

Original Investigation

Modeling the Health Effects of Expanding e-Cigarette Sales in the United States and United Kingdom

A Monte Carlo Analysis

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IMPORTANCE The prevalence of electronic cigarette (e-cigarette) use is increasing. Population health effects will depend on cigarette smoking behaviors, levels of dual use with conventional cigarettes, and e-cigarette toxicity.

OBJECTIVE To evaluate potential health effects of various scenarios of increasing promotion and use of e-cigarettes.

DESIGN, SETTING, AND PARTICIPANTS A base case model was developed using data on actual cigarette and e-cigarette use patterns that quantifies transitions from an initial state of no cigarette or e-cigarette use to 1 of 5 final states: never use of cigarettes or e-cigarettes, cigarette use, e-cigarette use, dual use of cigarettes and e-cigarettes, or quit. Seven scenarios were created that cover a range of use patterns, depending on how the e-cigarette market might develop, as well as a range of possible long-term health effects of e-cigarette use. Scenarios for changes from the base case were evaluated using Monte Carlo simulations. Separate sets of base case model parameters were evaluated for the US and UK populations.

MAIN OUTCOMES AND MEASURES We assigned unitless health "costs" for each final state on a scale of 0 to 100. Population health "costs" were compared with the base case (status quo) assuming e-cigarette use health "costs" from 1% to 50% as dangerous as conventional cigarette use health costs.

RESULTS Compared with the base case, a harm reduction scenario in which e-cigarette use increases only among smokers who are interested in quitting with more quit attempts and no increased initiation of e-cigarette use among nonsmokers, and another scenario in which e-cigarettes are taken up only by youth who would have smoked conventional cigarettes, had population-level health benefits regardless of e-cigarette health costs in both the United States and United Kingdom. Conversely, scenarios in which e-cigarette promotion leads to renormalization of cigarette smoking or e-cigarettes are used primarily by youth who never would have smoked showed net health harms across all e-cigarette health costs. In other scenarios, the net health effect varied on the basis of the health cost of e-cigarettes.

CONCLUSIONS AND RELEVANCE According to this analysis, widespread promotion of e-cigarettes may have a wide range of population-level health effects, depending on both e-cigarette health risks and patterns of use. Absent the primary effect of e-cigarette promotion being only to divert current or future conventional cigarette smokers to e-cigarette use, the current uncertainty about the health risks of e-cigarettes, increasing e-cigarette use among youth, and the varying health effects at different e-cigarette health costs suggest a potential for harm.

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While cigarette smoking prevalence is declining in the United States¹ and United Kingdom,² use of electronic cigarettes (also known as e-cigarettes or electronic nicotine delivery systems [ENDS]) has been increasing among both youth^{3,4} and adults.^{4,5} e-Cigarettes are marketed as less harmful to health than cigarettes, alternatives to cigarettes where smoking is prohibited, and as smoking cessation aids.⁶⁻⁸ The idea that e-cigarettes might be effective for smoking cessation, and the fact that they deliver lower levels of many toxins than cigarettes,^{7,9} has some endorsing e-cigarettes for tobacco harm reduction.⁹⁻¹⁴

The actual effects of e-cigarettes on population health will depend on multiple competing factors, including effects on cigarette initiation and cessation, levels of dual use (concurrent use of conventional cigarettes and e-cigarettes), and product toxicity. The long-term health risks of e-cigarettes remain to be defined,⁷ and actual use patterns are still emerging. However, there is increasing pressure on policymakers and regulators, including the US Food and Drug Administration,¹⁵ to make decisions about e-cigarettes now.

While some hope that e-cigarette use can promote smoking cessation or shift smokers to less toxic products,^{11,16,17} others worry that many youth will initiate nicotine addiction and that use of e-cigarettes will discourage successful smoking cessation.¹⁸⁻²⁰ Entry of the major cigarette companies into the e-cigarette market and lack of meaningful e-cigarette regulation^{7,18} further complicate the situation. We modeled a range of alternative scenarios to evaluate the potential health risks of increasing promotion and use of e-cigarettes in the United States and United Kingdom, highlighting the range of possible health outcomes and the effects of key variables, most notably long-term e-cigarette use health risks and rates of initiation among non-tobacco users and current cigarette smokers, on future population health.

Methods

A decision tree model, similar to the one that Mejia et al²¹ used to evaluate possible outcomes of promoting smokeless tobacco use for harm reduction, was developed by determining possible pathways in patterns of cigarette and e-cigarette use from an initial state of no product use to 5 final states: never use of cigarettes or e-cigarettes, cigarette use, e-cigarette use, dual use of cigarettes and e-cigarettes, or quit (Figure 1). It models the steady state after behavior changes and changes in product use patterns have been made in the real world and the emerging e-cigarette market has stabilized. This model was used in Monte Carlo simulations to estimate the health effects associated with a base case (simulating the status quo) and 7 alternative scenarios, covering a spectrum of population use patterns, depending on how the e-cigarette market develops,²² and what the long-term health effects of e-cigarettes turn out to be.

The Model

Following standard practice, we define current cigarette smoking as smoking at least 100 cigarettes per lifetime with most recent use in the past 30 days, and current e-cigarette use as

e-cigarette use on at least 1 of the past 30 days.²³ Dual use is defined as past 30-day use of both cigarettes and e-cigarettes. Those who initiate tobacco use with cigarettes are divided into those who are and are not interested in quitting smoking, with further division into subgroups based on e-cigarette use among those not interested in quitting and, for those interested in quitting, use of other tools for cessation (Figure 1).

The Base Case

The base case was created by assigning transition probabilities to each pathway in the tree on the basis of 2013 national estimates of cigarette use prevalence, e-cigarette use prevalence, quit ratios, and e-cigarette and cigarette use patterns among youth and adults. Most of these estimates are normally distributed; those with point estimates of transition probability of 0.5% or less are lognormally distributed. Table 1 presents the transition probabilities for the US and UK base cases.

Because most adult e-cigarette users are current or former smokers,^{5,32,36} e-cigarette initiation from nonusers was estimated to be from youth.^{25,26} As of June 2015, to our knowledge, there were no longitudinal studies on behavior of never smokers who initiate e-cigarette use. Therefore, patterns were based on susceptibility to use cigarettes among never smoking youth who use e-cigarettes and the ratio of current to ever e-cigarette use in this population.^{25,27,29}

In 2013, 17.8% of the US population currently used cigarettes,¹ and as of 2012, 21% were former smokers,²⁴ with a quit ratio of 55%.³⁷ Of the majority of current smokers (69%) who were interested in quitting in 2010, 75% made a quit attempt.³⁰ The prevalence of "every day" or "some day" e-cigarette use in the adult US population was 1.9% in 2012 through 2013.²³ In 2013, 19% of the UK population currently used cigarettes,² the quit ratio was 54%,² and current e-cigarette use prevalence was 3%.⁴

Health Costs

Following Mejia et al,²¹ we assigned unitless health "costs" for each final state on a scale of 0 to 100, with 0 for never product users and 100 for current cigarette smokers. Former smokers were assigned a health cost of 10, given that with more years of abstinence from smoking cigarettes, health risks associated with smoking approach those of nonsmokers, but risk of some malignant neoplasms and heart disease can exceed that of nonsmokers for more than 10 to 20 years after cessation.³⁸ Health costs were lognormally distributed; the same health costs were used in the US and UK models.

To bracket the unknown health risk of e-cigarette use, we investigated a range of possible e-cigarette use health costs from 1 (ie, 1% as harmful as current cigarette smoking) to 50 (ie, half as dangerous as conventional cigarette use) on the grounds that exposure to ultrafine particles^{7,39,40} and nicotine⁴¹ causes heart and noncancer lung disease, which, together, account for 56% of smokers' mortality.^{42(p668)}

Dual use of e-cigarettes and cigarettes was assigned a health cost of 95 on the assumption that e-cigarette users would consume fewer conventional cigarettes, which might lower cancer risk but is unlikely to affect cardiovascular risk,⁷ which is elevated with smoking even a few cigarettes a day.⁴³

Figure 1. Decision Tree Model and Mean Transition Probabilities for the Base Case



See Table 1 for the associated standard errors. NRT indicates nicotine replacement therapy.

Table 1. Transition Probabilities of the Base Case

	United States		United Kingdom	
Pathway	Probability (SE) ^a	Source	Probability (SE) ^a	Notes
Initiation				
To cigarette smokers	0.39 (0.01)	61% of US adults have never smoked >100 cigarettes, 18% are current smokers, 21% are former smokers ^{1,24}	0.42 (0.01)	58% of adults in the United Kingdom have never smoked cigarettes, 19% are current smokers, 23% are former smokers ²
To never use	0.60 (0.01)		0.57 (0.01)	
To e-cigarette initiators	0.01	0.9% of never-cigarette-smoking middle and high school students from 2011-2013 ever used e-cigarettes ²⁵	0.01	4% of never-cigarette-smoking Scottish youth have ever used e-cigarettes, 1% of whom tried e-cigarettes a few times ²⁶
e-Cigarette Use				
To quit	0.63 (0.01)	Among middle and high school students who never smoked cigarettes, intention to smoke cigarettes was 43.9% in ever e-cigarette users vs 21.5% in never users. ²⁵ The difference (22.4%) was divided among cigarette-only users and dual users. Approximately 1/3 of ever e-cigarette users among middle and high school students are current users. ²⁷ Among high school students, 17% used e-cigarettes only, 12% were dual users, 3% used cigarettes only, and 68% were nonusers ²⁸	0.72 (0.01)	Roughly 27.3% of never-smoking 10- to 11-year-olds in Wales who had ever used an e-cigarette were susceptible to start smoking cigarettes, compared with 8.7% of those who had never used an e-cigarette. ²⁹ The difference (18.6%) was divided among cigarette-only users and dual users. Roughly 25% of youth in the United Kingdom who have ever used e-cigarettes use them monthly or weekly ⁴
To cigarettes	0.04		0.03	
To e-cigarettes	0.15 (0.01)		0.11 (0.01)	
To dual user	0.18 (0.07)		0.14 (0.06)	
Cigarette Use				
No quit intent	0.31 (0.01)	69% of smokers interested in quitting in 2010 NHIS ³⁰	0.37 (0.01)	63% of smokers in the United Kingdom plan to quit smoking at all ³¹
Interested in quitting	0.69 (0.01)		0.63 (0.01)	
No Quit Intent				
Stable smoker	0.45	54% of daily smokers reported ever use of e-cigarettes in 2013 ³²	0.49	Adjusted to estimate current overall smoking prevalence (19%) and quit ratio (54%)
e-Cigarette trial	0.55 (0.02)		0.51 (0.02)	51% of smokers in the United Kingdom have ever tried e-cigarettes ⁴
e-Cigarette Use Not for Quitting				
To quit	0.65 (0.02)	Adjusted to estimate current overall smoking prevalence (18%), e-cigarette use prevalence (2%), and quit ratio (55%). More than 2/3 of current e-cigarette users are current cigarette smokers ³²	0.55 (0.02)	Adjusted to estimate current overall smoking prevalence (19%), e-cigarette use prevalence (3%), and quit ratio (54%). More than 2/3 of current e-cigarette users are current cigarette smokers ²
To cigarettes	0.18 (0.02)		0.18 (0.02)	
To e-cigarettes	0.05		0.07 (0.02)	
To dual user	0.12 (0.02)		0.20 (0.02)	
Interest in Quitting				
Quit attempt with e-cigarette	0.15 (0.01)	25% of those interested in quitting do not make quit attempt, 30% use NRT, and the remainder were unassisted ³⁰ ; 31% of those calling a quitline used an e-cigarette, approximately half using them for cessation ³³	0.18 (0.01)	Among adults in the United Kingdom, 22% currently use e-cigarettes and 83% cite quitting as a reason for starting use. ³⁴ Approximately 33% of adults in the United Kingdom who made at least 1 quit attempt in the past year reported using NRT over the counter in their attempt ³⁵
Quit attempt with NRT/medications	0.30 (0.01)		0.33 (0.01)	
Unassisted quit attempt	0.35 (0.01)		0.39 (0.01)	
No quit attempt	0.20 (0.01)		0.10 (0.01)	
Quit With e-Cigarette				
To quit	0.75 (0.02)	Adjusted to estimate current overall smoking prevalence (18%), e-cigarette use prevalence (2%), and quit ratio (55%)	0.75 (0.02)	Adjusted to estimate current overall smoking prevalence (19%), e-cigarette use prevalence (3%), and quit ratio (54%)
To cigarettes	0.12 (0.02)		0.10 (0.02)	
To e-cigarettes	0.05		0.05	
To dual user	0.08 (0.02)		0.10 (0.02)	
Quit With NRT and/or Medications				
To quit	0.80 (0.02)	Adjusted to estimate current overall smoking prevalence (18%), e-cigarette use prevalence (2%), and quit ratio (55%)	0.80 (0.02)	Adjusted to estimate current overall smoking prevalence (19%), e-cigarette use prevalence (3%), and quit ratio (54%)
To cigarettes	0.20 (0.02)		0.20 (0.02)	
To e-cigarettes	0		0	
To dual user	0		0	
Quit Unassisted				
To quit	0.70 (0.02)	Adjusted to estimate current overall smoking prevalence (18%), e-cigarette use prevalence (2%), and quit ratio (55%)	0.70 (0.02)	Adjusted to estimate current overall smoking prevalence (19%), e-cigarette use prevalence (3%), and quit ratio (54%)
To cigarettes	0.30 (0.02)		0.30 (0.02)	
To e-cigarettes	0		0	
To dual user	0		0	

(continued)

Table 1. Transition Probabilities of the Base Case (continued)

Pathway	United States		United Kingdom	
	Probability (SE) ^a	Source	Probability (SE) ^a	Notes
No Quit Attempt				
To quit	0	2010 NHIS: 25% of those interested in quitting made quit attempt ³⁰	0	Adjusted to estimate current overall smoking prevalence (19%), e-cigarette use prevalence (3%), and quit ratio (54%)
To cigarettes	1.00		1.00	
To e-cigarettes	0		0	
To dual user	0		0	

Abbreviations: NHIS, National Health Interview Survey; NRT, nicotine replacement therapy.

^a Estimates that were fixed did not have a standard error associated with them.

Table 2. Detailed Description of 7 Scenarios

Scenario	Effect on e-Cigarette Initiation by Nonsmokers	Effect on Interest in Quitting Among Smokers	Effect on e-Cigarette Use for Cessation Among Smokers
10% Absolute increase in e-cigarette use from cigarette initiators	Increase 10% (from 1% in the base case to 11%): all from those who would have started smoking cigarettes; 10% reduction in cigarette initiation	No change	No change
Harm reduction	No change	Increases by 20%	Doubles: 50% from those who would have made an unassisted quit attempt, 50% from those who would not have made a quit attempt
Decreased quit intentions with increased e-cigarette use for cessation	Doubles: 80% from those who would have started smoking cigarettes, 20% from never users	Decreases by 20%	Doubles: 1/3 from those who would have made an unassisted quit attempt, 1/3 from those who would have used NRT, and 1/3 from those who would not have made a quit attempt
5-Fold increase in e-cigarette initiation	Increase 5 times: 2/3 from those who would have started smoking cigarettes, 1/3 from never users	Decreases by 20%	Doubles: 1/3 from those who would have made an unassisted quit attempt, 1/3 from those who would have used NRT, and 1/3 from those who would not have made a quit attempt
Aggressive promotion	Increase 10 times: 50% from those who would have started smoking cigarettes, 50% from never users	Decreases by 25%	Triples: 1/3 from those who would have made an unassisted quit attempt, 1/3 from those who would have used NRT, and 1/3 from those who would not have made a quit attempt
Renormalization of smoking	Doubles: 50% from those who would have started smoking cigarettes, 50% from never users	Decreases by 25%	No change
10% Absolute increase in e-cigarette use from never users	Increase 10% (from 1% in the base case to 11%): all from those who would have been never product users; 10% reduction in never use	No change	No change

Abbreviations: NHIS, National Health Interview Survey; NRT, nicotine replacement therapy.

Scenarios

Each of the 7 scenarios models changes from the base case in e-cigarette use initiation, transition from cigarette to e-cigarette or dual use, and quitting, and reflects different ways that e-cigarette promotion could lead to increased product use, including estimates of the growth of the industry in the next few years some health^{11,18,22} or business⁴⁴ authorities have predicted. A brief description of each scenario follows, with more detailed descriptions in Table 2. The same scenarios were used for both the United States and the United Kingdom beginning from different base cases.

A 10% Absolute Increase in e-Cigarette Use From Cigarette Use Initiators

In this scenario, promotion and marketing of e-cigarettes diverts initiating cigarette smokers to e-cigarette use. There is a 10% absolute increase in e-cigarette initiation (ie, from 1% initiation in the base case to 11% initiation) and a corresponding 10% absolute reduction in initiating cigarette smokers. There is no effect on established cigarette smokers.

Harm Reduction

This scenario models what has been called the “best-case scenario,”²² in which e-cigarette use increases only among smokers, leading to increased interest in quitting and increased quit attempts among smokers who had not previously tried to quit, with no increased initiation of e-cigarette use among nonusers.

Decreased Quit Intentions With Increased e-Cigarette Use for Cessation

In this scenario, e-cigarette use patterns differ among smokers, with some using e-cigarettes for cessation and others continuing to smoke while using e-cigarettes in smokefree areas. On the basis of a study⁴⁵ in which intensive e-cigarette use (daily use for 1 month) was associated with smoking cessation whereas intermittent e-cigarette use (regular but non-daily use) was negatively associated with an indicator of motivation to quit, overall quit intentions among smokers in this scenario decrease by 20% while use of e-cigarettes for cessation doubles. An equal proportion of individuals now using

e-cigarettes for cessation come from those who would have made an unassisted quit attempt, those who would have used nicotine replacement therapy, and those who never would have made a quit attempt. e-Cigarette initiation doubles, mostly (80%) from people who would have started smoking cigarettes because 80% of middle school students who have ever used e-cigarettes have reported ever smoking cigarettes.³

A 5-Fold Increase in e-Cigarette Initiation

Following business projections that anticipate e-cigarette sales increasing from \$2 billion in 2013 to \$10 billion in 2017,⁴⁴ there is a 5-fold increase in e-cigarette initiation (one-third from never product users and two-thirds from initiating cigarette smokers). Similar to the previous scenario, there is a 20% decreased interest in quitting among smokers due to an increase in e-cigarette use in smokefree areas, and a doubling of e-cigarette use for cessation.

Aggressive Promotion

This scenario evaluates a greater increase in e-cigarette promotion, with a 10-fold increase in e-cigarette initiation (50% from never product users and 50% from initiating cigarette smokers, assuming greatly increased exposure of nonusers to e-cigarette advertising and products). Interest in quitting among smokers decreases by 25% while e-cigarette use for cessation increases 3-fold.

Renormalization of Smoking

This scenario assumes that increased promotion of e-cigarettes as alternatives to cigarettes and the tobacco industry's increasing involvement in the e-cigarette industry counter efforts to denormalize smoking in society. There is a doubling in e-cigarette initiation (50% from never product users and 50% from initiating cigarette smokers), a decrease in interest in quitting among smokers by 25%, and no change in use of e-cigarettes for cessation.¹⁷

A 10% Absolute Increase in e-Cigarette Initiation From Never Tobacco Users

This scenario models what has been deemed an unintended consequence of e-cigarette promotion for harm reduction,¹⁹ which is uptake of the product by many youth who never would have used tobacco. There is a 10% absolute increase in e-cigarette initiation and a corresponding 10% absolute reduction in never users. There is no effect on established cigarette smokers.

Monte Carlo Simulations

Monte Carlo simulations were run 100 000 times for each scenario to account for uncertainty in the transition probabilities (Table 1) and health costs. For each trial, a random set of parameter values for the base case was generated by the Crystal Ball software, version 11.1 (Oracle Software), based on the probability distributions defined in Table 1, and the total health cost is then calculated. The transition probabilities were modified according to each scenario, and the corresponding health costs were computed.

We computed the percentage of trials in each scenario showing a net health benefit or deficit compared with the base

case by subtracting the health cost of the base case from the health cost of each scenario for each of the 100 000 simulations. The net health effect was calculated by subtracting the percentage of trials with a health cost higher than the base case from the percentage with a health cost lower than the base case. This process was repeated for a range of e-cigarette health costs. A seed value of 999 was used for all calculations. Excel spreadsheets implementing the models, scenarios, and sensitivity analysis are available in supporting Excel files eSpreadsheet1 in [Supplement 1](#) and eSpreadsheet2 in [Supplement 2](#).

Sensitivity Analysis

Sensitivity analyses assessed the effect of the assumptions in the base case, the variable factors in the scenarios, and the health cost of each final state on the total health cost for each scenario by calculating the percentage of variance in the total health cost associated with changes in the values of the transition probabilities, health costs, and changes made in these values. Thus, the sensitivity analysis simultaneously considers the transition probabilities in the decision tree (Figure 1) and the changes to these transition probabilities assumed in the 7 scenarios. Transition probabilities were assumed to be normally distributed unless the point estimates were 0.5% or less, in which case they were assumed to be lognormally distributed. The health costs were lognormally distributed, and the between-scenario factors and base health cost of e-cigarettes were uniformly distributed over the range of possible values.

Results

The distributions of total health costs (including their 5th to 95th percentiles) for the base case and all scenarios at different e-cigarette health costs are summarized in [Table 3](#).

Base Case

The base case simulation for the United States yielded a prevalence of cigarette smoking of 18.2% (16.9% for cigarette only use plus 1.3% dual use), which is similar to the observed US adult cigarette smoking prevalence of 17.8%. The base case simulation for the United Kingdom yielded a total cigarette smoking prevalence of 19.2% (17.0% for cigarettes only plus 2.2% dual users), similar to the observed 19% smoking prevalence. The total health costs for the base case were 20.3 to 20.7 for the United States and 21.4 to 21.9 for the United Kingdom, depending on the e-cigarette health cost (Table 3).

Alternative Scenarios

The total health cost distribution for the harm reduction scenario is shifted down compared with the base case. This and the scenario of 10% absolute increase in e-cigarette initiation, all from those who would have been cigarette smokers, show a net health benefit at all e-cigarette health costs for both the United States and United Kingdom (Figure 2, Table 3). In contrast, in the scenarios of renormalization of smoking or 10% absolute increase in e-cigarette initiation, all from those who would have been never product users, there is a net health deficit at all e-cigarette health costs for both the United States and United Kingdom (Figure 2).

Table 3. Product Use Patterns and Distributions of Total Health Costs for the Base Case and 7 Scenarios for the United States and United Kingdom

Scenario	%					Mean Total Health Cost (5th-95th Percentile)			
	Never Use	Quit	Cigarette Use	e-Cigarette Use	Dual Use	e-Cigarette Cost = 1	e-Cigarette Cost = 10	e-Cigarette Cost = 25	e-Cigarette Cost = 50
United States									
Base case	59.9	21.1	16.9	0.7	1.3	20.3 (18.9-22.5)	20.4 (19.0-22.6)	20.5 (19.1-22.7)	20.7 (19.2-22.9)
10% Absolute increase in e-cigarette use from cigarette use initiators	59.9	22.4	12.8	2.1	2.8	17.7 (15.9-20.2)	17.9 (16.1-20.3)	18.2 (16.4-20.6)	18.7 (17.0-21.1)
Harm reduction	59.9	24.3	13.5	0.8	1.4	17.3 (15.7-19.8)	17.3 (15.7-19.9)	17.5 (15.9-20.0)	17.7 (16.1-20.2)
Decreased quit intentions with increased e-cigarette use for cessation	59.7	20.9	16.3	1.1	2.0	20.3 (18.8-22.5)	20.4 (18.9-22.6)	20.5 (19.1-22.8)	20.8 (19.4-23.0)
5-Fold increase in e-cigarette use initiation	58.5	22.0	15.4	1.6	2.5	20.0 (18.4-22.4)	20.2 (18.6-22.5)	20.4 (18.9-22.8)	20.8 (19.3-23.2)
Aggressive promotion	55.0	24.8	13.9	2.5	3.7	19.9 (18.0-22.7)	20.2 (18.2-22.9)	20.5 (18.6-23.3)	21.2 (19.3-24.0)
Renormalization of smoking	59.4	19.9	17.8	1.0	1.9	21.6 (20.2-23.7)	21.7 (20.3-23.8)	21.8 (20.4-24.0)	22.1 (20.7-24.2)
10% Absolute increase in e-cigarette use from never users	49.9	27.6	17.1	2.2	3.1	22.8 (20.8-25.8)	23.0 (21.0-26.0)	23.4 (21.4-26.3)	23.9 (21.9-26.9)
United Kingdom									
Base case	56.9	22.9	17.0	0.9	2.2	21.4 (19.9-23.8)	21.5 (20.0-23.9)	21.6 (20.1-24.0)	21.9 (20.3-24.3)
10% Absolute increase in e-cigarette use from cigarette use initiators	56.9	25.0	13.1	1.8	3.1	18.5 (16.7-21.2)	18.7 (16.9-21.4)	19.0 (17.2-21.7)	19.4 (17.6-22.1)
Harm reduction	56.9	27.3	12.4	1.1	2.3	17.3 (15.6-20.2)	17.4 (15.7-20.2)	17.6 (15.8-20.4)	17.8 (16.1-20.7)
Decreased quit intentions with increased e-cigarette use for cessation	56.7	22.2	16.6	1.4	3.1	21.8 (20.3-24.2)	21.9 (20.4-24.3)	22.1 (20.6-24.5)	22.5 (21.0-24.8)
5-Fold increase in e-cigarette use initiation	55.5	23.5	15.8	1.7	3.5	21.5 (19.8-24.0)	21.6 (19.9-24.1)	21.9 (20.2-24.4)	22.3 (20.6-24.8)
Aggressive promotion	52.0	26.8	14.2	2.4	4.5	21.2 (19.1-24.1)	21.4 (19.4-24.3)	21.8 (19.8-24.6)	22.4 (20.4-25.2)
Renormalization of smoking	56.4	20.9	18.6	1.2	2.9	23.5 (22.0-25.7)	23.6 (22.1-25.8)	23.8 (22.3-26.0)	24.1 (22.6-26.3)
10% Absolute increase in e-cigarette use from never users	46.9	30.3	17.1	2.0	3.6	23.6 (21.5-26.8)	23.8 (21.7-27.0)	24.1 (22.0-27.3)	24.6 (22.5-27.8)

Two scenarios (aggressive promotion and 5-fold increase in e-cigarette initiation) have net population level health effects that are between the 2 extremes for both the United States and the United Kingdom, although they are worse in the United Kingdom at any given e-cigarette health cost. In both the US and UK models, whether there is a net population health benefit or deficit in the aggressive scenario depends on the ultimate health cost of e-cigarettes (Figure 2, Table 3). The 5-fold increase in e-cigarette initiation scenario can have a population level health benefit or deficit in the United States depending on the health cost of e-cigarettes but is always at a deficit for the UK model. In the scenario in which there is decreased quit interest but increased e-cigarette use to quit among smokers, there is a slight health benefit at lower e-cigarette health costs in the United States and a net health deficit at all e-cigarette health costs for the United Kingdom.

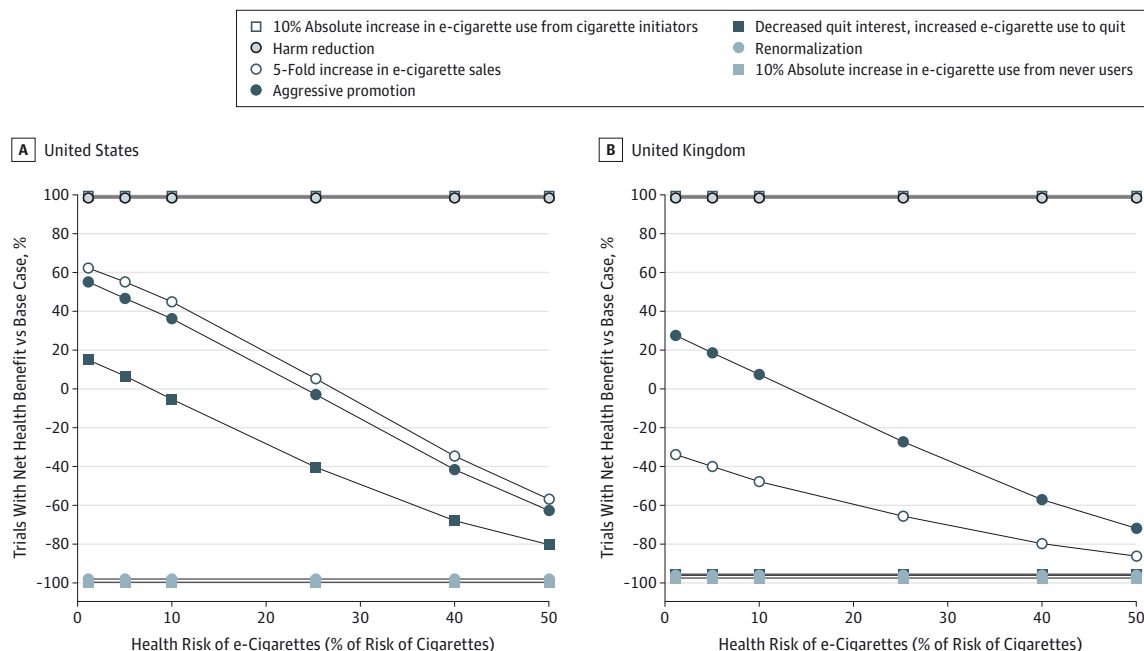
Sensitivity Analysis

In the overall model sensitivity analysis for both the United States and United Kingdom, the dominant assumption was the quitting health cost, followed by the e-cigarette health cost and the increase in interest in quitting among smokers. All other assumptions accounted for less than 10% of the variance.

Discussion

Our results suggest the importance of the (currently unknown) health risks of e-cigarettes in determining overall population health effects. For benefit across many e-cigarette health costs in both the US and UK models, most e-cigarette users need to be either current smokers interested in cessation (particularly smokers who had not previously attempted to quit) or people who

Figure 2. Probability of Each Scenario Having Net Health Benefit vs the Base Case as a Function of Mean e-Cigarette Health Costs



Percentages were calculated by subtracting the total percentage of trials in each scenario having a net health deficit from the total percentage of trials in each scenario having a net health benefit. The topmost scenarios always lead to lower population health costs, and the bottommost scenarios always lead to negative costs (lines for 10% absolute increase in e-cigarette use from cigarette

initiators, harm reduction, renormalization, and 10% absolute increase in e-cigarette use from never users in both the US and UK graphs are slightly shifted for display, as well as the line for decrease quit interest and increase e-cigarette use to quit in the UK graph; these are actually 99%-100%). (See Table 3 for prediction intervals for these curves.)

would have become cigarette users. These scenarios divert many people from smoking cigarettes to using e-cigarettes or quitting product use altogether, both of which have decreased health costs compared with smoking cigarettes and do not result in substantial e-cigarette use by never smokers. Conversely, if e-cigarettes lead to reversal of smoking denormalization and use is primarily in smokefree areas rather than for promotion of cessation, or a large number of youth who never would have smoked cigarettes start using the product, population-level harm is likely regardless of how harmful e-cigarettes turn out to be. These negative results occur because these scenarios include continued use of cigarettes among smokers, and e-cigarette use among individuals who never would have used cigarettes, which are more harmful than smoking cessation and never e-cigarette use, respectively.

For other scenarios (5-fold increase in e-cigarette initiation, aggressive promotion, decreased interest in quitting but increased e-cigarette use to quit), population-level health effects differ between the United States and United Kingdom and depend on e-cigarette health cost. The 5-fold increase in e-cigarette initiation and aggressive promotion scenarios have variable levels of health benefit or deficit depending on the health cost of e-cigarettes in both the United States and United Kingdom, but the net population health effect is always worse in the United Kingdom. While the decreased interest in quitting scenario shows a small net population health benefit at lower e-cigarette costs in the United States, it is always associated with a health deficit in the United Kingdom. These relatively negative outcomes in

the United Kingdom are because of higher baseline prevalence of cigarette smoking and e-cigarette use.

To date, e-cigarette safety assessment has focused primarily on chemical contents.⁴⁶⁻⁴⁹ e-Cigarettes generally contain lower levels of carcinogens, volatile organic compounds, and tobacco-specific nitrosamines than conventional cigarettes⁴⁷⁻⁴⁹ but more than US Food and Drug Administration-approved nicotine inhalers, a form of nicotine replacement therapy.⁴⁷ Diacetyl, an organic compound associated with respiratory disease, has been found at levels higher than deemed safe for exposure in many sweet-flavored e-cigarettes.⁵⁰ e-Cigarettes deliver ultrafine particles at levels comparable to or higher than cigarettes.³⁹ Ultrafine particles from cigarettes increase risk of cardiovascular disease⁵¹ and noncancer pulmonary disease.⁵² It will probably be several years before the combined health effects of these differences are determined.

If e-cigarette users defer cigarette quit attempts, it could lead to dual use of cigarettes and e-cigarettes. This carries higher health risk than complete tobacco abstinence, particularly for cardiovascular disease: risk of disease is increased even in those who smoke a few cigarettes per day,⁴³ and relative risk of mortality increases more sharply at low levels of exposure to fine particulate matter (such as from cigarette smoke) than higher levels.⁵¹

Increased e-cigarette marketing and promotion will expose more youth to these products. In 2014, hundreds of e-cigarette brands and thousands of different flavors were available online.⁶ Advertising expenditures by e-cigarette compa-

nies have been increasing in the United States⁵³ and United Kingdom.⁵⁴ Youth and young adults in the United States were increasingly exposed to e-cigarette television advertisements between 2011 and 2013,⁵⁵ and ever use and past-30-day use of e-cigarettes increased among US middle school and high school students during this time.^{3,56} Data from the 2014 Monitoring the Future study, a large US national study of adolescents, shows that e-cigarette use is surpassing conventional cigarette use in this population.⁵⁷

Which of these scenarios ultimately materializes will depend on the regulatory environment, including whether e-cigarette use is included in smokefree laws and regulations, what, if any, restrictions there are on advertising and promotion, and where and to whom e-cigarettes can be sold (including on the Internet). The probability of the more positive scenarios developing will be maximized if mass marketing of e-cigarettes is prohibited and promotion of e-cigarettes is limited to direct-to-consumer advertising directed at confirmed smokers.⁵⁸ Another alternative would be to limit availability of e-cigarettes to by prescription to smokers using them as part of a supervised smoking cessation program. For other scenarios, the health cost of e-cigarettes will be an important determinant in their population-level health effects (Figure 2).

This study is subject to a number of limitations. e-Cigarettes have only been available for a few years, and awareness and use patterns continue to evolve. Our simulations are based on current smoking behaviors among the general US and UK adult population and therefore may not be generalizable to specific populations with higher smoking prevalence, such as

those with mental illness. This is a model of the steady state after behavior changes and the market has stabilized rather than the dynamics of reaching that steady state. Given the short time on the market, long-term studies on use patterns, particularly among youth initiating e-cigarettes, are not available. These results are based on the US and UK markets and may not apply to other countries with different regulatory and marketing environments. As evidenced by the differences between the United States and United Kingdom, starting prevalences of cigarette and e-cigarette use are important in determining how different scenarios play out in different nations. As additional studies become available, or data from other countries are used, the transition probabilities can be adjusted in the spreadsheet in supporting Excel files eSpreadsheet1 and eSpreadsheet2 in the Supplement.

Conclusions

The net health effects of expansion of the e-cigarette market will depend both on the relative toxicity of the product and how use, marketing, and promotion of e-cigarettes are regulated and how, as a result, overall use patterns change. Absent the primary effect of e-cigarette promotion being only to divert current or future conventional cigarette smokers to e-cigarette use, the current uncertainty about the health risks of e-cigarettes, increasing e-cigarette use among youth, and the varying health effects at different e-cigarette health costs suggest that potential for harm remains.

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