Smoking and Mental Illness Comorbidity: Implications for Mortality Outcomes and Treatment Interventions

by

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Dedication

To my best friend and soulmate, Matty Wolford.

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Preface

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Abstract

Smoking and mental illness are leading contributors to mortality and morbidity in the U.S. They are also significantly associated with each other, as people with mental illness smoke at much higher rates compared to the general population. While it is known that people with mental illness have shorter life expectancies than people without, the extent to which this is associated with their increased smoking had previously been unknown. In Chapter 2, I use survival analysis and the National Health Interview Surveys 1997-2009 mortality follow-up data to construct lifetables by smoking and mental health status. I find that at age 40, never smokers with SPD lose approximately 5.3 years of life expectancy compared to current smokers with SPD who lose 14.9. Thus smoking is a primary driver of differences in life expectancy by mental health status.

In Chapter 3, I use simulation methods to adjust for recall error in national surveys and produce revised estimates of lifetime prevalence of major depression (MD) in the U.S. I develop a simple compartmental model of MD calibrated to data from the National Survey on Drug Use and Health (NSDUH). I show that over 40% of adults with lifetime MD underreport their histories of depression. After adjusting for recall error, 28.7% and 16.0% of women and men have lifetime MD compared to 15.6% and 9.5% when relying on self-report.

In Chapter 4, I develop the first model to evaluate the joint impact of smoking and mental health in the U.S. I calibrate a system dynamics model of smoking and depression comorbidity to NSDUH data 2005-2015 and show that the smoking prevalence disparity by depressive status is projected to widen over time. From 2016 to 2050, women and men with MD are expected to become increasingly more likely to smoke compared to their never depressed counterparts. Adults with current MD represent 6.7% of the adult population, but more than 640,000 smoking-attributable deaths are projected to occur in this group. While the proportion of smoking-attributable deaths among adults with depression is projected to decrease with time, even by 2050 parity with those who have no history of MD would not be achieved.

In Chapter 5, I evaluate the health gains associated with smoking cessation interventions that target patients with depression. I simulate the effects of widespread access to cessation treatment and increased utilization of mental health services among smokers with depression. Under a highly optimistic scenario that assumes all patients with depression receive cessation medication from their mental health professionals in 2018, less than 31,400 premature deaths would be avoided by 2050. This represents only about 5% of the nearly 600,000 smoking-attributable deaths that are projected to occur among adults with depression during the same period. Increases in the level of mental health service utilization would offer some additional but marginal health gains. While cessation interventions in mental health settings would reduce the smoking disparity by depression status, the mortality benefits associated with doing so are modest and should be pursued alongside more aggressive tobacco control strategies.

This dissertation advances knowledge about the impact of smoking and mental illness comorbidities on population health. It furthermore demonstrates the potential for systems science approaches to inform the epidemiology of behavioral health conditions, assess changes to tobacco use disparities over time, and evaluate the long-term effects of interventions.

Chapter 1 - Introduction

> *"The depression was burying me…I would smoke more to not be depressed, and then be more depressed because I was smoking. That was a vicious, vicious cycle." – Rebecca, age 57*[1]

Rebecca started smoking when she was a teenager, and was diagnosed with depression at age 33. She spent years feeling helpless to both her depression and her tobacco addiction, and finally found the motivation to quit smoking after she began losing her teeth. In the Centers for Disease Control and Prevention (CDC) *Tips from Former Smokers* campaign, she describes the cycle that kept her hostage during this time. Unfortunately, her experience is a common one for people with mental illness.

According to the National Survey on Drug Use and Health, of the 44.7 million adults in the United States with any mental illness, 1 in 3 are past month smokers.[2,3] For comparison, 1 in 5 adults with no mental illness smokes.[4] Although people without mental illness have benefited from significant declines in smoking over time, comparable trends have not been observed for people with mental illness.[5,6] Furthermore, an analysis using national cohort data showed that more recent birth cohorts of smokers have elevated psychiatric vulnerability, pointing to a shift in the smoking population, as it increasingly represents people with mental disorders.[7] In the U.S., people with mental illness smoke

at higher rates, with greater intensity, and are less successful at quitting than people without mental illness.[8-10] The likelihood of smoking among people with a mental disorder increases with the severity and with the number of other co-occurring psychiatric disorders.[8,11] These tobacco use disparities translate into higher burdens of tobacco-related disease and death for people with mental illness. More than half of all deaths among people with severe mental illness are due to cancer, heart disease, stroke, or other conditions caused by smoking.[12] People with behavioral health conditions are especially vulnerable to tobacco addiction, and as a result face a disproportionate share of the debilitating health conditions associated with smoking.

Why do people with mental illness smoke more?

One of the most common explanations for the persistent tobacco use disparity by mental health status is referred to as the 'self-medication hypothesis.' This hypothesis reasons that people with psychiatric disorders smoke more because the nicotine alleviates symptoms of their mental illness, thereby reducing negative affect and improving their physiological functioning.[13] Edward Khantzian proposed this hypothesis in 1985 as an explanation for widespread illicit drug use among people with psychiatric conditions.[14] He later updated his theory to emphasize that "it is not so much a psychiatric condition that one self-medicates, but a wide range of subjective symptoms and states of distress that may or may not be associated with a psychiatric disorder."[14] However the self-medication hypothesis has become less accepted as a way of understanding nicotine addiction among people with mental illness with more recent research.[15-19]

Research indicates that continued cigarette smoking may not alleviate psychiatric symptoms per se, but rather alleviates symptoms of nicotine withdrawal (e.g. irritability).[20] People with mental illness may be more vulnerable to cravings and nicotine withdrawal when trying to quit,[21] and also find the experience of smoking to be more rewarding than their mentally healthy counterparts.[22,23] In tests of whether cigarette smoking improves mood, data has shown that it is ineffective at reducing depressive symptoms.[24] It has been posited that because nicotine increases the rate at which medications metabolize, patients with schizophrenia may be smoking to alleviate the side effects of antipsychotic medications.[15] Evidence that nicotine allays medication side effects is mixed and somewhat difficult to reconcile with the apparent absence of a simultaneous reduction in the beneficial effects of such drugs.[15] Tests of cognition and attention behaviors among people with schizophrenia also indicated that nicotine is unlikely to produce the subjective additional benefits perceived by patients relative to mentally healthy people.[25] If the self-medication hypothesis holds, it follows that a reduction in smoking would lead to negative changes in mental health, which research has not demonstrated.[26] In a National Institute of Mental Health report, experts concluded that "overreliance on the self-medication hypothesis...may result in inadequate attention to other potential explanations."[22]

Instead, a growing body of research has investigated the possibility of other causal links between tobacco smoking and poor mental health.[22] Although it is difficult to ascertain causality based on observational data, a systematic review of longitudinal survey data demonstrates that depression and anxiety predict subsequent smoking and vice versa.[27] A 13-year prospective study of young women found that after adjusting for other mental health history and sociodemographic factors, baseline smoking predicted psychological

distress and depression at subsequent waves, and poor mental health at baseline predicted subsequent smoking.[28] Critiques of the self-medication hypothesis also point to evidence that indicates quitting smoking reduces anxiety, stress, and depressive symptoms.[29,30] A systematic review and meta-analysis of 26 tobacco cessation interventions found significant improvements to mental health following smoking cessation.[20] Another study using propensity score matching methods corroborates this finding.[31] Results from a Mendelian randomization analysis suggests that tobacco use could causally develop psychotic conditions: a gene variant related to smoking intensity was associated with schizophrenia in smokers but not never-smokers, though the study did not find similar results for depression.[32]

Tobacco industry tactics may have contributed to higher smoking (or delayed reductions to smoking) in populations with mental illness. Tobacco companies have funded research and scientific meetings that promote the idea that nicotine is helpful to people with schizophrenia as a form of self-medication.[33,34] Furthermore, the industry has a history of targeting people with mental illness as a base of consumers, typically as part of corporate social responsibility aims.[35] Industry documents show that marketing efforts included distributing free cigarette samples to psychiatric hospitals, drug treatment facilities, and homeless shelters. Companies have also cultivated relationships with and provided grants to service organizations that primarily serve the homeless or people with mental illness. Media marketing campaigns emphasized the benefits of smoking for stress relief and relaxation.[34,36]

Mental health professional norms likely have contributed to continued smoking among people with mental disorders. Historically, psychiatrists have been the least likely medical

specialty to address tobacco use in their patients, believing that they have other health problems that were more pressing or that quitting smoking would worsen their mental health.[37-39] Staff in mental health facilities often perceive smoking to be a secondary concern for their patients, and view nicotine as having a therapeutic role in patient's lives. Mental health professionals are sometimes under the impression that their patients do not want to quit,[39] despite the fact that smokers with depression and other disorders are motivated to quit smoking[40,41] and interventions have been shown to work for them.[42,43] At the same time, patients with severe mental illness do not view their mental health providers as avenues for cessation treatment, and report receiving little support or encouragement from them to quit.[38] Early efforts to implement smoke-free policies in psychiatric facilities were initially met with protest from mental health organizations concerned about how such policies would disrupt patient care, but a growing number of facilities eventually became smoke-free without issue.[33,44-48]

Shared underlying genetic and social vulnerability is an important and likely explanation for the co-occurrence of smoking with mental disorders.[49] In studies of twins, genetic factors that have been linked to nicotine dependence also predisposed individuals to major depression.[50] Numerous gene systems connected to smoking behaviors have been associated with psychiatric conditions, especially schizophrenia; this suggests that some genes can confer susceptibility to neuropsychiatric disorders.[51,52] Beyond genetics, people with mental illness are more likely to live in poverty, be less educated, be unemployed, lack social support—all social and environmental characteristics that have independently been associated with tobacco addiction.[53-55] Vulnerable populations are disproportionately affected by stress, discrimination, and homelessness, which are known

to be associated with substance use behaviors. This can have compounding effects, in which the interaction of low socioeconomic status with poor mental health leads to even worse smoking outcomes than when considered independently.[55,56]

Systems science and models of smoking

The dynamic nature of the relationship between poor mental health and tobacco addiction, and the potential for feedback mechanisms that reinforce both of these conditions simultaneously, makes their co-occurrence appropriate for the application of systems science methods. Systems science is a trans-disciplinary approach to the study of nonlinear, adaptive complex systems which emphasizes the inter-relatedness of components within a system and emergent effects generated that are larger than the sum of their individual parts. Systems science is no stranger to public health, as these methods have been used by researchers to develop computational models that improve knowledge about health disparities driven by feedback effects, how behaviors and contagions are spread through social networks, and dynamic interactions between humans and the environment.[57-61]

In the field of tobacco control, system science approaches are increasingly valued and utilized by government agencies to facilitate decision-making and long-term planning.[62-65] Numerous simulation models have been developed by researchers to evaluate tobacco use behaviors and the policy interventions to address them.[66-78] Such models have been used to estimate the impact of tobacco control on declines in smoking and on increasing life expectancy,[79,80] the potential impact of e-cigarettes and other novel tobacco products on changes to smoking and smoking-related mortality,[62,81-84] and the effects of peer

influences on the spread and clustering of smoking behavior.[85-90] To my knowledge, very few have studied comorbid smokers, and models that consider smoking and comorbid illness have mainly examined tobacco addiction co-occurrence with infectious diseases.[72,91] Although a systems dynamics model was previously employed to evaluate the effects of removing menthol cigarettes (which are primarily smoked by African-Americans) from the cigarette market,[92] existing simulation models of smoking generally have yet to consider marginalized populations.

Public health decision-makers and tobacco regulators have demonstrated an appreciation for the use of systems science methods to monitor population health and evaluate large-scale interventions. At the same time, tobacco control leaders are directing attention to the unaddressed smoking disparity between populations with and without mental illness. This presents a unique public health and research opportunity. This dissertation advances knowledge of the population health effects of smoking and mental illness co-occurrence using system dynamics modeling methods. System dynamics models are mathematical models characterized by feedback loops (between smoking and poor mental health), time delays between events (smoking uptake) and their outcomes (disease and death), compartments of individuals (never, current, and former smokers) and the flows between them (initiation and cessation rates)— features that make them particularly well-suited for my research agenda.[93]

Overview of chapters

Both smoking and mental illness independently contribute to premature death at the same time that their co-occurrence is driven by known and unknown etiological processes. But to what extent do populations with mental illness experience unequal health outcomes with respect to smoking? What are the consequences of smoking and mental illness comorbidity at the population level? How might they be addressed? These are questions I explore.

Previous research has established that people with mental disorders live shorter lives and have greater mortality risk than those without mental disorders.[94] However much of the existing literature on premature mortality for people with mental disorders fails to disentangle the contributions of smoking and serious mental illness to decreased life expectancy. How much of their reduced life expectancy is due to their mental illness or to their significantly higher smoking rates? In Chapter 2, I use survival analysis to generate lifetables and calculate life expectancy by smoking status and mental health status. I also estimate the smoking-attributable fraction of all deaths among people with serious mental illness. This is the first study to quantify the contribution of smoking to reduced life expectancy among people with serious mental illness.

In Chapter 3, I focus on people with major depression. Major depression is a commonly occurring mental disorder with a well-documented relationship to smoking behavior.[27,95] Screening for depression in the general population comes with challenges. Many people fail to accurately recall their past histories of mental health including depressive symptoms.[96,97] I develop a system dynamics model of major depressive episodes,

combining cross-sectional survey and cohort study data to adjust for recall error and estimate the lifetime burden of depression in the U.S. This model of major depression provides the foundation for a larger model that evaluates its concurrence with smoking.

In Chapter 4, I describe the first joint model of smoking and mental illness comorbidity in the U.S. I evaluate both smoking and depression in the adult population, projecting future population health outcomes from 2016 through the year 2050. This modeling approach is informed by longitudinal research on the effects of smoking and depression on each other, and estimates their interaction effects. It can evaluate the smoking disparity by mental health status, and changes in the tobacco and mortality burden for people with depression over time.

Next, I use the comorbidity model from Chapter 4 to understand how unequal health outcomes by depression status can be addressed through smoking cessation interventions that target patients with depression. Chapter 5 offers a glimpse into a hopeful future where cessation treatment is widely available, where mental health professionals fulfill their obligation to help patients quit, and where mental health care is more accessible to the people who need it.

Finally, I conclude by reflecting on the contributions that the collection of studies makes to the existing literature. I consider future research and policy directions prompted by this body of work and offer new questions worthy of inquiry.

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Chapter 2 - Smoking and the reduced life expectancy of individuals with serious mental illness

Background

The annual risk of death for individuals with mental disorders is more than twice that of the general population.[1] Not only do those with mental illness lose on average 10 years of potential life,[1] quality of life is reduced by the major contribution of these disorders to overall disability.[2] The impact of psychological distress on health is perhaps most exemplified by the more than 40,000 deaths due to suicide each year.[3] However a large proportion of deaths among those with mental disorders are ultimately due to chronic diseases such as heart disease, cancer, and stroke.[4] This may be due to social deprivation, risks associated with antipsychotic medications, and in particular, harmful health behaviors such as smoking.[4-9]

Though 19% of adults have some form of mental illness, previous estimates indicate that they account for nearly 40% of all cigarettes smoked in the U.S.[10] This figure could now be larger as people with mental illness make up an increasing proportion of the country's remaining smokers.[11] Prevalence of cigarette smoking varies by diagnosis; it can be as high as 46% among those with bipolar disorder and 59% among those who have schizophrenia.[12] On average, smoking rates are 70% higher among adults with any mental illness compared to the general population.[13] This translates into even greater

mortality risk for populations with psychiatric disorders. A previous study found that half of total deaths among those with schizophrenia, bipolar disorder, and depression are due to diseases linked to smoking.[14]

While tobacco use is a contributor to early death among those with psychiatric disorders, the extent to which smoking affects excess mortality, independent of mental illness, is unknown. Several studies examining mortality comparing populations with and without mental disorders adjust for confounding due to smoking. However these studies are restricted to veterans,[15,16] California-based or non-U.S. patient populations,[4,14] and middle-aged or elderly individuals.[17-20] These estimates cannot be generalized to the broader U.S. population, and often exclude the non-patient population, who do not seek or are unable to access mental health care.

I use nationally-representative data to estimate (1) the relative rates of death for smoking and serious psychological distress adjusting for relevant covariates, and (2) the impact of smoking on all-cause mortality and life expectancy among persons with serious psychological distress (SPD) in the U.S.

Methods

Data source

The National Health Interview Survey (NHIS) surveys the civilian, non-institutionalized U.S. population. Beginning in 1997, NHIS identified adults with serious psychological distress (SPD) according to the Kessler-6 (K-6) non-specific psychological distress scale. The survey asks respondents about the frequency over the past month with which they

have felt (1) nervous, (2) hopeless, (3) restless or fidgety, (4) so sad or depressed that nothing could cheer the respondent up, (5) that everything is an effort, and (6) worthless. Each item is scored 0-4 based on the response “none of the time”, “a little of the time”, “some of the time”, “most of the time”, or “all of the time.” Individuals with scores of 13 or greater are considered to have SPD. This measure is a validated tool for screening serious mental illness in the general population.[21,22]

Current smoking is defined as having smoked at least 100 cigarettes in one’s lifetime, and currently smoking every day or some days.[23,24] Former smokers have smoked at least 100 cigarettes but do not currently smoke. Nondrinkers are those who report zero alcohol use in the past year. Non-heavy drinkers report drinking in the past year, but no heavy drinking, where heavy drinking is defined as 5 or more drinks on one occasion. Individuals who have had any heavy drinking episodes in the past year are divided according to frequency of heavy drinking occasions: less than 3 heavy drinking days per week, and 3 or more heavy drinking days per week. Alcohol use categories were based on a study that found frequency of heavy drinking to better capture mortality risk compared to average daily consumption.[25]

Mortality follow-up data are available for a subsample of NHIS participants linked to death certificate information from the National Death Index from the date of survey through 2011.[26] Because NHIS only collects mortality data upon follow-up, all behavioral and demographic data are based on time of survey. The data thus do not allow for analysis of changing health status or behaviors over time. NHIS data for the years 1997-2009 were pooled to generate a final analytical sample of 328,110 individuals. I adhered to

recommended procedures from the National Center for Health Statistics to adjust pooled sampling weights for the mortality follow-up sample.[26]

Analysis

I used Cox regression models to estimate mortality hazard ratios stratified by 10-year age groups. Individuals age<25 were excluded from analyses because many people below this age have not yet attained their highest level of education. Survival models related time to death in years, and adjusted for smoking status, gender, race/ethnicity, education, age at baseline (continuous variable), marital status, and alcohol consumption. I also estimated mortality hazard ratios specifically for the population with SPD, stratified by gender, and adjusting for the aforementioned variables and year of birth.

The proportional hazards assumption was assessed for each covariate through interaction terms with log of time in years. As baseline mortality rates for lifetable construction are not available by race/ethnicity or alcohol consumption, I did not further stratify the NHIS cohort beyond age group and gender. Cox models did not include time-dependent variables for smoking, drinking, and SPD status since these are only available at baseline. Given the known correlation between mental illness and tobacco use, I tested for interactions between smoking status and SPD.

For comparison, I conducted similar survival analyses using national mortality follow-up data for other measures of mental illness, such as NHIS 2007 data for bipolar disorder and schizophrenia, and National Health and Nutrition Examination Survey (NHANES) data for anxiety disorder and depression. In general, small sample sizes resulted in very wide confidence intervals for the main coefficients of interest, and precluded lifetable

construction. Select results for the NHANES measure of depression are included at the end of this chapter (Appendix).

Smoking-attributable fraction

Mortality hazard ratios for current and former smoking were used to determine the smoking-attributable fraction (SAF) of preventable deaths among those with SPD. The calculation followed the CDC approach[27]:

$$\mathrm{SAF} = \frac{p_{cs}(RR_{cs} - 1) + p_{fs}(RR_{fs} - 1)}{p_{cs}(RR_{cs} - 1) + p_{fs}(RR_{fs} - 1) + 1}$$

where p_{cs} is the prevalence of current smoking in the population of interest, p_{fs} is the prevalence of former smoking, RR_{cs} is the relative risk of death for current smokers with SPD, and RR_{fs} is the relative risk of death for former smokers with SPD compared to never smokers with SPD.

Life expectancy

To estimate the impact of smoking and mental illness comorbidity on life expectancy, I developed lifetables by gender according to smoking and SPD status. Lifetables were constructed according to the Human Mortality Database (HMD) protocol.[28] I used the Cancer Intervention and Surveillance Modeling Network (CISNET) unadjusted never-smoker mortality rates as baseline rates, and assume these approximate the rates in never smokers without mental illness. The CISNET data have been used in the development of multiple validated models of smoking, mortality and lung cancer.[29-31] Baseline death rates were adjusted by applying the estimated age group-specific mortality

hazard ratios for SPD, current smoking, and former smoking. I report results based on the 2009 never-smoker death rates; results using the 1997-2008 CISNET death rates are available upon request.

Results

Table 2-1 presents characteristics of the study population at baseline according to SPD status. Persons with SPD comprise 3.1% of the population. From 1997 to 2011, 38,266 of all participants (9.5%) died at follow-up. A larger percentage of individuals with SPD died (14.2%) than did individuals without SPD (8.3%). Average follow-up time was 8.2 years. Mean age was 49.5 years and 49.8 years for the SPD and no-SPD samples respectively. Participants with SPD were significantly more likely to be smokers, less likely to have quit, more male, more likely to be black or Hispanic, less educated, less likely to be married, and more likely to be divorced or separated compared to those without SPD.

Table 2-1. Baseline sample characteristics by SPD status, NHIS 1997-2009

	No SPD	SPD	p-value
Avg years of follow-up (sd)	8.19 (3.84)	7.85 (3.94)	
Deaths (%)	35117 (8.3)	2013 (14.2)	<0.001
Male (%)	136741 (52.2)	3760 (41.0)	<0.001
Smoking status (%)			
Never smoker	169934 (48.0)	4369 (28.2)	<0.001
Current smoker	66036 (23.6)	4798 (48.1)	<0.001
Former smoker	74040 (28.4)	2335 (23.7)	<0.001
Education (%)			
High school or less	147443 (41.3)	7673 (62.9)	<0.001
Some college	83841 (28.8)	2781 (27.1)	<0.001
College grad	78471 (29.8)	1031 (10.0)	<0.001
Race/ethnicity (%)			
Hispanic	49433 (9.6)	2359 (11.7)	<0.001
White (Non-Hispanic)	204579 (77.1)	6870 (71.6)	<0.001
Black (Non-Hispanic)	43038 (9.3)	1813 (12.0)	<0.001
Other (Non-Hispanic)	14158 (4.0)	514 (4.7)	0.786
Age group (%)			
25-34	66614 (21.7)	2001 (19.0)	<0.001
35-44	70584 (24.5)	2738 (25.7)	0.074
45-54	61282 (22.3)	2992 (27.4)	<0.001
55-64	45524 (15.1)	1926 (16.1)	<0.001
65-74	35341 (9.4)	969 (6.4)	<0.001
75-84	24650 (5.6)	708 (4.1)	<0.001
85+	7556 (1.4)	229 (1.3)	0.966
Birth cohort (%)			
1912-1929	37844 (8.0)	1107 (6.1)	<0.001
1930-1939	34433 (9.3)	1040 (6.9)	<0.001
1940-1949	48180 (15.7)	2070 (16.7)	<0.001
1950-1959	64679 (23.2)	3022 (27.7)	<0.001
1960-1969	70521 (24.3)	2637 (24.7)	0.765
1970-1984	55894 (19.5)	1687 (17.9)	<0.001
Marital status (%)			
Never married	47559 (11.4)	2012 (14.5)	<0.001
Currently married	161494 (65.0)	3868 (45.6)	<0.001
Cohabiting	13276 (5.8)	622 (8.3)	<0.001
Divorced or separated	54032 (12.1)	3572 (24.1)	<0.001
Widowed	34435 (5.7)	1454 (7.5)	<0.001
Current drinking status (%)			
Nondrinker	50433 (20.3)	2957 (35.1)	<0.001
Non-heavy drinker	128795 (55.5)	3462 (40.4)	<0.001
Heavy drinker, <3 times per week	51781 (23.0)	1701 (21.0)	<0.001
Heavy drinker, 3+ times per week	2814 (1.2)	294 (3.5)	<0.001
No. of observations	311551	11563	

(%) represent weighted proportions; SPD = serious psychological distress;
Excludes individuals less than 25 years of age.

Table 2-2 and Table 2-3 present all-cause mortality hazard ratios by gender and age group adjusted for demographic and behavioral risk factors. Compared to those with at least a college degree, having a high school education or less significantly increased risk for death across all age groups except for those ages 85+. The hazard ratio was also higher for those with some college education, though this was not always significant for females. Risk of death was significantly greater for those who never married or who were divorced or separated compared to married individuals across most age groups. Relative to whites, black participants generally had higher mortality risk while Hispanic individuals had lower risk. Compared to non-drinkers, being a non-heavy drinker significantly reduced risk in most models. The effects of heavy drinking less than three times per week appeared to significantly reduce risk for some age groups, though results for more frequent heavy drinking were mixed and generally not statistically significant. My mixed results regarding heavy drinking could be explained by co-occurrence with smoking. When smoking variables were omitted in separate analyses, I noted that frequent heavy drinking increased mortality risk, though not significantly for most age groups.

Table 2-2. All-cause mortality hazard ratios by age group – Males

Age group	25-34	35-44	45-54	55-64	65-74	75-84	85+
Current smoker	1.811***	1.617***	2.257***	2.758***	2.717***	2.077***	1.334
	(1.377 - 2.382)	(1.352 - 1.935)	(1.942 - 2.623)	(2.383 - 3.191)	(2.400 - 3.077)	(1.781 - 2.422)	(0.932 - 1.911)
Former smoker	1.458**	1.081	1.191**	1.438***	1.487***	1.311***	1.216***
	(1.010 - 2.103)	(0.851 - 1.374)	(1.017 - 1.393)	(1.252 - 1.651)	(1.335 - 1.655)	(1.205 - 1.426)	(1.059 - 1.396)
SPD	1.703*	2.101***	1.768***	1.483***	2.098***	1.489***	1.783**
	(0.960 - 3.021)	(1.570 - 2.811)	(1.408 - 2.219)	(1.202 - 1.831)	(1.698 - 2.592)	(1.155 - 1.919)	(1.108 - 2.871)
Age	1.101***	1.119***	1.072***	1.093***	1.114***	1.107***	
	(1.054 - 1.151)	(1.088 - 1.150)	(1.052 - 1.094)	(1.074 - 1.112)	(1.098 - 1.130)	(1.092 - 1.121)	
High school or less	2.166***	1.961***	1.714***	1.741***	1.347***	1.231***	1.151*
	(1.480 - 3.170)	(1.553 - 2.476)	(1.454 - 2.020)	(1.504 - 2.014)	(1.211 - 1.497)	(1.116 - 1.358)	(0.982 - 1.350)
Some college	1.846***	1.658***	1.416***	1.407***	1.230***	1.049	1.059
	(1.240 - 2.750)	(1.305 - 2.107)	(1.192 - 1.683)	(1.199 - 1.651)	(1.072 - 1.412)	(0.934 - 1.179)	(0.867 - 1.294)
Hispanic	1.154	1.084	1.067	0.812***	0.821***	0.671***	0.749*
	(0.810 - 1.646)	(0.858 - 1.368)	(0.884 - 1.289)	(0.695 - 0.950)	(0.711 - 0.947)	(0.568 - 0.793)	(0.561 - 1.001)
Black, NH	1.489**	1.381***	1.486***	1.265***	1.206***	0.906	0.626***
	(1.069 - 2.074)	(1.104 - 1.727)	(1.260 - 1.753)	(1.100 - 1.455)	(1.083 - 1.344)	(0.778 - 1.054)	(0.471 - 0.832)
Other race, NH	1.022	1.337	1.022	1.196	0.689***	0.730**	0.790
	(0.540 - 1.935)	(0.912 - 1.962)	(0.755 - 1.384)	(0.953 - 1.502)	(0.528 - 0.899)	(0.541 - 0.984)	(0.547 - 1.141)
Never married	1.678***	2.052***	1.907***	1.759***	1.449***	1.148	1.139
	(1.255 - 2.244)	(1.695 - 2.485)	(1.629 - 2.232)	(1.474 - 2.099)	(1.256 - 1.671)	(0.958 - 1.376)	(0.804 - 1.613)
Cohabiting	0.832	1.344*	1.214	1.191	0.824	1.109	0.177*
	(0.552 - 1.253)	(0.985 - 1.834)	(0.905 - 1.628)	(0.919 - 1.544)	(0.624 - 1.087)	(0.799 - 1.540)	(0.026 - 1.192)
Divorced/separated	1.273	1.652***	1.710***	1.444***	1.349***	1.159**	0.977
	(0.841 - 1.929)	(1.368 - 1.995)	(1.501 - 1.948)	(1.282 - 1.626)	(1.226 - 1.484)	(1.016 - 1.321)	(0.688 - 1.389)
Widowed†		1.116	2.035***	1.842***	1.192***	1.079*	1.240***
		(0.428 - 2.910)	(1.421 - 2.915)	(1.500 - 2.262)	(1.073 - 1.326)	(0.989 - 1.176)	(1.099 - 1.400)
Non-heavy drinker	0.882	0.658***	0.605***	0.594***	0.736***	0.719***	0.807***
	(0.587 - 1.325)	(0.533 - 0.812)	(0.529 - 0.691)	(0.528 - 0.669)	(0.677 - 0.799)	(0.661 - 0.781)	(0.708 - 0.920)
Heavy drinker, <3 times per week	0.742	0.699***	0.615***	0.709***	0.684***	0.804**	0.763
	(0.501 - 1.099)	(0.567 - 0.862)	(0.531 - 0.712)	(0.621 - 0.809)	(0.594 - 0.788)	(0.673 - 0.961)	(0.502 - 1.161)
Heavy drinker, 3+ times per week	1.086	1.041	1.146	0.968	0.977	1.158	1.021
	(0.546 - 2.160)	(0.719 - 1.507)	(0.879 - 1.493)	(0.751 - 1.249)	(0.774 - 1.234)	(0.827 - 1.622)	(0.450 - 2.320)
No. of observations	24841	27763	24484	17648	12183	7161	1708

*** p<0.01, ** p<0.05, * p<0.1; 95% CI presented below hazard ratios; Reference groups omitted from table: never smoker, college graduate, non-Hispanic, white NH, married, nondrinker; NH = non-Hispanic; Ages 85+ are top-coded; †Widowed coefficient for ages 25-34 could not be estimated due to collinearity with the mortality variable.

Table 2-3. All-cause mortality hazard ratios by age group – Females

Age group	25-34	35-44	45-54	55-64	65-74	75-84	85+
Current smoker	1.425**	3.199***	2.484***	2.845***	2.782***	2.269***	1.332**
	(1.027 - 1.979)	(2.578 - 3.969)	(2.109 - 2.926)	(2.453 - 3.300)	(2.485 - 3.115)	(1.996 - 2.579)	(1.018 - 1.743)
Former smoker	0.920	1.304*	1.425***	1.736***	1.655***	1.580***	1.165**
	(0.571 - 1.482)	(0.955 - 1.780)	(1.175 - 1.727)	(1.499 - 2.011)	(1.495 - 1.831)	(1.459 - 1.711)	(1.024 - 1.327)
SPD	3.584***	1.904***	2.148***	1.677***	1.693***	1.587***	1.335
	(2.287 - 5.615)	(1.398 - 2.594)	(1.687 - 2.735)	(1.327 - 2.119)	(1.335 - 2.149)	(1.260 - 1.999)	(0.931 - 1.915)
Age	1.073***	1.092***	1.108***	1.073***	1.118***	1.104***	
	(1.018 - 1.130)	(1.052 - 1.134)	(1.080 - 1.137)	(1.051 - 1.095)	(1.100 - 1.135)	(1.088 - 1.120)	
High school or less	2.586***	1.395**	1.567***	1.493***	1.315***	1.226***	0.999
	(1.639 - 4.081)	(1.062 - 1.834)	(1.264 - 1.943)	(1.239 - 1.799)	(1.136 - 1.522)	(1.078 - 1.394)	(0.835 - 1.195)
Some college	2.134***	1.157	1.395***	1.215**	1.088	1.074	0.852
	(1.320 - 3.450)	(0.872 - 1.534)	(1.118 - 1.741)	(1.003 - 1.470)	(0.925 - 1.279)	(0.939 - 1.230)	(0.687 - 1.057)
Hispanic	0.685*	1.148	0.893	0.864	0.772***	0.831*	0.730
	(0.441 - 1.064)	(0.859 - 1.535)	(0.679 - 1.174)	(0.663 - 1.126)	(0.638 - 0.934)	(0.679 - 1.018)	(0.493 - 1.081)
Black, NH	1.138	1.528***	1.414***	1.424***	1.061	0.946	0.828*
	(0.716 - 1.808)	(1.209 - 1.932)	(1.151 - 1.738)	(1.210 - 1.677)	(0.935 - 1.204)	(0.835 - 1.072)	(0.664 - 1.034)
Other race, NH	1.017	0.632	0.954	0.858	0.837	0.722*	0.802
	(0.476 - 2.172)	(0.317 - 1.259)	(0.623 - 1.461)	(0.580 - 1.269)	(0.609 - 1.150)	(0.519 - 1.004)	(0.452 - 1.423)
Never married	1.742***	1.392**	1.539***	1.655***	1.287**	1.615***	1.052
	(1.208 - 2.512)	(1.062 - 1.824)	(1.216 - 1.947)	(1.335 - 2.050)	(1.045 - 1.583)	(1.333 - 1.957)	(0.744 - 1.486)
Cohabiting	0.600	1.087	1.143	0.783	0.946	0.642	0.796
	(0.311 - 1.157)	(0.748 - 1.581)	(0.838 - 1.559)	(0.499 - 1.228)	(0.588 - 1.522)	(0.322 - 1.279)	(0.325 - 1.947)
Divorced/separated	1.164	1.239*	1.296***	1.367***	1.160**	1.211**	1.121
	(0.782 - 1.733)	(0.979 - 1.568)	(1.097 - 1.531)	(1.182 - 1.582)	(1.010 - 1.333)	(1.037 - 1.415)	(0.800 - 1.571)
Widowed	1.875	1.586	1.556***	1.546***	1.287***	1.188***	1.065
	(0.456 - 7.708)	(0.858 - 2.930)	(1.173 - 2.063)	(1.307 - 1.829)	(1.169 - 1.418)	(1.076 - 1.310)	(0.869 - 1.305)
Non-heavy drinker	0.591***	0.658***	0.597***	0.569***	0.584***	0.731***	0.757***
	(0.399 - 0.875)	(0.524 - 0.826)	(0.507 - 0.703)	(0.502 - 0.645)	(0.533 - 0.641)	(0.679 - 0.788)	(0.671 - 0.853)
Heavy drinker, <3 times per week	0.641**	0.579***	0.702***	0.510***	0.606***	0.946	0.592
	(0.422 - 0.972)	(0.418 - 0.804)	(0.555 - 0.889)	(0.393 - 0.662)	(0.460 - 0.799)	(0.661 - 1.353)	(0.300 - 1.167)
Heavy drinker, 3+ times per week	0.306	0.996	0.944	1.118	1.968**	0.647	0.495***
	(0.040 - 2.359)	(0.468 - 2.118)	(0.490 - 1.818)	(0.508 - 2.459)	(1.172 - 3.305)	(0.252 - 1.664)	(0.333 - 0.735)
No. of observations	27408	29574	25698	17906	12709	8705	2485

*** p<0.01, ** p<0.05, * p<0.1; 95% CI presented below hazard ratios; Reference groups omitted from table: never smoker, college graduate, non-Hispanic, white NH, married, nondrinker; NH = non-Hispanic; Ages 85+ are top-coded; †Widowed coefficient for ages 25-34 could not be estimated due to collinearity with the mortality variable.

Hazard ratios were as expected for my variables of interest, with current smoking, former smoking, and SPD significantly increasing risk of death for males and females across most age groups. Mortality risk for current smoking increased by age group and was highest for males ages 55-64 and females ages 35-44 and 55-64. Risk for death among former smokers was also greatest among middle aged groups, declining for older age groups.

In earlier runs, interaction terms between former smoking and SPD were found to be insignificant, and so were left out of the final models. The interaction term between current smoking and SPD was significant only for males ages 85+. The large male 85+ interaction term and its low precision translated into inflated mortality estimates. In favor of more conservative and precise hazard ratios, I omitted this term from the final model presented here and used for lifetable construction.

The proportional hazards assumption was satisfied for most covariates included in the age-stratified models at the $p<0.05$ level, which suggests that the relative hazard is constant over time –a requirement for Cox models. I ran models stratified by the remaining covariates, and found that this did not noticeably affect estimates for my main variables of interest: current smoking, former smoking, or SPD.

Table 2-4 shows estimated mortality ratios among persons with SPD by gender. Current smoking substantially increases risk of death for both males and females – approximately doubling the hazard relative to persons with SPD who have never smoked. Former smoking also increases the relative hazard rates, but was only statistically significant for

females. As anticipated, mortality hazard ratios were considerably greater for those who have never married relative to married individuals, and Hispanic individuals had significantly reduced risk relative to non-Hispanic whites. All covariates in these models satisfied the proportional hazards assumption based on non-significance of time-interaction terms.

Table 2-4. All-cause mortality hazard ratios – SPD population

SPD population	Males	Females
Current smoker	2.093***	1.887***
	(1.492 - 2.938)	(1.513 - 2.354)
Former smoker	1.212	1.367***
	(0.891 - 1.650)	(1.091 - 1.713)
Age	1.057***	1.078***
	(1.025 - 1.091)	(1.045 - 1.113)
High school or less	1.343*	1.688**
	(0.967 - 1.866)	(1.117 - 2.550)
Some college	1.187	1.309
	(0.826 - 1.706)	(0.851 - 2.013)
Hispanic	0.679**	0.581***
	(0.503 - 0.916)	(0.413 - 0.817)
Black, NH	0.898	1.032
	(0.652 - 1.237)	(0.829 - 1.286)
Other race, NH	0.594	0.558**
	(0.314 - 1.123)	(0.341 - 0.914)
Never married	1.839***	1.432**
	(1.381 - 2.449)	(1.022 - 2.007)
Cohabiting	0.823	0.723
	(0.483 - 1.400)	(0.409 - 1.280)
Divorced/separated	1.279**	1.011
	(1.021 - 1.601)	(0.789 - 1.297)
Widowed	1.063	1.162
	(0.764 - 1.479)	(0.923 - 1.463)
Non-heavy drinker	0.925	0.660***
	(0.736 - 1.163)	(0.539 - 0.807)
Heavy drinker, <3 times per week	0.965	0.844
	(0.729 - 1.276)	(0.622 - 1.146)
Heavy drinker, 3+ times per week	1.466*	1.038
	(0.963 - 2.230)	(0.575 - 1.872)
Year of birth	0.970**	1.002
	(0.942 - 0.999)	(0.971 - 1.034)
No. of observations	3045	5269

Mortality hazard ratios were applied to estimate the smoking-attributable fraction of deaths among persons with SPD. This calculation was based on 46.2% smoking prevalence for SPD males (95% CI: 44.3%-48.1%) and 40.8% for females (95% CI: 39.5%-42.2%), and 25.9% former smoking prevalence among males (95% CI: 24.2%-27.6%) and 18.5% among females (95% CI: 17.3%-19.7%). Using confidence interval limits for both hazard ratios and prevalence estimates, the smoking attributable fraction ranged from 16%-53% among males and 18%-42% among females. Based on point estimates, approximately 36% and 30% of all deaths among males and females with SPD are due to smoking. For comparison, 26% of all deaths among people without SPD are smoking-attributable.

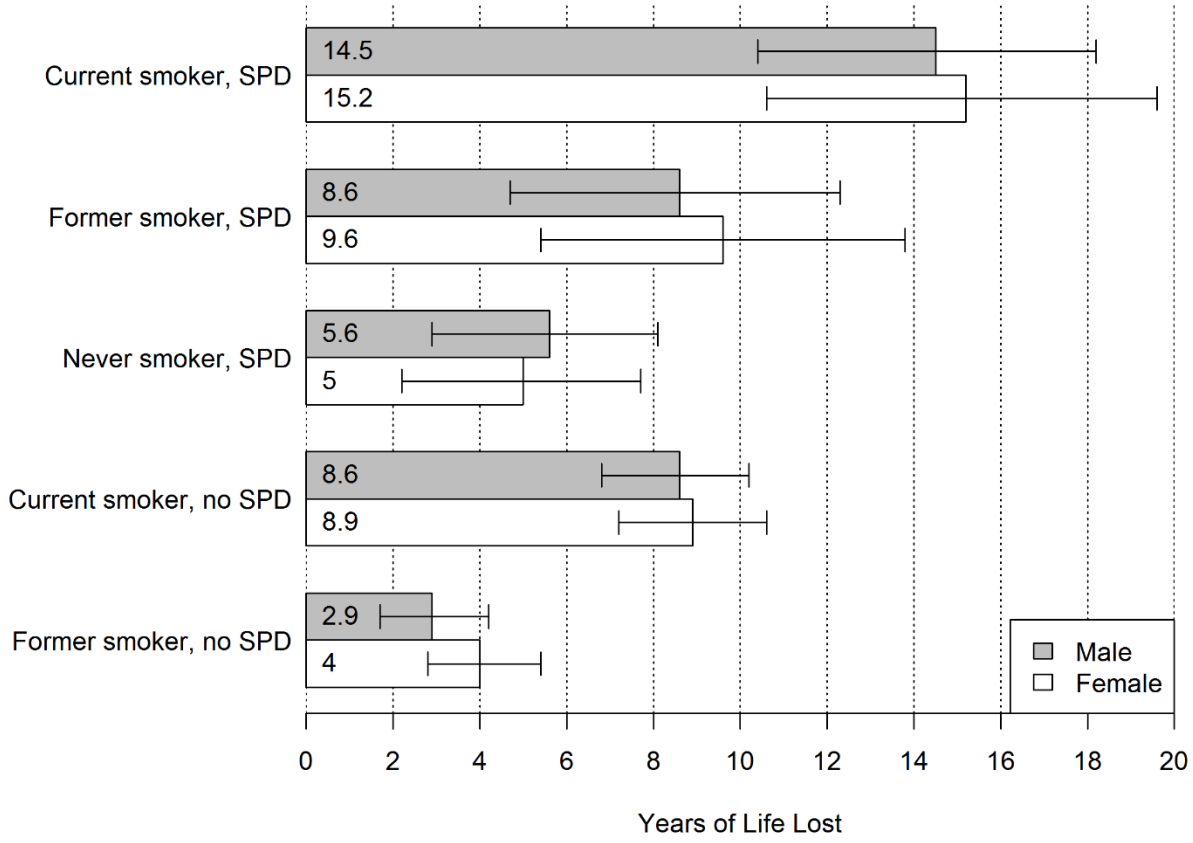
Figure 2-1 presents years of potential life lost at age 40 compared to never smokers without SPD. Confidence bands represent reduced life expectancy using the 95% confidence intervals for each hazard ratio applied to baseline never-smoker death rates. Results at other ages are available upon request.

Smoking with SPD costs individuals 14.9 years of life expectancy (average across males and females) compared to never smoking and not having SPD. For never smokers, having SPD reduces life expectancy by approximately 5.3 years. Thus, smoking accounts for nearly two-thirds of the overall difference in life expectancy between smokers with SPD and never smokers without SPD.

Among individuals with SPD, being a current smoker reduces life expectancy by approximately 9.55 years compared to not smoking, and the difference in life expectancy

is maintained even when evaluating across confidence intervals. Those with SPD who have quit smoking have 5.75 more years of life compared to those who are current smokers. However confidence bands overlap for former and current smokers with SPD.

Figure 2-1. Life expectancy reduction at age 40 by smoking and SPD status



SPD = serious psychological distress; Estimates represent the difference in life expectancy between each group and never smokers without SPD; Life expectancy in never smokers without SPD is 41.6 years for men and 43.7 for women at age 40; Confidence bars represent estimates using the lowest and highest hazard ratio estimates (95% CI) applied to the reference group's mortality rates.

Discussion

To my knowledge, this is the first study to quantify the specific contribution of smoking to reduced life expectancy among persons with serious mental illness. My findings that SPD and smoking both independently reduce life expectancy corroborate previous research.[1,32] However, I show that the difference in life expectancy between current smokers with SPD and never smokers without SPD is primarily due to smoking, which contributes to nearly two-thirds of the life years lost. I also find that one-third of all deaths among persons with SPD can be attributed to smoking.

The analyses show the clear benefit to quitting smoking regardless of one's mental health status. Former smokers with SPD have roughly 5 years of additional life compared to current smokers. However, the impact of serious mental illness on early death among former smokers is still strong, as their life expectancy is similar to that of current smokers who do not have SPD. Other results are generally consistent with existing literature on the effects of other demographic and behavioral risk factors for mortality, including research on the protective benefits of moderate drinking.[33]

This study is strengthened by its use of nationally representative data and the most historically comprehensive mental health measure available in the U.S., as annual screening for SPD among adults began as early as 1997. Although non-specific psychological distress is not a diagnostic measure, it is a scale that significantly predicts serious psychiatric disorders in the general population.[21,22] Furthermore, in separate analyses using the National Health and Nutrition Examination Survey (NHANES) and the

Patient Health Questionnaire (PHQ-9), a validated screening tool for clinical depression, I found smoking relative risks estimates consistent with those reported here (Appendix).

Screening for SPD in the general population also captures individuals who are not receiving treatment. Thus my study has the advantage of being generalizable to the non-patient population. However, NHIS does not survey homeless, military, incarcerated, or institutionalized groups known to have higher prevalence of smoking and mental disorders.[34-38] Thus my analyses might underestimate the true impact of smoking and mental illness on mortality due to the exclusion of these groups, particularly those in psychiatric institutions.

My estimations of the contribution of smoking to the excess mortality of persons with SPD may be conservative. This is because I use a general estimate of mortality risk for never smokers, one that inherently includes never smokers with SPD, as a baseline rate. Thus I might be underestimating the magnitude of differences in life expectancy. Moreover, I have not adjusted for the fact that persons with SPD smoke more cigarettes per day than do smokers without SPD.[12,39] Higher daily cigarette consumption likely contributes to even greater mortality risk, potentially exacerbating the effects.

My study is limited by the lack of data on mental health and smoking status for individuals over time. Health and behavioral data on NHIS respondents are collected at baseline and do not reflect their status upon follow-up. Unfortunately this is the nature of cross-sectional national health surveys, which at most collect longitudinal mortality data for a subsample. Other longitudinal data sources with more comprehensive information may be able to address this issue, but are generally not representative of the U.S. population.

Previous studies have reported on the excess mortality among those with mental illness in other countries. A global meta-analysis estimated roughly a decade of potential life lost for individuals with mental disorders;[1] This study suggests that much of this life expectancy reduction may be due to smoking. The finding that ~33% of deaths among persons with SPD are attributed to smoking is similar to estimates reported for UK patients with mental disorders.[40] Researchers there have also shown that smoking among those patients contributes to substantial economic costs and total years of life lost at the population level.[40] The work further examines differences in life expectancy at the individual level by age, gender, and smoking and mental health status.

There may be considerable variation in life expectancy and smoking attributable mortality by type of mental disorder, and level of disease severity. Future research should examine the effect of smoking on mortality for specific psychiatric disorders. Research could further parse out mortality among individuals with mental illness by cause of death. Though much of the mortality cost is due to smoking, mental illness may account for a larger portion of the decrease to quality of life, which I did not examine here.

The fact that smoking and serious mental illness comorbidity reduce life expectancy by nearly 15 years is appalling considering that the former can be avoided completely and the effects of the latter can be mitigated through effective prevention and treatment efforts. Though life expectancy is already reduced for individuals with mental disorders, important gains could be made by aiding those with mental illness to quit smoking, or by preventing them from ever starting to smoke.

Appendix

Supplementary materials, including more detailed lifetables, can be found online through the *American Journal of Preventive Medicine.*[41]

The following tables are results using the PHQ-9 measure for depression.

Table 2-5. All-cause mortality hazard ratios by age group, NHANES 2005-2010

Ages	25-34	35-44	45-54	55-64	65-80	Full sample
Current smoker	5.164**	2.171	2.964***	2.241***	2.547***	2.578***
	(1.284 - 20.770)	(0.585 - 8.057)	(1.430 - 6.145)	(1.276 - 3.937)	(1.748 - 3.711)	(1.890 - 3.516)
Former smoker†		0.674	1.893	1.178	1.336	1.359
		(0.059 - 7.637)	(0.718 - 4.987)	(0.577 - 2.402)	(0.917 - 1.947)	(0.896 - 2.061)
Depressed	1.642	1.998	1.211	1.244	1.915***	1.628***
	(0.373 - 7.215)	(0.601 - 6.638)	(0.631 - 2.325)	(0.733 - 2.109)	(1.184 - 3.099)	(1.159 - 2.288)
Male	3.136	0.774	1.681	1.180	1.748***	1.490***
	(0.794 - 12.378)	(0.248 - 2.418)	(0.886 - 3.190)	(0.763 - 1.824)	(1.338 - 2.284)	(1.168 - 1.902)
High school or less	1.666	3.181	2.322*	1.452	1.886**	1.920***
	(0.130 - 21.320)	(0.409 - 24.755)	(0.877 - 6.151)	(0.752 - 2.802)	(1.070 - 3.326)	(1.387 - 2.657)
Some college	4.245	3.306	2.464	1.339	1.624	1.836***
	(0.385 - 46.804)	(0.343 - 31.885)	(0.699 - 8.680)	(0.600 - 2.992)	(0.871 - 3.031)	(1.212 - 2.783)
Hispanic	1.153	0.745	0.690	1.301	0.692	0.824
	(0.184 - 7.217)	(0.296 - 1.875)	(0.326 - 1.461)	(0.724 - 2.338)	(0.442 - 1.084)	(0.636 - 1.067)
Black, NH	4.118*	0.404	1.625	2.252***	1.018	1.386***
	(0.920 - 18.426)	(0.118 - 1.387)	(0.868 - 3.044)	(1.378 - 3.681)	(0.672 - 1.540)	(1.094 - 1.754)
Other race, NH†				0.769	2.031	0.772
				(0.099 - 5.971)	(0.634 - 6.505)	(0.277 - 2.150)
Age	0.851*	1.235	1.368	1.050	1.051	1.117**
	(0.710 - 1.021)	(0.772 - 1.976)	(0.886 - 2.113)	(0.862 - 1.278)	(0.943 - 1.171)	(1.025 - 1.217)
Year of birth		1.199	1.195	1.006	0.942	1.033
		(0.811 - 1.772)	(0.820 - 1.742)	(0.854 - 1.184)	(0.848 - 1.046)	(0.950 - 1.124)
No. of observations	2438	2502	2541	2326	2624	12,418

*** p<0.01, ** p<0.05, * p<0.1; 95% CI presented below hazard ratios; Reference groups omitted from table: never smoker, college graduate, non-Hispanic, white NH; NH = non-Hispanic; †Coefficients for former smoker 25-34 and other race, NH ages 25-54 could not be estimated due to collinearity with the mortality variable.

Table 2-6. Smoking attributable fraction (SAF) of deaths, NHANES 2005-2010

SAF	0.60 (0.20 - 0.83)
P1	0.42 (0.38 - 0.46)
P2	0.20 (0.17 - 0.24)
RR1	4.24 (1.83 - 9.84)
RR2	1.69 (0.58 - 4.98)
P1 = current smoker prevalence among those with depression; P2 = former smoker prevalence among those with depression; RR1 = mortality hazard ratio for current smokers with depression relative to never smokers with depression; RR2 = mortality hazard ratio for former smokers with depression relative to never smokers with depression; 95% CI presented below estimates.	

The National Health and Nutrition Examination Survey (NHANES) began screening for depression annually in 2005 using the Patient Health Questionnaire-9 (PHQ-9). This nine-item questionnaire screens for the nine criteria for major depressive disorder according to the Diagnostic and Statistical Manual on Mental Disorders (DSM-IV) and is a widely used and validated measure for depression. The PHQ-9 asks about frequency of experiencing 1) little interest or pleasure in doing things 2) feeling down, depressed, or hopeless, 3) trouble falling or staying asleep, or sleeping too much, 4) tired or having little energy, 5) poor appetite or overeating, 6) bad about oneself or like a failure, 7) trouble concentrating, 8) moving more slowly than usual or being fidgety and restless, 9) suicidal thoughts, over the past two weeks. Each item is scored 0-3 for “not at all,” “several days,” “more than half the days,” and “nearly every day.” Depression is defined as score of 10 or greater. Data from the NHANES 2005-2006, 2007-2008, and 2009-2010 cycles were linked to the 2011 National Death Index mortality follow-up.

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Chapter 3 – Lifetime prevalence of major depressive episodes and adjustment of recall error through simulation modeling

Background

The National Survey on Drug Use and Health (NSDUH) is one of the main sources of surveillance information on population mental health in the U.S. According to the NSDUH, an estimated 16.2 million adults (6.7% of the population) have had at least one episode of major depression (MD) in the past year.[1] Of these individuals, nearly two-thirds experienced severe impairment due to MD, affecting their home management, relationships with others, social life, and ability to work. MD is the most common mental disorder in the general population and a leading contributor to disability worldwide.[2] In the U.S., MD accounts for 8.3% of all years lived with disability, and carries the heaviest disability burden of any mental and behavioral disorder.[3] People with MD have shorter life expectancies and increased risk of death, including suicide.[4-7] MD is also associated with significant productivity loss.[8,9] Still, the extent of the burden of depression and its impact on population health is likely misestimated by available survey data.

Cross-sectional surveys such as NSDUH assess lifetime history of psychiatric disorders retrospectively. This is problematic, as longitudinal studies have shown that retrospective assessments are prone to underreporting.[10] For example, the Baltimore Epidemiological Catchment Area (ECA) Study found that over a 25-year follow-up period, lifetime

prevalence of MD was nearly 3 times greater (4.5% vs. 13.1%) using cumulative evaluations compared to retrospective evaluations.[11] Moreover, cross-sectional surveys that cover a broad age range unexpectedly show that the lifetime prevalence of MD declines, rather than increases, with age.[12] For example, the National Comorbidity Survey –Replication (NCS-R) identified lifetime prevalence of MD as 16.6% for all adults, where MD increased as expected through ages 18-44, then dropped to 10.6% of those above age 60.[13] This pattern could be explained by differential mortality and symptomatic differences in depression among older adults,[14] or differences in MD incidence by birth cohort. However, failure to recall earlier depressive episodes,[15] particularly among older people, could also result in decreasing lifetime prevalence with age.

Surveys of population mental health such as the NSDUH provide timely assessments of psychopathology, which is useful for service planning. However, they may underestimate lifetime prevalence of MD due to their reliance on retrospective reporting. On the other hand, prospective cohort studies that address recall bias are costly to implement, often specific to a particular geographic location (e.g., Baltimore site of the ECA), or have only a few waves of data (e.g., National Epidemiologic Survey of Alcohol and Related Conditions; NESARC). In the absence of sufficient data to fully estimate the burden of MD in the population, simulation modeling approaches can fill in gaps in our understanding of the epidemiology of depression.[16-18]

Simulation modeling is an analytic approach that uses existing information to represent processes that contribute to the observed data. To date, very few models of depression consider the issue of declining lifetime prevalence of MD with age. One microsimulation study using data from Australia and the Netherlands addressed recall error to re-estimate

lifetime depression prevalence in the population.[19] Another discrete event simulation study investigated decreasing lifetime prevalence of MD by age in Canada.[20] No such analysis has used simulation modeling to evaluate the potential impact of recall error on prevalence estimates of lifetime depression in the U.S.

In this chapter, I develop a system dynamics model of MD episodes, combining both annual cross-sectional NSDUH data and prospective cohort data from the Baltimore ECA, to explicitly model recall error and associated mismeasurement of MD. I use this model to generate incidence and recall error parameters that do not yet exist in the literature, and to ultimately produce revised national estimates for lifetime prevalence of MD.

Methods

Data sources

The NSDUH is an annual nationally-representative household cross-sectional survey of ~70,000 civilian noninstitutionalized people ages 12 and above. The NSDUH assesses MD using criteria derived from the Diagnostic and Statistical Manual of Mental Disorders (DSM).[21] I use data for the adult (age ≥18) population (~50,000 respondents), because survey questions for MD differ between youth and adults, and are thus not comparable for combined analysis.[22,23] The survey is directed by the Substance Abuse and Mental Health Services Administration (SAMHSA) Center for Behavioral Health Statistics and Quality and conducted by RTI International.[23] Data on drug, alcohol, and tobacco use are collected as well as mental health indicators such as psychological distress and depressive symptoms. The survey ensures respondent confidentiality as no personally identifying information is included with survey responses. Participants use audio

computer-assisted self-interview software to respond to sensitive questions and receive a $30 incentive at the end of the survey. This data source represents the most historically comprehensive information on patterns of depression[24] with comparable measures for the years 2005-2015.

The Baltimore Epidemiologic Catching Area (ECA) Study is a longitudinal survey that follows a 1981 baseline cohort of 3,481 adult household residents in East Baltimore and repeats assessments in 1993, 1996, and 2004. Participants provide information about their depressive episodes based on the question “During that year, was there ever a time when you were feeling sad, depressed, or blue, and had some of these other problems like [list of DSM-IV criteria for MDD]?”[25-27] Memory anchors with key life events are used to help place periods of depression within each respondent’s personal life history.

Measures

A MD episode is a period lasting two weeks or more during which the respondent reports experiencing at least five of the following nine symptoms: 1) depressed mood most of the day, 2) markedly diminished interest or pleasure in activities most of the day, 3) significant changes in weight or appetite, 4) insomnia or hypersomnia, 5) psychomotor agitation or retardation, 6) fatigue, 7) feelings of worthlessness, 8) diminished ability to think or concentrate, and 9) recurrent thoughts of death or suicide ideation. These symptoms were asked about both over their lifetime and in the past year. The NSDUH measure of MD does not apply DSM hierarchy exclusions for episodes due to illness, bereavement, and/or substance use disorders.

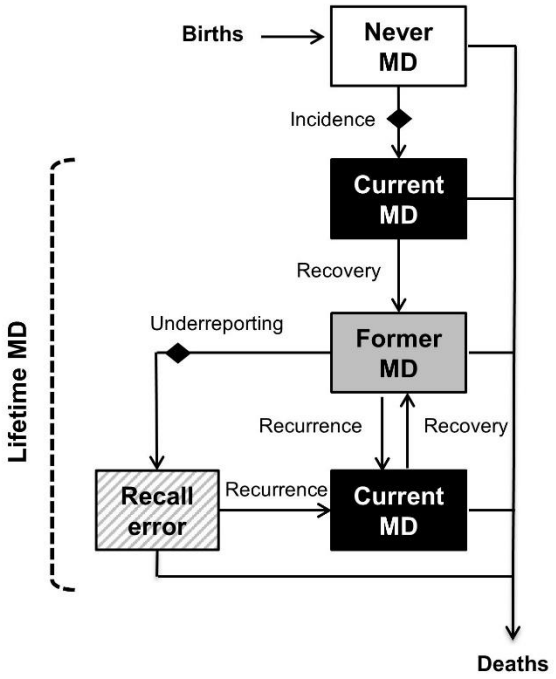
Model overview

There are three possible MD states for the population in the model. I define *current MD* (black) as an episode within the past 12 months, including a first or recurrent episode. I define *former MD* as individuals who report a lifetime history of at least one MD but have not had an episode within the past year (gray). I define *never MD* as those who report no lifetime history of MD (white). A key innovation of this model is that it includes a 'recall error' compartment for people who report no lifetime history of MD, but who are actually *former MD*.

Figure 3-1 provides an overview of the model structure. I use a compartmental model with separate stocks (boxes) for each depressive state and transition probabilities governing the flow (arrows) of individuals moving across them. This model evaluates aggregate-level patterns and does not track individual trajectories of depression (e.g. episode duration, number of previous episodes).

There are three possible MD states for the population in the model. I define *current MD* (black) as an episode within the past 12 months, including a first or recurrent episode. I define *former MD* as individuals who report a lifetime history of at least one MD but have not had an episode within the past year (gray). I define *never MD* as those who report no lifetime history of MD (white). A key innovation of this model is that it includes a 'recall error' compartment for people who report no lifetime history of MD, but who are actually *former MD*.

Figure 3-1. Model diagram of depressive states and transitions



MD = Major Depression; Diamond = annual probabilities estimated during model calibration; Never MD = individuals with no lifetime history of MD; Current MD = individuals with a past year MD; Former MD = individuals with lifetime history of MD but no MD episode in the past. Recall error = individuals who report no lifetime history of MD but are modeled as former MD.

I simulate a population in which all individuals begin in the *never MD* state at age zero based on U.S. Census Bureau population estimates for the years 2005-2015.[28] While I exclude children from the data sources, the model simulates individuals from birth until death, with onset of depression occurring as early as age 12. I model a 'burn-in' period in which the population is simulated beginning in 1900, with new births and deaths each year, so that the model achieves observed depression patterns by 2005.

Table 1 shows parameters used or calibrated for the model. As individuals age each year, they may have a first MD episode according to age at onset of MD incidence rates from the Baltimore ECA Study.[25] The ECA study identified 71 new cases of MD among 1,920 respondents representing 23,698 person-years of exposure. This study found that incidence peaked when respondents were in their 30s, with a smaller peak during their 50s. Because the Baltimore ECA did not include incidence rates for females ages < 22 and males ages < 29, where no data are available, I estimate the probability of a first MD episode for younger ages, 12-21 in females and 12-28 in males, during model calibration.

Following a first MD episode, individuals can recover into the *former MD* compartment. Annual recovery probabilities are treated as identical for males and females, and as constant across all ages. I calculated recovery and recurrence transition probabilities based on data from the Baltimore ECA.[26] Likelihood of recovering from an episode is the same regardless of whether individuals are in a first or subsequent episode, based on evidence showing no significant difference in rates of recovery by number of prior episodes.[29]

Table 3-1. Model parameters

Parameter	Model estimates
1st MD incidence probabilities	Age at onset of MD episode incidence for females ages 22+ and males age 29+ in the Baltimore-ECA cohort study.[25] Cubic natural splines for MDE incidence with knots at ages 13 and 18 were used to estimate probabilities among females ages 12-21 and males ages 12-28.
MD recovery probabilities	Annual probability of recovery calculated from 85% cumulative recovery from 1st MD over 10 years in the Baltimore-ECA cohort study.[26] Annual probability = $1 - (1 - Cumulative\ Incidence)^{(1/Duration\ in\ Years)}$

	$= 1 - (1 - 0.85)^{(1/10)} = 0.173$).
MD recurrence probabilities	Annual probability of recurrence calculated from 45% cumulative recurrence after 1st MD over 10 years in the Baltimore-ECA cohort study.[26] Annual probability $= (1 - (1 - 0.45)^{(1/10)} = 0.058)$.
Annual probability of death	Age, gender, and birth-cohort specific death probabilities from the Human Mortality Database, which relies on information from the National Vital Statistics System.[30]
Relative risk of mortality for lifetime history of MD episodes	Pooled relative risk of mortality for people with lifetime history of MD (RR=1.71, , 95% CI: 1.54 to 1.90) estimated from a meta-analysis of 43 studies.[5]

Former MD individuals can shift into the 'recall error' compartment based on calibrated estimates for the annual probability of underreporting past episodes. Since the aim is to assess the extent to which individuals fail to report histories of MD, I assume no inaccuracies due to overreporting of depressive episodes. Like those who are *former MD*, this group can then have a recurrent MD episode.

Finally, individuals across all compartments exit the model based on age, birth-cohort, and year-specific death probabilities. I applied an elevated risk of death to all ages among those with lifetime MD using a pooled relative risk of mortality (RR=1.71, , 95% CI: 1.54 to 1.90) from a meta-analysis of 43 studies,[5] that is nearly identical to an estimate from another review.[31] All surviving individuals exit the model by death at age 99. I developed the model using R version 3.1.3.[32] Given known differences in depression patterns by gender, I model females and males separately.[33]

Calibration

I calibrate the model to reproduce NSDUH depression patterns by age and gender using the 'Bhat' and 'splines' packages in R.[32,34] Specifically, I fit NSDUH data across three MD states and five age groups (18-25, 26-34, 35-49, 50-64, 65+) for a total of 15 distinct groups for males and females. I use the Davidon-Fletcher-Powell optimization algorithm to search for parameter estimates that minimize the sum of squared differences between the model and the NSDUH data for the years 2005-2015. During calibration, I fitted individuals in the 'recall error' compartment as part of the *never MD* population.

Parameter estimation

I estimate parameters for first onset of MD for females ages 12-21 and males ages 12-28 using cubic natural splines to identify coefficients for the annual age-specific probability of a first MD. This extends previously reported curves for age at MD onset to include youth and young adults,[25] and ensures that the model produces accurate estimates by age 18. The splines are given three degrees of freedom with knots at age 13 and 18. I assume no episodes of MD occur prior to age 12, because data suggest that only 0.50-0.75% of children show signs of depression by age 11.[35]

During calibration, I estimate underreporting for each of five age groups to align with the NSDUH data and allow annual probabilities to range from 0 to 1. Because the NSDUH top-codes all ages above 65, I estimate the same probabilities for the entire 65-99 category. The model assumes zero probability of underreporting of past MD among individuals ages < 18.

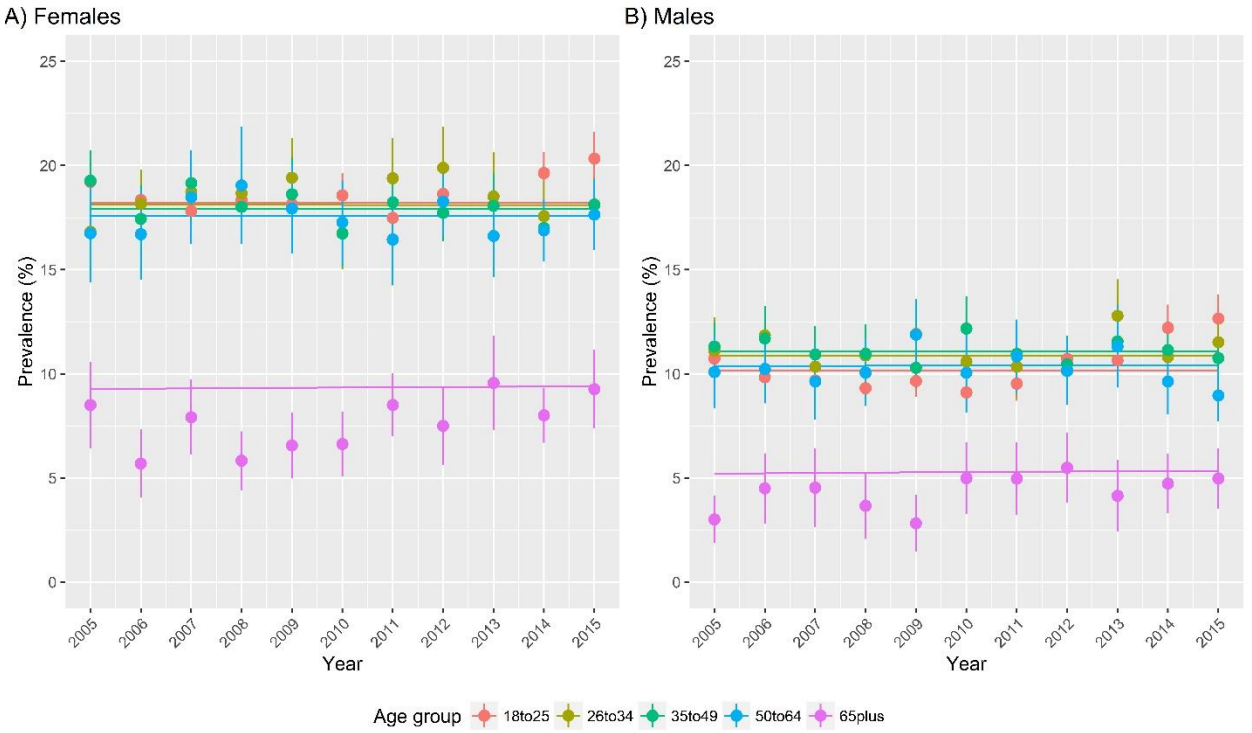
Sensitivity analysis

I assess the impact of three parameters: recovery, recurrence, and the relative risk of mortality among people with a history of MD, on two main outcomes of interest: (1) the proportion of the adult population that fails to recall past history of MD and (2) lifetime prevalence of MD. These parameters are assessed with Latin hypercube sampling, which enhances efficiency and reduces the number of model runs necessary to produce accurate estimates, using the package 'pse' in R.[36,37] I sample 200 parameter combinations, with each run re-fitting and re-estimating splines coefficients for MD incidence probabilities and age group-specific underreporting probabilities. Since there is substantial uncertainty surrounding the parameters for recovery and recurrence from MD. I sample values from a uniform distribution range that halved (50% decrease) and doubled (100% increase) base estimates. Values for the relative risk of mortality associated with ever having a MD episode are sampled from the normal distribution (RR = 1.71, 95% CI: 1.54-1.90) for the relative risk of mortality associated with MD.[5]

Results

In the NSDUH, for all age groups except for ages 65+, lifetime prevalence of MD fluctuated slightly from year to year but generally ranged from 16.5% to 20.3% for females, and 9.0% to 12.8% for males (Figure 3-2). Lifetime prevalence was markedly lower in the oldest age group, with point estimates ranging from 5.7% to 9.5% for females, and from 2.8% to 5.6% for males.

Figure 3-2. Lifetime MD prevalence by age group without recall error adjustment, United States, 2005-2015.



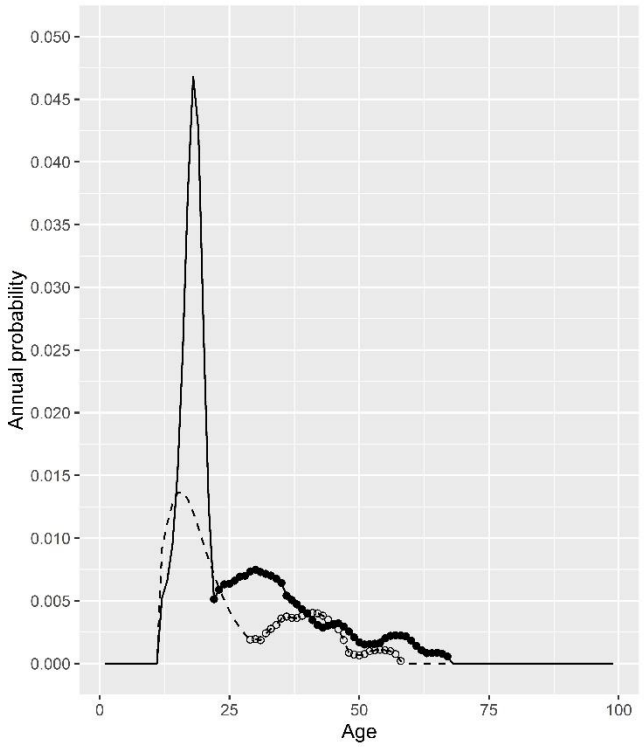
MD = Major Depression; Lines = model estimates without recall error adjustment; Dots = National Survey on Drug Use and Health data with 95% confidence interval bands (vertical lines).

After calibration, the model estimates for lifetime MD prevalence by age group without recall error adjustment corresponded closely to the NSDUH data as shown in Figure 3-2. For comparison, I categorize individuals with recall error in the model as *never MD*. For females, when those with recall error were excluded from lifetime MD estimates, prevalence decreased slightly with each successive age group, before dropping dramatically for the oldest age group. By the year 2015, prevalence was 18.2% for 18-25 year olds, 18.1% for 26-34 year olds, 17.9% for 35-49 year olds, 17.6% for 50-64 year olds, and 9.4% for ages 65 and above. For males, lifetime prevalence increased slightly,

then decreased, with age: lifetime MD prevalence was 10.2% for 18-25 year olds, 10.9% for 26-34 year olds, 11.1% for 35-49 year olds, 10.4% for 50-64 year olds, and 5.3% for those 65+ in the year 2015. Model estimates for each age group were relatively stable over time, with <0.1% absolute changes in prevalence over the 11-year period. For a comparison that includes recall error adjustment, see Appendix Figure 3-6.

I present the probabilities of first lifetime MD episode as used in the model in Figure 3-3. Black dots and circles represent previously reported data from the Baltimore ECA for women ages ≥ 22 and men ages ≥ 29.[25] Earlier research from the Baltimore ECA among adults showed bimodal MD incidence distributions, with peaks in the 30s and 50s age ranges. The calibrated estimates show higher risk of a first episode at younger ages for both females (solid line) and males (dashed line). Annual probabilities of first MD episode peak at age 18 among females (0.047) and at age 16 among males (0.014). This is 6.3 times greater than the highest peak based on previously reported data (0.008 at age 30), and 3.4 times greater than the highest previously reported rate among men (0.004 at age 40). Among youth and young adults, extrapolated probabilities of MD onset were substantially lower for males than for females, though the splines show a wider and more rounded peak.

Figure 3-3. Annual probability of 1st major depressive episode

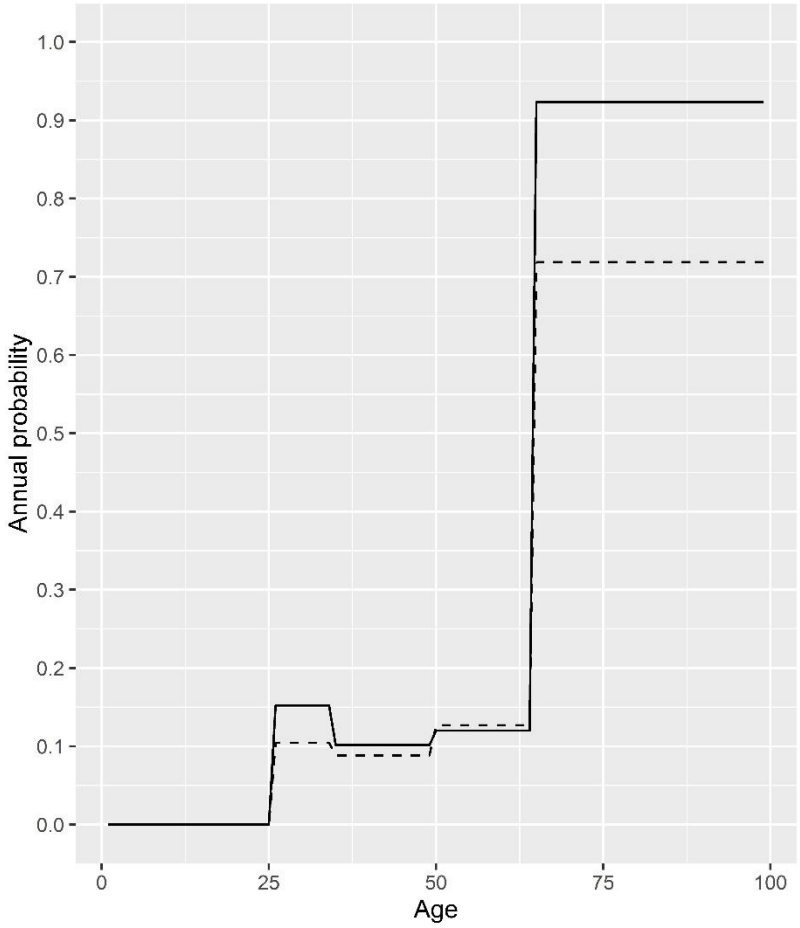


Solid line = Females ages 12-21 calibrated model estimates; Dashed line = Males ages 12-28 calibrated model estimates; Black Dots = incidence probabilities for female age at onset of major depressive disorder (MDD) in the Baltimore Epidemiological Catchment Area (ECA) Study; Circles = incidence probabilities for male age at onset of MDD in the Baltimore ECA Study.

I identified consistent patterns for the probability of underreporting a past MD episode for females (solid line) and males (dashed line), as shown in Figure 3-4. The calibrated model estimated zero probability of underreporting past MD for both males and females ages 18-25. The estimated proportion of *former MD* individuals who do not report their past episodes was higher for females (15.2%) than for males (10.5%) for those ages 18-25 and similar for ages 26-34 (10.1% vs. 8.8%) and 35-49 (12.0% vs. 12.7%). Probabilities of underreporting were dramatically higher for those ages 65+, with 92% and 71.9% of *former MD* females and males do not report their histories of MD. This represents more

than seven-fold and five-fold increases compared to the preceding age groups for females and males respectively.

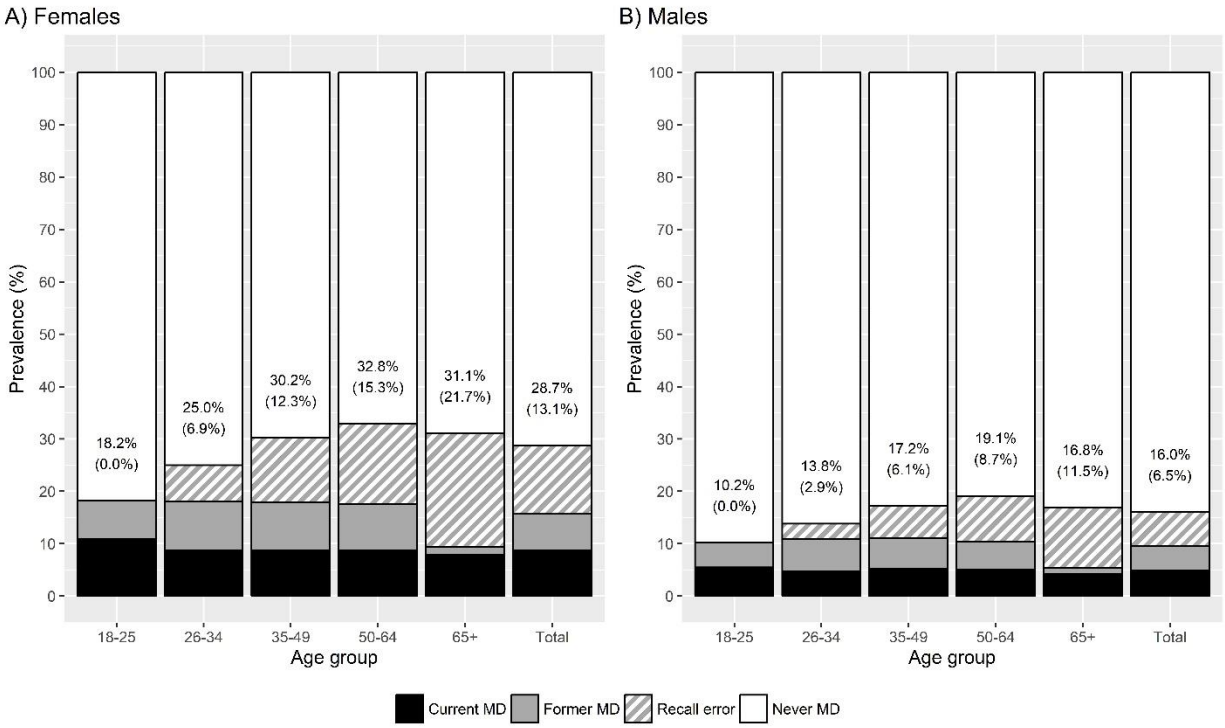
Figure 3-4. Past major depressive episode underreporting probabilities by age, United States



Solid line = Females; Dashed line = Males; model estimates calibrated for age groups 18-25, 26-34, 35-49,50-64, and 65+. Annual probabilities for individuals age <18 fixed at zero.

The model estimates 13.1% of women and 6.5% of men failed to report their histories of MD (Figure 3-5). Sensitivity analysis showed that 95% of values for the proportion of adults that underreport a past episode ranged from 8.6% to 16.9% for females and 4.2% to 8.5% for males (Appendix Figure 3-7). Individuals who fail to report their past depression represent an increasing share of those with lifetime MD with each successive age category; this proportion is lowest for ages 26-34 when 6.9% of females and 2.9% of males make up this group, and highest for ages 65+ at 21.7% of females and 11.5% of males. People who fail to report their past depression make up more than two-thirds of those with lifetime MD at age 65+.

Figure 3-5. Adult lifetime MD prevalence by age group with recall error adjustment, United States, 2015



MD = Major Depression; Distribution of the adult population with current MD (black), former MD (gray), former MD with recall error (diagonal hatching

pattern), and never MD (white). Numbers represent the percent of individuals with lifetime MD. Numbers in parentheses represent the percent of individuals with recall error who fail to report lifetime MD.

Figure 3-5 shows estimated prevalence of lifetime MD by age group and gender in 2015. Approximately 10% of women and 6% of men had *current MD*, and this remained relatively constant across age groups. The recall-corrected model estimated that 28.7% of women and 16.0% of men had a lifetime history of MD. During sensitivity analysis, 95% of estimates for lifetime prevalence of MD fell between 27.8% and 31.3% among females and between 15.4% and 17.6% among males (Appendix Figure 3-7). The proportion of the population with a lifetime history of MD increases with age until peaking in the 50-64 age group, where 32.8% of females and 19.1% of males had a history of a MD in their lifetimes, then decreases for those ages 65 and above to 31.1% and 16.9% respectively. Thereafter, the oldest 65+ age group shows slightly lower lifetime MD prevalence compared to younger adults, due to differential mortality.

Discussion

This simulation model quantifies the impact of recall error on lifetime prevalence of MD in the general U.S. population. I found that more than 40% of adults with a lifetime history of MD failed to report their history of MD in cross-sectional surveys. This indicates that lifetime prevalence of MD is considerably higher after accounting for underreporting among those without a current MD. The findings corroborate simulation studies from other countries that show lifetime prevalence of depression is dramatically higher than indicated

by retrospective analyses.[19,38] Our recall-corrected estimates also show the expected pattern of increasing lifetime prevalence with age, with a minor decrease in the oldest age group that can attributed to differential mortality.

This model is strengthened by its relative structural simplicity, its remarkably close fit with 11 years of nationally-representative survey data, and the use of age-cohort specific mortality rates. This simple yet comprehensive simulation model derives parameters for MD onset, recovery, and recurrence from the nation's longest-running psychiatric epidemiologic prospective cohort study. Furthermore, sensitivity analysis suggests that even with considerable uncertainty surrounding the extent to which adults underreport their past episodes, lifetime MD prevalence estimates fall within relatively narrow ranges.

I also found that the probability of a first MD episode is higher during adolescence than adulthood. By extrapolating probabilities to younger ages, I report plausible depression incidence data that could not otherwise be obtained through survey data. Youth and adult measures for depression are not directly comparable, nor are they generally used within the same surveys.[14] Our incidence estimates also support other data that show depressive symptoms become increasingly prevalent during adolescence.[35,39]

There are several alternative explanations for the lower lifetime MD prevalence among adults ages 65+ beyond recall error. They may interpret prior depressive symptoms differently, potentially in a more positive manner.[40] For example, older adults are less likely to endorse depressive symptoms, and when they do experience symptoms they are more likely to be categorized as 'minor' depression.[41,42] If MD incidence is rising over time, as some have argued,[43] it is possible that earlier birth cohorts have lower rates of

depression compared to recent birth cohorts. Even if the absence of a real increase in incidence, more recent cohorts may have greater mental health awareness, making them more likely to report symptoms. Finally, because people with depression have increased mortality risk, a larger proportion of them would be deceased in the oldest age group so their absence would lead to lower lifetime MD prevalence. However differential mortality does not explain unchanging patterns of lifetime MD prevalence during ages 25-64 when recall error still occurs. Because the U.S. population is aging[44] and recall error increases with age, this will further underestimate the true lifetime burden of depression.

Findings should be interpreted in light of study limitations. Because the public-use NSDUH data does not disaggregate its oldest age group, underreporting parameters were estimated for all individuals in this group. This results in a notable 'jump' in probabilities from the 50-64 age group to ages 65+. I previously used cubic natural splines to estimate the annual probability of forgetting which generated smoother curves across all ages. However, I found that using a 0 to 1 probability for each age group was both simpler to implement and capable of achieving a similar fit with survey data during calibration.

In the absence of reliable age-specific depression mortality rates, I had to apply a single relative risk of mortality point estimate for all individuals with lifetime MD. Some studies suggest that there is in fact no increased risk of death associated with major depressive disorder alone, and existing estimates may be confounded by concurrent health decline.[45] However the model does not consider differences by sociodemographic groups, and individuals with depression are more likely to live in poverty which puts them at higher risk of mortality overall.[46] This study also does account for high smoking rates among

those with depression, when smoking contributes substantially to mortality and reduced life expectancy among people with mental illness.[47,48] Even if depression itself confers a relatively small increase in mortality risk, individuals in the population with a history of depression are likely to still have higher probabilities of death. Although it is unclear how mortality risk for depression would change over the life course, sensitivity analysis show that varying a single mortality estimate did not change the study conclusions.

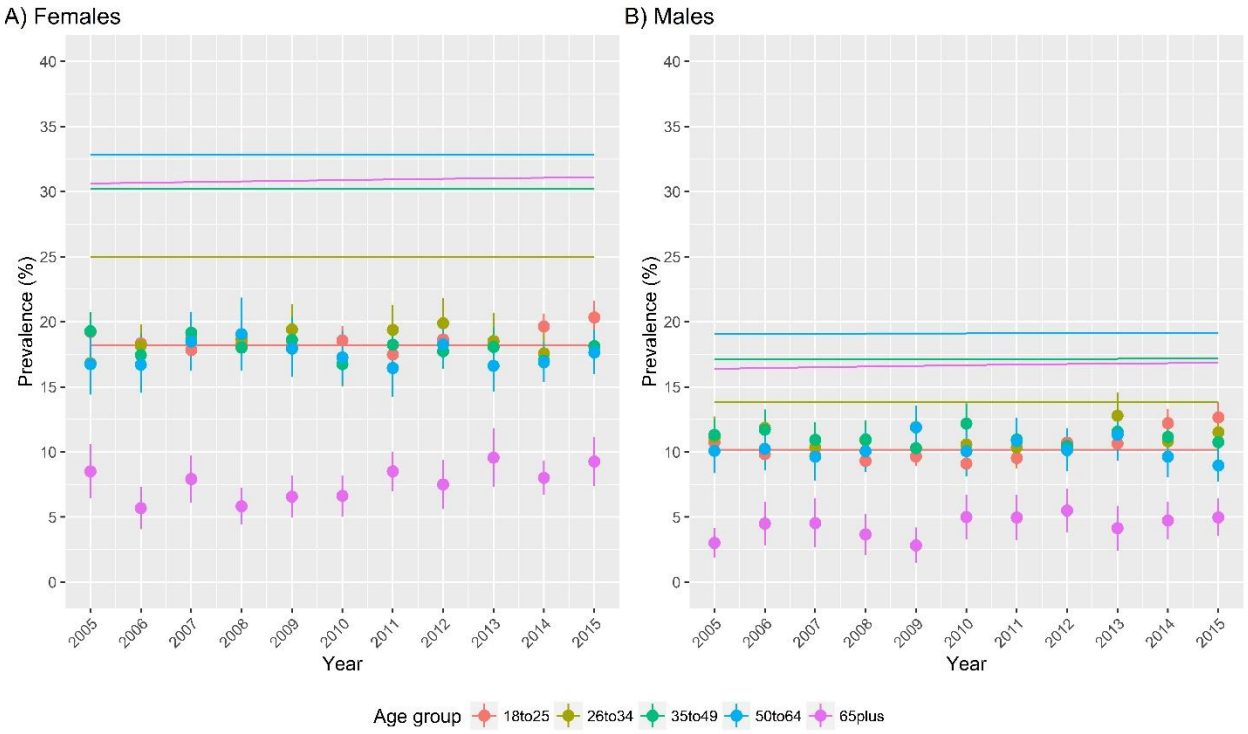
Due to the limited years of survey data, I were unable to examine period or cohort effects that may contribute to variation in lifetime MD prevalence, as discussed above. The NSDUH does not distinguish between depressive episodes associated with unipolar depression and bipolar disorder, so the exclusion of individuals with bipolar disorder would slightly lower prevalence estimates. In addition, recovery and recurrence rates were derived them from a single cohort study. However sensitivity analyses revealed that varying these parameters did not change the inferences drawn from the model: recall error plays a significant role in the severe underestimation of lifetime MD prevalence based on survey data.

High probabilities of recall error of MD episodes are an inevitable consequence of assessing depression symptoms in the general population. However, the alternative of relying on reports of clinical diagnosis would still substantially underestimate the burden of depression because ~37% of adults with MD do not receive any treatment for their depression.[49] Future studies should evaluate how survey inaccuracies lead to underestimation of the economic and disability burden of depression in populations. Research should also investigate who exactly fails to report their past experiences with depression and why. It is likely that such individuals have mild symptoms, episodes of

relatively short duration, or only a single episode across their lifetime. The stigma associated with having a history of a mental disorder is another likely explanation for their widespread underreporting. Future research should investigate the factors that contribute to under-reporting and recall error, and evaluate the implications of these underestimates for understanding the social, economic, and disability burden of depression in the population.

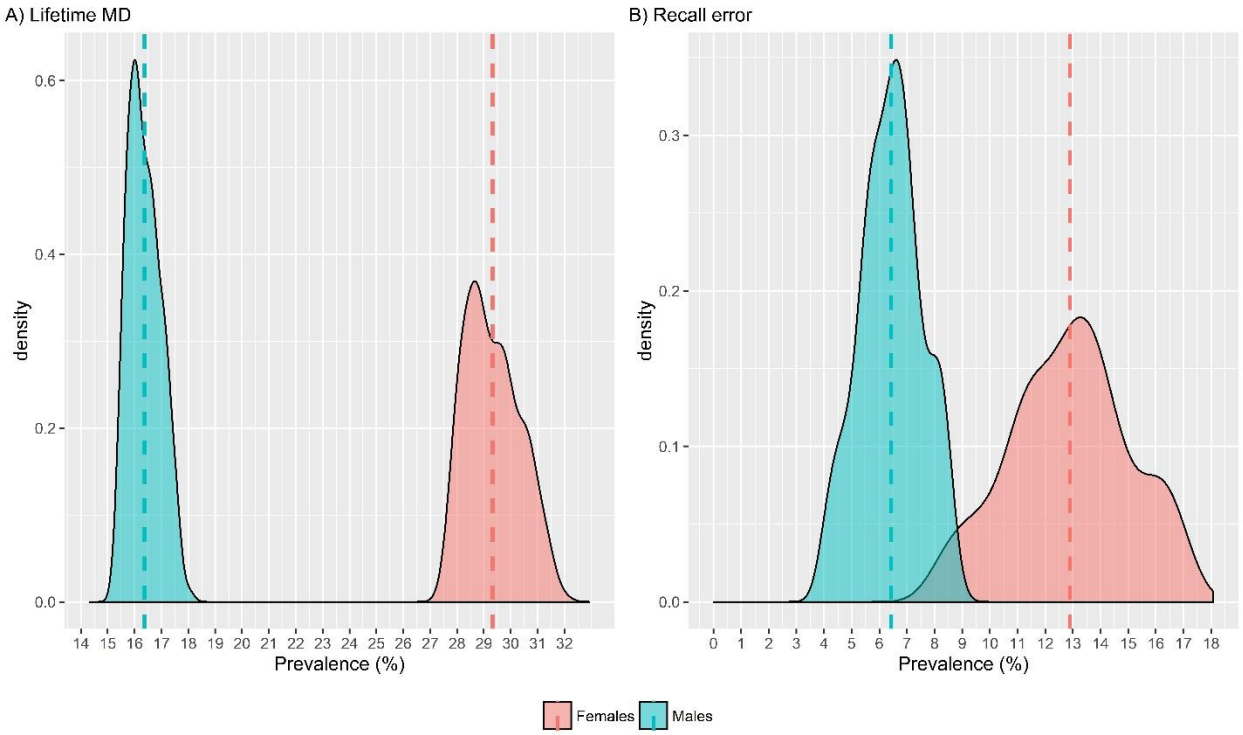
Appendix

Figure 3-6. Lifetime MD prevalence by age group with recall error adjustment, United States, 2005-2015



MD = Major Depression. Lines = model estimates with recall error (underreporting) adjustment; Dots = National Survey on Drug Use and Health data with 95% confidence interval bands (vertical lines).

Figure 3-7. Uncertainty distributions of lifetime MD prevalence and recall error, adults ages 18-99, United States



MD = Major Depression; Red = Females; Blue = Males; Vertical dashed line = mean value; A) Latin hypercube sampling results for lifetime MD prevalence with 95% of values for females between 27.8% and 31.3% and for males between 15.4% and 17.6% among males; B) Latin hypercube sampling results for the proportion of adults with former MD that underreport lifetime MD, with 95% of estimates from 8.6%-16.9% for females and from 4.2%-8.5% for males.

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Chapter 4 - Modeling smoking-related mortality and disparities for adults with depression

Background

Tobacco use and major depression are leading causes of death and disability in the U.S.[1] According to the National Survey on Drug Use and Health (NSDUH), 17.8% of adults are past 30-day smokers, and at least 1 in 6 Americans experiences major depression (MD) in their lifetime.[2-4] Annually approximately 6.7% of the U.S. adult population has had a MD episode in the past year, representing 16.2 million people.[5] Smoking and depression are also highly associated with each other,[6] and smokers with comorbid mental illness are considered a high priority group for intervention."[7] The disparity in smoking rates between those with and without depression is substantial. Based on the 2015 NSDUH, 31.2% of women and 35.8% of men with current MD are smokers, compared to 16.7% of women and 23.6% of men with no lifetime history of MD. Not only are people with depression more likely to start smoking, they are also less likely to quit.[8-10] The health burden for smokers with depressive disorders is high – they have elevated risk for disease and death due to their tobacco use,[11-14] as well as for their depression per se. In Chapter 2, I showed that for smokers with serious mental illness, much of their reduced life expectancy may be due to smoking alone.[15]

The mechanisms that lead to higher observed smoking rates among the depressed are not well-understood; however, recent longitudinal studies and systematic reviews have concluded that the relationship between depression and smoking is likely bi-directional.[16,17] Smoking and depression comorbidity is likely due to a combination of shared risk factors and neurobiological mechanisms.[18-20] Research supports the notion that smoking increases one's susceptibility to depression through neurophysiological changes,[21-23] and nicotine dependence has been shown to cause mood fluctuation and heighten stress pathways.[24-26] Other studies suggest that underlying genetic and social vulnerability may partly explain their co-occurrence.[27-29] Yet the association between smoking and depression remains, even after adjusting for demographic covariates[30-32] and other psychiatric disorders[33,34]. Major depression is a risk factor for future smoking and nicotine dependence,[35-38] and tobacco use predicts subsequent symptoms of depression by contributing to psychological distress and worse cognitive functioning.[24,35,39-43] These feedback effects imply that changes in either mental well-being or smoking behavior is likely to have effects on the other. Though people with mental illness are as motivated to quit smoking as the general population,[44,45] traditional tobacco control policies may have limited effectiveness for individuals whose mental states compromise aspirations for longer-term health and who may be inherently more susceptible to nicotine addiction.[46,47]

To date, very few population models of smoking have accounted in detail for differences in smoking patterns by relevant social factors, and none of have considered differences by mental health status.[48-55] Similarly, although some health economic[56-61] and dynamic models[62,63] for depression exist, these do not explicitly account for smoking comorbidity.

A model of smoking and mental illness comorbidity can be used to evaluate the potential effects of health interventions with the potential to reduce tobacco use disparities and the burden of smoking in populations with behavioral health conditions.

In this chapter, I develop a model of smoking and depression comorbidity in the U.S. adult population using a system dynamics approach. System dynamics models, also referred to as compartmental models, are composed of 'stocks' of homogeneous individuals within a health state (e.g. people with current MD) and 'flows' governed by differential equations characterizing the rates at which individuals move between health states (e.g. MD incidence or recovery).[64] These aggregate-level models are ideal for testing macro-level upstream policies in systems with nonlinearity, feedback loops, and time delays between events (e.g. smoking initiation) and future consequences (e.g. disease and death). A top-down system dynamics approach to studying smoking and depression comorbidity is ideal given these feedback effects, as well as the long time lag between smoking, depression, or interventions, and their subsequent impacts on population health outcomes.

The model considers the dynamics of major depression and smoking behaviors, projecting future smoking prevalence by depressive state, depression prevalence, and smoking-attributable deaths from 2016 to 2050.

Methods

Data Sources

I develop and validate the model using data from the National Survey on Drug Use and Health (NSDUH), an annual nationally representative survey of the non-institutionalized population in the U.S. adults ≥18+. Data on smoking behaviors, and depressive episodes are publicly available through the NSDUH for the years 2005-2015. The NSDUH provides consistent measures for smoking and includes data on depression and mental health service utilization from 2005 to 2015.[65] Though the NSDUH is a cross-sectional survey, compared to other surveys of mental health in the U.S., it is currently the most historically comprehensive data source, with annual data that enables analyses of trends in depression and tobacco use over time by mental health status.[66]

Measures

I use modified definitions for cigarette smoking in order to be consistent with other input data sources used in the model, and to simulate permanent smoking cessation without relapse (see next section). The standard definition for current smoking in the NSDUH is smoking part or all of a cigarette at least once in the past 30 days (Table 4-1. Smoking definitions comparisonTable 4-1). For this model, *current smokers* are individuals who smoked at least 100 cigarettes in their lifetime and smoked anytime within the past year. *Former smokers* are those who have smoked at least 100 cigarettes in their lifetime but who have not smoked at any point in the last year. This stricter definition for current smokers includes those who have quit smoking less than one year prior to survey assessment and avoids the problem of modeling cessation relapse in the model by

categorizing former smokers as those who likely have permanently quit. *Never smokers* are defined as those who have never smoked at least 100 cigarettes in their lifetime. Table 4-1 compares the model definitions with those used in national surveys and in other modeling studies.

Table 4-1. Smoking definitions comparison

	Current smoker	Former smoker	Never smoker
National Health Interview Survey (NHIS)	Currently smokes every or some days and has smoked at least 100 cigarettes in their lifetime	Smoked at least 100 cigarettes in their lifetime and does not currently smoke	Smoked less than 100 cigarettes in their lifetime
National Survey on Drug Use and Health (NSDUH)	Smoked part or all of at least one cigarette in the past 30 days	Has ever smoked part or all of a cigarette but not within the past 30 days	Has never smoked part or all of a cigarette
Cancer Intervention and Surveillance Modeling Network (CISNET) lung consortium	Smoked at least 100 cigarettes in their lifetime and smoked within the past 2 years	Smoked at least 100 cigarettes in their lifetime and last smoked more than 2 years ago	Smoked less than 100 cigarettes in their lifetime
Modified definition used by model	Has smoked at least 100 cigarettes in their lifetime and has smoked part or all of a cigarette within the past year	Smoked at least 100 cigarettes in their lifetime but has not smoked at all within the past year	Smoked less than 100 cigarettes in their lifetime

The NSDUH adult depression modules screen for lifetime and past year experience of a MD episode. The survey uses MD episode criteria derived from the Diagnostic and Statistical Manual or Mental Disorders (DSM-IV) – an individual must report at least five of the following nine symptoms for at least two weeks: 1) depressed mood most of the

day, 2) markedly diminished interest or pleasure in activities most of the day, 3) significant changes in weight or appetite, 4) insomnia or hypersomnia, 5) psychomotor agitation or retardation, 6) fatigue, 7) feelings of worthlessness, 8) diminished ability to think or concentrate, and 9) recurrent thoughts of death or suicide ideation.[67] MD prevalence in the NSDUH is greater than estimates reported elsewhere,[68,69] as the NSDUH does not exclude depressive episodes caused by illness, bereavement, substance use or other psychiatric disorders such as bipolar disorder.[70]

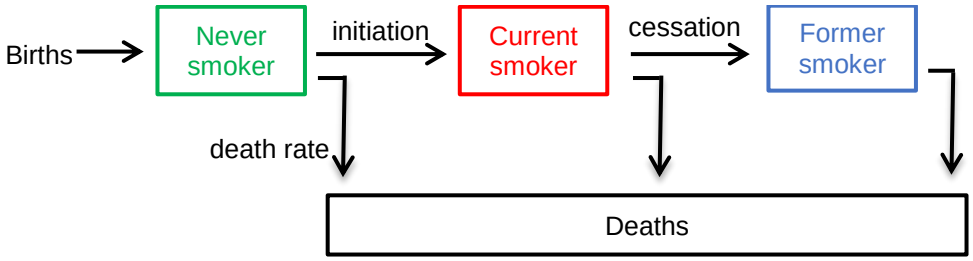
For this model, people with *current MD* have had a MD episode in the past year. Those who with *former MD* have had a MD in their lifetime, but not in the past year. Those who are *never MD* have never had a MD episode in their lifetime. Cross-sectional surveys of depression that rely on retrospective evaluations have been known to lead to substantial underestimation of lifetime history of depression.[71] The model explicitly accounts for the probability of recall error, so that individuals reporting no lifetime history of depression may actually be formerly depressed. Rates of recall bias by age were estimated during model calibration (See Chapter 3).

I developed this model by first separately fitting smoking-only and depression-only sub-models to smoking and depression data respectively. Once I calibrated both of these sub-models, I combined them into the full smoking and depression comorbidity model and re-calibrated to fit survey data on smoking prevalence by depressive status and vice versa. The full model of smoking and depression comorbidity specifically integrates and estimates known and unknown interaction effects between smoking initiation and cessation, and depression onset, relapse and recovery. I conducted all analyses using R version 3.1.3.[72]

Smoking sub-model

I consider three mutually exclusive smoking states in the smoking-only sub-model (Figure 4-1): never smoker, current smoker, and former smoker. Individuals are added to the model at birth as never smokers who can become current smokers, and then former smokers, based on initiation and cessation probabilities developed by the Cancer Intervention and Surveillance Modeling Network (CISNET) lung consortium.[73] Probabilities age, gender, and birth cohort were derived from the National Health Interview Surveys (NHIS) 1965-2015. CISNET projections for future smoking initiation and cessation rates have been used in several smoking modeling analyses.[50-55,74] The model assumes no relapse to smoking among former smokers as is consistent with previous models of population smoking[48] and aligns with CISNET net annual cessation rates where cessation is defined as a successful quit of at least two years with no relapse. Individuals exit the model through death or after reaching age 99. Age, gender, and birth cohort-specific mortality rates for never smokers, former smokers, and current smokers are based on CISNET estimates as well.[75,76]

Figure 4-1. Smoking sub-model diagram



To calibrate the smoking sub-model, I adjust each age group's initiation and cessation probabilities by applying scaling factors that modify the initial CISNET estimates. I

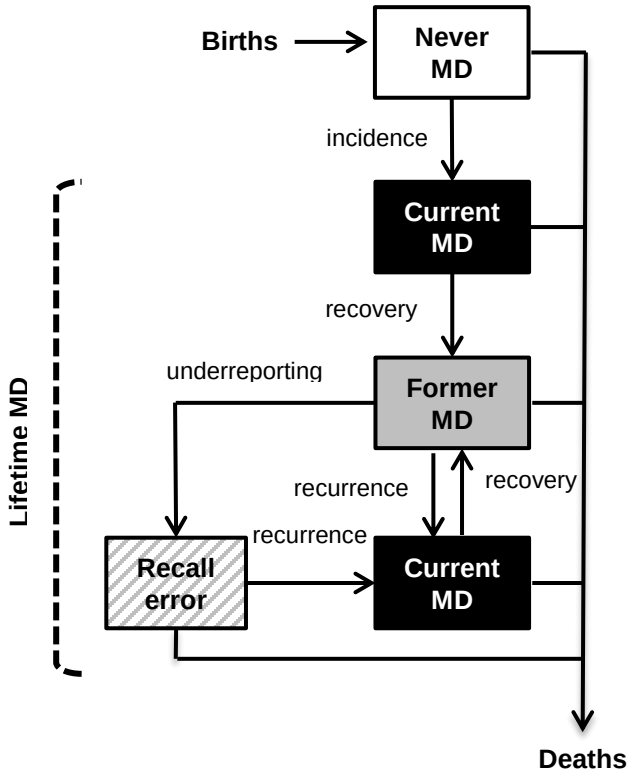
minimized the sum of squared differences between the model and smoking prevalence data by age group for both males and females in order to estimate these scaling factors. Calibration for this sub-model is necessary because the estimated probabilities were developed using the NHIS, whereas the full combined model utilizes data from the NSDUH. Differences in their respective survey designs and sample populations, the NSDUH has been shown to consistent yields higher smoking prevalence estimates compared to the NHIS.[77]

Depression sub-model

In the depression sub-model (Figure 4-2), individuals are born as never depressed and may transition to a first onset MD episode based on incidence data from the Baltimore Epidemiological Catching Area (ECA) Study,[78] the nation's longest-running psychiatric epidemiological cohort study. Because incidence data for females ages<22 and males ages <29 do not exist, I estimate the annual probability of a 1st MD episode at younger ages as part of calibration using cubic natural splines to fit the sub-model to NSDUH data. This sub-model, and the parameterization and calibration approach used for its development, has been described in greater detail in Chapter 3. Individuals may recover from a 1st MD episode and shift into a formerly depressed category. To address recall bias in retrospective assessments of depression,[71] I estimated the probability that individuals with former depression will underreport their past histories of depressive episodes during sub-model calibration. Formerly depressed individuals may also have a recurrent MD episode and subsequently recover.[79] MD age-specific incidence rates are

assumed to remain constant going into the future, as NSDUH data show no visible trends in depression patterns by age for the 2005-2015 period.

Figure 4-2. Depression sub-model diagram



Comorbidity model

The combined model of smoking and depression comorbidity includes 15 mutually exclusive smoking and depressive states (Figure 4-3) and can project future smoking and depression prevalence for the U.S. population ages≥18 from 2015 to 2050. I model males and females separately, as females have higher risk for depression and earlier ages at onset, while males have higher smoking and mortality rates.[80]

Each cohort is born into a never-smoking and never-depressed state at age 0 using Census Bureau projected population sizes.[81] The model is initialized in the year 1900 with the 1900 birth cohort, and new birth cohorts added each year such that by the year 1999, the model includes the entire population ages 0-99. Individuals leave the model according to smoking and depression-specific mortality rates or after age 99. A relative risk of mortality is applied to smoking status-specific mortality rates for individuals with histories of depressive episodes. This depression-associated mortality relative risk is estimated during model calibration.

I project future smoking and MD prevalence in the U.S. female and male adult populations, assessing baseline trends under a 'status quo' scenario. Main outcomes of interest are smoking prevalence by depressive state, MD prevalence, and population deaths attributable to smoking. Smoking prevalence can be projected by tracking flows into the stock of current smokers due to smoking initiation (α), and flows out of this stock due to smoking cessation (β) or death (μ).[48] MD prevalence can similarly be forecasted by following inflows due to incidence or recurrence (γ) and outflows due to recovery (ρ) or death (μ). For example, the number of people with current MD in a given smoking state s at time t is calculated accordingly:

$$\mathrm{MD}_{\mathrm{a,t,s,g}} = \mathrm{MD}_{\mathrm{a-1,t-1,s,g}} \times (1 + \gamma_{\mathrm{a-1,t-1,s,g}}) \times (1 - \rho_{\mathrm{a-1,t-1,s,g}}) \times (1 - \mu_{\mathrm{DE,a-1,t-1,s,g}})$$

Likewise, the number of smokers in a given depressive state d at time t can be determined as follows:

$$\mathrm{CS}_{\mathrm{a,t,d,g}} = \mathrm{CS}_{\mathrm{a-1,t-1,d,g}} \times (1 + \alpha_{\mathrm{a-1,t-1,d,g}}) \times (1 - \beta_{\mathrm{a-1,t-1,d,g}}) \times (1 - \mu_{\mathrm{CS,a-1,t-1,d,g}})$$

where:

$MD_{a,t,s,g}$ = number of individuals with MD at age a in year t in smoking state s and gender g
$CS_{a,t,d,g}$ = number of current smokers at age a in year t in depressive state d and gender g

d = never MD, current MD, or former MD
s = never smoker, current smoker, or former smoker
g = gender specifying male or female

$\gamma_{a,t,s,g}$ = incidence or recurrence of MD at age a in year t for smoking state s and gender g
$\rho_{a,t,s,g}$ = recovery rate from MD at age a in year t for smoking state s and gender g
$\alpha_{a,t,d,g}$ = smoking initiation rate at age a in year t for depressive state d and gender g
$\beta_{a,t,d,g}$ = smoking cessation rate at age a in year t for depressive state d and gender g
$\mu_{a,t,d,s,g}$ = death rate at age a in year t for smoking state s, depressive state d, and gender g

With known population sizes and numbers of individuals for each category, smoking and MD prevalence can be determined and the number of deaths that occur can be tracked over time.

Model Calibration

To calibrate the model, I minimized the sum of squared differences between the survey and model data with the Davidon-Fletcher-Powell optimization algorithm in the `Bhat` package in R.[82] Given initial values and their corresponding upper and lower limits, the algorithm searches the parameter space for estimates of scaling factors and interaction effects between smoking and depression that enable the model to reproduce smoking and depression patterns by age group as observed in the NSDUH from 2005-2015. The

initial lower bounds assume that current or former smoker status does not confer health advantages with respect to depression onset, recovery or recurrence compared to never smokers. The calibration process refines existing parameter estimates and generates plausible values that do not otherwise exist in the literature, such as depressive episode recovery rates by smoking status. Where possible, initial values as used in the optimization were drawn directly from the literature.

Figure 4-3. Smoking and depression model diagram

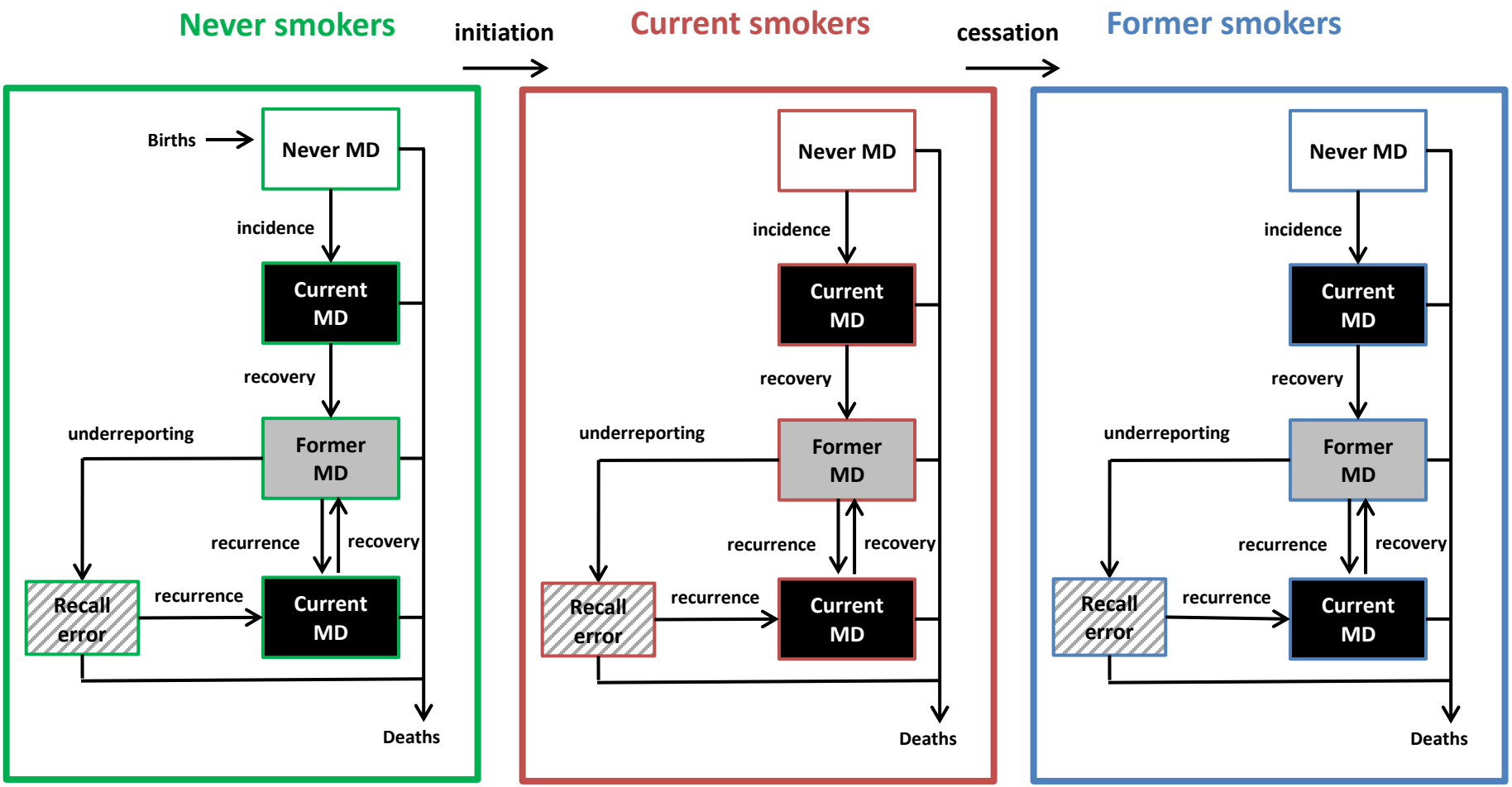


Table 4-2 summarizes input parameters as used in the model, including the smoking and depression sub-models. During calibration, I estimated parameters for interaction effects including effects that raise the probability of MD onset and recurrence (γ) or reduce the likelihood of recovery (ρ) among current or former smokers. I also re-estimated effects of depression on smoking behaviors such that those with current depression had increased probability of smoking initiation (α) and lower odds of cessation (β). Existing mortality estimates for depression control for sociodemographic factors that are not accounted for in this population model.[11] Therefore I modified death rates (μ) by re-estimating the relative risk of mortality associated with having a history of depression.

Table 4-2. Model parameters

Parameter	Source	Estimates derived from calibration
MDE incidence rates (γ)	- Age at onset of Major Depressive Disorder for females ages 22+ and males age 29+ in the Baltimore-ECA cohort study.[78]	- Cubic natural splines for MDE incidence females ages<22 and males ages <29 with knots at ages 13 and 18 (See Chapter 3). - Probability of DE incidence among current and former smokers[17,83]
MDE recurrence rates (γ)	- Annual probability of recurrence calculated from 45% cumulative recurrence after 1st DE over 10 years in the Baltimore-ECA cohort study.[79]	- Increased probability of recurrence among current smokers.
MDE recovery rates (ρ)	- Annual probability of recovery calculated from 85% cumulative recovery from 1st DE over 10 years in the Baltimore-ECA cohort study.[79]	- Recovery rates among current and former smokers.
Smoking initiation rates (α)	- Annual CISNET smoking initiation probabilities by age, gender, and birth cohort.[84]	- Increased probability of initiation among people with current depression.[17]
Smoking cessation rates (β)	- Annual CISNET smoking cessation probabilities by age, gender, and birth cohort.[84]	- Lower odds of cessation among smokers with current depression.[10]
Death rates by smoking status (μ)	- All-cause mortality rates by age, birth cohort, and gender for never smokers, current smokers, and former smokers.[75]	- Increased mortality risk among people with lifetime history of depression.[11]

Sensitivity Analysis

Because parameter uncertainty might have greater influence in dynamic models due to nonlinear feedback,[85] I conducted sensitivity analyses on the current smoking and depression interaction effect estimates derived from calibration to evaluate the sensitivity of model outcomes to each of these parameters (See Appendix Table 4-4). I used Latin hypercube sampling for parameter space exploration in the `pse` package in R which efficiently samples from across parameter combinations to cover the full range of possible model outcomes.[86,87] For both the male and female models, 200 parameter combinations were sampled from within uniform distributions with minimum and maximum values based on the 95% confidence intervals generated during model calibration, or qualitatively reasonable values when such intervals failed to be generated. Partial rank correlation coefficients were used to evaluate associations between parameters and imprecision for three main model outcomes: 1) smoking prevalence among adults with current depression, 2) the prevalence ratio between those with current and never depression, and 3) the number of smoking-attributable deaths among people with depression.

Smoking Attributable Mortality

To assess smoking-attributable mortality, I sum the number of smoking-attributable deaths (SAD) for both former smokers and current smokers across all ages and both gender using an approach used in previous models.[76,88] The total deaths are calculated by first multiplying the current and former smoker prevalences ($prev_{cs,\,fs}$) by the corresponding population sizes (P) for each age group and gender, and then again by the

difference in mortality rates between current or former smokers and never smokers ($\mu_{cs,fs,ns}$) as follows:

$$SAD = \sum_{age,gender} P\left(prev_{cs} \times (\mu_{cs} - \mu_{ns}) + prev_{fs} \times \left(\mu_{fs} - \mu_{ns}\right)\right)$$

This determines the number of deaths attributable to current and former smoking for a given population.

Results

The smoking sub-model showed close correspondence with the NSDUH 2005-2015 age-group specific prevalences for never, current and former smoking following calibration. The model initiation and cessation probabilities for males and females are shown in Appendix

Figure 4-8 and Figure 4-9. CISNET input initiation probabilities were increased for youth ages<18 and decreased for adults, while cessation probabilities were generally decreased to match model with NSDUH data.

With calibrated smoking inputs, age-group specific smoking prevalence in the model followed the same pattern as observed in the NSDUH data

Appendix. Figure 4-10 and Figure 4-11). The model estimates that for women, current smoking prevalence decreased from 23.4% in 2005 to 18.9% in 2015, which is consistent to the NSDUH decrease from 24.2% (95% CI: 23.1%, 25.3%) to 18.5% (95% CI: 17.8%, 19.2%). Likewise, for men, the model showed a decrease in total smoking prevalence from 29.8% in 2005 to 24.6% in 2015, consistent with survey data showing a similar decline from 30.3% (95% CI: 29.1%, 31.4%) to 24.4% (95% CI: 23.4%, 25.3%).

The depression sub-model demonstrated good fit with NSDUH data on never (including those who fail to recall past episodes), current, and former depression for males and females ages 18-64, as shown in Appendix Figure 4-12 and Figure 4-13. Calibrated estimates for onset of a first depressive episode and recall error by age are described in detail in Chapter 3. The model overestimates current MD prevalence and underestimates former MD for the oldest group ages ≥65. When the relative risk of mortality for those with a lifetime history of depression was increased, this slightly improved model fit with survey data for the oldest age group. No discernible trends in the prevalence of depression were observed in either the model or survey data over time.

For the entire adult population, the depression sub-model estimates were close to their corresponding NSDUH prevalence estimates for the 2005-2015 period. Current MD prevalence in the model was 8.2% on average for females, compared to 8.4% (95%CI 8.2%, 8.6%) in the NSDUH. For males, current depression prevalence was 4.7% for this period compared to 4.8% (95% CI: 4.7%, 5.0%) based on survey data.

To calibrate the full model of smoking and depression comorbidity, parameters for both sub-models were held constant while interaction effects were adjusted to: 1) increase the relative risk of a 1st MD episode among current smokers, 2) decrease the odds of smoking

cessation for people with a history of MDE, 3) increase the effects of current depression on subsequent smoking initiation, and 4) decrease the likelihood that current smokers would recovery from a MD episode. Higher relative risks of mortality applied to those with a history of MD were re-estimated for both men and women during calibration. Table 4-3 shows the adjusted interaction effect estimates. Calibration demonstrated that under reasonable parameter bounds, ideal fit was achieved when former smoking status had no effect on depression incidence, recovery, or recurrence rates. Furthermore, calibration estimates showed that the model performed best when current MD status increased the probability of smoking initiation by nearly 3 times compared to those without current MD.

Table 4-3. Model estimates derived from calibration

Parameter	Description	Initial value	Lower limit	Upper limit	Estimate (Females)	Estimate (Males)
$RRcs\_dep1$	Relative risk of 1st MD episode among current smokers vs. never smokers	1.70	1	5	1.41	1.06
$RRfs\_dep1$	Relative risk of 1st MD episode among former smokers vs. never smokers	1.48	1	5	1.00	1.00
$ORhdep\_quit$	Odds ratio for smoking cessation among people with a history of MD compared vs. never depressed	0.81	0	1	0.98	0.93
Efs_depr	Effect of former smoking on probability of recurrent MD episode vs. never smoking	N/A	1	5	1.00	1.00
Ecs_depr	Effect of current smoking on probability of recurrent MD episode vs. never smoking	1.37	1	5	1.00	1.10
$Edepr\_smkinit$	Effect of MD on smoking initiation	1.40	1	5	4.73	2.99

$deprecovSF\_fs$	Effect of former smoking on probability of recovering from MD episode	N/A	0	1	1.00	1.00
$deprecovSF\_cs$	Effect of current smoking on probability of recovering from MD episode	N/A	0	1	0.73	0.75
$RRmd$	Relative risk of mortality among people with history of MD vs never MD[11]	1.71	1	10	5.54	2.53

Under a status quo scenario, the model shows that all depressive subgroups experience decreasing smoking prevalence over time, with a rising proportion of never smokers in each group for females and males (Figure 4-4 and Figure 4-5). Among those in the model who have no history of MD, smoking prevalence is projected to decrease for females (males) by 45% (37%) between 2016 and 2050 from 17.3% to 9.5% (from 24.2% to 15.3%). When excluding never MD females (males) in the recall error category, the prevalence is 18.0% (males: 24.3%) in 2016 to 9.8% (15.3%) in 2050, also representing a 45% (37%) decrease. By comparison, females with current MD have consistently higher smoking rates during this period, with 31.2% (males: 36.0%) smoking in 2016, decreasing by 38% (31%) to 19.2% (24.8%) prevalence in 2050. For females (males) who are formerly depressed, excluding those with recall error, current smoking prevalence decreases from 27.5% (males: 32.7%) to 15.4% (21.4%), representing a 43% (33%) decrease. Former smoker prevalence is relatively similar across each subpopulation.

Figure 4-4. Smoking projections by depression subgroup, Females ages 18+

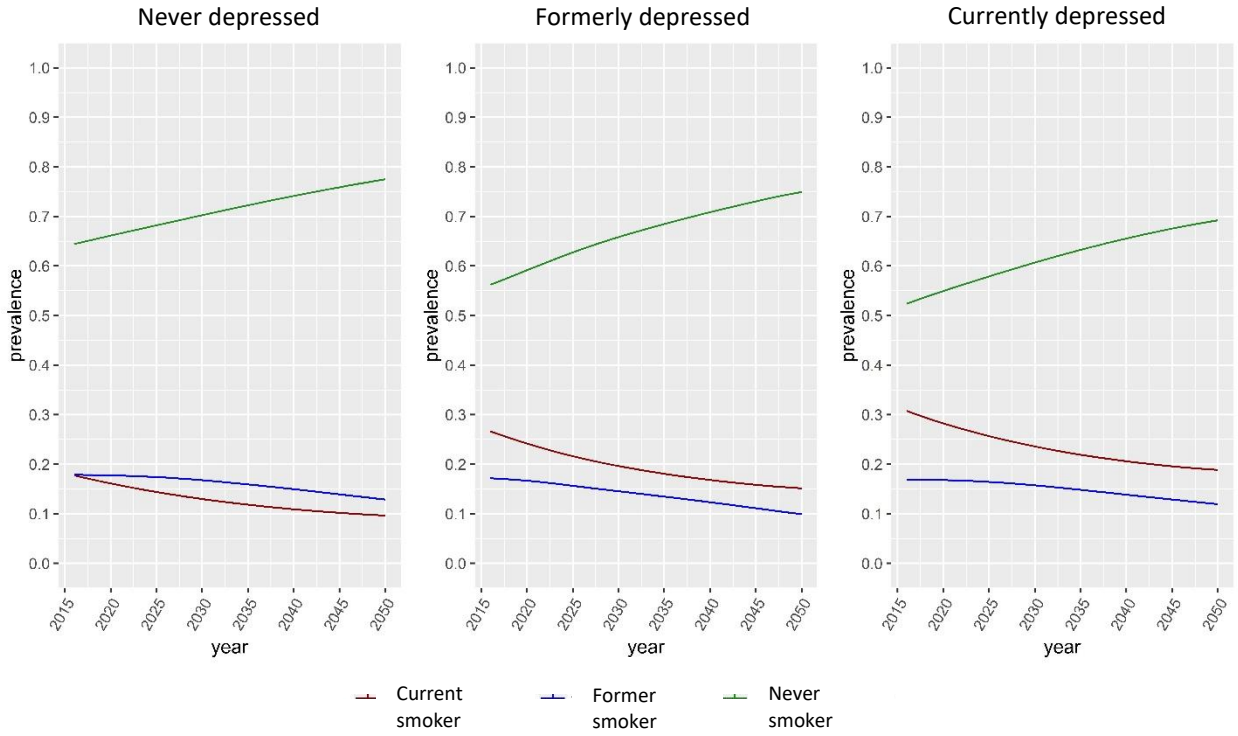
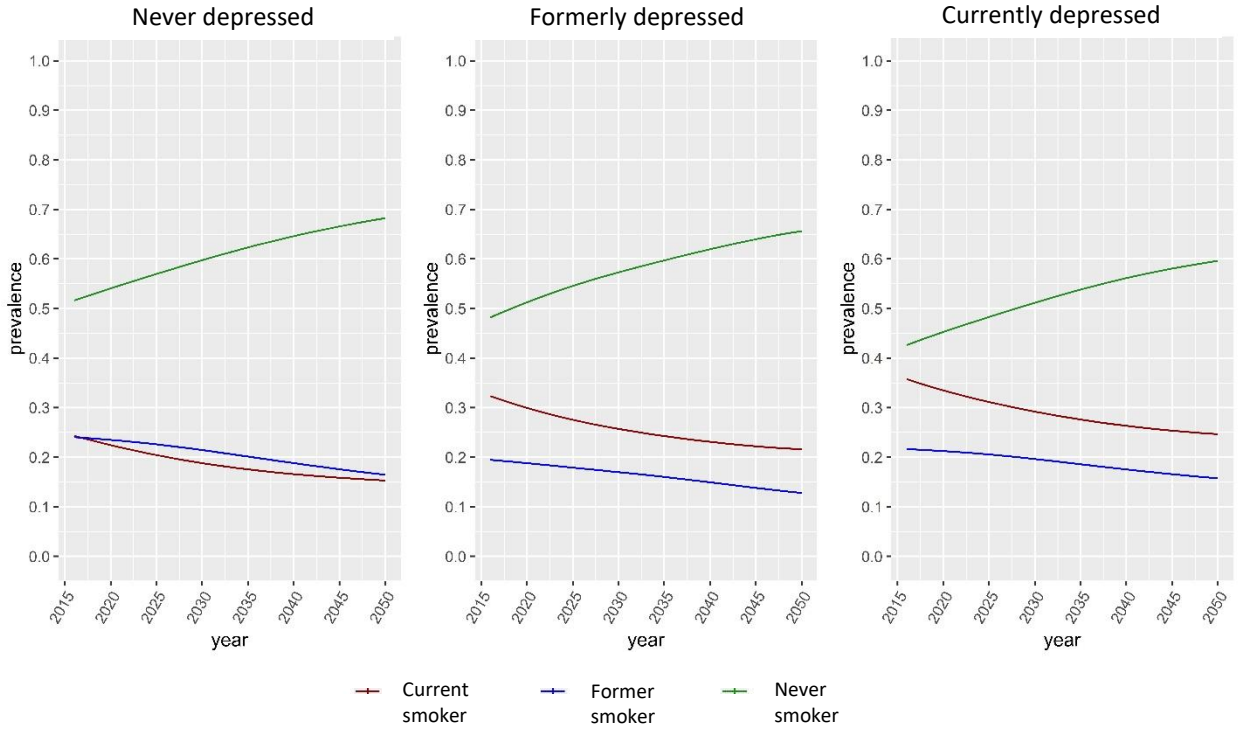
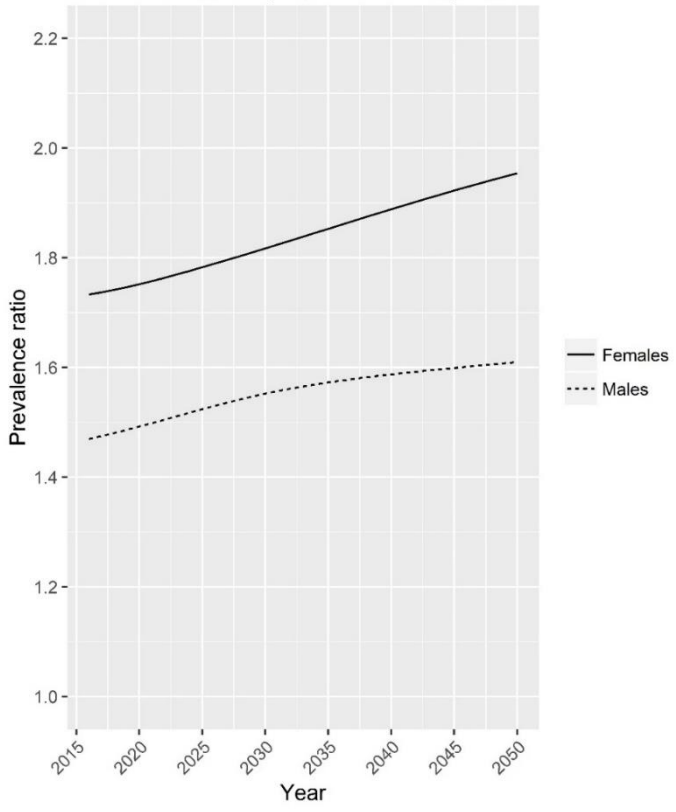


Figure 4-5. Smoking projections by depression subgroup, Males ages 18+



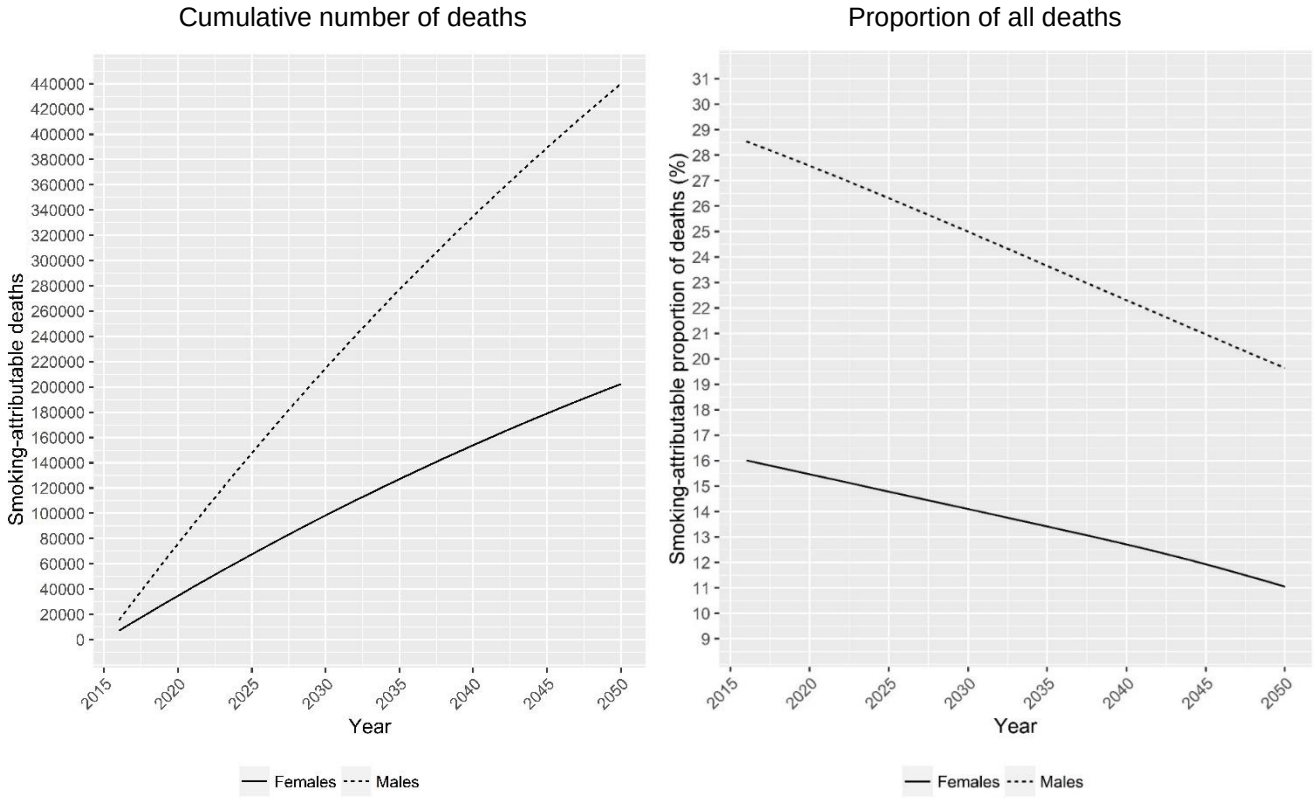
The prevalence ratio comparing smoking among adults with current depression with adults who have never been depressed is projected by the model to increase over time (Figure 4-6). For women, the smoking disparity between those with current and never depression increases from 1.73 in 2016 to 1.96 in 2050. For men, the ratio rises from 1.48 to 1.62. When excluding individuals who fail to report past MDEs from the never depressed population, the prevalence ratio is even larger. For the adult female population, it rises from 1.80 in 2016 to 2.02 in 2050, such that women with current depression projected to be twice as likely to smoke by 2050 compared to women who have never been depressed. For men, removed recall error individuals did not change the prevalence ratio increase. By 2050, men with depression will be more than 60% more likely to be smokers compared to men without a history of depression.

Figure 4-6. Current-to-never MD smoking prevalence ratio, ages 18+



The model estimates that 642,250 smoking-attributable deaths (SADs) will occur among people with current depression from 2016 to 2050 (202,262 deaths among women and 439,987 deaths among men) (Figure 4-7). The number of annual SADs is expected to decline from 22,604 (women: 7,096, men: 15,508) in 2016 to 14,377 by the year 2050 (women 4,491, men: 9,886). In 2016, smoking-attributable deaths represent 16.4% and 28.6% of all deaths among women and men with depression. This proportion is 65% and 33% higher than for women and men without a history of depression, for whom SADs represent 9.9% and 21.4% of all population deaths. By 2050, the model estimates that SADs will represent 11.4% and 19.7% of all deaths among women and men with depression, compared to 7.1% and 14.7% among women and men without a history of depression.

Figure 4-7. Smoking-attributable deaths among adults with MD



Partial rank correlation coefficients measuring the linear associations between each model outcome and each interaction effect (after removing the effects of other parameters) are shown in Appendix Figure 4-14, Figure 4-15, and Figure 4-16. Parameters for the relative risk of MD onset among current smokers ($RRcs\_dep1$), the effect of smoking on depression recurrence (Ecs_depr), and the effect of current MD on smoking initiation ($Edepr\_smkinit$) showed strong positive linear relationships with smoking prevalence among adults with depression and the current-to-never MD smoking prevalence ratio. Parameters for the odds of cessation among people with any history of MD ($ORhdep\_quit$) and the reduced probability of MD recovery among smokers ($deprecovSF\_cs$) showed clear negative linear relationships with these model outcomes. These directions of association also held true for smoking and depression interaction effects and the number of SADs among adults with depression, but the magnitudes of association were slightly more modest. Unlike outcomes for smoking prevalence and prevalence ratios, the number of SADs was responsive to changes in the relative risk of mortality for people with histories of depression ($RRmd$). There was a clear negative linear relationship between this depression mortality parameter and the number of SADs among adults with depression.

Discussion

This study presents results from the first joint model of smoking and depression comorbidity in the U.S. To my knowledge, it is also the first computational model of smoking to explicitly model a population with behavioral health comorbidities. The model integrates three of the best available data sources on smoking and depression patterns in the U.S. First, the underlying sub-model uses re-scaled CISNET age-gender-cohort specific smoking initiation and cessation inputs derived from the NHIS 1965-2015. Second, depression parameters are taken from the nation's longest-running psychiatric epidemiological survey, the Baltimore Epidemiological Catching Area Follow-up Study (See Chapter 3). I furthermore utilize the NSDUH, the only nationally representative dataset with consecutive years of data on depression and smoking for trend assessment.

I show that under current trends smoking prevalence is projected to decline for people with and without MD from 2015-2050. The finding that smoking prevalence is declining across the population overall is consistent with that of other simulation models.[89] Though this is encouraging news in some respects, the model results also demonstrate that in the absence of intervention, nearly 600,000 adults with current MD are projected to die premature deaths due to smoking from 2018 to 2050. While people with current MD make up <7% of the U.S. population, the proportion of tobacco-related deaths in this subpopulation is considerably higher (16.4% and 28.6% of all deaths among women and men with depression) than for people without a history of MD (9.9% and 21.4% of all deaths).

The prevalence ratio between those with current MD and with no history of MD is rising, indicating that despite the overall decrease in smoking, the smoking disparity by mental health status will widen over time. By 2050, women with MD are projected to be twice as likely to be smokers compared to women without a history of MD, whereas men with MD will be 1.6 times as likely to be smokers. Although the smoking prevalence disparity between women with and without MD is greater than for men, the proportion of smoking-attributable deaths is still larger for men. Accordingly to the model, more than 1 in 4 deaths among men with depression and approximately 1 in 6 among women can be attributable to smoking annually. In contrast, 1 in 5 and 1 in 10 deaths among men and women who have never been depressed can currently be attributed to smoking. It would take until 2050 for this statistic to be achieved for men and women with current depression. Differences in attributable deaths by gender are driven by both the higher prevalence of smoking among men and the higher prevalence of depression among women.

The smoking prevalence estimates reported here are higher than those reported by either the NHIS or the NSDUH. Both surveys use definitions of smoking that do not consider high probabilities of relapse among recent former smokers. I classify anyone who has smoked at all within the past year as current smokers, which includes former smokers who quit less than a year ago. For comparison, the NSDUH considers past 30-day smokers and the NHIS considers ‘everyday’ or ‘some-day’ cigarette smokers to be current smokers. Although this approach translates into higher prevalence estimates, the definition avoids considering temporary quitters as former smokers, and simplifies the model by avoiding the need to model relapse from quitting. It further improves the model fit by aligning my measures for current and former smoking more closely with those used

by the CISNET lung consortium in their previously validated models (Shown in Table 4-1).[73,90]

Strengths and limitations

This model is limited by the relatively few years of survey data available for calibration. Thus, larger trends in adult depression prevalence beyond the 11-year period of observation may not be captured by the current model. There has been mixed evidence about the existence of temporal trends in depression prevalence. Earlier research did not find significant trends in depression from 1990 to 2003.[91] A recent study using the NSDUH data found that depression prevalence has been rising for specific subgroups, including youth ages 12-17.[92] Nonetheless the NSDUH data in our analysis shows no evidence of any increasing or decreasing trends of MD for any adult age-groups. The NSDUH depression measures for adolescents differ from that of adults and are not appropriate for combined analyses, so it is unclear how changes in youth depression would translate into trends for the adult population.[93] If rates of depression are increasing over time, the results shown here are likely to underestimate the true burden of depression in the population, as well as the extent of smoking-attributable mortality among those with depression.

Another limitation of this model is that it does not account for other sociodemographic factors associated with both smoking and depression. For example, disparities in smoking by depression status are even more prominent when considering differences by socioeconomic status.[94] The current model does not further disaggregate the population beyond age and gender, because introducing too much population heterogeneity can dramatically increase the number of unique states in the model, leading to 'state

explosion'.[95] It would be problematic to calibrate a model with a large number of states to survey data when small numbers in specific subgroups would also lead to unstable estimates (e.g. wide confidence intervals). Although existing literature on the dynamics of smoking and depression comorbidity generally do not consider additional characteristics beyond age and gender, future work, including individual-based or agent-based models, could evaluate smoking disparities by mental health status across more diverse populations.

Moreover, the model specification allows for analysis at the population-level, but does not examine duration or frequency of depressive episodes at the individual level. The model simplifies these aspects of the course of depression. In future work, the model can be extended to represent depression at more granular levels.

The study is also limited by data sources that do not survey the homeless, imprisoned, or institutionalized populations, where depression is highly prevalent.[96] While absolute projections cannot be generalized beyond the civilian, non-institutionalized population, the relative trends may still be applicable to other populations. Depression is also known to be comorbid with other psychiatric disorders; this analysis does not evaluate depression effects independent of other mental disorders. Considering that smoking outcomes are worst among those with multiple mental disorders,[97] this is an unfortunate limitation of the study. If these groups were included, the burden of both smoking and depression in the U.S. population, and the smoking disparity by depressive status would likely be much larger.

The lack of comparable data sources beyond the NSDUH that assess both smoking and depression prevents validation of this model with other historical data. Comparison of the model outputs with real-world data would increase confidence in the results shown here. In the absence of such data, the model outputs corroborate existing research showing the potential for the burden of tobacco to continue disproportionately affecting people with mental illness even as the population experiences declines in smoking prevalence.[98-100]

Implications for practice and research

Despite long-standing recommendations that smoking cessation counseling and services be integrated as part of mental health treatment,[101-104] only 38% of mental health treatment facilities in the U.S. offer tobacco cessation counseling while 25% offer nicotine replacement therapy.[105] Furthermore, numerous barriers to accessing cessation treatments for Medicaid recipients have been documented, even when cessation treatment is covered.[106] In Chapter 5, I use this model to evaluate the impact of hypothetical large-scale cessation interventions that could reduce the burden of tobacco-related disease and death for people with depression. Future research could also evaluate the population-level impact of other interventions that target smokers with depression, including the use of smartphone applications, web-based platforms, or tailored telephone quitlines.[107,108] The use of e-cigarettes among people with mental illness has also been rising,[109,110] and may offer a less harmful alternative for smokers who are unable or unwilling to overcome their nicotine addiction.

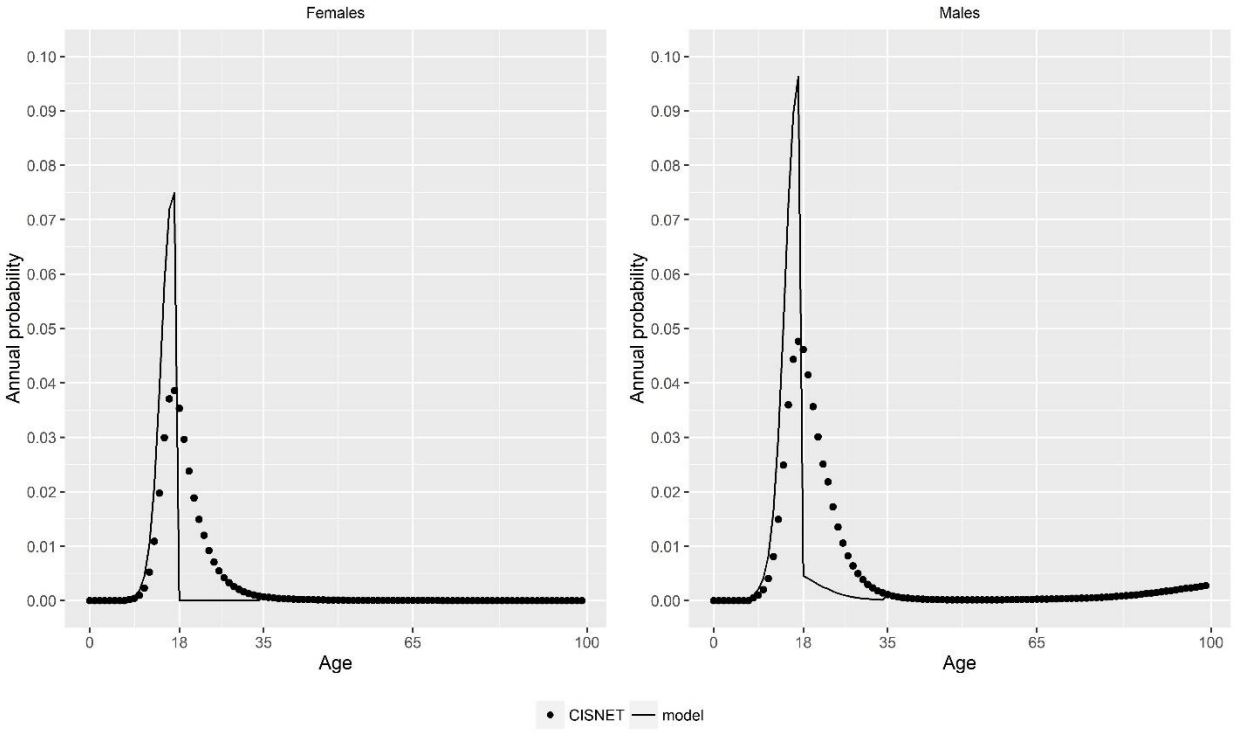
This study demonstrates that unless major changes to the policy and treatment environment for smokers with depression are implemented, disparities in smoking and smoking-attributable mortality by depression status are projected to persist and widen.

The application of simulation models, such as the one presented here, can offer public health decision-makers a view of what can be achieved with concerted public health action, or what can be expected without it.

Appendix

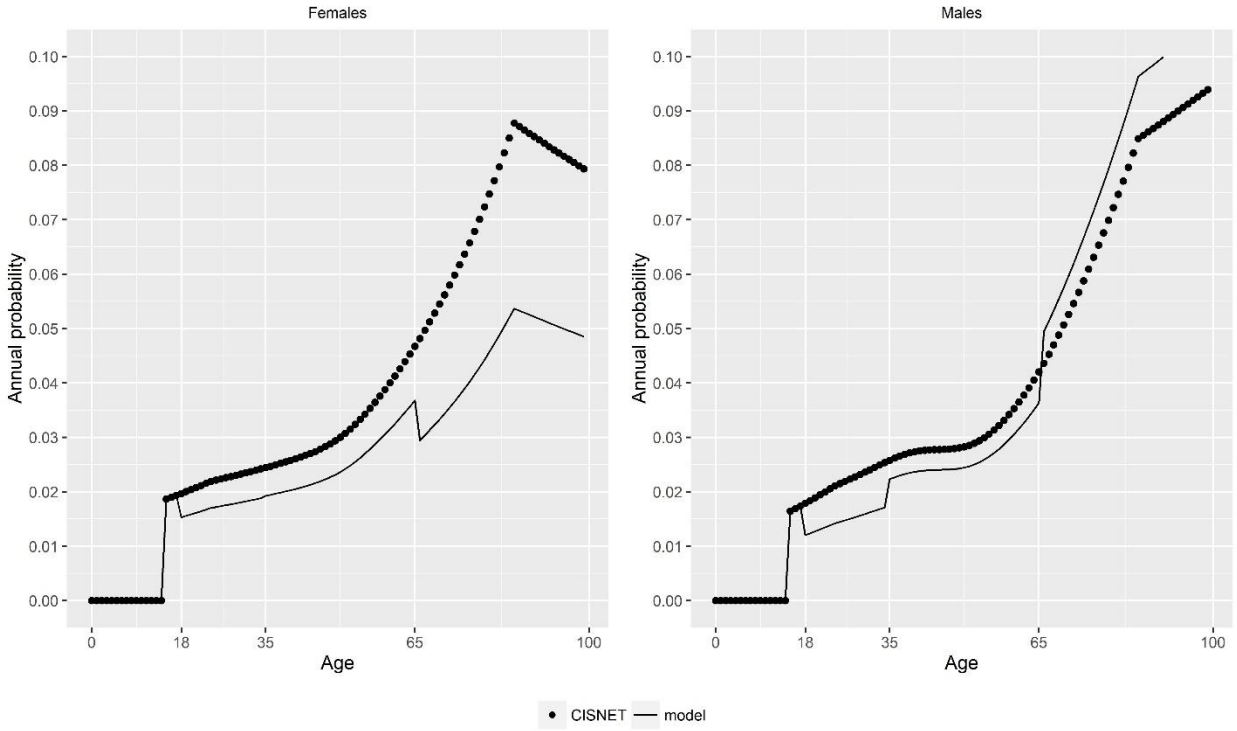
The NSDUH uses a different definition for smoking than data from CISNET or the NHIS that leads to higher overall smoking prevalence estimates. To adjust for this, the annual smoking initiation probabilities were calibrated to approximately double the original CISNET data for females and males for ages <18. Initiation was scaled to zero for females ages ≥18 and males ages ≥35, and to 10% of original CISNET probabilities for males ages 18-34. Cessation probabilities were reduced by 21-22% for females ages 18-64, and then by 39% for ages≥65. For males, the calibrated sub-model reduced annual cessation estimates by 33% for ages 18-34, then by 13% for ages 35-64. Cessation probabilities for males ages ≥65 were increased by 13%.

Figure 4-8. Smoking initiation probabilities



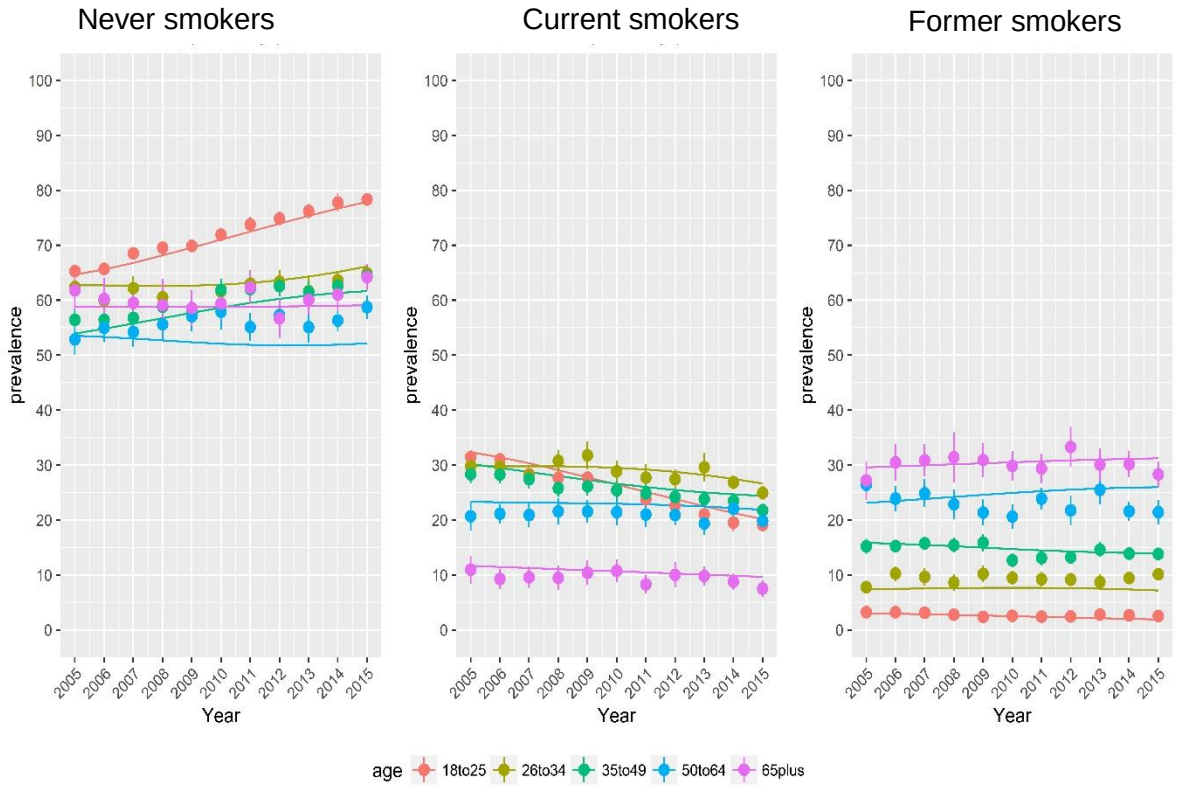
Female (left) and male (right) annual probabilities of smoking initiation. Data shown are for the year 2005. Dots = input data developed by the CISNET lung consortium. Lines = model calibrated probabilities.

Figure 4-9. Smoking cessation probabilities



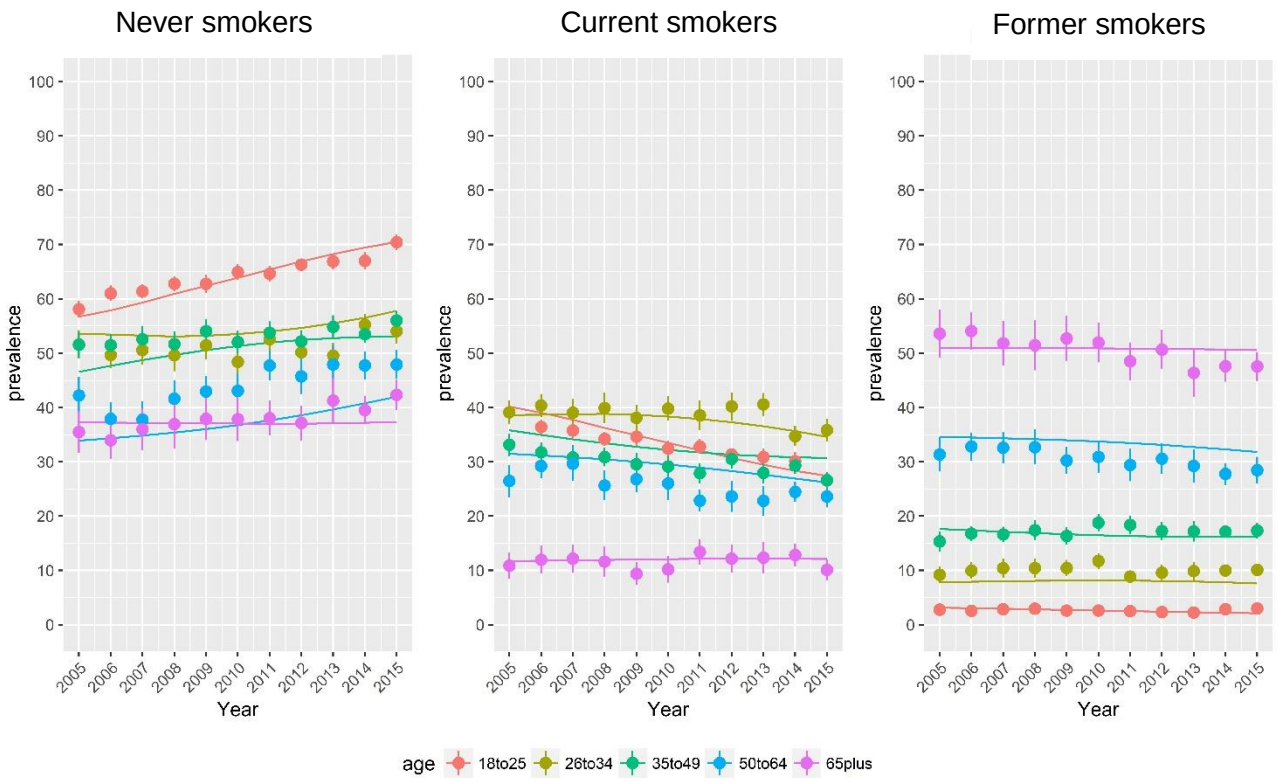
Female (left) and male (right) annual probabilities of smoking cessation. Data shown are for the year 2005. Dots = input data developed by the CISNET lung consortium. Lines = model calibrated probabilities.

Figure 4-10. Comparison of smoking sub-model and survey data, females ages 18+



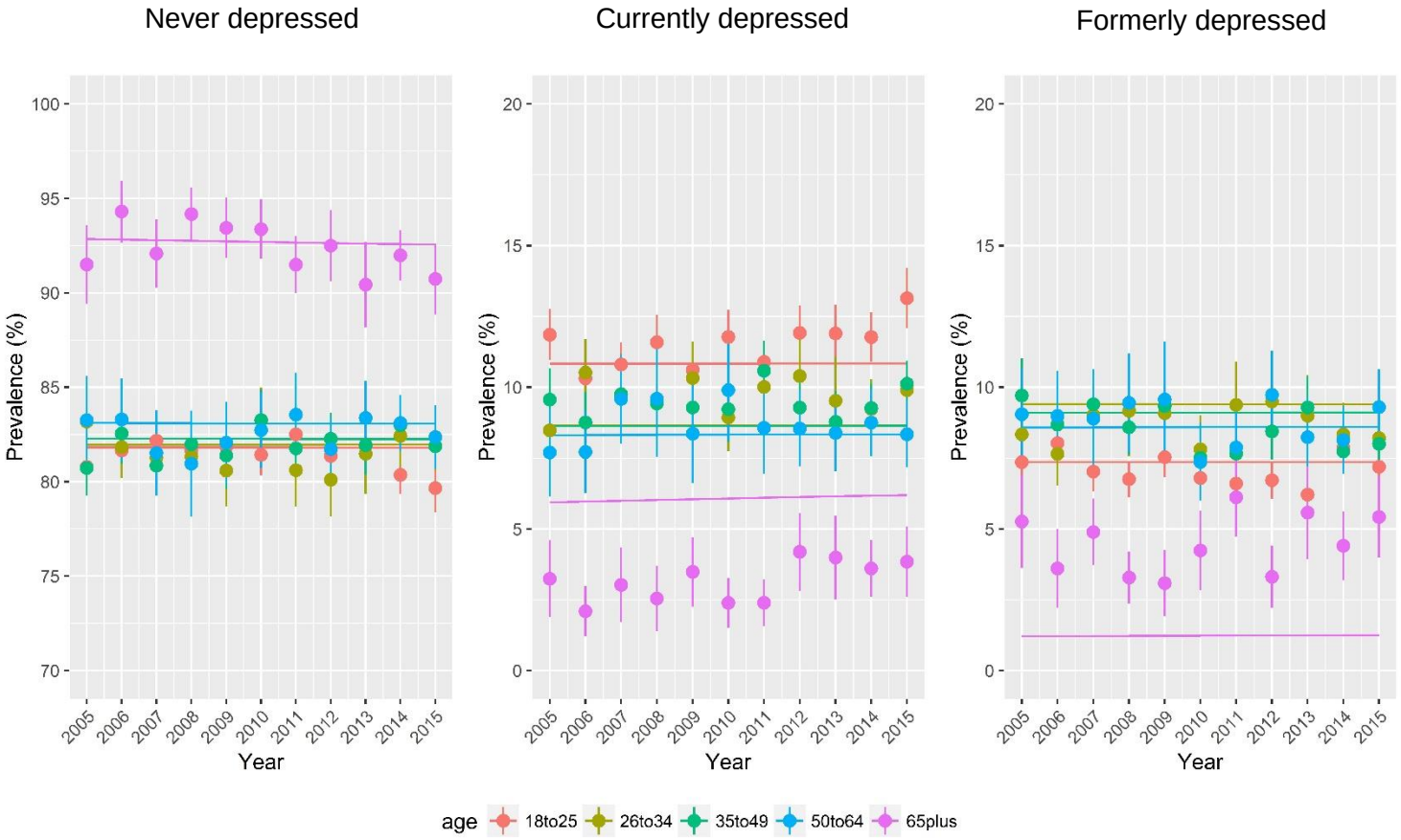
Left panel = never smoker prevalence. Middle panel = current smoker prevalence. Right panel = former smoker prevalence. Dots with vertical lines represent point estimates from the 2005-2015 NSDUH and their corresponding 95% confidence intervals. Lines represent age-group prevalence generated by the calibrated sub-model.

Figure 4-11. Comparison of smoking sub-model and survey data, males ages 18+



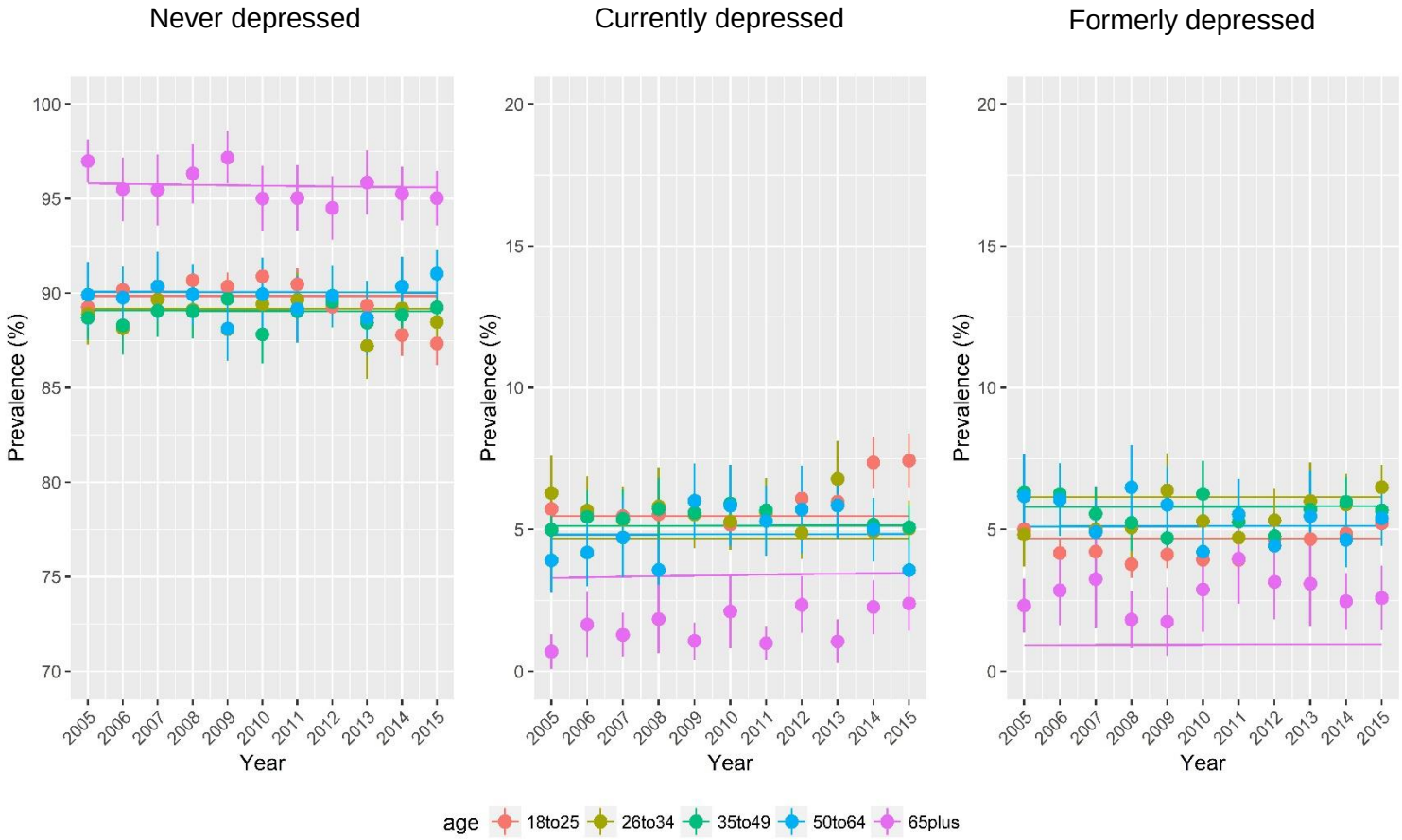
Left panel = never smoker prevalence. Middle panel = current smoker prevalence. Right panel = former smoker prevalence. Dots with vertical lines represent point estimates from the 2005-2015 NSDUH and their corresponding 95% confidence intervals. Lines represent age-group prevalence generated by the calibrated sub-model.

Figure 4-12. Comparison of depression sub-model and survey data, females ages 18+



Left panel = never depressed prevalence (includes recall error). Middle panel = current depression prevalence. Right panel = former depression prevalence. Dots with vertical lines represent point estimates from the 2005-2015 NSDUH and their corresponding 95% confidence intervals. Lines represent age-group prevalence generated by the calibrated sub-model.

Figure 4-13. Comparison of depression sub-model and survey data, males ages 18+



Left panel = never depressed prevalence (includes recall error). Middle panel = current depression prevalence. Right panel = former depression prevalence. Dots with vertical lines represent point estimates from the 2005-2015 NSDUH and their corresponding 95% confidence intervals. Lines represent age-group prevalence generated by the calibrated sub-model.

Table 4-4. Latin hypercube sampling distributions

Parameter	Description	Females			Males		
		Estimate	Min.	Max.	Estimate	Min.	Max.
$RRcs\_dep1$	Relative risk of 1st MDE among current smokers vs. never smokers	1.41	1.00	2.00	1.06	1.00	2.00
$ORhdep\_quit$	Odds ratio for smoking cessation among people with a history of MDE compared vs. never depressed	0.98	0.50	1.00	0.93	0.50	1.00
Ecs_depr	Effect of current smoking on probability of recurrent depressive episode vs. never smoking	1.00	1.00	2.00	1.10	1.00	2.00
$Edepr\_smkinit$*	Effect of depression on smoking initiation	4.73	2.36	9.46	2.99	1.55	4.45
$deprecovSF\_cs$	Effect of current smoking on probability of recovering from depressive episode	0.73	0.50	1.00	0.75	0.50	1.00
$RRmd$*	Relative risk of mortality among people with history of MDE vs never MDE	5.54	3.08	7.98	2.53	1.27	6.21

*Parameter distributions derived as 95% confidence intervals during model calibration
Uniform distributions assumed for all parameters.

Figure 4-14. Partial rank correlation coefficients: smoking prevalence among adults with MD

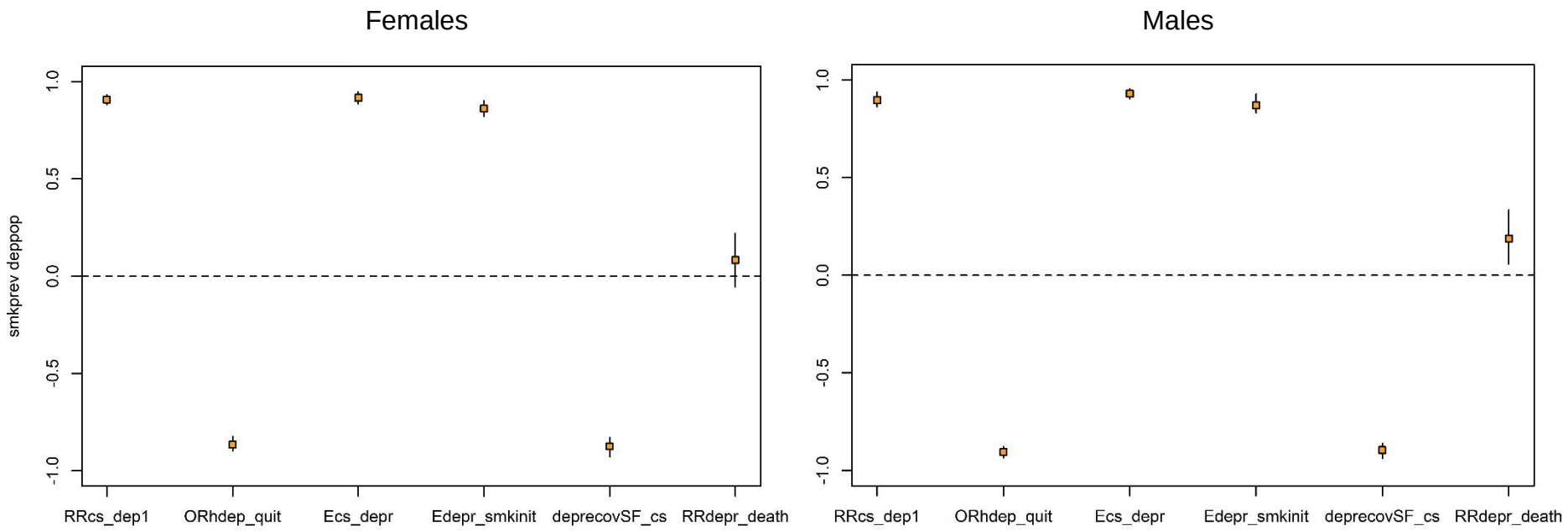
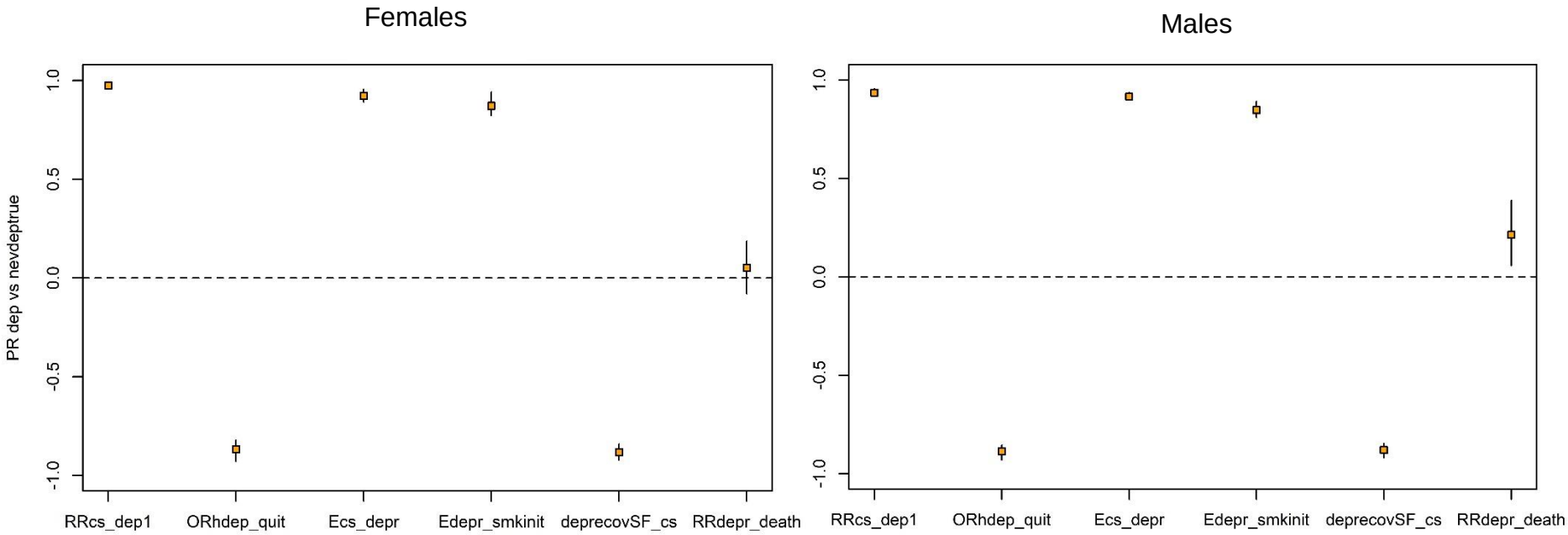
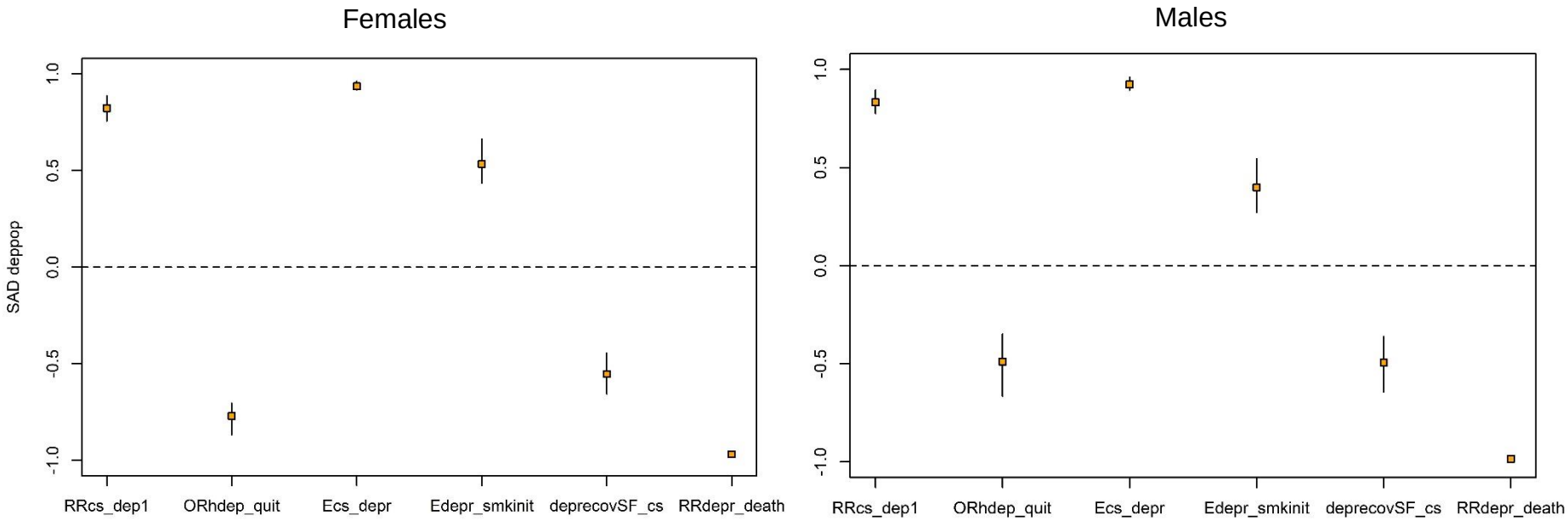


Figure 4-15. Partial rank correlation coefficients: current-to-never MD smoking prevalence ratio



Smoking prevalence among never depressed adults excludes recall error.

Figure 4-16. Partial rank correlation coefficients: smoking-attributable deaths among adults with MD



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Chapter 5 – Simulating the potential impact of widespread cessation treatment for smokers with depression

Background

Smoking rates in the U.S. have continued to plummet for the general population, but the rate of decline has been slower for people with health comorbidities.[1] As a result, people with mental illness continue to face a disproportionate burden of tobacco-related disease and premature death.[2,3] In particular, people with major depression (MD) make up 6.7% of the adult population,[4] but model estimates described in Chapter 4 show that more than 640,000 smoking-attributable deaths will occur in this group between 2016 and 2050. The proportion of all deaths that can be attributed to smoking in the depressed population will continue to be greater than for the population without histories of MD even as smoking prevalence is projected to decline for the entire population. In the absence of major intervention, men and women with MD will become increasingly likely to smoke compared to their never depressed counterparts. In sum, the smoking disparity between those with and without depression is expected widen.

The need for effective interventions that reduce the mental illness tobacco use disparity is well-documented.[5-8] Numerous researchers and national organizations already recommend providing smoking cessation counseling and treatments to patients with mental illness.[6,9-11] Experts have observed that few mental health settings have fully

implemented recommendations to integrate smoking cessation treatment with mental health care.[9,10,12-15] In a 2016 nation-wide assessment, only 37.6% of all public and private mental health treatment facilities reported offering cessation counseling, with an even smaller proportion (25.2%) offering nicotine replacement therapy.[16] Smoking cessation significantly reduces depression, while increasing positive affect and quality of life, thereby further justifying integrating smoking cessation programs into mental health settings.[17]

Still, such interventions would not reach the proportion of smokers with depression who do not use mental health services at all. Wider use of mental health services could lead to further declines in smoking, if health professionals offer cessation treatment for patients with depression. A recent study also found that individuals receiving mental health treatment in the past year were significantly more likely to have quit smoking compared to those who did not receive treatment (37.2% vs. 33.1%, p-value = 0.005), even after adjusting for substance use treatment, mental illness severity, and other sociodemographic characteristics.[1] Increased use of mental health services can then improve mental well-being, and in so doing, reduce propensity for smoking.

The long-term impacts of interventions to address smoking in populations with mental illness are challenging to evaluate using traditional research methods. Randomized controlled trials are limited by short time frames for follow-up, and are resource and time-intensive. However, modeling approaches can simulate intervention scenarios that cannot be readily tested in the real-world, evaluating their potential impact over time. Specifically, systems dynamics models can explore the range of effects of policy levers, identifying conditions under which the greatest public health gains can be made.[18-21]

Recent national reports have highlighted the utility of modeling for tobacco control aims.[22-25] Such models can guide macro-level decision-making for policymakers and practitioners interested in optimal strategies to address tobacco use disparities.[26]

The model described in the previous chapter examines future smoking, depression, and mortality outcomes under a status quo scenario that assumes no changes to usual care. I now extend this model to evaluate the impact of cessation treatment strategies on population health outcomes, including: a) provision of smoking cessation treatment by mental health professionals, and b) increased mental health treatment utilization in the population of smokers with current MD.

Methods

Model overview and extension

I adapt a previously calibrated system dynamics model of smoking and depression comorbidity (Chapter 4) to simulate the impact of cessation interventions targeting smokers with current depression in the U.S. A diagram of the model is shown in Figure 5-1. The population is born into a never smoker and never MD state, based on Census Bureau population projections.[27] From there, individuals may flow into and out of various smoking and depressive states based on annual rates of smoking initiation and cessation, or depression incidence, recovery, and recurrence. The base model was calibrated to data from the National Survey on Drug Use and Health (NSDUH) 2005-2015, and adjusts transition rates to account for interactions between smoking and depression (Chapter 4).

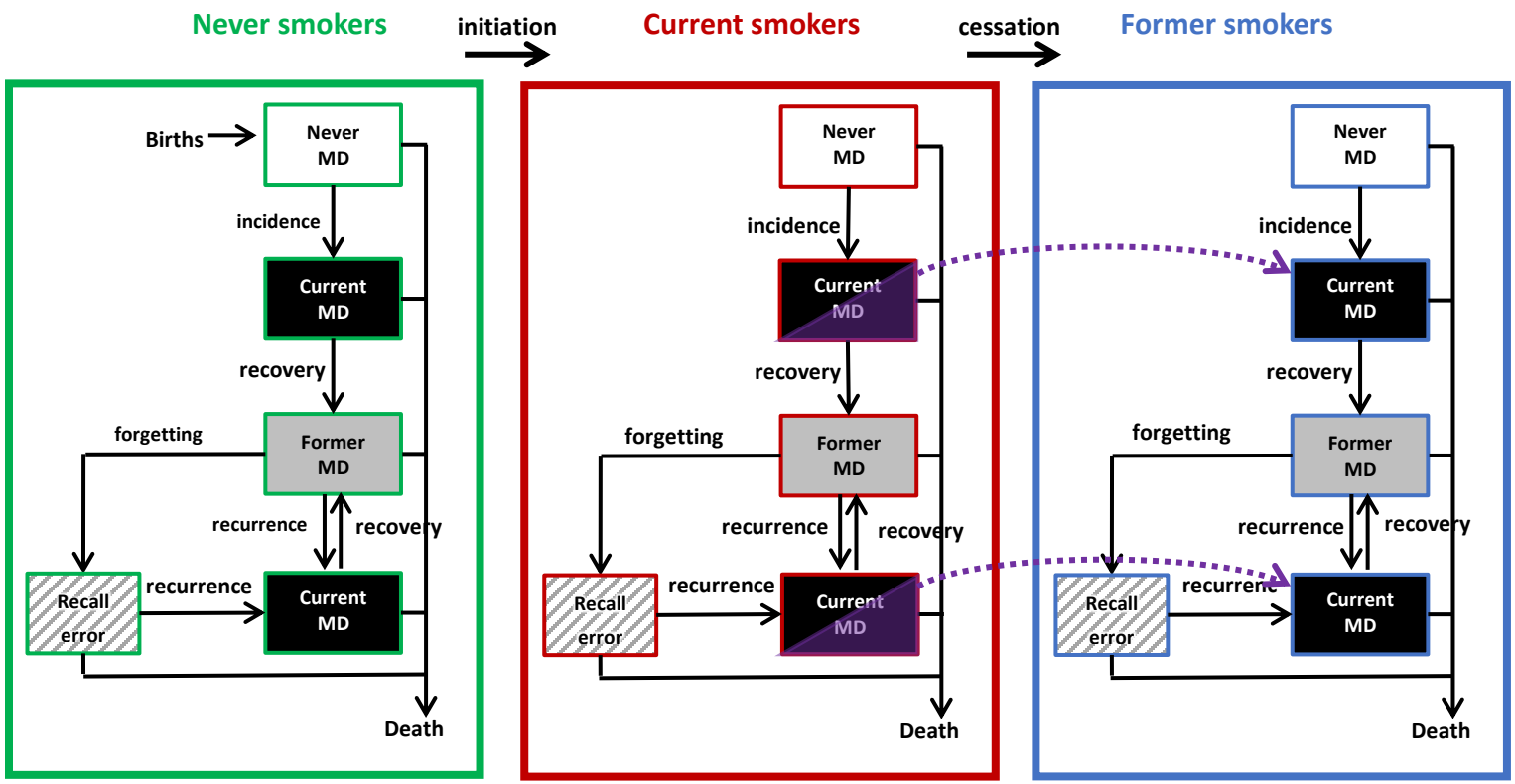
Individuals with current MD are those who report at least 5 out of 9 DSM-IV criteria for a major depressive episode lasting for a two-week period or longer within the past year (Figure 5-1, black compartments). Individuals who are never MD report no lifetime history of a major depressive episode (white compartments). Since recall error is common when screening for depression,[28] I report findings for the never MD population excluding individuals who have had past MD but report no lifetime history of it (gray-white diagonal hatching pattern). Current smokers are individuals who have smoked at least 100 cigarettes in their lifetime, and smoked at all within the past year (red outline).

Smokers with current MD quit based on annual cessation probabilities that are age, gender, and birth cohort-specific developed by the Cancer Intervention and Surveillance Modeling Network (CISNET) lung consortium with data from the National Health Interview Surveys 1965-2015.[29] Smokers who talk to health professionals about their depression are represented in purple in Figure 5-1. Their probabilities of quitting (purple dashed arrow) are increased when health professionals provide them with cessation treatment.

I model four hypothetical treatment interventions within the comorbid patient population seeking treatment for depression effective in the year 2018, including: A) any cessation treatment (including behavioral counseling, pharmacological treatment, or a combination), B) any cessation treatment + 10% increase in the proportion of smokers seeing health professionals for their depression, C) pharmacological treatment, and D) pharmacological treatment + 20% increase in the proportion of smokers seeing health professionals for their depression. To cover a wider range of possible joint impact, scenario B combines a conservative cessation treatment effect size with a smaller increase to mental health service utilization, while scenario D combines a larger treatment

effect size with a greater increase to utilization. I evaluate the prevalence ratio between those with current and never depression, the proportion of all deaths that are smoking-attributable, and the number of premature deaths avoided under each of these scenarios. All analyses were conducted in R.[30]

Figure 5-1. Smoking and depression model extension



MD = Major Depression;

= Smokers who talk to health professionals about their depression; = Cessation treatment.

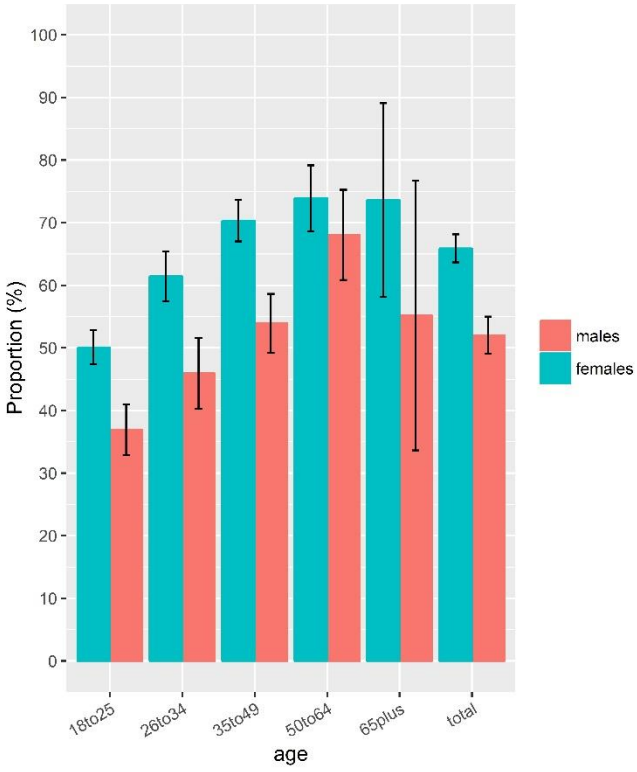
Mental health treatment utilization

I operationalize mental health treatment utilization as the proportion of all smokers with current MD who reported seeing or talking to a health professional about their depression within the past year. Beginning in 2010, the National Survey on Drug Use and Health (NSDUH) began asking whether adults saw a health professional for their depression, where a health professional includes: a general practitioner or family doctor, other medical doctor, psychologist, psychiatrist or psychotherapist, social worker, counselor, other mental health professional, nurse, occupational therapist, or other health professional. Thus, the sites for professional intervention for depression vary widely. As no visible trends were apparent from 2010-2015, I pooled across these years for mental health treatment utilization patterns, and applied these estimates to the comorbid population for each respective age group and gender, as shown in Figure 5-2. Baseline mental health treatment utilization rates were held constant at these proportions through 2050.

I re-calibrate the model to integrate the extension (Figure 5-1) by minimizing the sum of squared differences between the model output and NSDUH estimates of the proportion of comorbid people who see health professionals for their depression. I perform this minimization with the Davidon-Fletcher-Powell optimization algorithm in the Bhat package of R.[30,31] Because of the continuous out-flow of individuals from compartments, the final treatment seeking rates are effectively lower than the initial values supplied to the model. To ensure that the model's rates match those of survey estimates, I re-estimate the set of initial values necessary to accomplish this. Appendix Table 5-2 compares calibrated inputs with their final effective proportions. I similarly estimate initial values that translate

into 10% and 20% increases in the level of mental health treatment utilization across each age group as shown in Appendix Figure 5-7.

Figure 5-2. Smokers with MD who saw a health professional for their depression within the past year, NSDUH 2005-2015



Cessation intervention

Since smoking cessation interventions vary widely, and are implemented under heterogeneous conditions, I rely on estimates from a recent meta-analysis of randomized controlled trials that evaluated the effectiveness of cessation interventions for adult smokers with current depression across multiple mental health settings.[32] The review considers interventions tested on people solely with current depression, excluding studies of people with a history of depression or with mental health disorders other than

depression. Interventions evaluated are psychological and/or pharmacological in nature, and are implemented in clinical, primary care, mental health outpatient, home visit, or hospital settings.

Long-term smoking abstinence is evaluated as 7-day point prevalence at the 6- or 12-month follow-up period. Most studies used biochemical validation (e.g. carbon monoxide or cotinine verification) to assess abstinence. Examples of the types of cessation interventions evaluated include cognitive behavioral therapy, provision of nicotine gum, exercise and counseling, mood management counseling, health education, bupropion with counseling and NRT, among others. Because several of the behavioral-based cessation interventions failed to translate into significant changes in quitting, this moderated the overall combined risk ratio (RR); the meta-analyses showed that the probability of cessation increased by 13.7% across 16 interventions combined (RR = 1.137, 95% CI: 1.001-1.291) relative to comparison condition (no receipt of the cessation treatment under evaluation). When analyses were restricted to pharmacological interventions only, the RR for long-term abstinence was 1.588 (95% CI: 1.230-2.049) compared to placebo condition. These interventions provided patients with varenicline,[33] nicotine gum,[34] nicotine replacement therapy,[35] bupropion,[36] and nicotine patch.[37] The RRs and their confidence bounds are applied to annual cessation probabilities among comorbid smokers who are in contact with health professionals for their depression.

Premature deaths avoided

I compare all model outcomes under intervention scenarios with the status quo scenario (Chapter 4) in which there are no changes to patterns of mental health treatment

utilization or to provision of smoking cessation treatment for people with depression. To estimate the greatest possible health gains associated with integrating smoking cessation treatment in mental health settings, I assume that at baseline it is not available.

I evaluate the number of premature deaths avoided under each intervention scenario by first summing the total number of smoking-attributable deaths (SAD) among people with current depression following the approach described in Chapter 4:[23]

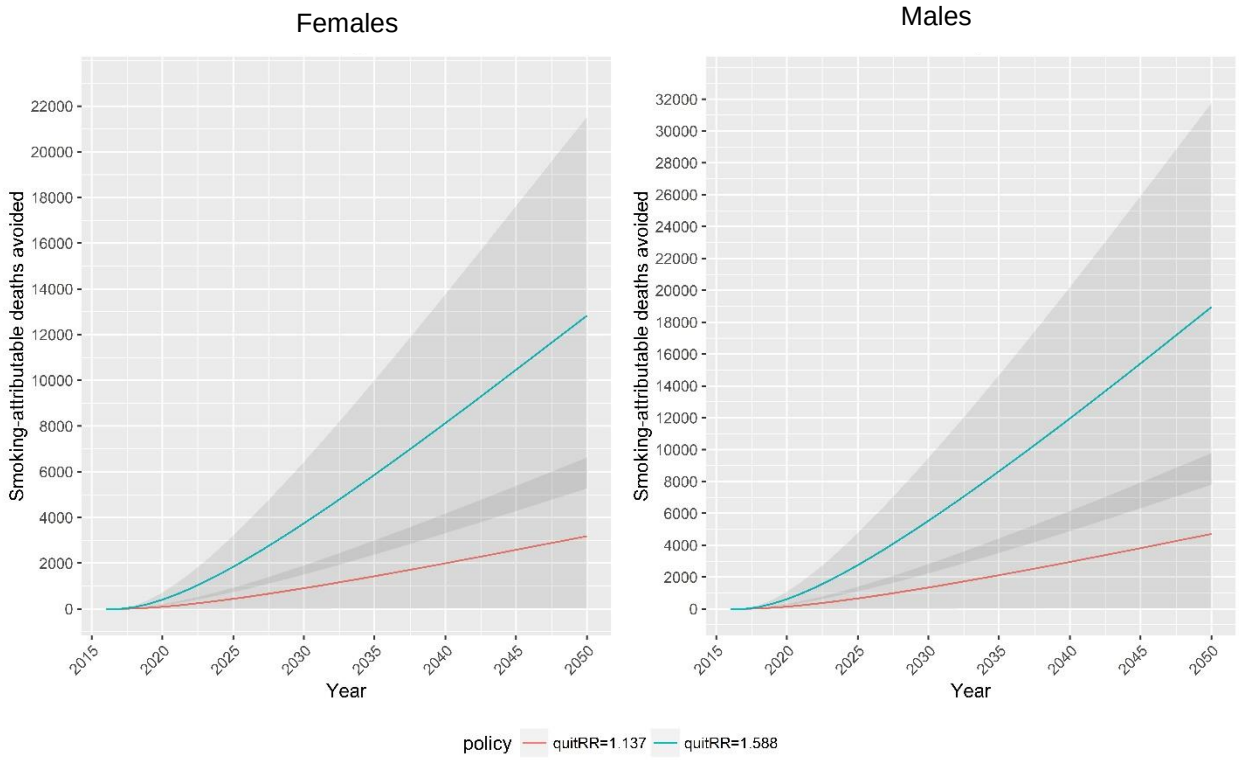
$$SAD = \sum_{age,gender} P\left(prev_{cs} \times (\mu_{cs} - \mu_{ns}) + prev_{fs} \times \left(\mu_{fs} - \mu_{ns}\right)\right)$$

I then calculate the difference between this value and that under the status quo to determine the number of premature deaths avoided under each intervention scenario.

Results

When no changes to mental health treatment utilization patterns are modeled, 52.0% of men and 65.9% of women smokers with depression talked to a health professional about their depression (Figure 5-2). The model estimates depicted in Figure 5-3 show that if these adults received any cessation treatment (red line with 95% CI estimates shown as gray ribbons), this would lead to 3,092 total premature deaths avoided (95% CI: 23 to 6,428) among women and 4,679 premature deaths avoided among men (95% CI: 34 to 9,753) by the year 2050. The provision of pharmacological treatment would lead to a greater number of premature deaths avoided by 2050: 12,472 among women (95% CI: 5,124 to 20,940) and 18,889 among men (95% CI: 7,778 to 31,643).

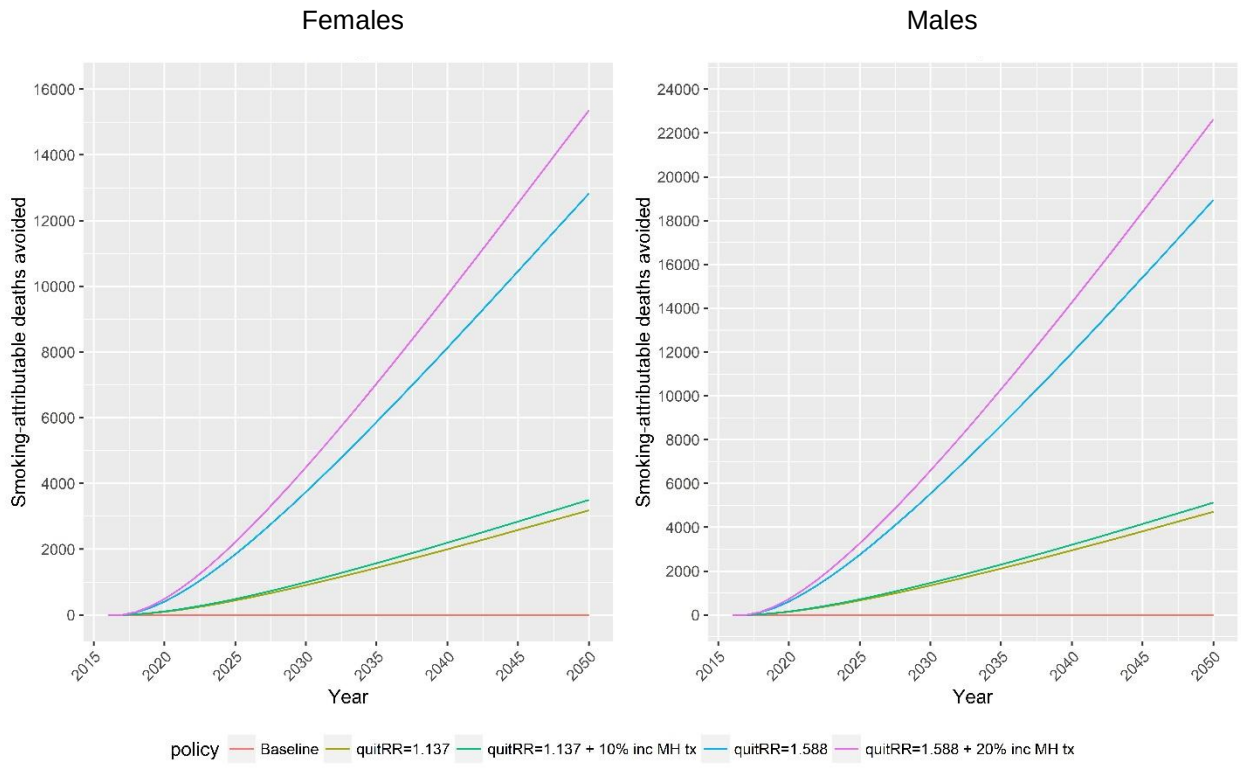
Figure 5-3. Cumulative number of premature deaths avoided: cessation treatment only



When cessation treatment is provided in conjunction with increases in the proportion of smokers who see health professionals for their depression, some additional health gains are achieved. Appendix Figure 5-8 shows that under a baseline scenario, smoking prevalence among women decreases by 35.8% (men: 28.7%) from 29.9% (34.8%) in 2018 to 19.2% (24.8%) in 2050. With any cessation treatment, female (male) smoking prevalence decreases by 36.4% (29.1%) over this time period. Any cessation treatment considered jointly with a 10% increase in mental health treatment utilization leads to 36.4% decline for women and 29.2% for men. Figure 5-4 shows that an additional 308 and 420 female and male premature deaths would be avoided by 2050 with this 10% increase (green line). Provision of pharmacological treatment alone leads to 38.2% and 30.5% decline in female and male smoking prevalence by 2050 (Appendix Figure 5-8).

When this is paired with a 20% increase in mental health treatment utilization, the model estimates a 38.7% and 30.9% decrease in smoking for women and men, with an additional 2,458 and 3,688 number of premature deaths avoided (Figure 5-4, purple line).

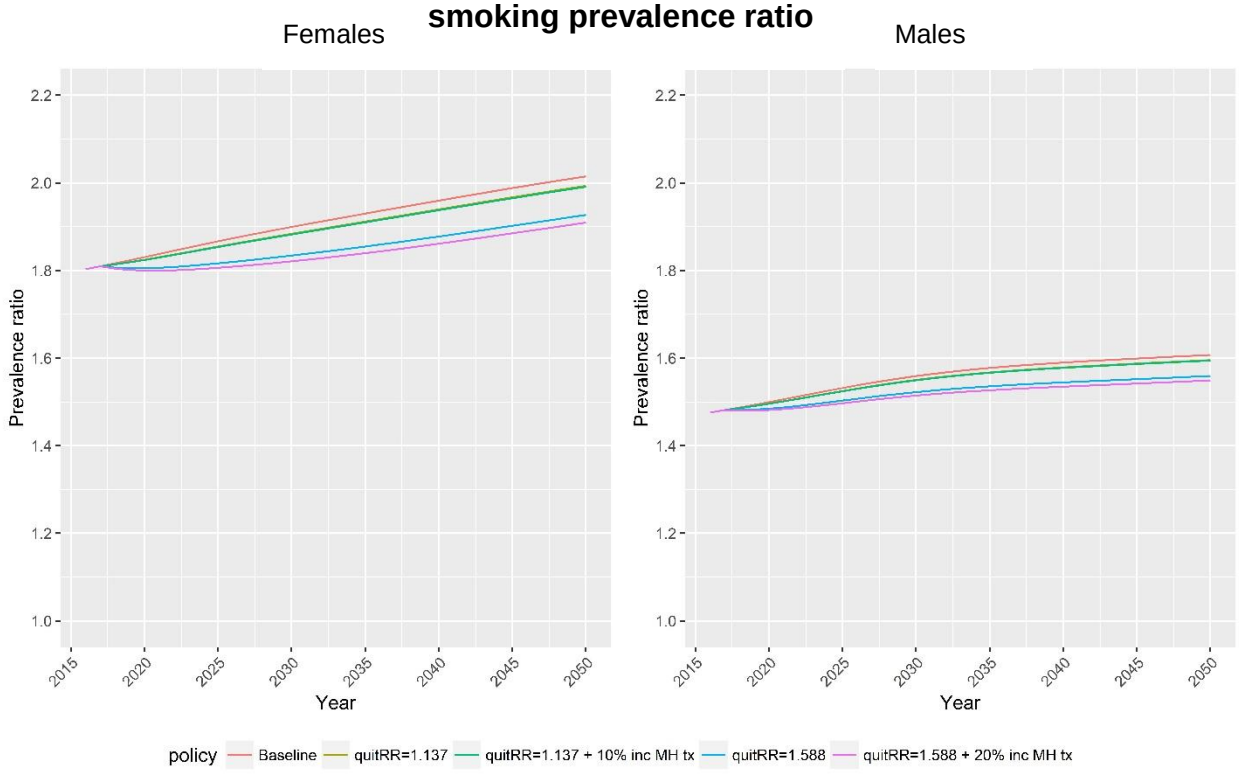
Figure 5-4. Cumulative number of premature deaths avoided



Under the status quo scenario, the smoking prevalence ratio between those with current MD and those with never MD (excluding individuals with recall error) increases over the 2018-2050 period from 1.81 to 2.02 for females and from 1.50 to 1.62 for males (Figure 5-5). Results where adults with never MD include those with recall error are shown in Appendix Figure 5-9. This rising disparity is moderated with more progressive treatment intervention scenarios. Under an intervention scenario where any cessation treatment is offered with no change to levels of mental health service utilization, this ratio does not change. When coupled with a 10% increase in utilization, the prevalence ratios decrease

is again marginal: 1.99 for women and 1.61 for men. With provision of pharmacological cessation treatment, the ratio for women reaches 1.93 by 2050, and 1.91 when tied to a 20% increase in comorbid smokers seeking treatment for their depression. Likewise, for men, pharmacological treatment alone would curb the prevalence ratio increase to 1.57 by 2050 and to 1.56 if combined with a 20% increase in mental health treatment seeking.

Figure 5-5. Current-to-never MD (excludes recall error) smoking prevalence ratio



With more progressive intervention scenarios also come greater reductions in the proportion of deaths attributable to smoking among people with current MD (Figure 5-6). In the year 2018, 16.1% and 28.2% of all female and male deaths in the comorbid population can be attributed to smoking. By 2050 these proportions are projected to decline to 11.4% and 19.7% under a status quo treatment scenario. When smokers who

see health professionals for their depression receive any cessation treatment, this proportion declines to 11.1% for females and 19.5% for males, and only marginally to 11.1% and 19.4% in conjunction with a 10% increase in mental health treatment utilization. Delivery of pharmacological treatment to patients leads to lower smoking-attributable proportions of all deaths by 2050: 10.5% for females and 18.8% for males. The model estimates a modest change to this proportion when pharmacological treatment is combined with a 20% increase in utilization: 10.3% for females and 18.6% for males by 2050. Table 5-1 summarizes all smoking-related outcomes by the year 2050 among the adult population with current MD.

Figure 5-6. Proportion of deaths attributable to smoking, adults with depression

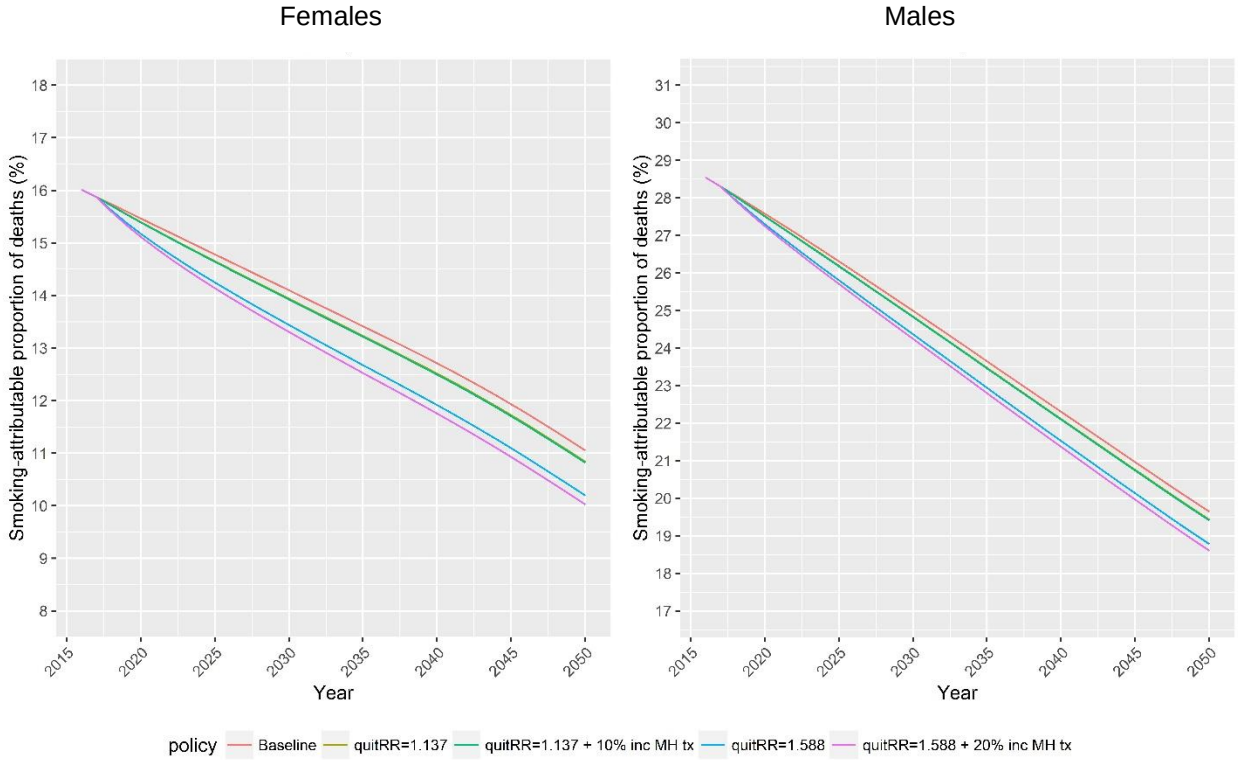


Table 5-1. Model summary of smoking outcomes for adults with major depression by 2050

	Females					Males				
Scenario	**Smoking prevalence**	**Prevalence decrease from 2018**	**Current-to-never MD PR**	**% of deaths attributed to smoking**	**# of premature deaths avoided**	**Smoking Prevalence**	**Prevalence decrease from 2018**	**Current-to-never MD PR**	**% of deaths attributed to smoking**	**# of premature deaths avoided**
Baseline 'status quo'	19.2%	35.8%	2.02	11.7%	0	24.8%	28.7%	1.62	19.7%	0
Any cessation Tx	19.0%	36.4%	2.02	11.1%	3,092	24.7%	29.1%	1.62	19.5%	4,679
Any cessation treatment + 10% MH Tx increase	19.0%	36.4%	1.99	11.1%	3,400	24.6%	29.2%	1.61	19.4%	5,099
Pharmacological cessation Tx	18.5%	38.2%	1.93	10.5%	12,472	24.2%	30.5%	1.57	18.8%	18,889.
Pharmacological cessation Tx + 20% MH Tx increase	18.3%	38.7%	1.91	10.3%	14,930	24.0%	30.9%	1.56	18.6%	22,577

PR = prevalence ratio; MH = mental health; Tx = treatment

Discussion

This study is the first to evaluate the potential population health benefit of widespread smoking cessation treatment for people with a common mental disorder: major depression. I develop a simulation model with nationally-representative data to quantify a missed public health opportunity for smokers with depression. Under the model assumptions, I find that if at the point of care, health professionals provided cessation treatment to their patients with depression, 7,771 to 31,361 premature deaths could potentially be averted by the year 2050. Doing so would moderately curb the rising smoking disparity between those with MD and those with no history of it, and reduce the proportion of all deaths that can be attributed to smoking among people with depression.

The results shown here offer first estimates of the population-level health impact of cessation treatment interventions for people with depression given several limitations. This model does not account for population heterogeneity and the complex treatment needs of people with multiple behavioral health conditions. Cessation treatment options vary widely across healthcare contexts and need to be adapted for the setting (inpatient vs. outpatient) and the patients, especially those with other co-occurring psychiatric disorders. Smokers with serious mental illness may have complicated healthcare profiles that differ considerably from patients included in randomized controlled trials. This study does not further disaggregate the population by other sociodemographic characteristics such as socioeconomic status. Research shows that disparities in smoking by depression status are even more pronounced when taking level of education and income into account.[38]

Another limitation is that the randomized controlled trials on which the treatment effect estimates are based may not be generalizable to smokers with depression in real-world settings. For example, while one trial did not require a desire to quit for participation,[11] another recruited patients from smoking cessation clinics who were already motivated to quit.[33] The meta-analysis risk ratios were based on evaluations of the efficacy of different cessation treatment interventions.[32] Efficacy studies generally overestimate the true 'real-world' effectiveness of interventions, and the extent to which they can be generalized outside the context of a clinical trial.[39,40] On the other hand, the true effects of cessation interventions included in the meta-analysis may be underestimated because of the inclusion of interventions that failed to translate into significant improvements in smoking abstinence, as well as the use control arm conditions that generally exceeded standard care (e.g. including behavioral smoking cessation counseling in both the intervention and control arm[34,35,37]).

The modeling assumptions used in this study are generous. The analysis assumes that all depressed patients seeking mental health services are interested in quitting smoking. Although research has demonstrated that many adults with depression want to quit smoking,[41] others may be reluctant to quit based on the erroneous belief that doing so could worsen their mental health[42] or unwilling to quit altogether. Secondly, I assume that their providers universally offer them cessation treatment. Health professionals are commonly under the misconception that smoking can interfere with patients' mental health recovery, despite evidence indicating that cessation confers mental health benefits including reducing depressive symptoms.[43-47] Surveys show that mental health professionals believe that their patients have other immediate problems to address, hold

permissive attitudes towards their patient's continued smoking, and of greater concern, health providers commonly believe their patients with mental illness are not interested in quitting.[48] Furthermore, qualitative research indicates that health providers are not perceived as sources of smoking cessation support by people with severe mental illness,[49] though this may be less applicable to people with common mental health disorders like depression.

I furthermore simulate optimistic scenarios with improved access to and utilization of mental health services. Despite passage of the Mental Health Parity and Addiction Equity Act, the level of insurance coverage for mental health care varies, with a significant proportion of behavioral care needs addressed out-of-network with high out-of-pocket costs.[50] Mental health service uptake is hindered by the well-documented stigma surrounding the use of treatment.[51] Although women have higher rates of depression than men, men stand to benefit the most from such interventions given both their higher smoking prevalence and lower utilization of mental health services compared to women.

Finally, the status quo scenario assumes little to no integration of cessation treatment in mental health services at baseline which inflates the overall health gain estimates. The level of smoking cessation treatment integration has very likely increased since the Affordable Care Act (ACA) was implemented. More than a third of mental health facilities report offering cessation help to patients, and while it is unclear how this translates into patient utilization at the individual level,[52] these improvements mean progress towards achieving the public health gains estimated by this study is already taking place

Policy implications

Public health leaders and professional organizations have long called for the integration of smoking cessation treatment into standard care for patients with mental illness.[5-7,9,10,14,53] Yet barriers to the widespread use of cessation treatment, even in general health settings, persist. The ACA greatly increased coverage for tobacco cessation treatment in private health insurance plans and under Medicaid. Tobacco treatment coverage is now required for non-grandfathered private health marketplace plans, as well as some newly eligible beneficiaries in states with Medicaid expansions. Policies that mandate coverage of tobacco dependence treatment in private insurance plans can still fail to translate into actual patient utilization of such services. Some private insurance plans only provide access to treatment for patients who meet medically necessary prerequisites; others do not make it clear to patients that this is a covered benefit.[3,54]

The Medicaid population has much higher smoking rates and higher levels of psychological distress compared to people with private insurance or other coverage.[55] When coupled with high utilization rates, Medicaid coverage of cessation treatment can significantly reduce population smoking.[56] States that elected to expand Medicaid experienced increases in quitting among low-income adults.[57] While Medicaid expansion plans cover tobacco cessation treatment without cost-sharing, they may still impose cost-sharing and limits on the number of quit attempts per year, or require counseling and prior authorization to receive cessation medications.[58,59] Under traditional Medicaid plans, cessation benefits must be covered for pregnant women, but are not required to do so for all enrollees. As a result, there is wide variation in state Medicaid programs' coverage and promotion of cessation medications.[60,61] In a qualitative study examining low utilization rates among Medicaid recipients in Kansas, barriers described included failure

of physicians to prescribe treatments and a lack of patient awareness of treatment coverage.[62] It is unclear what incentives exist to encourage physicians to prescribe cessation treatments, as Medicaid coverage is generally based on capitated payments. The ability of enrollees to access cessation treatment coverage is also at risk as more states are adding Medicaid work requirements.[63] Smokers and people with mental illness make up a disproportionate share of Medicaid enrollees[55] and continue to encounter barriers to treatment access despite recent policy reforms.

While there is clear value in broad system-wide interventions to help people with depression quit smoking, the health gains associated with widespread delivery of cessation treatment specifically in mental health settings might be modest. The model shows that under the most highly optimistic treatment scenario evaluated, less than 5% of the 597,255 premature smoking-attributable deaths among adults with depression during the 2018-2050 period would be averted. These results should not dissuade decision-makers from actively promoting smoking cessation treatments, which are known to be highly cost-effective, including for people with depression and other psychiatric conditions.[64-66] However given the investment required to provide them comprehensively, including the costs of broadening access to mental health services, provision of cessation treatment in mental health settings should be pursued in conjunction with other approaches.

Tobacco control strategies outside of the clinical setting can reduce smoking in populations with mental illness. Smoking cessation telephone quitlines are effective at helping smokers quit, especially when tailored for those with mental health conditions. In a recent randomized control trial, a specialized quitline designed for patients with mental

health conditions increased the likelihood of quitting compared to use of a standard quitline.[67] Smoke-free air laws implemented in restaurants and bars have been shown to reduce smoking for people with some specific psychiatric conditions.[68] Suggestive evidence also indicates that people with mental disorders are also sensitive to changes in price,[69] and would therefore be responsive to increases in tobacco taxes. Other research suggests that e-cigarettes may be just as effective at helping smokers with mental illness quit as nicotine replacement therapy,[70] although whether they can serve as cessation aids remains a topic of strong debate.[71,72] If e-cigarettes or other novel nicotine delivery products can deliver on their promise of harm reduction, strategies to promote their use among smokers with mental illness who would otherwise not quit may be worth pursuing.

Notably, the Food and Drug Administration recently announced its intention to explore regulations that would reduce the level of nicotine in cigarettes to non-addictive levels, using a simulation model to evaluate the potential public health benefits of doing so.[73,74] This regulation would undoubtedly have enormous impact on the lives of people with mental illness. Randomized controlled trials are now being conducted to evaluate the impact of very low nicotine cigarettes on the smoking behavior of people with comorbid mood and/or anxiety disorders.[75] Early evidence from a clinical trial showed that smokers with depressive symptoms are equally responsive to changes in the level of nicotine in their cigarettes as smokers without depressive symptoms.[76]

In sum, far more aggressive strategies are needed to markedly reduce tobacco-related disease and death for people with depression, and to achieve these reductions in fewer years. This should include efforts to prevent smoking initiation among youth and youth

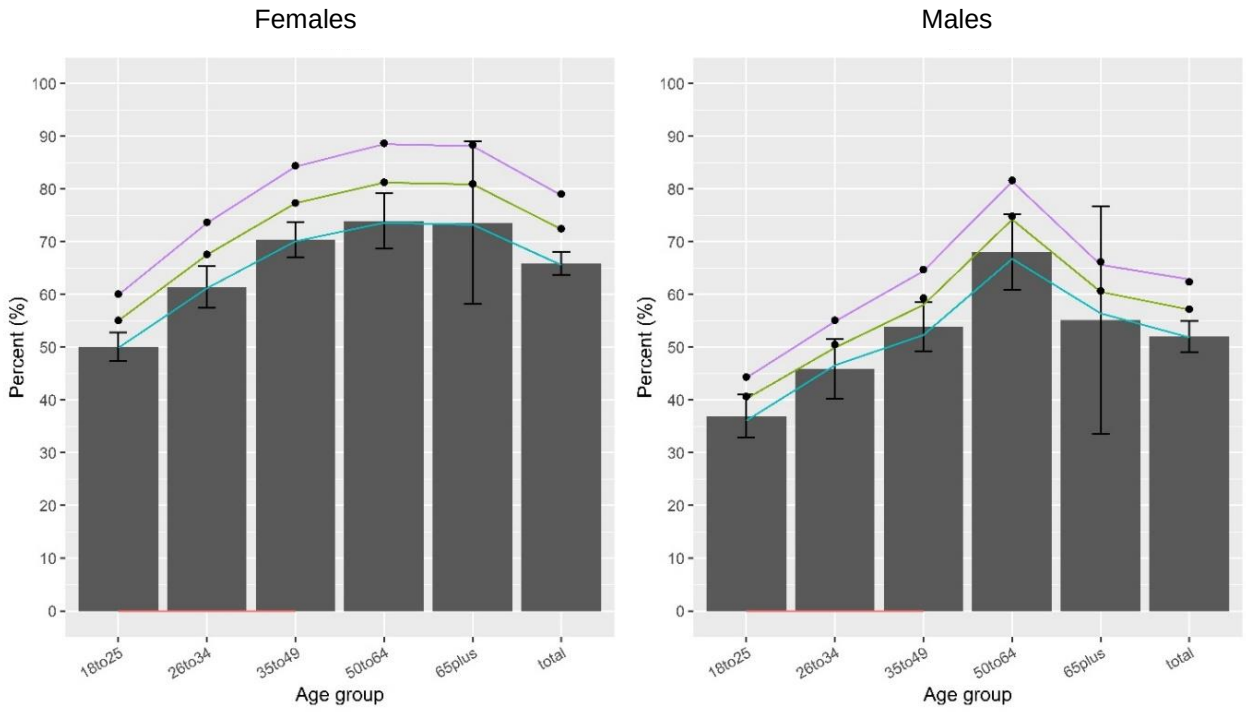
adults with depressive symptoms. As people with mental illness are increasingly represented in the country's remaining smoking population,[77] tobacco control and mental health advocates are now confronted with the important challenge of improving the policy and treatment environment for comorbid smokers. The task ahead is enormous and it may require new and innovative strategies beyond those evaluated here.

Appendix

Table 5-2. Proportion of smokers seeing health professionals for depression

Males	Baseline distribution		10% proportional increase		20% proportional increase	
Age group	Calibrated input	Final	Calibrated input	Final	Calibrated input	Final
18 to 25	57.0%	37.0%	63.3%	40.6%	69.7%	44.3%
26 to 34	49.6%	45.9%	50.5%	50.5%	55.8%	55.1%
35 to 49	55.2%	53.9%	62.6%	59.3%	70.0%	64.7%
50 to 64	75.7%	68.0%	83.2%	74.8%	90.6%	81.6%
65+	42.8%	55.2%	43.1%	60.7%	47.0%	66.2%
Females	**Baseline**		**10% increase**		**20% increase**	
Age group	Calibrated input	Final	Calibrated input	Final	Calibrated input	Final
18 to 25	63.8%	50.1%	70.1%	55.1%	76.5%	60.1%
26 to 34	71.1%	61.4%	78.2%	67.6%	85.3%	73.7%
35 to 49	73.7%	70.3%	81.1%	77.4%	88.5%	84.4%
50 to 64	74.8%	73.9%	82.3%	81.3%	89.7%	88.7%
65+	72.6%	73.6%	79.9%	81.0%	87.2%	88.3%

Figure 5-7. Mental health treatment utilization among smokers with depression



Bars represent the percent of smokers with a past year major depressive episode (MDE) for the NSDUH 2010-2015 period who reported that they "saw a health professional for their MDE within the past year." Vertical black lines are the corresponding 95% confidence intervals. Teal line = final distribution following calibration to NSDUH estimates. Green line = final calibrated values assuming a 10% increase in utilization. Purple line = final calibrated values assuming a 20% increase in utilization.

Figure 5-8. Smoking prevalence among adults with depression

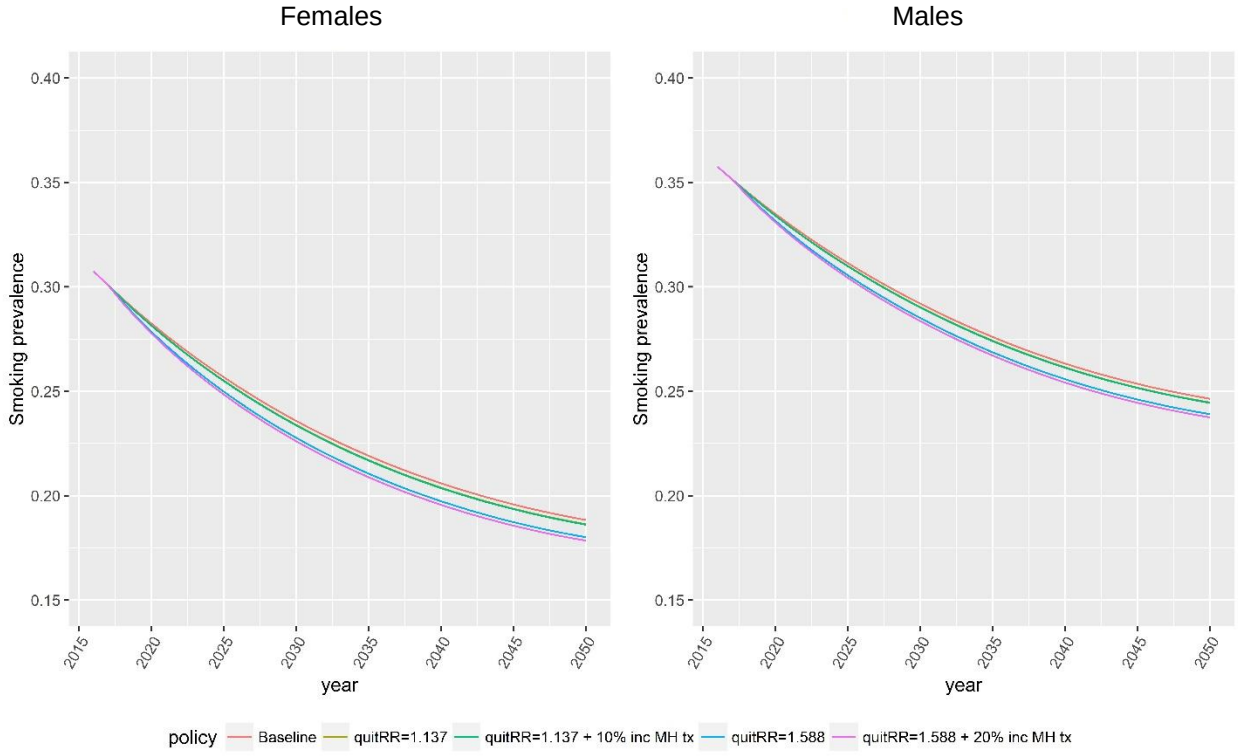
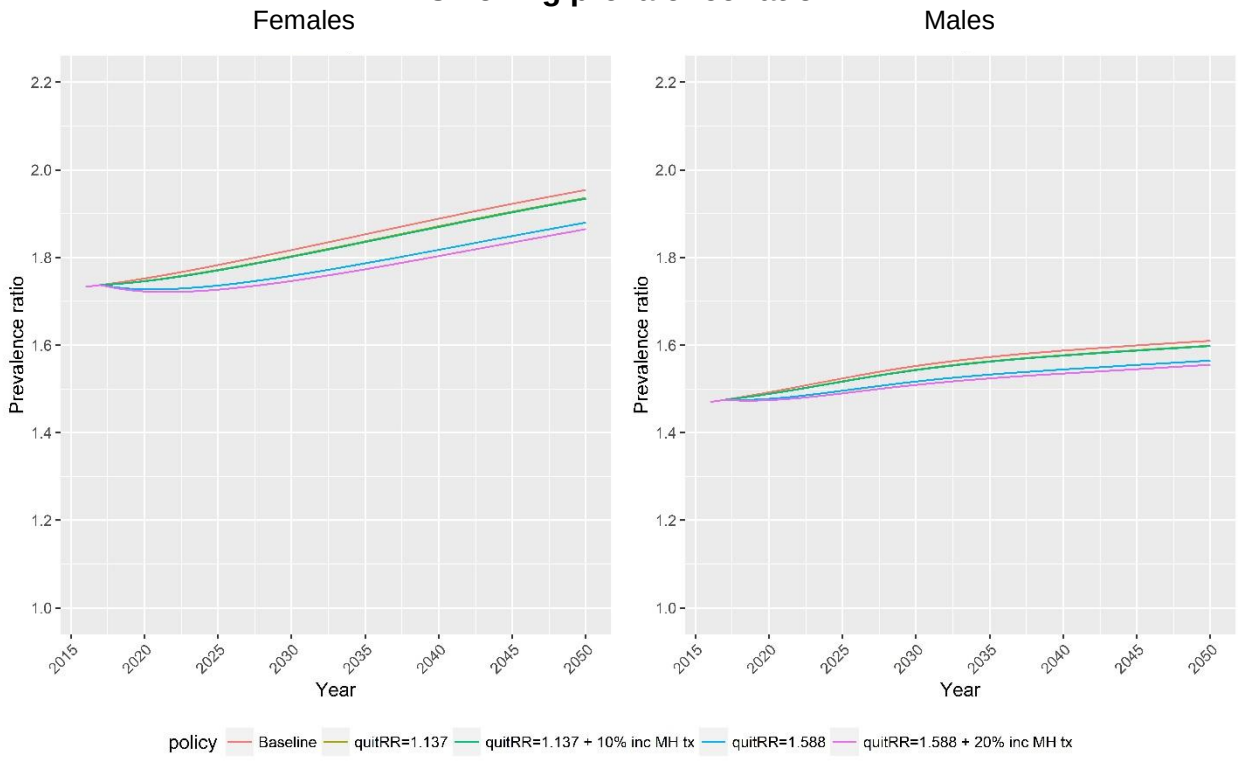


Figure 5-9. Current-to-never depression (includes recall error) smoking prevalence ratio



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Chapter 6 – Conclusion

"When life gives you a wake-up call, answer it." – Rebecca, former smoker[1]

Faced with the debilitating health consequences of her smoking, Rebecca was finally able to quit after 36 years as a smoker, and she has since offered this advice to countless smokers across the country. Public health agencies are now also waking up to the crisis of smoking among people with mental illness: Rebecca's inclusion in the CDC's *Tips from Former Smokers* campaign marks the first time that a national tobacco education campaign has specifically targeted smokers with mental health conditions. What was once described as a hidden epidemic,[2] is now receiving national attention as strategic partnerships are forming around the issue.[3] In October 2016, the American Cancer Society and the Smoking Cessation Leadership Center convened more than 16 leading organizations in Atlanta with the ambitious shared goal of driving down smoking rates in populations with mental illness.[4] These recent partnerships between major organizations offer promising opportunities for large-scale change.[3,5] Researchers have increasingly turned their focus to this tobacco use disparity as well. The literature on smoking and mental illness has grown significantly in the last two decades, improving our understanding of and ability to address this particular tobacco burden.[6]

The work presented here is part of that larger undertaking. We now know that smoking is the primary driver of differences in life expectancy between those with and without serious mental illness (Chapter 2). I found that while smokers with serious psychological distress (SPD) lose roughly 15 years of life expectancy at age 40, never smokers with SPD only lose 5. Adults with SPD who quit smoking live 5-6 years longer than those who continue. Prior to this study, estimates of the reduced lifespan of people with mental illness failed to disentangle the mortality risk associated with psychological distress from that produced by smoking.

Next, I modeled the epidemiology of depression—a necessary precondition to modeling its comorbidity with smoking—and discovered that current estimates of the lifetime burden of depression in the U.S. are inaccurate (Chapter 3). Over 40% of adults likely fail to report a past depressive episode. National cross-sectional data and modeling analyses suggest that lifetime experience with major depressive episodes are nearly twice the reported rate for women (15.6% vs. 28.7%) and almost 70% higher than the estimate for men (9.5% vs. 16.0%). The experience of depression is far more common than what available survey data indicate, a sign that estimates of its lower prevalence should be met with skepticism, and that efforts to improve the mental health of the nation must be redoubled.

Using this as an underlying sub-model, I turned to the development of a system dynamics model of the relationship between smoking and depression (Chapter 4). The vicious cycle that Rebecca and other depressed smokers find themselves in has major implications at the population level. In the absence of large-scale strategies that address disparate smoking rates between those with depression and those without a history of it, the gap is

projected to widen over the next several decades. By then women with depression will be twice as likely to smoke as they are now. Men with depression will be 1.6 times as likely to smoke. Adults with major depression only make up 6.7% of the population,[7] but from 2016 to 2050, more than 640,000 smoking-attributable deaths are expected to occur in this group.

Finally, I simulated the potential health gains associated with aggressive smoking cessation treatment for people with depression (Chapter 5). Research has shown that both pharmacological and general cessation interventions are effective at helping patients with depression quit.[8] If starting in 2018 every adult smoker seeing a mental health professional for their depression received cessation treatment, thousands of premature deaths could be avoided, the tobacco use disparity between those with and without depression would narrow, and the proportion of deaths among people with depression that are smoking-related would decline. However, this would only represent approximately 5% of the nearly 600,000 smoking-attributable deaths that would occur in this population between 2018 and 2050.

Future work

These findings prompt further questions. Thus far I have examined mortality outcomes, yet both smoking and depression are leading contributors to disability. Future modeling efforts could measure the extent to which interventions alleviate the disability burden from comorbid smokers. What impact would smoking and depression comorbidity have on other health metrics, such as disability-adjusted life years? Even if the health gains associated with providing cessation treatment in mental health settings are modest, other

benefits including improved quality of life and increased productivity have yet to be quantified. Although these studies provide estimates of the impact of interventions on smoking outcomes, additional work could evaluate the effects of such interventions on depression outcomes, given the dynamic relationship between smoking and depression.[9,10] How might cessation treatment influence mental health outcomes? How might mental health interventions influence smoking outcomes? What would be the associated costs?

The model I developed can be refined to assess more specific healthcare environments including mental health outpatient and primary care settings. Outside of the U.S., many high-income countries have health care systems better equipped for the widespread delivery of mental health services and smoking cessation medications. What are the projected population health outcomes in these other contexts?

Future research could explore the potential impact of other types of cessation interventions. Effective strategies need not take place in a health care context. New smartphone applications or web-based platforms could facilitate smoking cessation but have not been evaluated with smokers who have mental illness.[11] Telephone quitlines when tailored for people with mental health conditions have been shown to be more effective than standard smoking cessation quitlines.[12]

To date, there is limited research evaluating the costs and benefits of different tobacco control interventions for people with mental illness. Decision-makers and organizations committed to reducing the toll of smoking on communities with behavioral health comorbidities need evidence comparing potential health interventions with each other.

Research in this area could help public health leaders determine how resources dedicated to this issue are allocated—this includes information that assesses the opportunity costs associated with pursuing one approach over another. Simulation modeling methods can be used to evaluate and compare the impact of interventions, forecasting both health and economic outcomes in the near and distant future.[13-16] Other large-scale tobacco control strategies may confer larger health benefits than providing cessation treatment to smokers with mental illness.

Modeling methods could prove useful in evaluating tobacco harm reduction strategies for smokers with mental illness in particular. E-cigarette use has been rising not just in the general population, but also among smokers with mental illness.[17] Smokers with mental health conditions are just as or more likely to use e-cigarettes than smokers without.[18] Smokers who are unable to quit, but wish to cut back the number of cigarettes they are smoking or substitute their cigarettes completely, may turn to e-cigarettes. Though still controversial,[19] how might patterns of e-cigarette use (or other novel nicotine delivery products) among people with mental disorders shape the tobacco use disparity? If such devices are equally effective at helping smokers with mental illness quit compared to typical cessation treatments, as some research indicates,[20] then their widespread availability to consumers would facilitate uptake among those unable or unwilling to abstain from nicotine altogether.

Should the Food and Drug Administration follow through on its plans reduce nicotine in cigarettes to non-addictive levels, the impact of such broad-scale regulations on smokers with mental illness are important.[21,22] The model I developed could be applied to evaluate

the population-level impact of a nicotine reduction strategy for smokers with depression and tobacco use disparities by mental health status.

Other studies could evaluate innovative interventions that prevent smoking initiation among young people with symptoms of depression, or consider uptake of e-cigarettes among people with mental illness as a means of quitting. Smoking and depression are social processes driven in part by spillover or social network influences.[23,24] Other models could explicitly simulate the impact of interventions on communities where networks of smokers with mental illness may cluster.

A great deal of the existing research focuses on helping smokers with mental illness quit smoking, whereas little addresses preventing young people with behavioral health conditions from starting to smoke. Just as tobacco cessation and mental health treatment should be integrated, so too should tobacco prevention and mental health promotion strategies. Like smoking, depression also has its onset during adolescence and young adulthood (see Chapter 3). The feedback cycle between smoking and depressive symptoms suggests that early smoking prevention could lead to even greater mental health gains in the long-run.

In pursuing these new research questions, it is important to recognize that the effectiveness of intervention strategies will differ by type of mental disorder diagnosis, degree of severity, and level of baseline interest in quitting. The smoking patterns of people with depression may be more similar to the general population than to people with schizophrenia, for example. Not all smokers with mental illness will be interested in quitting, and researchers should consider every stage of their quitting process: from

motivating the smoker to make a quit attempt, to the quit attempt itself, to relapse prevention.[25]

This body of work puts forth the argument that the time to view smoking and mental health as separate public health issues is over. Together they represent a complex system capable of generating better or worse health outcomes, smaller or larger disparities, depending on how quickly we take action. Research now shows that in the next three decades, hundreds of thousands of people with depression could die early deaths from smoking. It is time to answer the call.

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