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Modeling the population health impact of accurate and inaccurate perceptions of harm from nicotine

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Abstract

Background Scientific evidence clearly demonstrates that inhaling the smoke from the combustion of cigarettes is responsible for most of the harm caused by smoking, and not the nicotine. However, a majority of U.S. adults who smoke inaccurately believe that nicotine causes cancer which may be a significant barrier, preventing switching to potentially reduced risk, non-combustible products like electronic nicotine delivery systems (ENDS) and smokeless tobacco (ST). We assessed the population health impact associated with nicotine perceptions.

Methods Using a previously validated agent-based model to the U.S. population, we analyzed nationally representative data from the Population Assessment of Tobacco and Health (PATH) study to estimate base case rates of sustained (maintained over four waves) cessation and switching to non-combustible product use, by sex. Nicotine perception scenarios were determined from PATH data. The overall switch rate from smoking in Wave 4 to non-combustible product use in Wave 5 (3.94%) was stratified based on responses to the nicotine perception question "Do you believe nicotine is the chemical that causes most of the cancer caused by smoking cigarettes?", (four-item scale from "Definitely not" to "Definitely yes"). The relative percent change between the overall and stratified rates, corresponding to each item, was used to adjust the base case rates of switching, to determine the impact, if all adults who smoke exhibited switching behaviors based on responses to the nicotine perceptions question. The public health impact of nicotine perceptions was estimated as the difference in all-cause mortality between the base case and the four nicotine perception scenarios.

Results Switch rates associated with those who responded, "Definitely not" (8.39%) resulted in a net benefit of preventing nearly 800,000 premature deaths over an 85-year period. Conversely switch rates reflective of those who responded, "Definitely yes" (2.59%) resulted in a net harm of nearly 300,000 additional premature deaths over the same period.

Conclusions Accurate knowledge regarding the role of nicotine is associated with higher switch rates and prevention of premature deaths. Our findings suggest that promoting public education to correct perceptions of harm from nicotine has the potential to benefit public health.

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Keywords Nicotine perceptions, Misperceptions, Public health impact, Population modeling, Tobacco harm reduction

Background

Combustible cigarettes are the most harmful of all tobacco products and the leading cause of preventable death in the U.S [1] which have been attributed to more than 400,000 premature deaths every year [2]. The morbidity and mortality from smoking cigarettes are primarily due to serious diseases such as lung cancer, chronic obstructive pulmonary disease (COPD), and heart disease [1]. The harm from cigarette smoking is caused by inhaling the smoke from combustion, which contains more than 7,000 chemicals. The Food and Drug Administration (FDA) has identified a number of these chemicals in cigarette smoke as harmful and potentially harmful constituents (HPHCs) and classified many of them as carcinogens, respiratory or cardiovascular toxicants, reproductive and developmental toxicants, or addictive [3]. Non-combustible tobacco products such as electronic nicotine delivery systems (ENDS)[1]; oral tobacco products e.g., smokeless tobacco, snus, and nicotine pouches; and heated tobacco products either do not contain or have substantially lower levels of these HPHCs compared to cigarettes and therefore can be potentially less risky than cigarettes. Public health authorities, including the FDA, acknowledge that not all tobacco products carry the same amount of risk but instead exist on a risk continuum, with combustible cigarettes considered the most risky and non-combustible products considered much less. Adults who smoke, particularly those who don't want to quit completely, may reduce their risks of smoking-related diseases by switching from cigarettes to non-combustible products. Therefore, making available products that deliver nicotine in a less risky manner to adults who smoke, particularly those who don't want to quit, is critical to reducing the risk of smoking-related diseases for such individuals. However, despite the knowledge that smoking cigarettes is harmful, there are nearly 30 million adults in the U.S. that continue to smoke [4]. One of many potential factors preventing adults who smoke from switching to potentially reduced risk alternatives is misperceptions of nicotine harm.

The vast majority of adults who smoke believe that nicotine is the chemical in cigarettes that causes cancer [5–7]. For example, researchers from FDA report that about 75% of people either were unsure of the relationship between nicotine and cancer or incorrectly believed that nicotine causes cancer [8]. The researchers posit that the incorrect beliefs regarding nicotine causing cancer, could discourage adults who smoke from switching to nicotine-containing non-combustible alternatives that may reduce their risks to smoking-related diseases. The observations regarding misperceptions of the harm from nicotine have been consistently reported across many studies. In a U.S. based study, 65% of people who smoke believed nicotine causes lung cancer and 71% believed it caused oral cancer [9]. Furthermore, a nationally representative study found that two-thirds of adults who smoke responded that "nicotine is a cause of cancer" [10, 11]. An International Tobacco Control (ITC) survey conducted from 2002 to 2008 found that more than half of U.S. adults who smoke incorrectly reported that nicotine is the cause of cancer, and this proportion significantly increased over time [6].

Nicotine misperceptions also impact attitudes and beliefs towards nicotine replacement therapy (NRT). Shiffman et al. found that a majority of adults who currently smoke and those who had formerly smoked (defined as having quit smoking within the last year) perceived NRT products to be just as harmful as smoking and they were significantly less likely to use NRT in future quit attempts [12]. Moreover, Snell et al., report that nicotine misperceptions could impede efforts to encourage people who smoke to transition to potentially reduced risk sources of nicotine, either to support cessation efforts or to replace cigarette smoking [13]. However, the net impact of nicotine misperceptions on a population level has not been investigated.

The purpose of this research was to estimate the public health impact associated with varying adults who smoke perceptions of nicotine harm using a computational health impact model. To our knowledge, this is the first analysis of the potential public health impact that focuses on outcomes based on real-world evidence regarding adults who smoke holding either accurate or inaccurate risk perceptions of nicotine. We applied a validated agent-based model to simulate individuals representative of the U.S. population and associated smoking behaviors [14].We projected changes in smoking prevalence and all-cause mortality outcomes (the number of premature deaths) among adults who smoke over an 85-year period and compared the outcomes associated with accurate perceptions of nicotine harm versus misperceptions.

Methods

We started with a base case scenario which represents the status quo. In the base case, the rate of switching to non-combustible use is representative of a population of adults who smoke with their existing perceptions of nicotine harm. We compared the base case to four nicotine

[1] Electronic nicotine delivery systems, e-cigarettes, e-vapor products.

perception scenarios in which the rate of switching to non-combusted use is adjusted based on stratified transition probabilities associated with the responses to the question "Do you believe nicotine is the chemical that causes most of the cancer caused by smoking cigarettes?" from Wave 4 data of the Population Assessment of Tobacco and Health (PATH) Study (R04_AC9120, four-item scale from "Definitely not" to "Definitely yes"). Each nicotine perception scenario modeled the population impact expected to occur if all adults who smoke held the same level of perception of nicotine harm as those in each response group from "Definitely not" to "Definitely yes". We modeled nicotine perception scenarios corresponding to each response rather than dichotomizing them into correct versus incorrect, as other researchers have done [8, 10, 11] to determine the population health impact associated with each response on this perception scale. The public health impact of nicotine perceptions was estimated as the difference in all-cause mortality and cigarette prevalence among adults who smoke, between the base case and each nicotine perception scenario.

In this research, we use a validated Agent-Based Population Model (ABM) as previously described [14–16] which projects future cigarette prevalence and all-cause mortality beginning in the year 2000. The ABM begins by initializing a hypothetical population of 2.81 million agents (1/100th of the year 2000 U.S. population) that is representative of the U.S. population for age, sex and tobacco use status. The model is iterated 100 times to simulate the entire U.S. population. The initial population mirrors the age and sex distribution data from the year 2000 U.S. Census. Each agent in the initial population was assigned to one of three tobacco use statuses representative of people who have never smoked, people who currently smoke and people who formerly smoked. Tobacco use status was assigned by sex and ages ≥ 18 using information from the National Health Interview Survey (NHIS) Sample Adult Questionnaire data for the year 2000. In our analysis of NHIS data, we defined status of individuals who were currently and previously smoking based on every day or some days definitions and having smoked 100 cigarettes criteria, commonly used by the Centers for Disease Control and Prevention (CDC) to estimate tobacco use prevalence for the U.S. adult population [17]. Since NHIS does not provide tobacco use information for ages < 18 years, tobacco use status assigned to the younger U.S. population, ages 10–17, by sex were estimated from the 2000 National Youth Tobacco Survey (NYTS). The NYTS is a nationally representative survey of middle and high school students focused exclusively on patterns of tobacco use. In analysis of the NYTS, we used past 30 days and lifetime use of 100 cigarettes or more to define use statuses.

Each agent in the initial population was assigned tobacco use history which was updated over the 100-year simulation timeframe from year 2001 to 2100. Agents who were representative of individuals who smoke or who previously smoked were assigned with their associated years of smoking and/or years stopped smoking and the age(s) at which the agent initiated and/or stopped smoking. Age and sex-specific probabilities from U.S. birth cohort smoking history data developed by Jeon et al. were used to assign when agents in the current smoking or former smoking statuses in the model's starting population initiated or stopped smoking [18]. The age and sex specific cigarette smoking initiation and cessation probabilities were generated by Tam et al. who used NHIS surveys administered from 1964 to 2015 to estimate birth cohort smoking histories [19] and details of the methodological approach and the resulting data are available on the Cancer Intervention and Surveillance Modelling Network website (CISNET, https://resources.cisnet.cancer.gov/projects/ - Publication Support and Modeling Resources).

Once the initial population was generated, the following algorithms were executed in 1-year time intervals throughout the simulation time frame:

Mortality sub-model

A mortality sub-model was used to estimate the survival probability of each agent based on their age, sex and current or former tobacco use history. The mortality sub-model was developed using data from a Kaiser Permanente (KP) Medical Care Program Cohort study [20], which included number of deaths, person- years, smoking status, age, sex, years smoked, and years since quitting smoking. The KP Study data were adjusted using the Human Mortality Database (HMD) to be representative of the U.S. population in the Year 2000. Mortality rates throughout the simulation time frame were further adjusted to account for expected age-specific changes in mortality over time using the methodology described by Carter et al., [21].

Transition sub-model

At each time interval within a simulation, agents were provided with an option to change or maintain their current tobacco use status. These decisions were governed by the agent's defined current tobacco use status, age and sex specific transition probabilities.

Population update

The age of agents who survive at each time interval was increased by 1-year increments. New agents are added to the population each year to account for birth and net immigration based on U.S. Census projections [22]. We assigned agents who entered the population via

immigration with tobacco use status and history similar to that used for the initial population.

We projected ABM scenarios through the year 2100. The public health impact of varying perceptions of nicotine harm was quantified as the difference in adult prevalence and cumulative all-cause deaths for ages 35–85 between the base case and nicotine perception scenarios. We used the 35–85 age range since it is expected that most smoking mortalities occur within this range [1].

Base case scenario inputs

The base case scenario models smoking prevalence and all-cause mortality where cigarette smoking continues to be the predominant tobacco use behavior. Transition probabilities, by and sex, for initiation from individuals that never smoked to currently smoking to smoking cessation to a state where they were established as previously smoking were obtained from CISNET, where the smoking history of U.S. birth cohorts was reported using NHIS data [18]. CISNET transition probabilities are available by age (0–99), sex and year through 2015. CISNET initiation probabilities by sex and age are updated each year in the model from 2001 to 2015, at which point they were held constant for the remaining simulation timeframe. Cessation probabilities in CISNET are based on at least two years of successful smoking cessation. This is an important consideration since minimal relapse has been reported [23] after a period of two years which minimizes the relapse transition between individuals who were previously smoking back to smoking cigarettes. The CISNET smoking cessation probabilities were updated by model each year between 2001 and 2013 with the corresponding yearly estimates. Beginning in the year 2014, former smoking state was split to differentiate individuals that successfully quit smoking and do not use non-combustible products from those who successfully quit smoking but who now use non-combustible products. The non-combustible use status represents the proportion of people who previously smoked who completely switched to non-combustible product use. Figure 1 provides a diagram of the base case tobacco use states and transitions.

To differentiate individuals who previously smoked from those who use non-combustible products, beginning in 2014 transitions from current smoking to former smoking and current smoking to non-combustible product use were estimated using data from Wave 1 (W1) 2013/2014 to Wave 5 (W5) 2018/2019 of the PATH study which is funded by the FDA Center for Tobacco Products (CTP) and administered by the National Institute on Drug Abuse (NIDA). The PATH study was designed to generate longitudinal epidemiologic data on tobacco-use behavior and health in the U.S. population [24].

As of 2022, five waves of PATH data are publicly available for analyses [25]. In our analysis of PATH, we identified adults who smoke (n=6,349) in W1 as those who reported smoking at least 100 cigarettes in their lifetime and currently smoke every day or some days. Adults who previously smoked were identified as W1 adults who smoke who no longer smoked in subsequent waves and did not use ENDS (defined in PATH to include products such as e-cigarettes, e-hookahs, e-cigars, e-pipes, personal vaporizers, vape pens, and hookah pens) or smokeless tobacco (ST, defined in PATH to include moist loose snus, snuff, dip and spit or chewing tobacco or snus every day or some days). Non-combustible product use was identified as W1 adults who smoke who no longer smoked but also indicated every day or someday use of ENDS and ST in subsequent waves. We calculated successful quitting and switching as people who smoked in W1 who transitioned to either former smoking or non-combustible product use in W2 (2015/2016) and maintained their status through W5 (an approximate 3-year of follow up). W1 adults who smoke who indicated they had not used ENDS or ST every day or some days in W2

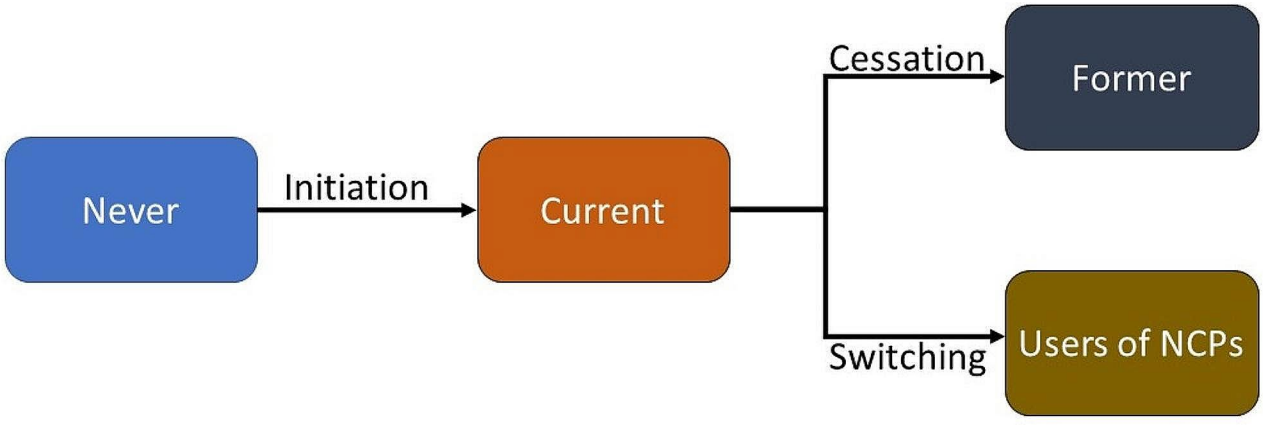

Fig. 1 Schematic of the base case tobacco use states and transitions. Footnote: Never = Individuals who have never smoked cigarettes; Current = Individuals who are currently smoking cigarettes; Former = Individuals who have previously smoked cigarettes; NCP = non-combustible products

but had used in any subsequent wave, W3 through W5, were excluded from our analysis. This was done to ensure that the transition rates reflected long-term sustained behavior. Estimates from five waves of PATH were used to obtain successful quitting/switching probabilities, which follows a similar methodology as CISNET successful smoking cessation calculation. We observed higher successful cigarette cessation probabilities based on the PATH study data which aligns with observations from existing research that indicates a recent increasing trend in cigarette cessation [26]. We applied PATH cessation probabilities to account for recent changes in smoking prevalence observed between 2014 and 2018 since they were not captured in the CISNET cessation rates.

The all-cause mortality probability assigned to use of non-combustible products was based on the excess relative risk (ERR) of non-combustible product use compared to cigarette smoking. We applied an ERR of 10%, which reflects a reasonable aggregate estimate for the various non-combustible tobacco products. An ERR of 10% is slightly higher than the estimate of 9% for current ST product use relative to smoking [27]. Applying a multi-criteria decision analysis (MCDA) model developed by an international expert panel convened by the Independent Scientific Committee on Drugs [28], the authors assigned the relative importance of different types of harm related to the use of nicotine-containing products compared to cigarette smoking. The panel estimated a relative risk of 5% for snus and 4% for ENDS products relative to smoking. An ERR value of 10% represents a conservative choice for non-combustible use in the model given that this tobacco use state is representative of exclusive or other combinations of use of ST and ENDS. Additionally, we do not allow transitioning to former non-combustible use, therefore agents entering the non-combustible use state carry their former smoking risk in addition to the ERR for current non-combustible use throughout the remaining simulation timeframe.

Nicotine perception scenarios

Nicotine perception scenarios were simulated in which all adults who smoke transition to non-combustible product use at rates associated with different levels of perception of nicotine harm. PATH W4 (2016–2018) data were used to assess adults who smoke perceptions of nicotine harm based on their responses to the question "Do you believe nicotine is the chemical that causes most of the cancer caused by smoking cigarettes?" (R04_AC9120, four-item scale from "Definitely not" to "Definitely yes"). We choose W4 as the baseline wave to analyze the levels of nicotine perception because, in addition to also being a true cross-sectional wave due to sample replenishment, it is more recent compared to W1 (2013–2014) and may reflect the current state of nicotine perception among adults who smoke.

Nicotine perception scenario inputs were developed by first estimating the overall rate of switching from smoking to non-combustible product use based on longitudinal analysis of PATH W4 (2016–2018) and W5 (2018–2019). The analysis included W4 adults who smoke (18+) that responded to the nicotine perception question (i.e., "Definitely not", "Probably not", "Probably yes" or "Definitely yes") ($n=6886$) following the same definitions used to define individuals who smoke and individuals who use non-combustible products in the base case. The overall switching rate was then stratified by W4 adults who smoke perceptions of nicotine harm. We did not estimate switching rates by age or sex to preserve sample size for each of the nicotine perception response groups.

A total of four nicotine perception scenarios were simulated corresponding to each of the four responses to the question "Do you believe nicotine is the chemical that causes most of the cancer caused by smoking cigarettes?". The model inputs corresponding to each nicotine perception scenario were estimated by adjusting the base case sustained switching rates with the relative percent change between the W4 to W5 overall and stratified transition rates corresponding to each different level of nicotine perception. Relative percent changes were calculated as the stratified rate associated with one level of the nicotine harm perception minus the overall rate divided by the overall[2] rate of smoking to non-combustible product use between W4 and W5. Relative percent changes were used to adjust the base case rates by sex to avoid over estimation of switching behavior. Switching rates between W4 to W5 would not be expected to be comparable to the sustained 1-year switching rate used in the base case since W5 is a follow up study conducted approximately two years after W4 data collection and may not reflect sustained switching. Therefore, we only applied relative percentage changes between the overall and stratified switching rates to the base case to evaluate the population impact associated with various levels of nicotine harm perception. In each scenario we assume that all adults who smoke will exhibit the switching behavior associated with the specific response groups.

The difference in overall prevalence and all-cause mortality between the base case and each nicotine perception scenario was used to quantify the population health impact corresponding to adults who smoke perceptions of nicotine harm.

[2] Relative Change = (Stratified Rate − Overall)/Overall.

Results

Base case PATH estimates

Based on our analysis of PATH W1 to W5, 3.92% male and 4.35% female adults who smoke transitioned to former smoking in W2 and remained through W5. Adults who smoked in W1 transitioned to non-combustible product use in W2 and maintained use of non-combustible products through W5 at a rate of 1.32% and 0.44%, male and female respectively.

Nicotine perception scenario PATH estimates

Table 1 shows the demographics characteristics of W4 adults who smoke overall and by perception of nicotine harm. We note that striking differences were observed among the different age and race/ethnicity subgroups in response to the nicotine perceptions question. While the nicotine misperceptions of harm were high across all age subgroups, they trended to be higher among the 45+age subgroup. More than 70% of adults who smoke in the 45+age subgroup responded "Definitely yes" or "Probably yes" regarding harm from nicotine, compared to ~50–55% for those in the lower age groups. Additionally, a higher proportion (~76%) of adults who smoke in the Non-Hispanic Black and Hispanic subgroups indicated higher perceptions of nicotine harm compared to the Non-Hispanic Whites (~58%). The data in Table 1 are important as the observed differences may result in different rates of switching to non-combustible product use between demographic subgroups. Modeling can theoretically be used to investigate population health impacts by demographic characteristics, however the sample sizes needed to provide robust input estimates have limited most models to include only age and sex variables. We focused our simulations on the overall group of W4 adults who smoke (18+) due to sample size and model limitations (i.e., current model is not capable of utilizing population inputs by race or economic status) however it is important to consider the data in Table 1 when interpreting the results.

Table 1 AS demographics by nicotine perception held

Characteristic	Total	Perception of nicotine harm: "Do you believe nicotine is the chemical that causes most of the cancer caused by smoking cigarettes?"			
		Definitely yes	Probably yes	Probably not	Definitely not
	7007	1338	2943	2090	515
Sex					
Female	46.38%	19.01%	45.99%	28.95%	6.04%
Male	53.62%	18.06%	43.19%	31.64%	7.11%
Age					
18–24	8.15%	13.79%	36.36%	36.85%	12.99%
25–44	45.47%	16.84%	39.97%	35.52%	7.67%
45+	46.38%	21.02%	50.36%	24.18%	4.44%
Race/Ethnicity					
Non-Hispanic White	68.78%	13.47%	44.42%	35.02%	7.09%
Non-Hispanic Black	13.08%	33.94%	43.08%	17.57%	5.41%
Non-Hispanic Others	5.42%	19.06%	43.02%	31.21%	6.7%
Hispanic	12.71%	29.63%	46.89%	18.26%	5.21%
Education					
LT College	57.39%	22.45%	46.92%	25.19%	5.44%
Some College	31.70%	14.08%	41.74%	36.58%	7.59%
College Grad	10.91%	9.64%	40.32%	40.33%	9.7%
Smoking Behavior					
Every Day	76.32%	18.51%	45.52%	29.84%	6.13%
Some Day	23.68%	18.58%	41.12%	32.12%	8.18%

The overall transition rate for W4 adults who smoke who completely switched to non-combustible product use by W5 was estimated to be 3.94%. Figure 2 shows the proportions of W4 adults who smoke that comprise of each response group and their associated transition rates to non-combustible product use in W5. As shown in Figs. 2, **6**.61% of W4 adults who smoke ($n=515$ shown in Table 1) responded "Definitely not". Of those adults who smoke who responded, "Definitely not", 8.39% quit smoking and switched to non-combustible product use by W5, more than twice the overall rate. This is in contrast with 18.52% ($n=1338$ in Table 1) of adults who smoke who responded, "Definitely yes", of which 2.59% switched to exclusive non-combustible product use at W5.

Table 2 provides the base case transition rate inputs by sex, relative percent change adjustments and the final rates used in each of the four nicotine perception scenarios. As shown in Table 2, the switch rates among adults switching from smoking cigarettes to using non-combustible products who had accurate nicotine risk perceptions (responding "Definitely not") was more than twice compared to those who had nicotine risk misperceptions (responding "Definitely yes") Also included in Table 2 are relative percent change adjustments corresponding to 95% confidence limits of the transition rates calculated as the ratio of the upper and lower 95% confidence limit of the transition rate associated with one level of the nicotine harm perception over the overall transition rate of smoking to non-combustible product use between W4 and W5. Sensitivity scenarios were conducted based on these 95% confidence limits (Table 2) of the stratified transition rates.

Table 3 shows adults who smoke prevalence projections between 2014 and 2100 for the base case and nicotine perception scenarios. Under the base case scenario, which reflects a mix of nicotine perceptions, the model predicts a relative change of -58.9% (i.e., a 58.9% reduction) in adult smoking prevalence between the years 2014 and 2100. Adult smoking prevalence decreases further over the same period when the transition rate to non-combustible product use is adjusted to correspond

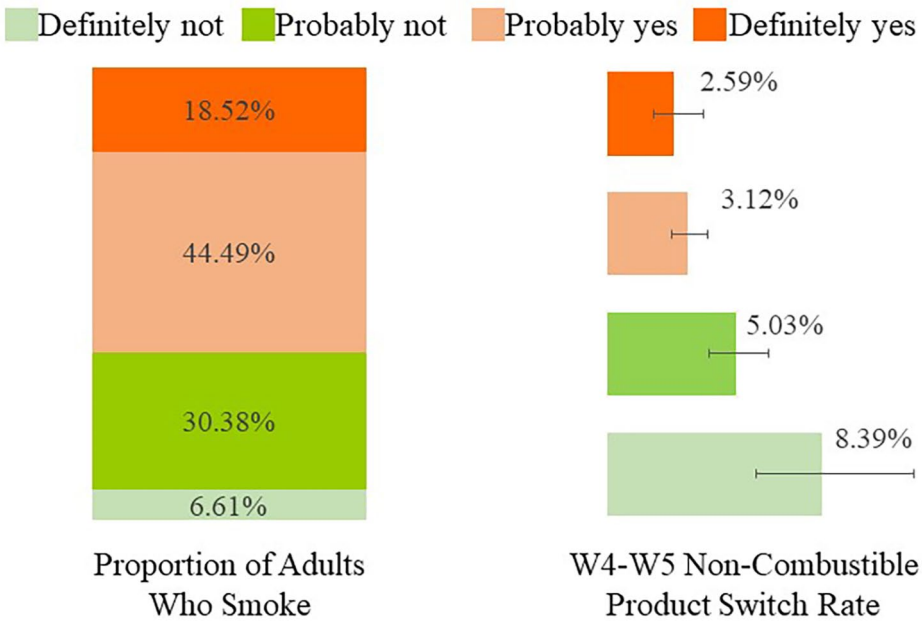

Fig. 2 Proportions of Wave 4 adults who smoke that comprise each response group and their associated switch rates to non-combustible product use in Wave 5. Footnote: Analysis based on PATH data from Waves 4 and 5. Error bars represent 95% confidence intervals for each response group switching rate

Table 2 Nicotine perception scenario switch rates for adults who switch from smoking cigarettes to using non-combustible products

Nicotine Perception Scenario	Base case Switch Rates		Relative % change Adjustment*	Switch Rates corresponding to each Nicotine Perception Scenario**	
	Male	Female		Male	Female
Definitely not	1.32	0.44	113% (47%,204%)	2.81	0.94
Probably not			28% (1%, 60%)	1.69	0.56
Probably yes			-21% (-1%, -37%)	1.04	0.35
Definitely yes			-34% (-5%, -55%)	0.87	0.29

*Relative percent changes corresponding to 95% confidence limits of the stratified switch rates are shown. **Switch rate calculated as Base Rate + Base Rate * Relative % change adjustment

to nicotine harm perceptions held by all the adults who smoke in the simulation similar to the "Definitely not" and "Probably not" response groups with relative changes of -63.7% and −60.2%, respectively. The model predicted slightly higher smoking prevalence in the nicotine perception scenarios if all adults who smoke in the simulation held nicotine harm perceptions similar to the "Probably yes" and "Definitely yes" response groups resulting in relative changes of -57.8% and −57.1%, respectively.

Figure 3 shows the predicted population health impact as cumulative premature deaths prevented through the year 2100. The nicotine perception scenarios in Fig. 3 resulting in cumulative premature deaths prevented greater than zero correspond to a net population health benefit. On the other hand, differences less than zero indicate an increase in smoking attributable mortality. Additionally, cumulative premature deaths prevented equal to zero indicate no change from the base case would be expected. The error bars in Fig. 3 show the results of additional sensitivity simulations

Table 3 AS Prevalence 2014–2100 (Ages 18+)

Scenario/year	2014	2025	2050	2075	2100	Relative Change
Base case	17.0%	11.2%	7.5%	7.1%	7.0	-58.9%
Definitely not	16.8%	10.2%	6.5%	6.2%	6.1	-63.7%
Probably not	17.0%	11.0%	7.2%	6.9%	6.7	-60.2%
Probably yes	17.0%	11.4%	7.7%	7.3%	7.2	-57.8%
Definitely yes	17.0%	11.5%	7.8%	7.4%	7.3	-57.1%

Relative change is calculated as (Y2100-Y2014)/Y2014

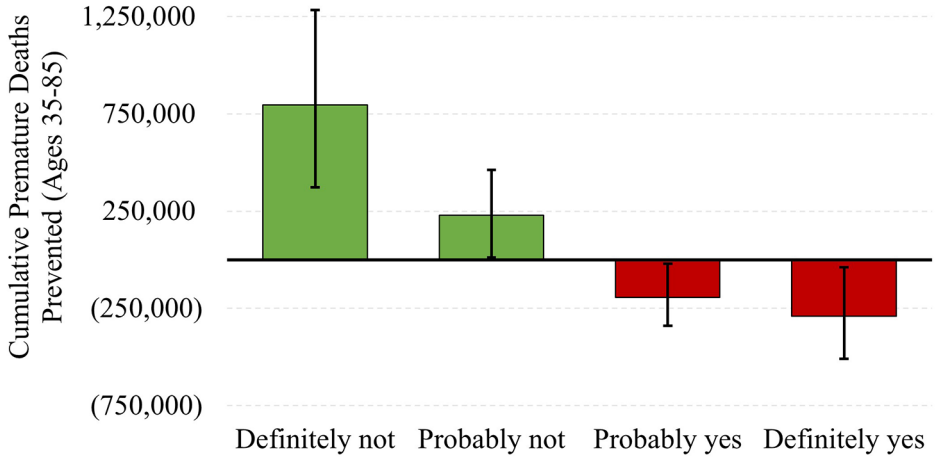

Fig. 3 Predicted population health impact as cumulative premature deaths prevented through to the year 2100. Footnote: The error bars indicate the results of additional sensitivity simulations corresponding to adjustments from the relative percent change of the overall W4-W5 switch rate and the 95% confidence limits of the stratified switch rates by nicotine perception response groups. The scenarios corresponding to "Definitely not" and "Probably not" both result in positive net public health gains of approximately 800,000 and 200,000 premature deaths prevented over the simulation time frame, respectively

Table 4 Cumulative deaths prevented (base - nicotine perception scenario)

Scenario/year	2025	2050	2075	2100
Definitely not	19,688	311,133	569,885	796,530
Probably not	5,395	86,384	161,207	228,390
Probably yes	-2,128	-72,207	-135,723	-194,735
Definitely yes	-11,376	-103,339	-200,652	-290,491

corresponding to adjustments from the relative percent change of the overall W4-W5 switch rate and the 95% confidence limits of the stratified switch rates by nicotine perception response groups. The scenarios corresponding to "Definitely not" and "Probably not" both result in positive net public health gains of approximately 800,000 and 200,000 premature deaths prevented over the simulation time frame, respectively.

Table 4 shows the predicted population health impact as cumulative premature deaths prevented from 2025 to 2100 in 25-year intervals. As shown in Table 4 the population health risks and benefits associated with varying perceptions of nicotine harm are seen as early as 2025.

Figure 4 show the ranges corresponding to sensitivity scenarios in which the adjustments to the base case rates are based on the 95% confidence intervals of the switching rates (see Table 2) for the "Definitely not" and Definitely yes" response groups. The upper and lower 95% confidence limits associated with the "Definitely not" response group results in a net population health benefit between 373,000 and 1.3 million premature deaths prevented (shaded region in Fig. 4 labeled Definitely not). The upper and lower 95% confidence limit corresponding to the "Definitely yes" response group results in a net population health risk between approximately 40,000 and 509,000 additional premature deaths (shaded region in Fig. 4 labeled Definitely yes). Figure 4 illustrates that if all the adults who smoke exhibit the switching behavior corresponding to those who responded "Definitely not" then a net population benefit could be expected. On the other hand, the behavior associated with adults who smoke with misperceptions regarding the role of nicotine in the harm caused by smoking result in net population risk. The shaded regions in Fig. 4 do not overlap indicating a clear difference in the health outcomes of these two groups.

Discussion

The objective of this study was to estimate the public health impact associated with varying perceptions of nicotine harm using computational modelling. While it is imperative for individuals to understand that nicotine is addictive, it is equally important for them to understand that nicotine is not the main reason why cigarette smoking is harmful to health. A clear trend in the rate of switching to non-combustible product use was observed across the nicotine harm perception response scale. We forecasted substantial benefits to public health if adults who smoke have correct perceptions of nicotine harm and negative consequences from continuing to maintain misperceptions regarding nicotine. Applying to all adults who smoke, switch rates associated with those who responded that nicotine is "Definitely not" the chemical that causes the cancer caused by smoking, resulted in *preventing* nearly 800,000 premature deaths with an upper estimate of 1.3 million over an 85-year period to 2100. The lower switch rate associated with those who responded "Definitely yes" correspondingly

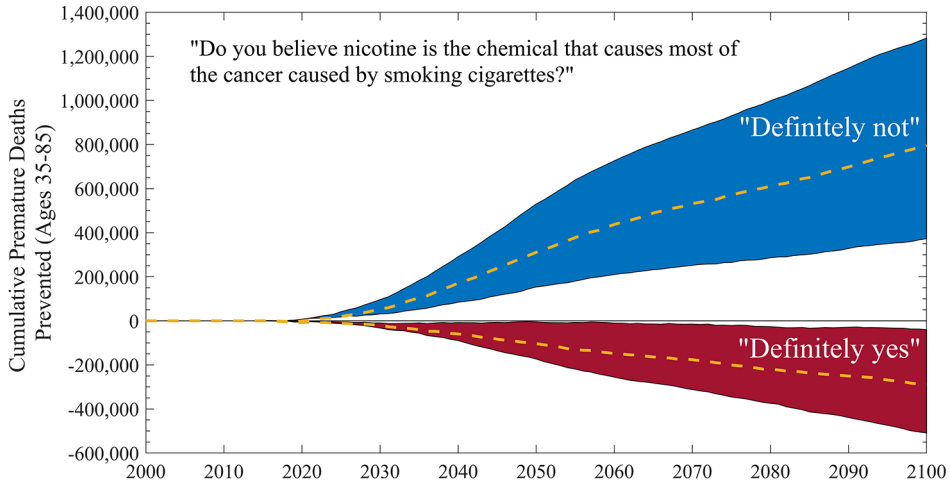

Fig. 4 Ranges of cumulative premature deaths prevented corresponding to sensitivity scenarios for the "Definitely not" and Definitely yes" response groups. Footnote: The adjustments to the base case rates are based on the 95% confidence intervals of the switching rates for the "Definitely not" and Definitely yes" response groups. The upper and lower 95% confidence limits associated with the "Definitely not" response group results in *a net population health benefit* between 373,000 and 1.3 million premature deaths prevented (shaded region labeled "Definitely not"). The upper and lower 95% confidence limit corresponding to the "Definitely yes" response group results in *a net population health risk* between approximately 40,000 and 509,000 additional premature deaths (shaded region labeled "Definitely yes"). Note: The shaded regions do not overlap, indicating a clear difference in the outcomes of these two groups

resulted in increasing deaths attributable to smoking by an additional 300,000 by the year 2100 if all adults who smoke held this misperception. Our findings indicate that, if left unchecked, increases in the proportion of adults who smoke who hold misperceptions of nicotine harm could have negative impacts on harm reduction efforts and public health. This is particularly important for "older" and Non-Hispanic Black and Hispanic adults who smoke. Our observations of higher prevalence of nicotine misperceptions, particularly in those individuals in the older age subgroups (Table 1) are comparable to those reported recently by Rubenstein et al. [29]. As indicated by the authors, the higher levels of nicotine misperceptions in these individuals, could be a barrier to switching to non-combustible products. Overall, our results illustrate the potential long-term public health gains that could be made through campaigns aimed at correcting perceptions of nicotine harm among all adults who smoke rather than the current status quo which has been described as a "quarantine of information" [30]. The trend from risk to benefit across the nicotine perception scenarios indicates that even a modest shift in perceptions of nicotine harm could have positive impacts on public health.

Our analysis of PATH W4 data are consistent with previous research indicating that a majority of adults who smoke (63% responded "Definitely" or "Probably yes") have misperceptions regarding the role of nicotine as a cause of cancer from smoking [5, 6, 8, 10, 11, 13]. Borland et al. reported nicotine harm perceptions are continuing to trend in the wrong direction with a significant decline observed (OR=0.97, $p=0.002$) among people reporting that nicotine is not the chemical that causes most of the cancer [6].

Incorrectly believing that nicotine causes cancer could discourage adults who smoke from switching to safer nicotine containing alternatives from cigarettes. Nicotine misperceptions could be erroneously associated with perceived harm of non-combustible products. Wilson et al. found that correct perceptions of nicotine harm were associated with correctly perceiving e-cigarettes to be less harmful than smoking [31]. Studies have shown that adults who smoke who perceive ENDs to be less harmful than smoking are more likely to switch. Kim et al. reported that switching to ENDS was nearly three times higher for adults who smoke who perceived ENDS to be less harmful than smoking [32]. Similarly, Snell et al. report that misperceiving nicotine to be a main cause of smoking-related cancers was associated with lower odds for ENDS use (adjusted odds ratio (AOR)=0.59; 95% confidence interval (CI)I: 0.49, 0.71; $p<0.01$) [13]. Therefore, the findings from our analyses support the notion reported in published literature. Substantial benefit can be manifested if all adults who smoke accurately understand that nicotine is not responsible for the harm related to smoking related diseases.

Moreover, misperceptions regarding the harm from nicotine also impacts the attitudes and beliefs of adults who smoke toward NRTs. Shiffman et al. report that a majority of adults who smoke (66%) perceived NRT products to be just as harmful as smoking or were unsure [12]. These individuals were less likely to have used NRT in the

past (odds ratio (OR)=0.45, 95% CI: 0.39–0.53) and less likely to consider using NRT during future quit attempts (OR=0.60, 95% CI=0.51–0.71). Additionally, Snell et al. reported lower odds of NRT use (AOR: 0.84; 95% CI: 0.71, 0.99; p=0.04) among those individuals who made a quit attempt during the study period [13]. Therefore, nicotine misperceptions could not only impede efforts to encourage adults who smoke to transition from cigarettes to potentially reduced risk sources of nicotine, but also to support cessation efforts.

The results of our findings should be considered in the context of the limitations of the model due to the assumptions. In this study we made several assumptions to simplify the modeling framework. For example, we assumed that initiation rates for smoking to be unchanged between both the base case and nicotine perception scenarios. Additionally, we assumed that the prevalence of immigrating populations, who were smoking and had previously smoked, to be the same as the starting population. This can be a limitation of our approach, since immigrating populations can be vastly different between countries, for example in New Zealand "Asians" including mostly Chinese and Indian people have the lowest smoking prevalence in NZ. Very few Chinese women smoke.(https://www.smokefree.org.nz/smoking-its-effects/facts-figures.Accessed-May, 2024). The model outcomes are not expected to be greatly impacted since these assumptions impact both the base case and the nicotine perception scenarios and the population health impact is evaluated by comparing the outcomes between the scenarios. Thus, changes to total prevalence and all-cause deaths would be impacted to a similar extent in both the base case and nicotine perception scenarios. However, it is important to consider that correcting the misperceptions should be targeted to adults who smoke and minimize any "spillover" reach to youth. Additionally, as the focus of this research is on cigarette smoking prevalence and smoking attributable all-cause mortality, we did not consider relapse from non-combustible product use back to cigarette smoking. Because the base case rate of switching to non-combustible product use is based on long-term analysis, spanning over roughly four years, (PATH W2-W5), this is a reasonable assumption since minimal relapse back to smoking is expected after two years [33]. Moreover, we assumed cessation from non-combustible product use as nonexistent, a conservative assumption, since it excludes any additional potential population health benefit resulting from long term cessation of non-combustible product s. We also made a simplifying assumption that the impact of initiation to non-combustible product use among those not currently using tobacco products was minimal. While potential increases in initiation of non-combustible products due to corrected perceptions of nicotine harm alone would be expected to decrease the overall net benefit, a concurrent decrease in smoking initiation and potential increases to non-combustible product cessation could act to counterbalance impacts due to initiation by people who have never used tobacco. Various population health models examining the impact of ENDS on the population have shown that the public health benefit associated with rates of smoking cessation and switching generally far outweighs possible increases to initiation [34–37]. In a recent model evaluating the impact of introducing a novel oral nicotine product, we found that initiation would have to increase by more than 3000% before the benefit of adults who smoke switching was outweighed [38]. Finally, we acknowledge that, as cited by some researchers [39, 40], number of premature deaths due to an exposure may not be precisely assessed, even under optimal conditions. However, such an approach is reasonable and has been used by authoritative bodies like the Food and Drug Administration [41] to make regulatory decisions regarding public health impact.

The benefit associated with correcting perceptions of nicotine harm is dependent on the relative risk of the non-combustible product category as compared to smoking. In our model, we assumed that the ERR of non-combustible products was a single value of 0.1. This estimate is derived from the epidemiological evidence for smokeless tobacco products [42] which is a reasonable and conservative assumption, representative of other non-combustible products. Current estimates of the relative risk of the various non-combustible products (e.g., snus and ENDS products) have been reported to be slightly lower than smokeless tobacco [28, 42, 43].

Conclusion

Accurate knowledge regarding the role of nicotine is associated with higher switch rates and prevention of premature deaths. Our findings suggest that promoting public education to correct nicotine misperceptions has potential to benefit public health. Despite the inherent uncertainty of a modeling approach, this research highlights the potential public health benefit of a harm reduction strategy for current adults who smoke, especially those who don't want to stop smoking. Providing information to adults who smoke about the role of nicotine and the relative risk of non-combustible products compared to smoking would be crucial to removing barriers to adults who smoke transitioning to non-combustible products, potentially lower harm sources of nicotine. However, dissemination of this information should be considered in the context of interpretation by individuals who have never used tobacco, including youth. In conclusion, correcting the inaccurate perceptions of the harm from nicotine may promote switching to non-combustible products among adults who smoke but don't want

to stop smoking. The switching behavior will accelerate the decline in smoking prevalence and has the potential to substantially reduce premature smoking-related mortality.

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TH and RMK developed the concept, LW generated the model inputs from PATH dataset, EL and MS provided strategic direction, all authors contributed towards the writing and review of the manuscript.

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