sci* 5(2):169-81. doi: 10.18001/trs.5.2.8.

57. Levy, D. T., K. E. Warner, K. M. Cummings, D. Hammond, C. Kuo, G. T. Fong, J. F. Thrasher, M. L. Goniewicz and R. Borland. 2019b. "Examining the Relationship of Vaping to Smoking Initiation among Us Youth and Young Adults: A Reality Check." *Tob Control* 28(6):629-35. doi: 10.1136/tobaccocontrol-2018-054446.

58. Levy, D. T., Z. Yuan, Y. Li, D. Mays and L. M. Sanchez-Romero. 2019c. "An Examination of the Variation in Estimates of E-Cigarette Prevalence among U.S. Adults." *Int J Environ Res Public Health*.
71. Miller, C. R., D. M. Smith and M. L. Goniewicz. 2020. "Changes in Nicotine Product Use among Dual Users of Tobacco and Electronic Cigarettes: Findings from the Population Assessment of Tobacco and Health (Path) Study, 2013-2015." Subst Use Misuse 55(6):909-13. doi: 10.1080/10826084.2019.1710211.

72. Mirbolouk, M., P. Charkhchi, S. Kianoush, S. M. I. Uddin, O. A. Orimoloye, R. Jaber, A. Bhatnagar, E. J. Benjamin, M. E. Hall, A. P. DeFilippis, W. Maziak, K. Nasir and M. J. Blaha. 2018. "Prevalence and Distribution of E-Cigarette Use among U.S. Adults: Behavioral Risk Factor Surveillance System, 2016." Ann Intern Med 169(7):429-38. doi: 10.7326/M17-3440.

73. Morean, M., S. Krishnan-Sarin and S. S. O'Malley. 2018. "Comparing Cigarette and E-Cigarette Dependence and Predicting Frequency of Smoking and E-Cigarette Use in Dual-Users of Cigarettes and E-Cigarettes." Addict Behav 87:92-96. doi: 10.1016/j.addbeh.2018.06.027.

74. National Academy of Sciences, Engineering and Medicine. 2018. Public Health Consequences of E-Cigarettes

75. Nelluri, B., K. Murphy, F. Mookadam and M. Mookadam. 2016. "The Current Literature Regarding the Cardiovascular Effects of Electronic Cigarettes." Future Cardiol 12(2):167-79. doi: 10.2217/fca.15.83.

76. Nutt, D. J., L. D. Phillips, D. Balfour, H. V. Curran, M. Dockrell, J. Foulds, K. Fagerstrom, K. Letlape, R. Polosa, J. Ramsey and D. Sweanor. 2016. "E-Cigarettes Are Less Harmful Than Smoking." Lancet 387(10024):1160-2. doi: 10.1016/S0140-6736(15)00253-6.

77. Poland, B. and F. Teischinger. 2017. "Population Modeling of Modified Risk Tobacco Products Accounting for Smoking Reduction and Gradual Transitions of Relative Risk." Nicotine Tob Res 19(11):1277-83. doi: 10.1093/ntr/ntx070.

78. Ratajczak, A., W. Feleszko, D. M. Smith and M. Goniewicz. 2018. "How Close Are We to Definitively Identifying the Respiratory Health Effects of E-Cigarettes?". Expert Rev Respir Med 12(7):549-56. doi: 10.1080/17476348.2018.1483724.

79. Robertson, L., J. Hoek, M. L. Blank, R. Richards, P. Ling and L. Popova. 2019. "Dual Use of Electronic Nicotine Delivery Systems (Ends) and Smoked Tobacco: A Qualitative Analysis." Tob Control 28(1):13-19. doi: 10.1136/tobaccocontrol-2017-054070.

80. Rosenberg, M. A., E. J. Feuer, B. Yu, J. Sun, S. J. Henley, T. G. Shanks, C. M. Anderson, P. M. McMahon, M. J. Thun and D. M. Burns. 2012. "Chapter 3: Cohort Life Tables by Smoking Status, Removing Lung Cancer as a Cause of Death," Risk Anal 32 Suppl 1:S25-38. doi: 10.1111/j.1539-6924.2011.01662.x.

81. Royal College of Physicians,. 2016. "Nicotine without Smoke: Tobacco Harm Reduction." Vol. London: RCP.

82. Ryan, H., A. Trosclair and J. Gfroerer. 2012. "Adult Current Smoking: Differences in Definitions and Prevalence Estimates–Nhis and Nsduh, 2008." J Environ Public Health 2012:918368. doi: 10.1155/2012/918368.

83. Shahab, L., M. L. Goniewicz, B. C. Blount, J. Brown, A. McNeill, K. U. Alwis, J. Feng, L. Wang and R. West. 2017a. "Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users: A Cross-Sectional Study." Ann Intern Med. doi: 10.7326/M16-1107.
84. Shahab, L., M. L. Goniewicz, B. C. Blount, J. Brown and R. West. 2017b. "E-Cigarettes and Toxin Exposure." *Ann Intern Med* 167(7):525-26. doi: 10.7326/L17-0315.

85. Soneji, S., J. L. Barrington-Trimis, T. A. Wills, A. M. Leventhal, J. B. Unger, L. A. Gibson, J. Yang, B. A. Primack, J. A. Andrews, R. A. Miech, T. R. Spindle, D. M. Dick, T. Eissenberg, R. C. Hornik, R. Dang and J. D. Sargent. 2017. "Association between Initial Use of E-Cigarettes and Subsequent Cigarette Smoking among Adolescents and Young Adults: A Systematic Review and Meta-Analysis." *JAMA Pediatr* 171(8):788-97. doi: 10.1001/jamapediatrics.2017.1488.

86. Soneji, S. S., H. Y. Sung, B. A. Primack, J. P. Pierce and J. D. Sargent. 2018. "Quantifying Population-Level Health Benefits and Harms of E-Cigarette Use in the United States." *PLoS One* 13(3):e0193328. doi: 10.1371/journal.pone.0193328.

87. Stanton, C. A., E. Sharma, K. C. Edwards, M. J. Halenar, K. A. Taylor, K. A. Kasza, H. Day, G. Anic, L. D. Gardner, H. T. Hammad, M. Bansal-Travers, J. Limpert, N. Borek, H. L. Kimmel, W. M. Compton and A. Hyland. 2020. "Longitudinal Transitions of Exclusive and Polytobacco Electronic Nicotine Delivery Systems (Ends) Use among Youth, Young Adults and Adults in the USA: Findings from the Path Study Waves 1-3 (2013-2016)." *Tob Control* 29(Suppl 3):s147-s54. doi: 10.1136/tobaccocontrol-2019-055574.

88. Strong, D. R., J. Pearson, S. Ehlke, T. Kirchner, D. Abrams, K. Taylor, W. M. Compton, K. P. Conway, E. Lambert, V. R. Green, L. C. Hull, S. E. Evans, K. M. Cummings, M. Goniewicz, A. Hyland and R. Niaura. 2017. "Indicators of Dependence for Different Types of Tobacco Product Users: Descriptive Findings from Wave 1 (2013-2014) of the Population Assessment of Tobacco and Health (Path) Study." *Drug Alcohol Depend* 178:257-66. doi: 10.1016/j.drugalcdep.2017.05.010.

89. Tam, J., D. T. Levy, J. Jeon, J. Clarke, S. Gilkeson, T. Hall, E. J. Feuer, T. R. Holford and R. Meza. 2018. "Projecting the Effects of Tobacco Control Policies in the USA through Microsimulation: A Study Protocol." *BMJ Open* 8(3):e019169. doi: 10.1136/bmjopen-2017-019169.

90. Taylor, K. A., E. Sharma, K. C. Edwards, M. J. Halenar, W. Kissin, K. A. Kasza, H. Day, G. Anic, L. D. Gardner, H. T. Hammad, L. C. Hull, M. Bansal-Travers, J. Limpert, N. Borek, H. L. Kimmel, W. M. Compton, A. Hyland and C. Stanton. 2020. "Longitudinal Pathways of Exclusive and Polytobacco Cigarette Use among Youth, Young Adults and Adults in the USA: Findings from the Path Study Waves 1-3 (2013-2016)." *Tob Control* 29(Suppl 3):s139-s46. doi: 10.1136/tobaccocontrol-2020-055630.

91. Tegin, G., H. M. Mekala, S. K. Sarai and S. Lippmann. 2018. "E-Cigarette Toxicity?". *South Med J* 111(1):35-38. doi: 10.14423/SMJ.00000000000000749.

92. Thun, M. J., A. D. Lopez and P. Hartge. 2013. "Smoking-Related Mortality in the United States." *N Engl J Med* 368(18):1753. doi: 10.1056/NEJMc1302783.

93. S. Department of Health and Human Services, . . 2014. "The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General." Vol. Atlanta, GA.

94. S. Food and Drug Administration, Center for Tobacco Products. 2020, "Rules and Regulations". Retrieved May 22, 2020 (https://www.fda.gov/tobacco-products/rules-regulations-and-
guidance/rules-and-regulations).

95. S. Food and Drug Administration, Center for Tobacco Products., National Institutes of Health and National Institute on Drug Abuse. 2019. "Population Assessment of Tobacco and Health (Path) Study " . Washington, DC.

96. Unger, M. and D. W. Unger. 2018. "E-Cigarettes/Electronic Nicotine Delivery Systems: A Word of Caution on Health and New Product Development." J Thorac Dis 10(Suppl 22):S2588-S92. doi: 10.21037/jtd.2018.07.99.

97. Vallone, D. M., M. Bennett, H. Xiao, L. Pitzer and E. C. Hair. 2018. "Prevalence and Correlates of Juul Use among a National Sample of Youth and Young Adults." Tob Control. doi: 10.1136/tobaccocontrol-2018-054693.

98. Vallone, D. M., A. F. Cuccia, J. Briggs, H. Xiao, B. A. Schillo and E. C. Hair. 2020. "Electronic Cigarette and Juul Use among Adolescents and Young Adults." JAMA Pediatr. doi: 10.1001/jamapediatrics.2019.5436.

99. Voos, N., L. Kaiser, M. C. Mahoney, C. M. Bradizza, L. T. Kozlowski, N. L. Benowitz, R. J. O'Connor and M. L. Goniewicz. 2019. "Randomized within-Subject Trial to Evaluate Smokers' Initial Perceptions, Subjective Effects and Nicotine Delivery across Six Vaporized Nicotine Products." Addiction 114(7):1236-48. doi: 10.1111/add.14602.

100. Wagener, T. L., E. L. Floyd, I. Stepanov, L. M. Driskill, S. G. Frank, E. Meier, E. L. Leavens, A. P. Tackett, N. Molina and L. Queimado. 2016. "Have Combustible Cigarettes Met Their Match? The Nicotine Delivery Profiles and Harmful Constituent Exposures of Second-Generation and Third-Generation Electronic Cigarette Users." Tob Control. doi: 10.1136/tobaccocontrol-2016-053041.

101. Wang, T. W., A. S. Gentzke, M. R. Creamer, K. A. Cullen, E. Holder-Hayes, M. D. Sawdey, G. M. Anic, D. B. Portnoy, S. Hu, D. M. Hom, A. Jamal and L. J. Neff. 2019. "Tobacco Product Use and Associated Factors among Middle and High School Students - United States, 2019." MMWR Surveill Summ 68(12):1-22. doi: 10.15585/mmwr.ss6812a1.

102. Warner, K. E. 2014. "Tobacco Control Policies and Their Impacts. Past, Present, and Future." Ann Am Thorac Soc 11(2):227-30. doi: 10.1513/AnnalsATS.201307-244PS.

103. Warner, K. E., D. W. Sexton, B. W. Gillespie, D. T. Levy and F. J. Chaloupka. 2014. "Impact of Tobacco Control on Adult Per Capita Cigarette Consumption in the United States." Am J Public Health 104(1):83-9. doi: 10.2105/AJPH.2013.301591.

104. Warner, K. E. and D. Mendez. 2019. "E-Cigarettes: Comparing the Possible Risks of Increasing Smoking Initiation with the Potential Benefits of Increasing Smoking Cessation." Nicotine Tob Res 21(1):41-47. doi: 10.1093/ntr/nty062.

105. Watkins, S. L., S. A. Glantz and B. W. Chaffee. 2018. "Association of Noncigarette Tobacco Product Use with Future Cigarette Smoking among Youth in the Population Assessment of Tobacco and Health (Path) Study, 2013-2015." JAMA Pediatr 172(2):181-87. doi: 10.1001/jamapediatrics.2017.4173.
106. Weitkunat, R., P. N. Lee, G. Baker, Z. Sponsiello-Wang, A. M. Gonzalez-Zuloeta Ladd and F. Ludicke. 2015. "A Novel Approach to Assess the Population Health Impact of Introducing a Modified Risk Tobacco Product." *Regul Toxicol Pharmacol* 72(1):87-93. doi: 10.1016/j.yrtph.2015.03.011.

107. Yingst, J. M., J. Foulds, S. Veldheer, S. Hrabovsky, N. Trushin, T. T. Eissenberg, J. Williams, J. P. Richie, T. T. Nichols, S. J. Wilson and A. L. Hobkirk. 2019. "Nicotine Absorption During Electronic Cigarette Use among Regular Users." *PLoS One* 14(7):e0220300. doi: 10.1371/journal.pone.0220300.

108. Zhu, S. H., Y. L. Zhuang, S. Wong, S. E. Cummins and G. J. Tedeschi. 2017. "E-Cigarette Use and Associated Changes in Population Smoking Cessation: Evidence from Us Current Population Surveys." *BMJ* 358:j3262. doi: 10.1136/bmj.j3262.

Tables

**Table 1. Data and initial parameters for the US Smoking and Vaping Model**
| **Input parameters** | **Description** | **Data source or estimate** |
|----------------------|----------------|---------------------------|
| Population           | Population by age, gender, and year (2013-2060) | US population projections (Center for Disease Control and Prevention 2019) |
| Mortality rates      | Mortality rates by age, gender, and year for never, current, and former smokers (2013-2060) | CISNET Lung Group,(Holford et al. 2014a, Holford, Levy and Meza 2016, Jeon et al. 2018, Tam et al. 2018) available on the CISNET website (CISNET 2016). |
| Expected life years  | Expected life years remaining of never smokers by age, gender, and year (2013-2060) | CISNET Lung Group,(Holford et al. 2014a, Holford, Levy and Meza 2016, Jeon et al. 2018, Tam et al. 2018) available on the CISNET website (CISNET 2016). |
| Smoking prevalence   | Current and former smoking prevalence by age and gender for initial year | CISNET Lung Group,(Holford et al. 2014a, Holford, Levy and Meza 2016, Jeon et al. 2018, Tam et al. 2018) available on the CISNET website (CISNET 2016). |
| NVP relative risk multiplier | Excess risk of NVP use measured relative to excess smoking risks (mortality rate of current smokers – mortality rate of never smokers) | NVP mortality risks estimated to be 5% that of smoking excess risk for both genders at all ages, based on multi-criteria decision analysis (Nutt et al. 2016) and independent review (McNeill et al. March 2020). |
| NVP Switching rate   | Rate of switching from smoking cigarettes to exclusive NVP use | Ranges from 0.6%-4.0%, estimated by age group and gender using prospective analysis from PATH data 2013-2018 |
| Smoking initiation multiplier in the NVP Scenario | Ratio of smoking initiation rate in the NVP Scenario to the No-NVP Scenario | 75% of No-NVP smoking initiation rate, based on (Levy et al. 2019b). |
| NVP initiation multiplier in the NVP Scenario | Ratio of NVP initiation rate in the NVP Scenario to the No-NVP Scenario | 50% of No-NVP smoking initiation rate, based on recent studies (Cullen et al. 2019, Hammond et al. 2019, Miech et al. 2019b, Miech et al. 2019c). |
| Smoking cessation multiplier in the NVP Scenario | Ratio of smoking cessation rate in the NVP Scenario to the No-NVP Scenario | 100% of the No-NVP smoking cessation rate |
| NVP cessation multiplier in the NVP Scenario | Ratio of NVP cessation rate in the NVP Scenario to the No-NVP Scenario | 100% of the No-NVP smoking cessation rate |

Notes: NVP= nicotine vaping product. No-NVP Scenario refers to values in the absence of NVP use. NVP Scenario refers to values with NVP use.
Table 2. Smoking prevalence (%), validation of US SAVM against the NHIS, by age and gender, 2013-2018
| Age   | Source | 2013   | 2014   | 2015   | 2016   | 2017   | 2018   | Relative difference 2013-2018 |
|-------|--------|--------|--------|--------|--------|--------|--------|------------------------------|
| US Males |
| 18+   | SAVM   | 21.4   | 20.4   | 19.4   | 18.5   | 17.5   | 16.7   | -22.2%                       |
| NHIS  | 20.3   | 18.8   | 16.7   | 17.5   | 15.8   | 15.8   | -22.2%                       |
| 95% CI| 19.5-21.2 | 17.9-19.7 | 15.9-17.6 | 16.7-18.4 | 15.0-16.6 | 15.0-16.6 | -22.2%                       |
| 18-24 | SAVM   | 19.9   | 18.2   | 16.6   | 15.3   | 14.2   | 13.3   | -33.0%                       |
| NHIS  | 21.6   | 18.6   | 15.2   | 14.6   | 12.1   | 8.5    | -60.8%                       |
| 95% CI| 18.6-21.4 | 15.9-18.0 | 12.5-17.2 | 11.9-14.5 | 9.7-10.5 | 9.7-10.5 | -60.8%                       |
| 25-44 | SAVM   | 27.3   | 26.3   | 25.2   | 24.0   | 22.8   | 21.6   | -21.0%                       |
| NHIS  | 23.1   | 22.9   | 19.7   | 20.6   | 19.3   | 19.1   | -17.2%                       |
| 95% CI| 21.6-21.4 | 18.2-22.2 | 19.0-17.2 | 17.7-17.5 | 17.5-17.5 | 17.5-17.5 | -17.2%                       |
| 45-64 | SAVM   | 20.4   | 19.5   | 18.6   | 17.8   | 17.1   | 16.3   | -19.9%                       |
| NHIS  | 21.6   | 19.3   | 17.8   | 19.4   | 17.3   | 18.3   | -15.2%                       |
| 95% CI| 20.2-21.3 | 17.7-18.0 | 16.5-17.2 | 15.9-18.0 | 15.9-18.6 | 15.9-18.6 | -15.2%                       |
| 65+   | SAVM   | 12.2   | 11.9   | 11.5   | 11.0   | 10.6   | 10.2   | -16.6%                       |
| NHIS  | 10.6   | 9.7    | 9.8    | 10.2   | 9.0    | 9.9    | -6.3%                        |
| 95% CI| 9.3-11.0 | 8.5-11.1 | 8.9-11.5 | 7.9-10.2 | 8.7-11.1 | 8.7-11.1 | -6.3%                        |
| US Females |
| 18+   | SAVM   | 15.9   | 15.2   | 14.5   | 13.8   | 13.2   | 12.6   | -20.7%                       |
| NHIS  | 15.4   | 14.9   | 13.5   | 13.6   | 12.1   | 12.0   | -22.1%                       |
| 95% CI| 14.7-15.7 | 12.8-14.2 | 12.9-14.2 | 11.5-12.8 | 11.3-12.6 | 11.3-12.6 | -22.1%                       |
| 18-24 | SAVM   | 15.0   | 13.7   | 12.5   | 11.5   | 10.6   | 9.9    | -33.7%                       |
| NHIS  | 15.4   | 14.8   | 11.1   | 11.4   | 8.5    | 7.3    | -52.6%                       |
| 95% CI| 13.0-17.8 | 9.0-13.3 | 9.4-13.3 | 6.5-10.5 | 5.2-9.4 | 5.2-9.4 | -52.6%                       |
| 25-44 | SAVM   | 20.6   | 19.9   | 19.2   | 18.5   | 17.7   | 16.9   | -17.6%                       |
| Ages       | NHIS  | NHIS 95% CI | SAVM | SAVM 95% CI | 95% CI |
|------------|-------|-------------|------|-------------|--------|
| 45-64      |       |             |      |             |        |
| SAVM       | 16.2  | 16.8-19.3   | 15.6 | 14.9-17.1   | 16.8-18.0 |
| NHIS       | 18.1  | 16.8-19.3   | 15.8 | 16.8-17.1   | 15.3-18.0 |
| 65+        |       |             |      |             |        |
| SAVM       | 8.2   | 6.6-8.6     | 7.4  | 6.5-8.6     | 6.8-8.7 |
| NHIS       | 7.6   | 6.6-8.6     | 7.6  | 6.5-8.6     | 7.3-8.6 |

Notes: Current smokers in the NHIS (National Health Interview Survey) are those who have smoked at least 100 cigarettes lifetime, and currently smoke cigarettes some days or every day.

Table 3. Nicotine vaping product prevalence (%), validation for US SAVM against NHIS by age and gender in year 2018

| US Males |
|----------|
| Ages     | 18+   | 18-24 | 25-44 | 45-64 | 65+   |
| SAVM     | 3.0   | 7.5   | 4.2   | 1.4   | 0.5   |
| NHIS     | 3.1   | 6.8   | 4.7   | 1.5   | 0.6   |
| NHIS 95% CI | 2.7-3.5 | 4.8-8.8 | 3.8-5.6 | 1.0-1.9 | 0.3-0.9 |

| US Females |
|------------|
| Ages       | 18+   | 18-24 | 25-44 | 45-64 | 65+   |
| SAVM       | 1.8   | 4.9   | 2.4   | 1.0   | 0.4   |
| NHIS       | 1.5   | 3.1   | 1.9   | 1.3   | 0.5   |
| NHIS 95% CI | 1.3-1.8 | 1.8-4.5 | 1.4-2.3 | 1.0-1.7 | 0.3-0.7 |

Notes: CI= confidence interval. NVP users from NHIS (National Health Interview Survey) are those who use NVPS at least 10 of the past 30 days.

Table 4. Baseline SAVM outcomes under NVP Scenario vs. No-NVP Scenario, all cohorts including new births, US, by gender, in years 2013-2060, ages 18-99
|                     | Year | 2013  | 2018  | 2023  | 2060  | Cumulative^a |
|---------------------|------|-------|-------|-------|-------|--------------|
| **US Males**        |      |       |       |       |       |              |
| **No-NVP Scenario** |      |       |       |       |       |              |
| Smokers (%)         |      | 21.4% | 19.2% | 17.4% | 12.2% | -            |
| SADs                |      | 280,925 | 277,980 | 274,943 | 219,947 | 12,555,272 |
| LYLs                |      | 3,668,313 | 3,551,197 | 3,389,252 | 2,275,317 | 141,511,570 |
| **NVP Scenario**    |      |       |       |       |       |              |
| Smokers (%)         |      | 21.4% | 16.7% | 12.9% | 4.5%  | -            |
| NVP users (%)       |      | 0.0%  | 2.1%  | 3.8%  | 8.8%  | -            |
| FS-NVP users (%)    |      | 0.0%  | 0.9%  | 1.5%  | 1.6%  | -            |
| SVADs               |      | 280,925 | 271,354 | 261,620 | 171,734 | 11,264,274 |
| LYLs                |      | 3,668,313 | 3,406,256 | 3,098,328 | 1,243,989 | 112,777,500 |
| **Difference**      |      |       |       |       |       |              |
| SADs averted        |      | 0     | 6,626 | 13,323 | 48,214 | 1,290,997   |
| LYLs averted        |      | 0     | 144,941 | 290,924 | 1,031,327 | 28,734,070 |
| **US Females**      |      |       |       |       |       |              |
| **No-NVP Scenario** |      |       |       |       |       |              |
| Smokers (%)         |      | 15.9% | 14.1% | 12.7% | 8.7%  | -            |
| SADs                |      | 110,815 | 106,875 | 106,031 | 86,296  | 5,024,120   |
| LYLs                |      | 1,405,272 | 1,369,936 | 1,318,238 | 822,514  | 54,081,266 |
| **NVP Scenario**    |      |       |       |       |       |              |
| Smokers (%)         |      | 15.9% | 12.6% | 10.1% | 4.1%  | -            |
| NVP users (%)       |      | 0.0%  | 1.2%  | 2.2%  | 5.5%  | -            |
| FS-NVP users (%)    |      | 0.0%  | 0.6%  | 1.0%  | 1.0%  | -            |
| SVADs               |      | 110,815 | 103,063 | 98,981  | 68,794  | 4,481,391   |
| LYLs                |      | 1,405,272 | 1,301,979 | 1,192,904 | 485,330  | 43,949,321 |
| **Difference**      |      |       |       |       |       |              |
| SADs averted        |      | 0     | 3,812 | 7,050  | 17,502 | 542,729     |
| LYLs averted        |      | 0     | 67,957 | 125,335 | 337,185 | 10,131,945 |
| **Both genders**    |      |       |       |       |       |              |
| Difference          |      |       |       |       |       |              |
| SADs averted        |      | 0     | 10,438 | 20,373 | 65,716 | 1,833,727   |
| LYLs averted        |      | 0     | 212,898 | 416,259 | 1,368,512 | 38,866,015 |
| SADs averted        |      | 0.0%  | 2.7%  | 5.3%  | 21.5% | 10.4%       |
| (%) | 0.0% | 4.3% | 8.8% | 44.2% | 19.9% |
|-----|------|------|------|-------|-------|
| LYLs averted (%) |      |      |      |       |       |

Notes: NVP = nicotine vaping product, SADs = smoking attributable deaths, SVADs = smoking and vaping attributable deaths, LYLs = life-years lost, FS-NVP = former smokers using NVPs.

a Cumulative is the sum of SADs/SVADs or LYLs over the years 2013-2060.

b No-NVP Scenario refers to the values of smoking prevalence (%), SADs, and LYLs in the absence of NVP use.

c NVP Scenario refers to values of smoking prevalence (%), exclusive NVP prevalence (%), former smokers using NVP prevalence (%), SVADs, and LYLs with NVP use.

Table 5. Sensitivity analysis: Smoking attributable deaths and deaths averted in the No-NVP Scenario and NVP Scenario across parameter changes, both genders, ages 18-99, 2013-2060
| Scenario | NVP relative risk (Risk_{NVP})^a = 5% | NVP relative risk (Risk_{NVP}) = 40% | Relative Change (5% vs 40%)^d |
|----------|----------------------------------|----------------------------------|----------------------------------|
| No-NVP Scenario | Total SADs | Total SADs |  |
| | 17,579,392 | 17,579,392 |  |
| NVP Scenario with parameter changes from baseline | Averted SADs and SVADs^b | Relative Change (vs. baseline estimate)^c | Averted SADs and SVADs^b | Relative Change (vs. baseline estimate)^c |
| Baseline estimate^e | 1,833,727 | 0.0% | 1,061,490 | 0.0% | -42.1% |
| 50% of switch rate,^f no decay^g | 1,124,559 | -38.7% | 636,758 | -40.0% | -43.4% |
| 200% of switch rate, no decay | 2,756,913 | 50.3% | 1,611,641 | 51.8% | -41.5% |
| 100% of switch rate, 10% annual decay | 1,102,703 | -39.9% | 619,565 | -41.6% | -43.8% |
| 100% of switch rate, annually increase of 5% in the first five years | 2,036,207 | 11.0% | 1,182,961 | 11.4% | -41.9% |
| 25% of smoking initiation | 1,938,925 | 5.7% | 1,212,317 | 14.2% | -37.5% |
| 125% of smoking initiation multiplier | 1,737,970 | -5.2% | 924,283 | -12.9% | -46.8% |
| 25% of NVP initiation^l | 1,836,013 | 0.1% | 1,104,549 | 4.1% | -39.8% |
| 75% of NVP initiation | 1,831,576 | -0.1% | 1,020,458 | -3.9% | -44.3% |
| 50% of smoking cessation^l | 224 | -100.0% | -934,792 | -188.1% | -41800% |
| 150% of smoking cessation | 2,913,448 | 58.9% | 2,254,369 | 112.4% | -22.6% |
| 50% of NVP cessation^k | 1,782,054 | -2.8% | 686,449 | -35.3% | -61.5% |
| 150% of NVP cessation | 1,864,824 | 1.7% | 1,291,320 | 21.7% | -30.8% |

Notes: NVP= nicotine vaping product, LYLs= life-years lost

^a The NVP relative risk multiplier is the mortality risk of NVPs as a percentage of the excess mortality risk of smoking.
b The absolute reduction in life-years lost in the NVP Scenario compared to the No-NVP Scenario over 2013-2060.

c The relative percent change in averted LYLs for each NVP Scenario is compared to the initial NVP Scenario (best estimate). A negative (positive) value implies that changing the parameter will decrease (increase) the averted LYLs in the specific scenario relative to averted LYLs in the initial NVP Scenario.

d The relative percent change in averted LYLs between scenarios with NVP risk multipliers of 5% vs. 40% is calculated as \((\text{Averted LYLs with 40\% NVP risk} - \text{Averted LYLs with 5\% NVP risk}) / \text{Averted LYLs with 5\% NVP risk})\).

e The initial values for each input parameters in NVP Scenario are as following. NVP switching rate with no decay for males females): 4\% (2.5\%) for ages 24 and below, 2.5\% (2.0\%) for ages 25-34, 2.5\% (1.6\%) for age 35-44, 1.3\% (1.4\%) for ages 45-54, 1.2\% (1.4\%) for ages 55-64, and 0.6\% (1.0\%) for ages 65 and above; smoking initiation multiplier = 75\%; NVP initiation multiplier = 50\%; Smoking cessation multiplier= NVP cessation multiplier =100\%

f NVP switching rate is the annual rate at which current smokers switch to NVPs.

g Annual decay rate is the exponential rate of decline in switching rates over time.

h Smoking initiation multiplier is relative to smoking initiation in the No-NVP Scenario.

i NVP initiation multiplier is relative to smoking initiation rates in the No-NVP Scenario.

j Smoking cessation multiplier is relative to smoking cessation in the No-NVP Scenario.

k NVP cessation multiplier is relative to smoking cessation rates in the No-NVP Scenario.

Table 6. Sensitivity analysis: Life-years lost and averted life years lost in the No-NVP Scenario and NVP Scenario across parameter changes, both genders, ages 18-99, 2013-2060
| Scenario | NVP relative risk \((\text{Risk}_{\text{NVP}}) = 5\%\) | NVP relative risk \((\text{Risk}_{\text{NVP}}) = 40\%\) | Relative Change \((5\% \text{ vs } 40\%)\) |
|----------|----------------------------------|----------------------------------|--------------------------|
| No-NVP Scenario | Total LYLs 195,592,836 | Total LYLs 195,592,836 | |
| NVP Scenario with parameter changes from baseline | Averted LYLs \(^b\) | Relative Change \((\text{vs. baseline estimate})^c\) | Averted LYLs \(^b\) | Relative Change \((\text{vs. baseline estimate})^c\) |
| Baseline estimate \(^e\) | 38,866,015 | 0.0\% | 22,647,153 | 0.0\% | -41.7\% |
| 50\% of switch rate, no decay \(^g\) | 24,568,915 | -36.8\% | 13,852,732 | -38.8\% | -43.6\% |
| 200\% of switch rate, no decay | 56,957,653 | 46.5\% | 33,756,316 | 49.1\% | -40.7\% |
| 100\% of switch rate, 10\% annual decay | 23,976,479 | -38.3\% | 13,438,461 | -40.7\% | -44.0\% |
| 100\% of switch rate, annually increase of 5\% in the first five years | 42,877,168 | 10.3\% | 25,119,390 | 10.9\% | -41.4\% |
| 25\% of smoking initiation \(^h\) | 42,143,294 | 8.4\% | 27,380,768 | 20.9\% | -35.0\% |
| 125\% of smoking initiation | 35,915,686 | -7.6\% | 18,383,498 | -18.8\% | -48.8\% |
| 25\% of NVP initiation \(^l\) | 38,925,863 | 0.2\% | 23,991,685 | 5.9\% | -38.4\% |
| 75\% of NVP initiation | 38,810,575 | -0.1\% | 21,372,002 | -5.6\% | -44.9\% |
| 50\% of smoking cessation \(^j\) | 13,772,377 | -64.6\% | -5,035,938 | -122.2\% | -136.6\% |
| 150\% of smoking cessation | 55,337,637 | 42.4\% | 41,046,115 | 81.2\% | -25.8\% |
| 50\% of NVP cessation \(^k\) | 38,048,498 | -2.1\% | 16,364,318 | -27.7\% | -57.0\% |
| 150\% of NVP cessation | 39,411,329 | 1.4\% | 26,857,771 | 18.6\% | -31.9\% |

Notes: NVP= nicotine vaping product, LYLs= life-years lost

\(^a\) The NVP relative risk multiplier is the mortality risk of NVPs as a percentage of the excess mortality risk of smoking.
The absolute reduction in life-years lost in the NVP Scenario compared to the No-NVP Scenario over 2013-2060.

The relative percent change in averted LYLs for each NVP Scenario is compared to the initial NVP Scenario (best estimate). A negative (positive) value implies that changing the parameter will decrease (increase) the averted LYLs in the specific scenario relative to averted LYLs in the initial NVP Scenario.

The relative percent change in averted LYLs between scenarios with NVP risk multipliers of 5% vs. 40% is calculated as \((\text{Averted LYLs with 40\% NVP risk} - \text{Averted LYLs with 5\% NVP risk}) / \text{Averted LYLs with 5\% NVP risk}\).

The initial values for each input parameters in NVP Scenario are as following. NVP switching rate with no decay for males females): 4\% (2.5\%) for ages 24 and below, 2.5\% (2.0\%) for ages 25-34, 2.5\% (1.6\%) for age 35-44, 1.3\% (1.4\%) for ages 45-54, 1.2\% (1.4\%) for ages 55-64, and 0.6\% (1.0\%) for ages 65 and above; smoking initiation multiplier = 75\%; NVP initiation multiplier = 50\%; Smoking cessation multiplier= NVP cessation multiplier =100\%

NVP switching rate is the annual rate at which current smokers switch to NVPs.

Annual decay rate is the exponential rate of decline in switching rates over time.

Smoking initiation multiplier is relative to smoking initiation in the No-NVP Scenario.

NVP initiation multiplier is relative to smoking initiation rates in the No-NVP Scenario.

Smoking cessation multiplier is relative to smoking cessation in the No-NVP Scenario.

NVP cessation multiplier is relative to smoking cessation rates in the No-NVP Scenario.

**Figures**
Figure 1

a. Transitions between Smoking States in the No-NVP Scenario
b. Transitions between Regular Smoking and Nicotine Vaping Product Use States in the NVP Scenario

Notes: NVP = nicotine vaping product

- Smoking initiation includes initiation into regular cigarette use net of any experimental NVP use and includes those who become regular dual users who smoke and regularly use NVPs.
- NVP initiation includes initiation into regular NVP use net of any experimental cigarette use.
- Switching after age 35 includes those regular smokers who quit smoking and switch to regular NVP and are considered before former smokers using NVPs.
- Switching before age 35 includes those regular smokers who quit smoking and switch to regular NVP use, and considered exclusive NVP users due to the reduced risks of quitting smoking before age 35.
- Smoking cessation includes cessation from regular cigarette use and dual users who quit both cigarette and NVP use, but may include those who quit smoking and temporarily use NVP.
- Former smoker using NVPs cessation includes those former smokers who quit NVPs and remain former smokers.
- NVP cessation includes those exclusive NVP users who quit NVP use.
Figure 2

a. Male smoking prevalence (ages 18 and above), original and scaled SAVM and NHIS, 2013-2018
b. Female smoking prevalence (ages 18 and above), original and scaled SAVM and NHIS, 2013-2018

Supplementary Files

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- SupplementtoPopMetricSAVMmodelpaper20210226.docx