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A novel microsimulation model of tobacco use behaviors and outcomes

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ABSTRACT

Background and Objective: Tobacco policymakers must consider how emerging products will change cigarette smoking behaviors and clinical outcomes. Our objective was to develop, calibrate, and validate a novel individual-level microsimulation model to project cigarette smoking behaviors and associated mortality risks. Unlike most tobacco models, our new model would explicitly include smoking relapse.

Methods: We developed the Simulating Tobacco and Nicotine Outcomes and Policy (STOP) model, in which individuals transition monthly between tobacco use states (current, former, or never) depending on rates of initiation, cessation, and relapse. Simulated individuals face tobacco use-stratified mortality risks. For US women and men, we performed internal validation of the model structure with a Cancer Intervention and Surveillance Modeling Network (CISNET) model. We then incorporated smoking relapse and calibrated cessation rates to reflect the difference between a transient quit attempt and sustained abstinence. We performed external validation with the National Health Interview Survey (NHIS) and the linked National Death Index. Comparisons were based on root-mean-square error (RMSE).

Results: In internal validation, STOP-generated projections of current/former/never smoking prevalence fit CISNET-projected data well (coefficient of variation [CV]-RMSE ≤15%). After incorporating smoking relapse, multiplying the CISNET-reported cessation rates for women/men by 7.75/7.25, to reflect the ratio of quit attempts to sustained abstinence, resulted in the best approximation to CISNET-reported smoking prevalence (CV-RMSE 2%/3%). In external validation using these new multipliers, STOP-generated cumulative mortality curves for 20-year-old current smokers and never smokers each had CV-RMSE ≤1% compared to NHIS. In simulating those surveyed by NHIS in 1997, the STOP-projected prevalence of current/former/never smokers annually (1998-2009) was similar to that reported by NHIS (CV-RMSE 12%).

Conclusions: The STOP model, with relapse included, performed well when validated to US smoking prevalence and mortality. STOP provides a flexible framework for policy-relevant analysis of tobacco and nicotine product use.

Keywords: tobacco, nicotine, model, validation, calibration, relapse

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The STOP microsimulation model captures individual-level tobacco use behaviors and outcomes.
- The model is novel in incorporating relapse, a key factor in nicotine addiction.
- We validated STOP model results with those of another model and, in a partially dependent manner, with empirical data.
- We validated with multiple outcomes, including smoking prevalence and mortality.
- This analysis did not account for some aspects of heterogeneity in tobacco use behaviors.

INTRODUCTION

In the US, tobacco smoking reduces life expectancy by over a decade and accounts for over $200 billion in healthcare costs annually, approximately 9% of all healthcare costs in the country.[1,2] Though the prevalence of cigarette smoking among adults has decreased in the US, from 42% in 1965 to 14% in 2017, the decline has not been seen in all segments of society.[3,4] Meanwhile, tobacco treatment interventions, including behavioral therapy and pharmacotherapy, remain underutilized.[5]

Novel tobacco and nicotine products, including electronic cigarettes (e-cigs) and heated tobacco products, raise many new behavioral, clinical, and policy questions.[6,7] Trial- and cohort-based data to fully inform these questions will not be available for many years. In the meantime, a timely way to address these questions is via modeling.

Simulation models provide a critical complement to more traditional research approaches.[8–14] Indeed, the Food and Drug Administration and the National Academies of Sciences, Engineering, and Medicine in the past year called for modeling studies to project the long-term effects, including both potential harms and benefits, of novel tobacco and nicotine products and regulatory policies to address them.[15,16] While multiple model-based studies of tobacco and nicotine products have been published,[17–25] most report aggregate trends, are focused at the population rather than individual level, and do not explicitly account for smoking relapse, a key component of the natural history and resource utilization of smoking cessation attempts. Our objective was to develop, calibrate, and validate a novel, individual-level microsimulation model that directly addresses the mechanics of smoking initiation, cessation, and relapse, and the associated clinical outcomes. The intended application of the model is to inform clinical and public health policy.

METHODS

Analytic overview

We developed a microsimulation model of tobacco- and nicotine-related behaviors, clinical outcomes, and treatments: the Simulating Tobacco and Nicotine Outcomes and Policy (STOP) model. In this analysis, we focused on cigarette smoking among US women and men to demonstrate that the STOP model, in simulating individuals' month-by-month smoking behaviors, can match historical smoking prevalence and mortality data. Our methods included: 1) performing internal validation to assess the model structure compared to another model; 2) incorporating smoking relapse and then calibrating smoking cessation probabilities to reflect the difference between a quit attempt and sustained abstinence; and 3) using our new relapse parameters, performing external validation to compare model outputs for mortality and for prevalence of current, former, and never smokers over time to empirical data from the National Health Interview Survey (NHIS) (table 1).

Table 1. Characteristics of internal and external validation analyses for a new microsimulation model of smoking behaviors and outcomes.

Analysis	STOP-generated output of interest	Comparator	Measure of goodness of fit
Internal validation[a]	1950 birth cohort prevalence of never, current, and former smokers, ages 0-70 years, by sex	CISNET-modeled 1950 birth cohort prevalence of never, current, and former smokers, ages 0-70 years, by sex	RMSE
External validation: mortality	Cumulative mortality by age, sex, and smoking status	Cumulative mortality and mortality rates of 1997-2009	MAPE and RMSE

		NHIS respondents by age, sex, and smoking status	
External validation: smoking prevalence	Prevalence of never, current, and former smokers, annually, 1998-2009	NHIS never, current, and former smoking prevalence, annually, 1998-2009	RMSE

STOP: Simulating Tobacco and Nicotine Outcomes and Policy model. CISNET: Cancer Intervention and Surveillance Monitoring Network. NHIS: National Health Interview Survey. RMSE: root-mean-square error. MAPE: mean absolute percentage error. [a]The initial internal validation did not include smoking relapse. In the subsequent calibration step, we incorporated smoking relapse and calibrated cessation to achieve a good fit to the CISNET-modeled 1950 birth cohort prevalence of never, current, and former smokers.

Because there is no consensus criterion by which to compare model-generated results to surveillance data, expert guidance suggests choosing a criterion appropriate for the model structure and data sources.[26] Similar to methods used in validating other models, we chose root-mean-square error (RMSE, for cumulative risks and time-varying prevalence estimates) and mean absolute percentage error (MAPE, for mortality rates) to evaluate the goodness-of-fit between STOP model results and data sources.[26–32] We applied the coefficient of variation of RMSE (CV-RMSE) as a relative measure of error.

Model structure

The STOP model is an individual-level Monte Carlo microsimulation.[33,34] An individual enters the model with age and smoking status defined by random realizations from specified probability distributions. The model follows a state-transition framework: individuals transition monthly through various cigarette smoking states reflecting never, current, or former smoking status. Transitions between these states depend on age- and sex-stratified monthly smoking initiation and cessation probabilities. For ex-smokers there are monthly relapse probabilities (figure 1). Monthly mortality probabilities depend on age, sex, and smoking status. Those who quit smoking retain the all-cause mortality probabilities of current smokers until they have remained abstinent for a defined period of time (e.g., five years), after which the mortality probabilities decline.[1,8,35]

Individuals are simulated in series: for each simulated person, the model tracks smoking behavioral events (smoking initiation, quit attempt, relapse) and the duration spent in each smoking state. Upon an individual's death, the next simulated person enters the model. Once a cohort large enough to attain stable estimates has been simulated, summary statistics are calculated, including mean number of quit attempts, life expectancy, and the monthly prevalence of never, current, and former smokers.

Internal validation

Overview and outcome comparisons

We conducted internal model validation (technical verification) by simulating the US population born in 1950, following them monthly until the year 2020, and then comparing STOP results to those from modeling studies from the Cancer Intervention and Surveillance Modeling Network (CISNET) Lung Working Group (table 1 and supplementary text).[26] We selected the 1950 birth cohort because smoking prevalence in the US peaked in the 1960s, which was the smoking initiation period (adolescence) for these individuals, and data collection frequency increased concurrently. We compared STOP-generated results to CISNET-reported results for the prevalence of female and male current, former, and never smokers over time.[35]

We used CV-RMSE to assess the goodness of fit of the six sets of prevalence curves.[27,30] First, RMSE was calculated as the square root of the average of the squared difference between STOP-projected prevalence (among all simulated individuals who are alive) and CISNET-projected prevalence at each year of age. Then, we calculated CV-RMSE by dividing RMSE by mean modeled prevalence, representing the relative error.

Input parameters for initial internal validation

For the initial internal validation exercise, we used data from CISNET modeling studies, which were derived from NHIS and were stratified by birth cohort (table 2).[36,37] Specifically, we used CISNET age- and sex-stratified smoking initiation and cessation rates and smoking-stratified mortality rates among US women and men born in 1950, converting them to monthly probabilities. The CISNET smoking cessation rates reflected a direct transition from current smoker to former smoker after at least two years of sustained abstinence.[36] This initial internal validation exercise did not include smoking relapse.

Table 2. STOP model input parameters applied in validation exercises.

Variable	Internal validation	External validation: mortality	External validation: smoking prevalence
Source	CISNET	NHIS 1997-2009	NHIS 1997
Baseline cohort characteristics			
Women/Men, %[a]	---	52/48	52/48
Initial age, mean, years (SD)	0	39.7 (21.4)	39.1 (20.7)

Minimum/maximum age, years	---	18/84	18/84
Initial prevalence of never/current/former smokers[b], %	100/0/0	56/22/22	52/25/23
Years since cessation among former smokers, mean (SD)	---	15.6 (12.7)	14.4 (11.9)
Smoking behavior events			
Monthly smoking initiation probability, by age and sex	0-0.0093	0-0.0063	
Monthly smoking cessation probability, by age and sex	0-0.015	0-0.035	
Clinical events			
Monthly mortality probability[c], by age and sex, x 10^{-4}			
Never smokers	0-12.8	0.4-95.2	
Current smokers	0-34.6	0.4-136.1	
Former smokers	Multiplier applied	0-111.5	
Source: based on smoking studies or calibrated			
Monthly relapse probability[d] (*t* = months since cessation)	$P_{Relapse} = 0.62*e^{-0.33*t}$		
Cessation rate multiplier (calibrated), women/men	7.75/7.25	7.75/7.25	7.5/7
Initiation rate multiplier (calibrated), women/men	---	---	0.9/1.0

Former smoker mortality multiplier, applied to never smoker mortality, by sex and age at quit[e]	1.0-2.2	---	---

STOP: Simulating Tobacco and Nicotine Outcomes and Policy. CISNET: Cancer Intervention and Surveillance Modeling Network. NHIS: National Health Interview Survey. SD: standard deviation. The numbers show model input parameters applied in internal validation (left), external validation of mortality (center), and external validation of smoking prevalence (right).

[a]In internal validation, we simulated cohorts of either all women or all men from birth. Thus, no distributions of initial age are displayed.

[b]Prevalence of each smoking status displayed here is the mean over all strata, but in the model these were stratified by 5-year age group and sex from ages 18 to 84.

[c]Additional details about mortality data are in supplementary table 2.

[d]This is based on relapse probabilities reported in smoking cessation intervention trials, focusing on placebo arms.[38–41]

[e]CISNET-derived former smoker mortality rates are often lower than CISNET-derived never smoker mortality rates for the 1950 birth cohort – a relationship with questionable face validity. We therefore adapted former smoker mortality multipliers for the internal validation from Thun et al.[35]

Incorporating smoking relapse and calibrating cessation probabilities

A novel aspect of the STOP model is the explicit inclusion of smoking relapse. Relapse is critical to projecting both short-term and long-term impacts of smoking cessation interventions and novel tobacco and nicotine products.

The STOP model distinguishes between three states for those who have ever smoked: 1) Current Smoker; 2) Smoker who Recently Stopped; 3) Former Smoker (figure 1). This enables a differentiation between: 1) transient quit attempts: transition from the Current Smoker state to the Smoker who Recently Stopped state, with a relatively high rate of early relapse back to the Current Smoker state; and 2) sustained abstinence: transition from the Smoker who Recently Stopped state to the Former Smoker state, with a lower rate of later relapse back to the Current Smoker state.

Following the initial internal validation of the STOP model (without relapse), we added probabilities of smoking relapse and then recalibrated the model by adjusting the previously-applied smoking cessation probabilities. First, we modeled relapse as an exponential decay function of time since quit, such that the highest risk of relapse was in the first month after a quit attempt. The coefficient and time constant are based on relapse probabilities in smoking cessation trials (table 2).[38–41] Second, we calibrated the previously-applied cessation probabilities (derived from CISNET cessation data) by a multiplier to reflect: 1) a quit attempt rather than sustained abstinence; and 2) the higher likelihood of making a quit attempt rather than attaining sustained abstinence in a given month. This multiplier represents the average number of quit attempts, lasting at least one month, prior to attaining sustained abstinence. We compared our multipliers to published data on the average number of quit attempts required to attain sustained abstinence.[42] Our overall aim for this calibration step was to identify a STOP-generated current smoker prevalence curve with an RMSE <0.01 compared to the CISNET model-generated current smoker prevalence curve, in line with previously described methods.[30]

External validation

Overview and outcome comparisons

For external validation, we compared STOP model results to NHIS data rather than to the results of another model (CISNET).[26,43] We accounted for smoking initiation, smoking cessation, and mortality. Because NHIS data do not explicitly report relapse, we incorporated smoking relapse and the best-fitting cessation multipliers found in the interval validation calibration step. We compared two outcomes: mortality and smoking prevalence (table 1 and supplementary text).

First, to project and validate mortality outcomes, we simulated the population surveyed by NHIS from 1997 through 2009 (supplementary text). We used MAPE to compare STOP-generated mortality rates to those derived from NHIS, stratified by age, sex, and smoking status. MAPE was the mean absolute value of the percent difference between STOP and NHIS values. We also produced curves of cumulative mortality from STOP-generated results and from NHIS data, stratified by sex and by current/never smoking status. We compared the four sets of cumulative mortality curves by the RMSE and CV-RMSE (STOP versus NHIS) from age 20 years until age 84 years (goal RMSE <0.01). We did not generate cumulative mortality curves for former smokers in this step because mortality risks depend on age at cessation, and this heterogeneous group would include people who quit smoking at a variety of ages.[1,35]

Second, with those surveyed by NHIS in 1997 as the input cohort, we used the STOP model to project the prevalence of current, former, and never smokers each year from 1998 to 2009. In a two-way sensitivity analysis, we re-calibrated cessation multipliers along with initiation multipliers with the goal of identifying multipliers that would minimize the CV-RMSE of STOP-reported current smoker prevalence compared to NHIS current smoker prevalence. The initiation multipliers were applied to smoking initiation rates for never smokers. We then compared the cessation multipliers from this step with those from the internal validation calibration step.

Input parameters

The initial distributions of age, sex, and smoking status for the population simulated in the external validation exercises came from two sources: aggregated 1997-2009 NHIS data for the mortality external validation, and 1997 NHIS data for the smoking prevalence external validation (table 2 and supplementary figure 1). We obtained NHIS data in aggregate for years 1997-2009 from the Integrated Public Use Microdata Series.[44] These data provided initial distributions of smoking status and years of abstinence for former smokers (to inform relapse risks). From these 1997-2009 NHIS data, we derived age- and sex-specific smoking initiation and cessation rates using self-reported age at initiation and age at cessation variables (supplementary table 1). As in our internal validation exercises, we converted the cessation rates to quit attempt rates by incorporating relapse rates and cessation multipliers.

The NHIS data include linked National Death Index (NDI) mortality outcomes through 2011 for respondents for whom mortality data are available. We calculated mortality rates by age, sex, and smoking status of the same NHIS respondents (supplementary table 1).

Patient and public involvement

We did not involve patients or the public in our work.

RESULTS

Internal validation

Initial internal validation, without relapse

The STOP-projected prevalence of current, former, and never smokers over time fit CISNET-projected data well for the 1950 birth cohort in the US (figure 2, blue line vs. red dotted line, RMSE <0.03, CV-RMSE 15%/7% for women/men). The STOP-estimated prevalence of current smokers at age 25 years, approaching peak prevalence for the 1950 birth cohort, was 40% for women and 54% for men, compared to CISNET estimates of 38% and 52%.

Incorporating smoking relapse and calibrating cessation probabilities

After incorporating smoking relapse, the prevalence of current smokers far exceeded that reported by the CISNET model, as expected since many of those who would have become former smokers reverted to being current smokers (figure 2, pink dashed lines). We then aimed to reflect all quit attempts rather than only transitions to sustained abstinence. In rough calibrations, we found that the optimal multiplier would be between 5 and 10 when applied to cessation rates from the previous step. In finer calibrations, we varied the multiplier across the range of 5 to 10 in increments of 0.25. We found that multiplying the CISNET-reported cessation rates by 7.75 for women and by 7.25 for men best approximated the CISNET-projected prevalence of current smokers, with RMSE 0.004/0.008 and CV-RMSE 2%/3% for women/men (figure 2, black lines). These multipliers fall within the published range of values for average number of quit attempts needed for successful abstinence.[42,45,46]

External validation

Mortality

In simulating the 1997-2009 NHIS population along with smoking relapse, we found that the age-, sex-, and smoking-stratified mortality rates generated by the STOP model were a good fit to those derived from NHIS (MAPE 7%, examples in supplementary table 2). The cumulative mortality curves for 20 year-old female and male current smokers and never smokers were similar between STOP projections and NHIS-derived data, with RMSE <0.01 and CV-RMSE ≤1% (figure 3). For those alive at age 20 years who continued to smoke until death, the STOP model predicted median life expectancy (counting years from birth) of 77.5 years for women and 72.5 years for men. These are similar to the median life expectancies for 30 year-old smokers reported by Jha et al. (also derived from NHIS data): 77 years for women and 72 years for men.[1]

Smoking prevalence

Using those surveyed by NHIS in 1997 as the input cohort, the STOP-projected prevalence of current, former, and never smokers each year from 1998 to 2009 was similar to that reported by NHIS, with overall RMSE 0.04 and CV-RMSE 12% for both women and men (ages 30-84 years combined; supplementary figure 2 shows results specifically for ages 40-44 years). Compared to NHIS, the STOP model slightly underpredicted never smoker prevalence and slightly overpredicted former smoker prevalence in later years. In the two-way sensitivity analysis, we found that cessation multipliers of 7.5/7.0 for women/men and initiation multipliers of 0.9/1.0 resulted in the best overall fit (lowest RMSE) of STOP-projected current smoker prevalence compared to that reported by NHIS (supplementary figure 3).

DISCUSSION

We developed, calibrated, and validated STOP, a novel microsimulation model of tobacco use behaviors and outcomes. Our initial model input parameters included smoking initiation and cessation and smoking-stratified mortality, and we demonstrated internal validity compared to the CISNET model. After incorporating relapse, we calibrated smoking cessation probabilities to reflect quit attempts rather than sustained abstinence. We then validated STOP model output with: 1) smoking prevalence over time reported by the CISNET model for US women and men born in 1950; 2) age-, sex-, and smoking-stratified mortality rates and cumulative mortality reported by the NHIS-NDI linked database for the years 1997-2009; and 3) prevalence of current, former, and never smokers by sex from 1998 to 2009 reported by NHIS, using 1997 NHIS-reported population characteristics as inputs.

The STOP model simulates individual-level tobacco use behaviors and associated clinical outcomes. Most existing tobacco models simulate at the population level or lack the capacity to consider smoking initiation and (non-sustained) quit attempts throughout a lifetime.[18,23–25,37,47,48] The individual-level details of STOP can be employed to simulate and compare behaviors and interventions. While this validation and calibration analysis focused on cigarette smoking because of the availability of historical data for comparisons, we intend to broaden the use of STOP to include e-cigs. Longitudinal cohort studies and clinical trials are examining the effects of e-cig use on tobacco smoking behaviors and clinical outcomes over long time horizons, but data are needed now to inform guidelines and policy around these novel products.[15,40,49,50] Results from multiple distinct, validated models can help motivate policy decisions, and consistency of policy recommendations across unique, independent models reinforces confidence in their recommendations.[51–55]

A novel aspect of the STOP model is the incorporation of smoking relapse, reflecting the understanding of nicotine addiction and tobacco use as a chronic relapsing condition.[41,45,56–59] This key feature enables an important distinction between a quit attempt and sustained abstinence. This distinction is missing from most tobacco models and indeed from many epidemiologic studies of smoking and smoking cessation, which consider the transition from “current” to “former” smoker to be an abrupt one that results in sustained abstinence. Incorporating relapse required calibrating cessation rates by applying multipliers. The cessation multipliers that provided the best fits to empirical data are in line with published data regarding the number of quit attempts required before sustained abstinence is achieved.[42,45,46] The slightly higher multiplier needed for women compared to men is consistent with NHIS data showing that among ever smokers (current smokers plus former smokers) aged 60 years and above, a greater proportion of women compared to men are former smokers.[44]

Many trials of smoking cessation interventions follow patients for a few months or up to one year, but they do not report subsequent relapse. By including relapse, the STOP model can combine data from short-term trials of smoking cessation interventions with data from natural history studies of smoking and smoking cessation to project longer-term outcomes. In capturing changes in an individual’s smoking behaviors over time, the STOP model can assess the efficacy of tobacco cessation interventions both in the short-term, by the interventions promoting quit attempts, and in the long-term, by the interventions reducing relapse and promoting sustained abstinence. The flexibility to integrate data from a variety of sources is a strength of modeling analyses.

Going forward, we plan to use the STOP model to study contemporary rather than historical populations and to predict future tobacco use. As no empirical data exist with which to validate model output of future tobacco use, we validated STOP model output against historical populations. Most US historical data on smoking prevalence and smoking-associated mortality are based at least in part on NHIS, the oldest ongoing survey of smoking prevalence in the US.[1,4,60,61] We compared STOP model output to CISNET model output, to NHIS itself, and to results from a study by Jha et al.,[1] all of which used NHIS data. We demonstrated internal validity of STOP compared to CISNET model results when using CISNET input parameters and then added relapse probabilities and cessation multipliers. We demonstrated external validity, in a partially dependent manner, of STOP compared to NHIS data when using some NHIS-derived input parameters plus the external relapse probabilities and cessation multipliers from our internal validation. Though independent external validation sources are ideal, dependent sources can still be useful, especially in this scenario where most of the available US historical smoking prevalence, behavior, and mortality data are derived from NHIS.[26] Of note, in a two-way sensitivity analysis in which we simultaneously varied the smoking initiation and cessation multipliers to achieve a close fit to NHIS smoking prevalence data, the optimal cessation multipliers were very similar to those we found in our internal validation calibration step, demonstrating the robustness of these multipliers across different sets of assumptions.

In an external validation exercise, the STOP model projection for never smoker prevalence from 1998 to 2009 was slightly lower than that reported by NHIS, and the STOP model projection for former smoker prevalence was slightly higher than NHIS data. In NHIS, former smokers were self-defined but on average had been abstinent for over a decade. NHIS considered those who smoked “some days” to be current smokers. STOP formally labels these people, who may have been abstinent from smoking for only a very short duration, former smokers but assigns them the mortality risks of current smokers (until a defined period of abstinence). Thus, one would expect the STOP model to predict a higher prevalence of former smokers than NHIS, as seen in our results. Immigration could also account for some of the difference between NHIS data and STOP model-generated results: immigrants were surveyed in NHIS but our model analysis does not account for them. Smoking prevalence differs between the immigrant and non-immigrant populations.[62,63]

The STOP model has features, and will have applications, not described in this analysis. We developed the model to incorporate resource utilization. The STOP model can capture the healthcare costs associated with being a current, former, or never smoker, as well as the costs of tobacco cessation interventions. By incorporating the chronic relapsing nature of nicotine addiction, the STOP model can account for the resources required for recurrent cessation interventions (e.g., restarting the same or a different intervention after smoking relapse), an important consideration in cost-effectiveness and policy analyses. Ultimately, we will use the STOP model to evaluate behavioral and clinical outcomes, costs of care, and cost-effectiveness of tobacco cessation interventions, programs, and policies. An overarching goal is to provide information that can inform decision makers – including clinicians, public health officials, and policymakers – on cost-effective interventions that reduce the clinical and economic burden of tobacco use. The model can eventually assess the impact of different financing options for tobacco cessation interventions – for example, annual versus lifetime insurance coverage limits. The flexibility in the STOP model structure will allow for analyses beyond US populations, including settings where smoking-related behaviors and clinical outcomes may be different from those in the US.[64]

The STOP model has limitations. Its projections are limited by the degree of specificity of available data – for example, age, sex, and birth year stratifications of smoking behavioral transitions. However, probabilities of these transitions can be varied in sensitivity analysis. STOP does not include dynamics such as the effects of one person's smoking on another person's smoking behaviors. Smoking is associated with other factors not directly captured by STOP, including race, socioeconomic status, mental illness, and other substance use, but different populations can be separately simulated in the model with input parameters specific to that population. There is considerable heterogeneity in smoking behaviors, including cigarettes consumed per day and daily versus nondaily smoking. STOP enables stratification by intensity of smoking, which can be used to represent amount or frequency of smoking.

In conclusion, STOP is a novel, individual-level microsimulation model that captures tobacco-related behaviors – importantly including relapse – and outcomes with a goal of informing decision making around tobacco cessation interventions and tobacco policy. We have demonstrated that the model is well-calibrated and validated to historical cohorts. We plan to use the model for policy-relevant analysis of contemporary patient-level and population-level care while reflecting real-life tobacco use and cessation behaviors.

AUTHOR CONTRIBUTIONS

Specific contributions are as follows:

KPR – study conception, study design, data analysis, data interpretation

AJB – study design, data analysis, data interpretation

DEL – study design, data interpretation

PT – data analysis, data interpretation

EPH – study design, data interpretation

TH – study conception, study design, data analysis

BO – study design

LY – data analysis, data interpretation

FMS – study design, data analysis, data interpretation

ADP – study design, data interpretation

KAF – study design, data interpretation

MCW – study design, data interpretation

NAR – study conception, study design, data interpretation

RPW – study conception, study design, data interpretation

KPR drafted the first version of the manuscript. All authors critically reviewed the manuscript for important intellectual content and approved the final submitted version.

COMPETING INTERESTS

NAR receives royalties from UpToDate, Inc., is a consultant for Achieve Life Sciences, and has been an unpaid consultant for Pfizer. All other authors report no competing interests.

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FIGURE LEGENDS

Figure 1. Overview of tobacco use states and transitions in Simulating Tobacco and Nicotine Outcomes and Policy (STOP) microsimulation model.

This is a simplified, stylized depiction of smoking states and transitions – for example, dimensions such as age and sex are not represented in the figure. The ovals represent possible cigarette smoking states or the deceased state. The arrows represent monthly transitions by which an individual can switch to a different state. The "Abstinence, sustained" transition is depicted by a dashed line because there is not a monthly probability of transition – instead, the transition occurs after an individual has spent a user-defined duration (e.g., one year) in the "Smoker who recently stopped" state. Numerical examples of the transition probabilities are in supplementary table 1.

Figure 2. Internal validation and calibration exercise: STOP-generated results and CISNET-generated results for current smoking prevalence over time for US people born in 1950.

STOP: Simulating Tobacco and Nicotine Outcomes and Policy model. CISNET: Cancer Intervention and Surveillance Modeling Network.

Panel A depicts women, Panel B depicts men. The red dotted line shows results from the CISNET model. The other three lines show STOP-generated results after each step of our parameterization and calibration process. The blue line includes parameterization of smoking initiation and cessation, but not relapse. The pink dashed line includes smoking relapse as based on published studies. The black line includes calibration of smoking cessation probabilities to reflect quit attempts and relapse before sustained abstinence.

Figure 3. External validation: STOP model results and NHIS/NDI results for cumulative mortality of current smokers and never smokers from age 20.

STOP: Simulating Tobacco and Nicotine Outcomes and Policy. NHIS: National Health Interview Survey. NDI: National Death Index. CV-RMSE: coefficient of variation of root-mean-square error.

Panel A depicts women, Panel B depicts men. Within each panel, the STOP results and the NHIS data are not easily distinguishable because they are essentially overlapping. Current smokers are those who continue to smoke until death. NHIS was linked to NDI for mortality data.

Figure 1

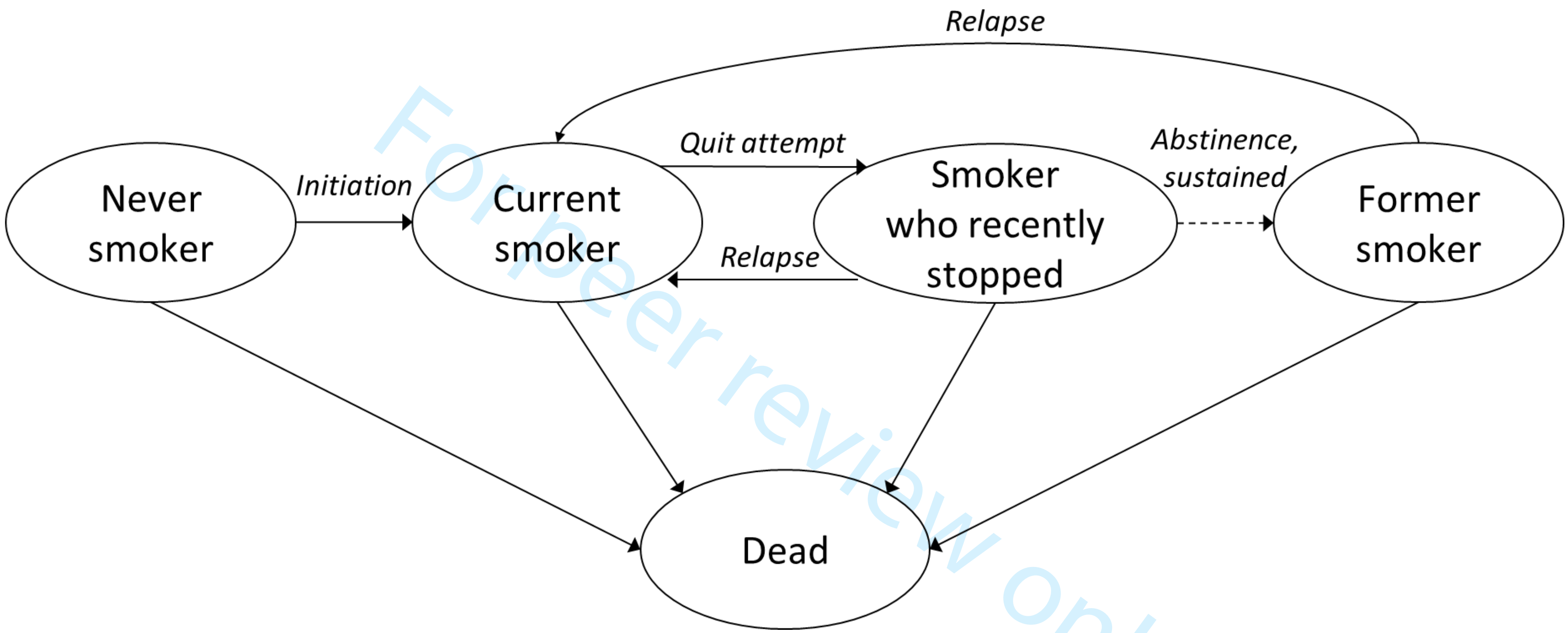

Relapse
Quit attempt
Abstinence,
sustained
Never
smoker
Initiation
Current
smoker
Smoker
who recently
stopped
Relapse
Former
smoker
Dead

Figure 2

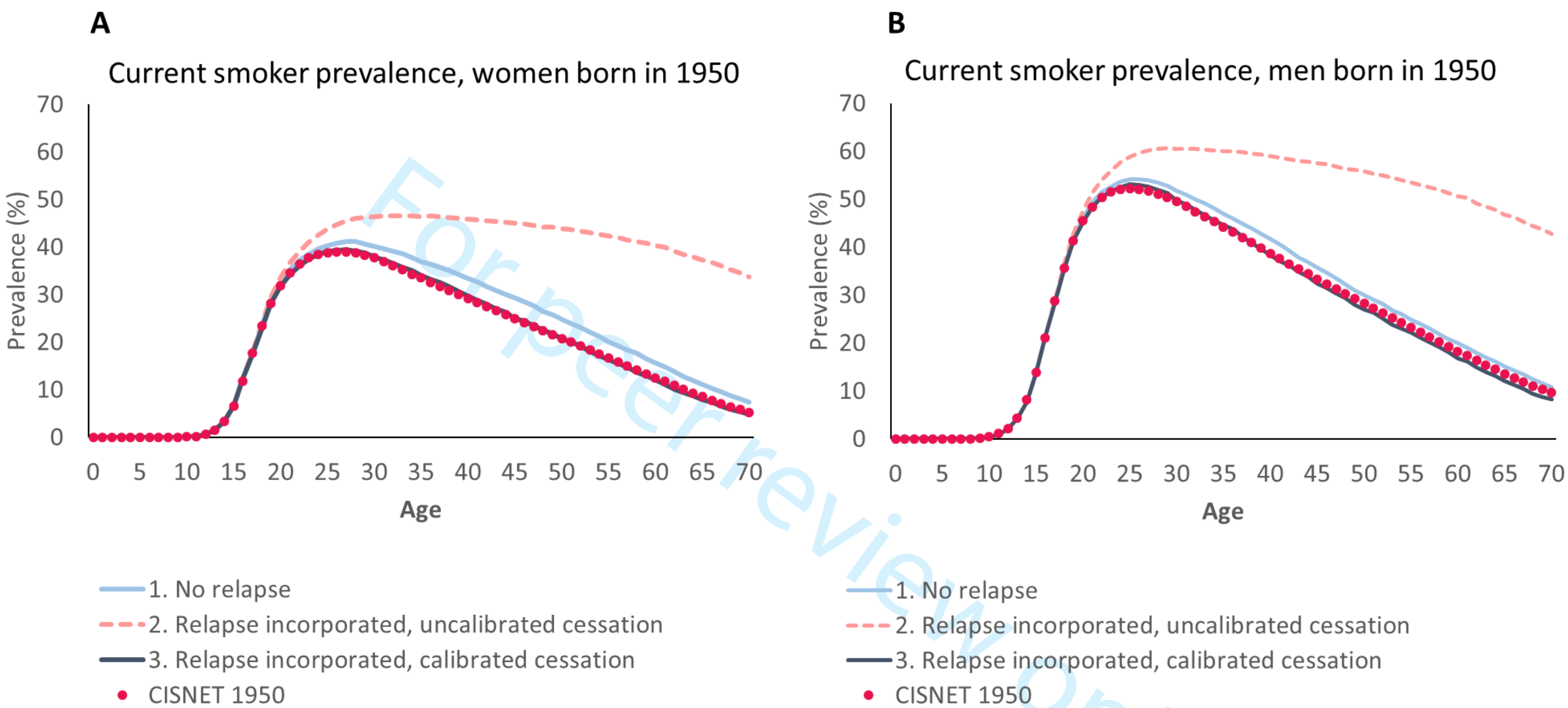
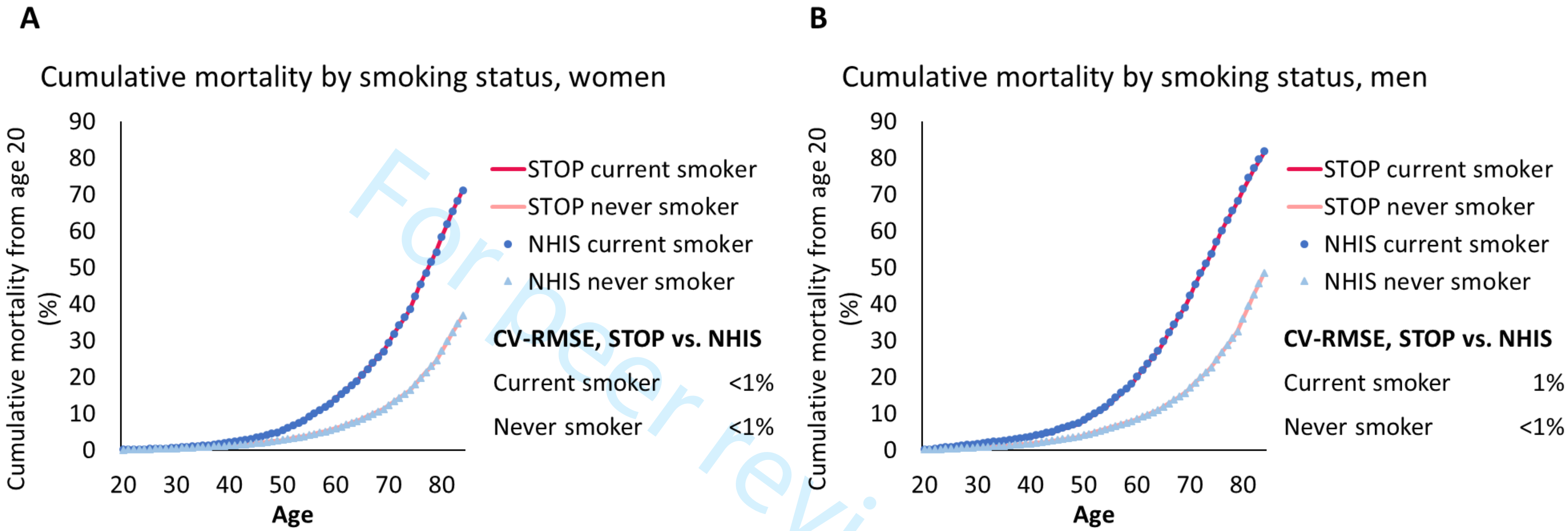

A
Current smoker prevalence, women born in 1950
Prevalence (%)
70
60
50
40
30
20
10
0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70
Age
1. No relapse
2. Relapse incorporated, uncalibrated cessation
3. Relapse incorporated, calibrated cessation
CISNET 1950
B
Current smoker prevalence, men born in 1950
Prevalence (%)
70
60
50
40
30
20
10
0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70
Age
1. No relapse
2. Relapse incorporated, uncalibrated cessation
3. Relapse incorporated, calibrated cessation
CISNET 1950

Figure 3


A
Cumulative mortality by smoking status, women
Cumulative mortality from age 20 (%)
Age
STOP current smoker
STOP never smoker
NHIS current smoker
NHIS never smoker
CV-RMSE, STOP vs. NHIS
Current smoker <1%
Never smoker <1%
B
Cumulative mortality by smoking status, men
Cumulative mortality from age 20 (%)
Age
STOP current smoker
STOP never smoker
NHIS current smoker
NHIS never smoker
CV-RMSE, STOP vs. NHIS
Current smoker 1%
Never smoker <1%

A novel microsimulation model of tobacco use behaviors and outcomes

Supplement

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Table of Contents

METHODS: SUPPLEMENTARY TEXT

CISNET Model

The Cancer Intervention and Surveillance Modeling Network (CISNET) is a collaboration of National Cancer Institute-supported investigators modeling the impact of interventions on population incidence and mortality of various types of cancer, including lung cancer. The Yale CISNET-Lung models, for subsequent analyses of cancer care interventions, used data from the National Health Interview Survey (NHIS) to generate detailed smoking initiation and cessation rates, stratified by birth year, age, and sex, and mortality rates, stratified by birth year, age, sex, and smoking status.[1,2]

National Health Interview Survey (NHIS)

NHIS is a yearly in-person questionnaire administered to the civilian noninstitutionalized population of the US which, since 1965, has collected information on individual smoking status. Since 1991, the smoking section of the NHIS has first queried “ever smoker” status – defined as having smoked at least 100 cigarettes in one’s lifetime – then asked ever smokers, “Do you NOW smoke cigarettes every day, some days or not at all?” which resulted in the classification of occasional smokers as current smokers, even though they initially may have said they did not smoke now. Regardless of response to the second question, participants were asked about the frequency of their smoking.[3]

Use of NHIS data in the Simulating Tobacco and Nicotine Outcomes and Policy (STOP) model

We downloaded NHIS and linked National Death Index (NDI) data from the Integrated Public Use Microdata Series (IPUMS) Health Surveys for the years 1997-2009.[4] We obtained basic demographic information, smoking status and behavioral variables, and death status/year of death reported through 2011. For all derivations below, we excluded those with unknown smoking or mortality status. Only people 18 years of age or older were surveyed about tobacco use, and since ages 85+ years are censored, we excluded those as well.

External validation - mortality

From the pooled 1997-2009 data, we used the IPUMS-recoded and -constructed survey weights adjusting for differential representation in the smoking sub-sample and NDI follow-up. Because of the NHIS sampling design, weights must be used so that the survey respondents can be collectively expanded to represent the civilian noninstitutionalized population of the US. These weights represent a surveyed individual's inverse probability of being included in both the survey supplement, which contains questions about smoking, and the NHIS-NDI linked mortality files.

Smoking cessation inputs: We derived age- and sex-stratified cessation rates using the NHIS variable that reported years since respondents (former smokers) quit smoking. We excluded quit ages before age 16 years (due to perceived inconsistency of coding of the "time since quit" variable – some entries implied negative quit age) and included quit ages through age 85 years.

Smoking initiation inputs: Similarly, we derived initiation rates, also age- and sex-stratified, using the variable that reported years since the respondent (a current or former smoker) started to smoke regularly. We used initiation rates from ages 6 to 61 years, the last age for which data are consecutively available for both women and men.

Mortality inputs: We calculated mortality rates by age, sex, smoking status, and five-year age group using the smoking status variable and NDI reporting through 2011. The rates were calculated from a follow-up period beginning in the respondent's survey year and ending in 2011 or the year of her/his death, whichever came first.

Input cohort: We derived initial cohort characteristics for this analysis from the NHIS 1997-2009 pooled dataset: current, former and never smoking prevalence by five-year age group from age <20 to 84 years; mean (standard deviation [SD]) age adjusted for bounding of the distribution; sex distribution; and mean (SD) time since quit bounded by a minimum quit age of 16 years.

Output comparison: We compared STOP model output for mortality to NHIS/NDI-reported mortality in the form of mortality rates and cumulative mortality from age 20 years.

External validation – smoking prevalence

From the NHIS 1997 data, using the same survey weights as above:

Smoking cessation, smoking initiation, and mortality inputs: We used the same cessation, initiation, and mortality rate inputs as for the mortality validation.

Input cohort: We derived input cohort characteristics for this analysis from the 1997 NHIS data: current, former, and never smoking prevalence by five-year age group from age <20 to 84 years; mean (SD) age adjusted for bounding of the distribution; sex distribution; and mean (SD) time since quit bounded by a minimum quit age of 16 years.

Output comparison: Starting with the 1997 NHIS respondents and following them each year from 1998 to 2009, we compared STOP projections to NHIS data regarding prevalence of current, former, and never smokers by five-year age group from age 30 to 84 years.

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8 Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction* 2004;**99**:29–38.

Supplementary Table 1. Examples of transition probabilities in the simulation model.

Parameter	Value	Reference
Smoking initiation probability, monthly, by age and sex	0-0.0063	Derived from NHIS 1997-2009 data
Cessation probability, monthly, by age and sex	0-0.035	Derived from NHIS 1997-2009 data
Relapse probability, monthly, by time since cessation	$P_{Relapse} = 0.62 {*} e^{-0.33 {*} t}$	[5–8]
Never smoker mortality probability, monthly, by age and sex, x 10^{-4}	0.4-95.2	Derived from NHIS/NDI 1997-2009 data
Current smoker or recently quit smoker mortality probability, monthly, by age and sex, x 10^{-4}	0.4-136.1	Derived from NHIS/NDI 1997-2009 data
Former smoker mortality probability, monthly, by age, sex, and time since cessation[a], x 10^{-4}	0-111.5	Derived from NHIS/NDI 1997-2009 data
Time to transition from “recently stopped” to “former smoker”	5 years	Assumption

NHIS: National Health Interview Survey. NDI: National Death Index. STOP: Simulating Tobacco and Nicotine Outcomes and Policy.

[a]These former smoker mortality probabilities were used only in the external validation exercises, comparing STOP model output to NHIS/NDI results. In internal validation comparing STOP model output

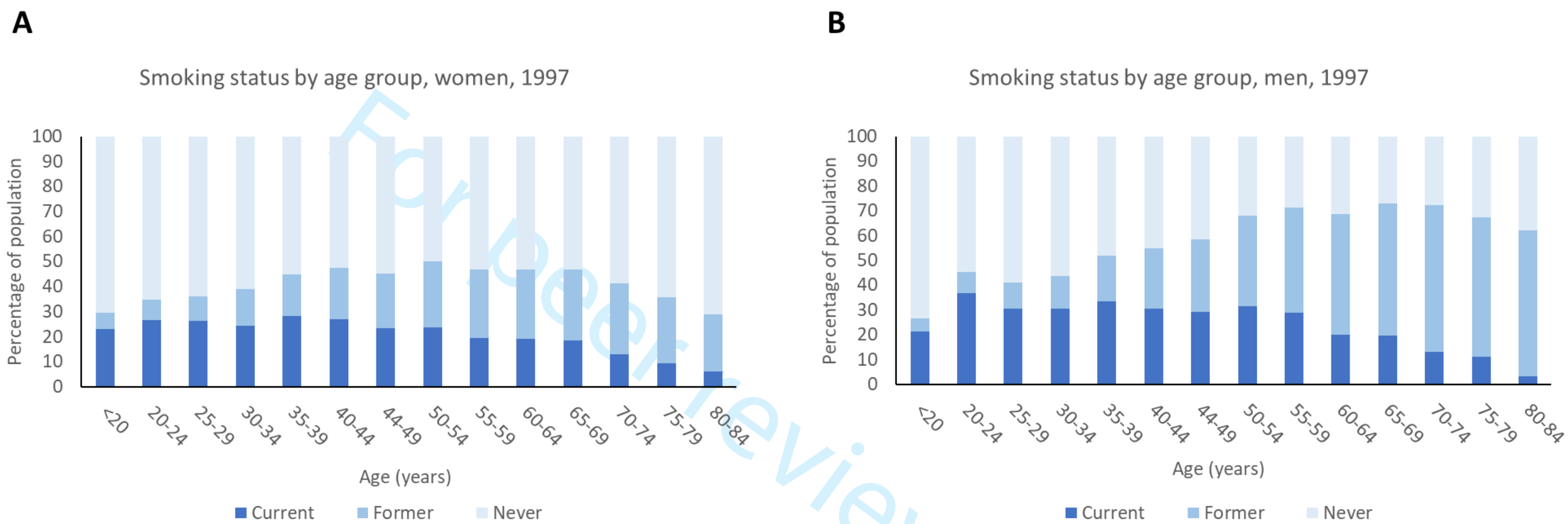
to the CISNET model results, we applied multipliers to never smoker mortality rates to derive former smoker mortality rates and then converted these to probabilities.

Supplementary Table 2. Selected age- and sex-specific annual mortality rates: STOP model output versus NHIS-derived mortality.

Women						
	Current smoker		Former smoker		Never smoker	
Age group, years	STOP	NHIS/NDI	STOP	NHIS/NDI	STOP	NHIS/NDI
40-44	0.0023	0.0023	0.0017	0.0015	0.0012	0.0012
50-54	0.0071	0.0071	0.0035	0.0029	0.0025	0.0025
60-64	0.0147	0.0146	0.0087	0.0079	0.0051	0.0051
Men						
	Current smoker		Former smoker		Never smoker	
Age group, years	STOP	NHIS/NDI	STOP	NHIS/NDI	STOP	NHIS/NDI
40-44	0.0031	0.0034	0.0028	0.0025	0.0018	0.0018
50-54	0.0094	0.0096	0.0059	0.0053	0.0042	0.0043
60-64	0.0233	0.0232	0.0114	0.0099	0.0067	0.0066

STOP: Simulating Tobacco and Nicotine Outcomes and Policy. NHIS: National Health Interview Survey. NDI: National Death Index.

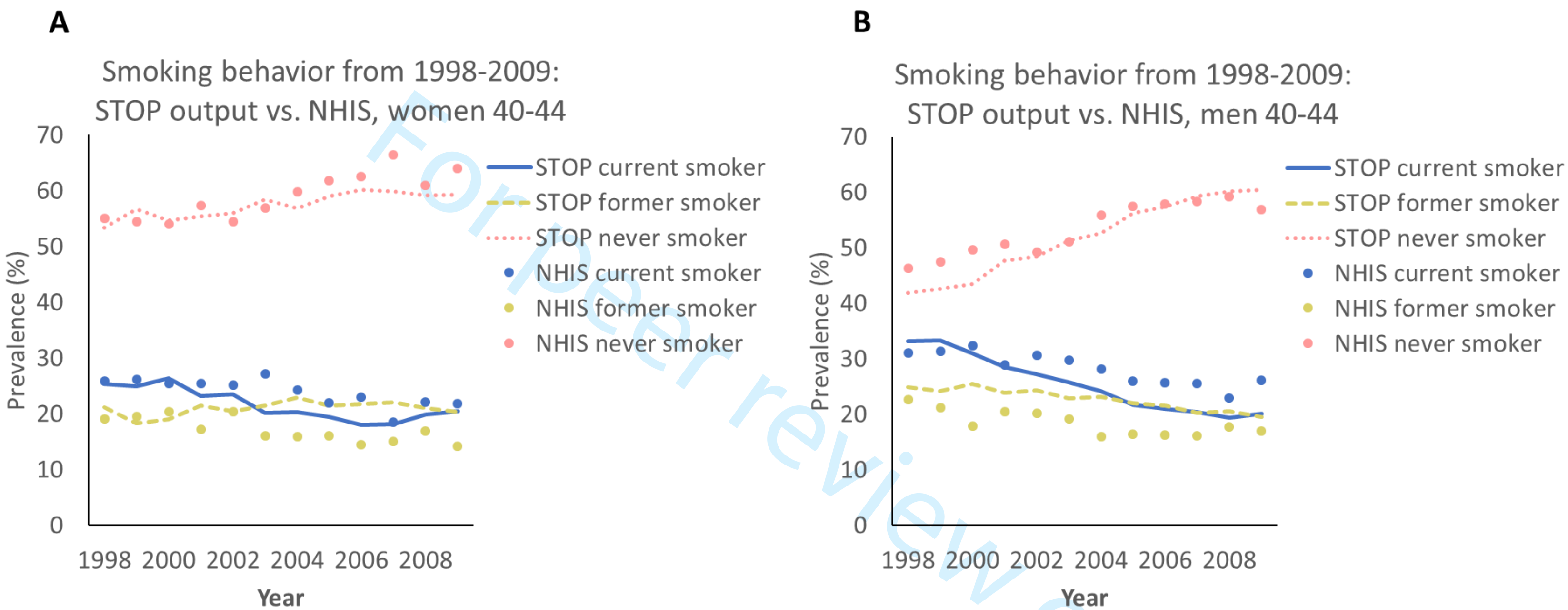
Supplementary Figure 1. Smoking status by age group and sex in 1997: STOP model inputs for the external validation exercise of smoking prevalence.



STOP: Simulating Tobacco and Nicotine Outcomes and Policy. NHIS: National Health Interview Survey.

Panel A depicts women; Panel B depicts men. For each age group, the prevalence of current, former, and never smokers is entered as STOP model input. The external validation analysis of smoking prevalence, using weighted NHIS 1997 survey respondent data as inputs, projects smoking prevalence annually from 1998 to 2009.

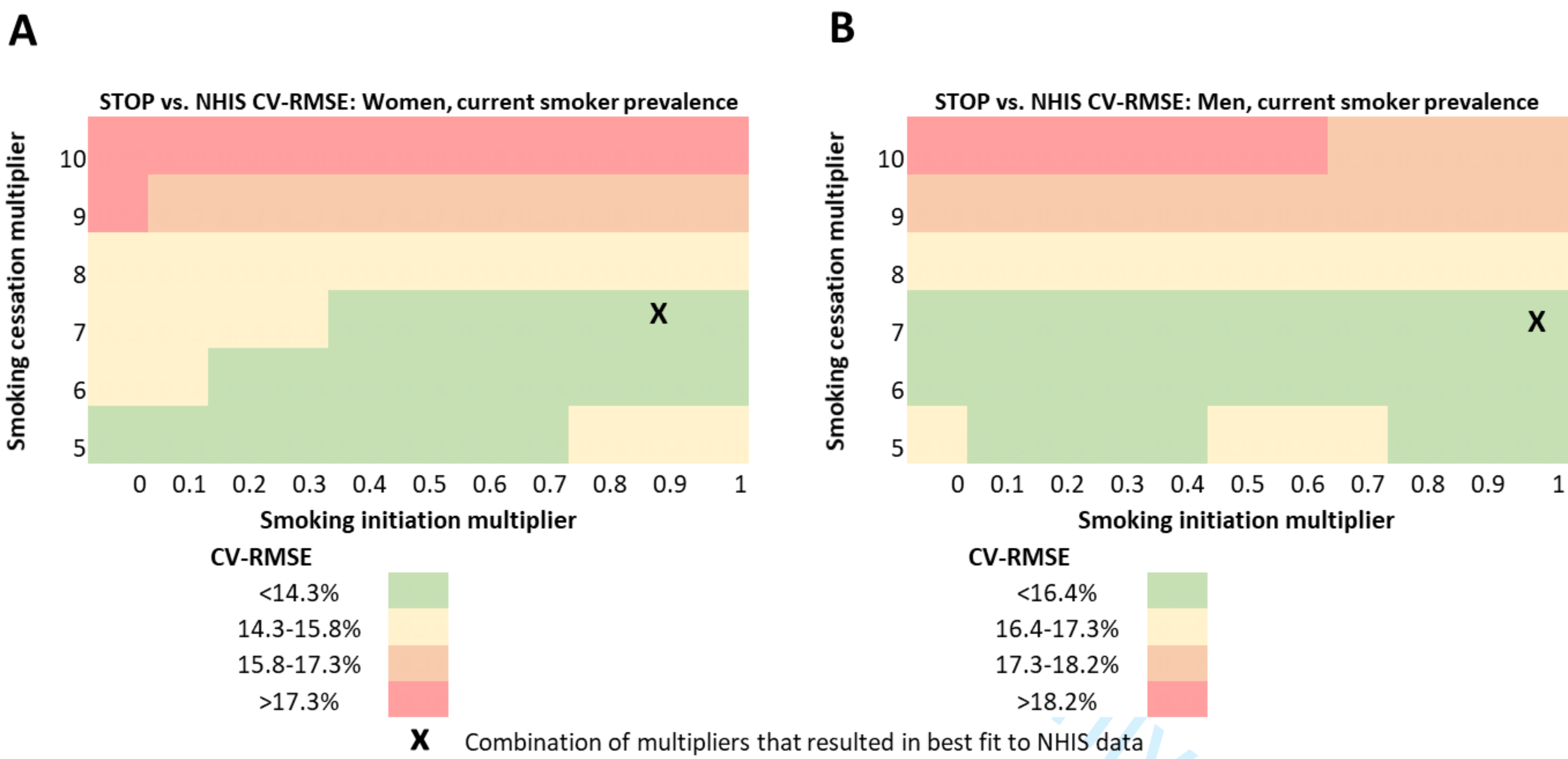
Supplementary Figure 2. External validation: STOP model results and NHIS results for prevalence of current, former, and never smokers each year from 1998 to 2009.



STOP: Simulating Tobacco and Nicotine Outcomes and Policy. NHIS: National Health Interview Survey. NDI: National Death Index.

Panel A depicts women, Panel B depicts men. The STOP model cohort had the age and smoking status distribution of the 1997 NHIS survey respondents (Supplementary Figure 1). The STOP-generated results reflect a microsimulation that included probabilities of smoking initiation, smoking cessation, smoking relapse, and mortality.

Supplementary Figure 3. Two-way sensitivity analysis of smoking initiation and smoking cessation multipliers for external validation exercise.



STOP: Simulating Tobacco and Nicotine Outcomes and Policy. NHIS: National Health Interview Survey. CV-RMSE: coefficient of variation of root-mean-square error.

Panel A depicts women; Panel B depicts men. The multipliers were applied to the original cessation and initiation rates derived from pooled 1997-2009 NHIS data and used in the STOP model. The horizontal axis shows the multiplier applied to smoking initiation rates (subsequently converted to probabilities) in the STOP model, and the vertical axis shows the multiplier applied to smoking cessation rates (subsequently converted to probabilities). Colored cells represent the CV-RMSE of STOP model-generated versus NHIS-reported current smoking prevalence among people ages 30-84 years from 1998 to 2009.

BMJ Open

A novel microsimulation model of tobacco use behaviors and outcomes: calibration and validation in a US population

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A novel microsimulation model of tobacco use behaviors and outcomes: calibration and validation in a US population

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ABSTRACT

Background and Objective: Tobacco policymakers must consider how emerging products will change cigarette smoking behaviors and clinical outcomes. Our objective was to develop, calibrate, and validate a novel individual-level microsimulation model to project cigarette smoking behaviors and associated mortality risks. Unlike most tobacco models, our new model would explicitly include smoking relapse.

Methods: We developed the Simulation of Tobacco and Nicotine Outcomes and Policy (STOP) model, in which individuals transition monthly between tobacco use states (current, former, or never) depending on rates of initiation, cessation, and relapse. Simulated individuals face tobacco use-stratified mortality risks. For US women and men, we conducted cross-validation with a Cancer Intervention and Surveillance Modeling Network (CISNET) model. We then incorporated smoking relapse and calibrated cessation rates to reflect the difference between a transient quit attempt and sustained abstinence. We performed external validation with the National Health Interview Survey (NHIS) and the linked National Death Index. Comparisons were based on root-mean-square error (RMSE).

Results: In cross-validation, STOP-generated projections of current/former/never smoking prevalence fit CISNET-projected data well (coefficient of variation [CV]-RMSE ≤15%). After incorporating smoking relapse, multiplying the CISNET-reported cessation rates for women/men by 7.75/7.25, to reflect the ratio of quit attempts to sustained abstinence, resulted in the best approximation to CISNET-reported smoking prevalence (CV-RMSE 2%/3%). In external validation using these new multipliers, STOP-generated cumulative mortality curves for 20-year-old current smokers and never smokers each had CV-RMSE ≤1% compared to NHIS. In simulating those surveyed by NHIS in 1997, the STOP-projected prevalence of current/former/never smokers annually (1998-2009) was similar to that reported by NHIS (CV-RMSE 12%).

Conclusions: The STOP model, with relapse included, performed well when validated to US smoking prevalence and mortality. STOP provides a flexible framework for policy-relevant analysis of tobacco and nicotine product use.

Keywords: tobacco, nicotine, model, validation, calibration, relapse

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The STOP microsimulation model and our calibration and validation methods capture monthly individual-level tobacco use behaviors and outcomes, including relapse, a key factor in nicotine addiction.
- We validated STOP model results with those of another model and, in a partially dependent manner, with empirical data.
- We validated with multiple outcomes, including smoking prevalence and mortality.
- This analysis did not account for some aspects of heterogeneity in tobacco use behaviors.

INTRODUCTION

In the US, tobacco smoking reduces life expectancy by over a decade and accounts for over $200 billion in healthcare costs annually, approximately 9% of all healthcare costs in the country.[1,2] Though the prevalence of cigarette smoking among adults has decreased in the US, from 42% in 1965 to 14% in 2018, the decline has not been seen in all segments of society.[3,4] Meanwhile, tobacco treatment interventions, including behavioral therapy and pharmacotherapy, remain underutilized.[5] Novel tobacco and nicotine products raise many new clinical and policy questions.[6,7] Trial- and cohort-based data to fully inform these questions will not be available for many years. In the meantime, a timely way to address them is via modeling.

Simulation models provide a critical complement to more traditional research approaches.[8–14] Indeed, the Food and Drug Administration and the National Academies of Sciences, Engineering, and Medicine recently called for modeling studies to project the long-term effects, including both potential harms and benefits, of novel tobacco and nicotine products and regulatory policies to address them.[15,16] While multiple model-based studies of tobacco and nicotine products have been published,[17–25] most report aggregate trends, are focused at the population rather than individual level, and do not explicitly account for smoking relapse, a key component of the natural history and resource utilization of smoking cessation attempts. A current challenge of projecting longer-term clinical and economic outcomes of short-term tobacco cessation studies lies in capturing the many smoking quit attempts and relapses.[26,27] A new model that intentionally examines relapse would extend trial results by projecting outcomes beyond the time horizon of trials, when many relapses occur. Our objective was to develop, calibrate, and validate a novel, individual-level microsimulation model that directly addresses the mechanics of smoking initiation, cessation, and relapse, and the associated clinical outcomes. The intended applications of the model include projecting the downstream impact of clinical and public health policy decisions and informing the design of tobacco treatment trials.

METHODS

Analytic overview

We developed a microsimulation model of tobacco- and nicotine-related behaviors, clinical outcomes, and treatments: the Simulation of Tobacco and Nicotine Outcomes and Policy (STOP) model. In this analysis, we focused on cigarette smoking among US women and men to demonstrate that the STOP model, in simulating individuals' month-by-month smoking behaviors, can match historical smoking prevalence and mortality data. Our methods included: 1) performing internal validation to ensure the accuracy of the mathematical calculations; 2) conducting cross-validation with another model; 3) incorporating smoking relapse and then calibrating smoking cessation probabilities to reflect the difference between a quit attempt and sustained abstinence; and 4) using our new relapse parameters, performing external validation to compare model outputs for mortality and for prevalence of current, former, and never smokers over time to empirical data from the National Health Interview Survey (NHIS) (table 1).

Table 1. Characteristics of cross-validation and external validation analyses for a new microsimulation model of smoking behaviors and outcomes.

Analysis	STOP-generated output of interest	Comparator	Measure of goodness of fit
Cross-validation[a]	1950 birth cohort prevalence of never, current, and former smokers, ages 0-70 years, by sex	CISNET-modeled 1950 birth cohort prevalence of never, current, and former smokers, ages 0-70 years, by sex	RMSE

External validation: mortality	Cumulative mortality by age, sex, and smoking status	Mortality rates of 1997-2009 NHIS respondents by age, sex, and smoking status, and cumulative mortality	MAPE and RMSE
External validation: smoking prevalence	Prevalence of never, current, and former smokers, annually, 1998-2009	NHIS never, current, and former smoking prevalence, annually, 1998-2009	RMSE

STOP: Simulation of Tobacco and Nicotine Outcomes and Policy model. CISNET: Cancer Intervention and Surveillance Monitoring Network. NHIS: National Health Interview Survey. RMSE: root-mean-square error. MAPE: mean absolute percentage error. [a]The initial cross-validation did not include smoking relapse. In the subsequent calibration step, we incorporated smoking relapse and calibrated cessation to achieve a good fit to the CISNET-modeled 1950 birth cohort prevalence of never, current, and former smokers.

Because there is no consensus criterion by which to compare model-generated results to surveillance data, expert guidance suggests choosing a criterion appropriate for the model structure and data sources.[28] Similar to methods used in validating other models, we chose root-mean-square error (RMSE, for cumulative risks and time-varying prevalence estimates) and mean absolute percentage error (MAPE, for mortality rates) to evaluate the goodness-of-fit between STOP model results and data sources.[28–34] We applied the coefficient of variation of RMSE (CV-RMSE) as a relative measure of error.

Smoking definitions

Similar to NHIS and the Cancer Intervention and Surveillance Modeling Network (CISNET, which used NHIS data), we defined Never Smokers as those who had smoked <100 cigarettes in their lifetime.[35–37] Among others (ever smokers), NHIS defined current smokers as those who reported currently smoking every day or some days. NHIS considered ever smokers who reported no smoking at the time of interview to be former smokers, regardless of the duration of abstinence. CISNET considered former smokers to be those who had quit smoking at least two years prior to interview; those with a shorter period of abstinence were still considered current smokers.

To better distinguish relapse and mortality risks among those with short-term or long-term abstinence, the STOP model includes three states for those who have ever smoked: 1) Current Smoker; 2) Recent Quitter (short-term abstinence); 3) Former Smoker (long-term abstinence) (figure 1). This enables a differentiation between: 1) transient quit attempts: transition from the Current Smoker state to the Recent Quitter state, with a relatively high rate of early relapse back to the Current Smoker state; and 2) sustained abstinence: transition from the Recent Quitter state to the Former Smoker state, with a lower rate of later relapse back to the Current Smoker state.

STOP model structure

STOP is an individual-level Monte Carlo microsimulation.[38,39] An individual enters the model with age and smoking status defined by random realizations from specified probability distributions. STOP follows a state-transition framework: individuals transition monthly through various cigarette smoking states (figure 1). Transitions between these states depend on age- and sex-stratified monthly smoking initiation and cessation probabilities. Ex-smokers have monthly relapse probabilities (figure 1). Monthly mortality probabilities depend on age, sex, and smoking status. Those who quit smoking retain the all-cause mortality probabilities of current smokers until maintaining abstinence for a defined period of time, after which the mortality probabilities decline.[1,8,40]

Individuals are simulated in series: for each simulated person, the model tracks smoking behavioral events (smoking initiation, quit attempt, relapse) and the duration spent in each smoking state. Upon an individual's death, the next simulated person enters the model. Once a cohort large enough to attain stable estimates has been simulated, summary statistics are calculated, including mean number of quit attempts, life expectancy, and the monthly prevalence of never, current, and former smokers. For the purpose of model output displays, those in the Recent Quitter state are considered "former smokers." We use a constant simulated population size of one million to obtain stable estimates of these "average" outcomes of interest.

Internal validation

We conducted internal model validation by comparing model outputs to expected results and by conducting sensitivity analysis.

Cross-validation

Overview and outcome comparisons

We conducted cross-validation by simulating the US population born in 1950, following them monthly until 2020, and then comparing STOP results to those from CISNET modeling studies (table 1 and supplementary text).[28] We selected the 1950 birth cohort because smoking prevalence in the US peaked in the 1960s, which was the smoking initiation period (adolescence) for these individuals, and data collection frequency increased concurrently. We compared STOP-generated results to CISNET-reported results for the prevalence of female and male current, former, and never smokers over time.[40]

We used CV-RMSE to assess the goodness-of-fit of the six sets of prevalence curves.[29,32] First, RMSE was calculated as the square root of the average of the squared difference between STOP-projected prevalence and CISNET-projected prevalence at each year of age. Then, we calculated CV-RMSE by dividing RMSE by mean modeled prevalence, representing the relative error.

CISNET Model

CISNET is a collaboration of National Cancer Institute-supported investigators modeling the impact of interventions on population incidence and mortality of various types of cancer, including lung cancer. The Yale CISNET-Lung models, for subsequent analyses of cancer care interventions, used data from NHIS to generate detailed smoking initiation and cessation rates, stratified by birth year, age, and sex, and mortality rates, stratified by birth year, age, sex, and smoking status.[37,41]

Input parameters for initial cross-validation

For the initial cross-validation exercise, we used data from CISNET modeling studies, which were derived from NHIS through 2009 and were stratified by birth cohort (table 2).[37,41] Specifically, we used CISNET age- and sex-stratified smoking initiation and cessation rates and smoking-stratified mortality rates among US women and men born in 1950, converting them to monthly probabilities. The CISNET smoking cessation rates reflected a direct transition from current smoker to former smoker after at least two years of sustained abstinence.[41] This initial exercise used the same input parameters as CISNET and did not include smoking relapse.

Table 2. STOP model input parameters applied in each validation exercise.

Input parameter	Cross-validation	External validation of mortality	External validation of smoking prevalence
Input parameters from CISNET (for cross-validation), NHIS 1997-2009 (for external validation of mortality), or NHIS 1997 (for external validation of smoking prevalence)			
Baseline cohort characteristics			
Women/Men, %[a]	---	52/48	52/48
Initial age, mean, years (SD)	0 (followed a birth cohort)	39.7 (21.4)	39.1 (20.7)
Minimum/maximum age, years	---	18/84	18/84
Initial prevalence of never/current/former smokers[b], %	100/0/0	56/22/22	52/25/23
Years since cessation among former smokers, mean (SD)	---	15.6 (12.7)	14.4 (11.9)
Smoking behavior events			
Monthly smoking initiation probability, by age and sex	0-0.0093	0-0.0063	0-0.0063
Monthly smoking cessation probability, by age and sex	0-0.015	0-0.035	0-0.035
Mortality			

Monthly mortality probability[c], by age and sex, x 10^{-4}			
Never smokers	0-12.8	0.4-95.2	0.4-95.2
Current smokers	0-34.6	0.4-136.1	0.4-136.1
Former smokers	Multiplier applied (see last row)	0-111.5	0-111.5
Input parameters derived from smoking studies or from authors' calibration			
Monthly relapse probability[d] (*t* = months since cessation)	$P_{Relapse} = 0.62*e^{-0.33*t}$	$P_{Relapse} = 0.62*e^{-0.33*t}$	$P_{Relapse} = 0.62*e^{-0.33*t}$
Cessation rate multiplier (calibrated), women/men	7.75/7.25	7.75/7.25	7.5/7
Initiation rate multiplier (calibrated), women/men	---	---	0.9/1.0
Former smoker mortality multiplier, applied to never smoker mortality, by sex and age at quit[e]	1.0-2.2	---	---

STOP: Simulation of Tobacco and Nicotine Outcomes and Policy. CISNET: Cancer Intervention and Surveillance Modeling Network. NHIS: National Health Interview Survey. SD: standard deviation. The numbers show model input parameters applied in cross-validation (left column), external validation of mortality (center column), and external validation of smoking prevalence (right column).

[a]In cross-validation, we simulated cohorts of either all women or all men from birth. Thus, no distributions of initial age are displayed.

[b]Prevalence of each smoking status displayed here is the mean over all strata, but in the model these were stratified by 5-year age group and sex from ages 18 to 84.

[c]Additional details about mortality data are in supplementary table 2.

[d]This is based on relapse probabilities reported in smoking cessation intervention trials, focusing on placebo arms.[42–45]

[e]For the 1950 birth cohort, some CISNET-derived former smoker mortality rates are lower than CISNET-derived never smoker mortality rates – a counterintuitive relationship otherwise unexplained. We therefore adapted former smoker mortality multipliers for the cross-validation from Thun et al.[40]

Incorporating smoking relapse and calibrating cessation probabilities

The STOP model specifically includes smoking relapse, critical to projecting both short-term and long-term impacts of smoking cessation interventions and novel tobacco and nicotine products.

Following the initial cross-validation of the STOP model (without relapse), we added smoking relapse probabilities and then recalibrated the model by adjusting the previously-applied smoking cessation probabilities. First, we modeled relapse as an exponential decay function of time since quit, such that the highest risk of relapse was in the first month after a quit attempt. The coefficient and time constant are based on relapse probabilities in smoking cessation trials (table 2).[42–45] Second, we calibrated the previously-applied cessation probabilities (derived from CISNET cessation data) by a multiplier to reflect:

1) a quit attempt rather than sustained abstinence; and 2) the higher likelihood of making a quit attempt rather than attaining sustained abstinence in a given month. This multiplier represents the average number of quit attempts, lasting at least one month, prior to attaining sustained abstinence. We compared our multipliers to published data on the average number of quit attempts required to attain sustained abstinence.[27] Our overall aim for this calibration step was to identify a STOP-generated current smoker prevalence curve with an RMSE <0.01 compared to the CISNET model-generated current smoker prevalence curve, similar to previously described methods.[32]

External validation

Overview and outcome comparisons

For external validation, we compared STOP model results to NHIS data.[28,36] We accounted for smoking initiation, smoking cessation, and mortality. Because NHIS data do not explicitly report relapse, we incorporated smoking relapse and the best-fitting cessation multipliers found in the cross-validation calibration step. We compared two outcomes: mortality and smoking prevalence (table 1 and supplementary text).

First, to project and validate mortality outcomes, we simulated the population surveyed by NHIS from 1997 through 2009 (supplementary text). To compare STOP-generated mortality rates to those derived from NHIS – stratified by age, sex, and smoking status – we used MAPE, the mean absolute value of the percent difference between STOP and NHIS values. We also produced curves of cumulative mortality from STOP-generated results and from NHIS data, stratified by sex and by current/never smoking status. These curves reflect 20-year-old current smokers who continue to smoke until death or 20-year-old never smokers who never start smoking. We compared the four sets of cumulative mortality curves by RMSE and CV-RMSE (STOP versus NHIS) from age 20 years until age 84 years (goal RMSE <0.01). We did not generate mortality curves for 20-year-old former smokers because mortality risks for those who stop smoking prior to age 20 are similar to those of never smokers.[1] Also, mortality risks depend on age at cessation, and at older ages this heterogeneous group would include people who quit smoking at a variety of ages.[1,40]

Second, with those surveyed by NHIS in 1997 as the input cohort, we used the STOP model to project the prevalence of current, former, and never smokers each year from 1998 to 2009. In a two-way sensitivity analysis, we re-calibrated cessation multipliers and initiation multipliers with the goal of identifying multipliers that would minimize the CV-RMSE of STOP-reported current smoker prevalence compared to NHIS current smoker prevalence. The initiation multipliers were applied to smoking initiation rates for never smokers. We then compared the cessation multipliers from this step with those from the cross-validation calibration step.

Input parameters

Initial distributions of age, sex, and smoking status for the population simulated in the external validation exercises came from two sources: aggregated 1997-2009 NHIS data for the mortality external validation, and 1997 NHIS data for the smoking prevalence external validation (table 2 and supplementary figure 1). We obtained NHIS data in aggregate for years 1997-2009 from the Integrated Public Use Microdata Series.[35] We used NHIS data through 2009 because those were the data used in the CISNET studies, which were our comparator in cross-validation exercises.[37,41] These data provided initial distributions of smoking status and years of abstinence for former smokers (to inform relapse risks). From these 1997-2009 NHIS data, we derived age- and sex-specific smoking initiation and cessation rates using self-reported age at initiation and age at cessation variables (supplementary table

1). As in our cross-validation exercises, we converted the cessation rates to quit attempt rates by incorporating relapse rates and cessation multipliers.

The NHIS data included linked National Death Index (NDI) mortality outcomes through 2011 for respondents for whom mortality data were available. We calculated mortality rates by age, sex, and smoking status of the same NHIS respondents (supplementary table 1).

Patient and public involvement

We did not involve patients or the public in our work.

Ethics statement

This study was approved by the Partners Human Research Committee (2019P001772).

RESULTS

Cross-validation

Initial cross-validation, without relapse

The STOP-projected prevalence of current, former, and never smokers over time fit CISNET-projected data well for the 1950 birth cohort in the US (figure 2, blue line vs. red dotted line, RMSE <0.03, CV-RMSE 15%/7% for women/men). The STOP-estimated prevalence of current smokers at age 25 years, approaching peak prevalence for the 1950 birth cohort, was 40% for women and 54% for men, compared to CISNET estimates of 38% and 52%.

Incorporating smoking relapse and calibrating cessation probabilities

After incorporating smoking relapse, the prevalence of current smokers far exceeded that reported by the CISNET model, as expected since many of those who would have become former smokers reverted to being current smokers (figure 2, pink dashed lines). We then aimed to reflect all quit attempts rather than only transitions to sustained abstinence. In rough calibrations, we found that the optimal multiplier would be between 5 and 10 when applied to cessation rates from the previous step. In finer calibrations, we varied the multiplier across the range of 5 to 10 in increments of 0.25. We found that multiplying the CISNET-reported cessation rates by 7.75 for women and by 7.25 for men best approximated the CISNET-projected prevalence of current smokers, with RMSE 0.004/0.008 and CV-RMSE 2%/3% for women/men (figure 2, black lines).

External validation

Mortality

In simulating the 1997-2009 NHIS population along with smoking relapse, we found that the age-, sex-, and smoking-stratified mortality rates generated by the STOP model were a good fit to those derived from NHIS (MAPE 7%, examples in supplementary table 2). Cumulative mortality curves for 20 year-old female and male current smokers and never smokers were similar between STOP projections and NHIS-derived data, with RMSE <0.01 and CV-RMSE ≤1% (figure 3). For 20-year-olds who continued to smoke until death, the STOP model predicted median life expectancy (counting years from birth) of 77.5 years for women and 72.5 years for men.

Smoking prevalence

Using those surveyed by NHIS in 1997 as the input cohort, the STOP-projected prevalence of current, former, and never smokers each year from 1998 to 2009 was similar to that reported by NHIS, with overall RMSE 0.04 and CV-RMSE 12% for both women and men (ages 30-84 years combined; supplementary figure 2 shows results specifically for ages 40-44 years). Compared to NHIS, the STOP model slightly underpredicted never smoker prevalence and slightly overpredicted former smoker prevalence in later years. In the two-way sensitivity analysis, we found that cessation multipliers of 7.5/7.0 for women/men and initiation multipliers of 0.9/1.0 provided the best overall fit (lowest RMSE) of STOP-projected current smoker prevalence compared to that reported by NHIS (supplementary figure 3).

DISCUSSION

We developed, calibrated, and validated STOP, a novel microsimulation model of individual-level tobacco use behaviors and outcomes. Our initial model input parameters included smoking initiation and cessation and smoking-stratified mortality, and we demonstrated cross-validity compared to the CISNET model. After incorporating relapse, we calibrated smoking cessation probabilities to reflect quit attempts rather than sustained abstinence. We then validated STOP model output with: 1) smoking prevalence over time reported by the CISNET model for US women and men born in 1950; 2) age-, sex-, and smoking-stratified mortality rates and cumulative mortality reported by the NHIS-NDI linked database for the years 1997-2009; and 3) prevalence of current, former, and never smokers by sex from 1998 to 2009 reported by NHIS, using 1997 NHIS-reported population characteristics as inputs.

Most existing tobacco models simulate at the population level or lack the capacity to consider smoking initiation and (non-sustained) quit attempts throughout a lifetime.[18,23–25,37,46,47] The individual-level details of STOP can be employed to simulate and compare behaviors and interventions. While this calibration and validation analysis focused on cigarette smoking because of the availability of historical data for comparisons, we intend to broaden the use of STOP to include electronic cigarettes (e-cigs). Longitudinal cohort studies and clinical trials are examining the effects of e-cig use on tobacco smoking behaviors and clinical outcomes over long time horizons, but data are needed now to inform guidelines and policy around these novel products.[15,44,48,49] Results from multiple distinct, validated models can help motivate policy decisions, and consistency of policy recommendations across unique, independent models reinforces confidence in their recommendations.[50–54]

A novel aspect of the STOP model is the incorporation of smoking relapse on a monthly basis, reflecting the understanding of nicotine addiction as a chronic relapsing condition with rapid cycles between use and cessation.[26,45,55–58] This key feature enables an important distinction between a quit attempt and sustained abstinence. This distinction is missing from most tobacco models and indeed from many epidemiologic studies of smoking and smoking cessation, which consider the transition from "current" to "former" smoker to be an abrupt one that results in sustained abstinence. Incorporating relapse required calibrating cessation rates by applying multipliers. The cessation multipliers that provided the best fits to empirical data are in line with published data regarding the number of quit attempts required before sustained abstinence is achieved.[27,55,59] The slightly higher multiplier needed for women compared to men is consistent with NHIS data showing that among ever smokers (current smokers plus former smokers) aged 60 years and above, a greater proportion of women compared to men are former smokers.[35] Calibration of cessation rates may compensate for other inaccuracies in model inputs or structure, though the pre-calibration (without relapse) STOP-generated results fit well with those of CISNET.

Many trials of smoking cessation interventions follow patients for a few months or up to one year, but they do not report subsequent relapse. By including relapse, the STOP model can combine data from short-term trials of smoking cessation interventions with data from natural history studies of smoking and smoking cessation to project longer-term outcomes including sustained abstinence. The flexibility to integrate data from a variety of sources is a strength of modeling analyses.

Going forward, we plan to use the STOP model to study contemporary rather than historical populations and to predict future tobacco use, while utilizing deterministic and probabilistic sensitivity analyses to account for uncertainty in future behavioral transition probabilities and mortality probabilities.[60] As no empirical data exist with which to validate model output of future tobacco use, we validated STOP model output against historical populations. Most US historical data on smoking prevalence and smoking-associated mortality are based at least in part on NHIS, the oldest ongoing survey of smoking prevalence in the US.[1,61–63] We compared STOP model output to CISNET model output, to NHIS itself, and to results from a study by Jha et al.,[1] all of which used NHIS data. We demonstrated cross-validity of STOP compared to CISNET model results when using CISNET input parameters and then added relapse probabilities and cessation multipliers. We demonstrated external validity, in a partially dependent manner, of STOP compared to NHIS data when using some NHIS-derived input parameters plus the external relapse probabilities and cessation multipliers from our cross-validation. Though independent external validation sources are ideal, dependent sources can still be useful, especially in this scenario where most of the available US historical smoking prevalence, behavior, and mortality data are derived from NHIS.[28] Of note, in a two-way sensitivity analysis in which we simultaneously varied the smoking initiation and cessation multipliers to achieve a close fit to NHIS smoking prevalence data, the optimal cessation multipliers were very similar to those we found in our cross-validation calibration step, demonstrating the robustness of these multipliers across different sets of assumptions.

In an external validation exercise, the STOP model projection for never smoker prevalence from 1998 to 2009 was slightly lower than that reported by NHIS, and the STOP model projection for former smoker prevalence was slightly higher than NHIS data. In NHIS, former smokers were self-defined but on average had been abstinent for over a decade. NHIS considered those who smoked "some days" to be current smokers, though some of them may have been in the midst of a short-duration quit attempt. STOP model output formally labels these people, who may be in the Recent Quitter state, , former smokers but assigns them the mortality risks of current smokers (until a defined period of abstinence). STOP reflects monthly quitting and relapsing behaviors whereas NHIS is an annual cross-sectional survey. Thus, one would expect the STOP model to report a higher prevalence of former smokers than NHIS, as seen in our results. Immigration could also account for some of the difference between NHIS data and STOP model-generated results: immigrants were surveyed in NHIS but our model analysis does not account for them. Smoking prevalence differs between the immigrant and non-immigrant populations.[64,65] On the other hand, STOP model-generated life expectancies were similar to the median life expectancies for 30-year-old smokers reported by Jha et al. (also derived from NHIS data): 77 years for women and 72 years for men.[1]

The STOP model has features, and will have applications, not described in this analysis. We developed the model to incorporate resource utilization. The STOP model can capture the healthcare costs associated with being a current, former, or never smoker, as well as the costs of tobacco cessation interventions. By incorporating the chronic relapsing nature of nicotine addiction, the STOP model can account for the resources required for recurrent cessation interventions (e.g., restarting the same or a different intervention after smoking relapse), an important consideration in cost-effectiveness and policy analyses. Ultimately, we will use the STOP model to evaluate behavioral and clinical outcomes, costs of care, and cost-effectiveness of tobacco cessation interventions, programs, and policies. An overarching goal is to provide information that can inform decision makers – including clinicians, public health officials, and policymakers – on cost-effective interventions that reduce the clinical and economic burden of tobacco use. The model can eventually assess the impact of different financing options for tobacco cessation interventions – for example, annual versus lifetime insurance coverage limits. The STOP model's flexibility will allow for analyses beyond US populations, including settings where smoking-related behaviors and clinical outcomes may be different from those in the US.[66]

The STOP model has limitations. Its projections are limited by assumptions and the degree of specificity of available data – for example, age, sex, and birth year stratifications of smoking behavioral transitions. While we have aimed to calibrate and validate the model with the best available historical data, any use of the model to project future outcomes should be approached with prudence. Calibration on historical data is no panacea because of concerns of calibration drift. Nonetheless, input parameter values can be varied in sensitivity analysis. STOP does not include dynamics such as the effects of one person's smoking on another person's smoking behaviors. Smoking is associated with other factors not directly captured by STOP, including race, socioeconomic status, mental illness, and other substance use, but different populations can be separately simulated in the model with input parameters specific to that population. There is considerable heterogeneity in smoking behaviors, including cigarettes consumed per day and daily versus nondaily smoking. STOP enables stratification by intensity of smoking, which can be used to represent amount or frequency of smoking.

In conclusion, STOP is a novel, individual-level microsimulation model that captures tobacco-related behaviors – importantly including relapse – and outcomes with a goal of informing decision making around tobacco cessation interventions and tobacco policy. We have demonstrated that the model is well-calibrated and validated to another model and to historical cohorts. We plan to use the model for policy-relevant analysis of contemporary patient-level and population-level care while reflecting real-life tobacco use and cessation behaviors.

AUTHOR CONTRIBUTIONS

Specific contributions are as follows:

KPR – study conception, study design, data analysis, data interpretation

AJB – study design, data analysis, data interpretation

DEL – study design, data interpretation

PT – data analysis, data interpretation

EPH – study design, data interpretation

TH – study conception, study design, data analysis

BO – study design

LY – data analysis, data interpretation

FMS – study design, data analysis, data interpretation

ADP – study design, data interpretation

KAF – study design, data interpretation

MCW – study design, data interpretation

NAR – study conception, study design, data interpretation

RPW – study conception, study design, data interpretation

KPR drafted the first version of the manuscript. All authors critically reviewed the manuscript for important intellectual content and approved the final submitted version.

COMPETING INTERESTS

NAR receives royalties from UpToDate, Inc., is a consultant for Achieve Life Sciences, and has been an unpaid consultant for Pfizer. All other authors report no competing interests.

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DATA STATEMENT

Data used to parameterize the model are publicly available at https://resources.cisnet.cancer.gov/projects and at https://nhis.ipums.org/nhis.

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FIGURE LEGENDS

Figure 1. Overview of tobacco use states and transitions in Simulation of Tobacco and Nicotine Outcomes and Policy (STOP) microsimulation model.

This is a simplified, stylized depiction of smoking states and transitions – for example, dimensions such as age and sex are not represented in the figure. The ovals represent possible cigarette smoking states or the deceased state. The arrows represent monthly transitions by which an individual can switch to a different state. The "Abstinence, sustained" transition is depicted by a dashed line because there is not a monthly probability of transition – instead, the transition occurs after an individual has spent a user-defined duration (e.g., one year) in the "Recent Quitter" state. Numerical examples of the transition probabilities are in supplementary table 1.

Figure 2. Cross-validation and calibration exercise: STOP-generated results and CISNET-generated results for current smoking prevalence over time for US people born in 1950.

STOP: Simulation of Tobacco and Nicotine Outcomes and Policy model. CISNET: Cancer Intervention and Surveillance Modeling Network.

Panel A depicts women, Panel B depicts men. The red dotted line shows results from the CISNET model. The other three lines show STOP-generated results after each step of our parameterization and calibration process. The blue line includes parameterization of smoking initiation and cessation, but not relapse. The pink dashed line includes smoking relapse as based on published studies. The black line includes calibration of smoking cessation probabilities to reflect quit attempts and relapse before sustained abstinence.

Figure 3. External validation: STOP model results and NHIS/NDI results for cumulative mortality of current smokers and never smokers from age 20.

STOP: Simulation of Tobacco and Nicotine Outcomes and Policy. NHIS: National Health Interview Survey. NDI: National Death Index. CV-RMSE: coefficient of variation of root-mean-square error.

Panel A depicts women, Panel B depicts men. Within each panel, the STOP results and the NHIS data are not easily distinguishable because they are essentially overlapping. Current smokers are those who continue to smoke until death. NHIS was linked to NDI for mortality data.

Figure 1

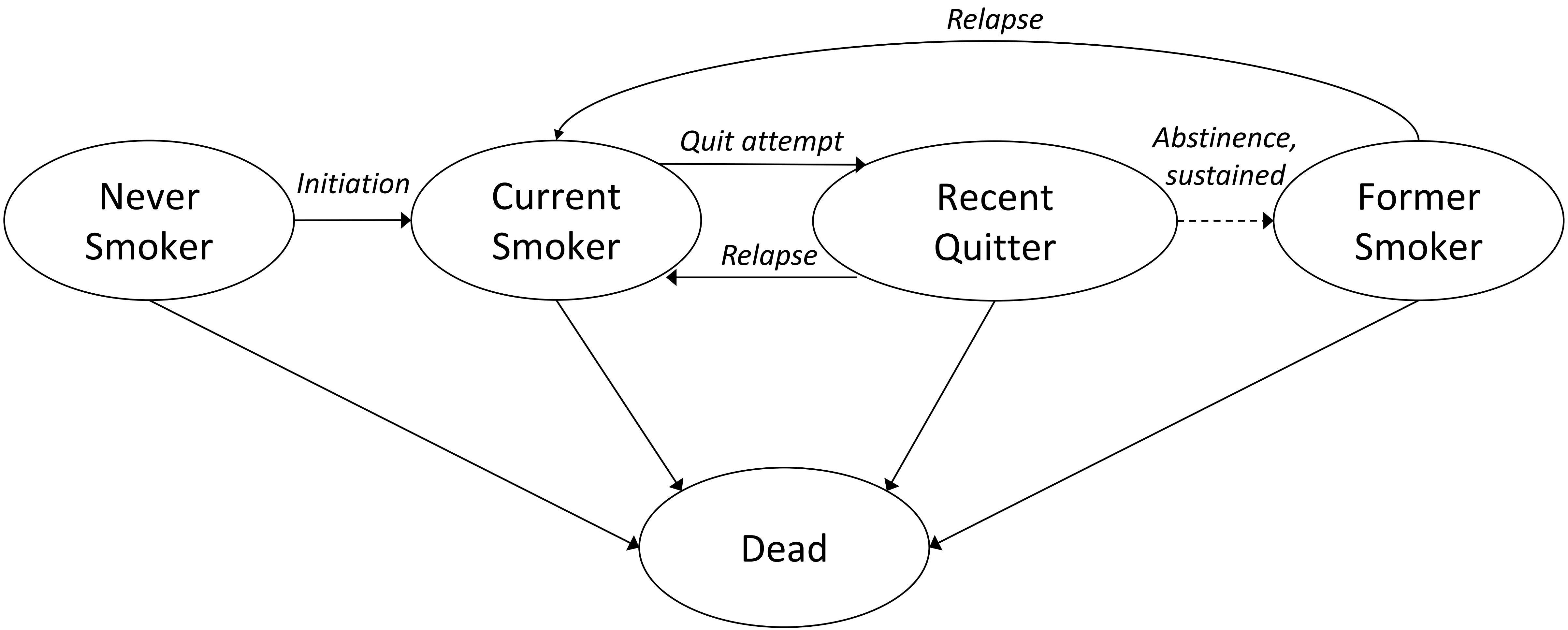

Relapse
Quit attempt
Abstinence, sustained
Initiation
Never Smoker
Current Smoker
Recent Quitter
Former Smoker
Relapse
Dead

Figure 2

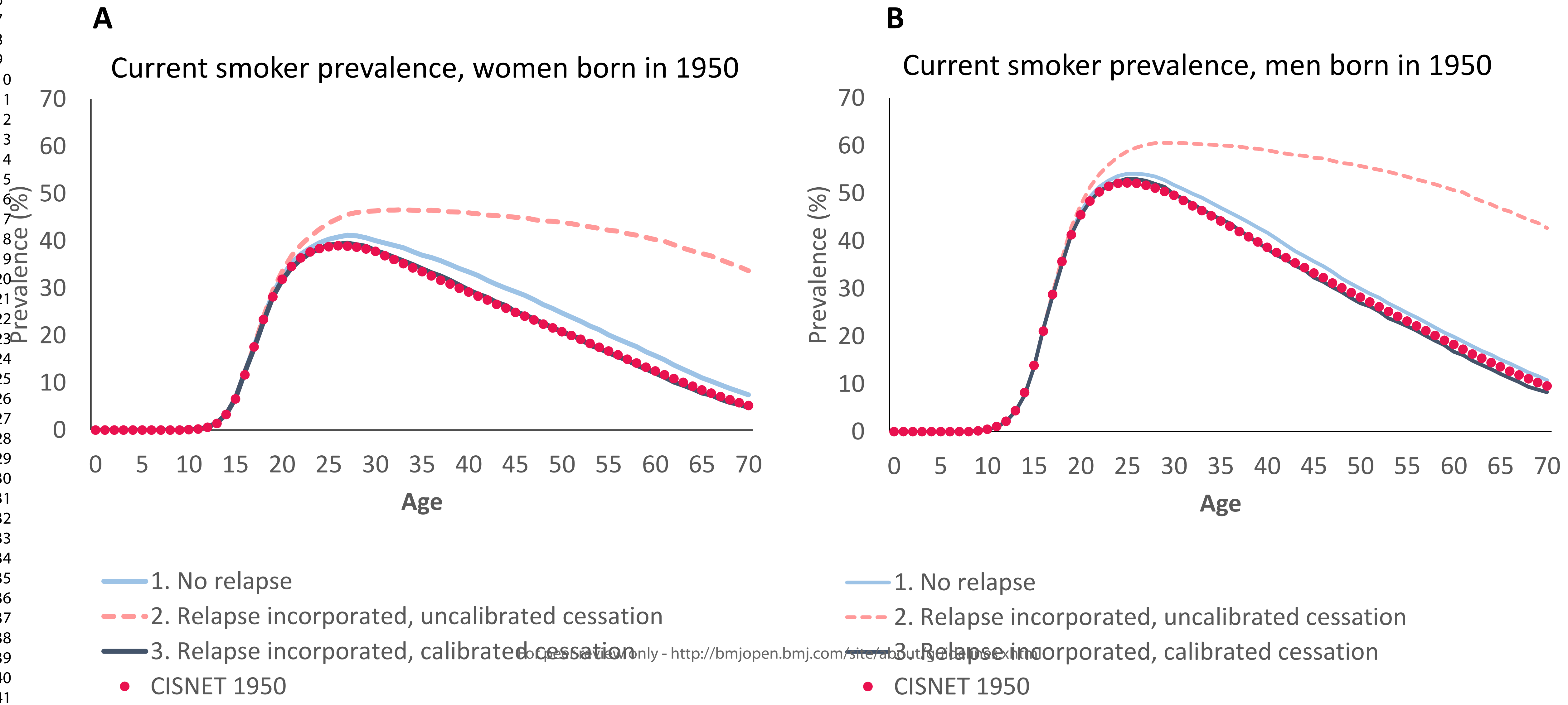
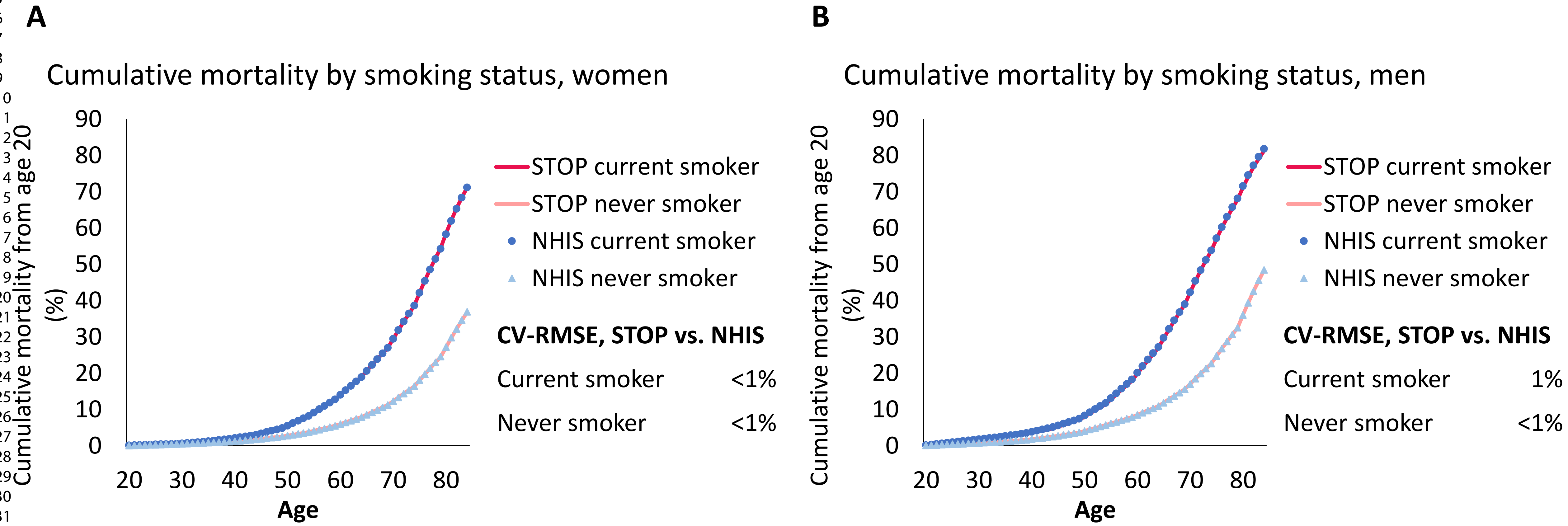

A
Current smoker prevalence, women born in 1950
Prevalence (%)
Age
B
Current smoker prevalence, men born in 1950
Prevalence (%)
Age
1. No relapse
2. Relapse incorporated, uncalibrated cessation
3. Relapse incorporated, calibrated cessation
CISNET 1950

Figure 3


A
Cumulative mortality by smoking status, women
Cumulative mortality from age 20 (%)
90
80
70
60
50
40
30
20
10
0
20
30
40
50
60
70
80
Age
STOP current smoker
STOP never smoker
NHIS current smoker
NHIS never smoker
CV-RMSE, STOP vs. NHIS
Current smoker <1%
Never smoker <1%
B
Cumulative mortality by smoking status, men
Cumulative mortality from age 20 (%)
Age
STOP current smoker
STOP never smoker
NHIS current smoker
NHIS never smoker
CV-RMSE, STOP vs. NHIS
Current smoker 1%
Never smoker <1%

A novel microsimulation model of tobacco use behaviors and outcomes:

calibration and validation in a US population

Supplement

Krishna P. Reddy, Alexander J.B. Bulteel, Douglas E. Levy, Pamela Torola, Emily P. Hyle, Taige Hou, Benjamin Osher, Liyang Yu, Fatma M. Shebl, A. David Paltiel, Kenneth A. Freedberg, Milton C. Weinstein, Nancy A. Rigotti, Rochelle P. Walensky

Table of Contents

METHODS: SUPPLEMENTARY TEXT

National Health Interview Survey (NHIS)

NHIS is a yearly in-person questionnaire administered to the civilian noninstitutionalized population of the US which, since 1965, has collected information on individual smoking status. Since 1991, the smoking section of the NHIS has first queried "ever smoker" status – defined as having smoked at least 100 cigarettes in one's lifetime – then asked ever smokers, "Do you NOW smoke cigarettes every day, some days or not at all?" which resulted in the classification of occasional smokers as current smokers, even though they initially may have said they did not smoke now. Regardless of response to the second question, participants were asked about the frequency of their smoking.[1]

Use of NHIS data in the Simulation of Tobacco and Nicotine Outcomes and Policy (STOP) model

We downloaded NHIS and linked National Death Index (NDI) data from the Integrated Public Use Microdata Series (IPUMS) Health Surveys for the years 1997-2009.[2] We obtained basic demographic information, smoking status and behavioral variables, and death status/year of death reported through 2011. For all derivations below, we excluded those with unknown smoking or mortality status. Only people 18 years of age or older were surveyed about tobacco use, and since ages 85+ years are censored, we excluded those as well.

External validation - mortality

From the pooled 1997-2009 data, we used the IPUMS-recoded and -constructed survey weights adjusting for differential representation in the smoking sub-sample and NDI follow-up. Because of the NHIS sampling design, weights must be used so that the survey respondents can be collectively expanded to represent the civilian noninstitutionalized population of the US. These weights represent a surveyed individual's inverse probability of being included in both the survey supplement, which contains questions about smoking, and the NHIS-NDI linked mortality files.

Smoking cessation inputs: We derived age- and sex-stratified cessation rates using the NHIS variable that reported years since respondents (former smokers) quit smoking. We excluded quit ages before age 16 years (due to perceived inconsistency of coding of the "time since quit" variable – some entries implied negative quit age) and included quit ages through age 85 years.

Smoking initiation inputs: Similarly, we derived initiation rates, also age- and sex-stratified, using the variable that reported years since the respondent (a current or former smoker) started to smoke regularly. We used initiation rates from ages 6 to 61 years, the last age for which data are consecutively available for both women and men.

Mortality inputs: We calculated mortality rates by age, sex, smoking status, and five-year age group using the smoking status variable and NDI reporting through 2011. The rates were calculated from a follow-up period beginning in the respondent's survey year and ending in 2011 or the year of her/his death, whichever came first. Because smoking behavior data were collected only at baseline in NHIS and not again at the time of death, there may have been some misclassification of smoking status (e.g., someone who was a current smoker at the time of NHIS assessment may have subsequently quit and later died but was still considered a current smoker). However, all-cause mortality rates do not significantly decrease until a few years after cessation, and we considered those who had quit smoking to have similar mortality risks to current smokers until five years of abstinence. This reflects contemporary studies in which former smokers were defined as those who had not smoked in the previous five years and data from large US cohort studies that indicate that the all-cause mortality risk in men who quit smoking does not fall below that of current smokers until five years of abstinence.[3,4]

Input cohort: We derived initial cohort characteristics for this analysis from the NHIS 1997-2009 pooled dataset: current, former and never smoking prevalence by five-year age group from age <20 to 84 years; mean (standard deviation [SD]) age adjusted for bounding of the distribution; sex distribution; and mean (SD) time since quit bounded by a minimum quit age of 16 years.

Output comparison: We compared STOP model output for mortality to NHIS/NDI-reported mortality in the form of mortality rates and cumulative mortality from age 20 years.

External validation – smoking prevalence

From the NHIS 1997 data, using the same survey weights as above:

Smoking cessation, smoking initiation, and mortality inputs: We used the same cessation, initiation, and mortality rate inputs as for the mortality validation.

Input cohort: We derived input cohort characteristics for this analysis from the 1997 NHIS data: current, former, and never smoking prevalence by five-year age group from age <20 to 84 years; mean (SD) age adjusted for bounding of the distribution; sex distribution; and mean (SD) time since quit bounded by a minimum quit age of 16 years.

Output comparison: Starting with the 1997 NHIS respondents and following them each year from 1998 to 2009, we compared STOP projections to NHIS data regarding prevalence of current, former, and never smokers by five-year age group from age 30 to 84 years.

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Supplementary Table 1. Examples of transition probabilities in the simulation model.

Parameter	**Value**	**Reference**
Smoking initiation probability, monthly, by age and sex	0-0.0063	Derived from NHIS 1997-2009 data
Cessation probability, monthly, by age and sex	0-0.035	Derived from NHIS 1997-2009 data
Relapse probability, monthly, by time since cessation	$P_{Relapse} = 0.62 * e^{-0.33*t}$	[5–8]
Never Smoker mortality probability, monthly, by age and sex, x 10^{-4}	0.4-95.2	Derived from NHIS/NDI 1997-2009 data
Current Smoker or Recent Quitter mortality probability, monthly, by age and sex, x 10^{-4}	0.4-136.1	Derived from NHIS/NDI 1997-2009 data
Former Smoker mortality probability, monthly, by age, sex, and time since cessation[a], x 10^{-4}	0-111.5	Derived from NHIS/NDI 1997-2009 data
Time to transition from Recent Quitter to Former Smoker	5 years[b]	Assumption, [3,4]

NHIS: National Health Interview Survey. NDI: National Death Index. STOP: Simulation of Tobacco and Nicotine Outcomes and Policy.

[a]These former smoker mortality probabilities were used only in the external validation exercises, comparing STOP model output to NHIS/NDI results. In cross-validation comparing STOP model output to

the CISNET model results, we applied multipliers to never smoker mortality rates to derive former smoker mortality rates and then converted these to probabilities.

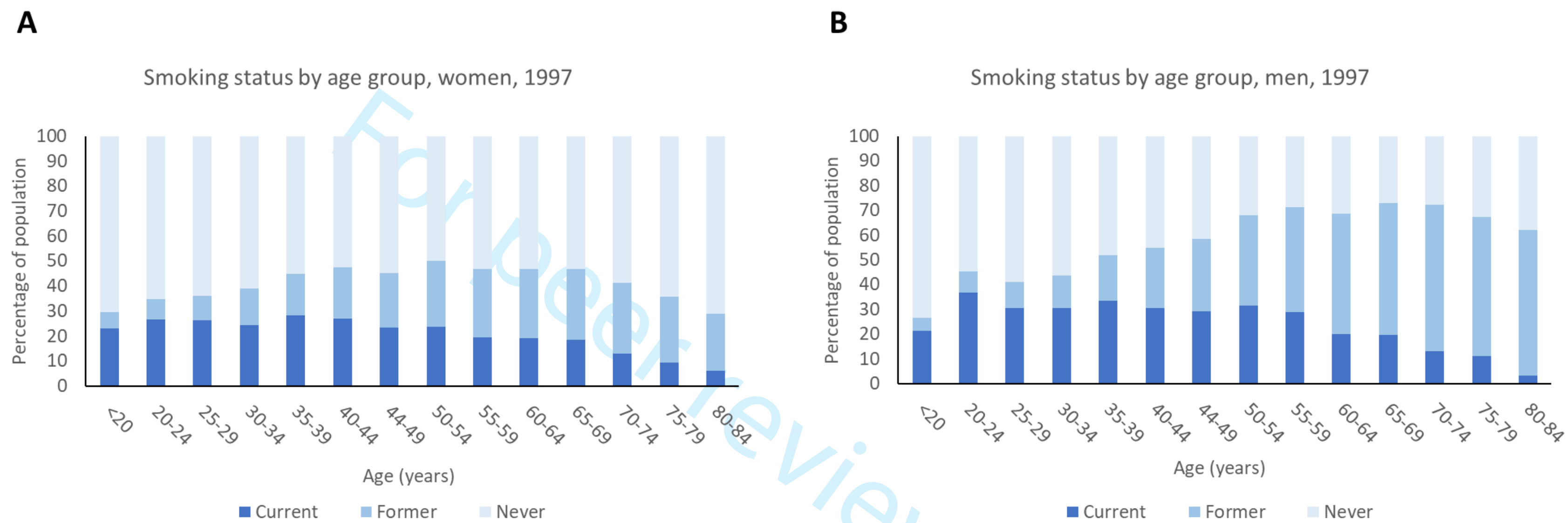
[b]This five-year abstinence period was based on data showing mortality risks by years since smoking cessation.[3,4] We performed an analysis in which we assumed that mortality risks decreased to "Former Smoker" levels immediately upon quitting smoking, but the model-generated results were not a better fit to NHIS data (results not shown).

Supplementary Table 2. **Selected age- and sex-specific annual mortality rates: STOP model output versus NHIS-derived mortality.**

Women						
	Current Smoker		Former Smoker		Never Smoker	
Age group, years	STOP	NHIS/NDI	STOP	NHIS/NDI	STOP	NHIS/NDI
40-44	0.0023	0.0023	0.0017	0.0015	0.0012	0.0012
50-54	0.0071	0.0071	0.0035	0.0029	0.0025	0.0025
60-64	0.0147	0.0146	0.0087	0.0079	0.0051	0.0051
Men						
	Current Smoker		Former Smoker		Never Smoker	
Age group, years	STOP	NHIS/NDI	STOP	NHIS/NDI	STOP	NHIS/NDI
40-44	0.0031	0.0034	0.0028	0.0025	0.0018	0.0018
50-54	0.0094	0.0096	0.0059	0.0053	0.0042	0.0043
60-64	0.0233	0.0232	0.0114	0.0099	0.0067	0.0066

STOP: Simulation of Tobacco and Nicotine Outcomes and Policy. NHIS: National Health Interview Survey. NDI: National Death Index.

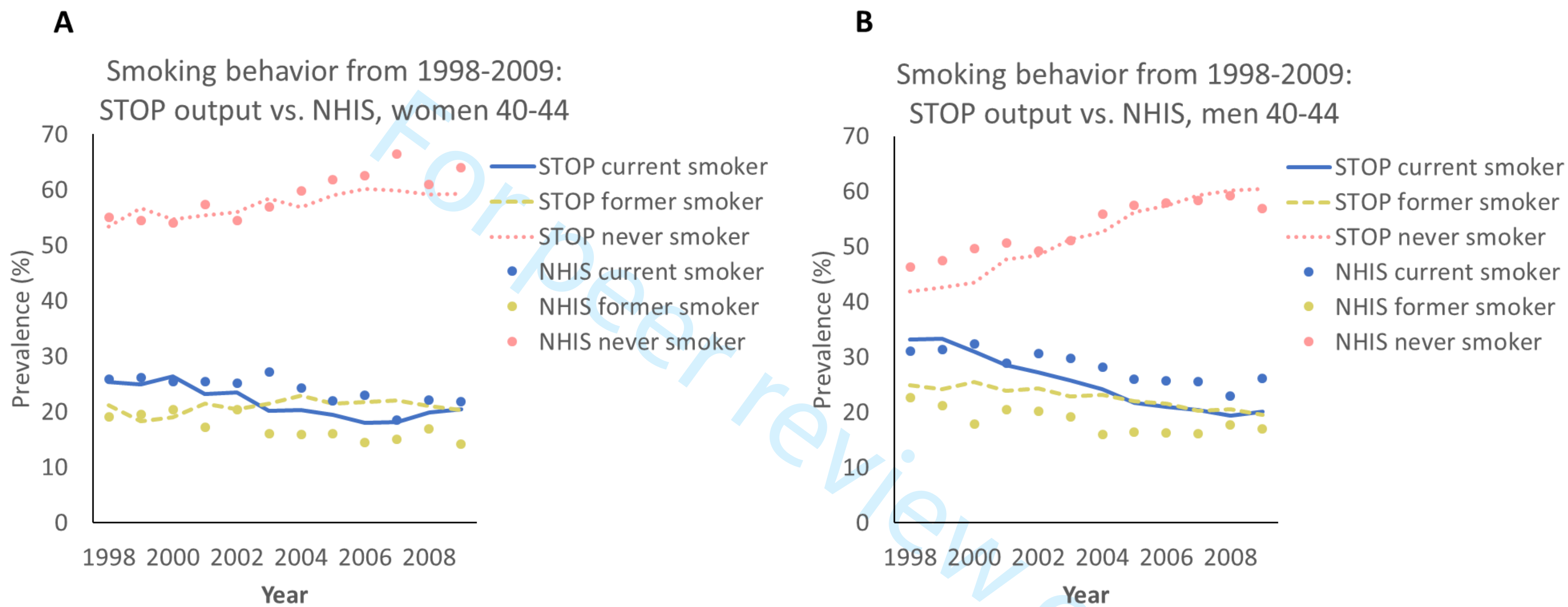
Supplementary Figure 1. Smoking status by age group and sex in 1997: STOP model inputs for the external validation exercise of smoking prevalence.



STOP: Simulation of Tobacco and Nicotine Outcomes and Policy. NHIS: National Health Interview Survey.

Panel A depicts women; Panel B depicts men. For each age group, the prevalence of current, former, and never smokers is entered as STOP model input. The external validation analysis of smoking prevalence, using weighted NHIS 1997 survey respondent data as inputs, projects smoking prevalence annually from 1998 to 2009.

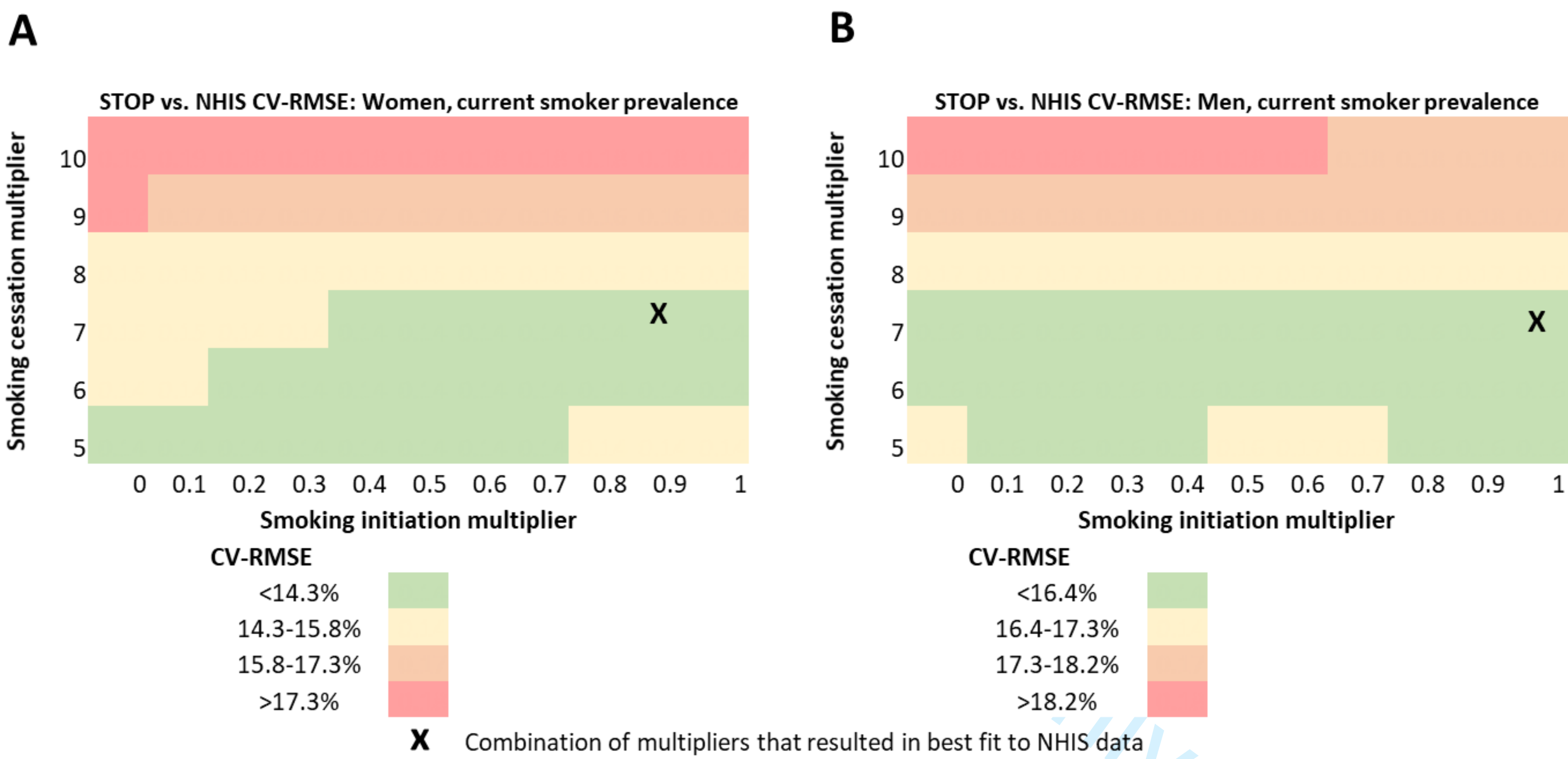
Supplementary Figure 2. External validation: STOP model results and NHIS results for prevalence of current, former, and never smokers each year from 1998 to 2009.



STOP: Simulation of Tobacco and Nicotine Outcomes and Policy. NHIS: National Health Interview Survey. NDI: National Death Index.

Panel A depicts women, Panel B depicts men. The STOP model cohort had the age and smoking status distribution of the 1997 NHIS survey respondents (Supplementary Figure 1). The STOP-generated results reflect a microsimulation that included probabilities of smoking initiation, smoking cessation, smoking relapse, and mortality.

Supplementary Figure 3. Two-way sensitivity analysis of smoking initiation and smoking cessation multipliers for external validation exercise.



STOP: Simulation of Tobacco and Nicotine Outcomes and Policy. NHIS: National Health Interview Survey. CV-RMSE: coefficient of variation of root-mean-square error.

Panel A depicts women; Panel B depicts men. The multipliers were applied to the original cessation and initiation rates derived from pooled 1997-2009 NHIS data and used in the STOP model. The horizontal axis shows the multiplier applied to smoking initiation rates (subsequently converted to probabilities) in the STOP model, and the vertical axis shows the multiplier applied to smoking cessation rates (subsequently converted to probabilities). Colored cells represent the CV-RMSE of STOP model-generated versus NHIS-reported current smoking prevalence among people ages 30-84 years from 1998 to 2009.

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A novel microsimulation model of tobacco use behaviors and outcomes: calibration and validation in a US population

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A novel microsimulation model of tobacco use behaviors and outcomes: calibration and validation in a US population

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ABSTRACT

Background and Objective: Simulation models can project effects of tobacco use and cessation and inform tobacco control policies. Most existing tobacco models do not explicitly include relapse, a key component of the natural history of tobacco use. Our objective was to develop, calibrate, and validate a novel individual-level microsimulation model that would explicitly include smoking relapse and project cigarette smoking behaviors and associated mortality risks.

Methods: We developed the Simulation of Tobacco and Nicotine Outcomes and Policy (STOP) model, in which individuals transition monthly between tobacco use states (current/former/never) depending on rates of initiation, cessation, and relapse. Simulated individuals face tobacco use-stratified mortality risks. For US women and men, we conducted cross-validation with a Cancer Intervention and Surveillance Modeling Network (CISNET) model. We then incorporated smoking relapse and calibrated cessation rates to reflect the difference between a transient quit attempt and sustained abstinence. We performed external validation with the National Health Interview Survey (NHIS) and the linked National Death Index. Comparisons were based on root-mean-square error (RMSE).

Results: In cross-validation, STOP-generated projections of current/former/never smoking prevalence fit CISNET-projected data well (coefficient of variation [CV]-RMSE ≤15%). After incorporating smoking relapse, multiplying the CISNET-reported cessation rates for women/men by 7.75/7.25, to reflect the ratio of quit attempts to sustained abstinence, resulted in the best approximation to CISNET-reported smoking prevalence (CV-RMSE 2%/3%). In external validation using these new multipliers, STOP-generated cumulative mortality curves for 20-year-old current smokers and never smokers each had CV-RMSE ≤1% compared to NHIS. In simulating those surveyed by NHIS in 1997, the STOP-projected prevalence of current/former/never smokers annually (1998-2009) was similar to that reported by NHIS (CV-RMSE 12%).

Conclusions: The STOP model, with relapse included, performed well when validated to US smoking prevalence and mortality. STOP provides a flexible framework for policy-relevant analysis of tobacco and nicotine product use.

Keywords: tobacco, nicotine, model, validation, calibration, relapse

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The STOP microsimulation model and our calibration and validation methods capture monthly individual-level tobacco use behaviors and outcomes, including relapse, a key factor in nicotine addiction.
- We validated STOP model results with those of another model and, in a partially dependent manner, with empirical data.
- We validated with multiple outcomes, including smoking prevalence and mortality.
- This analysis did not account for some aspects of heterogeneity in tobacco use behaviors.

INTRODUCTION

In the US, tobacco smoking reduces life expectancy by over a decade and accounts for over $200 billion in healthcare costs annually, approximately 9% of all healthcare costs in the country.[1,2] Though the prevalence of cigarette smoking among adults has decreased in the US, from 42% in 1965 to 14% in 2018, the decline has not been seen in all segments of society.[3,4] Meanwhile, tobacco treatment interventions, including behavioral therapy and pharmacotherapy, remain underutilized.[5] Novel tobacco and nicotine products raise many new clinical and policy questions.[6,7] Trial- and cohort-based data to fully inform these questions will not be available for many years. In the meantime, a timely way to address them is via modeling.

Simulation models provide a critical complement to more traditional research approaches.[8–14] Indeed, the Food and Drug Administration and the National Academies of Sciences, Engineering, and Medicine recently called for modeling studies to project the long-term effects, including both potential harms and benefits, of novel tobacco and nicotine products and regulatory policies to address them.[15,16] While multiple model-based studies of tobacco and nicotine products have been published,[17–25] most report aggregate trends, are focused at the population rather than individual level, and do not explicitly account for smoking relapse, a key component of the natural history and resource utilization of smoking cessation attempts. A current challenge of projecting longer-term clinical and economic outcomes of short-term tobacco cessation studies lies in capturing the many smoking quit attempts and relapses.[26,27] A new model that intentionally examines relapse would extend trial results by projecting outcomes beyond the time horizon of trials, when many relapses occur. Our objective was to develop, calibrate, and validate a novel, individual-level microsimulation model that directly addresses the mechanics of smoking initiation, cessation, and relapse, and the associated clinical outcomes. The intended applications of the model include projecting the downstream impact of clinical and public health policy decisions and informing the design of tobacco treatment trials.

METHODS

Analytic overview

We developed a microsimulation model of tobacco- and nicotine-related behaviors, clinical outcomes, and treatments: the Simulation of Tobacco and Nicotine Outcomes and Policy (STOP) model. In this analysis, we focused on cigarette smoking among US women and men to demonstrate that the STOP model, in simulating individuals' month-by-month smoking behaviors, can match historical smoking prevalence and mortality data. Our methods included: 1) performing internal validation to ensure the accuracy of the mathematical calculations; 2) conducting cross-validation with another model; 3) incorporating smoking relapse and then calibrating smoking cessation probabilities to reflect the difference between a quit attempt and sustained abstinence; and 4) using our new relapse parameters, performing external validation to compare model outputs for mortality and for prevalence of current, former, and never smokers over time to empirical data from the National Health Interview Survey (NHIS) (table 1).

Table 1. Characteristics of cross-validation and external validation analyses for a new microsimulation model of smoking behaviors and outcomes.

Analysis	STOP-generated output of interest	Comparator	Measure of goodness of fit
Cross-validation[a]	1950 birth cohort prevalence of never, current, and former smokers, ages 0-70 years, by sex	CISNET-modeled 1950 birth cohort prevalence of never, current, and former smokers, ages 0-70 years, by sex	RMSE

External validation: mortality	Cumulative mortality by age, sex, and smoking status	Mortality rates of 1997-2009 NHIS respondents by age, sex, and smoking status, and cumulative mortality	MAPE and RMSE
External validation: smoking prevalence	Prevalence of never, current, and former smokers, annually, 1998-2009	NHIS never, current, and former smoking prevalence, annually, 1998-2009	RMSE

STOP: Simulation of Tobacco and Nicotine Outcomes and Policy model. CISNET: Cancer Intervention and Surveillance Monitoring Network. NHIS: National Health Interview Survey. RMSE: root-mean-square error. MAPE: mean absolute percentage error. [a]The initial cross-validation did not include smoking relapse. In the subsequent calibration step, we incorporated smoking relapse and calibrated cessation to achieve a good fit to the CISNET-modeled 1950 birth cohort prevalence of never, current, and former smokers.

Because there is no consensus criterion by which to compare model-generated results to surveillance data, expert guidance suggests choosing a criterion appropriate for the model structure and data sources.[28] Similar to methods used in validating other models, we chose root-mean-square error (RMSE, for cumulative risks and time-varying prevalence estimates) and mean absolute percentage error (MAPE, for mortality rates) to evaluate the goodness-of-fit between STOP model results and data sources.[28–34] We applied the coefficient of variation of RMSE (CV-RMSE) as a relative measure of error.

Smoking definitions

Similar to NHIS and the Cancer Intervention and Surveillance Modeling Network (CISNET, which used NHIS data), we defined Never Smokers as those who had smoked <100 cigarettes in their lifetime.[35–37] Among others (ever smokers), NHIS defined current smokers as those who reported currently smoking every day or some days. NHIS considered ever smokers who reported no smoking at the time of interview to be former smokers, regardless of the duration of abstinence. CISNET considered former smokers to be those who had quit smoking at least two years prior to interview; those with a shorter period of abstinence were still considered current smokers.

To better distinguish relapse and mortality risks among those with short-term or long-term abstinence, the STOP model includes three states for those who have ever smoked: 1) Current Smoker; 2) Recent Quitter (short-term abstinence); 3) Former Smoker (long-term abstinence) (figure 1). This enables a differentiation between: 1) transient quit attempts: transition from the Current Smoker state to the Recent Quitter state, with a relatively high rate of early relapse back to the Current Smoker state; and 2) sustained abstinence: transition from the Recent Quitter state to the Former Smoker state, with a lower rate of later relapse back to the Current Smoker state.

STOP model structure

STOP is an individual-level Monte Carlo microsimulation.[38,39] An individual enters the model with age and smoking status defined by random realizations from specified probability distributions. STOP follows a state-transition framework: individuals transition monthly through various cigarette smoking states (figure 1). Transitions between these states depend on age- and sex-stratified monthly smoking initiation and cessation probabilities. Ex-smokers have monthly relapse probabilities (figure 1). Monthly mortality probabilities depend on age, sex, and smoking status. Those who quit smoking retain the all-cause mortality probabilities of current smokers until maintaining abstinence for a defined period of time, after which the mortality probabilities decline.[1,8,40]

Individuals are simulated in series: for each simulated person, the model tracks smoking behavioral events (smoking initiation, quit attempt, relapse) and the duration spent in each smoking state. Upon an individual's death, the next simulated person enters the model. Once a cohort large enough to attain stable estimates has been simulated, summary statistics are calculated, including mean number of quit attempts, life expectancy, and the monthly prevalence of never, current, and former smokers. For the purpose of model output displays, those in the Recent Quitter state are considered "former smokers." We use a constant simulated population size of one million to obtain stable estimates of these "average" outcomes of interest.

Internal validation

We conducted internal model validation by comparing model outputs to expected results and by conducting sensitivity analysis.

Cross-validation

Overview and outcome comparisons

We conducted cross-validation by simulating the US population born in 1950, following them monthly until 2020, and then comparing STOP results to those from CISNET modeling studies (table 1 and supplementary text).[28] We selected the 1950 birth cohort because smoking prevalence in the US peaked in the 1960s, which was the smoking initiation period (adolescence) for these individuals, and data collection frequency increased concurrently. We compared STOP-generated results to CISNET-reported results for the prevalence of female and male current, former, and never smokers over time.[40]

We used CV-RMSE to assess the goodness-of-fit of the six sets of prevalence curves.[29,32] First, RMSE was calculated as the square root of the average of the squared difference between STOP-projected prevalence and CISNET-projected prevalence at each year of age. Then, we calculated CV-RMSE by dividing RMSE by mean modeled prevalence, representing the relative error.

CISNET Model

CISNET is a collaboration of National Cancer Institute-supported investigators modeling the impact of interventions on population incidence and mortality of various types of cancer, including lung cancer. The Yale CISNET-Lung models, for subsequent analyses of cancer care interventions, used data from NHIS to generate detailed smoking initiation and cessation rates, stratified by birth year, age, and sex, and mortality rates, stratified by birth year, age, sex, and smoking status.[37,41]

Input parameters for initial cross-validation

For the initial cross-validation exercise, we used data from CISNET modeling studies, which were derived from NHIS through 2009 and were stratified by birth cohort (table 2).[37,41] Specifically, we used CISNET age- and sex-stratified smoking initiation and cessation rates and smoking-stratified mortality rates among US women and men born in 1950, converting them to monthly probabilities. The CISNET smoking cessation rates reflected a direct transition from current smoker to former smoker after at least two years of sustained abstinence.[41] This initial exercise used the same input parameters as CISNET and did not include smoking relapse.

Table 2. STOP model input parameters applied in each validation exercise.

Input parameter	Cross-validation	External validation of mortality	External validation of smoking prevalence
Input parameters from CISNET (for cross-validation), NHIS 1997-2009 (for external validation of mortality), or NHIS 1997 (for external validation of smoking prevalence)			
Baseline cohort characteristics			
Women/Men, %[a]	---	52/48	52/48
Initial age, mean, years (SD)	0 (followed a birth cohort)	39.7 (21.4)	39.1 (20.7)
Minimum/maximum age, years	---	18/84	18/84
Initial prevalence of never/current/former smokers[b], %	100/0/0	56/22/22	52/25/23
Years since cessation among former smokers, mean (SD)	---	15.6 (12.7)	14.4 (11.9)
Smoking behavior events[c]			
Monthly smoking initiation probability, by age and sex	0-0.0093	0-0.0063	0-0.0063
Monthly smoking cessation probability, by age and sex	0-0.015	0-0.035	0-0.035
Mortality			

Monthly mortality probability[d], by age and sex, x 10^{-4}			
Never smokers	0-12.8	0.4-95.2	0.4-95.2
Current smokers	0-34.6	0.4-136.1	0.4-136.1
Former smokers	Multiplier applied (see last row)	0-111.5	0-111.5
Input parameters derived from smoking studies or from authors' calibration			
Monthly relapse probability[e] (t = months since cessation)	$P_{Relapse}= 0.62*e^{-0.33*t}$	$P_{Relapse}= 0.62*e^{-0.33*t}$	$P_{Relapse}= 0.62*e^{-0.33*t}$
Cessation rate multiplier (calibrated), women/men	7.75/7.25	7.75/7.25	7.5/7
Initiation rate multiplier (calibrated), women/men	---	---	0.9/1.0
Former smoker mortality multiplier, applied to never smoker mortality, by sex and age at quit[f]	1.0-2.2	---	---

STOP: Simulation of Tobacco and Nicotine Outcomes and Policy. CISNET: Cancer Intervention and Surveillance Modeling Network. NHIS: National Health Interview Survey. SD: standard deviation. The numbers show model input parameters applied in cross-validation (left column), external validation of mortality (center column), and external validation of smoking prevalence (right column).

[a]In cross-validation, we simulated cohorts of either all women or all men from birth. Thus, no distributions of initial age are displayed.

[b]Prevalence of each smoking status displayed here is the mean over all strata, but in the model these were stratified by 5-year age group and sex from ages 18 to 84.

[c]Additional details about smoking behavior transitions are in supplementary table 1.

[d]Additional details about mortality data are in supplementary table 2.

[e]This is based on relapse probabilities reported in smoking cessation intervention trials, focusing on placebo arms.[42–45]

[f]For the 1950 birth cohort, some CISNET-derived former smoker mortality rates are lower than CISNET-derived never smoker mortality rates – a counterintuitive relationship otherwise unexplained. We therefore adapted former smoker mortality multipliers for the cross-validation from Thun et al.[40]

Incorporating smoking relapse and calibrating cessation probabilities

The STOP model specifically includes smoking relapse, critical to projecting both short-term and long-term impacts of smoking cessation interventions and novel tobacco and nicotine products.

Following the initial cross-validation of the STOP model (without relapse), we added smoking relapse probabilities and then recalibrated the model by adjusting the previously-applied smoking cessation probabilities. First, we modeled relapse as an exponential decay function of time since quit, such that the highest risk of relapse was in the first month after a quit attempt. The coefficient and time constant are based on relapse probabilities in smoking cessation trials (table 2).[42–45] Second, we calibrated the previously-applied cessation probabilities (derived from CISNET cessation data) by a multiplier to reflect: 1) a quit attempt rather than sustained abstinence; and 2) the higher likelihood of making a quit attempt rather than attaining sustained abstinence in a given month. This multiplier represents the average number of quit attempts, lasting at least one month, prior to attaining sustained abstinence. We compared our multipliers to published data on the average number of quit attempts required to attain sustained abstinence.[27] Our overall aim for this calibration step was to identify a STOP-generated current smoker prevalence curve with an RMSE <0.01 compared to the CISNET model-generated current smoker prevalence curve, similar to previously described methods.[32]

External validation

Overview and outcome comparisons

For external validation, we compared STOP model results to NHIS data.[28,36] We accounted for smoking initiation, smoking cessation, and mortality. Because NHIS data do not explicitly report relapse, we incorporated smoking relapse and the best-fitting cessation multipliers found in the cross-validation calibration step. We compared two outcomes: mortality and smoking prevalence (table 1 and supplementary text).

First, to project and validate mortality outcomes, we simulated the population surveyed by NHIS from 1997 through 2009 (supplementary text). To compare STOP-generated mortality rates to those derived from NHIS – stratified by age, sex, and smoking status – we used MAPE, the mean absolute value of the percent difference between STOP and NHIS values. We also produced curves of cumulative mortality from STOP-generated results and from NHIS data, stratified by sex and by current/never smoking status. These curves reflect 20-year-old current smokers who continue to smoke until death or 20-year-old never smokers who never start smoking. We compared the four sets of cumulative mortality curves by RMSE and CV-RMSE (STOP versus NHIS) from age 20 years until age 84 years (goal RMSE <0.01). We did not generate mortality curves for 20-year-old former smokers because mortality risks for those who stop smoking prior to age 20 are similar to those of never smokers.[1] Also, mortality risks depend on age at cessation, and at older ages this heterogeneous group would include people who quit smoking at a variety of ages.[1,40]

Second, with those surveyed by NHIS in 1997 as the input cohort, we used the STOP model to project the prevalence of current, former, and never smokers each year from 1998 to 2009. In a two-way sensitivity analysis, we re-calibrated cessation multipliers and initiation multipliers with the goal of identifying multipliers that would minimize the CV-RMSE of STOP-reported current smoker prevalence compared to NHIS current smoker prevalence. The initiation multipliers were applied to smoking initiation rates for never smokers. We then compared the cessation multipliers from this step with those from the cross-validation calibration step.

Input parameters

Initial distributions of age, sex, and smoking status for the population simulated in the external validation exercises came from two sources: aggregated 1997-2009 NHIS data for the mortality external validation, and 1997 NHIS data for the smoking prevalence external validation (table 2 and supplementary figure 1). We obtained NHIS data in aggregate for years 1997-2009 from the Integrated Public Use Microdata Series.[35] We used NHIS data through 2009 because those were the data used in the CISNET studies, which were our comparator in cross-validation exercises.[37,41] These data provided initial distributions of smoking status and years of abstinence for former smokers (to inform relapse risks). From these 1997-2009 NHIS data, we derived age- and sex-specific smoking initiation and cessation rates using self-reported age at initiation and age at cessation variables (supplementary table 1). As in our cross-validation exercises, we converted the cessation rates to quit attempt rates by incorporating relapse rates and cessation multipliers.

The NHIS data included linked National Death Index (NDI) mortality outcomes through 2011 for respondents for whom mortality data were available. We calculated mortality rates by age, sex, and smoking status of the same NHIS respondents (supplementary table 1).

Patient and public involvement

We did not involve patients or the public in our work.

Ethics statement

This study was approved by the Partners Human Research Committee (2019P001772).

RESULTS

Cross-validation

Initial cross-validation, without relapse

The STOP-projected prevalence of current, former, and never smokers over time fit CISNET-projected data well for the 1950 birth cohort in the US (figure 2, blue line vs. red dotted line, RMSE <0.03, CV-RMSE 15%/7% for women/men). The STOP-estimated prevalence of current smokers at age 25 years, approaching peak prevalence for the 1950 birth cohort, was 40% for women and 54% for men, compared to CISNET estimates of 38% and 52%.

Incorporating smoking relapse and calibrating cessation probabilities

After incorporating smoking relapse, the prevalence of current smokers far exceeded that reported by the CISNET model, as expected since many of those who would have become former smokers reverted to being current smokers (figure 2, pink dashed lines). We then aimed to reflect all quit attempts rather than only transitions to sustained abstinence. In rough calibrations, we found that the optimal multiplier would be between 5 and 10 when applied to cessation rates from the previous step. In finer calibrations, we varied the multiplier across the range of 5 to 10 in increments of 0.25. We found that multiplying the CISNET-reported cessation rates by 7.75 for women and by 7.25 for men best approximated the CISNET-projected prevalence of current smokers, with RMSE 0.004/0.008 and CV-RMSE 2%/3% for women/men (figure 2, black lines).

External validation

Mortality

In simulating the 1997-2009 NHIS population along with smoking relapse, we found that the age-, sex-, and smoking-stratified mortality rates generated by the STOP model were a good fit to those derived from NHIS (MAPE 7%, examples in supplementary table 2). Cumulative mortality curves for 20 year-old female and male current smokers and never smokers were similar between STOP projections and NHIS-derived data, with RMSE <0.01 and CV-RMSE ≤1% (figure 3). For 20-year-olds who continued to smoke until death, the STOP model predicted median life expectancy (counting years from birth) of 77.5 years for women and 72.5 years for men.

Smoking prevalence

Using those surveyed by NHIS in 1997 as the input cohort, the STOP-projected prevalence of current, former, and never smokers each year from 1998 to 2009 was similar to that reported by NHIS, with overall RMSE 0.04 and CV-RMSE 12% for both women and men (ages 30-84 years combined; supplementary figure 2 shows results specifically for ages 40-44 years). Compared to NHIS, the STOP model slightly underpredicted never smoker prevalence and slightly overpredicted former smoker prevalence in later years. In the two-way sensitivity analysis, we found that cessation multipliers of 7.5/7.0 for women/men and initiation multipliers of 0.9/1.0 provided the best overall fit (lowest RMSE) of STOP-projected current smoker prevalence compared to that reported by NHIS (supplementary figure 3).

DISCUSSION

We developed, calibrated, and validated STOP, a novel microsimulation model of individual-level tobacco use behaviors and outcomes. Our initial model input parameters included smoking initiation and cessation and smoking-stratified mortality, and we demonstrated cross-validity compared to the CISNET model. After incorporating relapse, we calibrated smoking cessation probabilities to reflect quit attempts rather than sustained abstinence. We then validated STOP model output with: 1) smoking prevalence over time reported by the CISNET model for US women and men born in 1950; 2) age-, sex-, and smoking-stratified mortality rates and cumulative mortality reported by the NHIS-NDI linked database for the years 1997-2009; and 3) prevalence of current, former, and never smokers by sex from 1998 to 2009 reported by NHIS, using 1997 NHIS-reported population characteristics as inputs.

Most existing tobacco models simulate at the population level or lack the capacity to consider smoking initiation and (non-sustained) quit attempts throughout a lifetime.[18,23–25,37,46,47] The individual-level details of STOP can be employed to simulate and compare behaviors and interventions. While this calibration and validation analysis focused on cigarette smoking because of the availability of historical data for comparisons, we intend to broaden the use of STOP to include electronic cigarettes (e-cigs). Longitudinal cohort studies and clinical trials are examining the effects of e-cig use on tobacco smoking behaviors and clinical outcomes over long time horizons, but data are needed now to inform guidelines and policy around these novel products.[15,44,48,49] Results from multiple distinct, validated models can help motivate policy decisions, and consistency of policy recommendations across unique, independent models reinforces confidence in their recommendations.[50–54]

A novel aspect of the STOP model is the incorporation of smoking relapse on a monthly basis, reflecting the understanding of nicotine addiction as a chronic relapsing condition with rapid cycles between use and cessation.[26,45,55–58] This key feature enables an important distinction between a quit attempt and sustained abstinence. This distinction is missing from most tobacco models and indeed from many epidemiologic studies of smoking and smoking cessation, which consider the transition from “current” to “former” smoker to be an abrupt one that results in sustained abstinence. Incorporating relapse required calibrating cessation rates by applying multipliers. The cessation multipliers that provided the best fits to empirical data are in line with published data regarding the number of quit attempts required before sustained abstinence is achieved.[27,55,59] The slightly higher multiplier needed for women compared to men is consistent with NHIS data showing that among ever smokers (current smokers plus former smokers) aged 60 years and above, a greater proportion of women compared to men are former smokers.[35] Calibration of cessation rates may compensate for other inaccuracies in model inputs or structure, though the pre-calibration (without relapse) STOP-generated results fit well with those of CISNET.

Many trials of smoking cessation interventions follow patients for a few months or up to one year, but they do not report subsequent relapse. By including relapse, the STOP model can combine data from short-term trials of smoking cessation interventions with data from natural history studies of smoking and smoking cessation to project longer-term outcomes including sustained abstinence. The flexibility to integrate data from a variety of sources is a strength of modeling analyses.

Going forward, we plan to use the STOP model to study contemporary rather than historical populations and to predict future tobacco use, while utilizing deterministic and probabilistic sensitivity analyses to account for uncertainty in future behavioral transition probabilities and mortality probabilities.[60] As no empirical data exist with which to validate model output of future tobacco use, we validated STOP model output against historical populations. Most US historical data on smoking prevalence and smoking-associated mortality are based at least in part on NHIS, the oldest ongoing survey of smoking prevalence in the US.[1,61–63] We compared STOP model output to CISNET model output, to NHIS itself, and to results from a study by Jha et al.,[1] all of which used NHIS data. We demonstrated cross-validity of STOP compared to CISNET model results when using CISNET input parameters and then added relapse probabilities and cessation multipliers. We demonstrated external validity, in a partially dependent manner, of STOP compared to NHIS data when using some NHIS-derived input parameters plus the external relapse probabilities and cessation multipliers from our cross-validation. Though independent external validation sources are ideal, dependent sources can still be useful, especially in this scenario where most of the available US historical smoking prevalence, behavior, and mortality data are derived from NHIS.[28] Of note, in a two-way sensitivity analysis in which we simultaneously varied the smoking initiation and cessation multipliers to achieve a close fit to NHIS smoking prevalence data, the optimal cessation multipliers were very similar to those we found in our cross-validation calibration step, demonstrating the robustness of these multipliers across different sets of assumptions.

In an external validation exercise, the STOP model projection for never smoker prevalence from 1998 to 2009 was slightly lower than that reported by NHIS, and the STOP model projection for former smoker prevalence was slightly higher than NHIS data. In NHIS, former smokers were self-defined but on average had been abstinent for over a decade. NHIS considered those who smoked “some days” to be current smokers, though some of them may have been in the midst of a short-duration quit attempt. STOP model output formally labels these people, who may be in the Recent Quitter state, former smokers but assigns them the mortality risks of current smokers (until a defined period of abstinence). STOP reflects monthly quitting and relapsing behaviors whereas NHIS is an annual cross-sectional survey. Thus, one would expect the STOP model to report a higher prevalence of former smokers than NHIS, as seen in our results. Immigration could also account for some of the difference between NHIS data and STOP model-generated results: immigrants were surveyed in NHIS but our model analysis does not account for them. Smoking prevalence differs between the immigrant and non-immigrant populations.[64,65] On the other hand, STOP model-generated life expectancies were similar to the median life expectancies for 30-year-old smokers reported by Jha et al. (also derived from NHIS data): 77 years for women and 72 years for men.[1]

The STOP model has features, and will have applications, not described in this analysis. We developed the model to incorporate resource utilization. The STOP model can capture the healthcare costs associated with being a current, former, or never smoker, as well as the costs of tobacco cessation interventions. By incorporating the chronic relapsing nature of nicotine addiction, the STOP model can account for the resources required for recurrent cessation interventions (e.g., restarting the same or a different intervention after smoking relapse), an important consideration in cost-effectiveness and policy analyses. Ultimately, we will use the STOP model to evaluate behavioral and clinical outcomes, costs of care, and cost-effectiveness of tobacco cessation interventions, programs, and policies. An overarching goal is to provide information that can inform decision makers – including clinicians, public health officials, and policymakers – on cost-effective interventions that reduce the clinical and economic burden of tobacco use. The model can eventually assess the impact of different financing options for tobacco cessation interventions – for example, annual versus lifetime insurance coverage limits. The STOP model's flexibility will allow for analyses beyond US populations, including settings where smoking-related behaviors and clinical outcomes may be different from those in the US.[66]

The STOP model has limitations. Its projections are limited by assumptions and the specificity of available data – for example, age, sex, and birth year stratifications of smoking behavioral transitions. While we have aimed to calibrate and validate the model with the best available historical data, any use of the model to project future outcomes should be approached with prudence. Calibration on historical data is no panacea because of concerns of calibration drift, and relapse rates could change over time due to changes in population-level nicotine dependence.[67] Nonetheless, input parameter values can be varied in sensitivity analysis. STOP does not include dynamics such as the effects of one person's smoking on another person's smoking behaviors. Smoking is associated with other factors not directly captured by STOP, including race, socioeconomic status, mental illness, and other substance use, but different populations can be separately simulated in the model with input parameters specific to that population. There is heterogeneity in smoking behaviors, including cigarettes consumed per day and daily versus nondaily smoking. STOP enables stratification by intensity of smoking, which can be used to represent amount or frequency of smoking.

In conclusion, STOP is a novel, individual-level microsimulation model that captures tobacco-related behaviors – importantly including relapse – and outcomes with a goal of informing decision making around tobacco cessation interventions and tobacco policy. We have demonstrated that the model is well-calibrated and validated to another model and to historical cohorts. We plan to use the model for policy-relevant analysis of contemporary patient-level and population-level care while reflecting real-life tobacco use and cessation behaviors.

AUTHOR CONTRIBUTIONS

Specific contributions are as follows:

KPR – study conception, study design, data analysis, data interpretation

AJB – study design, data analysis, data interpretation

DEL – study design, data interpretation

PT – data analysis, data interpretation

EPH – study design, data interpretation

TH – study conception, study design, data analysis

BO – study design

LY – data analysis, data interpretation

FMS – study design, data analysis, data interpretation

ADP – study design, data interpretation

KAF – study design, data interpretation

MCW – study design, data interpretation

NAR – study conception, study design, data interpretation

RPW – study conception, study design, data interpretation

KPR drafted the first version of the manuscript. All authors critically reviewed the manuscript for important intellectual content and approved the final submitted version.

COMPETING INTERESTS

NAR receives royalties from UpToDate, Inc., is a consultant for Achieve Life Sciences, and has been an unpaid consultant for Pfizer. All other authors report no competing interests.

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DATA STATEMENT

Data used to parameterize the model are publicly available at https://resources.cisnet.cancer.gov/projects and at https://nhis.ipums.org/nhis.

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FIGURE LEGENDS

Figure 1. Overview of tobacco use states and transitions in Simulation of Tobacco and Nicotine Outcomes and Policy (STOP) microsimulation model.

This is a simplified, stylized depiction of smoking states and transitions – for example, dimensions such as age and sex are not represented in the figure. The ovals represent possible cigarette smoking states or the deceased state. The arrows represent monthly transitions by which an individual can switch to a different state. The "Abstinence, sustained" transition is depicted by a dashed line because there is not a monthly probability of transition – instead, the transition occurs after an individual has spent a user-defined duration (e.g., one year) in the "Recent Quitter" state. Numerical examples of the transition probabilities are in supplementary table 1.

Figure 2. Cross-validation and calibration exercise: STOP-generated results and CISNET-generated results for current smoking prevalence over time for US people born in 1950.

STOP: Simulation of Tobacco and Nicotine Outcomes and Policy model. CISNET: Cancer Intervention and Surveillance Modeling Network.

Panel A depicts women, Panel B depicts men. The red dotted line shows results from the CISNET model. The other three lines show STOP-generated results after each step of our parameterization and calibration process. The blue line includes parameterization of smoking initiation and cessation, but not relapse. The pink dashed line includes smoking relapse as based on published studies. The black line includes calibration of smoking cessation probabilities to reflect quit attempts and relapse before sustained abstinence.

Figure 3. External validation: STOP model results and NHIS/NDI results for cumulative mortality of current smokers and never smokers from age 20.

STOP: Simulation of Tobacco and Nicotine Outcomes and Policy. NHIS: National Health Interview Survey. NDI: National Death Index. CV-RMSE: coefficient of variation of root-mean-square error.

Panel A depicts women, Panel B depicts men. Within each panel, the STOP results and the NHIS data are not easily distinguishable because they are essentially overlapping. Current smokers are those who continue to smoke until death. NHIS was linked to NDI for mortality data.

Figure 1

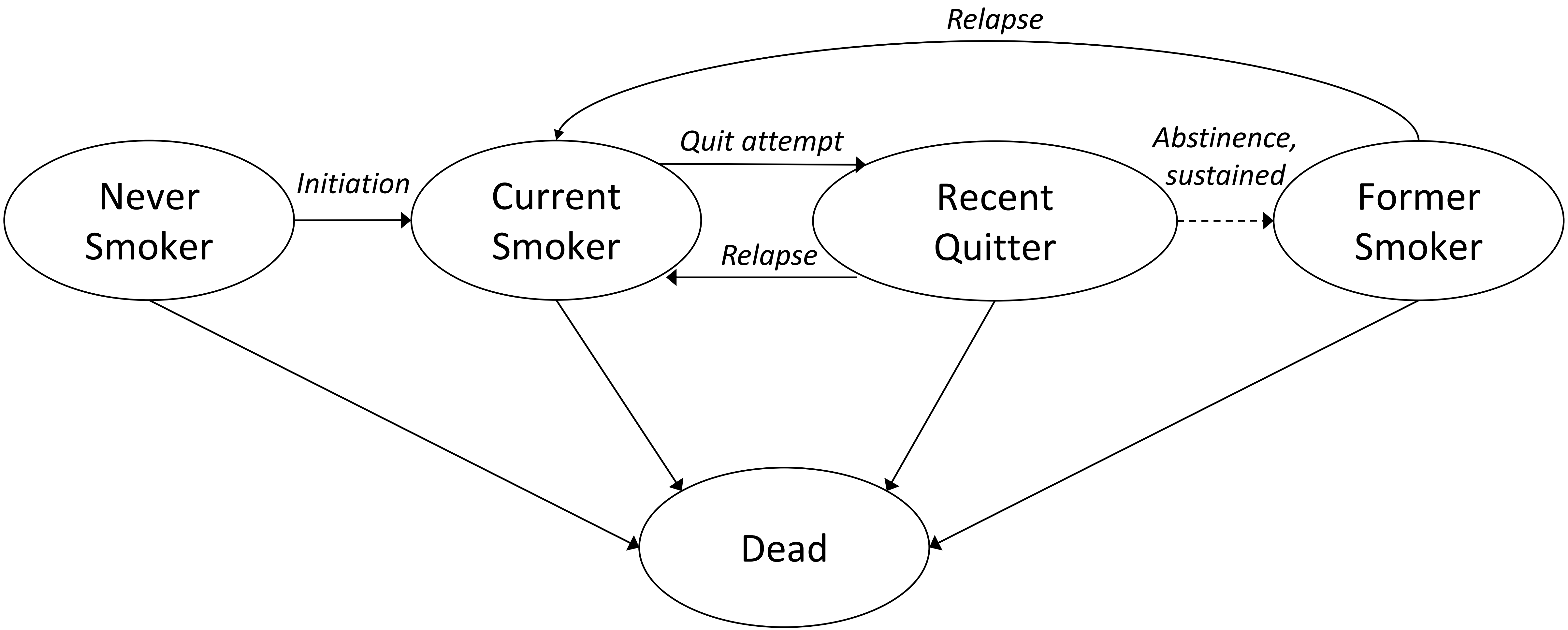

Relapse
Quit attempt
Abstinence,
sustained
Initiation
Never
Smoker
Current
Smoker
Recent
Quitter
Former
Smoker
Relapse
Dead

Figure 2

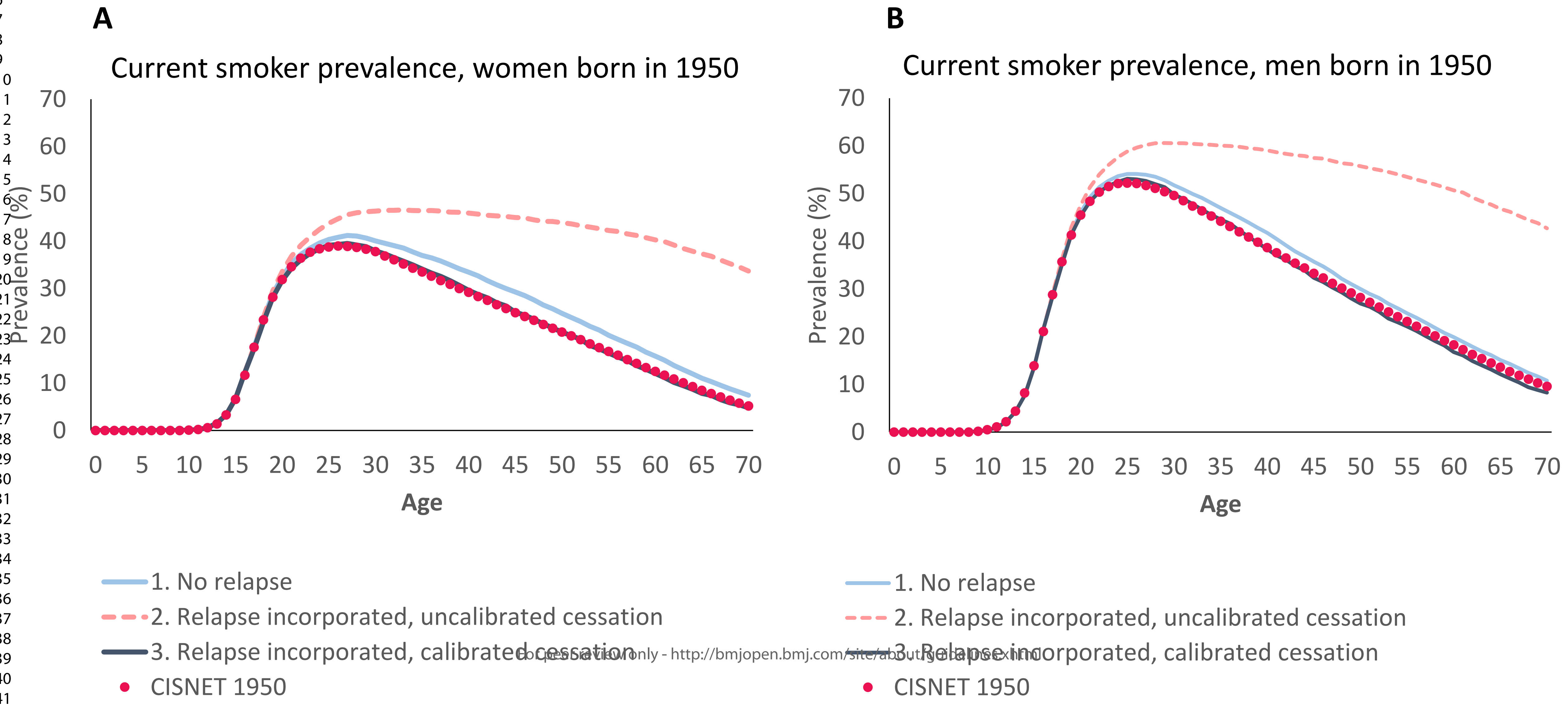
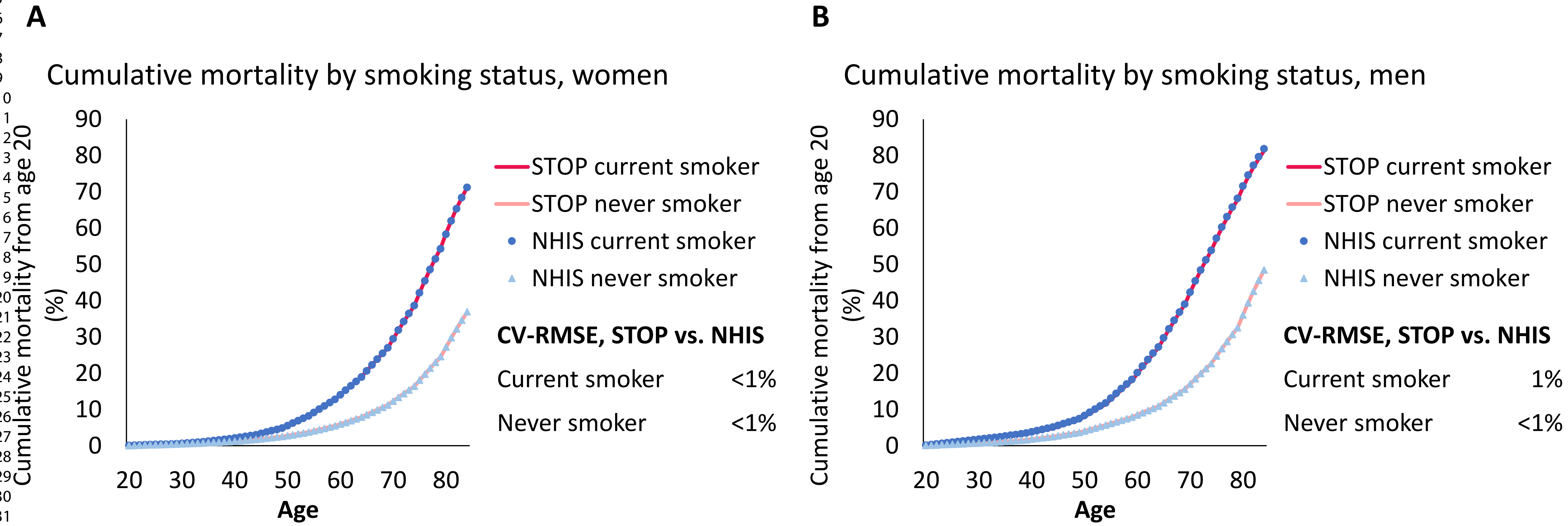

A
Current smoker prevalence, women born in 1950
Prevalence (%)
70
60
50
40
30
20
10
0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70
Age
B
Current smoker prevalence, men born in 1950
Prevalence (%)
70
60
50
40
30
20
10
0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70
Age
1. No relapse
2. Relapse incorporated, uncalibrated cessation
3. Relapse incorporated, calibrated cessation
CISNET 1950
1. No relapse
2. Relapse incorporated, uncalibrated cessation
3. Relapse incorporated, calibrated cessation
CISNET 1950

Figure 3


A
Cumulative mortality by smoking status, women
Cumulative mortality from age 20 (%)
0
10
20
30
40
50
60
70
80
90
20
30
40
50
60
70
80
Age
STOP current smoker
STOP never smoker
NHIS current smoker
NHIS never smoker
CV-RMSE, STOP vs. NHIS
Current smoker <1%
Never smoker <1%
B
Cumulative mortality by smoking status, men
Cumulative mortality from age 20 (%)
0
10
20
30
40
50
60
70
80
90
20
30
40
50
60
70
80
Age
STOP current smoker
STOP never smoker
NHIS current smoker
NHIS never smoker
CV-RMSE, STOP vs. NHIS
Current smoker 1%
Never smoker <1%

A novel microsimulation model of tobacco use behaviors and outcomes: calibration and validation in a US population

Supplement

Krishna P. Reddy, Alexander J.B. Bulteel, Douglas E. Levy, Pamela Torola, Emily P. Hyle, Taige Hou, Benjamin Osher, Liyang Yu, Fatma M. Shebl, A. David Paltiel, Kenneth A. Freedberg, Milton C. Weinstein, Nancy A. Rigotti, Rochelle P. Walensky

Table of Contents

METHODS: SUPPLEMENTARY TEXT

National Health Interview Survey (NHIS)

NHIS is a yearly in-person questionnaire administered to the civilian noninstitutionalized population of the US which, since 1965, has collected information on individual smoking status. Since 1991, the smoking section of the NHIS has first queried "ever smoker" status – defined as having smoked at least 100 cigarettes in one's lifetime – then asked ever smokers, "Do you NOW smoke cigarettes every day, some days or not at all?" which resulted in the classification of occasional smokers as current smokers, even though they initially may have said they did not smoke now. Regardless of response to the second question, participants were asked about the frequency of their smoking.[1]

Use of NHIS data in the Simulation of Tobacco and Nicotine Outcomes and Policy (STOP) model

We downloaded NHIS and linked National Death Index (NDI) data from the Integrated Public Use Microdata Series (IPUMS) Health Surveys for the years 1997-2009.[2] We obtained basic demographic information, smoking status and behavioral variables, and death status/year of death reported through 2011. For all derivations below, we excluded those with unknown smoking or mortality status. Only people 18 years of age or older were surveyed about tobacco use, and since ages 85+ years are censored, we excluded those as well.

External validation - mortality

From the pooled 1997-2009 data, we used the IPUMS-recoded and -constructed survey weights adjusting for differential representation in the smoking sub-sample and NDI follow-up. Because of the NHIS sampling design, weights must be used so that the survey respondents can be collectively expanded to represent the civilian noninstitutionalized population of the US. These weights represent a surveyed individual's inverse probability of being included in both the survey supplement, which contains questions about smoking, and the NHIS-NDI linked mortality files.

Smoking cessation inputs: We derived age- and sex-stratified cessation rates using the NHIS variable that reported years since respondents (former smokers) quit smoking. We excluded quit ages before age 16 years (due to perceived inconsistency of coding of the "time since quit" variable – some entries implied negative quit age) and included quit ages through age 85 years.

Smoking initiation inputs: Similarly, we derived initiation rates, also age- and sex-stratified, using the variable that reported years since the respondent (a current or former smoker) started to smoke regularly. We used initiation rates from ages 6 to 61 years, the last age for which data are consecutively available for both women and men.

Mortality inputs: We calculated mortality rates by age, sex, smoking status, and five-year age group using the smoking status variable and NDI reporting through 2011. The rates were calculated from a follow-up period beginning in the respondent's survey year and ending in 2011 or the year of her/his death, whichever came first. Because smoking behavior data were collected only at baseline in NHIS and not again at the time of death, there may have been some misclassification of smoking status (e.g., someone who was a current smoker at the time of NHIS assessment may have subsequently quit and later died but was still considered a current smoker). However, all-cause mortality rates do not significantly decrease until a few years after cessation, and we considered those who had quit smoking to have similar mortality risks to current smokers until five years of abstinence. This reflects contemporary studies in which former smokers were defined as those who had not smoked in the previous five years and data from large US cohort studies that indicate that the all-cause mortality risk in men who quit smoking does not fall below that of current smokers until five years of abstinence.[3,4]

Input cohort: We derived initial cohort characteristics for this analysis from the NHIS 1997-2009 pooled dataset: current, former and never smoking prevalence by five-year age group from age <20 to 84 years; mean (standard deviation [SD]) age adjusted for bounding of the distribution; sex distribution; and mean (SD) time since quit bounded by a minimum quit age of 16 years.

Output comparison: We compared STOP model output for mortality to NHIS/NDI-reported mortality in the form of mortality rates and cumulative mortality from age 20 years.

External validation – smoking prevalence

From the NHIS 1997 data, using the same survey weights as above:

Smoking cessation, smoking initiation, and mortality inputs: We used the same cessation, initiation, and mortality rate inputs as for the mortality validation.

Input cohort: We derived input cohort characteristics for this analysis from the 1997 NHIS data: current, former, and never smoking prevalence by five-year age group from age <20 to 84 years; mean (SD) age adjusted for bounding of the distribution; sex distribution; and mean (SD) time since quit bounded by a minimum quit age of 16 years.

Output comparison: Starting with the 1997 NHIS respondents and following them each year from 1998 to 2009, we compared STOP projections to NHIS data regarding prevalence of current, former, and never smokers by five-year age group from age 30 to 84 years.

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Supplementary Table 1. Examples of transition probabilities in the simulation model.

Parameter	Value	Reference
Smoking initiation probability, monthly, by age and sex	0-0.0063	Derived from NHIS 1997-2009 data
Cessation probability, monthly, by age and sex	0-0.035	Derived from NHIS 1997-2009 data
Relapse probability, monthly, by time since cessation	$P_{Relapse} = 0.62*e^{-0.33*t}$	[5–8]
Never Smoker mortality probability, monthly, by age and sex, x 10^{-4}	0.4-95.2	Derived from NHIS/NDI 1997-2009 data
Current Smoker or Recent Quitter mortality probability, monthly, by age and sex, x 10^{-4}	0.4-136.1	Derived from NHIS/NDI 1997-2009 data
Former Smoker mortality probability, monthly, by age, sex, and time since cessation[a], x 10^{-4}	0-111.5	Derived from NHIS/NDI 1997-2009 data
Time to transition from Recent Quitter to Former Smoker	5 years[b]	Assumption, [3,4]

NHIS: National Health Interview Survey. NDI: National Death Index. STOP: Simulation of Tobacco and Nicotine Outcomes and Policy.

[a]These former smoker mortality probabilities were used only in the external validation exercises, comparing STOP model output to NHIS/NDI results. In cross-validation comparing STOP model output to

the CISNET model results, we applied multipliers to never smoker mortality rates to derive former smoker mortality rates and then converted these to probabilities.

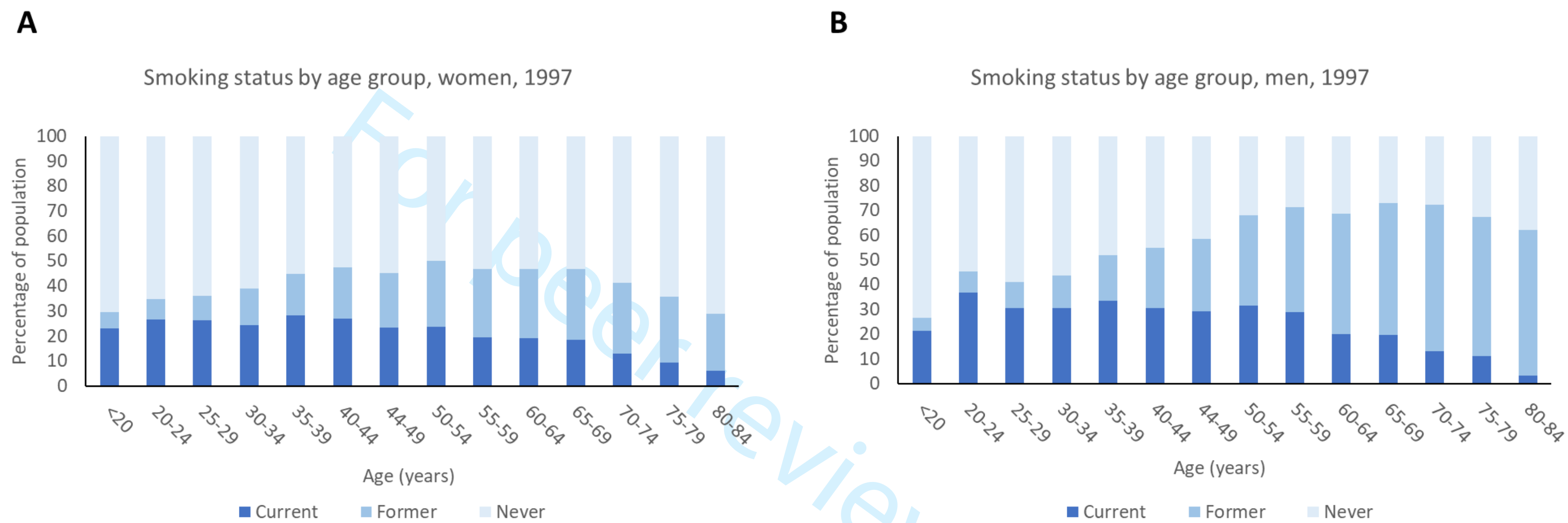
[b]This five-year abstinence period was based on data showing mortality risks by years since smoking cessation.[3,4] We performed an analysis in which we assumed that mortality risks decreased to "Former Smoker" levels immediately upon quitting smoking, but the model-generated results were not a better fit to NHIS data (results not shown).

Supplementary Table 2. Selected age- and sex-specific annual mortality rates: STOP model output versus NHIS-derived mortality.

Women						
	Current Smoker		Former Smoker		Never Smoker	
Age group, years	STOP	NHIS/NDI	STOP	NHIS/NDI	STOP	NHIS/NDI
40-44	0.0023	0.0023	0.0017	0.0015	0.0012	0.0012
50-54	0.0071	0.0071	0.0035	0.0029	0.0025	0.0025
60-64	0.0147	0.0146	0.0087	0.0079	0.0051	0.0051
Men						
	Current Smoker		Former Smoker		Never Smoker	
Age group, years	STOP	NHIS/NDI	STOP	NHIS/NDI	STOP	NHIS/NDI
40-44	0.0031	0.0034	0.0028	0.0025	0.0018	0.0018
50-54	0.0094	0.0096	0.0059	0.0053	0.0042	0.0043
60-64	0.0233	0.0232	0.0114	0.0099	0.0067	0.0066

STOP: Simulation of Tobacco and Nicotine Outcomes and Policy. NHIS: National Health Interview Survey. NDI: National Death Index.

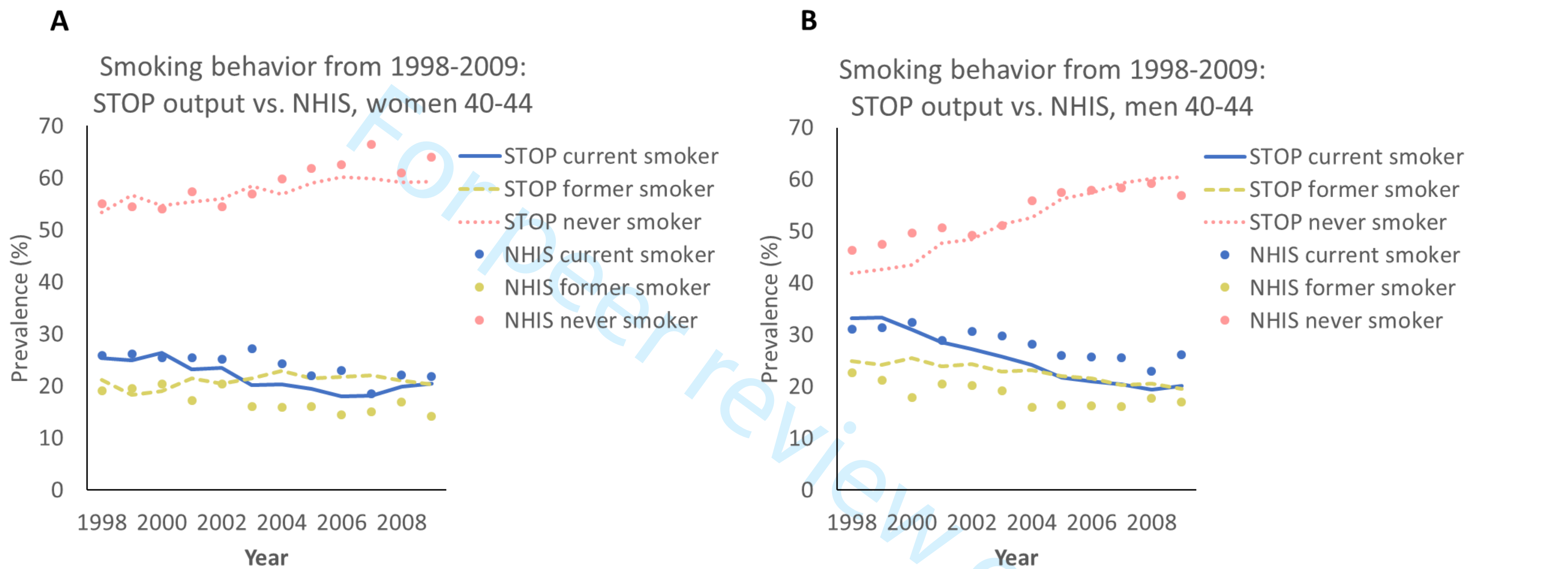
Supplementary Figure 1. Smoking status by age group and sex in 1997: STOP model inputs for the external validation exercise of smoking prevalence.



STOP: Simulation of Tobacco and Nicotine Outcomes and Policy. NHIS: National Health Interview Survey.

Panel A depicts women; Panel B depicts men. For each age group, the prevalence of current, former, and never smokers is entered as STOP model input. The external validation analysis of smoking prevalence, using weighted NHIS 1997 survey respondent data as inputs, projects smoking prevalence annually from 1998 to 2009.

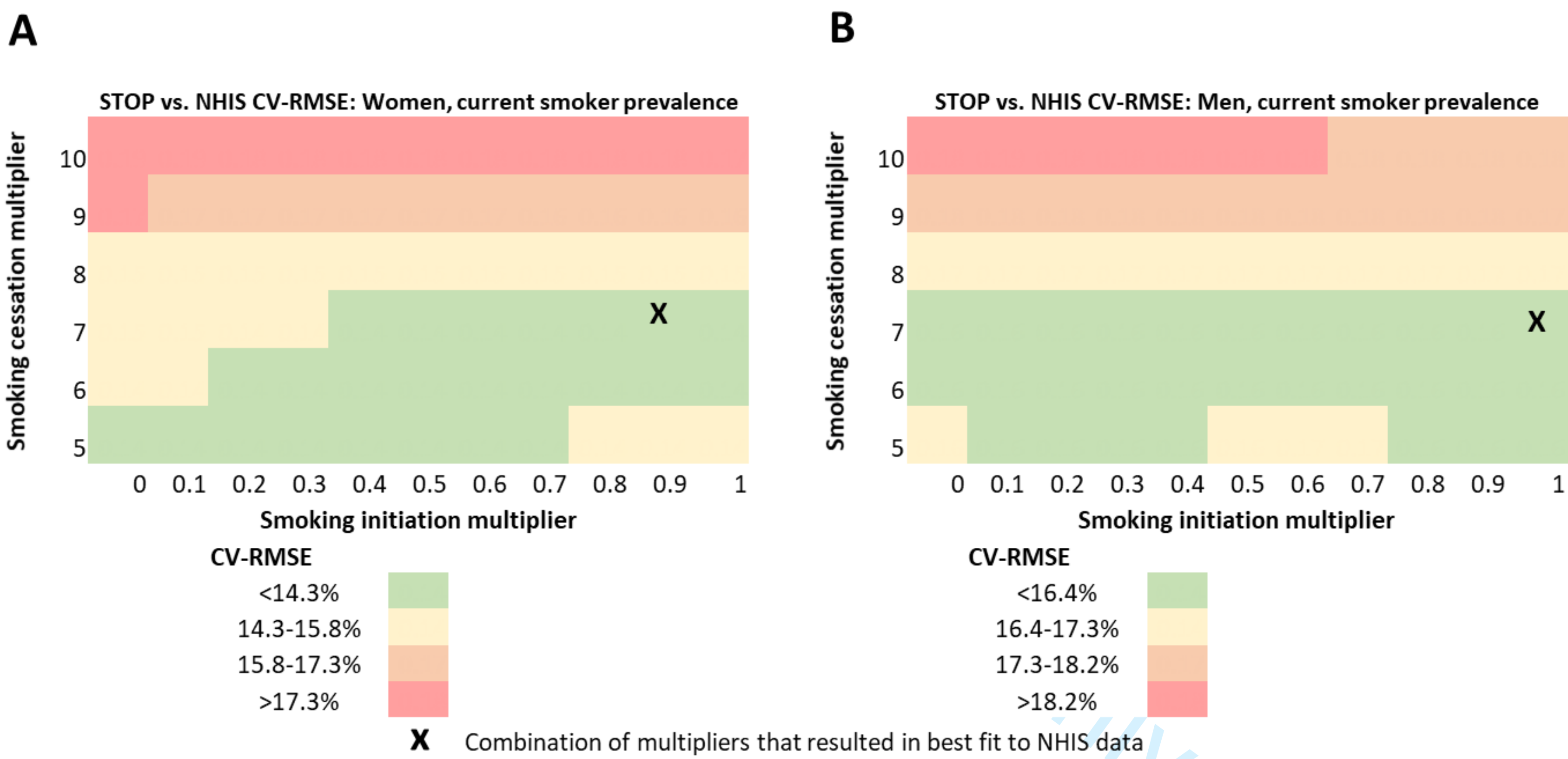
Supplementary Figure 2. External validation: STOP model results and NHIS results for prevalence of current, former, and never smokers each year from 1998 to 2009.



STOP: Simulation of Tobacco and Nicotine Outcomes and Policy. NHIS: National Health Interview Survey. NDI: National Death Index.

Panel A depicts women, Panel B depicts men. The STOP model cohort had the age and smoking status distribution of the 1997 NHIS survey respondents (Supplementary Figure 1). The STOP-generated results reflect a microsimulation that included probabilities of smoking initiation, smoking cessation, smoking relapse, and mortality.

Supplementary Figure 3. Two-way sensitivity analysis of smoking initiation and smoking cessation multipliers for external validation exercise.



STOP: Simulation of Tobacco and Nicotine Outcomes and Policy. NHIS: National Health Interview Survey. CV-RMSE: coefficient of variation of root-mean-square error.

Panel A depicts women; Panel B depicts men. The multipliers were applied to the original cessation and initiation rates derived from pooled 1997-2009 NHIS data and used in the STOP model. The horizontal axis shows the multiplier applied to smoking initiation rates (subsequently converted to probabilities) in the STOP model, and the vertical axis shows the multiplier applied to smoking cessation rates (subsequently converted to probabilities). Colored cells represent the CV-RMSE of STOP model-generated versus NHIS-reported current smoking prevalence among people ages 30-84 years from 1998 to 2009.