SIMULATION MODELING IN TOBACCO REGULATORY SCIENCE: WHERE ARE WE AND WHERE SHOULD WE GO NEXT?

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Proceedings of the CAsToR 2021 Symposium

An interactive three-day online symposium on the current state and future trends in computational modeling for tobacco regulatory science.

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Simulation Modeling in Tobacco Regulatory Science: Where are we and where should we go next?

PROCEEDINGS OF THE CASTOR 2021 SYMPOSIUM

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INTRODUCTION

Rafael Meza, PhD, University of Michigan
David Levy, PhD, Georgetown University
Principal Investigators, Center for the Assessment of Tobacco Regulations (CAsToR)

We are delighted to present these proceedings for the CAsToR Symposium 2021, held June 7-9, 2021. Our theme for this Symposium was "Simulation Modeling in Tobacco Regulatory Science: Where are we and where should we go next?" This three-day virtual meeting brought together many of the key researchers in both modeling and TRS for an incredibly rich and productive series of presentations and dialogues.

The Center for the Assessment of Tobacco Regulations (CAsToR) aims to provide evidence-based and expert-informed modeling of the behavioral and public health impacts of tobacco regulations. Funded through the Tobacco Centers of Regulatory Science (TCORS) 2.0 program, this multi-institutional Center includes experts in the field of tobacco regulatory science and modeling from the University of Michigan, Georgetown University, Yale University, the University of California San Francisco, and the University of Minnesota. The aims of this Symposium were to:

- Identify knowledge gaps in tobacco regulatory research that can be addressed by simulation (computational) modeling of tobacco behaviors, policies and health effects.
- Identify the utility of and challenges in using computational models in the context of a dynamic tobacco landscape within the current tobacco regulatory framework.
- Propose a plan to fill knowledge gaps and address challenges in conducting timely tobacco regulatory science research that uses tobacco simulation modeling.

Its program featured keynotes from leading tobacco control researcher Dr. Ken Warner and FDA Center for Tobacco Products Director Mitch Zeller, technical presentations from

academic experts, government leaders, consultants and emerging researchers, and daily panel discussions with key figures in the field.

More importantly, this was an interactive forum that engaged participants, highlighted by five group breakout sessions devoted to addressing core areas aligned with the objectives of the Symposium. The results of these breakout sessions, and their subsequent discussions with participants, are captured in these proceedings and serve as an important roadmap for future work in modeling and tobacco regulatory science.

In this challenging pandemic year, this virtual Symposium brought together a national group of stakeholders to discuss new ways for advances in modeling and tobacco regulatory science to help end the scourge of tobacco-related death and disease. The end result of this Symposium was a tremendous exchange of ideas and a base for future collaboration, which we are privileged to share with you in these proceedings.

Further information about this Symposium, including presenter information and recordings of live presentations, are available online at: https://tcors.umich.edu/Symposium2021.php

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PARTICIPANT LIST

Symposium moderators

Rafael Meza, PhD - University of Michigan

David Levy, PhD – Georgetown University

Keynote speakers

Kenneth E. Warner, PhD – University of Michigan

Mitchell Zeller, JD – US Food and Drug Administration

Presenters and facilitators

David Mendez, PhD – University of Michigan

Ritesh Mistry, PhD – University of Michigan

Douglas Luke, PhD – Washington University in St. Louis

Esther Salazar, PhD – US Food and Drug Administration

Jamie Tam, PhD – Yale University

Jody Sindelar, PhD – Yale University

Aylin Sertkaya, PhD – Eastern Research Group

Warren Bickel, PhD – Fralin Biomedical Research Institute, Virginia Tech

Raymond Niaura, PhD – New York University

Iris Yuefan Shao, MPH – Emory University

Thuy Le, PhD – University of Michigan

Ruoyan Sun, PhD – University of Alabama at Birmingham

Eric J. "Rocky" Feuer, PhD – National Cancer Institute

David B. Abrams, PhD – New York University

K. Michael Cummings, PhD MPH – University of South Carolina

Benjamin Apelberg, PhD MHS – US Food and Drug Administration

Clifford Douglas, JD – University of Michigan

Dorothy Hatsukami, PhD – University of Minnesota

Keynote: The Role of Simulation Modeling in Tobacco Research and Regulation: Yesterday, Today and Tomorrow

Kenneth E. Warner, PhD, University of Michigan.

Abstract

Simulation modeling in tobacco control plays an important role in applications including forecasting smoking prevalence and health outcomes, estimating the future impact of interventions, examining unintended intervention side effects, performing counterfactual or "what if" analysis of intervention strategies, and identifying research gaps and establishing priorities.

Future priorities include modeling of issues of relevance to the FDA and other policymaking bodies, developing standards of good practice for modeling, and educating tobacco control researchers about modeling, as well as future areas such as improving cost-effectiveness of modeling and exploring the use of artificial intelligence.

Introduction

My hope in this presentation is to inform other researchers about the value of simulation modeling, and how their knowledge and their research methods can work with modeling to contribute to informing and guiding tobacco regulatory science. I believe that regulatory science will be best informed by simulation modeling research combining the talents of modelers and non-modeling researchers who bring different perspectives to the research as well as skill sets.

So, why modeling? First of all, the obvious answer is that we want to address questions and issues that are of interest and importance. And they all tend to be rather complex: lots of variables, lots of interactions among them, and so on. Frankly, the real answer to "why modeling?" is because we can't address these questions effectively without modeling. Frequently, we're interested in future outcomes. For example, we can't wait ten years to find out what's going to happen ten years from now in terms of smoking prevalence – so we have to be able to make projections, and that's what modeling allows us to do.

According to Epstein (2008), we use a model *whenever* we try to project a future outcome: usually an implicit model that is "in our heads" with unspecified assumptions, untested internal consistency, and unknown logical consequences or relationships to actual data. Therefore, as he puts it, "[t]the choice … is not whether to build models; it's whether to build *explicit* ones." With explicit models, we understand precisely what assumptions are being made and what happens when we change those assumptions, and the results are replicable and data driven.

Simulation modeling in public health is now used for a wide range of purposes. For example, we've seen a lot of modeling related to COVID-19 and vaccination, predicting the likely course of infectious diseases and what control measures are likely to achieve over time. More generally, modeling is being used to try to develop a national plan to address future infectious disease epidemics and pandemics. It also is used to understand the evolution of chronic disease epidemics such as obesity and, obviously, the impact of smoking. And it can be used to assess cost-effectiveness of alternative approaches to reducing the health effects of diseases.

Modeling in tobacco control

What can modeling contribute specifically to tobacco control? Here are some of the areas where it is used:

- Forecasting smoking prevalence and health outcomes, for goal setting and other applications
- Estimating the future impact of interventions (such as policies, regulations, education and media campaigns, and cessation initiatives) on smoking prevalence and health outcomes
- Identifying the potential importance of unintended intervention side effects
- Assessing the past trajectory of smoking and health outcomes if existing interventions had not occurred, or if non-adopted interventions had been adopted
- Identifying research gaps and establishing priorities to improve data for future models

One element of special relevance is that the Family Smoking Prevention and Tobacco Control Act of 2009 requires the US Food and Drug Administration (FDA) to employ a public health standard, which means they have to evaluate population health impacts, a new field of regulatory science for FDA. For much of what the FDA does, namely the approval or non-approval of drugs, the standard is individual patient safety and efficacy. Assessing population health is much more challenging, and frankly, it's probably much more important. This means that simulation modeling is going to be an important method for evaluating modified and novel tobacco products going forward.

There are two principal categories of model types used in tobacco control: ***aggregate (compartmental)*** models, and ***individual (agent-based)*** models.

Aggregate or compartmental models track quantities describing homogeneous groups, one of the most obvious being the total number of smokers in the US population tracked over time. These models have stocks (aggregate quantities of interest, such as the number of smokers) and flows (rates of transition between stocks, such as smoking initiation, cessation or death rates).

For example, we may divide the overall population into age and gender groups, with smoking prevalence, initiation and cessation rates for these groups possibly differing from those of the other groups, and they can vary over time. But within each of these groups, at a given point in time, all members of the group are treated as if they are identical. One variation on the aggregate model, system dynamics models, are characterized by greater complexity, nonlinear reactions, and feedback effects.

Agent-based models track individuals as they interact with their environment through social networks. Their structure has three components: *agents*, *rules*, and *characteristics*. The *agents* themselves are individuals who have unique traits that are followed throughout the simulation, such as age, gender, socioeconomic status, and smoking status. These agents follow *rules* describing the behavior of the agents as they interact with each other and their environment. For example, if a non-smoking young person interacts with a same-age smoker, this interaction will increase the probability that the non-smoking individual will initiate smoking.

Choosing *characteristics* of the groups or individuals to include in these models depends on the purpose of the model. If modelers are interested in the effects of menthol cigarettes, for instance, their models have to distinguish initiation and cessation rates by type of cigarette (menthol or non-menthol). If modelers are not interested in menthol smoking per se, they can simply use rates of initiation and cessation averaged across these two types of cigarettes. Other examples of characteristics include the greater difficulty of quitting among lower socioeconomic status smokers, or the greater price sensitivity among young smokers.

There are many simulation models used among tobacco control researchers. Here at CAsToR at the University of Michigan and Georgetown University, models we employ include David Levy's SimSmoke model, the Mendez-Warner UM model, and the CISNET model used by Ted Holford, Rafael Meza and others. All of these are used frequently and have performed admirably.

How models for tobacco control are used

Now, let's look in more detail at the areas we have mentioned previously for how these models are used:

Forecasting smoking prevalence and health outcomes. This is the most basic use for tobacco control models, frequently under a variety of different circumstances or conditions.

One important application is goal setting. For example, every ten years the Department of Health and Human Services issues the Healthy People goals for the next ten years in all areas of public health. How has modeling been used as it relates to these goals? David Mendez and I published a study shortly after the 2010 goals had been produced (Mendez and Warner, 2000) that demonstrated why its smoking prevalence goal was simply unattainable – it would have required changes in the initiation rate and smoking cessation rate that basically were not conceivable.

Another approach to these 2010 prevalence goals took a very different and interesting tack: David Levy and his colleagues published a paper (Levy et al., 2010) asking what it would take to actually achieve these goals three years later, by 2013. Needless to say, this would have required aggressive tobacco control measures to achieve that goal in 2013, and it was not achieved. Similarly, these models are relevant to what would be needed to reach future goals, such as the Healthy People 2030 goal to reduce smoking prevalence to 5%. This goal could be achieved, but would require some pretty remarkable tobacco control efforts to get there.

Estimating the future impact of interventions. The impacts of numerous interventions have been evaluated using multiple models, including the following interventions:

- Taxation
- Smoke-free policies
- Advertising bans
- Warning labels (including graphic)
- Media campaigns
- Youth access laws (including T-21)
- Mandated cessation treatment
- Mandated cessation treatment coverage
- Educational programs
- Mandated less hazardous cigarettes
- Combinations of policies and interventions
- Possible future FDA interventions (including banning menthol and nicotine reduction)
- In some cases, multiple interventions

A natural next step would be to assess the cost-effectiveness of the interventions. Some examples of this include school-based educational programs, teen smoking cessation programs, raising the legal age of smoking, smoke-free workplaces, and comparisons of smoking cessation treatment alternatives. Unfortunately, the potential for contributions in this area greatly exceeds its realization to date.

Identifying unintended side effects. All restrictive policies and regulations produce undesired and sometimes unanticipated side effects. As such, simulations of the effects of each of these policies can include evidence-based parameter values for both the intended and, when expected, unintended impacts. That will permit formal quantitative analysis of the net benefits or costs of these policies.

For example, research indicates that imposing a minimum age of purchase for e-cigarettes is associated with increased rates of youth cigarette smoking (Friedman, 2015; Pesko et al., 2016). We also have research

finding that taxing e-cigarettes, perhaps to try to discourage youth smoking, increases adult smoking (Saffer et al., 2019). In both cases, we can estimate how much these might happen via modeling.

For another example, regarding nicotine reduction regulation, while we can anticipate some undesirable consequences, we have little empirical evidence on which to base specific parameter values. Indeed, the same holds for the direct desired effects. How much would a nicotine reduction regulation decrease smoking among existing adult smokers and over what period of time? How much would it reduce youth initiation of smoking?

Modeling can still help here, but will require creative use of sensitivity analysis. One example of this is the analysis by Apelberg et al (2018) evaluating nicotine reduction policy with use of sensitivity analyses. In all cases, modelers will need to use logic, existing evidence, and perhaps develop evidence.

Assessing the past trajectory of smoking and health outcomes. Simulation modeling is an important mechanism for estimating what would have happened in the absence of an intervention that was implemented. We refer to such analyses as counterfactual or "what-if" analyses. Simulation can be a very useful tool for dealing with this kind of fundamental uncertainty.

This is not to say the simulation will always give you the answer: it won't. But frequently it can put questions in perspective – helping, for example, to identify which uncertainties are most central to developing an answer in which you can have confidence, or evaluating what effects would have accompanied earlier intervention.

The other kind of counterfactual addresses the question of what would have happened had an intervention been adopted earlier than it was. These what-if analyses are immensely useful, often providing real insights about public health that likely could not exist in their absence.

Counterfactual analyses: some examples

As an example of modeling the absence of an intervention, Holford et al (2014) used modeling drawing on earlier work by CISNET to evaluate smoking outcomes in the absence of all tobacco control efforts subsequent to the first US Surgeon General's report in 1964. They concluded that from 1964-2012, 8 million additional deaths would have occurred had it not been for those public health initiatives, demonstrating why CDC ranked tobacco control as one of the ten most important public health contributions of the 20th century

As for examples of analysis of earlier interventions, Le and Mendez (2021) addressed the counterfactual question of what would have happened if menthol cigarettes were not available in the cigarette market beginning in 1980. Their paper estimated there would have been some 10.1 million fewer smokers between 1980 and 2018, and 378,000 fewer premature smoking deaths.

Another example is a study by Levy et al (2021) that used the CISNET model to evaluate how many smoking deaths would have been avoided with a policy limiting nicotine content in cigarettes to levels incapable of sustaining addiction beginning in 1964, 1975, or 1985. Had that occurred, the authors estimate that from 16 to 21 million smoking attributable deaths would have been avoided. Both of these studies can inform future FDA regulatory decision making regarding menthol in cigarettes.

Identifying research gaps and establishing priorities. All of the uses of simulation modeling addressed previously can help to identify research gaps and establish priorities for future modeling work.

Sensitivity analysis is often an important tool for this. Many simulations require the inclusion of variables for which there are no established values, or at least no well-established values. In these instances, standard practice is to use a value that seems reasonable in the base case analysis, and then perform a sensitivity

analysis in which multiple model runs examine the effect of variations in the value – in effect, to test the impact of that variable's uncertainty on the study's basic findings. Often there will be more than one such variable. That requires multiple sensitivity analyses.

A sensitivity analysis will produce one of two conclusions, both of which are valuable in establishing priorities for further study. In some cases, uncertainty about the variable's true value doesn't matter, because varying the number does not change the essential finding of the study, that is, whether the intervention in question makes a net positive contribution to the health of the public. In this case we do not need to invest scarce resources in trying to specify the value of the variable more precisely. In other cases, the uncertainty does matter, varying the number does change the essential finding of the study, and we know we need to invest in more research on what we have now identified to be a critically important variable.

Uncertainties characterize the real world just as they do simulation models, and through techniques such as sensitivity analysis, those uncertainties need not necessarily derail the analytical process, and hence, not the regulatory process either.

Simulation modeling for tobacco regulatory science: going forward

I'll close by looking briefly at some priorities for simulation modeling as we move forward.

In terms of subject matter, there are going to be a lot of issues of possible contemporary relevance to the FDA and other policymaking bodies. One of these is banning menthol in cigarettes – as noted above, we have had important studies on that already (Levy et al (2011), Le and Mendez (2021)), and more will be in print soon. Another is nicotine reduction – these studies date back over fifteen years (Tengs et al., 2005), and recent ones include the Apelberg et al (2018) and Levy et al (2021) studies mentioned earlier. Also, our TCORS project focuses specifically on nicotine reduction.

There are other regulations that FDA might consider as interests in the future. For example, increasing the pH of combusted tobacco products, which would make inhalation more unpleasant. Other ideas include maximum yields for various carcinogens, and the regulation of flavors in non-combusted products, the latter of which is a subject that lends itself very nicely to simulation modeling.

Whether the FDA chooses to permit or prohibit the marketing of various alternative products, we are seeing simulation models used in providing evidence to FDA about this from the manufacturers of these products, as well as from others. There are also issues relevant to policy makers outside of the FDA: for example, the effects of heavy taxation of combusted products and low taxation of non-combustible products is an obvious place where simulation could provide us important insights for policies that the FDA has no control over (Chaloupka et al., 2015).

Now, let's turn our attention to methods. There has been discussion about developing standards of good practice for modeling, particularly for modeling in tobacco control, as well as public health in general. Should we have standards for base case assumptions, so that all models use the same initial assumptions, and we would be able to compare them more directly?

At the other extreme of methods issues, is there a role for artificial intelligence (AI) in modeling for tobacco regulatory science? AI has been used in COVID modeling, and someday we may see AI modeling applied in evaluating tobacco regulatory science. Another issue discussed earlier is using modeling to produce more cost-effectiveness analyses: this has been employed relatively infrequently, but it is a logical and important addition to what modeling does well anyway.

Finally, should we be establishing standards for educating other tobacco control researchers about modeling? I hope that this symposium may lead non-modeler researchers to collaborate with colleagues skilled at modeling, as this has been a win-win situation in our experience.

In closing, here is a quote from the US Surgeon General's report from 2014 (USDHHS, 2014) that sums up this field well: "[I]n the next phase of tobacco control … models will be a key tool for designing strategies to address groups with high rates of prevalence and to hasten the end of the tobacco epidemic."

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Questions and answers

Q: You mentioned developing a reference model or reference modeling parameters for use in computational modeling around tobacco regulatory policies. Do any such model-like reference parameters exist in other fields? And if so, is there interest in developing one for our field?

A: We tend to use National Health Interview Survey (NHIS) data in our modeling when we're looking for smoking prevalence. We know that smoking prevalence rates vary substantially from one major national survey to another. So that's an example of where one could decide to go with one versus the other, although it's not clear which is inherently the best one. The answer is yes, you could choose some of these, but it would be a little bit challenging to get everybody on board and say that's the right answer.

Here is a really good example: smoking initiation. How do you define an initiation rate in our model? David Mendez and I use the 18-24 year old smoking prevalence rate as initiation. That's how we define it, while lots of other people define it in very different ways, including whether somebody is a current 30-day user of cigarettes. With the use of surveys, there are all kinds of different approaches to measuring something like initiation. So I think it would be difficult to do that, but it shouldn't be impossible.

Also, some of the standards that you might want to reference are not necessarily just quantitative figures – you may want to have processes. For example, there have been some standards set up by economists for cost effectiveness analysis to describe how you should go about it, rather than which specific numbers should be selected. So I think you want to think about both aspects.

Q: The real risk to population health appears to be in those who are smoking today and are age 35 and older. So how might these dynamics be modeled, since our current regulatory approach seems to be overweighted toward protecting youth today, and not really focused as much on the adult smoker?

The model that David Mendez and I use specifically asks when will smokers die, if they're going to die as a result of smoking, and it's got them by age, by smoking history, by how long they've quit smoking and so on. Realistically, of course, you're not looking at many deaths until you get further into middle age. So if you take those numbers and you add them up over time, current adult smokers are subject to an immediate risk of death, while young current smokers are not subject to a risk of death for many years.

One of the things we have not done in our model most of the time – and I believe most models do not do, but it's probably something we should all be thinking about – is discounting, because we're counting a year of death that occurs to, let's say, a current teenager 40 years from now the same as the year of a 60 year old dying today. Should they be valued equally? The concept of discounting argues that they should not. Saving a year of life today should be valued more highly than saving a year 40 years from now.

From an economist's point of view, you definitely should be discounting to take account of the difference in time. yet few of us do that in our models, in part simply because readers might have trouble understanding the concept of "discounted years of life lost." At a minimum, most models are taking the passage of time into account by identifying how far into the future lost life-years (or premature deaths) occur.

Keynote: Simulation Modeling and How it Informs the Work of FDA's Center for Tobacco Products

Mitch Zeller, JD, Director, FDA Center for Tobacco Products.

Abstract

This keynote presentation provides an overview of the US Food and Drug Administration (FDA)'s role in the regulation of tobacco products, together with case examples of how computational modeling has been employed for potential tobacco product standards, and how computational modeling can be used to inform premarket and postmarket review.

Background

To protect the public and create a healthier future for all Americans – particularly youth – Congress passed the Tobacco Control Act, which became law on June 22, 2009. In support of this Act, the FDA's goal is to reduce the harm from all regulated tobacco products across the entire U.S. population, by reducing the number of people who start using tobacco products, encouraging more people to stop using these products, and reducing the adverse health impact for those who continue to use these products.

When FDA began regulating all tobacco products intended for human consumption in an effort to protect the public health in 2009, the agency was granted the authority to regulate the manufacturing, marketing, and distribution of cigarettes, cigarette tobacco, roll-your-own, and smokeless tobacco, as well as "deem" products meeting the statutory definition of tobacco product by issuing a regulation. On August 8, 2016, a final rule went into effect that "deems" all products meeting the statutory definition of tobacco product, including components or parts (but excluding accessories), to be subject to FDA's tobacco product authorities, including:

- ENDS (e-cigarettes, e-cigars, vape pens, etc.)
- All cigars
- Pipe tobacco
- Nicotine gels
- Waterpipe (hookah)
- Dissolvables not already under the FDA's authority
- Future tobacco products

The FDA pursues a "public health" standard for these products, as tobacco cannot be regulated using FDA's traditional "safe and effective" standard; this public health standard takes into account the effects on both users and non-users of tobacco products and assesses their net population-level health impacts.

The Tobacco Control Act amended the Food, Drug, and Cosmetic Act to provide FDA authority for premarket review of new and modified risk tobacco products and post-market surveillance, along with product standards, testing and reporting of ingredients, reporting of harmful and potentially harmful constituents, adverse event reporting, new warning labels, and advertising and promotion restrictions. These efforts are entirely funded through industry-paid user fees based on market share, and not applications.

How the FDA is using its regulatory authority

As part of its role in regulating tobacco products, the FDA seeks to understand regulated products, restrict product changes to protect public health, prohibit modified risk claims that state or imply reduced exposure or risk without an order, and restrict marketing and distribution to protect public health. It also works to decrease the harms of tobacco products, and ensure industry compliance with FDA regulation through education, inspections, and enforcement.

The FDA also takes an educational role, designed to educate the public about FDA's regulatory actions. It also seeks to prevent youth initiation and encourage cessation via public education campaigns designed to create behavior change and expand the science base for regulatory action and evaluation.

Above all, the FDA uses its authority to now regulate e-cigarettes, cigars, hookah, and other tobacco products, in addition to cigarettes and smokeless products. Figure 1 shows an overview of the FDA's rulemaking process for tobacco, including Notices of Proposed Rulemaking (NPRM), solicitation and review of public comments, and the issuance of final rules.

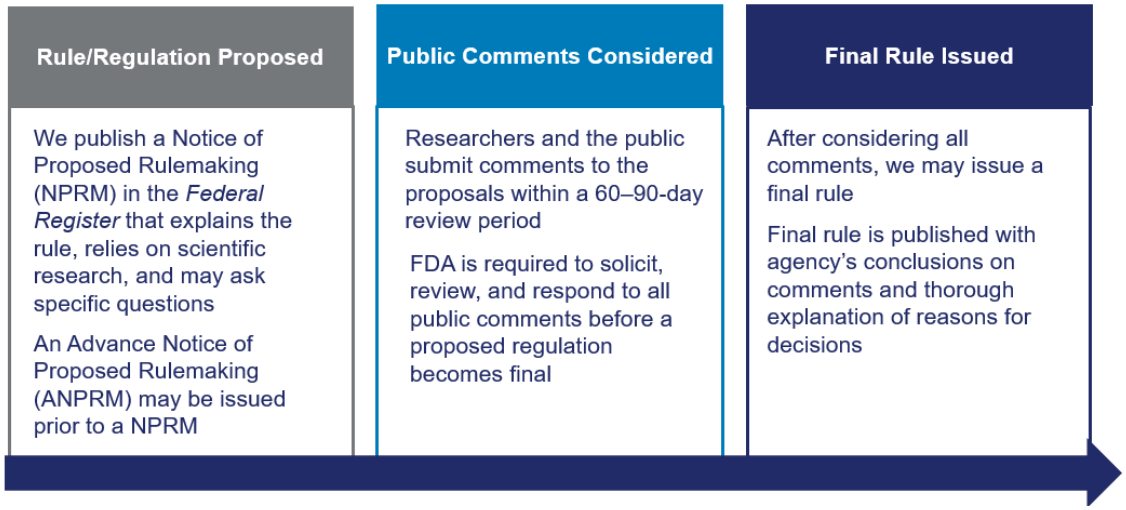

Figure 1. Summary of the FDA's tobacco regulation process.

Population health standards for FDA regulation of tobacco products

The FD&C Act requires FDA to apply a population health standard when making certain regulatory decisions. The standards that FDA's Center for Tobacco Products applies in implementing its regulatory authorities are described below:

Premarket Tobacco Product Applications (PMTA)
FDA can authorize the marketing of a new product under the premarket tobacco product application pathway if it is determined to be appropriate for the protection of public health. Appropriateness for the protection of the public health shall be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account (1) the increased or decreased likelihood that existing users of tobacco products will stop using such products, and (2) the increased or decreased likelihood that those who do not use tobacco products will start using such products.

Modified Risk Tobacco Product (MRTP) Applications
To market a product with a reduced risk claim, the FD&C Act requires FDA to determine if a proposed modified risk tobacco product (MRTP), as it is actually used by consumers, will (1) significantly reduce harm

and the risk of tobacco-related disease to individual tobacco users, and (2) benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

Tobacco Product Standards
FDA can issue product standards for tobacco products if they're appropriate for the protection of the public health. To do so, the FDA must consider scientific evidence concerning… (1) the risks and benefits to the population as a whole, including users and nonusers of tobacco products, of the proposed standard; (2) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (3) the increased or decreased likelihood that those who do not use tobacco products will start using such products.

Sources: Sections 907(a)(3)(A), 907(a)(3)(B) and 910(c)(4) of the FD&C Act

Examples of computational modeling for potential product standards

Decisions about tobacco product regulation often include the integration of multiple lines of evidence, such as product appeal, addictiveness, toxicity, and the product's impacts on tobacco product use behavior and disease risk. Computational modeling can be a useful tool to integrate such evidence to assess the potential impacts of new or modified risk tobacco products or new regulatory actions on short and long-term measures of tobacco product use, morbidity, and mortality. Here are three examples of how modeling has been used to inform regulation:

Potential impact of a reduced nicotine policy

In March 2018, the FDA issued an advance notice of proposed rulemaking, Tobacco Product Standard for Nicotine Level of Combusted Cigarettes, where they sought public comment for consideration in developing a product standard to lower nicotine to a minimally addictive or non-addictive level in cigarettes. An FDA-funded study published in the March 2018 issue of the New England Journal of Medicine quantified a range of potential impacts of reducing nicotine levels in cigarettes. (Apelberg et al, 2018), examining baseline versus reduced nicotine policy scenarios as shown in Figure 2.

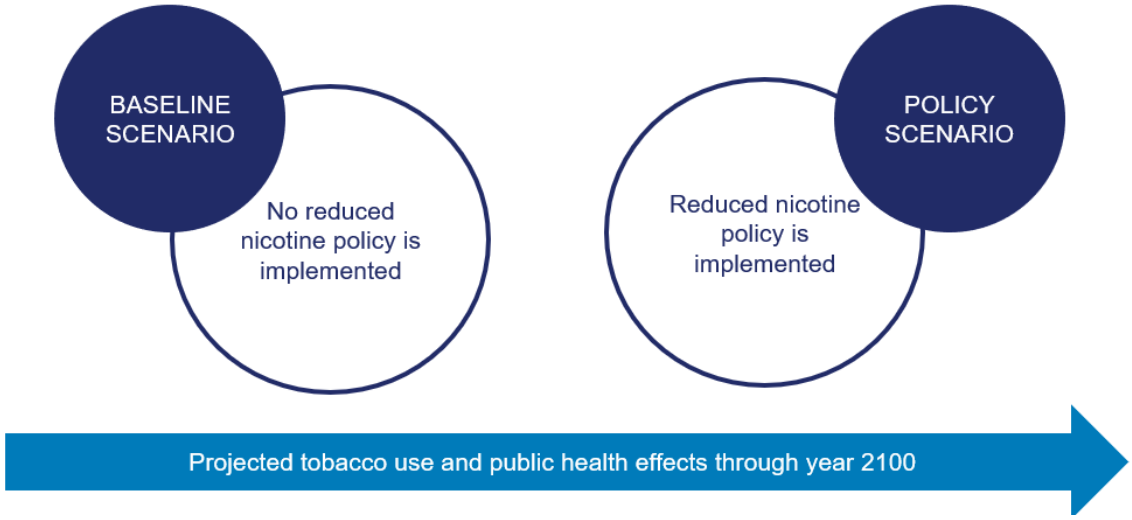

Figure 2. Model scenarios for reduced nicotine policy study (Apelberg et al, 2018)

A two-product model was used to project impacts of the proposed standard on tobacco use, morbidity, and mortality in the U.S., with Product 1 consisting of cigarettes (including very low nicotine cigarettes) and Product 2 consisting of non-combustible products (including e-cigarettes), as shown in Figure 3.

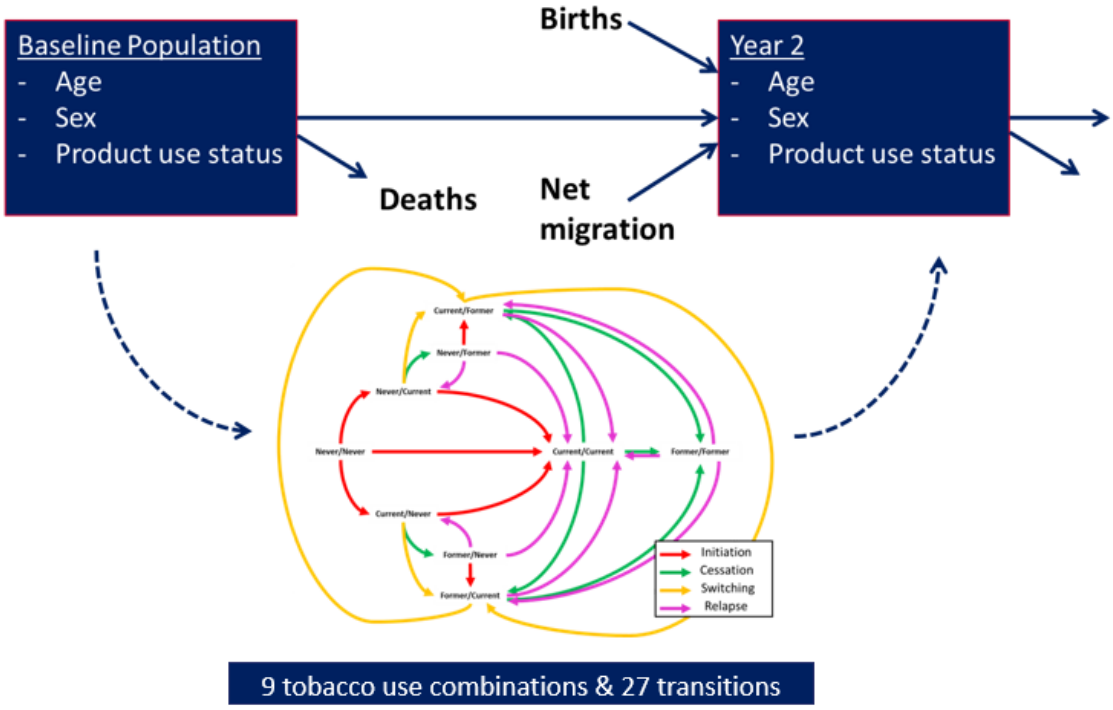

Figure 3. Model overview for reduced nicotine policy study (Apelberg, 2018)

To obtain inputs about the behavioral impacts of a reduced nicotine policy, the FDA conducted an expert elicitation through Industrial Economics, Inc. (IEc), with a panel of eight experts in tobacco science (6) and policy (2). Questions used asked experts about the anticipated impact of the policy on areas including cigarette smoking cessation, switching to products not covered by the policy, dual use of cigarettes and products not covered, cigarette smoking initiation, and initiation of products not covered.

Results of the nicotine model showed that approximately 5 million additional adult smokers would quit smoking within just one year after implementation, compared to the baseline scenario, with more than 134 million years of life gained among the U.S. population by the year 2100. Only about 1.4 percent of the U.S. adult population would smoke cigarettes by 2100, in part, because more than 33 million people would avoid becoming regular smokers, and by the year 2100, more than 8 million premature deaths from tobacco could be avoided.

Modeling studies for menthol cigarettes

The FDA's recent decision to pursue a menthol cigarette ban is an example where computational modeling can play an important role in characterizing the public health burden due to tobacco products, and assessing the potential public health impact of a regulatory action. One recent example of a modeling study related to menthol cigarettes is a study by Le and Mendez (2021), which estimated that menthol cigarettes were responsible for approximately 378,000 smoking-related premature deaths, 3 million life years lost and 10.1 million new smokers from 1980-2018. In addition, results from a previous study by Levy et al (2011) showed that over a 40-year period, between 323,000 and 633,000 deaths could be avoided under a menthol cigarette ban, almost one third of which would be among African-Americans.

Modeling the potential impact of a flavored cigar product standard

A 2019 study (Rostron et al, 2019) estimated the population health impact of prohibiting characterizing flavors in cigars, using data on U.S. cigar use, cigar-attributable mortality, and evaluations of the effect of local and national flavor restriction policies. This study estimated that prohibiting characterizing flavors would result in 800 fewer deaths per year due to increased cigar cessation among adults, and approximately 112,000 fewer cigar smokers among each cohort of 18-year-olds.

Computational modeling to inform premarket and postmarket review

The FDA commissioned a 2011 report from the Institute of Medicine (IOM), entitled *Scientific Standards for Studies on Modified Risk Tobacco Products* (IOM, 2011), including a section on the value of modeling. It discusses the potential utility of modeling in reviews of modified risk tobacco products (MRTPs), including synthesizing information from empirical studies, exploring complex interactions and systems that may be impractical to study empirically, exploring "what if" scenarios, and projecting short- and long-term effects of MRTP introduction. There were also words of caution for the use of modeling, with considerations for the conduct and reporting of model-based analyses including transparency, validation of models, and dealing with uncertainty.

The FDA now has a draft guidance to industry regarding modeling submitted for pre-market and postmarket review. In this draft guidance, the FDA has suggested that applicants should provide the following if they submit modeling:

- Explanations and justification of the technique used
- Assumptions used in the development of any models and parameters
- A listing of the parameters used in the analyses and/or models
- Data used to derive parameters or estimates and a rationale for the applicability of the data for the given parameter
- The results of various scenarios, including worst-case scenarios

Modelers can inform tobacco regulation and review by publishing studies that evaluate the potential impact of proposed regulations, and submitting comments in public dockets (www.regulations.gov).

Modeling requirements for IQOS postmarket review

On July 7, 2020, FDA authorized the IQOS System and Heatsticks from Philip Morris International (PMI) to be marketed with reduced exposure claims. This authorization included requirements for postmarket surveillance and studies to "determine the impact of the order on consumer perception, behavior, and health, and to enable the [FDA] to review the accuracy of the determinations upon which the order was based…"

This postmarket surveillance and studies requirement included studies of youth and adult use behavior along with consumer understanding and perceptions, a computational toxicology study, monitoring and reporting of serious and unexpected adverse events, and surveillance of new research study findings on the MRTPs, as well as modeling the impact of the MRTPs on population health. Modeling requirements in the IQOS order included the following:

- The model must incorporate data and information collected through postmarket surveillance and studies, e.g. the percentage of current smokers who switch completely to IQOS or become dual users, the percentage of former smokers who take up the use of IQOS, and the percentage of youth and young adults who initiate the use of IQOS.

- The model must incorporate the latest information on acute and long-term health effects of IQOS, including effects relative to cigarette smoking.
- Annual reporting must include a description of the methodology used, a copy of the model or its code, descriptions of all inputs and how they were derived, and a summary of results along with implications for whether the MRTPs continue to be appropriate to promote public health.

Challenges and future directions

It is difficult to accurately assess the "real-world" impact of a new product or new marketing in a pre-market setting, and there is uncertainty about the risk of a new product in the absence of long-term epidemiological evidence, as well as uncertainty about the impact of policies that have never been implemented before. Important sources of uncertainty may include: (1) structural assumptions of the model, (2) parameter inputs, and (3) variability among individuals in the population (IOM, 2011). Approaches to help address model uncertainty include transparency and documentation of model inputs and assumptions, comparisons of results across different modeling approaches, and quantifying how uncertainty in inputs translates into uncertainty in outputs.

Other challenges involved with modeling include identifying relevant inputs for new policies or new tobacco products and appropriately characterizing the uncertainty associated with projected estimates. The FDA decision-making provides opportunities for public input and comment regarding its processes, including the submission of new data or analyses for FDA consideration.

In closing, the FDA regulates tobacco products using a population health standard, which requires the consideration of individual risks and the impact of an action on the U.S. population. Computational modeling can be a useful tool to inform its regulatory actions by incorporating product risks and use behaviors to project the potential impacts of different regulatory decisions. Useful features of models to inform tobacco product regulation include the ability to model the uptake of new tobacco products, the relative impact of different regulatory options, and potential countervailing effects, such as tobacco product substitution.

Editor's note: Mr. Zeller's remarks are not a formal dissemination of information by FDA and do not represent Agency position or policy.

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Questions and answers

Q: No country yet has ever gone through with a nicotine standard. How does the FDA go about updating its modeling, or how do those who are interested in influencing the FDA proceed when real world evidence is produced after policies are put into place, that may or may not look the same as what was predicted from expert elicitations? How does expert elicitation need to be held up against other kinds of evidence?

A: That's a really important question. As regulators, we talk about changed circumstances and it is our job by law, but I would say there's a moral obligation and a public health imperative if circumstances have changed from either what we projected or what we expected, and we need to reconsider or re-evaluate a policy based upon new information, new evidence. That's our job. We are voracious consumers of that information. So anyone who has new information for us after a policy has been put into place, we have the power to reconsider, and Congress gave us the power to withdraw PMTA authorizations. So we are always in the business of receiving new information.

The nicotine product standard remains something that is under discussion in the still very new administration. It's under consideration. But that doesn't mean that the need for new information ends, even if it is confirmatory of what we already know. If a nicotine product standard were ever to go final, the likelihood that we will be sued is high. And a judge's responsibility under the Administrative Procedure Act to make an assessment about whether the final action that we took was or was not arbitrary and capricious comes down to the strength of the science.

This takes me back to the beginning of my answer, which is continue to give us new and more information, and help us make the administrative record for policies that have not yet gone into place as strong as they possibly can be, knowing the industry that we're dealing with and the likelihood that we will see them in court.

Compartmental Models in Tobacco Control Research

David Mendez, PhD, Department of Health Management and Policy
University of Michigan School of Public Health.

Abstract

This presentation provides a basic overview of component models used in tobacco control. It reviews terminology, modeling concepts and provides examples of sample component models, together with examples from the literature of how these models have been used in tobacco control research.

Introduction

This presentation is a brief discussion – aimed at non-modelers - about compartmental models, also known as aggregate models, because these are the most common type of model we use in tobacco control research.

For example, let's assume that we want to track the number of smokers in a population over time. While this population is very heterogeneous, and individuals have multiple unique characteristics including gender, age, gender, education, and socioeconomic status, we are only interested in tracking their smoking status and are going to simply classify them as never, current, or former smokers. So we can organize them in homogeneous groups, put them into buckets, and track the number of individuals in each bucket, as shown in Figure 1.

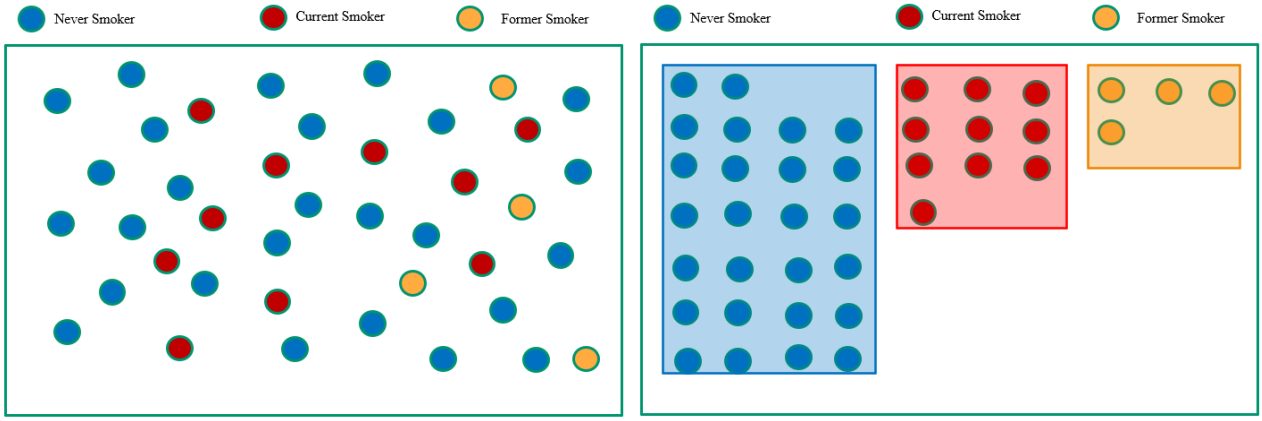

Figure 1. Tracking individuals by smoking status.

Now, suppose that we want to distinguish them further – for example, in three age groups, 0-17, 18-24, and older than 24, as shown in Figure 2. We can simply create more buckets if necessary and keep track of the number of individuals in these buckets.

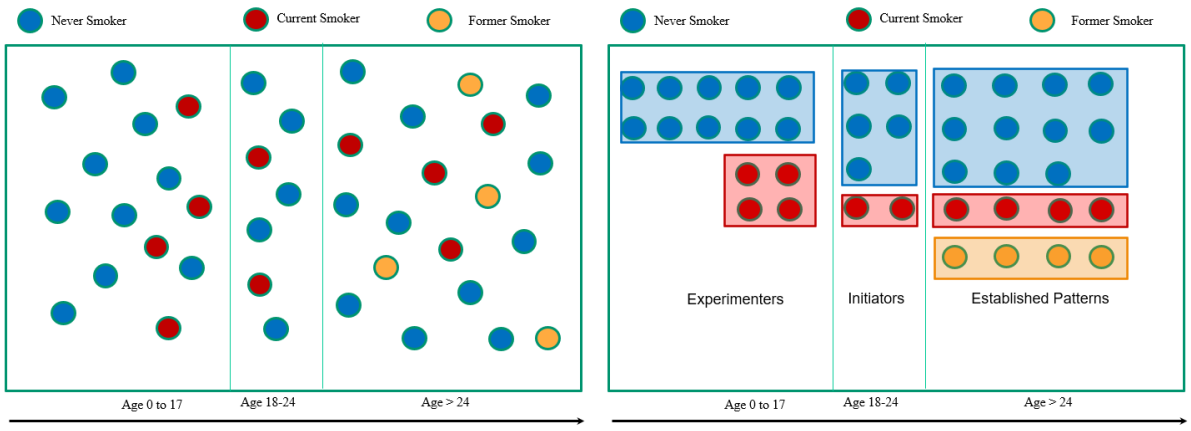

Figure 2. Tracking individuals by smoking status and age group.

And if we realize that we want to further divide the individuals by additional categories such as gender, socioeconomic status, or additional age groups, and if we think these characteristics can influence smoking behavior, the important factor is that the set of buckets at which we arrive comprise all the characteristics that are important to answer the question that we're trying to solve.

So how do we track the number of individuals in these compartments over time? Let's assume we have a snapshot of present time, from a census, with the number of former, never, and current smokers. From there, compartmental models follow a simple rule to predict the future that helps us set up the simulation:

Future = Present + Change
or
Smokers (t+1)= Smokers(t) + Change

We can now take all the individuals in these compartments and determine what changes. For the box of smokers, for example, we can look at rates of smoking initiation among never smokers, relapse among former smokers, cessation among current smokers, and death, as shown in Figure 3. That's how we arrive at the future. In this case we end up with 13 smokers, this time point becomes the new present, and we keep moving forward.

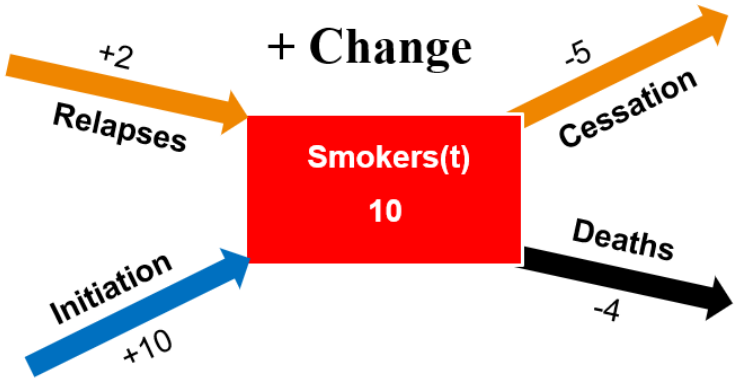

Figure 3. Sample change at a point in time for a compartmental model quantity.

These models are known in general as *stock and flow* models. The quantity of whatever we are tracking inside these buckets are what we call the stocks, and the transitions between compartments correspond to the flow. These flows can be defined in different ways. For example, one simple way is to have a constant rate multiplied by the appropriate stock – such as a smoking initiation rate multiplied by the number of never smokers. Figure 2 shows our stock of smokers at time *t*, with flows expressed as constant rates for initiation, relapse, cessation and death.

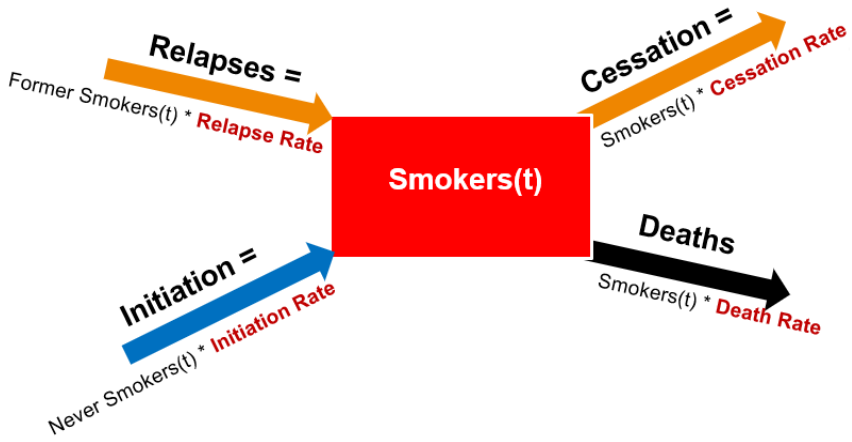

Figure 2. Stock and flow model of current smokers at time t.

Let's look at one parameter we will call the initiation rate, which we can think of as the probability over a certain period of time that a never smoker initiates smoking. This parameter can be affected by policy, and so we want to create policies that reduce the initiation rate. In this case we either have a rule to anticipate how the parameter is going to change or we treat it as a constant. When we have a fixed proportion, or even if we have a time-varying proportion, these are what we call Markov models. In many cases these are very useful in representing the overall transition of a system of behavior.

In some cases, however, we have a more complex way to define the flow. For example, in this case, the initiation rate can be expressed as a function of an exogenous parameter λ and the number of current smokers:

$f(\lambda, \text{Smokers}(t)) =$ Initiation rate due to exogenous and endogenous causes

This function could, for example, reflect an imitation component in the initiation rate: the more smokers, the more individuals that could be imitating their neighbor smokers. This model exhibits what we call a feedback loop, as shown in Figure 3. In cases like this, the number of smokers influences the value of the same compartment in the future, which can take place directly or indirectly through other compartments.

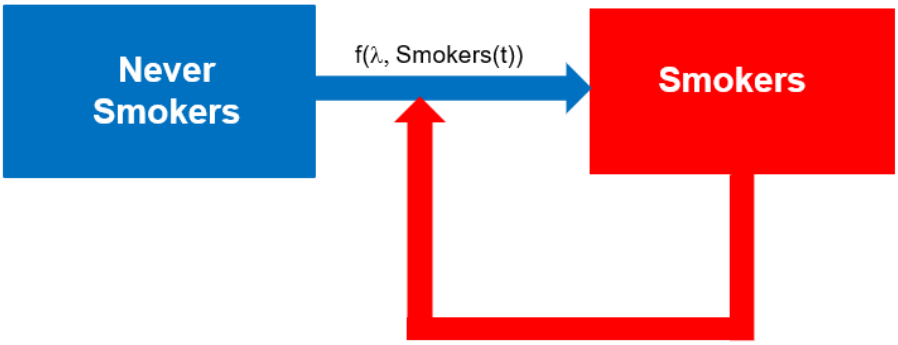

Figure 3. A feedback loop between current smokers and initiation of never smokers.

Figure 4 is an example of a basic compartmental model that keeps track of individuals by age, gender, and smoking status. The initiation and cessation rates are inputs that can be affected by policy, we have specific death rates by age, gender, and smoking status, and then we apply the same process described previously. So there are many examples of compartmental models and applications like these.

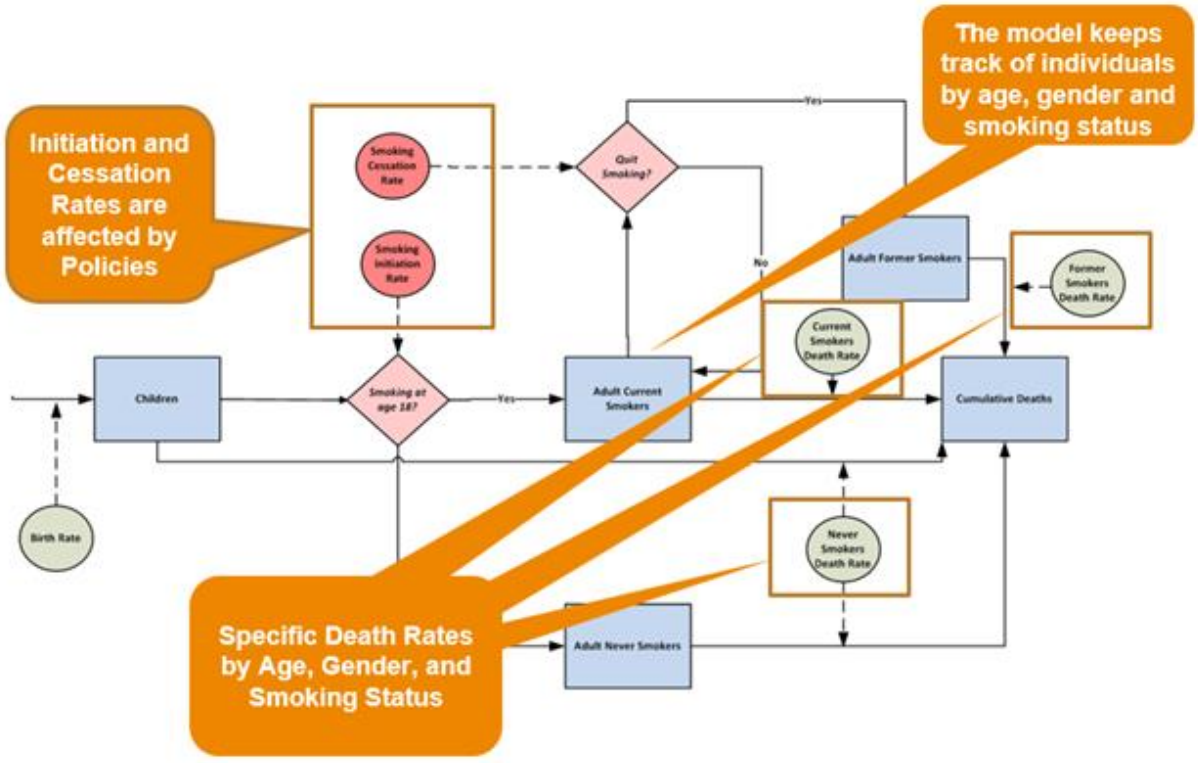

Figure 4. A compartmental model tracking individuals by age, gender, and smoking status.

Examples from the literature

Here are some examples of how compartmental models have been used in tobacco control research:

- **Status quo projections,** such as Tam et al (2020)'s study modeling smoking-attributable mortality among adults with major depression in the United States.
- **Estimation of policy effects,** such as a study by Levy et al (2011) modeling the future effects of a menthol ban on smoking prevalence and smoking-attributable deaths in the United States.

- **Feasibility analyses**, including Mendez and Warner (2000)'s analysis of why the US government's Healthy People 2010 goals for tobacco control were unattainable.
- **What-if scenarios**, including Warner and Mendez (2010)'s modeling of U.S. smoking prevalence with and without improvements in initiation and cessation rates, and implications for policy.
- **Counterfactual analyses**, such as Holford et al (2013)'s modeling of reductions in smoking-related mortality associated with implementation of tobacco control policies since 1964.
- **Parameter estimation**, such as Borracci and Mulassi (2015)'s simulation work on how tobacco use during adolescence may predict smoking during adulthood.
- **Multiproduct analyses**, such as Levy et al (2021)'s recent study on the public health implications of vaping in the United States.

Concluding thoughts

Compartmental models play an important role in tobacco control research. However, they do have some limitations. For example, they cannot fully represent the heterogeneity of individuals in the population. In addition, they cannot fully represent non-random connections and interactions among individuals.

As a result, modelers should recognize when heterogeneity and network effects are important enough to merit abandoning the compartmental or aggregate approach in favor of an individual-based model. Models, in general, can and should be designed to answer specific questions, given specific situations.

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Tobacco Town: A Computational Model for Exploring Environmental Effects of Retail Tobacco Control Policies

Douglas Luke, PhD, Center for Public Health in System Science, Washington University in St. Louis

Abstract

This presentation provides an overview of the examination of retail tobacco control policies and the use of agent-based models in tobacco control. We discuss our work with Tobacco Town, an agent-based model (ABM) used to model the impact of policies for tobacco retailers, with examples of the impact of retailer policies on travel time for purchasing tobacco in a sample metropolitan area.

Introduction

This presentation will discuss the case for retail tobacco control policies, look at the use of agent-based modeling and tobacco control science, and then combine the two and talk about Tobacco Town, which is an agent-based model used in retail policy research by ASPiRE (Advancing Science and Practice in the Retail Environment), an NCI-funded research center at Washington University in St. Louis.

The classic four-pronged approach to tobacco control is based around pricing, cessation support, smoke free policies and media campaigns. Kong (2020) has suggested that retail approaches can serve as a "vaccine booster" and act as a fifth approach to tobacco control, in areas such as product availability, pricing and promotion, age of sale, advertising and display, and retail licensure.

Why is this important? First, tobacco retailers are ubiquitous; for example, there are 27 tobacco retailers for every McDonald's in the US. Second, tobacco products remain the most heavily marketed and advertised product in the world: in 2018, the tobacco industry spent a million dollars an hour at these retail locations, marketing and selling these products. Third, there are critical inequities in the location of tobacco retailers. For example, you tend to find tobacco retailers in poorer parts of communities, and among populations of color, so some studies and modeling approaches have looked at retailer reduction as an appropriate health equity approach.

What do we mean when we talk about retail tobacco policies? Here are some examples of these policies:

- Tobacco retail licenses, to monitor retailers in a community
- License caps, to put an upper limit on how many retailers can be in a community
- Retailer buffers, to prevent retailers from being too close together
- Restrictions on product availability, such as menthol cigarettes
- Age limits on purchase, such as Tobacco 21 policies

When you reduce the number of retailers in a community, you increase the distance to retailers and to tobacco products. Costs often increase when there are fewer retailers in a community, there is reduced exposure to advertising, and there are reduced purchase opportunities. These are the mechanisms by which retail tobacco policies are hypothesized to work in communities.

Agent-based models

Agent-based models (ABMs) are computational simulations that take a bottom-up approach to study a complex system. These complex systems have individual agents that behave as a function of their characteristics and their interactions with each other in the environment, and it is those interactions among agents that often turn out to be very critical.

Agent-based models emphasize heterogeneity, which opens the door to research questions that might be harder to address using forecasting or compartmental models. They are also built within environments that are physical (such as where people live, go to school, or purchase tobacco) or social (such as social networks). They are designed to model emergent behavior, and Epstein (2008) notes that ABMs help focus on the mechanisms of a behavior, which in this case involves policy effects.

Hammond (2015) describes the components of an agent-based model using the acronym PARTE, with components as follows:

- Agent **P**roperties
- Agent **A**ctions
- Agent **R**ules
- **T**ime
- **E**nvironment

In this system, the agents themselves have properties. They can be people, but they can also be hospitals or businesses, for example. These agents themselves do things - so people might wake up and go to school, go to work, or purchase tobacco products. And when they choose these actions, they follow rules – for example, when they purchase tobacco products, they might prefer products that are cheaper or closer to where they live. All of this happens over time, within environments which can be physical, social, or both.

In public health, agent-based models have historically been used predominantly in the study of infectious diseases, which has been particularly important lately with COVID. But lately we have seen ABMs be used in other areas, in particular in behavioral prevention studies and policy research. And so these are different areas of chronic disease, public health policy and implementation of science as well.

Tobacco Town: An agent-based model for tobacco simulation

Tobacco Town is an example of an ABM that is particularly useful for public health policy research. Historically, there have been many types of studies you simply can't do in tobacco control, so we can use these models as virtual laboratories to model a baseline community, introduce a type of policy, and then see what happens to that virtual community.

One particularly useful benefit is when you model, you discover data gaps. For example, despite tremendous knowledge about the epidemiology of smoking, we discovered in our Tobacco Town model that we actually didn't know the answer to a pretty simple question: how far are people willing to travel to purchase cigarettes? This is something that can be added to the next generation of surveillance, research, and tobacco control efforts.

Tobacco Town is a series of models that has been developed over nearly ten years, using an agent-based model as a policy laboratory to study the potential effects of retail interventions. We work closely with community partners throughout all phases of this project, partly because we want this model to be useful for

policymakers in communities around the United States. In particular, we are building tailored models that are specific for a city like Washington, D.C. or Providence, Rhode Island.

Tobacco Town focuses on two kinds of environments, the built environment and the consumer environment. In the built environment, we can examine policies limiting retailers. Figure 1, for example, shows retailers in a community on the left hand side, as well as schools. The right hand side of this figure shows what happens If the community passes a policy restricting the proximity of tobacco retailers to schools, particularly among those wanting to purchase tobacco products.

Figure 1. Impact of a policy restricting tobacco retailer proximity to schools.

In the consumer environment, such as what we see when people enter tobacco stores, we can study policies such as minimum price laws or restrictions or bans on menthol cigarettes. Tobacco Town forms a framework under which we can model these and other interventions.

The building blocks of Tobacco Town include a lot of empirical data, including smoking characteristics, retailers and their locations, and pricing information. And then the actual rules that underlie the model are based on not just data, but broader sets of literature and theories, especially social science and health science theories; for example, travel and purchasing theories that suggest that people want to minimize the time they take to purchase commodities like cigarettes.

We also use real maps of real cities. In particular, we use a set of national synthetic population data. These are not real people, but they look just like real people. For example, we know where people live in certain cities based on their socio-demographic characteristics, as shown in Figure 2, and add on things like where the tobacco retailers are in those environments. This allows us to simulate people moving from their home to their work every day, and when they need to purchase cigarettes, the route they would take to purchase them – typically a route that minimizes both time and price. This forms the baseline, from which we can add policy interventions and model their impact – for example, how restrictions on retailer proximity to schools affects individual agent routes in the model.

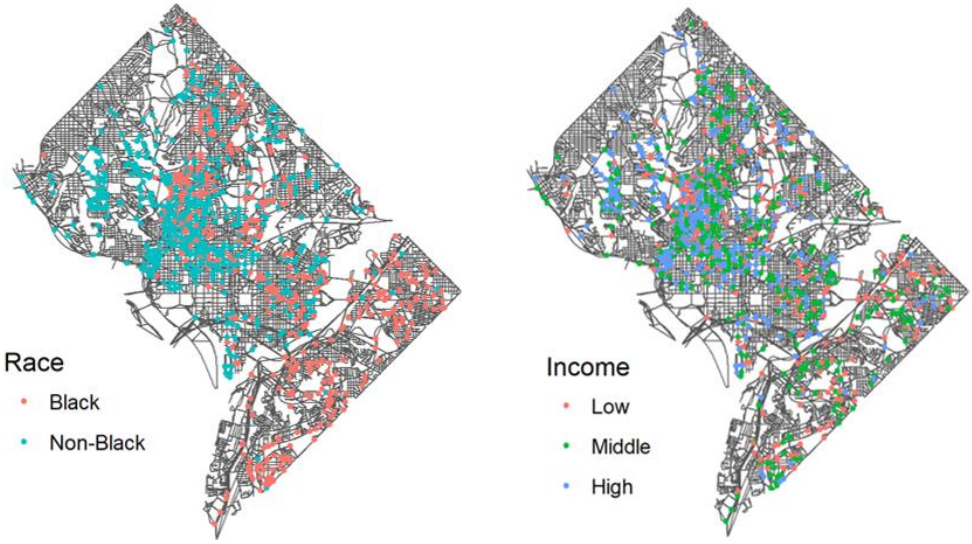

Figure 2. Socio-demographic characteristics of sample synthetic population data.

Findings from Tobacco Town modeling

So what are we learning in these Tobacco Town agent-based models? The first thing is that when we look at density reduction efforts, the effects are not linear. Consistent with decades of tobacco control policy research, we find that strong policies and multiple policies have larger effects and that any individual policy is never going to be enough.

A particular strength of ABMs is that policy effects are community-specific - what works in Providence may not work or may not work the same way in New York City, for example. And different kinds of policies work in different ways, which means they have different potentials for affecting disparities in behavior. Finally, we are learning that retailer density and proximity to retailers are not the same thing, even though they are highly related to one another. As an example, in Figure 3, the X axis shows retailer density in different kinds of communities, and then on the Y axis, we see an abstract cost estimate that combines time and money.

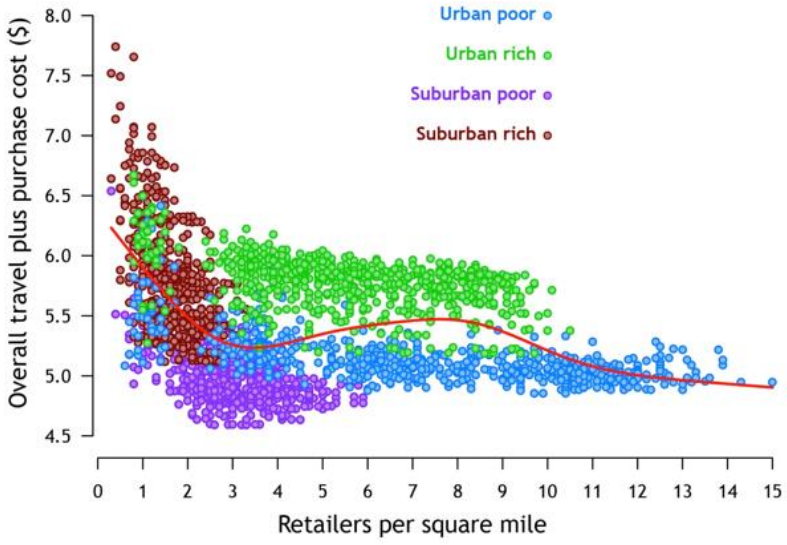

Figure 3. Overall travel time and purchasing cost versus tobacco retailer density for specific groups.

This figure shows that we do not really see a large effect on cost until density is driven down pretty low, which means that in high density urban environments you really have to reduce density quite dramatically in order to see an impact. In fact, it may not be feasible to pass policies to get density low enough where residents notice that they have to travel further or have to spend more money.

In this figure, where the colors represent different kinds of communities, and the dots are retailer density, we see that retailer density starts out quite differently based on socioeconomic level. As you look at different kinds of policies and start layering on the policies, we get to a point where we can both lower retailer density and reduce the disparities across community type.

We have also learned from our Tobacco Town models that density and proximity are not the same. For example, Figure 4 shows a model for Providence, Rhode Island, where the figure on the left shows current retailers, the center figure is a retailer-to-retailer policy where retailers are not allowed to be within two kilometers of each other. The next policy is a school policy where retailers are not allowed to be within two kilometers of a school.

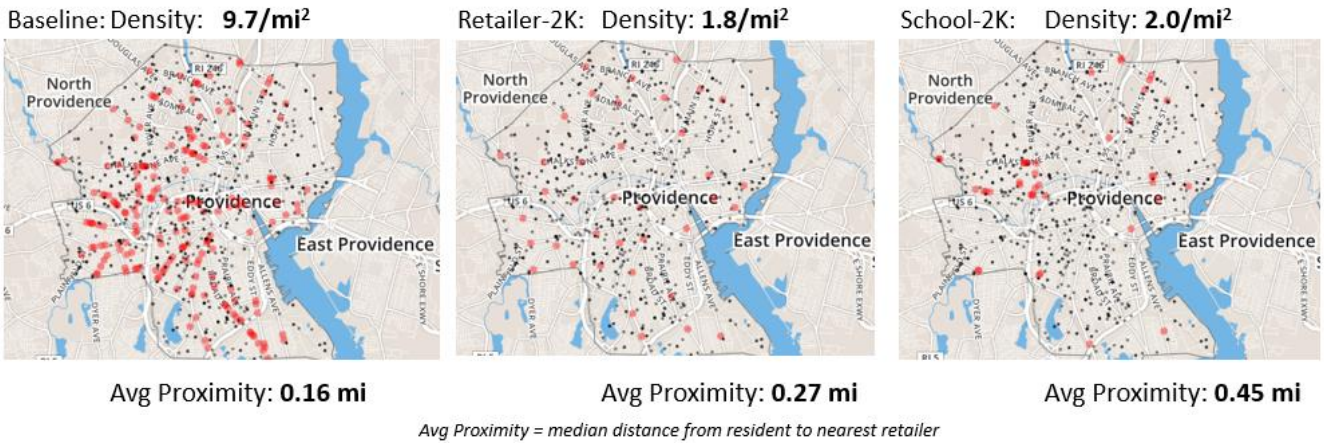

Figure 4. Impact of retailer-to-retailer versus retailer-to-school proximity policies for model of Providence, RI.

Compared with current figures of almost 10 retailers per square mile, both of these policies reduce density about the same, to around two retailers per square mile – however, they have very different effects on proximity, with about a quarter of a mile for the retailer policy and almost half a mile for the school policy. Moreover, the school-based policy clears out the tobacco swamps in entire neighborhoods. This kind of data is really important for policy makers.

We feel that by revealing these kinds of underlying mechanisms, policymakers can design policies that work best for their particular communities. We have been working with community partners throughout this project and are particularly excited about using the Tobacco Town model to answer questions for specific communities. We have created a dashboard that allows community policy makers to explore potential effects of these different sorts of retailer policies and see which ones affect density and proximity or which ones have the greatest potential for disparities reduction.

Conclusions

Some of the main early conclusions from our work with Tobacco Town models to date include:

- Policy mechanisms and effects are community specific
- Community engagement has been critical for all phases of agent-based model development and testing
- Agent-based models can reveal underlying mechanisms, which may provide an architecture for the tailored design of policies
- Also because of the focus on mechanisms, agent-based models hold critical promise for studying the rise and fall of tobacco-related disparities

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Questions and answers

Q: What things would be able to rapidly and effectively, without having to start from scratch, go from a model for Rhode Island to having models for, say, for all potential colleges?

A: I think there's a balance here. Sometimes you have a model that's a generic model that is just meant to be widely applicable. Other times you might build, from the ground up, a specific model for a particular context. In Tobacco Town, we've tried to have a little bit of a balance there. The first version of Tobacco Town only used abstract town types: poor urban, poor suburban, rich suburban, and so on.

Using the basic framework, though, the key for us for tailoring - and it wasn't all that complicated - was moving to geophysical data, i.e. maps for real towns. And then these synthetic populations that allow us to put people in realistic places on these maps. And then the third ingredient – and most critical for us – is that through ASPiRE. we have good data on where the retailers are located. So as soon as we have those three things, although it's not easy, we're able to look at how Tobacco Town is working for a specific town.

Q: You refer to theoretically based kinds of assumptions. How do you model the sensitivity around those model assumptions, and what else can you say about those inputs?

Agent-based models run the range of highly abstract models to highly empirically based models, and there are good and bad models of each kind. In the social sciences, there have been highly influential ABMs that are pretty abstract that reveal a dynamic that we didn't understand earlier. The other side of this is that it is

important to have these models be empirically based, especially in public health, where we're studying real policies that will be implemented in real places.

Notice I didn't say forecasting, or population risk, or national cancer rates anywhere in my presentation, because Tobacco Town is not about that. And so the agent-based model is focused on answering a particular kind of question. This is a transportation model in terms of the physical environment. So for us, we want to know how far people actually travel typically for purchasing tobacco products, and that's been hard for us to get at. Now we are hoping, through ASPiRE and others, that this will be added to other data sets. But there, for example, we are doing much more sensitivity analysis, because we don't have good estimates for that particular piece of information.

Population Modeling in Tobacco Regulation to Quantify the Risks and Benefits to the Population as a Whole

Esther Salazar, PhD, Center for Tobacco Products, Office of Science
U.S. Food and Drug Administration

Abstract

This presentation describes the use of a dynamic population model (DPM) for modeling tobacco regulatory issues, using an example from a DPM developed by the FDA in collaboration with Sandia National Laboratories for modeling the impact of new tobacco products or policies.

Overview

Population models have been used in tobacco regulatory science to model the potential impacts of regulatory policies on the population as a whole, including users and nonusers of tobacco products. They are also used to evaluate the potential population health impact associated with the introduction of new tobacco products through Premarket Tobacco Product Application (PMTA) and Substantial Equivalence (SE) pathways at the FDA.

Because of recent changes in the tobacco market – including the introduction of new products such as e-cigarettes, heated tobacco products such as IQOS, flavored tobacco products, and others – population modeling frameworks for tobacco use have been adapted to account for dual/poly use with new products, as well as switching between products

This presentation will discuss a modeling approach used by the FDA's Center for Tobacco Products (CTP), along with what we are learning about limitations and challenges for population modeling.

Examples of modeling strategies used by CTP

The Dynamic Population Model (DPM) is a multi-state dynamic population model used to assess the effects of product initiation, cessation, relapse, and dual use on product use prevalence and mortality attributable to tobacco use. Here are some examples of these models:

- In 2015, in collaboration with Sandia National Laboratories, CTP developed a DPM that can be used to evaluate the potential population health impact associated with the introduction of new tobacco products or policies (Vugrin et al., 2015).

- In 2018, CTP used a DPM to quantify the potential public health effects of enacting a regulation that makes cigarettes minimally addictive (nicotine product standard).

- On March 16, 2018, FDA issued an advance notice of proposed rulemaking (FDA, 2018) to develop a "Tobacco Product Standard for Nicotine Level of Combusted Cigarettes."

As a brief summary of the dynamic population model approach, we can highlight two scenarios using the DPM described in Vugrin et al. (2015), as shown in Figure 1. One is a one-product scenario, when we only focus on

one specific tobacco product – such as cigarettes – and the model can move from different tobacco use states (never, current, and former smokers) according to transition probabilities for cessation, relapse, and initiation. The other scenario is a two-product scenario – for example, cigarettes and non-combusted products. For this model scenario we have 9 tobacco use states, and can analyze transitions between these categories. In total, we have 27 transitions we can explore that involve initiation, cessation, switching, and relapse among the 9 states. As with the first scenario, this model can be used to estimate product use, prevalence and mortality attributable to tobacco use for the different products defined in the modeling framework.

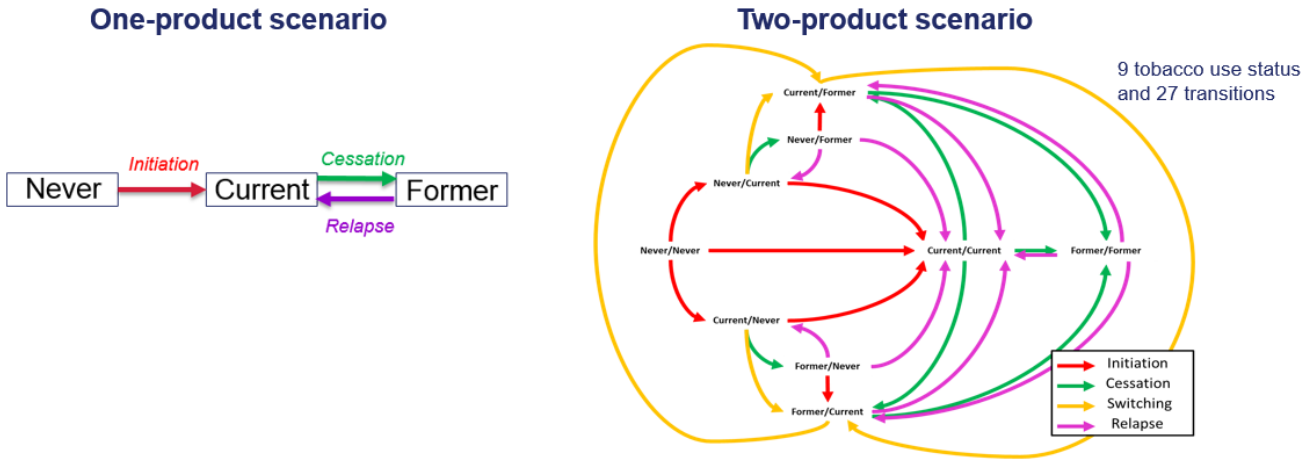


Figure 1. One-product and two-product scenarios for FDA dynamic population model (DPM).

At each discrete time step "t", the model updates each subpopulation "i", accounting for births, mortality. and net migration, as outlined in Figure 2.

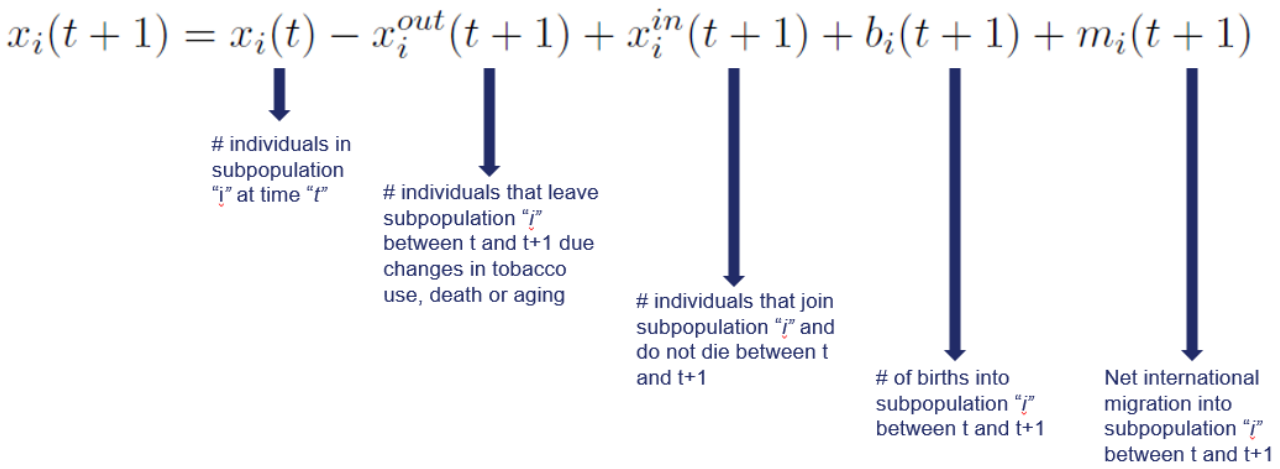


Figure 2. Updates to model at each time step.

The DPM is used to project the impact of hypothetical scenarios on tobacco use, morbidity and mortality in the United States. Examples of hypothetical scenarios include the introduction of a new tobacco product or the implementation of a new policy, such as a nicotine product standard, menthol ban, or other policies.

For a specified simulation period, the model simulates product use prevalence, morbidity. and mortality attributable to tobacco use, comparing between a baseline scenario versus a hypothetical scenario. The DPM is a deterministic model, and because of this feature, the model does not incorporate uncertainty. To account for uncertainty, we used Monte Carlo simulation to compute range estimates. A summary of input parameters to populate the model is described in Table 1.

Scenario	Input model parameter	Source
Baseline scenario	U.S. Population by sex and age	U.S. Census: National Population Projections
	Births and net international migration	U.S. Census National Population Estimates
	U.S. mortality rates and relative risk (all-cause) by smoking status, sex and age groups	National Health Interview Survey – Linked Mortality Files (NHIS-LMF)
	Tobacco-use status (never, current, dual, former) by sex, age groups and tobacco product use	National Health Interview Survey (NHIS), National Youth Tobacco Survey (NYTS), PATH
	Smoking transition behaviors by sex and age (initiation, cessation, relapse, switching)	Reconstructions of cohort smoking histories from NHIS data (CISNET estimates)
Hypothetical regulatory scenario	Regulatory-specific values to change transition behaviors. For example: • % reduction in smoking initiation • % increase in cessation • Changes in switching from one product to the other	Regulatory-specific expert elicitation, tobacco research papers

Table 1. Input model parameters for the FDA DPM.

Output data from this model for each year in the simulation period (in this case, from 2015 to 2100) includes:

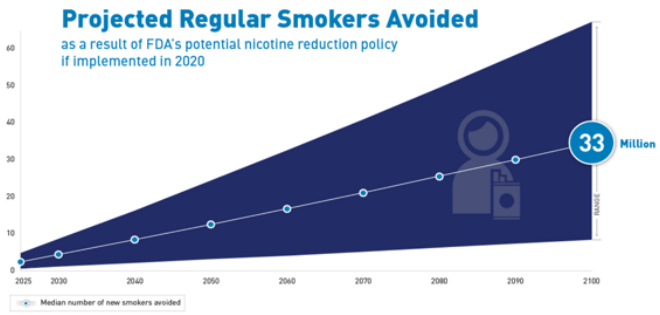
- U.S. population projections by sex, age, and tobacco use status
- Tobacco use prevalence (never, current, dual, former users)
- Projected regular smokers dissuaded
- Projected life-years gained
- Projected tobacco-attributable deaths prevented

Example: Modeling a potential nicotine product standard

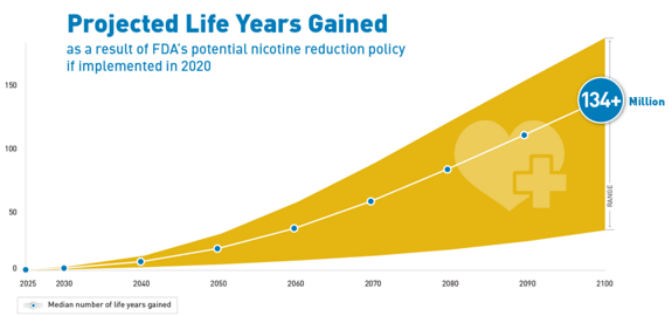
The following is an example of how this model can inform regulators for a given simulation period. The baseline and policy scenarios were as follows:

- Baseline scenario: Cigarette smoking would continue to decline based on recent trends in smoking initiation and cessation and CISNET projections.
- Policy scenario: A product standard is put in place in 2020 to lower levels of nicotine in cigarettes and other combustible tobacco products.

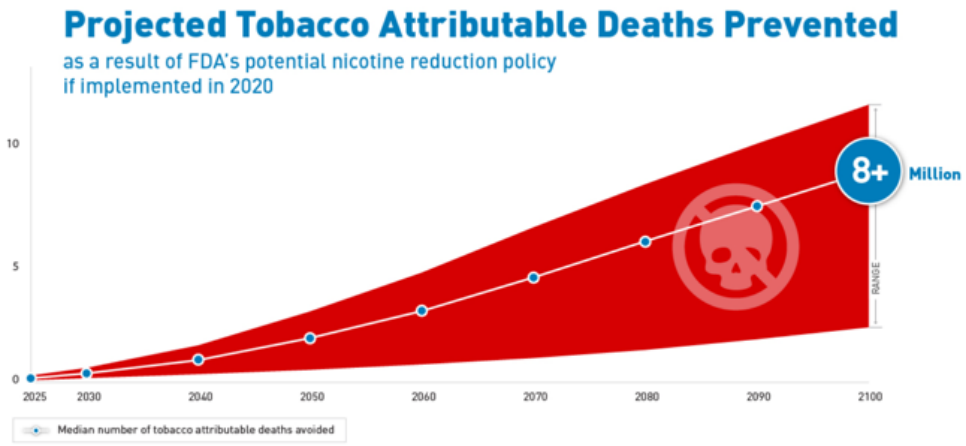
We can then model changes in prevalence, morbidity, and mortality during the simulation period. Results of this simulation are shown in Figure 3, showing that by 2100, 33 million people would avoid becoming regular smokers, more than 134 million years of life would be gained among the U.S. population, and more than 8 million premature deaths from tobacco could be avoided.



By 2100, 33million people would avoid becoming regular smokers



By 2100, more than 134 million years of life gained among the U.S. population



By 2100, more than 8 million premature deaths from tobacco could be avoided

Figure 3. Results of the DPM simulation for a potential nicotine product standard implemented in 2020 and a simulation period from 2015 through 2100.

Limitations of the dynamic population model

The dynamic population model does have some limitations in terms of construction of input model parameters as well as its modeling framework.

Regarding input parameters, although the model can be used to run stratified analyses (i.e., by race/ethnicity) and for different tobacco products, in some cases incorporating group-specific mortality estimates is not possible due to the lack of follow-up mortality data and small sample size for low-prevalence tobacco products.

To date, cause-specific (tobacco-related) mortality and morbidity data has not been incorporated – sometimes it would be helpful to present results related to specific diseases like lung cancer or other tobacco-related diseases, but this is not possible due to a lack of data for some low-prevalence tobacco products.

Also, some CTP-reported analyses using the DPM assume constant tobacco use transition rates (initiation, cessation, switching) over the simulation period. Finally, in terms of its modeling framework, DPM is a

deterministic model approach and does not incorporate uncertainty for model predictions. To account for uncertainty, Monte Carlo simulations were used.

Challenges for population modeling

Multiple challenges remain in the use of DPM, and in fact in other population models, for use in tobacco regulation. Two of the main ones surrounding the construction of input parameters are as follows:

- Tobacco use prevalence can be derived from complex surveys, such as NYTS for youth, NHIS for adults, and PATH and TUS-CPS for both. However, estimates can be different across surveys. Sensitivity analysis (or other analyses to account for input parameter uncertainty) is needed to assess the impact of various data sources on model outcomes.
- There is not enough mortality follow-up data to estimate mortality risk associated with the use of new tobacco products marketed in the U.S.

Future challenges surrounding the modeling framework include:

- Ideally, model outcomes (prevalence, morbidity and mortality) should be reported with uncertainty metrics (such as confidence intervals, standard errors, range values). Other modeling frameworks, such as probabilistic models or Bayesian approaches, could be explored to incorporate uncertainty.
- Micro-simulation (including agent-based modeling) could be used to simulate changes in tobacco use transitions under hypothetical regulatory scenarios. Results from micro-simulation analysis could provide model-based assumptions and input data to model the impact of regulatory scenarios.
- It may be difficult to incorporate available biomarker data from tobacco users into the model. However, biomarker data could be used on mortality/disease risk analysis; results from that analysis could help inform input model parameters.

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Tobacco Use and Comorbid Mental Health Conditions: A Modeling Challenge

Jamie Tam, MPH, PhD
Assistant Professor, Department of Health Policy and Management, Yale University.

Abstract

As an example of modeling tobacco-related health disparities, this presentation discusses the development and implementation of the Major Depression and Smoking (MDS) model, an aggregate model examining smoking behaviors and depression. It examines the key challenges that come with modeling tobacco use among people with a mental health condition, including data issues, model structure, interaction effects, and other issues.

Introduction

In the tobacco control space, tobacco-related health disparities are widely seen as the next major frontier: how we can facilitate reductions to smoking among the most vulnerable members of society. Disparities are also being incorporated into tobacco simulation modeling. This presentation shares some insights on modeling for a particularly important subset of the smoking population: people with mental health conditions.

Mental health conditions are surprisingly common in the population. As of 2019, an estimated 20.6% of US adults live with any mental illness (AMI), 5.2% with serious mental illness (SMI), and 7.1% with major depression (MD), while 17% of youth aged 6-17 experience a mental health disorder (NAMI 2020, NSDUH 2019). While specific serious mental health conditions have lower overall prevalence, such as schizophrenia and bipolar disorder, depression and anxiety are the most common types of mental illnesses.

Across all mental health conditions, people with mental health conditions are more likely to start smoking and to smoke more heavily, and are less likely to successfully quit compared to the general population. This group has a higher mortality risk, with differences in life expectancy primarily due to smoking. Furthermore, the higher the severity of mental illness, the more likely it is that the person smokes (Tam, 2016; Williams, 2013). For these reasons, experts have named smokers with mental health conditions as a priority population for intervention and a tobacco use disparity group.

Even as smoking rates have declined for the general population, they remain unacceptably high among people with mental illness, and this represents a largely unaddressed smoking disparity. Figure 1 shows data from the NSDUH showing trends in past 30-day smoking comparing people with and without AMI. AMI is defined as having a diagnosable mental, behavioral, or emotional disorder, other than a developmental or substance use disorder, based on the Diagnostic and Statistical Manual (DSM-IV), while smoking is defined as any cigarette use in the past 30 days. In 2019, smoking prevalence was 70% higher in the AMI population (NSDUH, 2019).

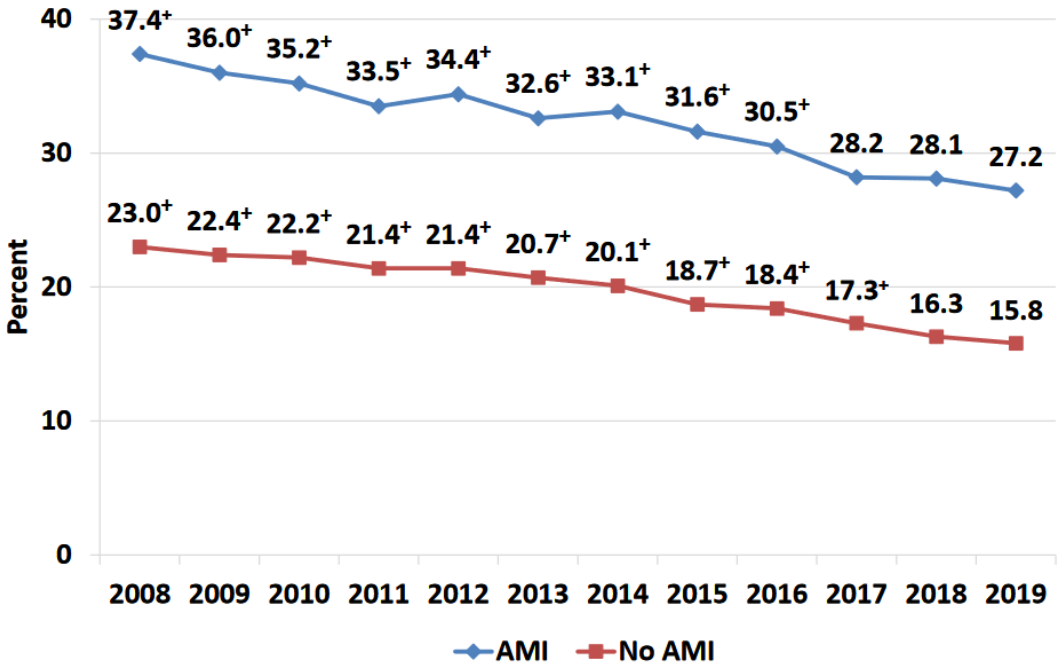

Figure 1. Smoking prevalence rates for people with and without any mental illness, 2008-2019. (Source: NSDUH)

Given this data, it is no surprise that a large percentage of deaths among people with mental illness are ultimately due to chronic diseases associated with smoking, and this is true across mental disorders. In my own work, I model smoking among people with major depression.

Modeling tobacco use and mental health

Why should people with mental health conditions be relevant to tobacco simulation modeling? The field of tobacco control is dealing with an increasingly complex remaining population of smokers—one that is disproportionately made up of society's most vulnerable groups. Smokers in more recent birth cohorts have been shown to have disproportionately high psychiatric vulnerability – that is, they are much more likely to have a comorbid behavioral health condition. Until recently, most tobacco models have focused on the general population, and some models have accounted for differences by race/ethnicity, while there appear to be only a couple of tobacco models that consider comorbidities.

In the model presented here, projections of smoking prevalence among people with current depression and people without a history of depression show that the prevalence ratio may be increasing over time, suggesting that even as smoking continues to decline, this gap will not be closing anytime soon.

We have a long way to go to address smoking disparities by mental health status, and models can help us get a birds-eye view of the underlying dynamics that are driving disparities, as well as help us identify optimal strategies for intervention. This presentation discusses the key challenges that come with modeling tobacco use among people with a common mental health condition such as major depression, including data and definitions, model structure, interaction effects, non-cigarette tobacco products, and other challenges.

Challenge #1: Data and definitions

The first challenge in modeling tobacco use with mental illness is a data challenge. Most of the tobacco simulation models that have been developed use the National Health Interview Survey (NHIS), which offers the most historically comprehensive assessment of smoking in the US going back to 1965. The NHIS, however, has very limited questions related to mental health; serious psychological distress (SPD) has been assessed since 1997, but this measure was discontinued as of 2019 and is not diagnosis specific. One 1999 supplement assessed depression, anxiety, and panic disorders; however these are not part of the annual assessment.

This situation is not ideal for modeling mental illness, where we want patterns of a diagnosable mental health condition that are assessed repeatedly over time. However, the good news is that as of 2019, generalized anxiety disorder and depression will be part of a new expanded mental health assessment for NHIS that will rotate every 3 years.

Other national surveys are state-specific (BRFSS), are cohort-based with fewer assessments (NESARC - National Epidemiologic Survey on Alcohol and Related Conditions, NCS) or in the case of PATH, have very few metrics for mental health that are useful for modeling diagnosable conditions. PATH includes a measure for perceived mental health and for diagnosis of schizophrenia, schizoaffective disorders, and psychosis – all of which are uncommon. That leaves us with the National Survey on Drug Use Health (NSDUH), which is the most historically comprehensive nationally-representative data source on smoking and depression, with consistent measures for depression since 2005. Table 1 shows a summary of mental health measures available in major current surveys.

Survey	Mental health measures	Assessments
NSDUH	Major Depressive Episodes (MDE), SPD, SMI, AMI, depression/anxiety diagnosis, suicidality	Annual cross-sectional
NHIS	SPD, depression/anxiety rotating core 2019-forward	Annual cross-sectional
BRFSS	SPD, MDE, Anxiety/depression for some states	Annual cross-sectional, state-based
PATH	Self-perceived mental health, schizophrenia/psychosis diagnosis	Wave 1 (2013-14), Wave 2 (2014-15), Wave 3 (201516), Wave 4 (2016-18)
NESARC	DSM diagnostic criteria for mental disorders	Wave 1 (2001-2002), Wave 2 (2004-2005), NESARC-III (2012-2013)
NCS	DSM mental disorders, MDE, suicidality, SMI, AMI	NCS-I (1990-1992), NCS-2/Replication (2001-2003), NCS-Adolescent (2001-2004)

Table 1. Comparison of mental health measures used in specific surveys.

Another data issue is calibrating a smoking-only model to the NSDUH data on smoking. Model inputs for smoking initiation and cessation are from the Cancer Intervention and Surveillance Modeling Network (CISNET), which relies on NHIS data. In developing the smoking components of the model, tobacco models have traditionally relied on NHIS, which employs a different definition for smoking, while smoking initiation and cessation inputs were developed by the CISNET Lung Consortium and generated using NHIS data. These inputs are age, gender, and birth cohort specific, providing detailed trajectories of smoking behaviors going back to 1965.

However, because these inputs were developed using the NHIS, and we are trying with this model to fit smoking commonness of the model to the NSDUH, we need to think carefully about what definitions we are using for both smoking and for mental health in the model.

In the NHIS, the official definition of smoking is "currently smoking every day or some days and having smoked at least one hundred cigarettes in your lifetime." NSDUH, in contrast, looks at smoking in the past 30 days, which generates much higher prevalence estimates. And when the CISNET lung group developed those modelling inputs, they assumed no relapse back to smoking, which means the current smoker group includes people who have recently quit but have a high probability of relapsing. So to align across these different data sources, the smoking definition used in this model retains the permanent quitting aspect of the system and inputs and also keeps the 100 cigarettes in a lifetime threshold used by the NHIS.

For depression, we used the NSDUH screening criteria shown below. There are no exclusions to these criteria due to illness, mourning, and substance use disorders, or other psychiatric disorders, which means that rates will be higher than those for surveys using these exceptions. Also it's important to note that this depression measure is based on that individual's self-reported symptoms – it does not ask, for example, whether the individual has been diagnosed with major depression by a physician. So in that respect, this measure for major depression captures more people.

Challenge #2: Model structure

We used the DSM-IV definition of a major depressive episode to inform different depression states in the model. Here, never depression (Never MD) represents someone who has no lifetime history of a major depressive episode. Someone with current major depression (Current MD) has had a depressive episode in the past year, which may or may not be their first onset episode. And then people with former depression (Former MD) are individuals who report no episode in the past year but a lifetime history of at least one episode.

Is this the appropriate model structure? Intuitively, it would seem so. But when fitting the model to the survey data, it became very clear that the structure itself needed to change. For example, NSDUH data showed a substantial drop in lifetime prevalence of MD for respondents aged 65 and over, when in fact with lifetime prevalence of any condition, you would expect it to increase with age as more people experience the condition within their lifetimes as they age. It turns out that the quality of lifetime assessments of depression is a problem across many surveys, not just the NSDUH, because of *recall bias*, that is, people failing to report their histories of depression over time.

To address this, we revised the model structure to reflect this tendency for people with histories of depression to fail to report their histories, with a new recall error compartment that represents individuals who self-report no lifetime history of a depressive episode but are in fact modeled as having a history of depressive episodes. Figure 2 shows how this model evolved to include this new recall error component.

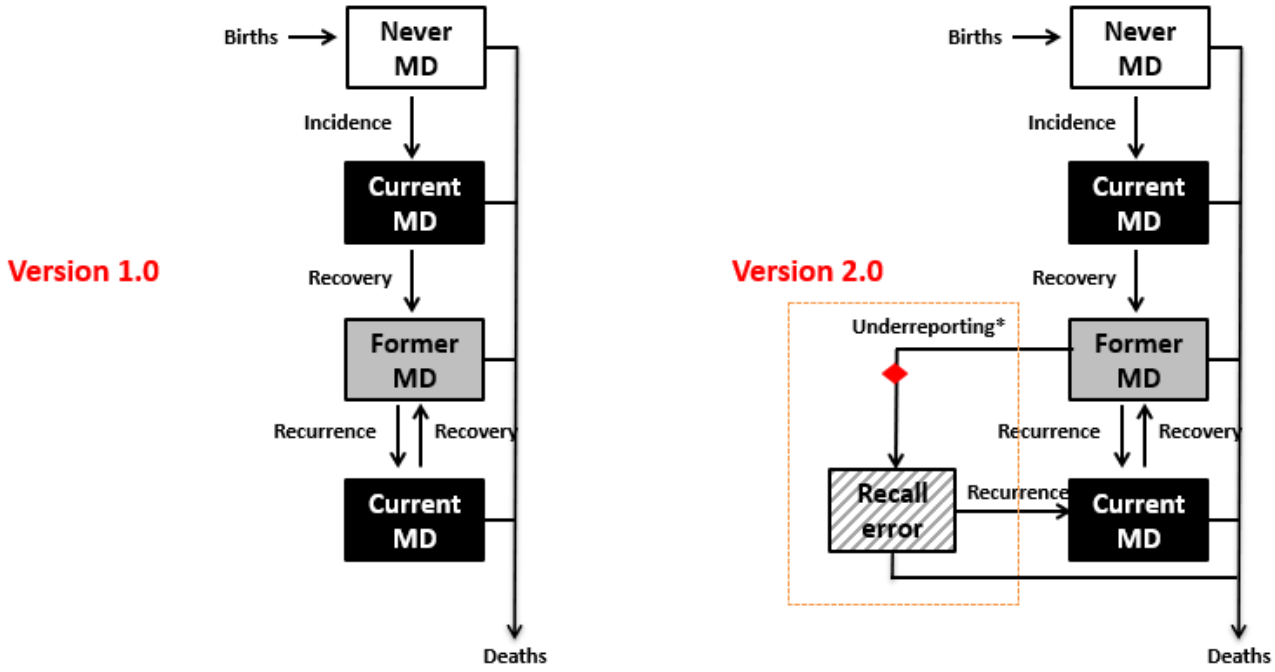

Figure 2. Mental health categories of model updated to include a recall error component.

Challenge #3: Smoking and mental health interactions

Another modeling factor involves potential interactions between smoking and mental health. A systematic review of smoking and depression found positive associations between smoking and subsequent depression and vice versa, even after controlling for confounders. Some longitudinal studies indicate that smoking may increase susceptibility to depression through neurophysiological changes, and that smoking increases the risk for suicide ideation and completion.

There is also research that shows quitting smoking reduces depressive symptoms suggestive of potential causal pathways, in studies following adolescents and adults. Over time, major depression puts individuals at risk for future smoking, initiation, and nicotine dependence, and having depression reduces the odds of successfully quitting. There are, of course, shared underlying genetic and social vulnerability characteristics that explain their high degree of co-occurrence, but even after accounting for these, there's literature showing how smoking and depression interact with each other (Wooten et al, 2020). Figure 3 summarizes some of the potential feedback effects affecting the model.

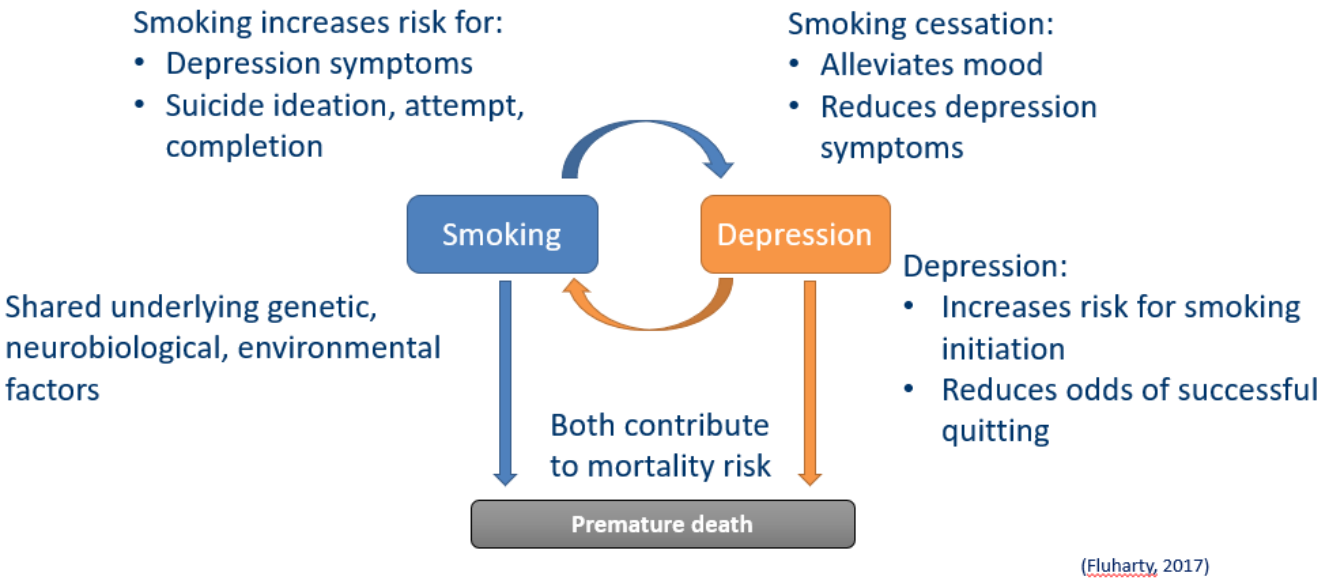

Figure 3. Potential feedback effects between smoking and depression.

The Major Depression and Smoking (MDS) model

Figure 4 shows the full Major Depression and Smoking (MDS) model, with 15 mutually exclusive health states. The simulated population is initialized into a never smoker and never depressed state at birth. Then each year, individuals flow across the smoking and depression compartments based on gender and age, specific smoking initiation probabilities, decision probabilities from CISNET, and depression incidence and recovery rates from some longitudinal studies of depression. And as discussed previously, there are interaction effects between smoking and depression.

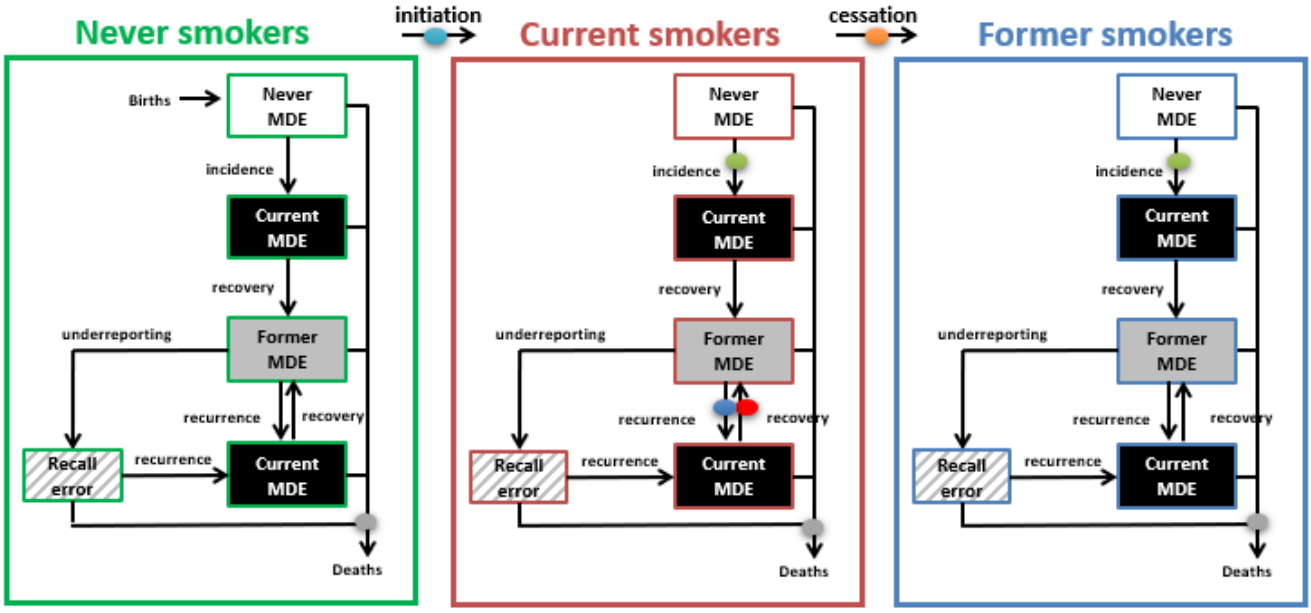

Figure 4. The Major Depression and Smoking (MDS) model.

Smoking status at baseline has been shown to increase the risk of a subsequent first major depressive episode (green dots). A history of depression also increases the odds of smoking initiation and decreases the odds of cessation (teal and orange dots). Being a current smoker also raises risk for recurrence of depressive episodes and influences the likelihood of recovering from depression (blue and red dots). Finally, we re-estimate the mortality risk associated with having a history of depression to adjust for further differential mortality in the depressed population that isn't accounted for (grey dots).

Figure 5 shows smoking prevalence by major depression status among women, after accounting for the interaction effects between smoking and depression in the model, and the model shows a strong correspondence with the NSDUH. Calibrated estimates were created for the interaction effects, based on relevant literature. Reported estimates will, of course, differ from the calibrated estimates, since other covariates like race, ethnicity, and socioeconomic status are not included in the model. One thing that came out of this calibration process was the importance of one particular parameter: the effect of depression status on subsequent smoking initiation. It is very important that we incorporate this parameter because of high smoking rates reported among young people with depression in the survey data as well.

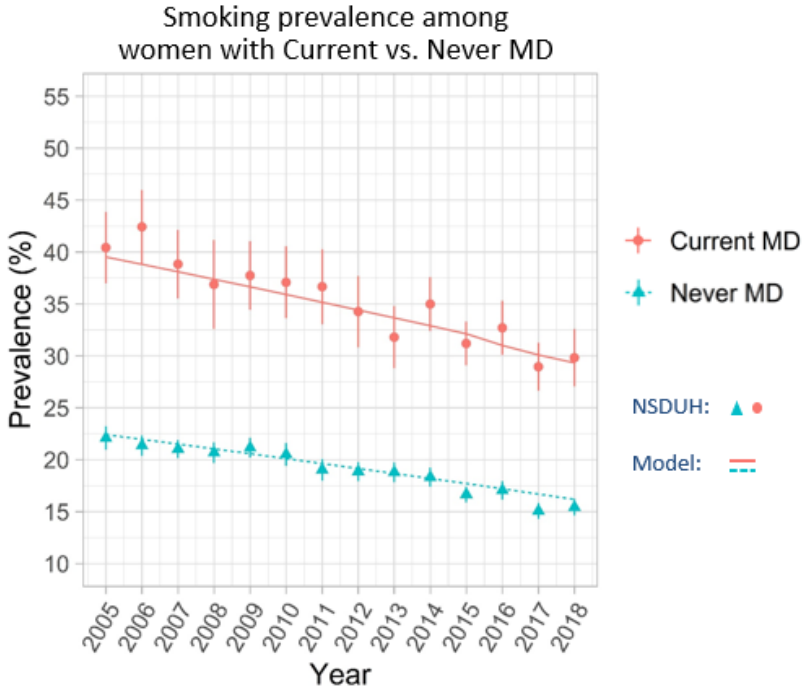

Figure 5. Model versus survey data (NSDUH) for smoking prevalence among women with Current MD versus Never MD status.

The fully calibrated MDS model shows that in the absence of bold action, smoking related disease and death will continue to disproportionately burden people with major depression, and this disparity is expected to persist and even rise over time for men and women. So under the status quo, little will change, and the smoking disparity may even widen. This model also shows how widespread cessation treatment for smokers with depression could have a public health benefit, but even with aggressive action, the benefits when focusing just on cessation treatment are relatively modest. Figure 6 shows recent analysis results from this model for specific treatment strategies versus medicated patient controls (mPC) (Tam et al, in press).

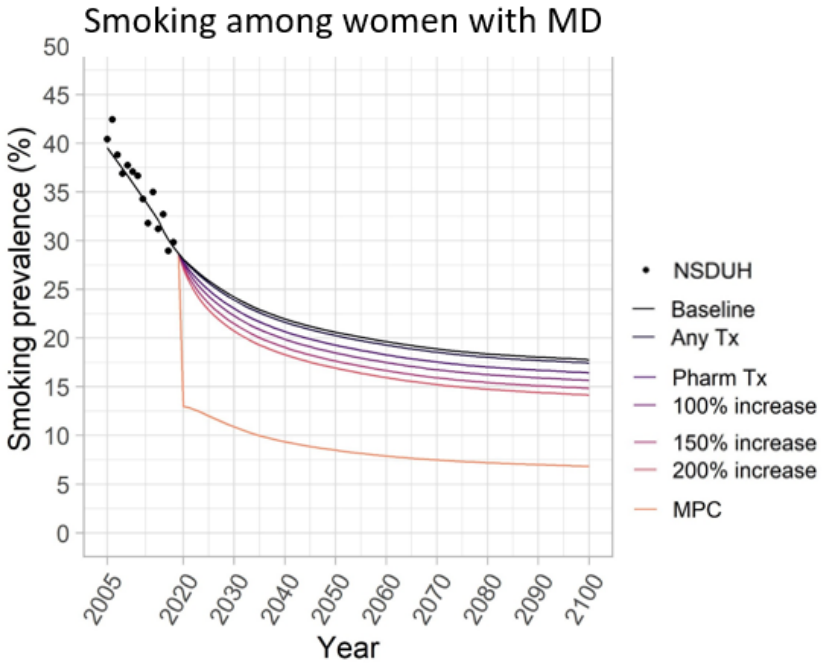

Figure 6. Model results projected from 2020 through 2100 (Source: Tam et al., in press)

Much of the conversation around smoking among people with mental health conditions has focused on integrating smoking cessation and treatment in mental health settings, so one of the things that we did with this model was evaluate gains under optimal treatment conditions, e.g. if all patients quit smoking. We found that while there would be gains associated with increasing smoking cessation treatment in mental health settings, the absence of a prevention focus does not change the disparity by much; that is, even if more people leave the smoking compartment who are depressed, the inflow into that compartment continues. So we can expect the disparity in smoking by mental health status to persist if we only focus on cessation.

Other challenges

A major challenge moving ahead is how to account for not only population heterogeneity but also product heterogeneity. There are other tobacco products that are not cigarettes that have not been modeled for these populations, including e-cigarettes, and smokers with depression are also more likely to use e-cigarettes than the general population. There is a lack of non-cigarette tobacco data for comorbid populations, and product use transition patterns may differ from the general population.

Finally, integrating information like cigarette use into a model like this can lead to a problem known as data explosion, where the number of compartments in the model increases exponentially with the integration of additional states. In this context, it is important to know when to abandon an aggregate approach for an individual based one.

To conclude, there are still some additional challenges that remain beyond population heterogeneity and tobacco product heterogeneity. There is also substance heterogeneity, e.g. people using more than one type of substance at a time. While this model focuses on people with comorbid mental health conditions, smokers are also more likely to have comorbid substance use disorders. Other ongoing trends could also impact model projections: for example, depression rates have been rising among young people, and COVID-19 and its associated disruptions will have an impact on how we can make projections for the future. These are some of the important but not insurmountable challenges on the road ahead.

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Questions and answers

Q: Could you elaborate on how to separate out the impact of smoking versus other substance use?

A: How we deal with multiple substances is a big, unanswered question. For example, when we talk about e-cigarette use, people are vaping marijuana as well. So even in our understanding of existing tobacco products, we have to take into consideration that people are vaping not just nicotine, but marijuana and other substances. I think that once you include multiple substances, the picture becomes very complicated very quickly. But there has been modeling work on other substance use disorders such as alcohol use disorder and opioid use disorders in that arena that we could really learn from.

Panel Discussion: Computational Models in Tobacco Research

Panel discussion with David Mendez, PhD, Douglas Luke, PhD, Esther Salazar, PhD and Jamie Tam, PhD; Moderated by Rafael Meza, PhD

Abstract

This is a summary of a panel discussion with presenters from the first day of the CAsToR Symposium, addressing audience questions on computational modeling issues in tobacco control in Q&A format.

Q: What happens when you have two models and they come up with different results? Can you reconcile those? Is it possible to combine microsimulation with macrosimulation in some way?

David Mendez: When you aggregate the model and get everybody behaving in the same way, then you should have the same output in a microsimulation model as in a macrosimulation model. That's why one of the first things that we do in the micro model is to dock the model. So we have a lot of heterogeneity in the population that we need to recognize. But if you have a compartmental model that produces some result, you simply go to your micro model and set parameters to be the same, to mimic the compartmental model.

So just to mimic the structure, when they produce the same thing, then you can let loose with heterogeneity and connections. And if there are different results, then you know that heterogeneity and those connections will matter. If there is no error in the structure, you dock your model, and then when you let all the same parameters vary according to how you think they should vary, any discrepancy must be gone.

Doug Luke: One of the things that I think is implied in David's response, especially around docking: I think modelers now expect there to be a lot more scrutiny and transparency in model development. We've all learned that when that doesn't happen, the models are not worth very much. This may sound like a cop out, but it's often apples and oranges when we compare models, and looking at the model agreeing is not the be all and end all. Often you learn as much from why these models don't seem to agree than if they actually agreed more, and there's so much that an agent-based model might be doing, like social interactions.

So if you've got social networks in there, you can be modeling something that is very much empirical, but possibly the compartmental models have no way of incorporating that, so the models are not converging. I think having models not being integrated, but connected - where you're using, let's say, micro simulation or agent-based models for one part of it, and then the results from that get put into a population level dynamic model, let's say – we're seeing more and more of that.

We're seeing in agent-based models much greater integration of social structure and social network information, which is incredibly helpful for public health types of applications. But these are complicated things, and we don't spend enough time talking to each other. And so multiple models where modelers, scientists, and community members are in some form of dialogue probably can really push the computational modeling community forward much faster than anything else.

Q: One of the challenges is that for many of the policies or regulations the FDA needs to consider, there isn't much data – one example is nicotine regulation, where then you relied on expert elicitations. But of course, those are hard to do. They are expensive, and modelers are not necessarily trained to do these. Would you consider using, for instance, the discrete choice experiments or experimental tobacco market

data to inform these policy effects? Also, what is your view about asking survey respondents about hypothetical responses to different policy scenarios, and then using those to inform the modeling?

Esther Salazar: This is very important, and directly related to the uncertainty in the input parameters. You mentioned a couple of examples: using a panel to get information from potential users of new products, or other ideas to get assumptions for different hypothetical policy scenarios. But this is actually most related to how we can incorporate the uncertainty into models of parameters that are related to policy scenarios.

If we can incorporate in the modelling framework itself uncertainties that are related to extreme scenarios - minimum to maximum scenarios - then we can quantify those uncertainties. For example, expert elicitation is expensive and also time consuming. However, at the end of the day, what we got from expert elicitation was a set of values that are mostly related to the minimum to maximum scenarios, and then these come with, for example, the incorporation of prior information.

For example, I mentioned about the Bayesian modelling framework that modelers can explore, that naturally will incorporate this type of uncertainty into the modeling framework itself. This is one of the challenges that we have as modelers - how to incorporate different tools into this modern framework, to be able to estimate or incorporate uncertainty around input parameters. We can explore ways to introduce assumptions for these parameters, and also to incorporate that uncertainty mathematically into the modelling framework.

David Mendez: My opinion is that what you are trying to do with a simulation model is reduce your uncertainty about an output. Either you want to know a certain structure, or you want to evaluate what's going to happen in the future. Depending on how certain your inputs are, you are going to have a range of variability in the model.

So if you have certain information that you think is valid, even though it has a lot of variability in the inputs, if it reduces your uncertainty of the output and it's logical, then you have to determine whether what you get in the output is enough to answer the question you're posing. If you are going to have a huge confidence interval from zero to one million and the input parameters are very loosely based, you don't have confidence that your output is going to be that helpful. So it depends on what you want to do; there should be certain levels of quality or certain levels of certainty in your output.

Doug Luke: It sounds like we're actually pretty much in agreement on this. We should be free to use evidence in whatever form it arrives if it enhances our model building. We talk about parameter estimation and the quality of the data that come in, and those are incredibly important. But David Freedman wrote a great paper called "Statistical Models and Shoe Leather[1]," and his point was, you can't stop thinking just because you've got an elegant statistical model or you have the best sort of data.

We haven't talked about this too much, but one of the things that models do is make it a little easier for us to think in causal language because that's what this is about. In my experience, it's the arguments we have with epidemiologists that tend to be the most frustrating, because it's not just how high quality a particular data source is, it's do you understand what's going on? Do you know what you're trying to model? Does the uncertainty inform the next iteration of the model in a way where knowledge is expanding? I think modeling and its effect on causal thinking is something that's really important for us.

Q: A lot of you have talked about using different datasets with different estimates. But that kind of leaves decision makers in a quandary. So how about we go to the next step where we can say, "OK, here's the different estimates – which should we rely on?" Can we move in that direction?

[1] Freedman, D. (1991). Statistical Models and Shoe Leather, *Sociological Methodology*, 21, 291-31.

Jamie Tam: I think it may depend on whether the use of different data sources leads to different conclusions, in the way that when multiple models reach similar qualitative conclusions, you can have a great deal more confidence in those qualitative conclusions, even if the numbers differ.

We talk about certain data sources as if they're the kind of gold standard for modeling, when there are many shortcomings, like even with the NHIS: landlines, telephone based surveys, survey response rates. How much more can we rely on these data sources as our "ideal data sources"? So I think it's helpful to have not only multiple models but multiple data sources that feed into our conclusions.

Esther Salazar: I would like to also mention that there is a big challenge of pulling this information together. For example, we have prevalence data from NHIS and from PATH. These two are a very good example because one is cross-sectional, and the other is a longitudinal survey. So how can we use different surveys that have different designs in the models that we are building? For example, if we notice that the prevalence change for one of them is 13 percent while the other is 10 percent, which one should we use? I think that is more related to how to also incorporate uncertainty into model parameters.

We can think of multiple strategies. One maybe is pulling the data together if we have similar designs. Another one is to try to get into different ranges for these different input parameters and to try to see if we can incorporate sensitivity analysis for those, or try to build a stochastic model to be able to incorporate uncertainty for those parameters. So the mathematical framework that we are using right now perhaps cannot be used to account for those changes in the model, in order to incorporate uncertainty and how to get into the pulling of the data. So we need to think about that carefully and try to see what the best solution is, or perhaps just try to think about sensitivity analyses that are appropriate to incorporate different input parameters from different surveys.

Q: This is directed to Doug Luke. Have you used Tobacco Town to examine compliance with underage sales laws? Second, some communities have enacted vaping flavor bans - have Tobacco Town models been used to estimate the intended and unintended consequences of those vaping flavor bans? Finally, are you accounting for other policies in Tobacco Town when you're using the model?

Doug Luke: We have not used Tobacco Town to examine compliance with underage sales laws, and we are also not applying Tobacco Town to vaping, although it is a future possibility, and we are looking at tobacco menthol bans.

One of the interesting things here is in the density literature in terms of mapping availability of products. The typical approach is to just do retailer density, but it gets more complicated when you think of product restrictions where we might have the same number of tobacco retailers in a community, but they're not selling the same things. So we're starting to think of something like product density, which is not tied to retailers but rather product availability in the community.

Also, you can't just develop a tobacco model and say let's use it for alcohol. That being said, we also as modelers do hold out the promise that once you develop a model – if you develop models or pieces of models that are based on certain underlying mechanics – that they can be applied in different situations. Certainly, for example, we are thinking that we can apply this model in D.C. and in Providence. So, as always, the devil is in the details. But I do think policy research will be dramatically enhanced by using more computational modeling approaches. It's just too hard to study real world policies and wait for them to happen. We have to have other ways of examining them.

Esther Salazar: I would like to mention something related to the construction of input parameters and the use of agent-based modeling; for example, for specific regions where we have different policies in place, trying

to see how these policies affect behavior in specific groups that we are interested in. Using simulations, we can understand how people will react to a specific policy in a specific region, and by repeating this analysis for different geographic regions we will be able to see how regulatory actions impact the population across the US. We can use the outputs from these agent-based models as input parameters to populate our population models to estimate the health benefits of regulatory actions in the population as a whole.

These are pieces we can explore, like using agent-based models for the construction of input parameters for hypothetical policies; for example, trying to see how the media is playing a role influencing youth to initiate tobacco use, how changes in tobacco use prevalence are related to the reception of media messages, and if this is going to impact initiation. There are some statistical analyses there that are related to the impact of messages from the tobacco industry, for example, sentiment analysis (or opinion mining) to explore how marketing of tobacco products is going to impact youth in their decisions about using a new product. So, we can use these types of underlying data to construct modeling approaches for microsimulation modeling at an individual level.

Q: I'd like to make a suggestion where I think that agent-based models can be especially useful. In Doug Luke's models, the focus is on retail. In vaping, that's kind of a section, but then there's the Internet and vape shops, which is kind of a different type of retail. Where I think agent based models can be useful is they can consider different choices that the individual can make between these different sources.

Doug Luke: One of the advantages is that you can have different kinds of agents in agent-based models, with diversity and heterogeneity. So you can have physical stores and the Internet as a type of store. This is a very complicated model, but at least in theory, you can incorporate that heterogeneity in that kind of model.

David Mendez: I think a very important point is that we are very concerned all the time about data to populate our model, to put parameters in our model, when the real value of a modeler is to come up with a structure that represents reality. So we have two things: data to populate the model and then the model specification - do we have the models that reproduce the phenomenon? That's modeling. And if you have a model that is very dependent on parameters, and it changes behavior when you change the parameters, then you are not in very good shape.

Right now we have models that are dependent on a lot of exogenous parameters. For example, Esther Salazar made a very good example about how to model the parameters - how to internalize, how to endogenize the initiation rate. Now I don't have to be looking at how this initiation rate is going to change. I modeled the initiation rate, so I use an agent-based model that's going to tell me how the initiation rate might be changing and so on. At a point, we should be looking for models that depend on very few parameters that we can easily obtain and that do not change the major outputs of what we're modeling. So when we get there, then we have something stable that can accommodate many different situations.

Two Methods to Estimate Parameters: Flavor Bans in E-cigarettes and Cigarettes

Jody Sindelar, PhD, Yale School of Public Health

Abstract

This presentation compares two strategies for parameter estimation for modeling the effects of tobacco product flavor bans, using a discrete choice experiment versus a quasi-experimental approach.

Introduction

In this presentation we are reporting on two methods to estimate parameters for the impact of flavor bans on e-cigarettes and cigarettes. One is a discrete choice experiment, which we have conducted across a series of publications. The other approach is an approach that we have used before for other applications and are using to be implemented shortly as a joint project with researchers from the University of Michigan. This approach is a quasi-experimental method using real world data.

Discrete choice experiments (DCE) are especially useful in cases when policies have not been implemented and/or there are no real world data. By comparison, quasi-experimental studies examine real world policy change and ongoing data, by looking at population response to policies implemented, using your own collected data or publicly available data.

Modeling a flavor ban

The US Food and Drug Administration (FDA) has had regulatory authority over tobacco products since 2009, and since 2016 this now includes authority over e-cigarettes and other tobacco products. The FDA is required to regulate to improve public health and needs to consider substitution across tobacco products by consumers in response to policies. States also have the power to restrict vaping, such as prohibiting indoor vaping or implementing age restrictions, and to regulate flavors (Sindelar, 2020).

FDA has begun to use its 'premarket approval' to take some flavored e-cigarettes off the market. So if you impose a ban on menthol cigarettes and people move to e-cigarettes, that could be considered good or bad. But if you impose a ban on flavored e-cigarettes and consumers move to cigarettes, that would be considered adverse to public health.

In one study (Buckell et al., 2018), we looked at how different flavor bans would impact public health using a discrete choice experiment, considering the impact on smoking and vaping. Should we ban menthol? Ban all flavors? Maintain the status quo? Ban similarly or differently across combustible cigarettes and e-cigarettes? Is there a heterogenous impact by demographics and types of smokers/vapers? What are the priorities – to reduce overall smoking, or to reduce the use of cigarettes or e-cigarettes?

Approach 1: Discrete choice experiment (DCE)

Overall, respondents make choices of products across attributes (such as flavor) and at different levels (such as menthol or fruit). We selected attributes and 'levels,' determined products for respondents to select among, as shown in Table 1, and developed the discrete choice experiment and an accompanying survey. Next, we

piloted it to improve the survey, then randomized the results to help us select the most impactful sets of questions and optimize the number of options for respondents.

	E-cigarette	Combustible cigarette
Flavor	Plain tobacco Menthol Fruit Sweet	Plain tobacco Menthol
Life years lost by average user	10 5 2 Unknown	10
Level of nicotine	High Medium Low None	High Medium Low
Price	$4.99 $7.99 $10.99 $13.99	$4.99 $7.99 $10.99 $13.99

Table 1. Attributes and levels used in constructing discrete choice experiment.

Our experimental design involved what is called a best/best DCE that allows choosing the top two options. It would not be realistic to ask respondents to select from all possible combinations, so they were presented with a defined set of 12 possible choices from the attributes and levels above, and there were three sets of choices randomized across respondents. They were then asked to select their first choice and second choice, or opt out to avoid having to make a forced choice. An example of these choices is shown in Figure 1.

Figure 1. Sample choices for best/best discrete choice experiment

The choices made by respondents formed the data to be analyzed. It was also important to have an accompanying survey along with the DCE, which we could use for control variables. Thus, the responses could be different depending on factors we wanted to control for in the analysis, such as socioeconomic status, demographics, smoking, vaping, history, current habits, or knowledge and perceptions about vaping. We then use these data as control variables and examine response heterogeneity by control variables.

Economists like the DCE model because it is based on an underlying utility function, such as this case where (i=individual; j=product, and c=choice set):

$$U_{ijc}\ (flavored\ cigarette) = Men\_Gcig + Tob\_Ecig + Men\_Ecig + Fru\_Ecig + None\text{-}of\text{-}these + \beta_{price}.Price_{jc} + \beta_{nicotine}.Nicotine_{jc} + \beta_{Health\ risk}.Health\ Risk_{jc} + \varepsilon_{ijc}$$

Basically, we are estimating a regression of respondent choices as a function of the different types of cigarettes as well as flavor, price, and nicotine. What they yield are called choice probabilities: the higher the utility, the more likely the choice here. The constants are a product interaction with the flavor, such as menthol and combustible cigarettes.

Looking at the results for a sample of adult current and recent smokers, as shown in Table 2, the coefficients on constant terms are measures of the preferences. This sample prefers the omitted category of tobacco cigarettes (as shown by the large negative coefficient on "none of these"), understandably prefers a lower price, and also prefers a medium level of nicotine and a healthier product.

Parameters	Coef. (s.e.)	Sig.
Constant: menthol combustible cigarette	−0.38 (0.035)	***
Constant: tobacco e-cigarette	−0.55 (0.037)	***
Constant: menthol e-cigarette	−0.88 (0.058)	***
Constant: fruit/sweet e-cigarette	−0.71 (0.040)	***
Constant: none of these *(omitted tob cig)*	−1.87 (0.049)	***
Price	−0.08 (0.002)	***
Nicotine: none *(omitted medium)*	−0.15 (0.024)	***
Nicotine: low	−0.04 (0.019)	*
Nicotine: high	−0.06 (0.015)	***
Health: unknown *(omitted 10 years lost)*	0.30 (0.033)	***
Health: 2 life years lost	0.37 (0.036)	***
Health: 5 life years lost	0.18 (0.027)	***

Table 2. Results from sample of adult current and recent smokers.

We then use this model to look at the interaction between the flavor-product constants and sociodemographic variables to examine heterogeneity – for example, how women or dual users have different preferences – and then use these results to create better predictions than assuming that all groups have the same preferences.

The key policy issue is that we use these results to predict the percentage of the population that selects each cigarette type, or none. These 'choice probabilities' sum to 1 in each scenario. They are not quantities but are 'choice shares' (e.g. the percentage of times that, for example, e-cigarettes are selected) and are used to make predictions under alternative regulatory bans, as we compare the 'status quo' (current regulations) to alternative regulations.

Table 3 shows the potential flavor ban policy options for which we predicted impact and compares current regulations (as of 2018) to alternatives shown, listing permitted flavors by cigarette type.

	Combustible cigarettes		E-cigarettes	
Policy	**Menthol**	**Fruit/sweet**	**Menthol**	**Fruit/sweet**
Current US Policy: ban fruit/sweet in ccig	Allowed	Banned	Allowed	Allowed
Alternative 1: ban all flavors	Ban	Ban	Ban	Ban
Alternative 2: only allow menthol ecig	Ban	Ban	Allow	Ban
Alternative 3: ban all ccig flavors	Ban	Ban	Allow	Allow
Alternative 4: only allow fruit/sweet ecig	Ban	Ban	Ban	Allow
Alternative 5: ban all ecig flavors	Allow	Ban	Ban	Ban

Table 3. Policy alternatives examined for flavor bans in combustible cigarettes and e-cigarettes.

Looking at the results of this analysis in Table 4, we see that if you wanted to minimize the amount of smoking in the population, you would ban menthol in combustibles (-5.2% change). However, if you wanted to maximize the amount of people selecting no tobacco product, then you would ban all non-tobacco flavored products (5.2% change). Conversely, if the goal is to reduce consumption of combustible cigarettes, banning only e-cigarette flavors – which is what is happening in some states – would be the worst thing you could do.

Maximize	**% change predicted market share compared to 'current'**		
	Ccig	Ecig	None
Ban e-cigarette flavors	8.3	-11.1	3
Ban menthol in combustible cigarettes	-5.2	3.8	1.6
Ban all non-tobacco flavors	2.7	-7.9	5.2

Table 4. Results of discrete choice experiment analysis for flavor bans.

This is one example that demonstrates the importance of these results for policy predictions. You can use discrete choice experiments when you don't actually have real world data to evaluate – so in this case, we chose the discrete choice experiment prior to real world flavor bans because the bans didn't yet exist and couldn't be analyzed with real world responses. DCEs are well attuned and rigorous methods that can help to assess policy implications.

Approach 2: Quasi-experimental approach

The second approach, in a project currently in progress jointly with the University of Michigan, is a quasi-experimental approach to estimate the impact of state level flavor bans. We can now analyze real world bans, analyzing states with and without bans, and also with or without Tobacco 21 laws, which are a confounder.

Our aim is to establish the cause-and-effect impact of flavor ban policies on smoking and vaping. We look at pre- and post-ban outcomes using a survey, and we consider that the policy change is exogenous to the smoker or the vaper. We gather our data using separate surveys of smokers and vapers, and compare their changes in use over time (November 2019 versus current) in states with versus without bans.

We cannot use this approach to examine the impact of flavor bans at the federal level because there is currently no overall, fully implemented ban on menthol in cigarettes, and it is difficult to assess the pre-

authority approval approach that the FDA is now using which is similar to a ban. Here, we are state-level impact to suggest the impact of federal policies.

How do we identify and measure the pre-post change through survey questions? State flavor bans occurred mainly prior to Thanksgiving 2019, we use this as a prompt to help the sample respondents report how much they were smoking and vaping then, and then ask how much they are smoking or vaping now. We also ask respondents if they have noticed an inability to buy flavored products – for example, they may not have noticed because they were not smoking or vaping then. If they did notice, we ask how they changed and why; here as well for example, they may have been too young to purchase tobacco products in a Tobacco 21state, or responded to a flavor ban.

The outcome of these surveys is change before and after the date that a law passed or when respondents noticed these laws, versus change across the same dates for those in non-ban states. We also take advantage of the fact that the passage of policies is exogenous to users, but we acknowledge that the policy is not necessarily randomly passed by states, thus we can control for characteristics of the state.

We conducted two national online surveys of users ages 18-32 with 2000 respondents to each survey:

- Survey 1: Regular vapers who vaped daily or on some days as of Thanksgiving 2019 (prior to the implementation of state flavor restrictions).
- Survey 2: Ever-smokers who smoked at least 100 cigarettes in their life and smoked daily or on some days as of Thanksgiving 2019. We also had information on dual users.

Our key outcomes are past versus current tobacco use, with outcomes including switching, quitting, and quantity used. Other outcomes include whether these bans changed their perceptions of riskiness, and for those who are not affected by an actual flavor ban, what their hypothetical response might be, as a supplement to the actual real-world exposure. We also measure control variables such as socio-economic and demographic information, state of residence and more.

Table 5 shows a summary of our outcomes, including whether respondents quit, continued to vape, started smoking any kind of e-cigarettes, or reduced use. We ask this for the states which were affected by a flavor ban on e-cigarettes and also the states for which there was a ban on menthol. But when we ask about menthol, we are asking more specifically whether they quit menthol smoking, quit smoking, or changed to non-menthol cigarettes.

Behavioral responses	State or local bans on flavored e-cigarettes (real-world)	Real-world MA ban or federal ban on menthol cigarettes
1) Quit…	• Vaping flavored e-cigarettes; quit all vaping	• Quit smoking menthol, quit smoking
2) If continue to vape any kind of ecig, reduce use	• Vape less frequently/intensely	• Smoke less frequently/intensely
3) Switch to or continue to use…	• Unflavored e-cigarettes • Different tobacco product (e.g. cigarettes)	• Non-menthol cigarettes • Menthol e-cigarettes • Unflavored e-cigarettes • Different tobacco product (e.g., cigars) • (hypothetical- flavored ecigs)
Also ask about: Efforts to circumvent bans/ change in perceptions/ response to hypothetical ban		

Table 5. Summary of behavioral response outcomes from quasi-experimental study on smoking and vaping behaviors.

We selected our states so as to have a good representation of states that passed a flavor ban and those that did not. Table 6 shows that we have three groups plus Massachusetts alone, showing whether they ban menthol, ban e-cigarette flavors, or have Tobacco 21 laws.

Groups/ States	States (names or number of)	Cigarette Menthol Ban	E-cigarette Flavors Ban	Tobacco-21 Laws	Vapers (N obs.)	Smokers (N obs.)
MA	MA	X	X	X		1000 from MA 500 from NJ, NY, RI
Group 1	MA, NJ, NY, RI		X	X	1000	
Group 2	13+DC			X	500	500 from Groups 2 & 3 Combined
Group 3	33				500	

Table 6. Survey group characteristics for quasi-experimental study of flavor bans and Tobacco 21 laws.

By comparing pre- and post-ban results across state groups, we can identify the impact of flavor bans on smoking and vaping. Similarly, we can identify the impact of a menthol cigarette ban on smoking and vaping by comparing across states, given that only Massachusetts has passed a menthol cigarette ban. In regressions, we can control for policy groupings and interactions; in essence, comparing states with flavored e-cigarette bans and Tobacco 21 laws versus states with only Tobacco 21 laws.

We will use separate analyses for the sample of smokers and vapers, and control for dual use. We can use logit, ordinal logit or multinomial logit , depending on the outcome (binary, multivariate). We will estimate linear regression models such as:

$$Y_i = \beta_x X + \delta_z Z + \varepsilon_i$$

where

Y_i is pre/post vaping or smoking, or changes in risk perceptions or hypothetical response.
β_x, is set of estimated impact of each control variable.
X_i is the set of 1) individual socio-economic/demographic characteristics and the history of smoking or vaping; 2) state fixed effects (sensitivity analyses); and 3) COVID-19 or EVALI factors.
δ_z is the set of estimated impacts
Z is the set of policy variables or groups of states.
ε_i is an error term assumed to be normally distributed.

Control variables include smoking and vaping histories, socio-economic and demographic status (e.g. age, gender, race, ethnicity, education, income), and other state tobacco policies and characteristics. We may also consider other state characteristics such as unemployment, poverty, race and others.

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Questions and answers

Q: How well do the results of discrete choice experiments predict actual health-related behaviors? In other words, how good are these DCEs at estimating what users actually might end up doing in one scenario or another?

A: The problem is that it's actually hard to know. For example, our discrete choice experiments were conducted when there were no flavor bans, and so we could not compare those results to the true impacts because we haven't seen any "true results". There is not an estimate of the impact of a federal e-cigarette flavor ban in the United States. The perfect counterfactual doesn't exist. Our results from discrete choice experiments may differ from expert opinions, but we can see if they're different, and we still don't know which is the correct or true outcome.

Expert Elicitation – Insights and Lessons Learned

Aylin Sertkaya, PhD, Eastern Research Group

Abstract

This presentation provides an overview of the expert elicitation (EE) process and its use in tobacco control, together with guidelines for employing expert elicitation and lessons learned from past projects involving its use.

Introduction

Expert elicitation (EE) is a structured method of systematically synthesizing the opinions of experts where there is uncertainty due to insufficient data/information. It is a heuristic scientific consensus method that can be quantitative or qualitative. This presentation will discuss insights and lessons gained from conducting expert elicitations for dozens of research projects commissioned by federal agencies.

Expert elicitation can be used to quantify ranges for poorly known parameters but can also be used to address qualitative issues such as definitions, assumptions, and causal models. The application areas for expert elicitations are quite diverse and range from nuclear engineering and forecasting environmental risk assessments to health technology assessments for pharmaceuticals.

The use of formal expert elicitation dates back to the 1950s. Since the early 1970s, decision analysts, modelers, economists, and others in the private and public sectors have used formal expert elicitations to obtain expert judgments to gather data not accurately known or available in an effort to put together the structure of the models, to develop causal relationships in complex economic or social phenomena, and to prioritize objectives.

There are many technical, administrative, political and procedural factors that influence the decision to conduct an expert elicitation, and for a given project, one needs to consider several factors when deciding whether to conduct an EE. According to the US Environmental Protection Agency (2009), some examples of when expert elicitation is desirable are when:

- Data of suitable quality is unavailable or unobtainable.
- Evidence and/or models are conflicting.
- Experts and financial resources to perform an expert elicitation are available.

Conversely, factors that make this less desirable include:

- When empirical data exists with a high degree of consensus.
- Insufficient expertise is available.
- Other less intensive and expensive methods for obtaining the information are available.

The expert elicitation process

Figure 1 shows an example of what a sample expert elicitation process looks like. There are a variety of expert elicitation protocols, but there is no universally accepted method. The method adopted often needs to be customized to the needs of the study, and this is usually an iterative process.

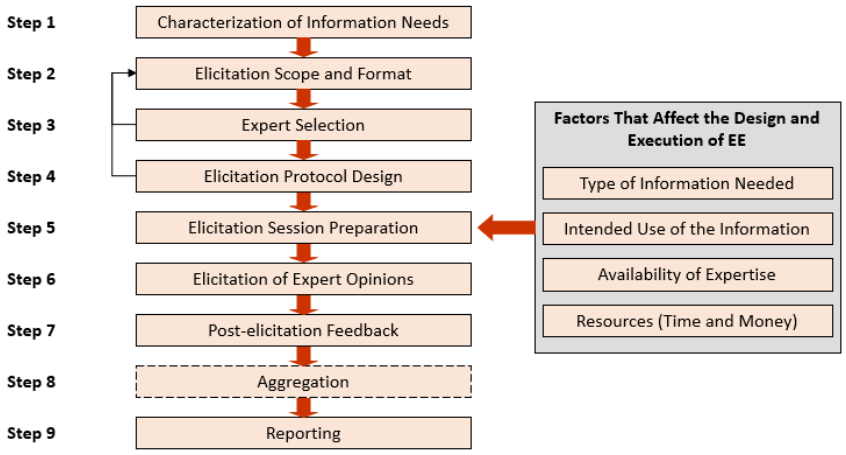

Figure 1. Overview of an expert elicitation process. (Source: Knol, Slottje, van der Sluijs et al. 2010)

The steps shown in this figure describe good practices, but the process of expert elicitation should not be approached as a routine procedure amenable to cookbook solutions. Each elicitation should be considered a special case and dealt with on its own terms.

Table 1 shows some examples of the use of expert elicitation in tobacco control research. These cover a wide range of topics and vary significantly in the number of experts used, the adopted protocol for the expert elicitation, the mode of administration, and the aggregation method.

Study	Objective	Type of EE	Expert Uncertainty	Number of Experts	Protocol	Mode	Aggregation
Trochim et al., 2003	To develop a conceptual framework that describes the tactics the tobacco industry uses to undermine tobacco control programs	Qualitative	Not assessed	34 (online); 13 (face-to-face)	Nominal Group Technique / Kaplan Method	Online & Face-to-face	Behavioral
Levy et al., 2004	Assess the relative risk of use of LN-SLT compared with cigarette smoking with respect to mortality, lung cancer, heart disease, and oral cancer	Quantitative	Self-assessed	9	Delphi (3 rounds)	Questionnaires	Mathematical (linear pool)
Pechey, Spiegelhalter and Marteau, 2013	To estimate the likely impact of plain packaging of tobacco products on smoking prevalence in adults and the percentage of children trying smoking	Quantitative	Self-assessed	33	Semi-structured Interviews	Telephone	Mathematical (linear pool)
Apelberg et al., 2018	To estimate the effect of reducing nicotine in cigarettes to minimally addictive levels on rates of cigarette-smoking cessation, switching from cigarette smoking to products excluded from the policy, dual use, cigarette-smoking initiation, and initiation of products excluded from the policy	Quantitative	Self-assessed	8	Delphi (1 round)	Questionnaires	Mathematical (linear pool)
Levy et al., 2021	To estimate the transitions from cigarette use to other combustible tobacco product, smokeless tobacco, novel nicotine delivery product use, or no tobacco use under a federal menthol cigarettes and cigar ban	Quantitative	Self-assessed	11	Delphi (2 rounds)	Questionnaires	Mathematical (linear pool)

Table 1. Examples of expert elicitation studies used in tobacco control.

The first study in this table is the only qualitative expert elicitation study versus the others, which were used to develop quantitative estimates. Its authors used expert elicitation to develop a conceptual framework to describe and categorize the different strategies the tobacco industry uses to undermine tobacco control programs. They also used behavioral aggregation by bringing the experts together after the first part of the elicitation to reach a consensus on this conceptual framework. Conversely, the fifth study, which the author was

personally involved in, was a quantitative expert elicitation aimed at getting transition probability estimates for use in tobacco simulation modeling. to estimate transitions from cigarette use to other tobacco products under a federal menthol cigarettes and cigars ban. The study included 11 experts and used self-administered questionnaires, using the Delphi method with two rounds, and expert responses were aggregated with equal weights using mathematical aggregation.

Some other examples of expert elicitation used in other areas include:

- The US Food and Drug Administration (FDA) has employed EE to estimate the frequency of inappropriate food handling practices in households and retail establishments by type of food, and to formulate a model of *Salmonella* transmission in tomatoes, as well as estimate the relative effectiveness of a range of tomato pre- and post-harvest practices in reducing the likelihood of salmonella contamination.
- The US Environmental Protection Agency (EPA) has used EE to determine particulate matter (PM) response for mortality, and to perform regulatory impact analysis of final PM National Ambient Air Quality Standards.
- The Intergovernmental Panel on Climate Change (IPCC) has used EE to address specific components of the climate change issue, including biomass, temperature gradient and others.

Five lessons for expert elicitation

Lesson 1: Select experts carefully

Who takes part in an expert elicitation can greatly affect its outcome and acceptability in the wider community. Generalists have substantial knowledge in a relevant discipline and a solid understanding of the context of the problem, and these types of experts are useful to include in elicitations involving context or model structure uncertainty, especially those where the problem is multidisciplinary in nature.

There are also subject matter experts, who are authorities in a given field of expertise and are useful to include in elicitations that require subject specific information, such as model parameters. And then there are normative experts, who have knowledge and practical experience that can support the elicitation; these are individuals with specializations in decision analysis, statistics, economics and psychology.

It is important to have a well balanced panel when there is a high degree of value diversity, high stakes, or when the results need to be accepted by a wide peer community. It is preferable to use a formal selection procedure to ensure that opposing views are presented on the panel. Common approaches to identifying experts include agency recommendations, literature reviews, citation analysis, and the use of the snowball approach, where you identify a few experts first and then allow those experts to recommend other experts.

In putting the panel together, one needs to recognize that understanding the body of available information is important but not sufficient to serve as an expert on an expert panel; Intuition and the ability to integrate information beyond the reported data are also very critical.

Lesson 2: Select an optimum number of experts

There is no absolute guideline on the number of experts to solicit for an expert panel. Two recent studies examined this, as shown in Figure 2, and concluded that the optimum number of experts for a panel ranges from as low as six to as high as 22 experts. However, one needs to be cognizant that there could be diminishing marginal returns for including additional experts in an expert elicitation, and the general feeling

among many practitioners is that beyond 12 experts, the benefit of including additional experts drops off sharply.

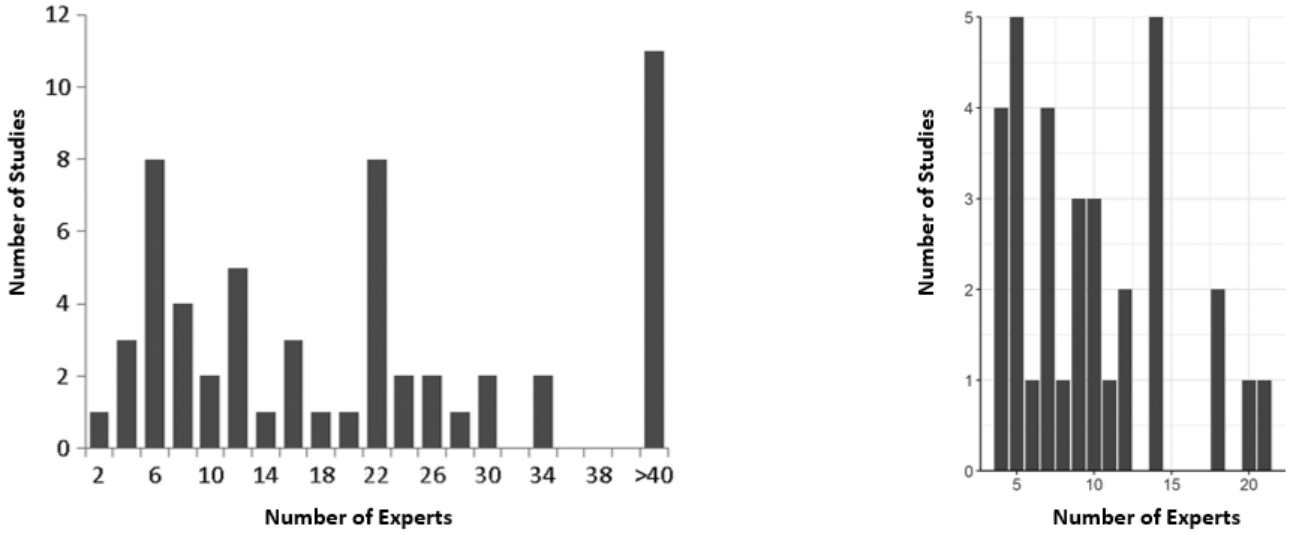

Figure 2. Two summaries of number of experts versus number of studies. (Sources: Butler, Thomas and Pintar, 2015; Colson and Cooke, 2018)

Lesson 3: Avoid the use of qualitative terms

The wording of questions and use of qualitative terms in an expert elicitation needs very careful consideration. Quantitative probability associated with a qualitative term varies significantly from expert to expert. For example, in one case when members of the Executive Committee of the EPA Science Advisory Board were asked to assign numerical probabilities to uncertainty words that had been proposed for use with EPA cancer guidelines, the range for terms such as "likely," "not likely," and "somewhere between likely and not likely" varied widely (Morgan, 2014).

This is also a reason that pre-testing of questions is highly recommended; slight phrasing of the same question has been shown to lead to differences in responses.

Lesson 4: Beware of heuristics and biases

Experts use various heuristics when judging certain information, and this may result in biases. All of us use heuristics in making judgments, not just experts. Some forms of bias include:

- Availability bias, which arises if the expert is affected by the ease of recall or the memory of recent experience.
- Anchoring and adjustment refer to the phenomenon of experts selecting a starting point as a first approximation and then adjusting this value to reflect supplementary information. Results end up being biased toward the anchor.
- Representative bias refers to inappropriate generalization of specific knowledge.
- Overconfidence leads to estimates that have narrow spread when, in fact, the true spread is larger, and this may be reduced by asking about high and low values before asking about the central tendency.

- Hindsight bias refers to the tendency of people to exaggerate the predictability of reported outcomes because they fail to think about how things could have turned out differently.
- Motivational bias arises when the responses are influenced by factors such as moral or professional responsibility, legal liability, or peer credibility.

Therefore, it is important to mitigate or minimize biases resulting from the use of heuristics in making judgments. Some ways to address this described by Kynn (2008) include:

- Familiarize the expert with the elicitation process.
- Use familiar measurements and ask questions within the expert's areas of expertise.
- Decompose elicitation into small distinct parts; perform combinatorial exercises using a computer.
- Be specific with wording – use a graphical representation if possible.
- Do not provide example numbers for the expert to anchor to.
- Ask the expert to discuss estimates and give evidence for and against.
- Provide feedback and allow the expert to reconsider.

Lesson 5: Prepare experts for the elicitation

To fully engage experts and to minimize attrition, and this is especially relevant for experts in situations involving large panels, it is important to prepare the experts for the elicitation. One should introduce the scope and purpose of the study. This may be provided in a briefing book that contains the outline of the nature of the problem, key literature or a summary of the literature, information about the expert elicitation procedure itself, and also information on heuristics and biases.

One may also provide training on how to think about probabilities and how to avoid biases. And it's also important to provide post-elicitation feedback, which can be instantaneous while the expert is completing the questionnaire if it's online, or it could be delayed after they've completed and submitted their responses. This allows the expert to reflect on their responses and make any adjustments needed.

In the expert observations that we have done, we have found that instead of providing a long briefing book, holding training webinars to familiarize the experts with the scope and format of the situation worked better in terms of engaging experts and minimizing attrition.

Additional insights

In closing, some additional insights for the expert elicitation process include the following:

- Expert responses can vary, and performance weighting of expert responses (aka classical model) performs better than equal weighting but only slightly.
- The jury is still out on different elicitation methods (Delphi vs. nominal group technique vs. decision conferencing, etc.).
- Expert elicitation is well suited for situations involving complex technical problems, unobtainable data, and conflicting conceptual models.
- Expert elicitation is not a substitute for rigorous empirical methods.
- Understanding the sources of differences between experts can lead to insights, consensus, and/or revision of the elicitation protocol, which in turn may be more valuable than any aggregate finding.

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Questions and answers

Q: For expert elicitation studies done by your group, I would like to hear more details on how diversity of expertise is insured. Specifically, I worry about how the use of traditional academic publication matrices, such as the h-index, will tend to produce experts who are older, whiter and male.

A: We do try to be cognizant of that, even though we have used the h-index and other similar methods. Ultimately, it's important to take a look at the composition of your panel and whether it's in balance – one person might have a high h-index, but you might opt to exclude them to introduce more diversity into your panel. As with anything in expert elicitation, that is a subjective determination done by the researchers and in collaboration with the agencies that are responsible for the studies.

Q: If the ranges are too varied, perhaps the results are not very helpful. So what is the usual practice to aggregate the values - do you use mean, median or another approach? How do you handle outliers?

A: We have never resorted to removing outliers; the reason that you select the expert to serve on the committee is because they have the relevant and applicable expertise. But in terms of aggregating responses, typically means and medians are used in a linear pool, and sometimes you might want to use a logarithmic pool. At other times, and this is actually a good practice in terms of reporting experience, you don't aggregate the responses; you report anonymized responses for each expert. Then possibly those are going to be used in, for instance, the modeling study – you can introduce some sort of a Monte Carlo simulation that would cull from different experts' responses rather than an aggregated expert response.

An Experimental Model of the Tobacco Marketplace

Warren K. Bickel, PhD
Addiction Recovery Research Center, Fralin Biomedical Research Institute, Virginia Tech

Abstract

This presentation introduces an experimental tobacco marketplace (ETM) model, which can be used to forecast the effects of new products and policies. This model involves live subjects making actual product purchases based on model assumptions.

Results are presented for five studies using the ETM model, modeling cigarette price and/or policy changes, three of which also studied illegal purchases following reduced nicotine standards or vaping bans.

Introduction

Tobacco control would benefit from estimates of the impact of new policies and products. No current method can adequately estimate the effects of a new regulation or tobacco product on the patterns of consumption and substitution. We have developed a new experimental method to examine the dynamic tobacco marketplace and forecast the effects of new products and policies, which we call the *experimental tobacco marketplace (ETM)*.

We organize these studies by taking cigarette smokers and other tobacco users and endowing them with as much money as they typically spend on their tobacco products. We then put them into an Amazon-like interface where we control all the products, all the prices and the conditions of their availability. The subjects will then work through several potential decision-making scenarios, one of which will then be randomly selected and actually made to come true, with the subject walking away with those products and any unspent money that we had allocated to them. We then typically follow up with them later, and they can return any unused product and get compensated for the return of those products.

What we are interested in are measures of elasticity, both intensity and demand elasticity – the sensitivity of subjects to a product's price and also substitution behavior. In this sense, we are talking about economic substitution: as we increase the price of a conventional product do we see another product that remains at a constant price show an increase in uptake? That would indicate a degree of substitution, and we can measure that degree.

The methods for these in-person laboratory studies involve doing an assessment session, exposing people to the products that they may not be familiar with, then engaging in ETM sessions under several scenarios. One of these scenarios will come true, they will walk away with product that they can use in their real world environment, and then we will follow up with them. We can then repeat the cycle several times if needed for a given experiment.

So why a complex experimental tobacco marketplace? Because the type and number of products in the marketplace alters demand elasticity and substitution. Figure 1 shows such an example from one of our studies.

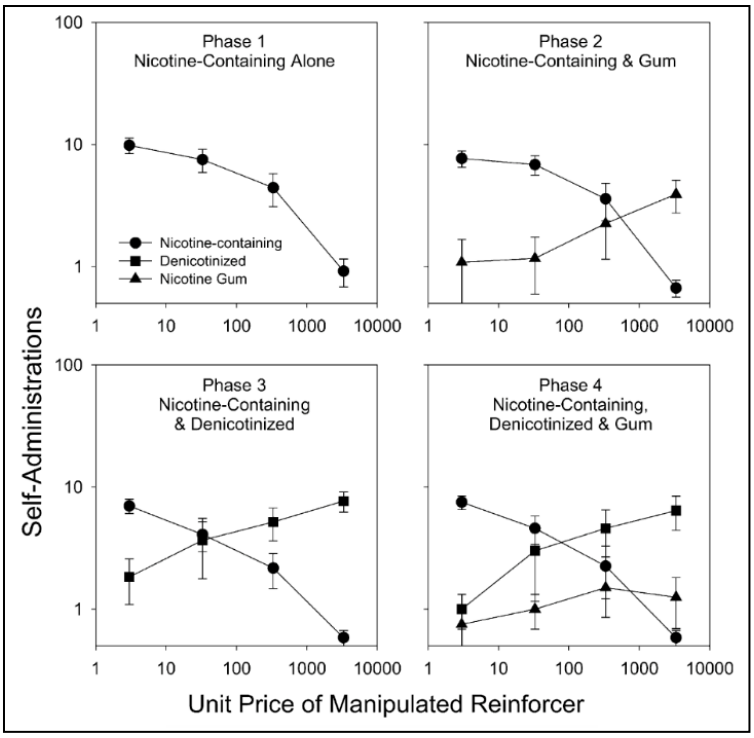

Figure 1. Demand elasticity and substitution for multiple tobacco products.

Example studies

Here we present examples of five studies using the ETM, two of which involve modeling increases in cigarette price and/or policy changes, and three of which involve illegal purchases following reduced nicotine standards or vaping bans.

Experiment 1: Effect of e-cigarette nicotine strengths on substitution

This was a study involving 25 smokers (within-subject), measuring cigarette and e-cigarette purchases across five prices of conventional cigarettes and four different e-liquid strengths (0, 6, 12, & 24mg/mL). Key findings, as shown in Figure 2, were as follows:

- Cigarette purchasing decreased as a function of cigarette price.
- E-Liquid purchasing increased as a function of both cigarette price and e-liquid strength.
- The 24 mg/mL e-liquid appears to function as the best substitute for cigarettes.

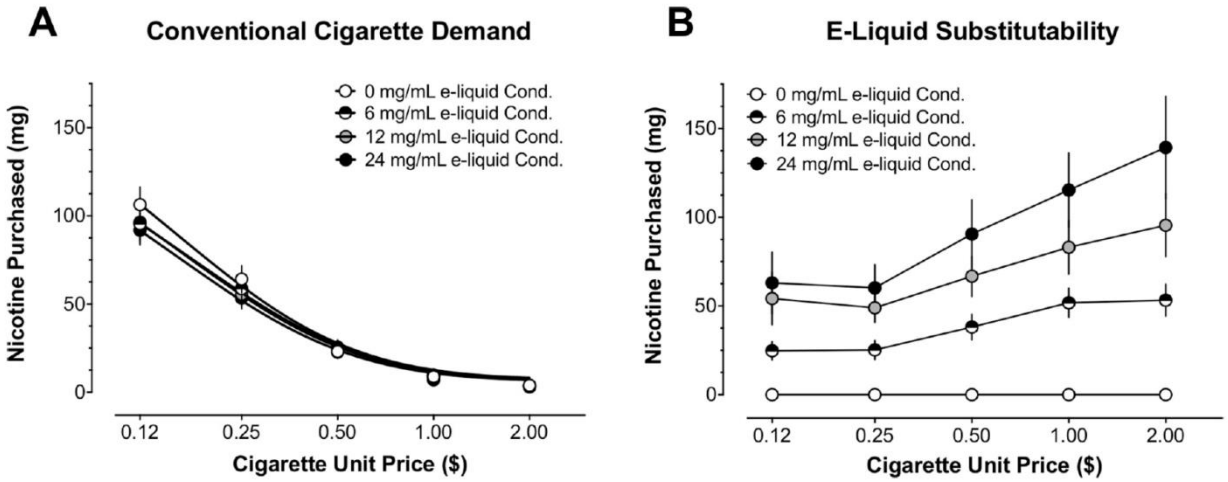

Figure 2. Conventional cigarette demand and e-cigarette substitutability across multiple cigarette prices. (Source: Pope et al., 2019)

Experiment 2: Integrated tax policy

This study involved 35 online smokers (within-subject), comparing tobacco parity taxation to harm reduction taxation. Tobacco parity taxation would impose a higher tax equally on all tobacco products other than medicinal nicotine or cessation products with the goal of encouraging cessation of all tobacco purchasing, while a harm reduction tax proposal would levy taxes in proportion to the product's level of harm, with the goal of transitioning tobacco users away from the most harmful products.

Subjects purchased products across 6 multiplicative tax factors. Key findings, as shown in Figures 3 and 4, were as follows:

- The total amount of nicotine(mg) purchased from tobacco/medicinal products was not significantly different between these two proposals.
- Higher taxes yielded lower overall demand.
- The tobacco parity proposal decreased purchasing of all tobacco products and increased purchasing of medicinal nicotine.
- The harm reduction proposal decreased purchasing of combustible products and resulted in greater purchases of ENDS and smokeless tobacco products.

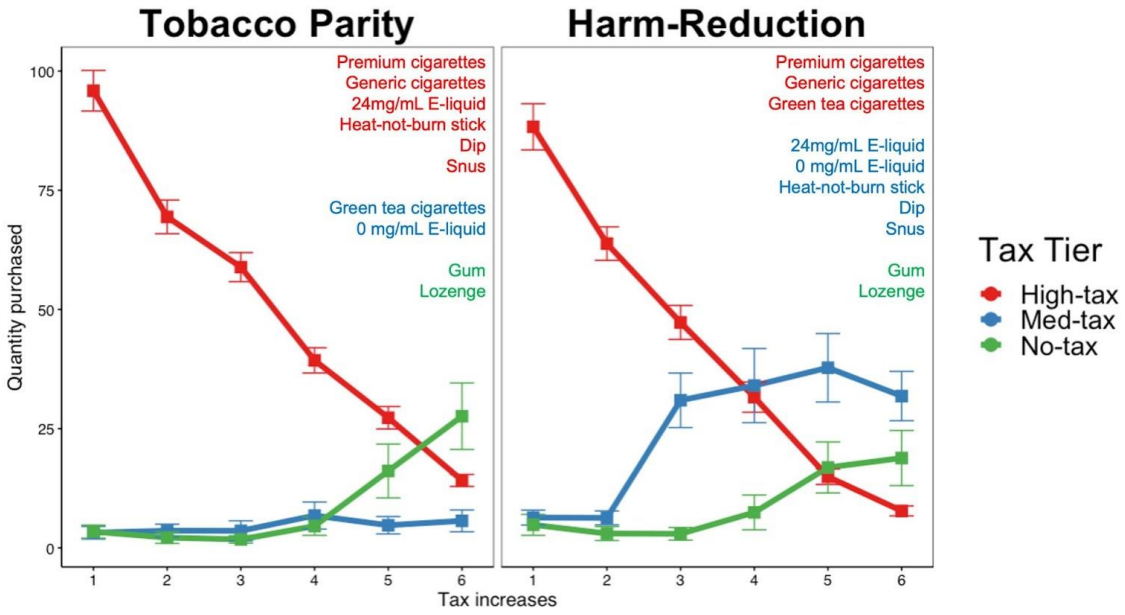

Figure 3. Product purchases versus tax level for tobacco parity and harm-reduction taxation. (Source: Freitas-Lemos et al., in submission)

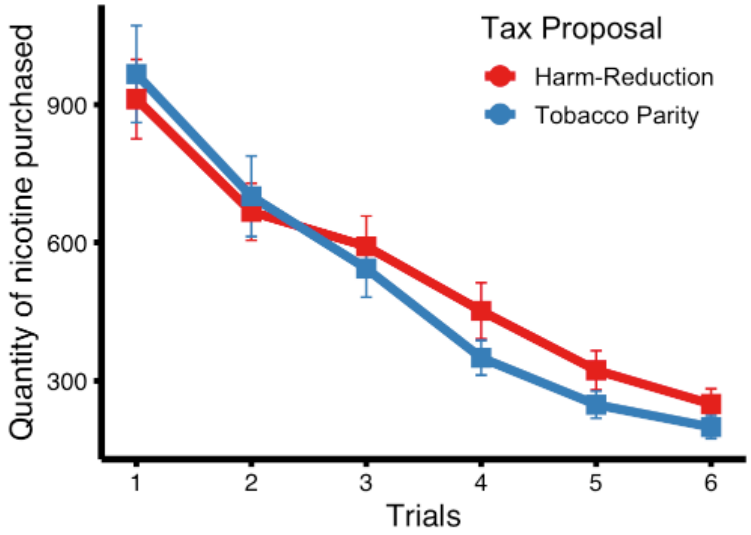

Figure 4. Quantity of nicotine purchased versus tax level for tobacco parity and harm-reduction taxation. (Source: Freitas-Lemos et al, in submission)

Experiment 3: Effects of reduced nicotine standards on illegal purchases

This is the first of three experiments presented here that involved an illegal experimental tobacco marketplace. Illicit trade in tobacco products is ongoing, and these products may contain adulterants not found in commercial products. The efficacy of mitigation strategies is unknown in this case, and there is an absence of empirical models.

This experiment involved 52 online smokers (between subjects) and compared purchasing decisions of very low nicotine legal cigarettes versus conventional cigarettes, measuring marketplace preference across five price trials. Key findings, summarized in Figure 5, were that price and product standards can alter substitutability between legal and illegal marketplaces and products.

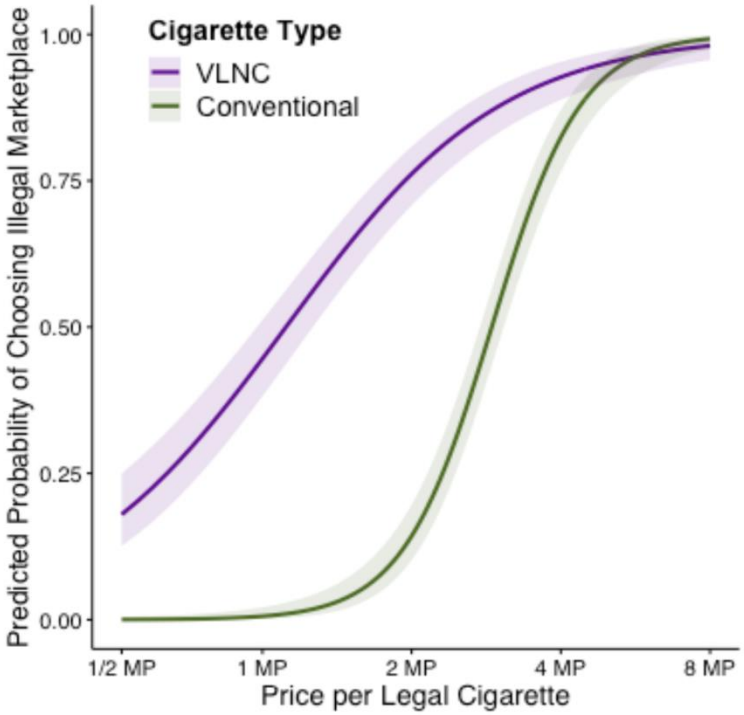

Figure 5. Probability of choosing illegal tobacco products by legal cigarette price, for VLNC and conventional cigarettes. (Source: Freitas-Lemos et al., manuscript in preparation(1))

Experiment 4: Effects of vaping bans on illegal purchases

This study involves 150 online smokers, e-cigarette users, and dual users (within-between subjects), examining purchases in the cases of no vaping ban, a full vaping ban, and bans on vaping of flavored products, as well as the impact of monetary fines for illegal purchases. Key findings, shown in Figures 6 and 7, were as follows:

- Bans increased illegal purchases, with the largest effect among exclusive e-cigarette smokers.
- Increasing cigarette price increased illegal purchasing, with the largest effect among exclusive cigarette smokers and dual users.
- The vaping ban produced greater illegal purchases as compared to the flavor ban.
- Monetary fines suppressed illegal purchasing, with exclusive e-cigarette users being the most resistant.

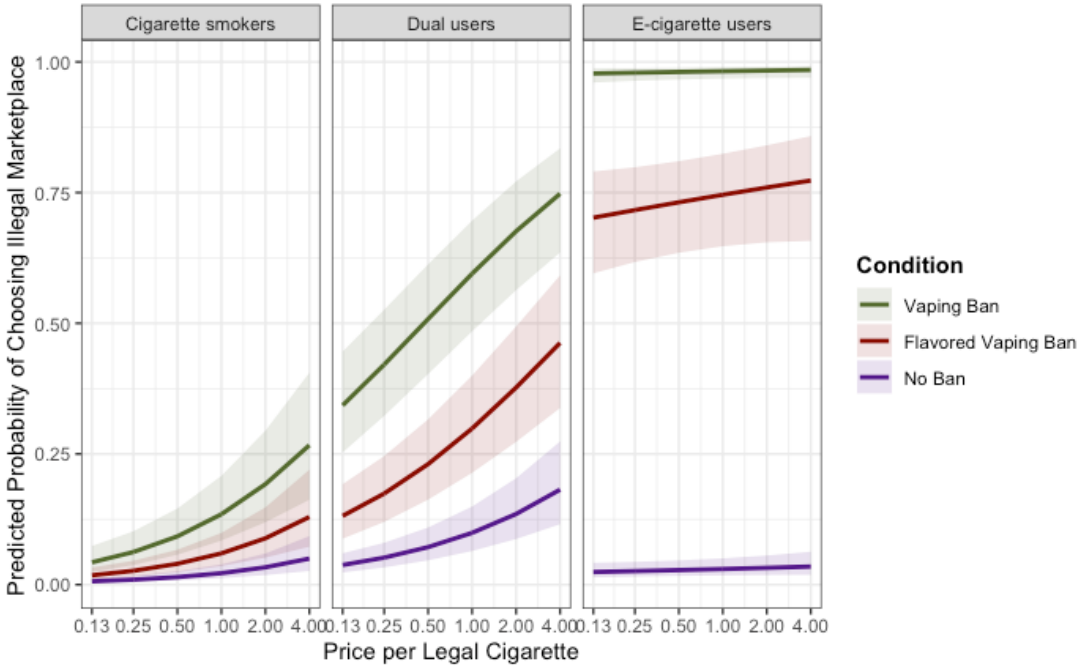

Figure 6. Predicted probability of choosing illegal marketplace by legal cigarette price, by vaping ban status. (Source: Freitas-Lemos et al., 2021)

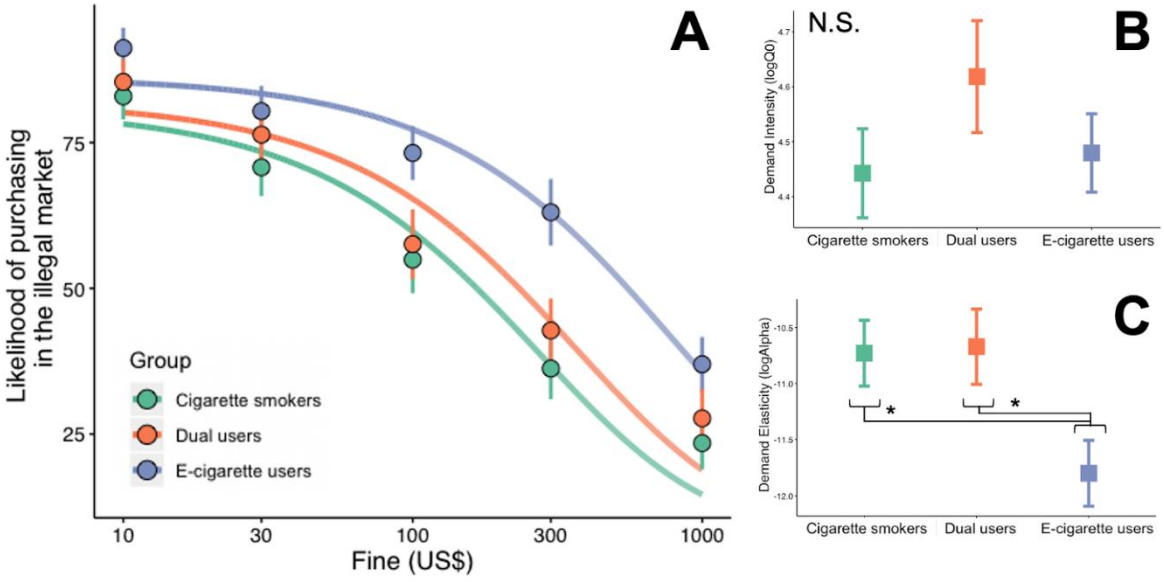

Figure 7. Impact of monetary fines on illegal tobacco purchases. (Source: Freitas-Lemos et al., 2021)

Experiment 5: Effects of vaping bans on illegal purchases – a systematic extension

This study extended the previous study to a sample of 452 smokers, e-cigarette users, and dual users from the US, Canada and England, using data from the ITC project. It examines the predicted probability of choosing illegal products across cigarette price levels, under the conditions of no ban, a vaping ban, a total flavor vaping ban, and a partial flavor ban.

Figure 8 shows that overall, across all three countries, we see the same general rank order of the impact of these different conditions engendering illicit purchases. However, we also see some clear country differences. This shows that we can get generalizable results from our more basic laboratory arrangement to broader groups of individuals across different countries, but can also be sensitive to local environments.

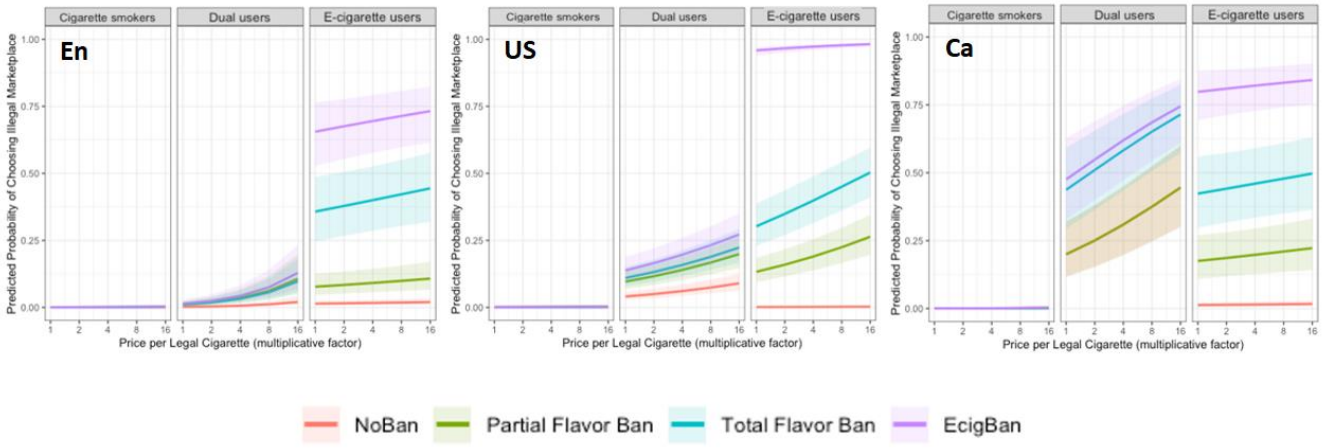

Figure 8. Projected probability of choosing illegal marketplace across tobacco use type and price in England, US and Canada. (Source: Freitas-Lemos et al., manuscript in preparation(2))

Conclusions

The experimental tobacco marketplace assesses the impact of policy on tobacco product demand and substitution. As we have shown here, it can be adapted to address a variety of questions of relevance to tobacco control. It can assess the generalizability of policy impact across different countries, and we believe that it could be a useful tool for tobacco control, regulatory science, and the modeling of future policies.

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Questions and answers

Q: When you look at the demand curve for cigarettes and the demand curve for alternatives like e-cigarettes with a taxation scheme where they tax them comparably versus one where you have a lower tax for the ENDS product, what happens to the overall demand for cigarettes at any given price? When we have differential taxation, do we see a greater decrease in demand at any given price?

A: These were all conventional cigarette smokers, so although we had these other products in the category, they were primarily using conventional cigarettes. What we did see at the initial tax increases was a move away from premium to more generic cigarettes, and then you can see at what point they finally sort of give up and start purchasing alternative products. So it varied by the type of tax condition and what the alternatives are.

Clearly with harm reduction, there was an earlier transition to products that we had in the mid-tax tier. And since there was really no nicotine available in the tobacco parity taxation in that tier, it took a little bit longer, and then we saw more transition to the nicotine. We are showing substitution, and with the differential pricing, the demand curve is actually lower when we have the harm reduction schema.

Q: What kind of information did respondents receive about the illegal market? You mentioned fines, but I'm wondering if to the respondent, are there any perceived negative consequences to purchasing through the illegal market, or barriers to accessing that illegal market?

First, this was an initial experiment. The number of things that we could potentially manipulate are innumerable. For example, we could put in a delay to receipt, or a probability that the product that you purchased is not actually the product that you receive in the illicit market, or that the quality of the product is lower. What we've done in these conditions is just to explain that this is an illicit market that has all the risk associated with illicit market purchase.

In a subsequent experiment, which was not presented here, we asked people if they purchased, how it would be? We did the profile of negative mood states and asked what would happen if you got caught? Then we measured the increase of negative mood states. So we take that the concept of buying from the illegal market is not without consequence for the consumer.

Of course, that could be amplified in any of these contexts as well by saying, for example, maybe you will become known to the authorities as an illegal purchaser. Your name could be put on a public website. And that's what we love about the experimental tobacco marketplace. It is robust in the number of things that we can explore, and the only thing that is thwarting us is our own creativity.

Generating Models Before Generating Parameters: A Bayesian Network Approach

Ray Niaura, PhD, NYU College of Global Public Health

Abstract

This presentation examines two examples of generating models for tobacco control, using a propensity score analysis and a Bayesian network model for modeling the association of e-cigarette use and cigarette smoking among youth using PATH data.

Introduction

This presentation discusses modeling strategies for tobacco control, using a running example involving high dimension data in the Population Assessment of Tobacco and Health (PATH) study youth sample, looking at the association of e-cigarette use and cigarette use longitudinally across the first three waves of data.

Our first example is a variation of propensity score analysis used to deal with the multitude of covariates assessed at baseline. Next, using exactly the same data set, we will talk about Bayesian networks to illustrate other approaches to data analysis. One advantage of Bayesian networks is structure learning, which basically means learning how these variables are associated with one another, providing insight about potential confounding variables. Finally, we will discuss whether identifying potential confounders tells us the whole story that we might want to know.

Example: An entropy balancing propensity score analysis

This first study (Xu et al., to appear) utilized what is called an entropy balancing approach to handle a multitude of covariates. Figure 1 shows the design of the analysis, in which we selected tobacco naive youth at Wave 1, classified exclusive e-cigarette users at Wave 2, and then looked at past 30-day cigarette smoking outcomes at Wave 3.

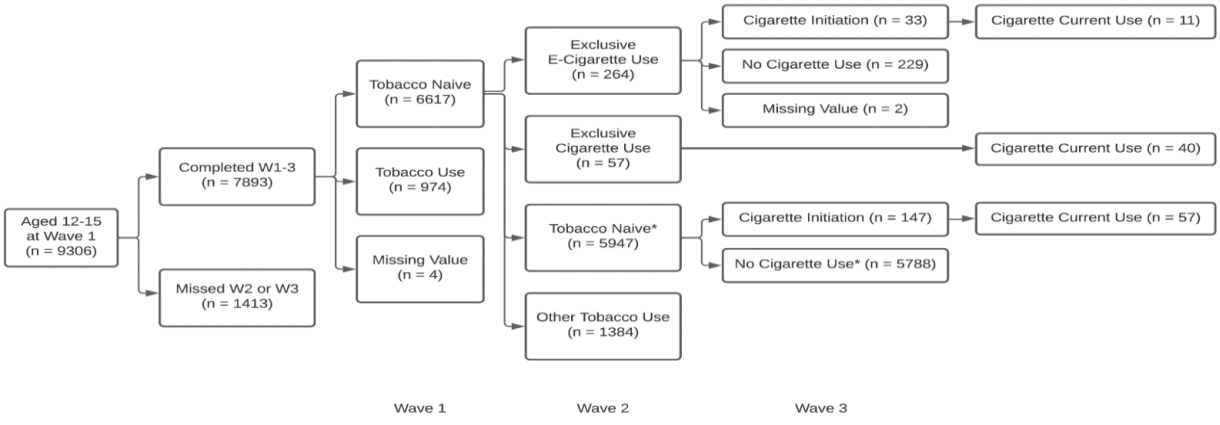


Figure 1. Design of propensity score analysis, based on PATH data.

The exposure was e-cigarette use at Wave 2, the outcome is past 30-day cigarette smoking at Wave 3, and we identified 55 pre-exposure, potentially confounding covariates at Wave 1, which is baseline. These include self- or parent-reported factors including sociodemographic (e.g., sex, race), interpersonal (e.g.,

depression, impulsivity, medical history), behavioral (e.g., alcohol use, drug use) and social environmental (e.g., living with smokers, parental monitoring) factors.

We then employed an entropy balancing approach, which is a multivariate reweighting method that adjusts the weight of each participant so that the covariate distributions in the reweighted data achieve balance (i.e., mean and variance), which obviates the need for propensity score matching. Survey weights were included in the model for estimating entropy balancing weights. This worked very well, getting a complete balance on all of the 55 covariates or potential confounders; standardized mean differences (SMD) of all 55 confounding variables after entropy balancing were close to zero.

Table 1 shows results from the outcome of the analysis, with the effects of initial e-cigarette exposure on tobacco-naive youth, and then one year later, on past 30-day cigarette use. When we perform this analysis with sampling weights only, the odds ratio for the effect of e-cigarette use on subsequent cigarette use is 5.16, and after we do the entropy balancing, that odds ratio decreases to 3.67. In a subsequent analysis examining the predictive power of initial cigarette use on continued cigarette use one year later, an odds ratio of 47.23 decreases to 21.98 after entropy balancing.

The Effects of E-cigarette Ever Use on Subsequent Combustible Cigarette Use

Outcome	Sampling Weights Only			EB + Sampling Weights		
Sample 1	B	SE	OR (95% CI)	B	SE	OR (95% CI)
Cigarette Initiation	1.79	0.25	5.99 (3.66, 9.78)	1.17	0.34	3.22 (1.65, 6.33)
Past 30-day Cigarette Use	1.64	0.34	5.16 (2.64, 10.03)	1.30	0.51	3.67 (1.35, 10.06)
Sample 2						
Past 30-day Cigarette Use	3.84	0.30	47.23 (26.14 85.34)	3.09	0.41	21.98 (9.86, 49.43)

Notes. EB = Entropy balancing; B: unstandardized regression coefficient; SE = standard error; OR = adjusted odds ratio. The first set of ORs was based on a model adjusted for sampling weights only. The second set of ORs was based on a model adjusted for sampling weights and entropy balancing weights, where the entropy balancing model also used sampling weights.

Table 1. Results for effects of e-cigarette use on subsequent combustible cigarette use, with and without entropy balancing. (Source: Xu et al., to appear)

Bayesian network approach

Next, we will discuss using a Bayesian network approach to analyze exactly the same data used in the previous example. Bayesian networks are a graphical representation of a compact joint probability distribution, showing probabilistic relationships between the variables. So Bayesian networks consist of nodes which are the circles that represent the variables, and arcs that are also sometimes called edges or arrows. An arc indicates that a relationship or association exists between the nodes, and the absence of an arc implies independence between the variables.

A huge challenge with Bayesian networks, as with any modeling, is that the number of potential networks is super-exponential, as shown in Figure 2; even with three nodes, for example, there are 25 possible networks. So if we are going to use tools like Bayesian network modeling to tell a story, we need to make sure that it's possible to do so in the space of algorithmic complexity.

Number of possible networks (models) grows super-exponentially with the number of nodes (variables)

Number of Nodes	Number of Possible Networks
1	1
2	3
3	25
4	543
5	29281
6	3.7815×10^{6}
7	1.13878×10^{9}
8	7.83702×10^{11}
9	1.21344×10^{15}
10	4.1751×10^{18}
...	...
47	8.98454×10^{376}

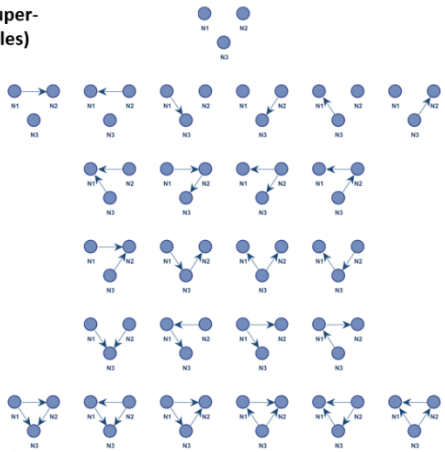
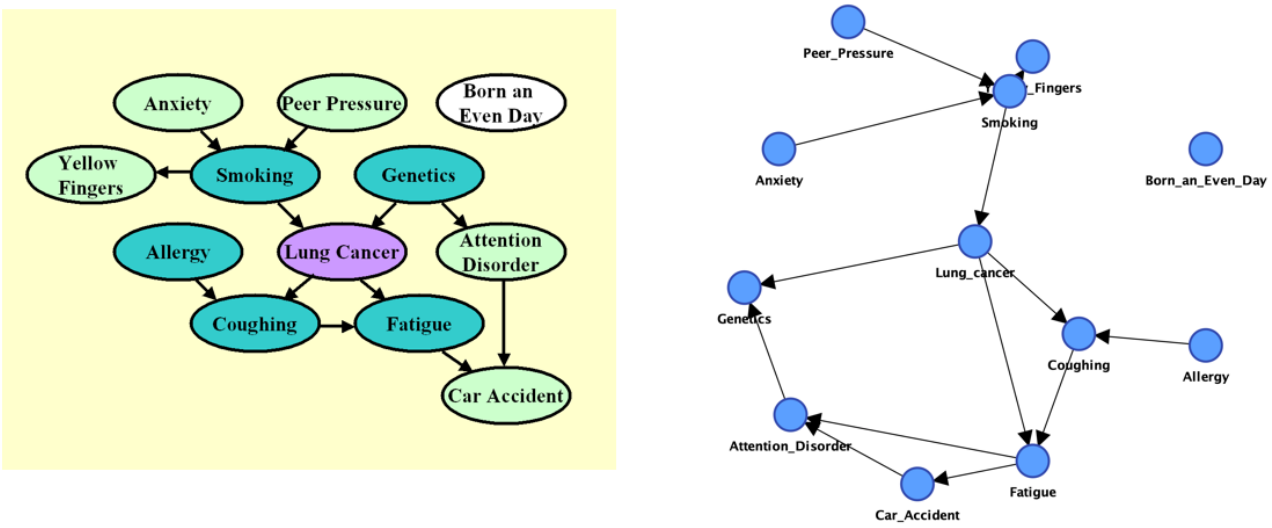


Figure 2. Exponentiality across Bayesian network nodes.

We use BayesiaLab, a proprietary software tool, to do our analysis. BayesiaLab uses algorithms to learn the network structure, so it searches that exponential space and uses score based algorithms - in this case, the minimum description length score that actually balances between model complexity and degree of fit of the data, based on the maximum likelihood estimation. Bayesian networks also support encoding prior knowledge in the network – for example, you can use prior distributions over the network parameters.

Figure 3 shows an example of what BayesiaLab can do. On the left is the data structure from something called the Causal Challenge that was issued several years ago. Researchers were sent this data set and did not know what the structure was, and had to use their favorite machine learning techniques to retrieve the structure. I ran the data through BayesiaLab, and we retrieved exactly the same structure, which is very reassuring because it tells us that the Bayesian networks software is doing its job.



Original Model

Learned Model

Figure 3. Original and learned model from the Causal Challenge dataset used to validate BaysiaLab.

Example: Network analysis using PATH data

Figure 4 shows a depiction of the data for our Bayesian network analysis of PATH data, which is still a work in progress. All of the variables are nodes, where Wave 1 includes all the covariates, at Wave 2 we have the exposure variable, and at Wave 3, we have the outcome smoking variable.

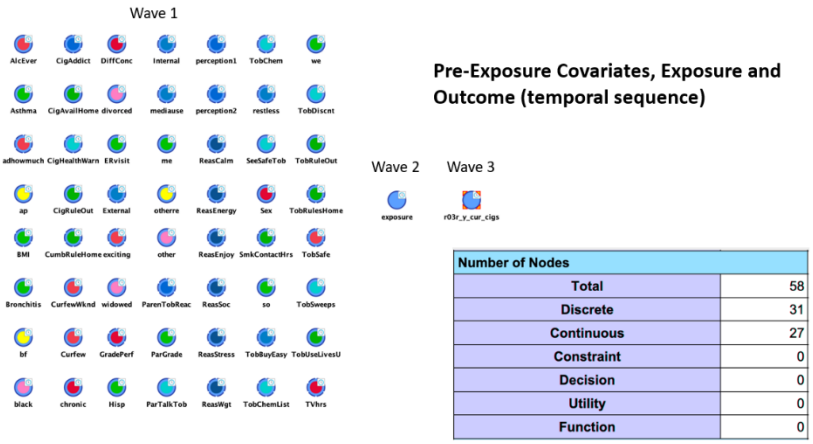


Figure 4. Data for Bayesian network analysis of PATH data.

Figure 5 shows a simple and computationally efficient structure learning algorithm, which is a minimum weight spanning tree, and it shows us that exposure and cigarette use are connected but not directly. There seems to be some variable that connects them. Given the exponentiality we discussed previously, if we are going to use tools like Bayesian network modeling to tell us a story, we need to make sure that it's possible to do so in the space of algorithmic complexity.

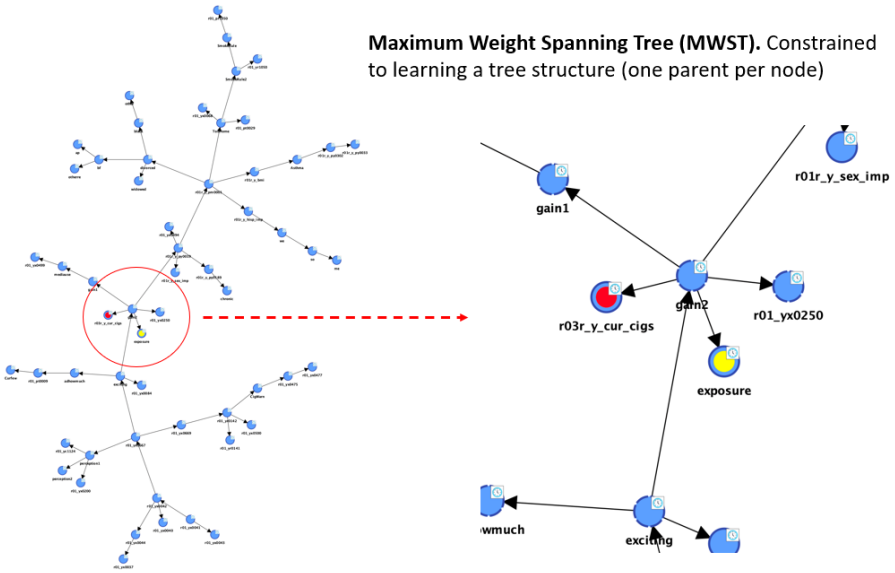


Figure 5. Minimum weight spanning tree (MSWT) relating exposure to e-cigarettes and cigarette use.

Figure 6 shows the results of a semi-supervised learning algorithm, where you can see all the covariates in a jumbled heap interconnected on the left, but then we see that there are connections to both e-cigarette exposure and the outcome. Notice, though, that there is no direct link between exposure and outcome. So we could think about these indirect links as possible confounders.

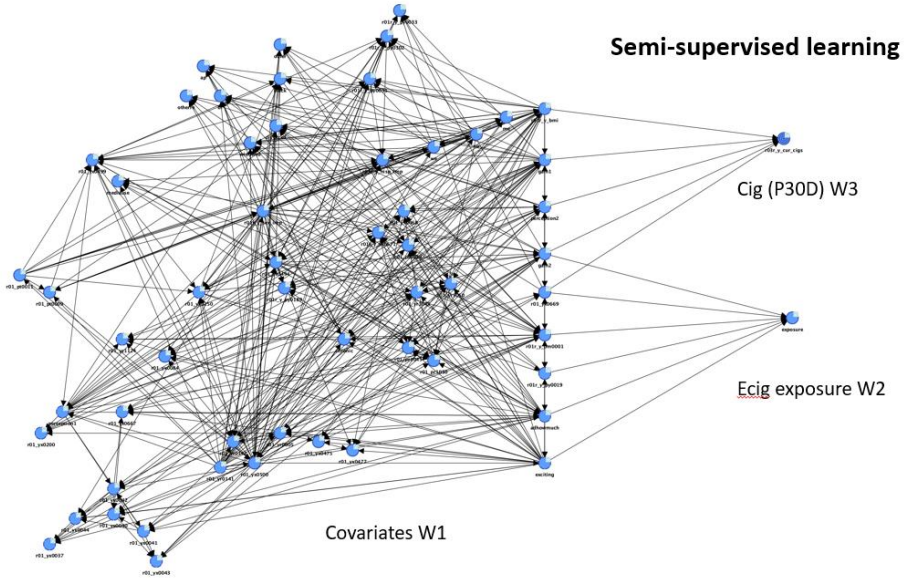


Figure 6. Results of semi-supervised learning algorithm.

Figure 7 shows what we did to simplify the approach, using a probabilistic structural equation model. Essentially, the algorithm clusters the covariates into a set of eight factors that are related to the outcomes themselves, and we were able to specify that there is, in fact, a temporal relationship here.

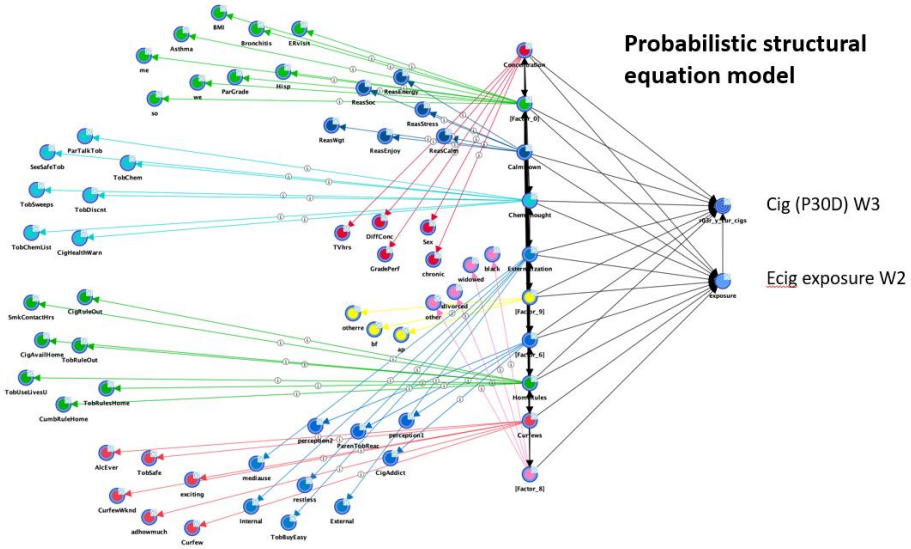


Figure 7. Results of probabilistic structural equation modeling.

Figure 8 shows the same set of data rerun just with the factors, and we see that we now have a direct connection between cigarette exposure and cigarette smoking. But notice that the factors themselves are highly intercorrelated and also have effects on both e-cigarette exposure and the smoking outcome, so these could be considered possible confounders. We have not delved into the true meaning of all of this yet; however this raises a cautionary flag to take a close look at the evaluation of causal modeling.

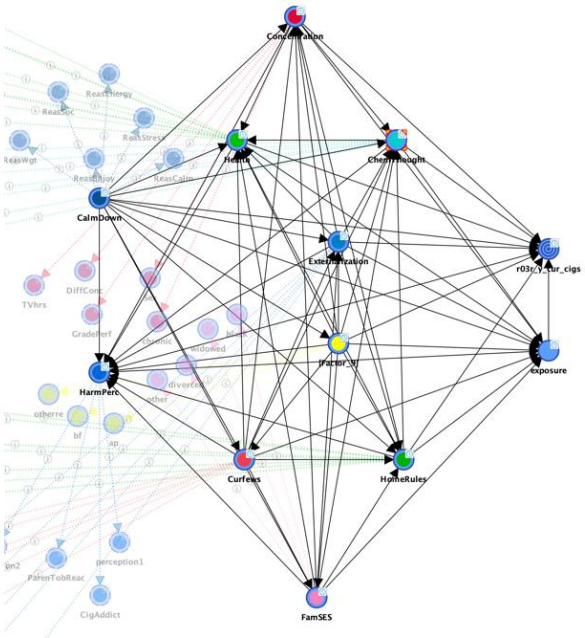


Figure 8. Additional analysis where structure learning was performed with just factors and outcome.

Looking at overall model performance in Figure 9, the short story is that the model does a pretty good job of predicting non-smoking outcomes, but it doesn't do a really good job of predicting smoking, which sounds a little strange, but it's actually true. If we look at our mutual information metric, the effects are very small in terms of shared information here between e-cigarette use and then subsequent smoking (2.65%), although if we did a conventional statistical test, it would be highly significant.

Confusion Matrix

Occurrences | Reliability | Precision

Value	0 (13053434.85)	1 (146010.98)
0 (13150545.09)	99.9348%	72.3359%
1 (48900.73)	0.0652%	27.6641%

Overall Precision: 99.1354%	Mean Precision: 63.7995%
Overall Reliability: 99.0133%	Mean Reliability: 90.8991%
Gini Index: 1.0529%	Relative Gini Index: 95.1818%
Lift Index: 1.0108	Relative Lift Index: 99.9724%
ROC Index: 97.5910%	
Calibration Index: 89.9159%	
Binary Log-Loss: 0.0279	
R: 0.5843	RMSE: 0.0849
R2: 0.3414	NRMSE: 8.4883%
Acceptance Threshold: Maximum Likelihood	

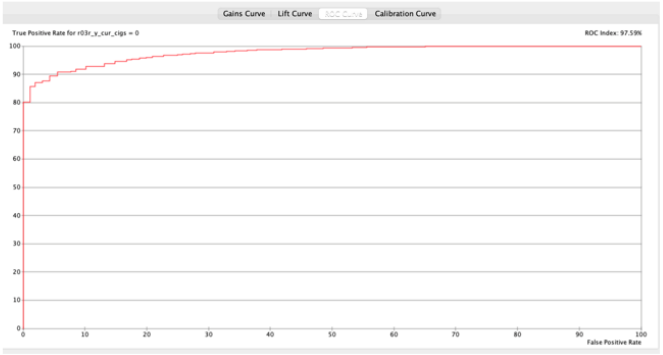


Figure 9. Results of overall model performance.

Figure 10 shows a tornado plot of total effects, with the effect of the exposure variable at the top and then, in rank order, the effects of other factors on the outcome. One thing we could do in the future is to decompose

the indirect effects and all the different pathways, which is something that you can do in a Bayesian network analysis that would be very hard to do in other types of contexts.

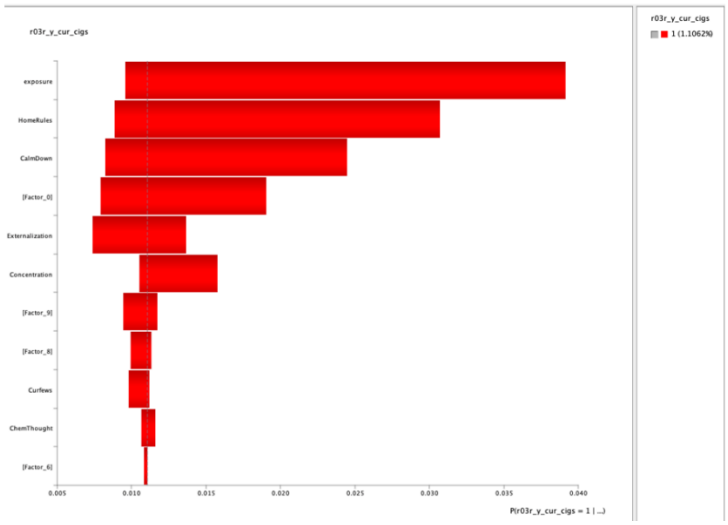


Figure 10. Tornado plot of total effects.

Finally, Figure 11 shows how you can set evidence with Bayesian networks. The left side shows the data as they are observed, so about 4.18 percent of this youth population use e-cigarettes at Wave 2, and of those, 1.1 percent actually smoked a cigarette. In the middle panel, we set the evidence so that 100 percent of the youth used e-cigarettes, and the increase in smoking went from 1.1 percent to 4.89 percent. On the right, if we set all e-cigarette use to zero percent, smoking goes from 1.1 percent to 0.94 percent. Here again, this corresponds to the idea that we can predict non-smoking better than we can predict smoking.

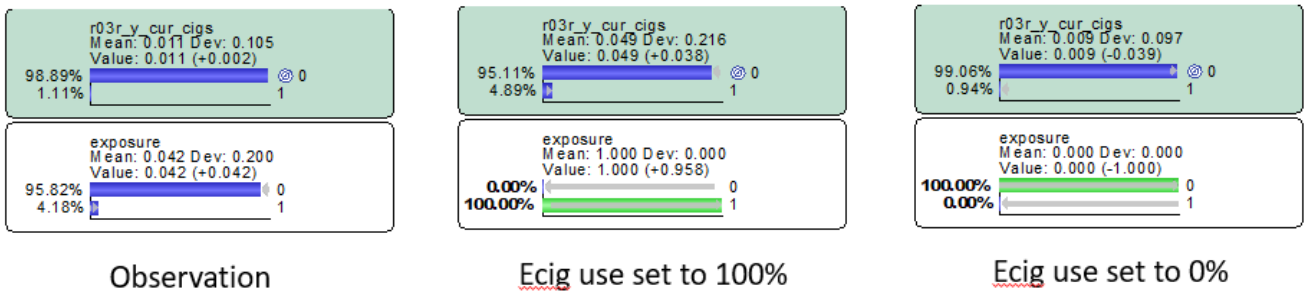


Figure 11. Results from setting evidence for e-cigarette use to observed data, 100 percent and zero percent.

References

Xu S, Coffman DL, Liu B, Xu Y, He J, Niaura, R. (To appear). Relationships Between E-cigarette Use and Subsequent Cigarette Initiation Among Adolescents in the PATH Study: An Entropy Balancing Propensity Score Analysis.

Questions and answers

Q: You were putting many covariates into the analysis, and then this is what you got. What if you were to start with a smaller number of covariates?

A: This is why I did the probabilistic structural equation modeling – because 55 covariates is a lot, and I was looking for a way to simplify those, in terms of whether they have some sort of correlated structure. So then we ended up with 8 variables rather than 55. But you could also do other things, such as things that experts agree ought to be confounding variables.

There are lots of ways to approach the covariate question. Propensities for modeling is another way, which is if you boil it all down into a single score. I don't know that any one of these approaches is necessarily the best or the right one - I think they all tell us different things.

Q: You describe the complex structure of the e-cigarette to cigarette relationship as largely not direct, at least not initially. Would you say that this provides pretty strong evidence, without an a priori model, for what might be called shared vulnerability or other factors that have to do with risk taking behavior in some way?

A: There are a lot of indirect effects, and that's why I think we need to kind of take a step back and understand what those mean. You can say that something is a confounder, but I don't know if that's the right word for a lot of these things. And notice that I didn't do a deep dive into interpreting what it all meant – that's going to take more work.

It's not just as simple as "we have this association, we controlled for X zillion covariates, and there was this residual effect, which we therefore call a causal effect." It's much more complex and much more interesting than that. So that's why this is a work in progress to be continued, to continue to try to tease apart some of those questions.

Q: Isn't the Bayesian modeling approach a type of machine learning approach to pick out the key variables? Would that be your interpretation?

A: Yes, it can be used along those lines. The machine learning here is finding the structure – in other words, the associations within the variables – and what it'll do is find a structure that's optimized. So in a sense, when you're looking at the optimized network, you're saying that there are real connections here.

Then you could ask how whatever the machine learning finds compares to other people's models, or other conceptual models. You could take the same variables and rearrange them differently in major networks, and then you can then test one model against another in terms of actual fit. So yes, you can try to get at that to see which variables are playing a role and where the significant pathways are.

Panel Discussion: Innovative Approaches to Generate Model Parameters

Panel Discussion with Jody Sindelar, PhD, Aylin Sertkaya, PhD, Warren Bickel, PhD and Raymond Niaura, PhD, with additional contributions from David Abrams, PhD, New York University and Cathy Backinger, PhD, US Food and Drug Administration
Moderated by David Levy, PhD and Rafael Meza, PhD

Abstract

This is a summary of a panel discussion with presenters from the second day of the CAsToR Symposium, addressing audience questions on generating parameters for tobacco regulatory science models, in Q&A format.

Q: Bayesian networks are a primarily empirical approach that rely on data. How might other methods be applied in this type of approach? Could you then incorporate, for example, an expert elicitation, or a discrete choice analysis, or an experimental market analysis on top of that, and see how that might affect the results?

Raymond Niaura: Absolutely, the answer is a thousand percent yes. Because, for example, doing elicitation - if you're building a model with a Bayesian network, you can conceptually specify a model, or you can have a group of experts specify the structure of a model. But then you're going to need parameter estimation, and how are you going to do that? Well, you use the expert elicitation methods that Aylin mentioned as one approach when there's no good data to draw from.

Likewise, I think that both the DCE and experimental marketplace methods for generating parameter values for some of these associations could be very complementary to a Bayesian network approach. So I see everything kind of swimming together in a really nice way. We should all be talking, sharing information, and seeing how we can use what people have developed, because there are other kinds of modeling approaches.

The thing I like about the Bayesian networks is that they are very user friendly in terms of being able to build models and populate the models with data and that sort of thing, so that's just my bias. But yes, I think it's pretty exciting.

David Levy: And that leads to kind of looking at it from the other perspective, too – can your process be used to help structure expert elicitation, discrete choice analysis, or experimental marketplaces?

Raymond Niaura: Yes, you can specify time series so you can have something called dynamic Bayesian networks, but you can then draw in influence arrows and say, what if a tax increase happens here, or what if these products are unavailable or what about illegal products and the black market? All of that can definitely be modeled in a network structure. But again, you'd need to have some ideas of what effects would be. So you'd have to get that information through the experimental marketplace or through the discrete choice experiments or through elicitation. But I see that as very compatible.

Rafael Meza: For instance, how much does available empirical data inform how you end up designing an expert elicitation? Maybe it's relatively easy to think about it conceptually - whatever the data is, is something you share with the experts, and maybe your questions are based on the current prevalence rates or what-have-you. I presume it's the same for discrete choice experiments as well as an experimental marketplace, just to help design the specific experiments that you're going to do.

David Levy: In particular, what you see in the real world can help inform the types of transitions that might be explicitly considered in an expert elicitation or discrete choice or experimental marketplace. So do others see value in how you might use empirical data, and then also how you might use one of the other approaches that's been described to bring together these two different approaches?

Jody Sindelar: I think it's a good idea to bring them all together, because when the question was "is a discrete choice experiment better or worse data?", I look across everything, and everything has a big weakness - like experimental data or the discrete choice experiment is called a stated preference, and that's what you say versus real world data. But real world data has big problems too. Like scanner data - you might think that's fabulous, but when they scan a cigarette pack, you don't know who smokes it, whether they store it, or whether they went to another store where it wasn't being scanned.

So I think that looking across approaches is really important because I don't think we have the global benchmark where we can compare everything to it and say, well, you're biased in this way or that way. And I think you need a really big sample - I believe in big "N's" and the nationally representative sample of smokers. So getting people coming together with even smaller samples might add up to more general truth. So I think that would be very good.

And I'll just say one other quick thing. I didn't go through the advantage of discrete choice experiments. Or how, like any other, there are really important methods that could produce a better outcome, like you can give people sample questions. A discrete choice experiment done well is a lot better than one that's just done without being thorough in how you increase the quality of data, the sample representation, and things like that.

Q: Why isn't the FDA setting up funded labs devoted to answering the policy regulatory questions that they are thinking about? Given the scalability and that you're limited only by your own imagination, it seems that you could be deploying study after study and getting a lot of incredible data. Why isn't this happening?

Warren Bickel: So to the FDA, I'm available! I think you're right. These methods are deployable. One of the things I think would be interesting is looking at consistency across the methods, and also the variations.

One of the values that the experimental tobacco marketplace uniquely has is we're always looking at a function. We're not looking at a data point - we're looking at a systematic manipulation of a variable, either dose or price, over and over again. And the beauty of that is that part of the replication crisis that confronts many fields, including some that overlap ours, is they're often looking at one point in a curve. And we all know curves can be curvilinear, and where you decide to compare can produce different outcomes. When you have a whole function, you have a deeper set of variables by which to explain the phenomena and are less likely to run into the issue of "I just picked the wrong two points."

Jody Sindelar: I think that's a wonderful idea, and with the discrete choice experiments, we have samples of about two thousand, and we have quotas so that they are nationally representative of a smoker or a vaper. And as I said, I strongly believe in large samples that should be representative of the population. And it's sometimes hard to fill specific quotas, but it can take up to two months to get two thousand people. And you can put in, again, anything you want. Like this time, in the real world survey we're doing right now, we asked about EVALI and COVID, so you can be timely and ask what would affect someone's decision right now. And we also have functions because we manipulate price from low to high, nicotine from low to high.

But really, you can do anything you want. The question what's the most important or what's the missing piece right there? And DCEs are very good when you don't have a real world option. So real world data is

sometimes better, but the DCEs can be useful because you can manipulate so many things at the same time. So it seems like a wonderful idea.

Raymond Niaura: Do you think that you would be able to find perhaps regional differences, say within the US, in terms of some of the results that you've shown us?

Jody Sindelar: Yes, in different situations. We sample by regions, but we know the state, so we could definitely show that. And I think it's important because the supply is different, and we're talking about this in the real world data. but we also know the policies are different. States have different underlying desires to pass laws to control tobacco, or the e-cigarette markets enter the West Coast and slowly get to the Midwest. So, yes, all those things - by age, by gender differences, by race, by region.

Aylin Sertkaya: I just want to make a quick comment on these types of primary data collections through natural discrete choice experiments from smokers or nonsmokers. I don't work for the FDA, but I've done a number of projects for the FDA. One of the hurdles for implementing that center that you might be envisioning is the Paperwork Reduction Act, which limits primary data collection efforts. Any time you reach out to more than nine entities or individuals, an agency needs a clearance from the Office of Management and Budget, which could take up to two years or more for each collection. So that's a hurdle.

Q: If the FDA or a regulatory or government agency needs an analysis of the impact of a policy, and there is little information, how long would it take to plan, conduct, execute and get results from an experimental market analysis, a discrete choice experiment, or an expert elicitation? Is this something that can be done within a year, within six months, within two months? What is the level of speed that could be achieved?

Warren Bickel: That's a great question. The way to think about it is what kind of question to answer: are you trying to understand a range of conditions, and then once you understand them, go large? I think that makes a lot of intuitive sense, and that's the value of the type of work that I'm doing right now. I'm getting a range of conditions, and that sets the occasion to say we have an idea of what the parameter space is, and now we can pick the optimal ones. And the fact that we can do it within-subject permits us to eliminate some sources of variability that otherwise might be noise, and allow a stronger understanding of some of the effects.

But those studies, at different scales, can be done rather rapidly online, assuming that there are people available to do them, and you can access them as you get into more refined samples. Let's say I want a dual user that uses e-cigarettes X amount and still smoke cigarettes X amount - it takes longer to identify them and accumulate them. But generally it's pretty quick, and for some of these studies, we can get the answer in a matter of months, not a year.

Raymond Niaura: It's a matter of resources, right? I mean, if you have enough money just to set up the studies, then you should be able to do them quickly.

Q: Would that be the same for DCEs and expert elicitations? Are we talking in terms of these different approaches being comparable in their timescale? Given the right resources, should you be able to do them all in a relatively quick time frame?

Aylin Sertkaya: Yes, that's applicable to expert elicitations too. I mean, as long as you have the resources and know the exact questions you want to ask, then doing the expert elicitation is fairly quick.

Jody Sindelar: With a discrete choice experiment, if you have the resources, you can do it. We now have a battery of a whole bunch of different surveys, so developing a new survey takes less and less time. It might take two months to get two thousand people with a nationally representative sample. It depends on whether

you want something harder to find online, like black menthol smokers with low education. One of the things about an online survey is that highly educated white women are probably most likely to be online, and that's why you have to set up quotas, and some quotas are hard to fill. And quasi-experimental studies also can be done. It's a longer discussion about how long they take, but that's another method that we have now to study real world policies.

David Abrams: I really love this conversation. I just wanted to throw out a couple of thoughts about how to increase the triangulation, the energy, and the resources. Raymond Niaura only just scratched the surface with what he did with BayesiaLab and three waves of data. PATH actually has five waves of data, and as you know, repeated measures on five data points on trajectories, transitions, and complex interrelationships between different products is hugely informative, even compared to three data points. So that's point number one. Clearly, Ray could do what he's doing, and add Wave 4 and Wave 5, and have even more interesting and perhaps stronger relationships as you follow the same people over three or four or five years out from baseline.

The second point is that you could pick a small, purposive subsample of existing PATH participants, who've already got three or four waves of data, to inform you of who you actually want to test in the real world with whatever a key subset of a discrete choice experiment might be, or something Warren's doing in his lab, or even something stimulated to inform an explicit elicitation.

So that kind of triangulation is usually met with resistance. The resistance is, oh, we can't touch the sample of 40 thousand households at all because there's reactivity and contamination and blah, blah, blah. Yet we have suggested that actually within a large sample like this, if you pick a purposive subsample of specific interest, and you still have a fairly large sample within that subsample, you could pick some of them at random and not necessarily contaminate in any big way the overall sample. And of course, you can use electronic web-based and other ways of sampling people in between the now two-year gap between each PATH survey that is now being conducted.

Finally, if we were concerned about reactivity of repeated measures or asking a few extra questions, if that would have helped us to get rid of smoking, we would have used it. But I don't think that reactivity is strong enough. And the advantages of informing policy by triangulating all these methods with actual real world samples informed by full waves of longitudinal data, to me are astronomical and a massive opportunity to be proposed for rapidly informing FDA hot button policy issues.

Warren Bickel: And to your point, the last thing I replicated, the effect of the flavor ban on illegal purchases, was done after we invited people who had already completed the ITC survey, to participate in an additional study. And that's where we got the subsample. But because it was after they did it, we have all that data that can be used to inform what we observed.

Jody Sindelar: I think the timeliness of that would be good, because one of the disadvantages, I think, with this rapidly changing regulatory environment is you have to be there when things are happening, not only to witness the change, maybe, but also to provide data before the change comes. So doing something on a more timely basis would be very helpful right now.

Q: One question that I have is about the challenges that you face doing these types of studies that are not traditional, and finding resistance from those who are not familiar or who might be skeptical about this. So how can we increase the reliability of the things that we're finding with these types of studies, and also the confidence in them? And what, if anything, needs to be done to educate the research community?

Warren Bickel: Certainly the experimental marketplace is relatively new, and of course, anything new is a question. I think the extent that we can show concordance across different measures would give strength to each of the measures, which would increase the extent that any estimates that come from these marketplace studies could be integrated into work. But there are definitely some people who question the experimental marketplace. We've gotten some people who are saying, "You know, it's an experiment - we don't want to experiment, we want to measure. We want epidemiology only."

Raymond Niaura: But you know, there are good stories to tell here. I mean, if we're scientists talking to scientists, we're going to expect that sort of criticism. But there's a gap between this really good stuff and the public at large. I don't know how to bridge that gap, but it seems to me it wouldn't take much to be able to translate the findings from DCE or an experimental marketplace into a story that a good science writer would be able to run with. It seems to me to be far closer to interesting phenomena than a lot of epidemiology.

Jody Sindelar: I think you can also point out that these mechanisms, like substitutability, have importance that comes up again and again; for example, if you pass a law to ban menthol in e-cigarettes, which is what states are doing, not realizing that you're sending people back to cigarettes sometimes. So you can't look at one without understanding the whole ecosystem, and I think that's important.

And also on the idea that everything should convert - I think if it actually does, that's great. But I think false precision is not as valuable as actually understanding the uncertainty. Another lesson I like to tell people is there is a certain amount of uncertainty, and also things change. Look at the e-cigarette market, where products come on and off the market, while states are passing laws. So having a sense that it is dynamic is better than a sense of false precision.

Q: Jody, could you comment more on how to measure uncertainty associated with parameters estimates using experimental methods, and how to incorporate those into population models?

Jody Sindelar: First, a couple of my co-authors calibrate their DCE to real world data, and there are ways to calibrate it to the real world data so we can reduce that kind of uncertainty. But the other kind of uncertainty we have is statistical uncertainty, because we have two thousand people in our sample and we know the confidence interval.

Because we can look at heterogeneity, it's not about reducing the confidence interval, but having more precise estimates. For example, young women behave differently than older men - we know that, for example, older smokers really want to have their cigarettes, and don't want to go to flavored e-cigarettes.

So we can look at how these things vary. If you looked at the whole pool, it might be very uncertain, but when you get to smaller subgroups you know with more certainty - and I'm not using that word statistically. But you know that these groups are heterogeneous, and pooling them, or at least not understanding the differences, can be a mistake.

Q: Dr. Cathy Backinger, Senior Science Advisor, Office of Science, FDA's Center for Tobacco Products*, has some comments on the earlier discussion about more rapid modeling studies for policy research.

Cathy Backinger: I just wanted to address an earlier question: why doesn't the FDA fund labs to be able to do some of this in more real time? I did want to say that, as you know, the federal government is not that nimble on being able to do any research really quickly. You all know when you submit a grant to NIH, it takes at least 10 months. So one of our goals in TCORS was to have this possibility for rapid response research. And of course, that is probably, in my estimation, not working as ideally as it could be. But we are trying to get some of these things to happen.

We can't talk about FDA's tobacco regulatory actions until they have been announced publicly. As such, we have to try to be as nimble as possible, and I think we're doing pretty well. And, you know, the Michigan and Georgetown TCORS is exactly that, trying to do modeling and trying to look at some of our policies as we announce them, to better approximate the impact of some of these policies, and evaluating or looking at policies at the state and community level.

I just wanted to raise that, and I totally acknowledge that we're not as nimble as we would like to be. And we need to have the peer reviewed scientific literature to help inform our direction. And, of course, the announcement in April of the menthol ban in cigarettes and menthol in all flavored cigars, it's going to take a while. And so thinking of the research now, because it's going to take some time, will be helpful and informative to the FDA.

Editor's note: Dr. Backinger's remarks are not a formal dissemination of information by FDA and do not represent Agency position or policy.

Q: Could the panel comment on the value of international between-country comparisons? The FDA only funds US studies, which may be a missed opportunity.

Warren Bickel: Yes, the International Tobacco Control (ITC) project, which is funded by NIH and also has collaborators who bring their own funding from other countries, provides a unique opportunity to explore that. And indeed, with the support of ITC, that has encompassed different countries. So apparently, at least at the level of NIH, there's openness to cross-country comparison.

David Levy: I feel that my involvement in both the ITC and CAsToR really has a very synergistic kind of effect. I would also point out that one of the cancer groups in England has put out a call for researching cancer. And so I think increasingly there's going to be work that is from different countries and that could really benefit and provide insight to the kind of modeling that we do in CAsToR.

Rafael Meza: I want to thank our speakers from this session, Jody Sindelar, Aylin Sertkaya, Warren Bickel, and Ray Niaura. Also, our thanks to David Abrams, Cathy Backinger, and everyone who has had a question. This has been a great discussion.

Social Network Structure and Cigarette Smoking Among Adolescents and Young Adults

Iris Yuefan Shao, MPH, Emory University

Abstract

This study examined social network structural characteristics among adolescents and young adults with different cigarette smoking behavior using adolescent and young adult waves of the Add Health study in-home friendship survey. We found differences in community structures between smoking status groups, and relationships between social network structural features and tobacco use for young adults but not adolescents.

Introduction

This presentation will discuss social network structure and cigarette smoking among adolescents and young adults. As background, Figure 1 shows recently updated data from the National Youth Tobacco Survey, showing that despite the decline in youth use of combustible tobacco products, there was no significant change in teen cigarette smoking from 2019 to 2020. In addition, the proportion of ever-smokers who initiated cigarette smoking in early adulthood more than doubled between the years 2002 and 2018, with the proportion of daily cigarette smokers who transitioned to daily smoking in early adulthood also increasing by about 20% in 2018.

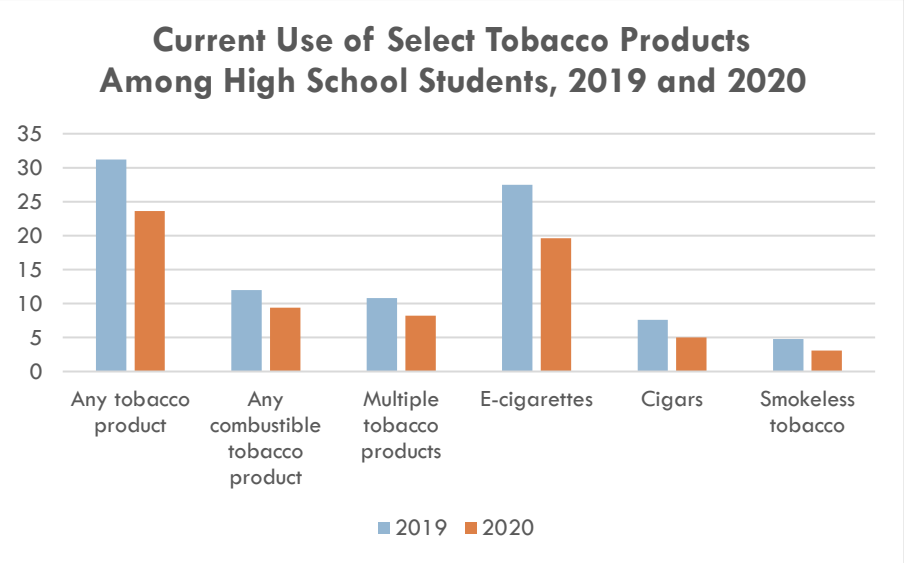


Figure 1. Current use of select tobacco products among high school students, 2019 and 2020. (Source: CDC MMWR, December 18, 2020. https://www.cdc.gov/mmwr/volumes/69/wr/mm6950a1.htm

Findings from an extensive number of sociological and epidemiologic studies have suggested the importance of social network in smoking behaviors among adolescents and young adults. Specifically, cigarette smoking behaviors have been shown to be correlated with one's friendship network. Exposure to smokers within the social network has also been observed to be associated with a higher likelihood of smoking and with high likelihood of smoking initiation among adolescents. Most well-known studies linking social network to cigarette smoking

among the younger population has been centered around the social contagion theory (the LeBon-Park-Blumer hypothesis), social norm theory and the concept of homophily (McPherson), where individuals are more likely to emulate the behaviors of friends, and where individuals with similar smoking behaviors tend to be in the same network cluster.

Modeling social network structure versus smoking behavior

This dynamic interplay between friendship ties and smoking behavior has been the foundation for the design of many tobacco control programs targeting youth. However, when thinking about effective smoking prevention measures, we might need to take into consideration the additional pathway linking social network to individual cigarette smoking behavior through social network structural characteristics, as shown on the right of Figure 2. In particular, social networks structural properties play an important role in shaping one's perceived network externality prior to decision making, which is defined as the perceived effect a product has on a user while others are using the same or a compatible type of product.

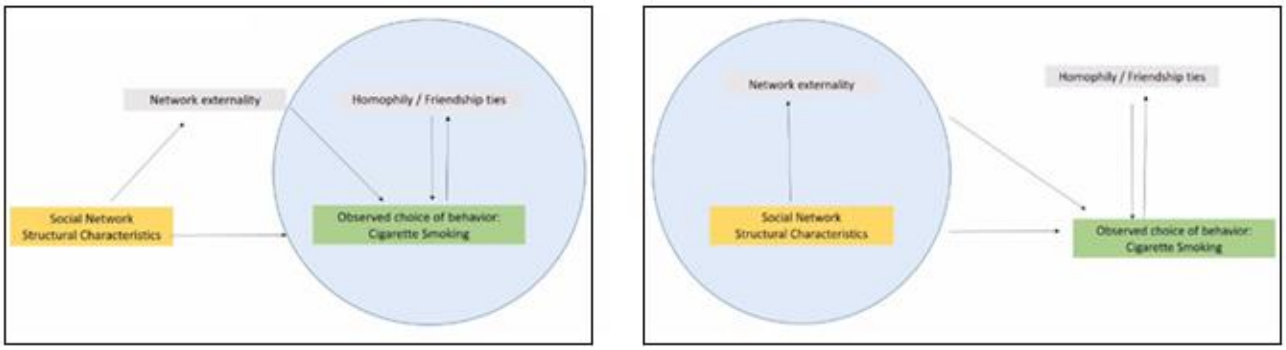


Figure 2. Traditional links between homophily/friendship and smoking behavior versus consideration of social network structural characteristics.

To date, there have been a very limited number of studies actually evaluating the association between social network structural features and tobacco use behavior. Further understanding of such pathways is particularly important when thinking about smoking prevention measures since network structural properties are key to network dynamics, including signaling and diffusion, which are both crucial to individual decision making in a social network, as well as information diffusion.

In this preliminary analysis, we aim to explore the social networks structural characteristics among adolescents and young adults with different cigarette smoking behavior using the Add Health study Wave I and III in-home friendship survey. In addition, the association between network structural properties and cigarette smoking behaviors were discussed in both of the waves. Details about the waves of this study are shown in Figure 3.

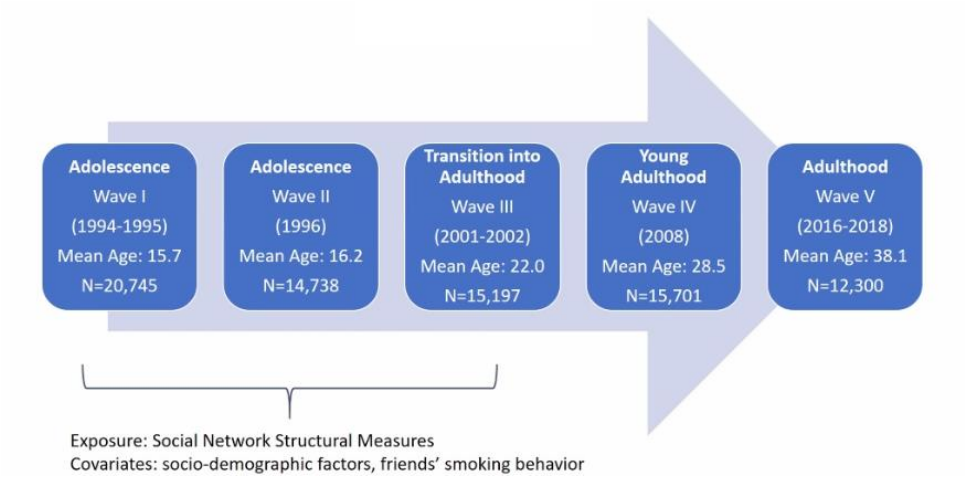


Figure 3. Waves of the Add Health survey.

Network structural features of interest include betweenness centrality, a local clustering coefficient and network diameter, and the additional centrality measure of indegree centrality, as shown in Table 1. That property was assessed because it informs a popular research question, as in whether popularity is associated with smoking behavior among young adults and adolescents.

Network structural features	
Betweenness centrality	The number of times a node acts as a bridge along the shortest path between two other nodes
Local clustering coefficient	Fraction of a pair of nodes' friends that are also friends with each other
Diameter	The shortest distance between two nodes in the network
Centrality measure	
Indegree centrality	Percentage of ties that belong to one particular group out of entire network ties

Table 1. Network structural features and centrality measure.

Using the Add Health in-home survey, we constructed several different networks, and associations between network structural characteristics and cigarette smoking were assessed using logistic regression. At baseline, there were 20,745 individual participants with a mean age of 16 years old, and by Wave III the mean participant age had reached 22 years of age. A majority of the adolescents were never smokers in Wave I, whereas in Wave III only 30 percent of young adults were never smokers. Higher proportions of individuals in Wave III also nominated a current smoker as a friend within the network, as compared to Wave I.

Figure 4 shows the overall friendship network with community detection methods, and Wave I's overall friendship network has a smaller number of subcommunities whereas as participants get to young adulthood in Wave III, the overall friendship network has started to form more clear and numerous subcommunities, suggesting that the overall network is now less compact.

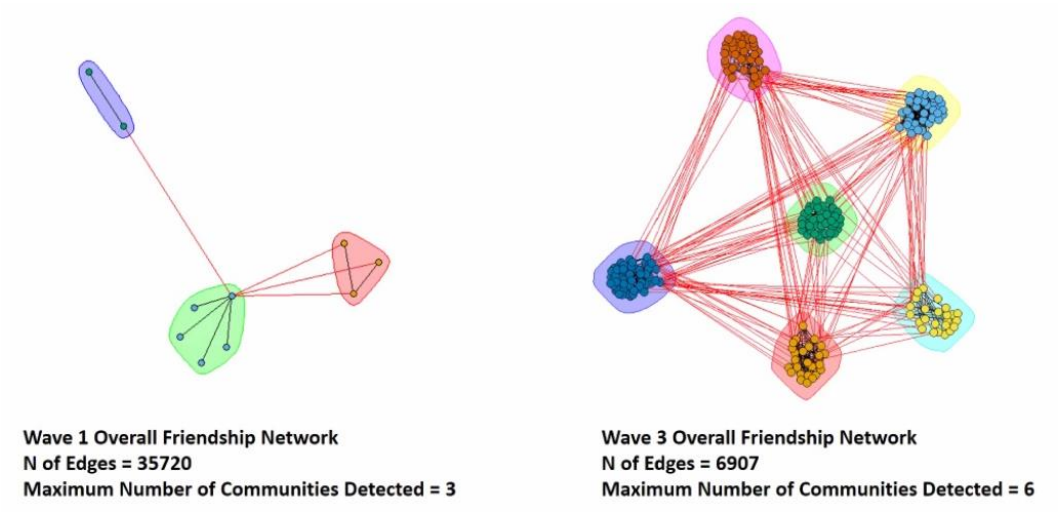


Figure 4. Wave I and III overall friendship network communities.

Looking at the friendship network stratified by smoking behavior at both waves, at Wave I there were only about 0.3% of adolescents who were current smokers, and 3% who were former smokers. Therefore, there was no clear subgroup in either of those populations, and the never smokers had three distinct subcommunities within the overall friendship network. At Wave III, however, we can see in Figure 5 that never smokers exhibit different community structures as compared to former smokers and current smokers, and current smokers and former smokers exhibit a smaller number of subcommunities and might be more compact than never smokers. The structures for current smokers and former smokers are relatively similar as compared to never smokers.

Figure 5. Wave III friendship network communities by smoking status.

Looking at regressions assessing the association between network structural features and network behavior in adolescents, we observed that the odds of smoking decreased by about 14% for each unit increase in indegree centrality. However, we did not find an association between other structural properties and smoking behavior among adolescents at Wave I using similar methods.

However, among the young adult friendship network, for every unit decrease in local clustering coefficient, which is a measure of the local level clustering of a social network, there was an approximate 40% decrease in the odds of being a current smoker as compared to being a never smoker. In addition, for every unit decrease in betweenness centrality there was about a 15% decrease in odds of being a current smoker as compared to being a never smoker. These findings indicate that current smoker networks are less compact,

with fewer friends functioning as bridges between ties among the young adult network, which is relatively different from the adolescent network findings.

Conclusions

To conclude, we can see that based on these two cross-sectional analyses, the macro level network structural characteristics differ by age as well as smoking status. In particular, clusters play an important role in differentiating networks among individuals with different smoking behaviors. Individual network structural characteristics such as betweenness centrality and local clustering coefficient were observed to be associated with cigarette smoking behavior among young adults but not adolescents.

However, there are several key limitations of this particular preliminary analysis. First of all, there is limited generalizability due to lack of an up-to-date data source about the population, and there could also be bias due to missing covariate information as well as missing network nodes due to the network survey design. The second limitation is the self-reported measure of tobacco use as well as network ties.

For the next step of this research, we might consider missing data imputation on the social network to impute the missing ties as well as missing nodes, to evaluate the coevolution between the social network structural features and smoking behavior. Second, we should consider incorporating structural features and parameters of simulation models, evaluating dynamics of adolescents and young adult smoking behavior, as well as the effectiveness of tobacco control measures on a social network.

Questions and answers

Q: Does the friendship network that you analyzed include relationships between family members or just friendship networks?.

A: We used the in-home survey of Waves I and III, where they nominate their friends. However, we did not specifically exclude those who are actually siblings or family members, which is worth exploring, because the strength of the network ties might actually differ if the person is in one of those categories. We may think about linking this data back to the main survey to identify those individuals in the future.

Q: Why did you choose the Add Health survey versus more recent data sources?

A: Add Health is one of the more nationally representative sources with relatively more comprehensive network information. It was also interesting to capture the differences between the networks among different developmental periods, for example, in adolescence and adulthood. However, there is a disadvantage that it is relatively dated as compared to newer datasets, and we may consider this for the future.

Q: Have you considered using Twitter or Facebook or other social media data to look at this type of relationship?

A: There actually has been a similar study on Facebook smoking status years ago. We did not really take advantage of Twitter or Facebook at this point because online behavior is also exhibited relatively differently as compared to these types of longitudinal studies. I think those data are really helpful in terms of looking at the online kind of interventions, as opposed to the more traditional smoking prevention measures or policy effectiveness, and might be of interest if we're looking at online intervention design.

An Estimation of the Harm of Menthol Cigarettes in the United States from 1980-2018

Thuy Le, PhD, University of Michigan School of Public Health.

Abstract

This presentation describes a model used to estimate the harm of menthol cigarettes in the United States, including excess smoking prevalence, smoking initiation and mortality due to menthol cigarette use. This model was mainly based on National Health Interview Surveys (NHIS) data from 1980 through 2018. The results of this simulation showed over 10 million excess smokers, three million life years lost, and 378,000 premature deaths attributable to menthol cigarettes over the period studied.

Introduction

This presentation describes an estimation of the harm of menthol cigarettes in the United States from 1980 to 2018, in collaboration with Dr. David Mendez.

Menthol cigarettes were first created in the 1920s and became widespread in the 1950s and 1960s. Menthol in cigarettes creates a cooling sensation in the throat and airways, masking irritation and harshness in cigarette smoke. Menthol flavoring is likely to encourage youth and young adults to initiate smoking and to delay smoking cessation, and there has been an ongoing debate over menthol flavored cigarettes in particular.

In 2011, the FDA Tobacco Products Scientific Advisory Committee reports indicated that the availability of menthol cigarettes in the market harms public health by increasing the number of smokers, with resulting premature deaths and morbidity. In 2013, and again in 2018, the FDA sought public comments, research results and other information on the impact of menthol cigarettes on smoking initiation, prevalence and other factors, to inform regulatory actions that the FDA might take on mentholated cigarettes. Finally in April 2021, the FDA announced plans to ban menthol cigarettes and flavored cigars.

Modeling the harm of menthol cigarettes

To quantify the harm caused by menthol cigarettes, we estimated the excess smoking prevalence, smoking initiation and mortality in the US from 1980 to 2018 that can be attributed to menthol cigarettes. We used a well-established simulation model of smoking prevalence and health effects to quantify the impact of menthol cigarettes on the US population during the period from 1980 to 2018.

Figure 1 shows an overview of this model. The blue boxes represent major compartments of the model, tracking the number of never smokers, current menthol and non-menthol smokers, and former smokers over time. The circles correspond to the model's parameters: red for menthol-specific parameters and green for the rest. The orange diamonds indicate the events of individuals becoming menthol and non-menthol smokers. Details of this model can be found in the FDA TPSAC menthol report (TPSAC, 2011).

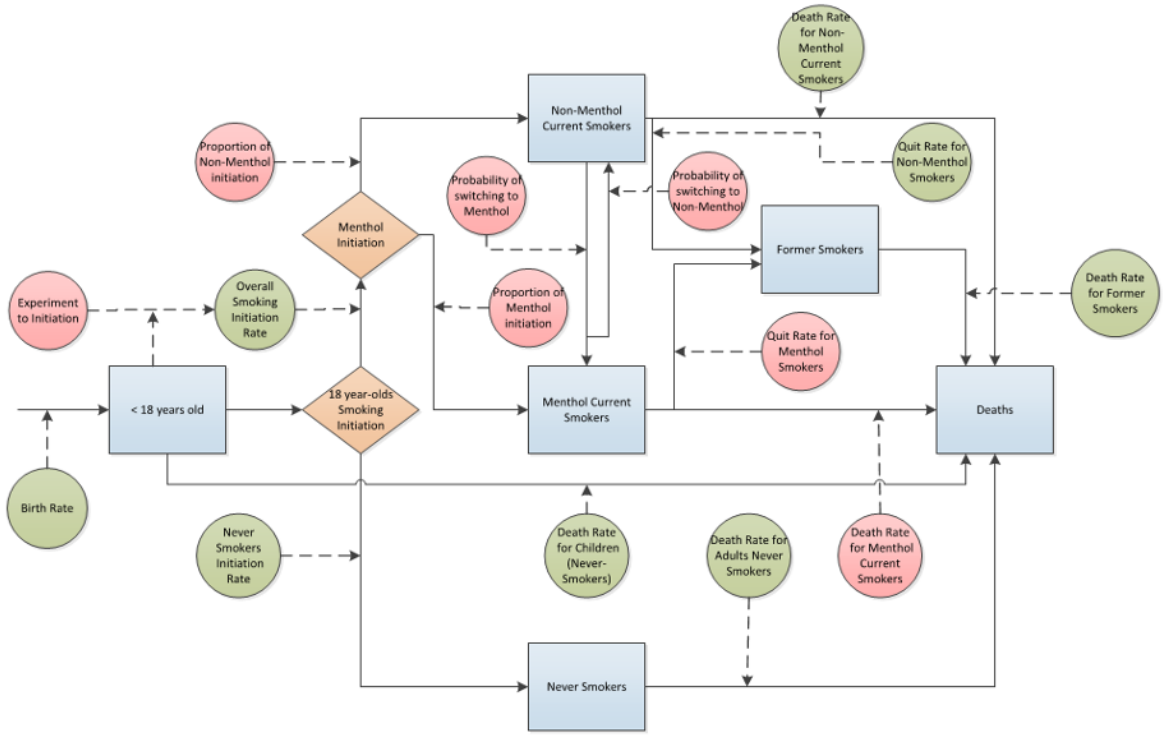


Figure 1. The dynamics of the menthol cigarettes model (TPSAC, 2011).

Data from various published sources was used to populate this model. For instance, menthol and non-menthol smoking prevalence data was taken from the 1980 to 2018 National Health Interview Surveys (NHIS). In order to estimate the potential harmful effects of menthol cigarettes, we first developed a simulation scenario using retrospective NHIS data to reproduce the US smoking trends from 1980 through 2018 (***status quo ante*** scenario). Then, we constructed an alternative scenario over the same period, in which menthol cigarettes were assumed to be nonexistent from 1980 through 2018 (***counterfactual*** scenario).

Finally, we compared the numbers of smoking-related premature deaths, life years lost and excess new smokers in the status quo ante and counterfactual scenarios, to quantify the public health harm attributable to menthol over the period from 1980 through 2018. Moreover, we also examined the individual contributions of changes in initiation and cessation due to menthol to the excess smoking-related deaths and life years lost. To do so, we performed two additional simulation runs in which we first set the initiation and then the cessation rate in the counterfactual scenario to their respective values in the status quo ante scenario.

As described, we simulated two different scenarios. Under the status quo ante scenario, the smoking initiation rate was taken as the average smoking rate among 18 to 24-year-olds in the 1980-2018 NHIS, and in this scenario there are menthol and non-menthol smokers. Previous studies have shown that the odds of becoming a regular smoker are higher among menthol experimenters. Therefore, under the counterfactual scenario, when the effect of menthol was removed, the smoking initiation rate would be lower.

Results

The results of this study are shown in Figure 2. The open circles represent the NHIS smoking prevalence, and triangles and solid circles represent simulated smoking prevalence in the status quo ante and counterfactual scenarios. The shaded region shows the 95% confidence band of the estimated prevalence in the

counterfactual scenario. This figure shows that the estimated smoking prevalence in the status quo ante scenario aligns very closely with the observed NHIS data, with pseudo-$R^2 = 0.98$.

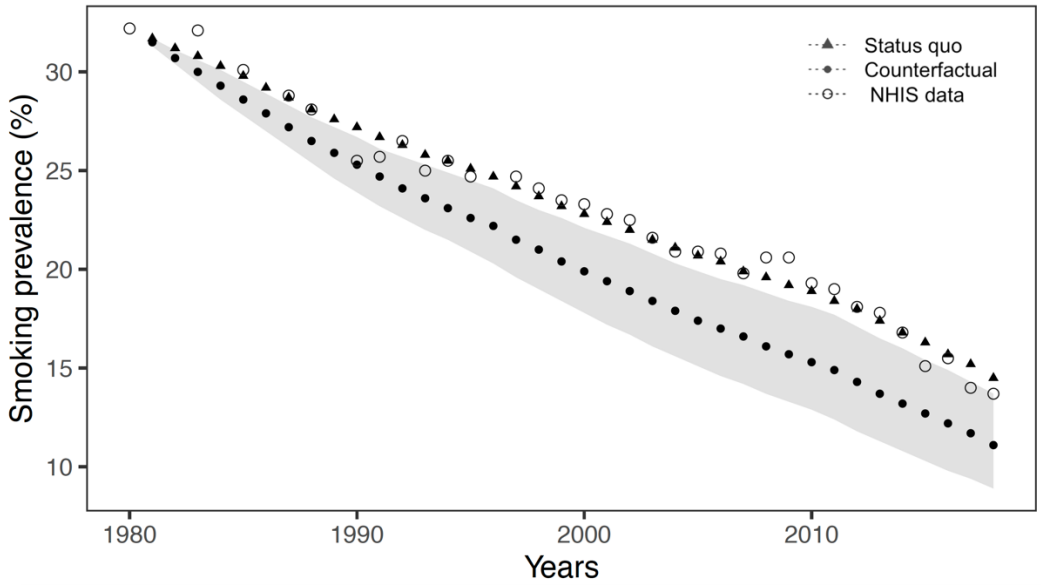


Figure 2. Results from status quo ante and counterfactual scenarios versus NHIS data.

Over this period, we found that menthol cigarettes were responsible for slowing down the decline in smoking prevalence by 2.6 percentage points. Without menthol cigarettes, the smoking prevalence in the US would have been about 11.1% in 2018 instead of 13.7%. About 10.1 million excess smokers (representing approximately 266,000 additional smokers per year), three million life-years lost, and 378,000 premature deaths (roughly 9,900 premature deaths per year) were caused by menthol cigarettes.

Moreover, from 1980 through 2018, 56% (44%) of smoking-related deaths due to menthol cigarettes were explained decreases in smoking cessation (by increases in smoking initiation respectively), and 65% (36%) of cumulative lives lost due to menthol were explained by decreases in smoking cessation (by increases in smoking initiation respectively).

Discussion and limitations

This work shows that menthol cigarettes have caused substantial harm to the population. From 1980 through 2018, these products were responsible for millions of excess smoking initiators and hundreds of thousands of smoking related deaths. Menthol cigarettes' harm stems not from the menthol substance itself, but from the changes in smoking initiation and cessation. This is a population rather than an individual health effect. While menthol smoking has been declining for decades now, and it is at historically low levels, menthol in other nicotine delivery products could exert the same effects as in cigarettes, stimulating the use of those products.

Limitations for this study included the following:

- First, the results rely on some key parameters taken from the literature. Therefore, the uncertainty of our results is associated with that of those parameters. As empirical research produces updated information about the sensitive parameters in the model, this will be incorporated in the analysis to reduce the uncertainty in the results.

- Second, the simulation model assumes population characteristics that may not be an appropriate representation for all situations – for example, homogeneity of compartments and proportionality of effects, among others.
- Finally, we modelled the US general population, and we know that the prevalence of menthol cigarette use is disproportionately high among African Americans. Therefore, menthol harm is certain also to be disproportionately higher among that group.

This work was supported by grants from the National Institutes of Health, National Cancer Institute and the Food and Drug Administration. We would also like to thank the members of the CAsToR Data Core for providing several pieces of the data used in this study.

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Questions and answers

Q: What do you do with the menthol smokers in the case of the counterfactual model scenario? Did you assume them as never smokers, or as a reduced number of regular smokers in the counterfactual? How did you make this decision?

A: We know that menthol encourages people to start smoking and delay smoking cessation. Therefore, in the counterfactual model, we consider that if we remove menthol in cigarettes, the initiation and the cessation rates would change. So then we evaluated how much change would be reasonable if we removed menthol cigarettes, and then we constructed the counterfactual model using the updated adjusted initiation and cessation rates.

Q: How do smokers who use menthol differ from those who don't use menthol, besides their initiation and cessation rates? Do these groups differ in other ways within the model?

In our model, they differ only in initiation rate and cessation rate, and they have the same mortality risk. According to some studies available in the literature, they discovered that there is no difference in mortality risk between menthol and non-menthol smokers. Moreover, we are doing a follow-up study on the African American population, and according to recent literature there is a significant change in the cessation multiplier.

Trends in Nicotine and Tobacco Product Use among U.S. Adolescents, 1999-2020

Ruoyan Sun, PhD, Department of Health Care Organization and Policy, University of Alabama at Birmingham School of Public Health

Abstract

This presentation looks at how adolescent use of nicotine and tobacco products has evolved since 1999, using data from the CDC's National Youth Tobacco Survey (NYTS). It also examines the use of a new measure, nicotine product days (NPD), which more accurately captures the true use of nicotine products and health risks from its consumption.

Introduction

The Centers for Disease Control and Prevention (CDC) closely monitor tobacco use trends among US adolescents via the annual National Youth Tobacco Survey (NYTS). Two key measures that they use are:

1. Current use of an individual tobacco product, defined as use within the last 30 days;

2. Any tobacco product use in the past 30 days, a binary variable referred to as ATP.

However, this ATP variable does not reflect utilization changes in the types of nicotine and tobacco product. It does not reflect the frequency of use, and an ATP value of 1 could vary from the use of a single product on a single day to the use of multiple products daily in the past 30 days. This variable also does not account for differential health risks associated with different products, and we know that some products, especially combustible products, cause greater health risks than others.

A new measure: nicotine product days (NPD)

Our research question was how to better assess changes in exposure to nicotine and tobacco products, and we propose the concept of nicotine product days (NPD), defined as the number of days that an individual consumed a nicotine product in the past 30 days. Compared with ATP, NPD permits quantitative comparison of changes in exposure to various products and can account for differential product risks by adding risk weight for each product.

Because this is being proposed as an alternative to the CDC's ATP measure, we are using the same data as the CDC. We took nationally representative data on youth tobacco use from all 16 waves of NYTS surveys from 1999 till 2020 and then constructed NPD by adding frequency of use data on nine nicotine and tobacco products in available years: cigarettes, cigars, chewing tobacco, dipped snuff, electronic cigarettes, bidis, hookah and kreteks. For each of these products, we gathered our data from the question, "During the past 30 days, on how many days did you smoke/use [product]?"

Here are two examples of NPD:

1. Students vaped 3 days and used hookah once last month: 3 + 1 = 4 NPD

2. Students smoked cigarettes 10 days and vaped 5 days last month: 10 + 5 = 15 NPD

By comparison, in both of these cases their ATP is 1.

Figure 1 shows the estimated NPD as well as the ATP for average high school and middle school students in the US from 1999 to 2020. The orange curves are for high school students, and the blue curves are for middle school students. The dashed lines in both cases are ATP values from the CDC, and the solid curves are our estimated NPD for high school and middle school students.

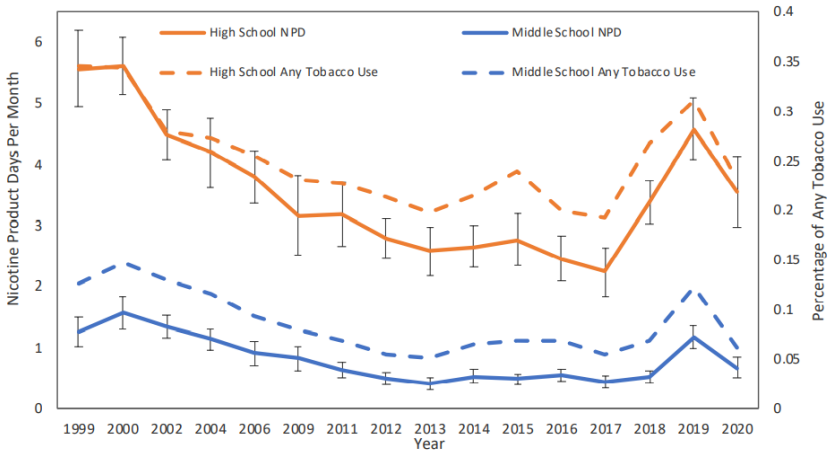

Figure 1. Nicotine product days (NPD) versus CDC any tobacco product (ATP) measure for high school and middle school students, 1999-2020.

What we see in general for both middle and high school students are similar trends between NPD and ATP through 2013, prior to electronic cigarette popularity among adolescents. However, NPD fell more rapidly than ATP for high school students, and the orange lines from 2013 to 2015 reflect reductions in frequency of product use for high school students that were captured only by our NPD measure and not by ATP, given that it is a binary measure. Both measures increase sharply for both high school and middle school students in 2018 and 2019 but drop steadily in 2020. These large increases in 2017 to 2019 are very concerning and are the reason public health authorities have labeled youth vaping an epidemic in the US.

Another feature of NPD is that it looks at the use of specific tobacco products. Figure 2 shows high school and middle school students' use of combustible, smokeless and electronic cigarettes over time. For e-cigarettes we only have data from 2014 onward; however, for most middle and high school students there has been a steady decrease in use of combustible cigarettes. Throughout this entire period from 1999 to 2020, smokeless tobacco use has largely stayed the same; however, the main changes are driven by electronic cigarettes, for which we do see a large increase from 2017 to 2019, and then a decrease in 2020.

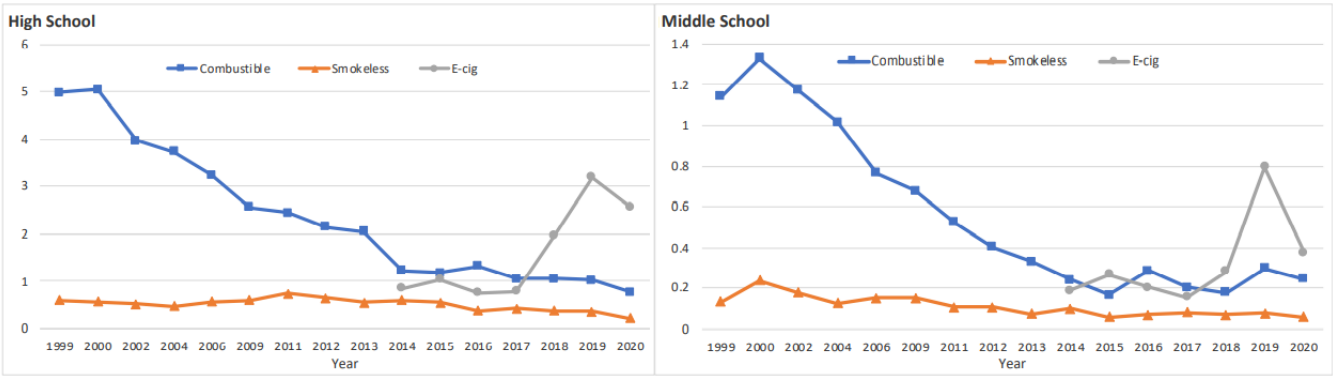

Figure 2. NPD for combustible, smokeless and e-cigarette products for high school and middle school students, 1999-2020.

Risk-adjusted NPD

We also introduced the concept of risk weights, composed from all risks associated with using a particular product as an adolescent, including risks potentially occurring during the adolescent years as well as long-term chronic disease risks. We also consider potential changes in utilization patterns. Given the uncertainty, we vary the possible risk weights for e-cigarettes from 10% to 100% of the risk of combustible cigarettes. Figure 3 shows weighted risk-adjusted NPD values for high school and middle school students. The risk stays low for electronic cigarettes, given its low risk values, and we actually have a steadily decreasing risk-adjusted NPD all the way from 1999 onward.

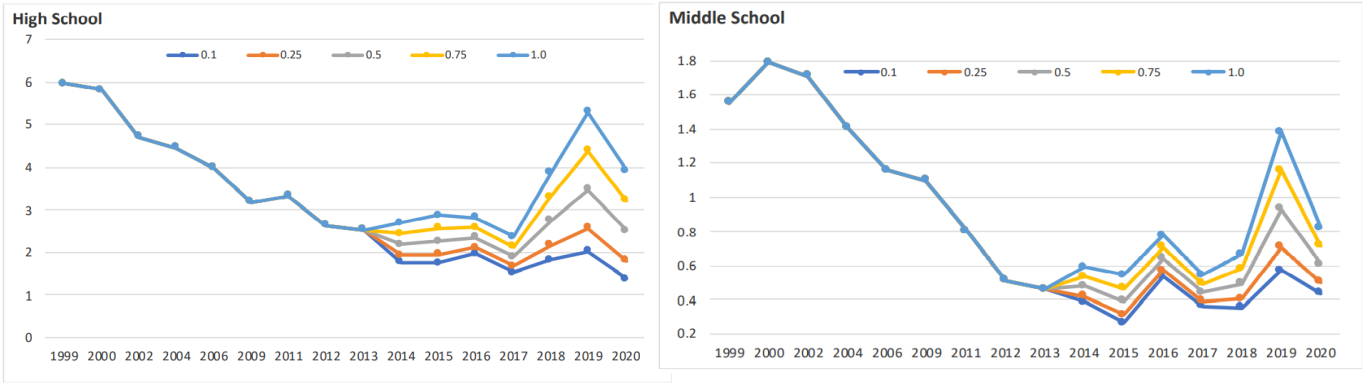

Figure 3. Weighted risk-adjusted NPD values for high school and middle school students.

Discussions and limitations

Mean NPD generally mirrors ATP for the period from 1999 to 2020. However, exposure to nicotine and tobacco products, assessed by NPD, declined prior to the popularity of e-cigarettes. This decline slowed and then reversed due to the upsurge of vaping. Using a low risk weight for e-cigarettes, risk-adjusted NPD continues to decrease post-2013 among middle and high school students.

Limitations of this approach include:

- NPD does not assess nicotine exposure directly but indirectly through exposure to nicotine and tobacco products.
- NPD does not incorporate information on intensity of use.
- NYTS does not distinguish vaping nicotine vs vaping THC.

Whether the health risks associated with nicotine and tobacco product use have increased or not due to the popularity of e-cigarettes depends on one's assessment of the risks associated with youth vaping. We hope that NPD represents a modest step forward in assessing adolescent exposure to nicotine and tobacco products.

Questions and answers

Q: How much do you think these results were affected by changes in NYTS question wording about e-cigarettes and other tobacco products between 2014 and after 2015? Previously they asked about smoking in the past 30 days and then had a checklist of other products.

A: The main purpose of our measure is comparing it with the CDC's any tobacco product (ATP) measure. We saw this change in their question, and largely speaking, if it affected their ATP it would have affected our NPD measure the same way. But that is a really good limitation to note for study periods since the survey changed.

Q: In terms of explaining the decrease in ATP seen in 2020 – other than EVALI or changes due to COVID – could it also be due to not being able to reach study participants who would have been reached if not for COVID? Do you see any differences in NYTS participants in 2020 compared to other years?

Not really. The 2020 survey was ended in March 2020 due to COVID, and we can say with confidence that COVID had no impact other than cutting short the period of time they did the surveys. However, this raises another issue: the Monitoring the Future (MTF) survey showed no change in vaping prevalence in 2020 versus the large change we saw for 2020 in NYTS. This is a huge gap, and we are not yet sure what this means, but it is something we should be aware of.

The CISNET Smoking History Generator and CAsToR microsimulation models: Past Applications, Current Developments, and Future Directions

Rafael Meza, PhD, University of Michigan

Abstract

This presentation discusses an overview of two modeling tools developed for tobacco use modeling and policy simulation, the Smoking History Generator and the Tobacco Policy Tool, together with examples of using both tools in practice.

Introduction

The Center for the Assessment of Tobacco Regulations (CAsToR) aims to provide evidence-based and expert-informed modeling of the behavioral and public health impacts of tobacco regulations. In this presentation, we will discuss its work with the Smoking History Generator and CAsToR micro-simulation models. Compared with earlier smoking models, we focus on how patterns change by generation or birth cohort, as well as by covariates. We also focus on modeling, in quite a bit of detail, the history in the US of smoking initiation, cessation, and intensity rates. This model has been expanded to consider policy effects and has been used to predict the impact of different US tobacco control policies on overall mortality and lung cancer prevalence.

Overview of Smoking History Generator

Figure 1 shows a schematic presentation of the model. Key data sources include the National Health Interview Survey (NHIS), the Cancer Prevention Studies (CPS-I and CPS-II), and the Human Mortality Database. These are integrated and serve as the inputs for the simulator that generates individual smoking histories.

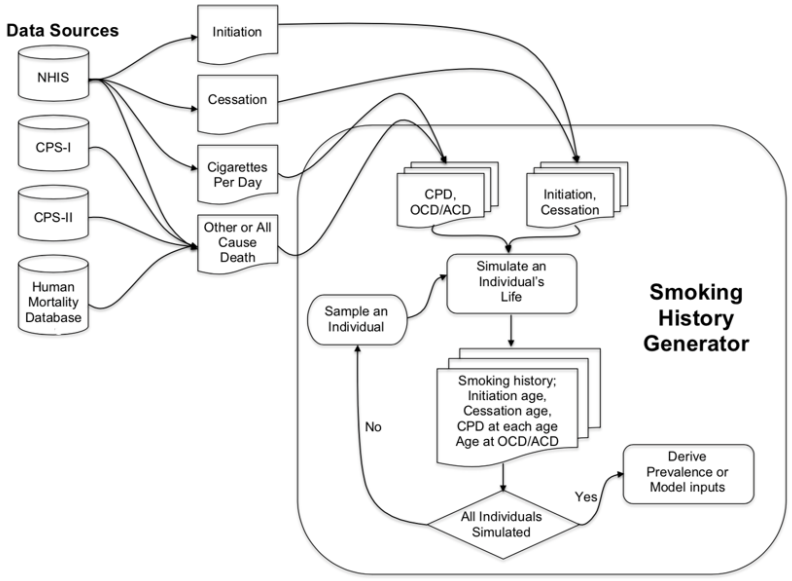

Figure 1. Schematic of Smoking History Generator.

One key input is initiation rates, and we have similar figures for cessation rates, shown in Figure 2 for different generations. As part of this work, we have been able to characterize the history of smoking in the US

in detail. For instance, we find stronger reductions in smoking cessation, particularly for recent birth cohorts, and the question is if this will continue or not, particularly in this era of more new products.

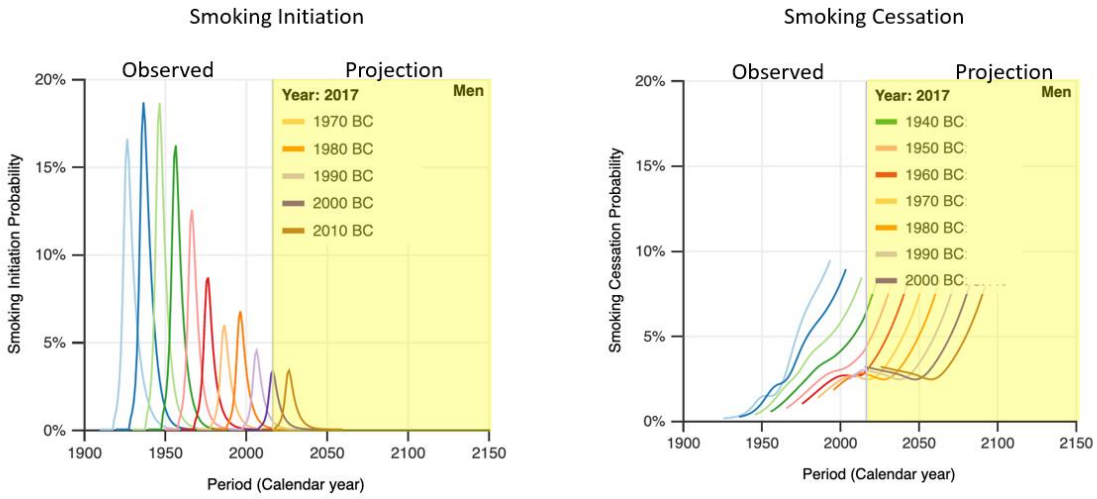

Figure 2. Observed and projected smoking initiation and cessation by birth cohort. (Sources: Holford et al., 2014; Jeon et al,. 2018; Tam et al., 2018)

We then use the simulator to generate individual smoking histories, which become the input for the CISNET lung cancer models. When we simulate a large number of individuals, we recover the patterns of smoking in the US population, and then if current trends by cohort or generation continue, we can project where we think smoking is going to go in the next few years. These, in turn, become inputs for the CISNET lung models that can model the number of lung cancer deaths in the US and predict where they are going to go. For instance, as smoking goes down, and the population share of never smokers increases, we actually expect an increase in the actual number of lung cancers among never smokers, as shown in Figure 3.

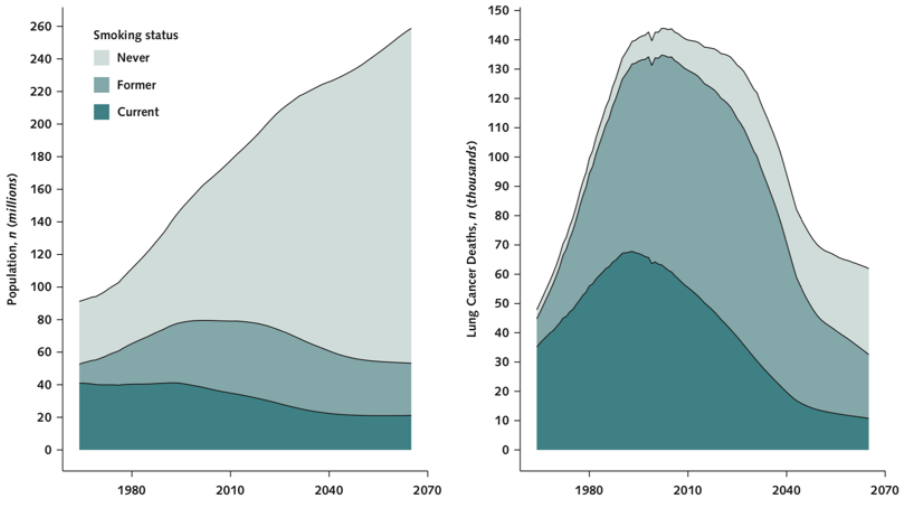

Figure 3. CISNET projected future smoking and lung cancer burden. (Source: Jeon et al, 2018)

The Tobacco Policy Tool

We've extended the Smoking History Generator to a Tobacco Policy Tool that modifies the initiation rates and cessation rates under policy scenarios, and then we repeat the simulations to compare the impact of different policies, as shown in Figure 4. In particular, the Smoking History Generator and the Tobacco Policy Tool have been used to generate the inputs behind a policy tool that we've developed, the website TobaccoPolicyEffects.org, where policy makers can examine the projected effects of four different policies.

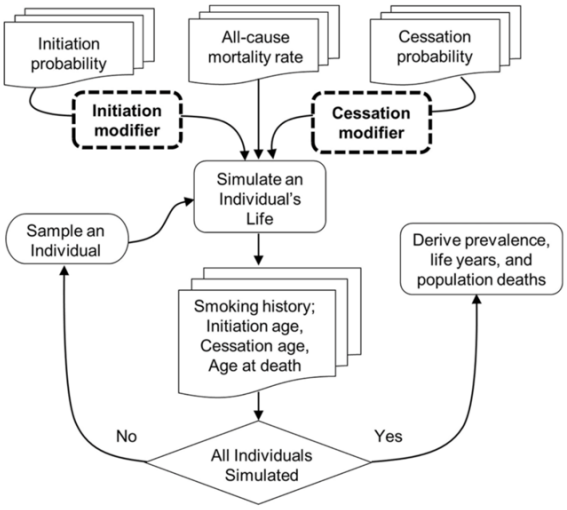

Figure 4. Schematic of Tobacco Policy Tool. (Source: Tam et al., 2018)

Figure 5 shows an example from TobaccoPolicyEffects.org where you can vary parameters - in this case, tax level - and then see the effect projected in the US or in specific states. We continue working within CISNET and within CAsToR to expand many of these applications and tools.

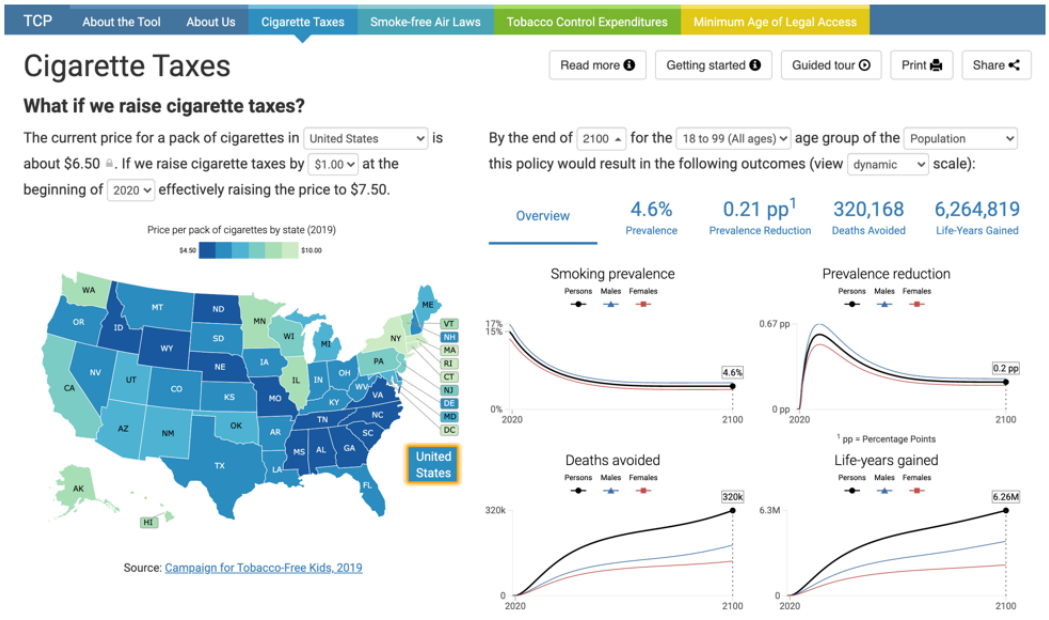

Figure 5. Sample screen from TobaccoPolicyEffects.org, modeling increase in cigarette taxes.

Other modeling examples

We are working hard to expand the Smoking History Generator to consider other sociodemographic groups. As one example, an extension of the Smoking History Generator now incorporates smoking and mortality factors for the non-Hispanic black population and can consider ENDS as well as smoking.

Figure 6 shows rates of initiation and smoking prevalence for non-Hispanic blacks (solid lines) and non-Hispanic whites (dashed lines) by birth cohort, showing a pattern by generation where prevalence is lower for non-Hispanic blacks early in life but increases later in life. We use this input to generate simulation models of smoking and health outcomes for US blacks and plan to extend this to other racial and ethnic groups.

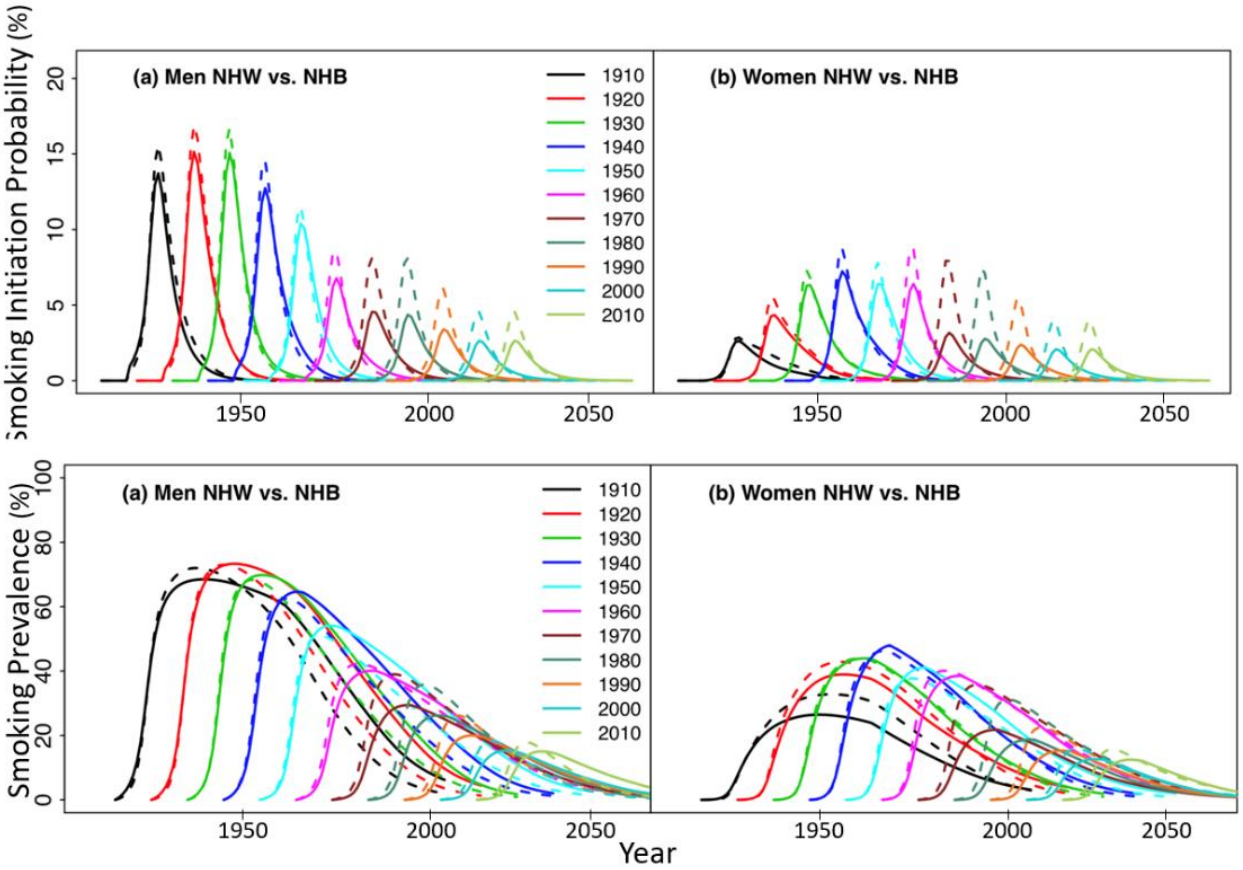

Figure 6. Smoking initiation probability and prevalence rates for non-Hispanic blacks versus non-Hispanic whites by birth cohort.

Figure 7 shows some results from this model, projected through 2100. The left hand side projects smoking prevalence under status quo for non-Hispanic black males and females if cessation trends continue by generation as they are now.

The right hand side of Figure 7 projects smoking-attributed mortality for this group between the status quo and a scenario representing the maximum potential reduction of premature mortality (MPRPM) that could be achieved if all non-Hispanic blacks quit smoking in 2020. This metric, proposed by Ken Warner and David Mendez, is a good example of new metrics that will allow us to compare the impact of different policies.

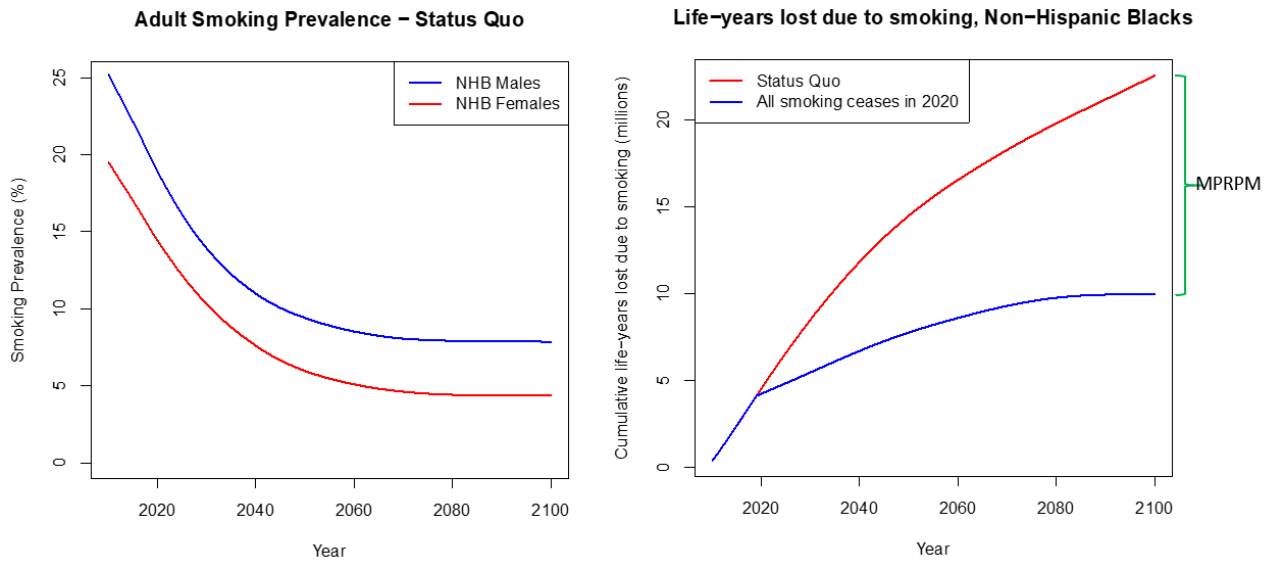

Figure 7. Modeling results for non-Hispanic blacks, projecting adult smoking prevalence under status quo assumptions (left side), and life-years lost due to smoking for status quo versus maximum potential reduction of premature mortality (MPRPM) (right side).

Another modeling example at CAsToR involves extending our simulation models to consider multiple products, such as combustible cigarettes and ENDS. For example, Brouwer et al. (2020) examined transition states between cigarettes and e-cigarettes, with a main schematic representation shown in Figure 8. We are trying to connect this kind of modeling with the data analysis that is also being conducted in CAsToR.

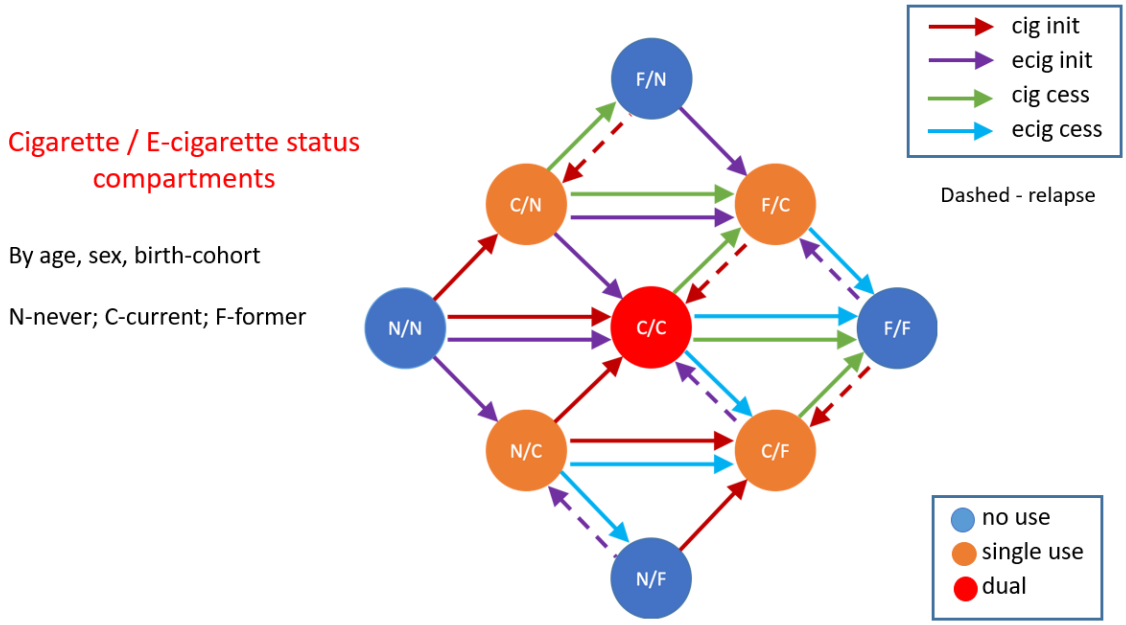

Figure 8. Schematic representation of transition states between cigarette and e-cigarette use. (Source: Brouwer et al., 2020)

Figure 9 shows results from this study, estimating transitions between cigarette and ENDS statuses, and then estimating transitions between categories of never use, non-current use, current exclusive use, and dual use.

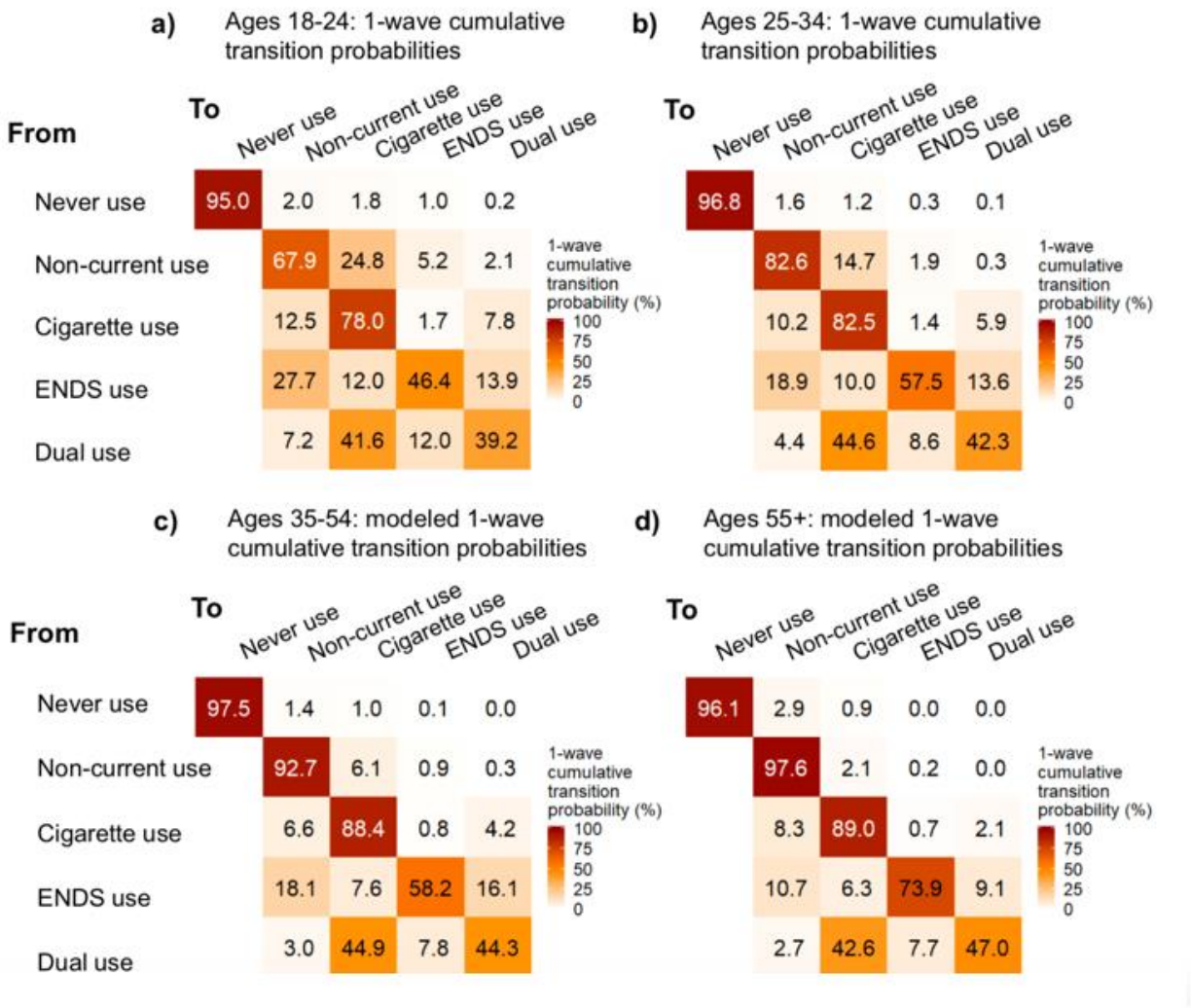

Figure 9. Results by age group of analysis of transitions between product use categories. (Source: Brouwer et al., 2020)

Future directions

Beyond our current efforts, some important future directions for our modeling efforts at CAsToR include:

- Extensions to other sociodemographic groups, including categories such as education, income, and state of residence
- Modeling of other tobacco-related conditions, such as the relationship between tobacco use and mental health, COPD, and cardiovascular disease
- Multiple tobacco products (Measurement of longitudinal exposure with different outcome metrics; explore product interactions)
- More advanced modeling methods and dissemination tools, including using multiple data sources in an automated and timely way, improving model accessibility, and training a new generation of modelers.

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Understanding the Public Health Consequences of Menthol Cigarettes: A Computational Modeling Approach

David Mendez, PhD, Department of Health Management and Policy
University of Michigan School of Public Health

Abstract

This presentation looks at the modeling process behind the 2011 TPSAC report on menthol in cigarettes and subsequent work on the harms of menthol as examples of using modeling to support public health regulation, together with open questions for the future.

Introduction

This presentation discusses an example of a process of developing a model that might be useful in generating ideas and policies for public health, using menthol in cigarettes as a case study.

The 2009 Family Smoking Prevention and Tobacco Control Act charged the Food and Drug Administration's (FDA) Tobacco Products Scientific Advisory Committee (TPSAC) with developing a report and recommendations that address "the issue of the impact of the use of menthol in cigarettes on the public health including such use among children, African Americans, Hispanics, and other racial and ethnic minorities."

One of the findings of this committee was that the evidence was insufficient to conclude that the substance menthol was harmful. Nevertheless, the TPSAC's recommendation was that the removal of menthol cigarettes from the marketplace would benefit public health in the United States. So why was a substance that is not harmful in cigarettes still recommended for removal?

The issue was that empirical results showed that individuals who experimented with menthol were more likely than those who experimented with non-menthol cigarettes to become regular smokers in adulthood, those who smoked mental cigarettes were less likely to quit, and there was increased evidence of increased addiction among menthol smokers. So this was a harm that they needed to evaluate. The TPSAC committee could not say that menthol was a harmful substance, but it was harmful in the way that the delay is quitting it allows more people to get addicted and smoke longer.

So is that effect of sufficient magnitude to warrant a concern at the population level? That's what the TPSAC committee wanted to evaluate. It was an interesting collaboration between myself, who had no prior experience with menthol, and a committee that was not that familiar with simulation modeling. Working closely with Jonathan Samet, Dorothy Hatsukami and Neal Benowitz, we went back and forth to figure out what was important to them and what to model. Instead of saying, "Let's look at the overall picture of menthol, and let's put in everything that happens or potentially happens with menthol," the idea was to produce a model that represented the harm, and the origins of the harm, that they were thinking about.

Modeling the impact of menthol

So we developed the model, and its conclusions were in the TPSAC report. Later, when we started CAsToR with a larger group of investigators, one of our priorities was to evaluate menthol harm. We obtained new parameters, updated the parameters for the model, and in collaboration with colleague Thuy Le, produced the results of what was the likely damage of menthol over the past 40 years - in other words, what portion of cigarette smoking harm can be attributed to menthol. A diagram of this model is shown in Figure 1.

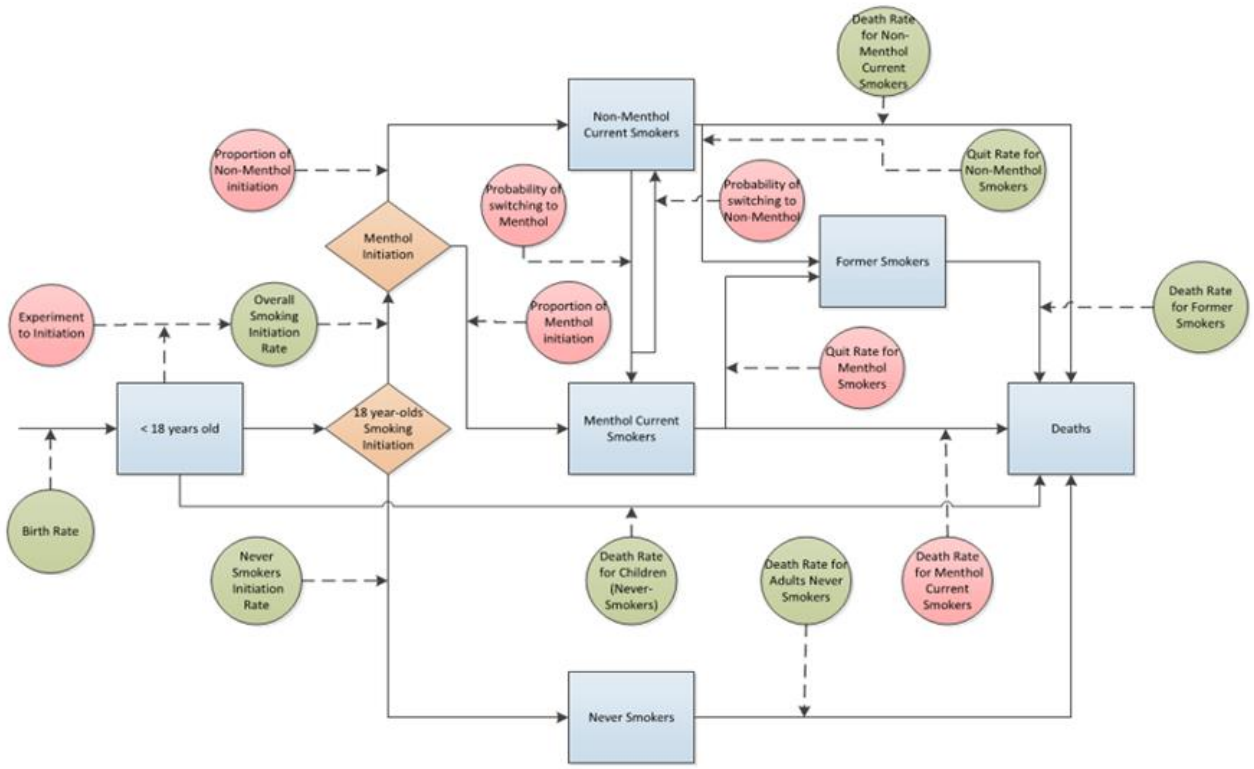

Figure 1. Block diagram of menthol cigarettes prevalence model.

Next we updated the TPSAC report, which is in process, because now we know that the harm due to menthol was substantial over the last 40 years. What about going forward? So if there is to be any action, it should not only be based on the past, but also the potential for damage going forward. We found that this damage is still very significant, both in the general population (Table 1) and more concentrated in the African-American population (Tables 2 and 3).

	Cumulative Excess Initiation				
	2020	**2030**	**2040**	**2050**	**2060**
TPSAC Report 2010-2050	2,288,534	4,429,326	6,710,101	9,124,867	
Update 2018-2060		1,261,941	2,282,866	3,333,301	4,389,620
	Cumulative Excess Premature Deaths				
	2020	**2030**	**2040**	**2050**	**2060**
TPSAC Report 2010-2050	17,182	67,182	164,590	327,565	
Update 2018-2060		79,381	200,851	333,694	465,458
	Cumulative Life-years Lost				
	2020	**2030**	**2040**	**2050**	**2060**
TPSAC Report 2010-2050					
Update 2018-2060		296,302	1,384,200	3,134,939	5,244,762

Table 1. Estimated public health effect of menthol in the general population,. TPSAC report vs updated parameters.

	Cumulative Excess Initiation				
	2020	2030	2040	2050	2060
TPSAC Report 2010-2050	461,273	859,101	1,262,086	1,656,005	
Update 2018-2060		292,761	533,250	778,295	1,023,171
	Cumulative Excess Premature Deaths				
	2020	2030	2040	2050	2060
TPSAC Report 2010-2050	4,716	16,381	35,250	66,524	
Update 2018-2060		34,282	71,999	104,660	134,807
	Cumulative Life-years Lost				
	2020	2030	2040	2050	2060
TPSAC Report 2010-2050					
Update 2018-2060		137,740	558,208	1,125,330	1,722,065

Table 2. Estimated public health effect of menthol on the African American population. TPSAC Report versus updated parameters.

	Cumulative Excess Premature Deaths			
	2030	2040	2050	2060
African American Population	34,282	71,999	104,660	134,807
Low Menthol AA Population	2,272	9,580	23,819	43,935
	Cumulative Life-years Lost			
	2030	2040	2050	2060
African American Population	137,740	558,208	1,125,330	1,722,065
Low Menthol AA Population	6,750	51,946	177,094	412,665

Table 3. Estimated public health effect of menthol on the African American Population vs a hypothetical low menthol African American population.

Figure 2 shows some of the results from this model. Over the next 40 years, African-Americans will bear 23 percent of excess smoking initiation due to menthol and almost 30 percent of premature deaths, despite representing just 12 percent of the population. Moreover, if African Americans were to use menthol in the same proportion as the general public, their share of premature deaths would drop to 9 percent.

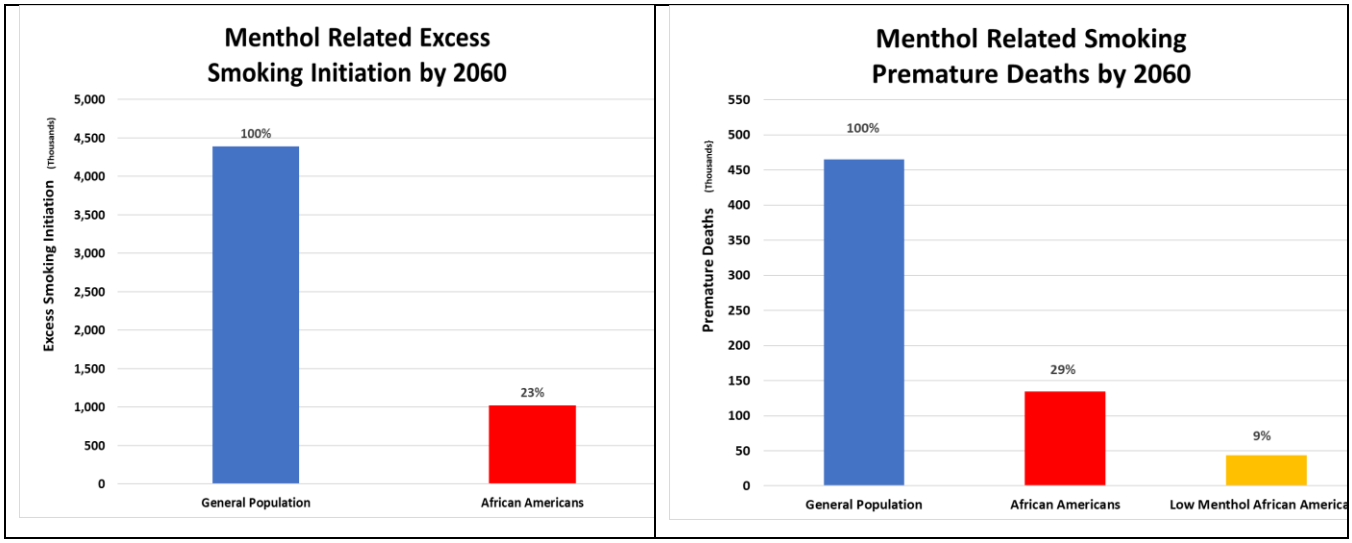

Figure 2. Excess smoking initiation and premature deaths projected due to menthol, 2020-2060.

Closing thoughts

We have just shown a specific example of the utilization of simulation modeling in public health, and its results speak directly to implications for public health. So how easy or difficult is it to put models like these together? Here are some of the issues that we need to discuss from here:

Training. Is it necessary to have formal training in modeling? How do we actually pick up the idea of what it is that you are going to model and how to express that process appropriately?

Collaboration. We should highlight the benefits of collaboration and complementary expertise in simulation analysis. For example, I have had the great benefit of working with Ken Warner for many years, and over time we have learned how each other thinks and have acquired expertise in each other's areas.

Expertise. Our experiences at CAsToR bring attention to the additional expertise that is often needed in the field of tobacco simulation. Having modelers with expertise in tobacco makes it much easier to contemplate and talk about ideas and get them to come to fruition. That is the model that we should be striving for: individuals with dual skills in methodology and technology.

Meaning of results. To put the meaning of quantitative simulation results into perspective, in 2011 David Levy produced a model that showed similar magnitudes of the harms of menthol as the model that we produced. This was very good because we didn't communicate at all with each other, so that lends some validity to our findings. But we are not looking to get exactly the same numbers; we want to present the magnitude of the problem, perform sensitivity analyses, and see if the magnitude of the problem remains in the same ballpark.

Meeting current needs. We need to discuss the value of computational modeling approaches to tobacco regulation. Solving questions that regulators are looking for is important, and it is a choice for researchers to be working on something that will respond directly to current needs. How can we anticipate that effectively?

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Modeling a Menthol Ban Using the Menthol SAVM (Smoking and Vaping Model)

David T. Levy PhD, Georgetown University

Abstract

This presentation describes the development of the Smoking and Vaping Model (SAVM) for exploring the impact of menthol in cigarettes, including model design, calibration, results, and future directions.

Introduction

The idea of using modeling to support the concept of a menthol ban for tobacco products goes back at least a decade, including previous modeling and empirical efforts. In this presentation we will look at our work modeling a menthol cigarette ban to examine the public health impact of such a ban, using recent data on smoking patterns from the Smoking and Vaping Model (SAVM) model, and in this case incorporating the potential role of the use of nicotine vaping products (NVPs) in such a ban.

A review of the literature showed strong existing evidence that a menthol ban would lead to an increase in smoking cessation. What was less clear, however, was its effect on initiation. While good evidence also exists that menthol is associated with cigarette smoking initiation, questions remained about what impact a menthol ban would have on initiation.

We considered the impact of a menthol ban that is applied to both cigarettes and cigars, so that substitution from menthol cigarettes to menthol cigars, especially little cigars, is not a major unintended consequence. For the design of the menthol ban scenario in Menthol SAVM, we modeled the allocation of would-be menthol smokers in the initiation process from never smokers, and switching and cessation processes from menthol and non-menthol smokers. For these parameters, we relied on an expert elicitation process (Levy et al. 2021a), as well as a review by Cadham et al. (2020), applying mean net transitions from the expert elicitation.

Development of the model

The expert elicitation for this project was developed through the Tobacco Centers of Regulatory Science (TCORS) in collaboration with Dr. Aylin Sertkaya. This process involved 11 experts, based on a review of the literature on menthol bans as well as an h-index based on a search of Scopus, to identify individuals who were among the most published authors on the topic of menthol tobacco. The final panel was based on these two criteria together with efforts to have a panel with diverse views, and two rounds of Delphi method sessions were conducted via the internet.

Initiation parameters

Initiation, as mentioned earlier, was a key concern. We ultimately decided to set up our questions thinking in terms of people who would initiate smoking by the age of 24, and what they would do in the event of a menthol ban. The decision tree that was used is shown in Figure 1.

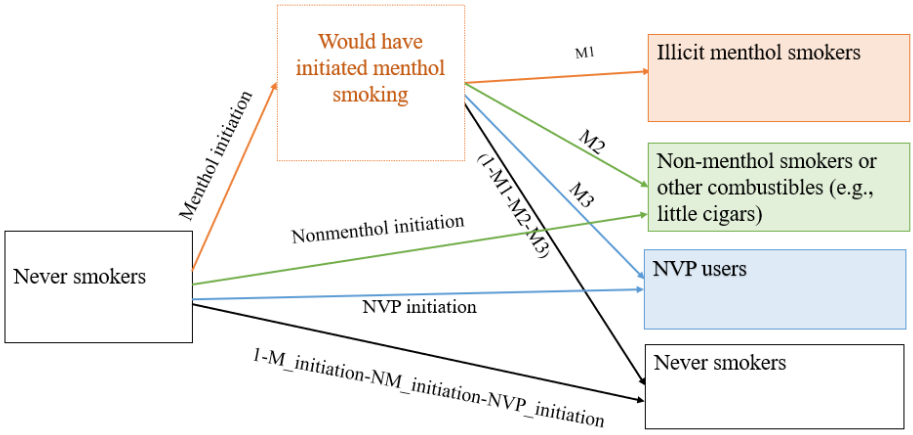

Figure 1. Transitions from never smokers under the Menthol Ban scenario, based on 100 youth and young adults who would have become menthol smokers by age 24 in the absence of a ban.

Results based on this tree are shown in Table 1. In this case, the status quo is people by the age of 24 who are menthol smokers, with the results showing, for the total population, what they do instead. The results were that 41.1 percent still smoke, 17.6 percent switch to novel nicotine delivery products (NNDP) such as e-cigarettes, and 39.1 percent use no tobacco or novel nicotine delivery products, so e-cigarettes did play an important role.

Population	Status Quo	Total Population with Menthol Ban			
Product Type	**Mean/ Median**	**Mean**	**Median**	**Min**	**Max**
Become non-menthol cigarette users (exclusively or with other products)	-	33.0	30.0	1.9	79.0
Become non-menthol cigar users (exclusively or with other products, but not cigarettes)	-	5.5	2.0	0.0	20.0
Become illicit menthol cigarette or cigar user	-	2.6	1.0	0.0	10.0
Total combustible use (status quo all menthol cigarettes)	100.0	41.1	46.0	3.5	83.0
Become exclusive smokeless tobacco or other oral tobacco product users	-	2.2	2.0	0.0	5.0
Become novel nicotine delivery product users (NNDP), such as e-cigarettes or heated tobacco products (exclusively or in combination with other products, but not cigarettes or cigars)	-	17.6	20.0	3.4	25.0
No tobacco or novel nicotine delivery product use	-	39.1	30.0	6.0	92.3

Table 1. Transition of would-be menthol smokers at age 12-24 in the Menthol Ban scenario from expert elicitation.

Cessation parameters

While existing estimates for cessation were available, we chose to develop these parameters in the context of a model, and evaluate alternatives. We first asked what kind of transitions menthol smokers would make in two years in the absence of a ban, and then looked at how that would change with a ban, as shown schematically in Figure 2.

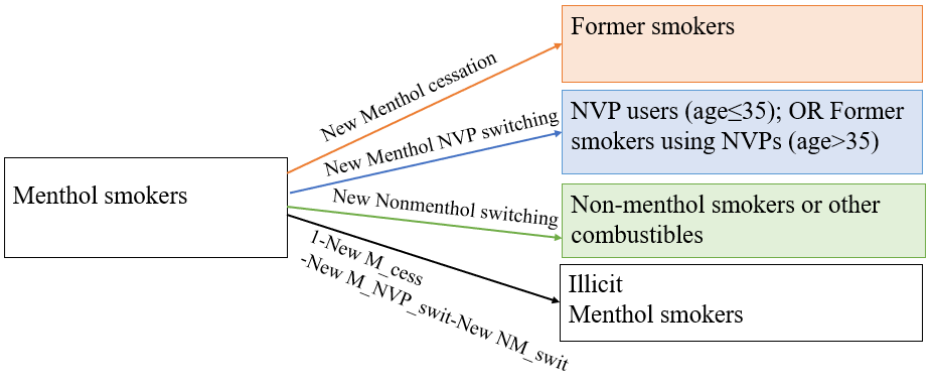

Figure 2. Primary transitions by menthol smokers in the Menthol Ban scenario, compared to cessation and switching transitions of menthol smokers in the absence of a menthol ban, i.e., the status quo.

Table 2 summarizes these transitions. Even without a ban, a sizable portion (12.5%) quit smoking, with 9.7 percent switching to e-cigarettes. Other results of what would happen to menthol smokers if there were a ban include increased cessation and e-cigarette use. Based on this, we looked at the difference and standardized that based on the percentage of menthol smokers in the status quo, and these gave us the transitions relevant to our model.

Product Type	No ban Mean	With ban Mean	Absolute difference	Percentage of the 67.9% menthol smokers in the Status Quo
Continue to be menthol cigarette smokers (exclusively or with other products)	67.9	0.0	-67.9	
Switch to non-menthol cigarettes (exclusively or with other products, except menthol cigarettes)	4.5	45.7	41.2	60.6%
Switch to cigars, especially little cigars, filtered cigars, or cigarillos (exclusively or with other products, but not cigarettes)	2.7			
Switch to non-menthol cigars, especially little cigars, filtered cigars or cigarillos (exclusively or with other products, but not cigarettes)		3.7	1.0	1.5%
Switch to illicit menthol cigarette or cigar use	0.0	5.7	5.7	8.4%
Total Combustible	75.2	55.2		
Switch to exclusive smokeless tobacco or other oral tobacco products	2.6	2.4	-0.2	-0.3%
Switch to novel nicotine delivery products (NNDP), such as e-cigarettes or heated tobacco products (exclusively or in combination with other products, but not cigarettes or cigars)	9.7	20.0	10.3	15.2%
Quit regular use of all tobacco or novel nicotine delivery products	12.5	22.5	10.0	14.7%

Table 2. Transition of menthol smokers at age 35-54 in the status quo and menthol ban scenario from expert elicitation.

Menthol SAVM model

These parameters were then used to create a model based on a simplified model of smoking and vaping, which focused on regular use and did not explicitly consider dual use (Levy et al. 2021b). Since nicotine vaping products (NVP) became more prevalent around 2013, this model was calibrated and validated over the period 2013-2020. We assumed that a menthol ban takes place in 2021, and compared the smoking and vaping rates and associated deaths with those under a status quo of no menthol smoking ban. This model assumed the same risks for menthol and non-menthol smoking, but did sensitivity analysis of NVP risk, and did

not explicitly model cigar (considered as combustibles) or smokeless tobacco use. A schematic of the transitions used is shown in Figure 3.

The focus for this model was on regular use, and in trying to simplify it, one of the decisions that was made was to focus on transitions to regular use. For example, if somebody used e-cigarettes for a short period of time, then became a smoker, ultimately what was important is that they became a regular smoker, and that was what we specifically modeled in SAVM. We decided – more controversially – not to explicitly include dual product users, who were incorporated with cigarette users. We chose at this point to keep things as simple as possible, until we understand more the interrelationships between dual use and ultimate regular use.

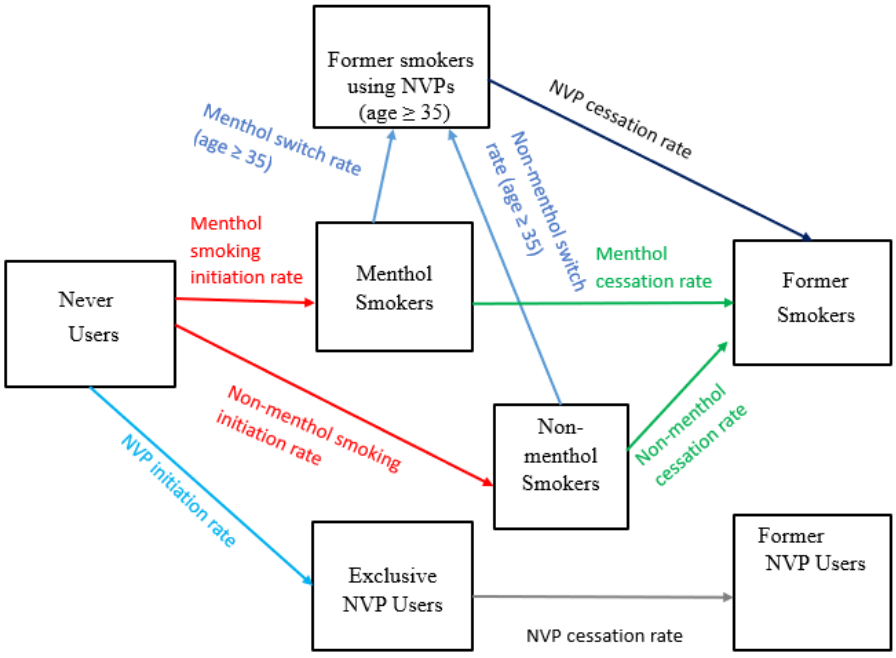

Figure 3. Transitions between smoking and nicotine vaping products (NVPs) use states in the Status Quo scenario.

Calibration of the pre-menthol model

We adjusted the rates of initiation and cessation to obtain a better fit of the model for smoking and NVP prevalence, particularly at younger ages. The main adjustment was in initiation, because of the drastic reduction in smoking rates among youth and young adults. This model also showed an upward trend in menthol use pre-ban.

The primary final adjustments involved reducing the percentage of smoking initiation and increasing the switching rate to NVPs at younger ages (e.g., through age 24), while reducing the cessation rate at older ages. We also adjusted the NVP switching rate from 2018 onward by reducing it by 10 percent annually starting in 2018 at all ages for both genders; otherwise, the low smoking initiation led to drastic reductions in smoking prevalence.

Table 3 shows the rates that were projected for the future for both menthol and non-menthol smokers, which were lower compared with past estimates; it was important for us to capture recent trends, and because cigarette use had been so drastically reduced in recent years, we incorporated that. At the same time, this model was flexible enough to consider variations in these initiation rates.

Menthol Status Quo				
Category/Year	2021	2026	2060	Cumulative Impact *
Menthol smoker	5.4%	4.5%	2.4%	-56%
Nonmenthol smoker	7.2%	5.7%	2.7%	-63%
All Smokers	12.6%	10.2%	5.1%	-60%
Former smoker	19.4%	18.4%	9.2%	-53%
Former NVP user	0.2%	0.6%	4.6%	1973%
Total SADs	380,525	377,046	282,457	14,217,294
Total LYL	4,694,635	4,425,092	2,401,706	143,238,275
Menthol Ban Scenario				
Category/Year	2021	2026	2060	Cumulative Impact *
Menthol smoker	5.4%	0.3%	0.1%	-98%
Nonmenthol smoker	7.2%	8.4%	4.2%	-41%
All Smokers	12.6%	8.7%	4.3%	-66%
Menthol smoker	77,455	6,792	2,557	271,469
Total	380,525	359,958	268,435	13,563,073
Total	4,694,635	4,113,651	2,182,890	131,927,198
Public Health Impacts				
Menthol Smoker	-	-92%	-97%	-
Nonmenthol Smoker	-	47%	58%	-
All Smokers	-	-15%	-15%	-
Overall NVP	-	23%	27%	-
Averted Deaths	-	17,088	14,022	654,221
Averted life-years lost	-	311,441	218,817	11,311,077

Table 3. Smoking and NVP prevalence, smoking and vaping attributable deaths, life-years lost and public health impact for both genders combined, ages 18 and above, 2021-2060.

Model results

Figures 4 and 5 show results from running the model. Figure 4 shows drastic reductions in menthol use and increases in non-menthol use, which are not as big proportionately because non-menthol smokers began at higher rates.

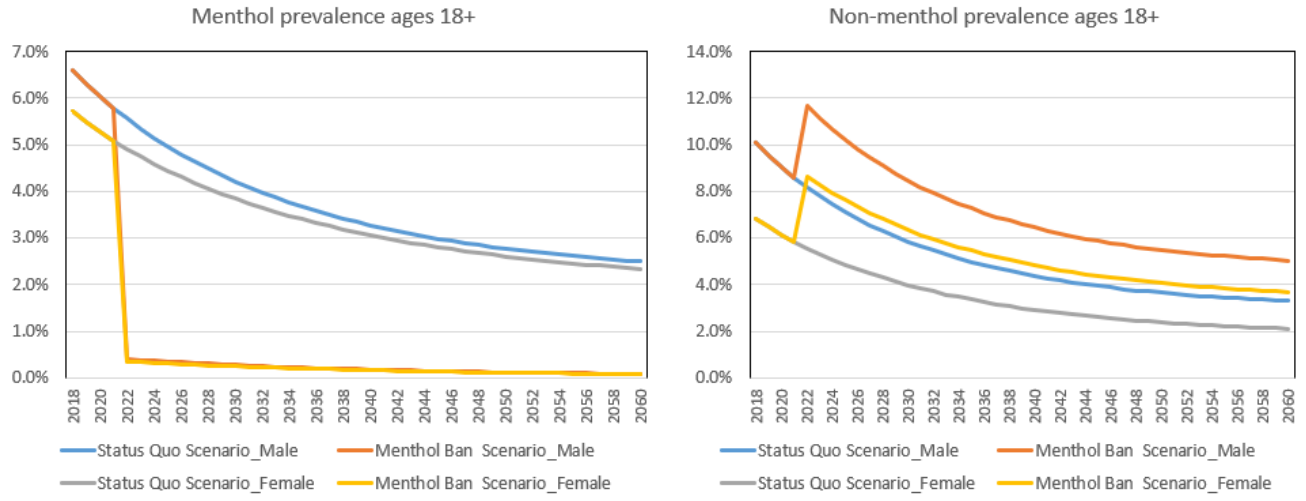

Figure 4. Prevalence rates: pre- and post-menthol ban.

Figure 5 gives an idea of the overall effects on cigarette use. We did find that there were what might be considered substantial reductions in cigarette use, which then translated to reductions in both cigarette and e-cigarette avertible deaths.

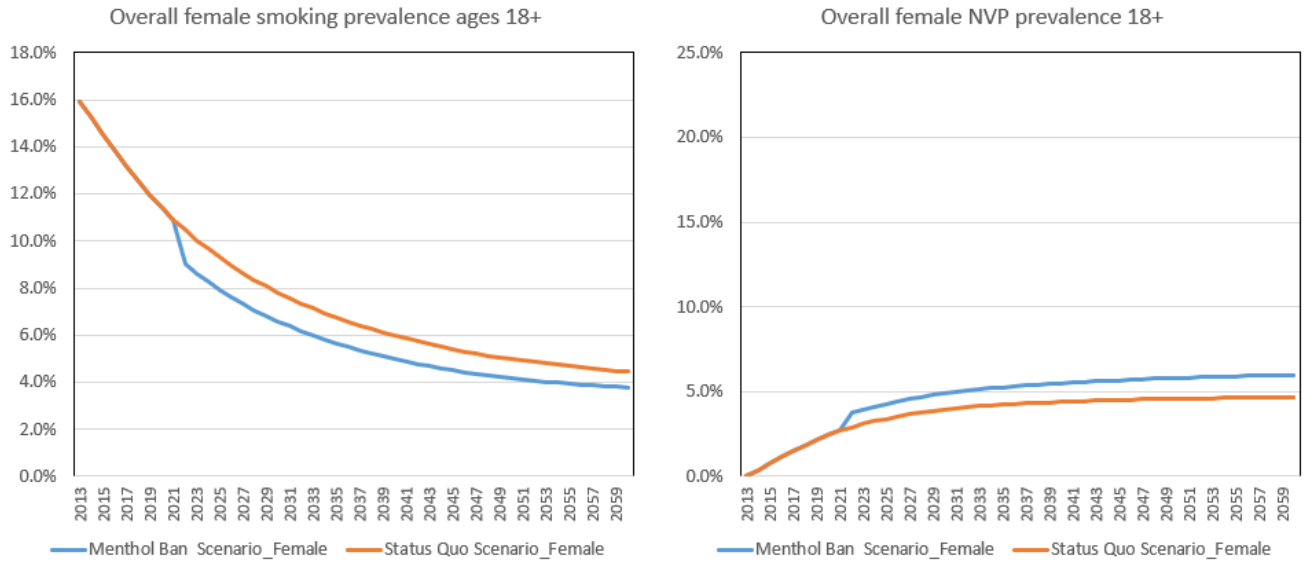

Figure 5. Impact on overall smoking and NVP prevalence.

Table 4 shows the results of our sensitivity analysis. This data shows that the results were particularly sensitive to the rate of switching from cigarettes to e-cigarettes, and to smoking cessation rates. This is an important implication of the model, because it tells us what is potentially important and what we need to understand to fully gauge the effects of a menthol ban.

Case	Description	Both genders combined	% change*
Smoking- and Vaping-Attributable Deaths Averted by Menthol Ban			
1	Base Case	654,221	-
2	5% instead of 15% NVP risk	687,209	5%
3	25% instead of 15% NVP risk	622,425	-5%
4	Increase overall smoking cessation rates by 50%	459,759	-30%
5	Reduce overall smoking initiation rates by 50%	617,576	-6%
6	Increase non-menthol cessation rates annually by 10%	845,972	29%
7	Menthol cessation rate same as non-menthol rate	461,006	-30%
8	Increase NVP cessation rates by 50%	668,766	2%
9	Increase NVP initiation rates by 100%	652,116	-0.3%
10	Menthol switching rate same as non-menthol rate	636,897	-3%
11	Increase overall switching rate by 50%	581,294	-11%
12	Reduce the annual decline in switching rate from 10% to 0%	504,624	-23%

Table 4. Sensitivity analysis of averted smoking- and vaping-attributable deaths and life-years lost to NVP relative risks and individual transition parameters, both genders combined, all ages, 2021-2060.

Conclusions

Some key points about this model include the following:

- It focuses on regular use and does not distinguish between dual and exclusive use.
- We also did not consider variations across subpopulations such as age, socio-economic level or race, although, for example, there are potentially important differences between African-Americans and the rest of the population because of the high rates of menthol use in the African-American population.
- Its results depend on the stability of transitions, including those related to NVPs (e.g., due to major changes in technology or surrounding events, such as COVID), as well as whether recent reductions in smoking will continue into the future.
- Finally, we did not include results on smokeless tobacco, to simplify the model as much as possible. We have the potential of bringing in smokeless, oral and heated tobacco products in the future.

In conclusion, we did find substantial improvements in public health through reduced smoking as a result of a menthol ban and saw major reductions in smoking-attributable deaths offset to some extent by the increase in NVP use. The results were sensitive to parameters, especially switching from cigarettes to e-cigarettes, while being relatively insensitive to single parameter variations of individual transitions and NVP risks.

We have now made the SAVM model available via the TCORS website, together with a 100-page user manual, and we plan on extending this model in the future to examine how a menthol ban would be influenced by a policy of restricted flavors in nicotine vaping products (NVPs). We strongly encourage others to engage in the modeling process as a way of looking at the potential effects of policies and thinking about the relevant transitions that we need to focus on in the future to truly understand patterns in tobacco use.

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Breakout Sessions: Future Directions in Tobacco Modeling

Moderated by Ritesh Mistry, PhD, University of Michigan

Abstract

A summary of discussions and recommendations is presented from five breakout sessions on future issues for modeling in tobacco regulatory science, facilitated by subject matter experts. Topics discussed include modeling priorities, training, translation, accessibility and collaboration, and engagement with industry.

Introduction

In the closing session of this Symposium, participants participated in one of five separate breakout sessions to discuss future modeling issues for tobacco regulatory science and make recommendations. These groups were hosted and facilitated by subject matter experts in their respective topic areas, followed by summary presentations by each facilitator. Specific breakout group topics and their facilitators were as follows:

Topic	Facilitator
Modeling Priorities	David Levy, PhD, Georgetown University
Training	David Mendez, PhD, University of Michigan
Timely Translation	Rafael Meza, PhD, University of Michigan
Model Accessibility and Collaboration	Jamie Tam, PhD, Yale University
Industry Engagement	Clifford Douglas, JD, University of Michigan

Chatham House Rule

To encourage open dialogue and a frank, free exchange of ideas, these breakout sessions were held in the spirit of the Chatham House Rule (www.chathamhouse.org), which state:

"When a meeting, or part thereof, is held under the Chatham House Rule, participants are free to use the information received, but neither the identity nor the affiliation of the speaker(s), nor that of any other participant, may be revealed."

While summaries of these breakout session discussions are being disseminated as part of the Symposium proceedings, the actual discussions and the identities of individual speakers within these breakout groups have not been recorded for dissemination. What follows are summaries informed by discussion comments as well as public presentations by individual breakout session facilitators.

Topic 1: Tobacco Regulatory Science: Modeling Priorities

This group's discussion centered on the most "wicked modeling tasks" facing tobacco regulatory science – in other words, what would be most important for modeling to support in TRS over the next decade.

A major theme that emerged from these discussions was thinking about harms in a more systematic way: in particular, thinking about the relative harms of newer products and how they compare, which remains

controversial. Another key theme was how best to aggregate products in terms of harms, in terms of the individual products themselves, the overlapping use of products, and relevant transitions between products.

This led naturally to the question of data sources and how to combine them. There has been a lot of discussion at this Symposium about different surveys and how they have different results. We also need to think about other sources of information, such as information that's collected rapidly over the Internet, as well as market and sales data, to give us a real way of capturing the most recent changes in use patterns. A related question is how we integrate this data with some of the methods that were discussed, such as discrete choice analysis, the experimental marketplace, and so on.

Finally, how do we make sure that the different ways in which we're modeling responds most directly to what is needed? At CAsToR, much of our work is related to the FDA, but we need to explore ways of ensuring that what we are doing is consistent with the needs of that stakeholder, as well as consider how our modeling work is relevant to other stakeholders.

Summary of specific ideas discussed in the breakout group

What are the top 3-5 major/most wicked modeling tasks facing tobacco regulatory science?

- Gathering data and modeling the effects of new and emerging products, on their own or modeling poly-product use
- Estimating the harm of non-combustible products on the continuum of harm, and looking at how we divide these products into categories for modeling
- Having truly dynamic computational models in a rapidly changing market
- Considering the impact of transitional or temporary use, versus focus on regular use of different products
- Seeing how reliable the effect sizes of policies over time are, especially for nicotine vaping products versus cigarette-oriented policies

How should we best work with different data sources?

- Working with data when estimates from different sources do not agree with each other
- Exploring broader sources of data to inform our models, such as internet surveys and sales data, to answer questions that policy makers have
- Distinguishing how to best use different datasets, and identify relevant categories/transitions over time

How do we make sure modeling responds to what is needed?

- Validating models in a way that speaks to regulators and stakeholders, and creating more community connection to modeling
- Looking at the value of considering industry structure and behavior

Topic 2: Training

Several issues came out of this discussion on training. One was a need for more formal training in what we call systems thinking, for modelers and non-modelers to have a global view of problems, and understand them in terms of inputs, outputs, processes, and how they are interconnected. There is also a need for more individuals

that have formal training in modeling or related fields such as math and systems science, who understand the most effective and efficient modeling approach for a problem, as well as the pitfalls of different approaches.

To better understand the behavior of the models that they are putting together, it would be ideal for those in the modeling community to also have tobacco expertise, as well as extra training on the U.S. health system and its possibilities for regulation. There was a consensus that it is better for people to have formal quantitative training at the undergrad or graduate level, and then provide them with tobacco and the social science expertise so they can communicate with other people on the team.

Other issues included having access to a range of related disciplines in social sciences and behavioral economics, and for everyone involved in the modeling process, the ability to share and disseminate ideas in ways that can be understood by other people. Finally, a key issue is what schools can do to prepare that subset of individuals who could put the engine together behind a systems thinking approach to tobacco modeling problems, and what complementary training or enhancement can be given to these people to get them the expertise they need.

Summary of specific ideas discussed in the breakout group

What kinds of formal modeling training would be helpful to tobacco modelers?

- Introduction to tobacco control in the US and the US tobacco regulatory framework
- Formal training in a quantitative field either at the undergrad or graduate level
- Multidisciplinary perspective in understanding modeling approaches, mathematics/statistics, tobacco control research, epidemiology, policy evaluation
- Provide an overview or brief introduction to the most used models
- Training in interdisciplinary collaboration
- Grant writing
- Software tools and programming
- Publishing modeling studies

Are there underrepresented disciplines in the field of tobacco modeling from which we can draw a new generation of investigators?

- Social scientists, behavioral scientists, and behavioral economists
- Machine learning/AI
- Economists
- Participatory modeling

Can the necessary modeling training be acquired "on the job"?

- Yes, from my experience! Working and learning at the same time
- Yes, but depends on mentoring and support

Action steps

- Take inventory of where our modelers are coming from

Topic 3: Timely Translation

Three main topics were discussed in this breakout group. The first was the timely translation of modeling results to support the regulatory process, including the relationship between regulatory decision makers and the modelers, and how that plays a role in translation. The group reflected on examples of collaboration and input between agencies and modelers, and while also acknowledging the constraints these agencies may have about being directive or prescriptive about modeling efforts, there was a consensus that direct input from decision makers is an important and unique aspect of the process.

A related issue is how rapid dissemination can be facilitated by direct collaborations with modelers and other tobacco researchers, particularly those who are collecting data, and that regulatory funders could highlight that these collaborations are possible – and even welcome or encouraged – to facilitate the development of joint projects that make this process faster.

The second topic was getting data in a more timely manner, so modelers can develop their models using the most recent and relevant information. For many current major data sources, the lag between collection and publication or release of this data is a challenge. Ideas include the use of other sources such as sales, marketing, and tax data, as well as other new sources to get timely estimates or bounds for the effects of policies. Here as well, direct collaboration between modelers and non-modelers, or modelers and data collectors, could be a great way of improving this.

The final topic discussed was publications and dissemination, including the use of preprints and other approaches for more rapid dissemination of results. While peer reviewed publication remains the goal everyone should aim for, preprints are having an increasing role in public health, and in tobacco control they can play a role in helping to disseminate modeling results in a more rapid fashion. A major issue will be the perspective of the FDA, NIH, and other decision makers about using information from preprints to support their decisions, which appears to be a possibility. The COVID-19 pandemic was a great example of how modelers were able to disseminate results and findings very rapidly through preprints, websites, and releases in GitHub and other channels, and participants felt this approach should be embraced and developed further.

Summary of specific ideas discussed in the breakout group

What are the barriers to or facilitators of rapid translation?

- Getting geocoding data for more recent waves would allow modelers to take advantage of natural experiments
- The confidentiality of regulatory agencies may be difficult for modelers to work within
- Data not necessarily being available in a timely manner. Possible solutions: priority access for modelers via direct collaboration with data collectors, new data collection approaches (ETM, DCEs, EEs), RFAs that encourage collaborations between modelers and data collectors
- Facilitators – direct collaboration with policy makers/regulators
- Perhaps contracting for a special issue of a journal on modeling tobacco might speed up the publication process
- Detailed information is lacking
- Use of special issues, monographs, reports
- Modelers develop tools (not just papers) that can be disseminated quickly

How can we rapidly respond to regulators' and policy makers' needs?

- Rapid publication
- Rapid access to data
- Developing infrastructure to generate model parameters

Should the FDA consider pre-prints, policy briefs, and other non-peer reviewed data?

- Look at the NBER model for economics
- Preprints are a way to speed up dissemination (while awaiting peer-review publication)
- Perhaps there can be lessons learned from the COVID-19 pandemic in terms of publishing research faster? Ask journals?
- The FDA's responsibility is to regulate. If we keep doing what we are doing now, are we going to make our goals?
- The FDA is a consumer of the science, but there may not be a way to have this inside the FDA
- Preprints are a way to get information out there, and then journals can do rapid turnaround if it is very important

How can we foster direct collaborations between regulatory agencies and decision makers with modeling teams?

- Can the CAsToR group bring in FDA staff as part of modeling? A sensitive issue is policy, but fundamental research can be more collaborative with the FDA
- How can we make data available to modelers in a timely manner? The FDA is receiving data; would the FDA be willing to ask companies to voluntarily provide data?
- With the cooperative agreement grants of TCORS it may be possible to have FDA staff serve as scientific advisors to CAsToR

Topic 4: Model Accessibility and Collaboration

This group had a very productive dialogue around model sharing and collaboration, accessibility, and transparency. Some of the key questions discussed included:

- How could we strengthen interdisciplinary collaboration in tobacco simulation modeling?
- How could we incentivize researchers to share models and work collaboratively to improve them?
- How might we develop structures that facilitate model verification and reproducibility?
- How might we encourage the creation and maintenance of a repository of models with standardized documentation?

Regarding interdisciplinary collaboration, the group discussed the issue of specific needs in modeling, particularly information that currently is not available to tobacco simulation models because that data has not been generated. Participants agreed that it is worthwhile to have modelers involved in conversations around surveillance and other kinds of data collection systems, to design information in a way that is conducive to the needs of modelers and non-modelers, and in that respect strengthen interdisciplinary collaboration.

As far as incentivizing researchers to share models and work collaboratively to improve them, we talked about the idea of having some kind of rotational program where people visit researchers and learn from

each other, specific to modeling – perhaps something similar to the CISNET Passport program could exist within the TCORS and CAsToR network.

With respect to the structures that facilitate model verification and reproducibility, the idea that had the most traction in our group discussion was an accessible online taxonomy of models, where each tobacco simulation model is described in a very standard way including input parameters, explicit assumptions, and other descriptive information. This could allow people to explicitly see how assumptions are similar or different, see which inputs are shared across multiple models, and look directly at code or inputs.

There would need to be a discussion about whether this would be a publicly accessible repository, and whose responsibility this would be – it would require labor to pull together the relevant information and synthesize and standardize it, and perhaps guidelines on how information should be reported to be part of this model repository. The group felt that the University of Michigan/Georgetown TCORS is positioned well to be an example when it comes to model accessibility and model sharing. The group also discussed the challenges of funding the development of such a repository, and how this would affect the scope of models that are in it.

Summary of specific ideas discussed in the breakout group

How could we strengthen interdisciplinary collaboration in tobacco simulation modeling?

- Identify different specific needs in modeling: input parameters, network-based data, etc. As modelers, can we be more explicit about the ongoing data needs and invite other researchers to be involved
- Encourage non-tobacco people to join tobacco modeling teams, who may have experience modeling other kinds of phenomena
- Train existing tobacco control researchers in simulation modeling, and attract their interest
- Encourage the use of tools developed for model accessibility, such as the "Tobacco Control Policy Tool"
- Encourage the participation of experts in other areas in modeling groups, to have a more holistic approach

How could academia incentivize researchers to share models and work collaboratively to improve them, and thereby avoid redundancies?

- Rotational program where someone learns directly from another team
- Symposiums like this that take place annually
- Encourage the development of programs like the TCORS/CASEL- and the CISNET Passport program, but to a wider audience. The program allows researchers to visit and work with other research groups.

How might we develop structures that facilitate model verification and reproducibility?

- Base case runs where different models can be compared with each other. These would be used on a common set of input parameters.
- Develop a taxonomy of models, with different input parameters and structures, describing to users the main characteristics of models
- Websites that include model code and input parameters (e.g. transition probabilities), with a comprehensive list of assumptions and limitations, targeted to modelers and non-modelers
- Look at CISNET model profiles on their website as an example, to see what aspects are similar and different

- Assumptions and mathematical frameworks are not always clearly stated. Share the code and have shared common inputs in a descriptive table comparing across models

How might we encourage the creation and maintenance of a repository of models with standardized documentation?

- Should include what is available currently and what is still needed going forward
- Identify an independent party to come up with guidelines to standardize the information that needs to be reported in the model repositories.
- This is a full time job! Make this someone's job.
- Seek consensus from a group of modelers and non-modelers who have a good understanding of the model development process

Action steps

- Create an accessible online repository with enough information to replicate the results, including a table showing the model specific characteristics, input data, assumptions and limitations
- Explore who would be funding this and who is going to do it
- University of Michigan/Georgetown TCORS is positioned well to encourage this as a practice
- Skills used for the DAD core at the University of Michigan/Georgetown TCORS may be similar to what is needed for the creation of a repository
- Expand and disseminate the use of the "Data Dissemination" project from CAsToR-TCORS
- Funding may or may not come from the FDA, depending on whether this is domestic-focused or global

Topic 5: Industry Engagement

This group had a robust and rich discussion regarding whether modelers in academia, and the research community more widely, should support and pursue engagement with industry – including, obviously, the major tobacco companies, but also others such as those involved in the production and marketing of vaping products. Three major questions were addressed:

- What value is added – or potentially added – to the research mission by the engagement of academic researchers with industry?
- How do we optimize and ensure ethically appropriate communications between modelers or researchers in academia with industry?
- What safeguards are needed in the event such engagement is pursued?

On the first point, it was recognized by all of the participants that this is a fraught area. The industry certainly has data that may be useful in developing models and conducting research, which has not always been available to the academic community. Upon request, the industry has been cautiously forthcoming in sharing information, but academics also appreciate the likelihood, if not the certainty, of the cherry-picked nature of what is disclosed or not disclosed.

The second question is about optimizing ethically appropriate engagement between academia and industry. One suggestion was that industry be asked to publish data openly that would be accessible in an open and available manner, that could then be accessed and analyzed. This would reduce concerns around developing

direct relationships with industry, and would create a more of an arm's length type of environment. And of course, there is always the concern that the industry is obviously guided by the profit motive and maximizing shareholder value, so disclosures around this are a critical feature.

On the question of safeguards needed, the group noted that different organizations or agencies approach this in different ways. For example, the NIH and subagencies such as NIDA do not regard the tobacco industry as a stakeholder, and this is taken into consideration with regard to funding and funder relations. The FDA on the other hand directly regards industry as a stakeholder and has much more direct interaction, such as collecting scientific information and submissions from industry in connection with regulatory applications such as PMTA and MRTP. Another observation involved the issue of quasi-industry data sources from firms under contract with the tobacco industry.

In terms of action steps, in addition to the earlier recommendation for industry to post data publicly, one suggestion was a possible event or symposium with the membership of SRNT to explore this topic in depth. And in general, it was recommended that we acknowledge and build awareness around these types of interactions, including how they might affect research and research funding, to avoid any type of actual or potential conflict.

Summary of specific ideas discussed in the breakout group

What value is added to the research mission by engagement of academic researchers with industry?

- NIH/NIDA policies on tobacco industry funding for grantees: https://www.drugabuse.gov/about-nida/advisory-boards-groups/national-advisory-council-drug-abuse-nacda/points-to-consider-regarding-tobacco-industry-funding-nida-applicants
- Background: Industry has data which may be useful in developing models and conducting research. Industry has access to data not available to the academic research community. This data is internal and sometimes regarded as proprietary. Industry-related models are few and far between but may be useful to the larger modeling community. Industry is "cautiously forthcoming," but this is a "fraught" area.
- Not every product negatively impacts public health. There may be opportunities to work together for public benefit; but the for-profit aspect of the industry is something to consider.
- Demand for healthier products by consumers applies to our field as well as others. For example: PMI claiming that switching from cigarettes to IQOS is safer and supporting this with data that would be useful to independent researchers. As a counterpoint, data from Poland indicates no switching to IQOS as was seen in Japan, and PMI is not talking about this.
- What about when industry comes to us as researchers for data? Data is publicly available via some information-sharing agreements; the industry should reciprocate (could build trust; but could be cherry-picked).

How do we optimize and ensure ethically appropriate communications between modelers in academia and industry?

- One way may be to ask industry to publish data openly which can then be analyzed (this would reduce bias and keep relationship at arms-length).
- Conflicts of interest must be kept in mind. Industry involvement may hurt this, as their goal is not public health – the industry is obviously guided by the profit motive and maximizing shareholder value.
- Meetings and messages may turn to "being bought," which we want to avoid as a real concern.

What safeguards are needed when academic researchers interact with industry researchers?

- Quasi-industry data sources are subject to these same risks of cherry-picking and fulfilling a narrative, but often they are seen as trusted sources of information even by the government; for example, see The Tax Burden on Tobacco, now hosted on the CDC website after being birthed by the Tobacco Institute.
- We must be aware that the industry may cherry-pick data, whether it be publicly available or not
- Some organizations do not see industry as stakeholder; consider funder relations and connections
- For the FDA, the industry is a stakeholder by legislation, while for NIH/NIDA this is not the case

Action steps

- The industry should post data publicly
- Consider a symposium on this topic, as these are big questions – perhaps with SRNT
- Take into account and build awareness about how interaction with industry may impact research and research funding.

Questions and answers

Q: The second group mentioned that everybody should really have systems thinking expertise. I agree with that on a high level. But the reality of the detailed modeler mathematician is probably just a dream – they can't possibly have all the detail that a team can. Your thoughts?

David Mendez: I totally agree with you. What I meant is that everybody should be trained in systems thinking, and not system modeling - there is a difference between the two. Systems thinking is a framework that you can use to conceptualize the problem and explain the problem to others and share ideas.

Let's say that you want to solve the issue of decreasing smoking prevalence. You can conceptualize elements of the problem, such as increasing cessation and decreasing initiation. We need scientists working in this area who can visualize and express ideas in this holistic manner, and discuss what parts are important.

Not everybody will be a systems modeler – that requires some training. But the most important part is how to communicate and formalize problems so you can transmit these ideas to others. It's about being an architect of a building rather than an engineer; we need engineers to support the pipes and understand the mathematics of the system that you are working on, but the value comes from the conceptualization of the problem. That's the architecture of the problem.

Rafael Meza: One of the things that we realize is that we need more modelers – not just because we are modelers, but because there is a big gap and a big need for people doing this kind of work. I think that there is certainly a big opportunity, and I encourage any young engineer or person in social sciences to consider this as a potential direction because there is really room and space for this.

Beyond that, familiarity and knowledge of modeling across the board at different levels is sorely needed, because in the end, the industry and FDA need to consider the public health impact of regulations and other products, and they need to conduct analysis in that regard. And they cannot only be evaluated by modelers, they need to be evaluated by the community in general. So it's great if you're a tobacco control person and can learn enough to evaluate the quality of people's modeling work.

Q: This kind of work could be really useful to states, regions, and localities that might be trying to do specific policies but may not have the resources of a full team who does this. Is there any way that modeling could be made more accessible to community members and not just researchers?

Jamie Tam: One thing that has definitely come out of the COVID-19 pandemic is broader public awareness of modeling and its relevance, along with many different visualization tools that are now available for people to kind of explore the effects of policy parameters. So I think that more work could be done in that arena – for example, developing a public website where model results are updated, and people can specify the state that they're interested in getting results for.

As for the point you raised about communities or states or localities that are interested in tobacco policies, I think there is definitely space for better tools that can help to facilitate the translation of models to the public. One challenge is that it's not really part of standard practice to do that kind of work, and so some of our conversation has been around how we create incentives for researchers or academics to invest that kind of effort into doing that.

Rafael Meza: That is a good point about COVID modeling, because we are seeing modeling for infectious disease taking place down to the state level. This is because infectious disease modeling is common enough that there are enough people out there able to do the local modeling. So I think that is part of the need for trying to expand the amount of expertise available. Here at the University of Michigan, we have just launched a Master's program in computational epidemiology and systems modeling, to really try and capitalize on this awareness of what modeling does and the role it can play in public health.

David Levy: I think what's really important here, that we don't see enough of – and what CISNET really does a good job of – is documenting the models. It's not just a matter of saying, "here's my equation," but of explaining the models and the modeling. I think that really needs to be more of a focus of modelers in general. For example, our aim should be to try to somehow get the different TCORS more involved with modeling, as a way of speaking to each other. That may be the most important aspect of modeling.

David Mendez: We have models everywhere. Every time you do a regression, it is a model. But the issue that we are dealing with here is a specific type of situation that we call systems modeling. If we are dealing with a population health problem, we are going to be dealing with multiple aspects of that problem, that interact in a certain way to produce an output. That is what systems thinking is – thinking about multiple components that inform how they interact and form a system.

Nowadays training and courses on this are required to get a Masters degree in public health. So even though you are doing a specific job of getting data, or getting parameters, or whatever, it is the ability to have the big picture that is fundamental to the whole business of modeling in tobacco control.

Jamie Tam: I think that visualizations can go a long way towards attracting interest while also simultaneously building comprehension around the model. So I think that some of the visualization tools and the dashboards that we've seen at this Symposium are a good step in that direction, and are all things that we can start to think about – for example, what a dashboard would look like for tobacco simulation models that deal more with federal regulations, or are specific to the work that's coming out of the TCORS.

Panel Discussion: Formulating a Plan to Move Forward

Panel Discussion with K. Michael Cummings, PhD MPH, David B. Abrams, PhD, Benjamin Apelberg, PhD, MHS, MPH, Dorothy Hatsukami, PhD, Clifford Douglas, JD and David Mendez, PhD
Moderated by Rafael Meza, PhD and David Levy, PhD

Abstract

This is a summary of the closing panel discussion with presenters from the third and final day of the CAsToR Symposium, addressing future directions in modeling and related issues for tobacco control and public health.

Rafael Meza: This closing panel discussion has a theme of "Formulating a plan to move forward." What are your thoughts in terms of where we should go? What are the key priorities, and what are the key topics and issues that that we should be thinking about as we move forward?

Mike Cummings: I am not a modeler, so I've been through David Levy's papers and his grant applications many times, and I keep learning every time I go through. Basically, what I see modeling doing is specifying relationships and their objectives, so there are different purposes for modeling. So for public health, I think it's really essential for regulators and decision makers to want to have science to help guide decision making in areas of uncertainty.

So why model? There are different purposes, but what to model is the data - we need more data, and we need better data. One of the things that I find as a non-modeler who does a lot of survey data collection is having the specification, the model, I learn where there are gaps in what we are measuring, so we can build better models and test those relationships better. So getting better data is really important.

And then how to model? We learned a lot about different modeling approaches: Bayesian modeling, agent-based modeling, cohort approaches and so on. Which ones work best? It gets a little bit into the weeds, but at some point we need to figure this out. They all contribute in different ways, triangulating an answer to the question. And then where to model? At the international, federal, state, local level? I think the answer is all of these, for different purposes.

Finally, who are we modeling for? Who are the consumers of this? Obviously, you start out with regulatory science, and we have the FDA that was given regulatory authority over tobacco products, but there are decision makers, Congress, state legislatures, the industry. Then there is the tobacco control community, which I think is frankly moving forward with policies that are probably ill conceived, not science-based, and may be doing more harm than good. And certainly modeling of the type that we've heard about over the last three days could be very helpful to try to get us back on track.

David Abrams: Just to echo what Mike said, a couple of points. I think finally we have a TCORS center that brings together the single most important mission of the FDA regulation: the public health standard, which is a population standard, to more rapidly reduce the death, disease burden and excess cost of largely a lifetime of continued smoking, that leads to a half a million premature deaths. And I think the single biggest priority of modeling is to place a much more precise spotlight on how it assures that we can answer that complex public health question. This includes users and nonusers, youth and adults in a single model that ends with the public health impact of saving half a million lives per year who die unnecessarily, largely from combusted tobacco.

I think we have tools, we have models, and we have a critical mass. But it hasn't been brought to bear in the strongest way possible to integrate into what David Mendez calls systems thinking. That means looking at the public health impact of the input stocks and flows of both youth and adults, and the harms of different products along the harm continuum, in a way that properly captures what the data are telling us. And it means looking at the ultimate outcome of optimizing saving lives in the best possible way. I don't think we've fully used all of those tools.

The biggest example of this is what was brought up about COVID. COVID modeling, within eight months, has become a news headline on every news channel, with flexible, rapid, real time input into its graphs by state and by other areas, where they are modeling what amounts to a half a million deaths. Looking at the urgency of that, what do we need to remind us that we have half a million deaths every single year from tobacco? I think we can do much more with the tools we have.

I don't think we are maximizing the utility of the five waves of PATH data to fully inform the longitudinal flows of youth, off-ramps, on-ramps, and the differential harm of the different products that have to simultaneously be looked at. And I think the biggest danger we see, that modeling in your center and going forward can prevent, is the narrow minded focus on one aspect of the system - like blind humans and elephants. You can pick youth gateway up, and ignore differential harm of different products, and ignore that it may be an off-ramp more than an on-ramp, when you use population impact as your outcome.

As David Levy has shown, and as Rafael Meza showed in his recent analysis study, the net rate of combusted harmful tobacco has dropped more rapidly and significantly, even as we worry about e-cigarettes going up. The differential impact of menthol and flavors, and of the kind of work Dorothy Hatsukami is doing with taking the nicotine out of the most combustible products, is all related to complex modeling, where you cannot just pick one piece of it and ignore all the others.

I think Benjamin Apelberg's study, that we participated in, on simulating the six to eight million lives saved if we took very low nicotine, also included the fact that we had alternative adequate nicotine-satisfying products in our equation. So we can't leave out one piece of the system and simply say that we saved eight million lives over the next few years because it was only very low nicotine products. It wasn't. It was the systems model that we were asked to comment on in the expert system group.

Finally, I think systems thinking with this modeling is the only way to address the public health standard. You can't leave a piece of it out. You can't talk about teens without adults. You can't talk about non-users without users. You can't talk about flows away from the most harmful products on the continuum. And modeling is the only way you can quantify and make explicit all of those aspects that matter, to the public health standard of saving a half a million lives per year more rapidly through regulation and policy, than we've ever done before.

I think we just saw the potential here that we have a lot of work to do to maximize and realize the value that modeling plays in informing the policy of the public health standard to save lives, and not to pick a piece of the model and leave out some of the other pieces for some other agenda that is more narrow, and perhaps more politically focused or more emotionally focused, than what the science is telling us.

Benjamin Apelberg: It's really great to see how much work is coming out of TCORS. As the FDA representative on this panel, I'll just reiterate or reinforce what was said, and what Mitch Zeller said on day one. I think it goes without saying that computational modeling is extremely valuable to informing FDA's regulatory actions.

As David just talked about, our standard is about population health. And this is really a way to take something that's very complex, understanding impacts on all these different groups and what that means, and translating that into something that's digestible and meaningful to people. I do think that some of the points that were raised throughout the last three days about where we could head are good ones that I wanted to flag – for one, thinking about what is the range of outcomes that we're looking at. I know that mortality has been a big focus, and the data tends to be much more readily available for mortality, but it makes it a little difficult to take into account the impacts to current users versus the impacts to youth. The timescales in which this is happening are quite different.

Making sense of that is sometimes a challenge. So how should we be thinking about those two different timescales for impact? I think the issues around health equity, and being able to understand not just what kind of impact a regulatory action might have overall, but what impact it might have with respect to disparities and improving health equity is also really valuable, and I'm glad to see that that's an area of focus.

Another point that was raised was that sometimes it can be really difficult to make sense of different modeling approaches, and the findings that are generated from them. What parts of these modeling approaches can be standardized? Are there common inputs for which there is a consensus – that could be used as a starting place? I think that could really help to take out some of the variability, in terms of trying to make sense of the findings of different models.

Rafael Meza talked about the Smoking History Generator, and there is probably more consensus that can be brought to bear on inputs like rates of initiation, cessation, mortality rates, and disease risk with respect to different types of products, so that we can all work off of one set or just a few sets of status quo scenarios, and then really begin to look at what are the implications of different policy options.

I think that direction could also be informative to industry, who are developing models and including those in their applications. And it sort of requires a deep dive to understand what each of these different models is doing under the hood and trying to make sense of those. So I think the leadership from this group can really contribute to moving in that type of direction. Thanks.

Editor's note: Dr. Apelberg's remarks are not a formal dissemination of information by FDA and do not represent Agency position or policy.

Rafael Meza: Thank you, Ben. I want to ask you one thing about your last point, and it is related to what I heard from Mitch Zeller – he was saying that there is a standard or some guidelines for the industry of how to do "what if" scenarios.

You just brought up the issue that maybe we could come up with a set of standard parameters that could be used, maybe for industry models or anyone else as the starting point; how can we make that happen? Because certainly we feel in CAsToR that we can play that role in terms of, for instance, releasing a set of initiation rates based on what's been fitted up to now that may be a status quo for anyone who wants to play. So do you see which mechanisms could help?

Benjamin Apelberg: What Mitch mentioned was a draft guidance - it's actually been out for quite a long time - it's not a final guidance, it was FDA's thinking at that time, and it's pretty high level. It essentially just states to document and be transparent to make it clear what you're doing. So there is potentially a lot more that could be done.

I think in the interim, just getting that information out there, whether it's publishing it, or making it available, or communicating those tools more broadly, would be valuable. And then there's probably a role for the FDA to be able to point to that as one source. Even if it's not part of a formal guidance or incorporated into some formal documentation, the industry is looking for direction and something that the Agency would support. A lot of that is on us as an Agency to communicate what we want to see, but I think that having the expertise to have generated this work, to be regularly publishing on it, just adds credibility to the data and information that you all put out there.

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Dorothy Hatsukami: I think what's really become apparent throughout this Symposium is the importance of an integrated, systematic and multidisciplinary research approach. Working with David Mendez on the TPSAC menthol report was very valuable and made my science much richer as a result of understanding the important key parameters for determining public health impact.

In terms of future directions, as a first step, it would be important to establish research priorities in tobacco regulatory science. Some of these priority areas could be reactive - that is, addressing the key issues that we are currently facing. For examples, what do we do with electronic cigarette flavors? What about nicotine dose? Should there be a cap on nicotine dose for electronic cigarettes?

]t would also be important to think proactively, that is, what are some of the regulatory measures that would have a significant impact on public health? For example, should we reduce the levels of nicotine content in cigarettes, and what kind of impact will it have on the use of alternative nicotine delivery systems?: What would happen if there were restrictions on these alternative products; for example, what if we had a reduced nicotine content product standard for cigarettes, but also had no electronic cigarette flavors or a nicotine cap on electronic cigarettes or other non-combustible tobacco products? Also, what would happen if we had a modified-risk claim on some of these alternative nicotine delivery systems in the context of a reduced nicotine product standard for cigarettes? It is important to consider various regulatory permutations that can maximize or reduce public health impact. So, identification of impactful current and future research priorities is an important first step.

The second step, of course, would be to identify the key parameters for addressing those priority topics. A systems approach as described in this symposium would be crucial to understanding what those key parameters might be.

Third, it would be important to develop a strategic research approach to address those key parameters. It was valuable to hear about all the different methodologies that could be used: the discrete choice experiments, the experimental marketplace, the quasi-experimental designs, and so on. In addition, traditional clinical trials can also provide information to populate the key parameters. These three steps will provide a more systematic approach to doing our science.

Rafael Meza: Great points, and thank you for laying that down so nicely. And I think an emerging theme is about this issue of prioritization, and I guess optimization, of the strategies. And to start really thinking about using the models to help inform what should be the priorities, and have that be a priority for the modeling. Cliff, what are your thoughts?

Cliff Douglas: I've been thinking throughout this discussion about the priority of always keeping in mind, how will or can this research be used? How can it have a direct effect, as some of you have emphasized, on informing the right audiences? Obviously, the FDA is a critical one, and we've heard about state and local

governments and the like. I also think in terms of some of the vehicles by which the information reaches those folks, the media is an important one.

In some cases, it is so critical that much of this information reaches decision makers that I think in terms of whom I want to share this with today – for example, the New York Times or the Wall Street Journal. Those are the big examples, but it's the way in which we can frame and provide this information to all of those different critical audiences.

It's all about the audience, whether it's members of Congress, or Federal agencies, or the Executive branch, as well as consumers. And consumers ultimately are making decisions based on this as well. And they don't even know this necessarily, but they receive a sort of trickle down of information that originates with the work that we all are doing. And how it reaches them, and in what form, is something that I would ask folks to always try to bear in mind, because of its direct relevance to, again, the issue in the cause of translation and communicating critical information to folks.

So it's kind of fun in the sense that there are multiple, quite heterogeneous audiences out there. And it's not always easy to know exactly how one thing should be framed for a given audience or multiple audiences. But those are things that we work out along the way.

So I've really been quite reassured, and I think if anything, further motivated to make the most of the work that's done through CAsToR, this TCORS and the extended group of people involved in this sphere. Because as several of you have said so well, this is going to have a direct impact on serving the net health impact mission of the population standard employed by the FDA, and by extension, the decision making that we see all over the country.

Unfortunately, as has also been said, too much of the decision making out there hasn't been reliant on this work. More of it needs to be. And again, it goes toward the primacy of our doing the best job we can at translating and communicating it to the public.

Rafael Meza: That is a great point that we need to talk about. I think it's really critical that we collaborate with people like you and others, who can help us translate and disseminate the work in multiple ways. It's also probably a topic that is relevant to the model accessibility discussions, because in the end, dissemination requires effective communication.

In closing, we will ask David Mendez to share his conclusions as a key member of this Symposium.

David Mendez: One thing that struck me along the way is that this is definitely not a solitary action. We need a strong collaboration among individuals with different expertise, who can make their contribution in many different ways - in their modeling, but also in what we call face validity - that it makes sense what we are doing.

Having a team to work with is extremely valuable, and getting to know that team and be comfortable, that's important. So I echo Dorothy's remark about how much more interesting it was when we got together a few years ago and talked about the menthol problem - what were the key parameters, what we intended to do, and so on. And that would not have happened if it was just done by one person in isolation. For example, my collaboration with Ken Warner here at the University of Michigan has been invaluable. Our expertise put together has produced a very fruitful collaboration.

And now with CAsToR, we feel more reinforced with more expertise and more modelers. So we're getting a community that is ready to launch and produce more output of this type. I remember the first conference of

modelers that was put together by David Levy back in 2000 - there were five people in the room, and look at what is happening now. So I think we have the momentum now.

I also want to reiterate something that David Abrams said about systems thinking. We now have the ability to see a comprehensive map of the problem. It is not about this part of the population, or this problem that we need to solve. Overall, we can now see how our actions in one part of the problem affect other parts of the problem.

We have discovered, now that we have this comprehensive map, that we are at a disadvantage compared with, for example, the tobacco industry. They have one single goal, which is to maximize their profit. We have multiple goals. Instead of saying we want to save as many lives as possible, we have to make our objective a little bit more concrete, because some individuals or some groups say their goal is to protect kids. Others say, no, I want to protect the adults, that's my goal. Another group may say that disparities is more important to protect. So we have a lot of different, well-intentioned groups that are focusing on different aspects.

Now we have the opportunity to look at the tradeoffs - to say that we are gaining in one part of the goal, but losing in another. We need to actually come up with an objective that we all agree on and a set of constraints that we agree on - that we want to save as many lives as possible, for example, but not at the expense of increasing disparities in an unruly manner. We need to specify that, and we can with a model.

There should be a way that we can compare the goals that different individuals or different factions have - are we harming kids now, or putting future adults at risk? So we can do something for adults now, and some people say that we are doing that at the risk of harming kids. Are we harming kids now, or are we taking a risk that they suffer 40 years from now? At some point you have to say, OK, I have a group of people that I can save now, for example, and a group of people at the same age with whom I can prevent something happening in 50 years. What do I get, and what is the trade?

So can we agree on some sort of common metric qualities, for those aspects with a common vision? More than anything, the fact that we have a view of a comprehensive model system thinking will make our communications a little bit easier on us, and have a common goal that we can understand and understand the tradeoffs. So that's something that modelling can do.

As an aside, I've heard a lot at this Symposium about what else we can do with modeling. I know we surely need more artificial intelligence embedded in tobacco research, because we're generating so much data that it is sometimes difficult to make sense of all the intricacies of the data. Can we just do some automatic processes that extract information that we can use to, say, generate hypotheses of modeling?

Also, right now, can we use our models as data? A model is a representation of an idea – it is a hypothesis. If you look at a group of experts and put a model together with little data, and they have a theory about how things should go, can we use that? Can we infuse that information into the estimation process of the data? Now we have extra knowledge that we put together, based on theory, that can extract parameters that are less noisy. Can we do that? We haven't done much of this. With that, I will stop here.

Rafael Meza: I really like the final points you were making, David. This discussion on measures and metrics is quite relevant, and I think we are in a unique position to help guide that discussion.

I think we all recognize that this closing panel has been extremely valuable and helpful, and that there is much more that we need to discuss. I would like to thank our panelists for your comments, and your participation throughout the Symposium. This has been a great session.