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Predicted Impacts of E-Cigarettes on US Mortality and Health Care Costs

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FDA guidance for MRTP applications requests estimation of morbidity as well as mortality impacts. How can we do this (without an overwhelming computation)?

1. Find recent cigarette-attributable healthcare costs and cigarette-attributable deaths for the same period.

2. Find the ratio: cigarette-attributable healthcare cost per cigarette-attributable death.

3. Multiply this by the predicted premature deaths avoided by the new product.

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Agenda: a model for avoided premature deaths, and extension to morbidity costs

- Model overview
- Cigarette smoking and CPD-Excess Risk modeling
- Output measures
- Sensitivity analysis
- Using avoided premature deaths to approximate avoided morbidity costs

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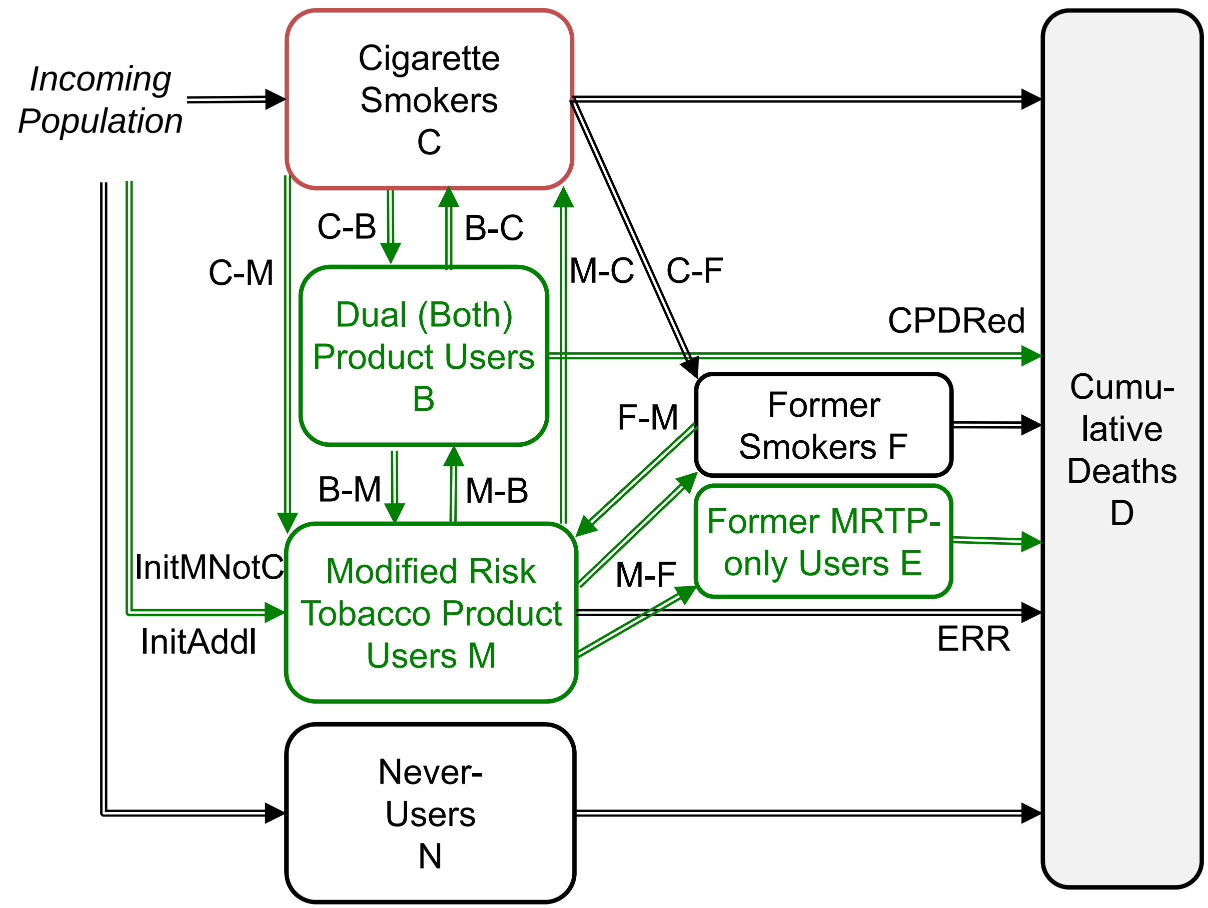
A “microsimulation” model simulated a population of 1 million over 2015-2100.

Loop to simulate each person *independently*. Inner loop steps through each year of the simulation period.

- **Initialize** each person by random draws from input distributions for age, sex, initial tobacco use status if already ≥ initiation age (C/F/N), and cigarettes per day (CPD) for ever-smokers.
- Each year after the first, increment age and **check if the person dies** that year, based on a random draw accounting for age, sex, and tobacco use history.
  - If so, end simulation of that person.
  - Otherwise, **update annual status** based on random draws:
    - If just reached initiation age (18), set initial status to C, M, or N.
    - C becomes B, M, or F, or remains C.
    - B becomes C or M, or remains B.
    - M becomes C, B, or F/E, or remains M.
    - F becomes M, or remains F.
    - E and N remain the same.



InitMNotC: would-be cigarette smokers who instead initiate an MRTP; InitAddl: would-be never-smokers who instead initiate an MRTP; CPDRed: reduction in CPD by dual users; ERR: Excess Relative Risk of death from the MRTP relative to cigarettes.

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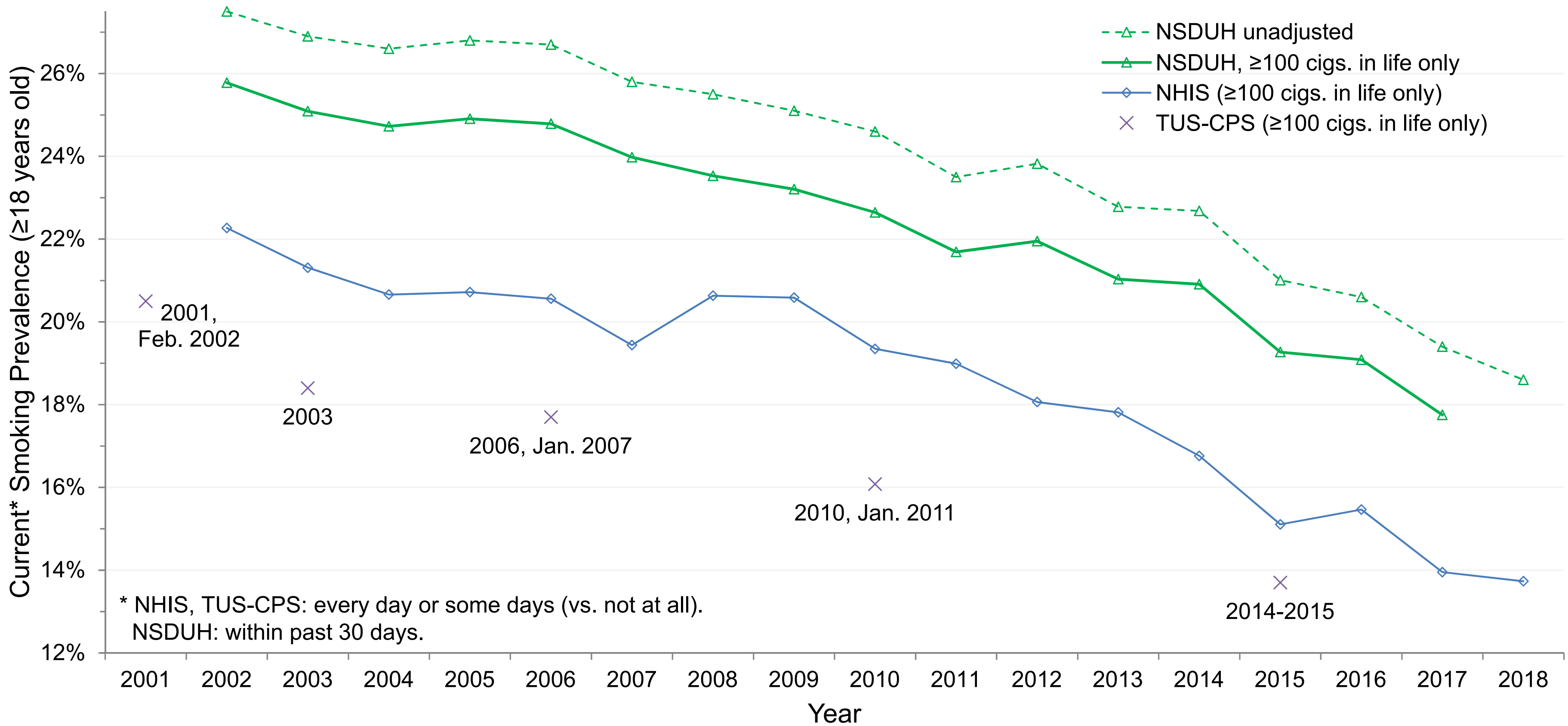
US smoking prevalence is declining faster in the e-cigarette era (last 5+ years).



NSDUH: National Survey on Drug Use and Health. NHIS: National Health Interview Survey.

Are e-cigarettes already lowering US smoking rates?

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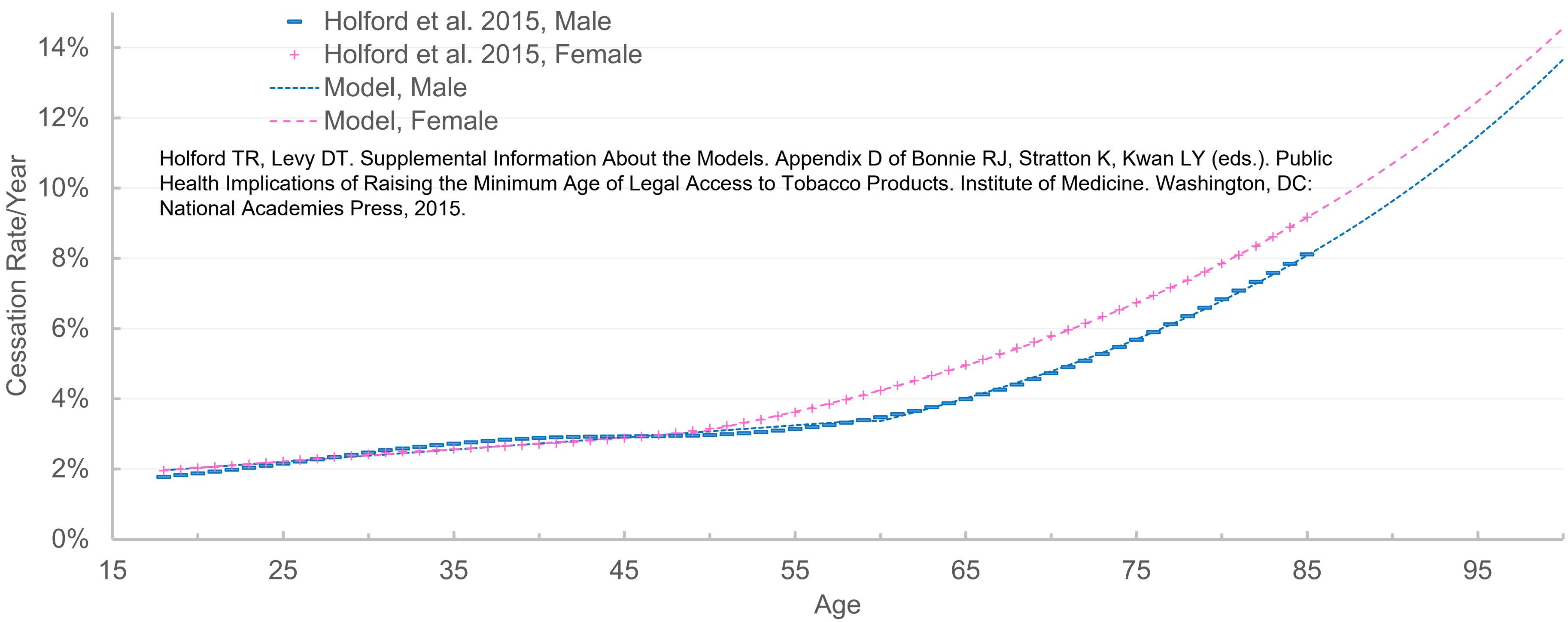
Cigarette cessation rate curves by age and sex were based on Holford et al. 2015. Initiation rates were based on NSDUH surveys.



Overall mean of 3.5% increased to 4.2% based on Mendez et al. 2017.*

Cigarette initiation rates used maximum NSDUH)smoking prevalence by age and sex through age 25, in the first model year (2015); thereafter, an annual decline was assumed, fitted to NSDUH data since 2002.

* Mendez D, Tam J, Giovino GA, et al. 2017. Has Smoking Cessation Increased? An Examination of the US Adult Smoking Cessation Rate 1990–2014. *Nicotine Tob Res*. 2017 Dec., 19(2):1418-1424

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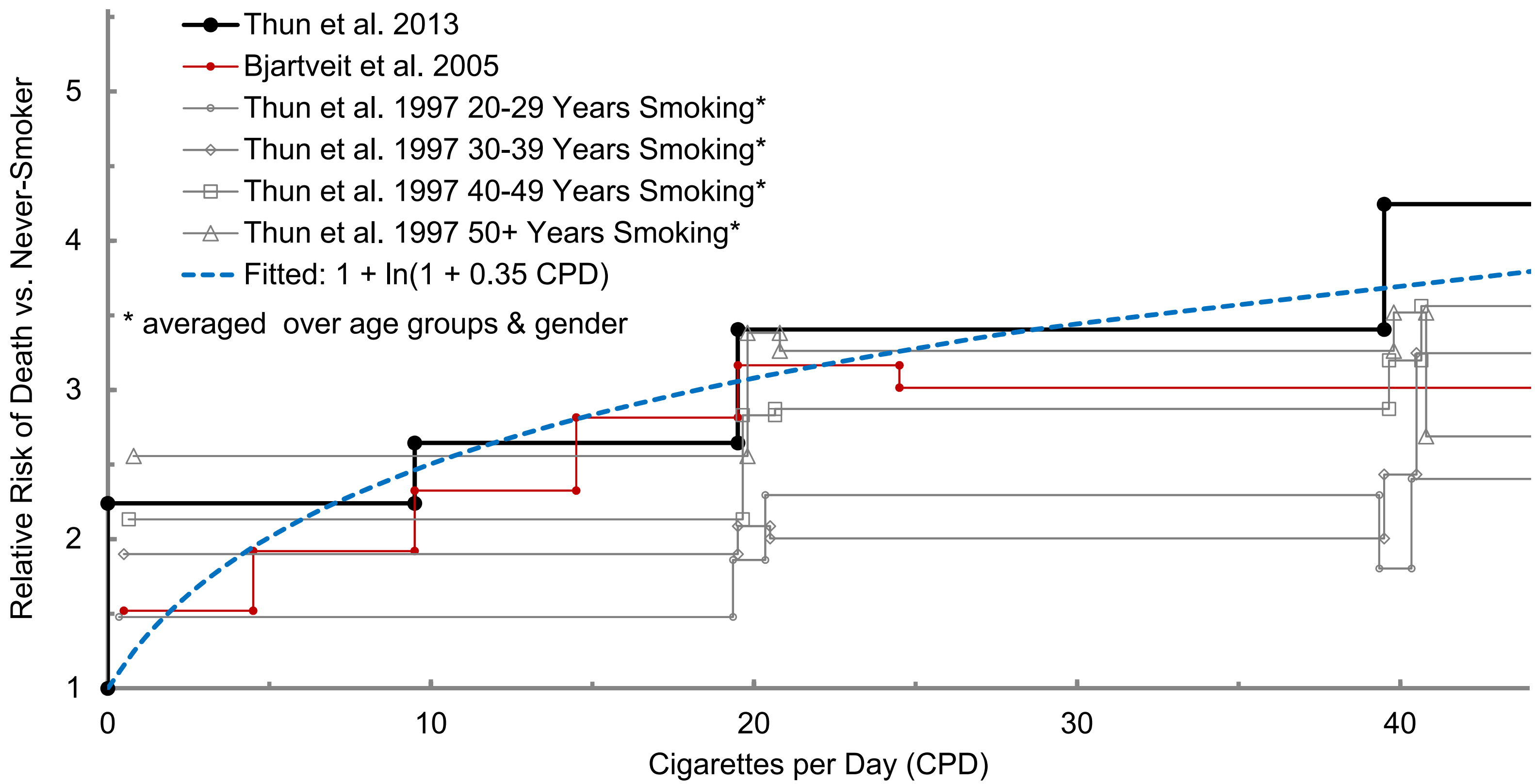
A simple relationship was assumed between CPD and Relative Risk (or Excess Risk ER = Relative Risk - 1).



Assumption: this curve applies to reducers as well as life-long smokers. For example, if a smoker with ER = 2.1 at 20 CPD reduces to 16 CPD while adding an MRTP with 10% ERR, ER becomes ln(1 + 0.35*16) + 10%(2.1) = 2.1: no net change.

Poland B, Teischinger F. Population Modeling of Modified Risk Tobacco Products Accounting for Smoking Reduction and Gradual Transitions of Relative Risk. *Nicotine Tob Res*. 2017 Nov 1;19(11):1277-1283.
Poland B, Larroque S. Does Reducing Cigarette Consumption Without Quitting Reduce Risk of Premature Death? Implications of a Model. SRNT Annual Meeting, San Francisco, CA, Feb. 20-23, 2019, Abstract POS2-90. https://www.jt-science.com/sites/default/files/2019-04/2019-p2.pdf

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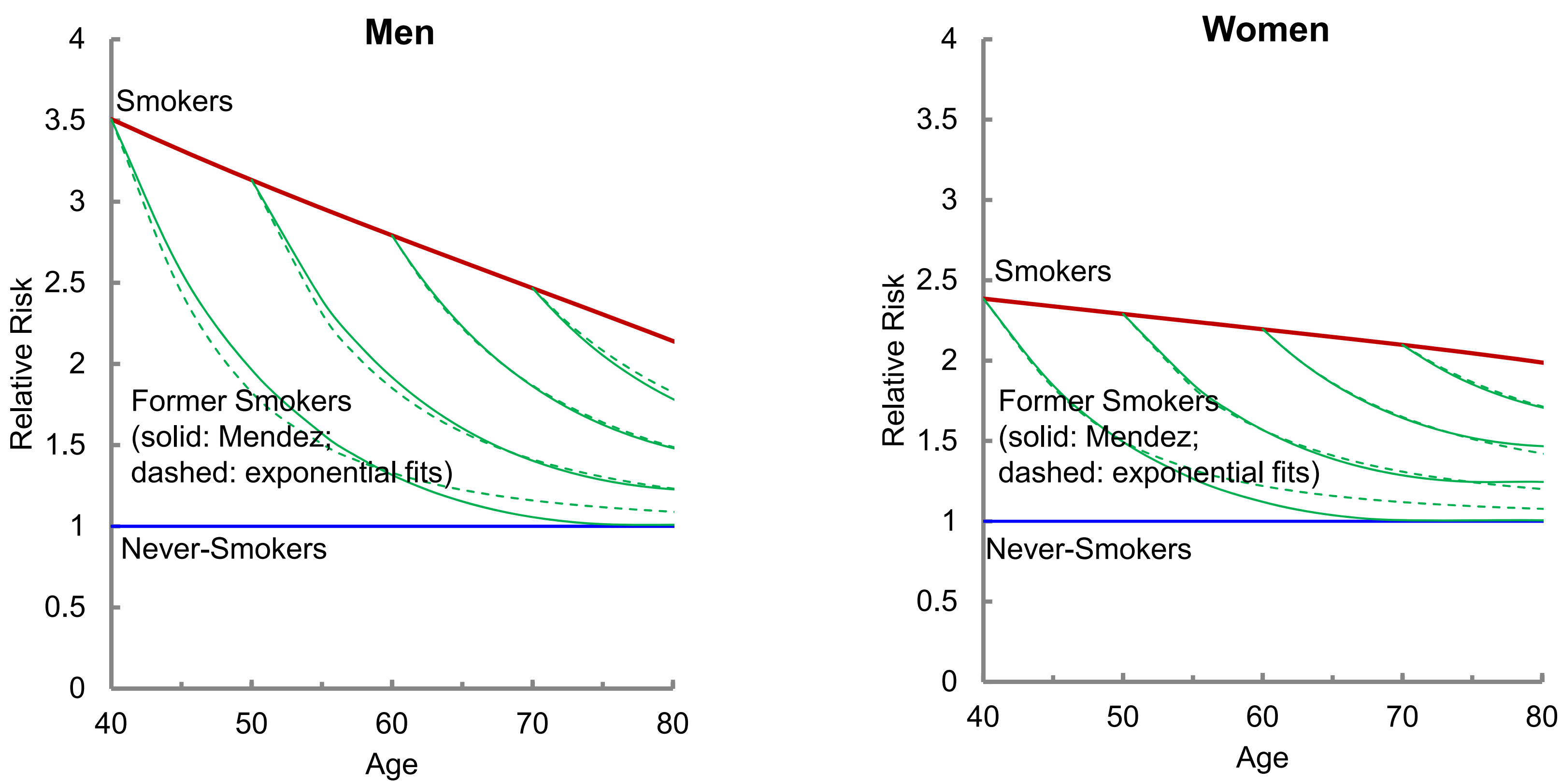
Relative Risk was modeled as declining exponentially after quitting, as a function of age and sex.



Mendez D, Warner KE 2001. The relative risk of death for former smokers: the influence of age and years-quit. Unpublished research monograph.
www.umich.edu/~dmendez/tobacco/RRiskmonograph.doc

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The same gradual Relative Risk (RR) change was applied to *any* change in RR (or ER).

- Excess Risk $ER(t) = ER(0) \exp(-k\,t) + ER_{eq}\,[1 - \exp(-k\,t)]$

  where ER_{eq} is equilibrium Excess Risk, and k is the exponential slope (a function of age and sex).
  - For a former smoker, $ER_{eq} = 0$, so $ER(t) = ER(0) \exp(-k\,t)$
  - For a new smoker, $ER(0) = 0$, so $ER(t) = ER_{eq}\,[1 - \exp(-k\,t)]$

- Thus, ER(*t*) always moves towards equilibrium (which is also changing).

- ER(*t*) was updated annually, providing a simple way to **account for a full tobacco product use history**.

Poland B, Teischinger F. Population Modeling of Modified Risk Tobacco Products Accounting for Smoking Reduction and Gradual Transitions of Relative Risk. *Nicotine Tob Res*. 2017 Nov 1;19(11):1277-1283

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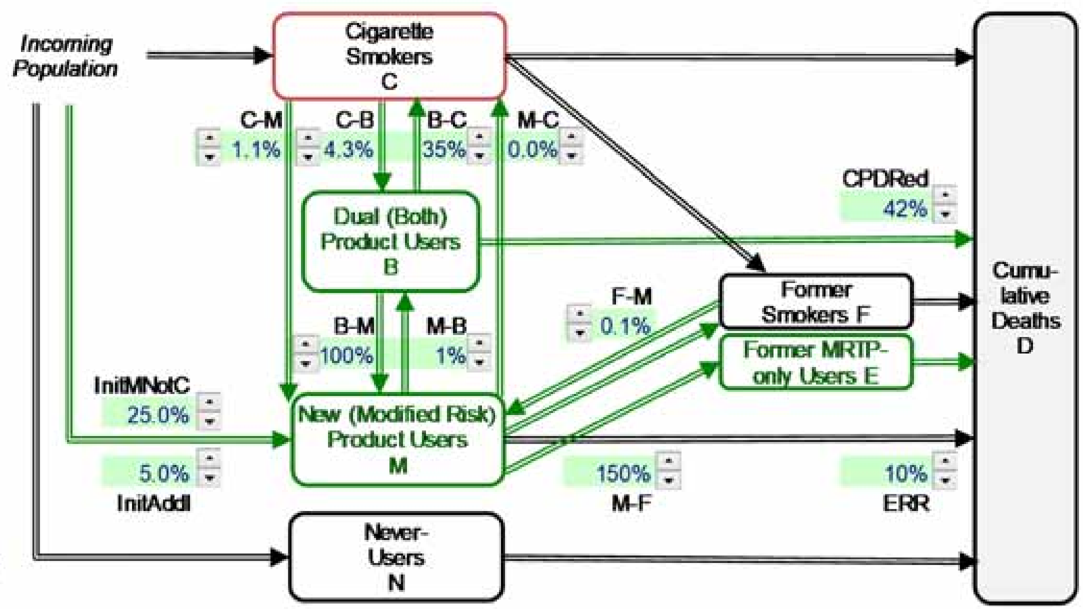
A dozen MRTP input parameters each had Low, Base, and High cases for sensitivity analysis.

Low	Base	High	
0%	25%	50%	1. **InitMNotC:** Would-be cigarette initiators who instead initiate MRTP (% of cigarette initiators in no-MRTP scenario)
0%	5%	10%	2. **InitAddl:** MRTP initiators--additional beyond would-be cig.-initiators (% of cig. initiators in no-MRTP scenario)
0.0%	0.1%	0.5%	3. **F-M:** Rate former smokers initiate (relapse to) MRTP (% of former cigarettes-only smokers/yr)
0%	4.3%	8.6%	4. **C-B:** Rate cigarette-only smokers add MRTP (% of cig-only smokers/yr)
0%	1%	2%	5. **M-B:** Rate MRTP (only) users add cigarettes (% of MRTP-only users/yr)
0%	42%	84%	6. **CPDRed:** Reduction in cig. use level by dual users (% of level without MRTP)
100%	150%	200%	7. **M-F:** Quit rate for MRTP (only) users (% of cigarette quit rate)
20%	35%	50%	8. **B-C:** Rate dual users quit MRTP (continuing cigarettes) (% of dual users/yr)
75%	100%	125%	9. **B-M:** Cigarette quit rate for dual users (% of cigarette-only quit rate)
5%	10%	25%	10. **ERR:** Proportion of cig. smoker Excess Risk experienced by MRTP users
0.0%	1.1%	2.2%	11. **C-M:** Rate cigarette-only smokers switch completely to MRTP (%/yr)
	0%	1%	12. **M-C:** Rate MRTP-only users switch completely to cigarettes (%/yr)



Simulate 1,000,000 individuals through year 2100

☑ Also simulate no MRTP
☐ Also simulate low & high ERR

By also simulating a no-MRTP scenario, we calculated Avoided Premature Deaths.

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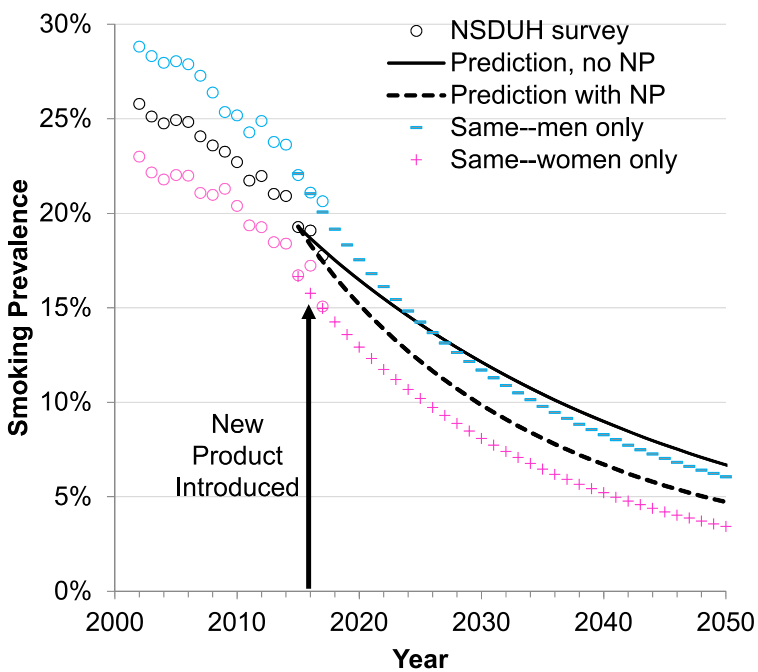
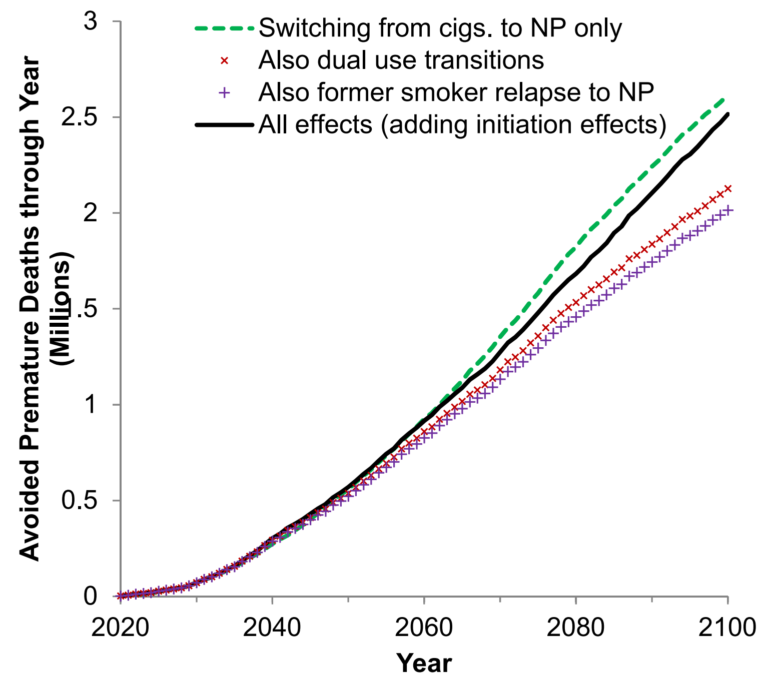
The model was validated with NSDUH prevalence data and used to project avoided premature deaths.

Avoided premature deaths = deaths occurring later *with* MRTP *minus* deaths occurring later *without* MRTP.

Comparison with data



Avoided premature death breakdown



Avoided total (cumulative) deaths don't work well in later years, because those whose deaths are avoided initially die eventually.

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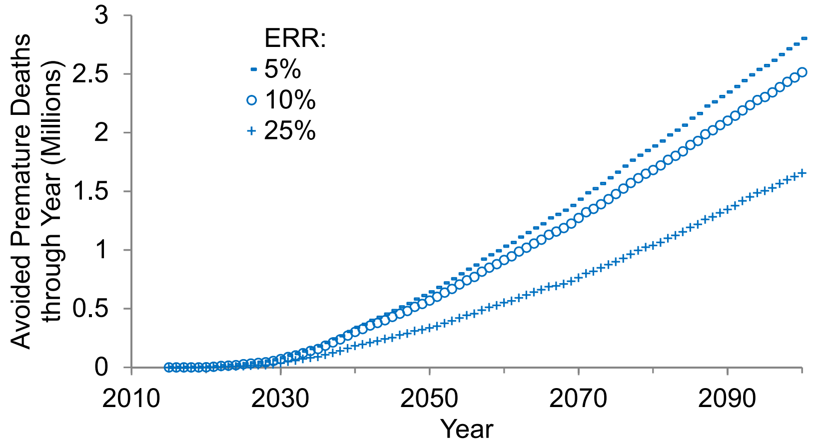
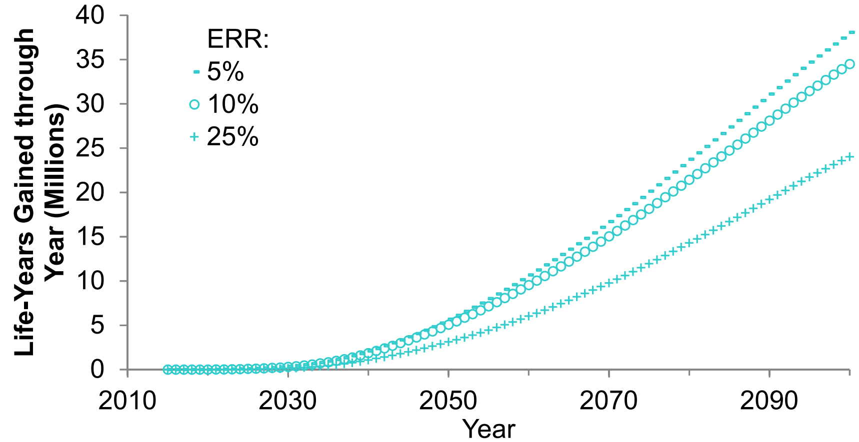
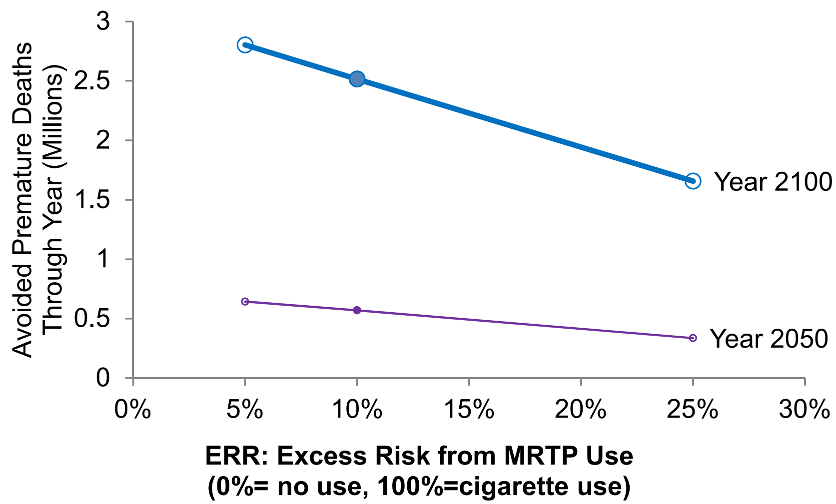
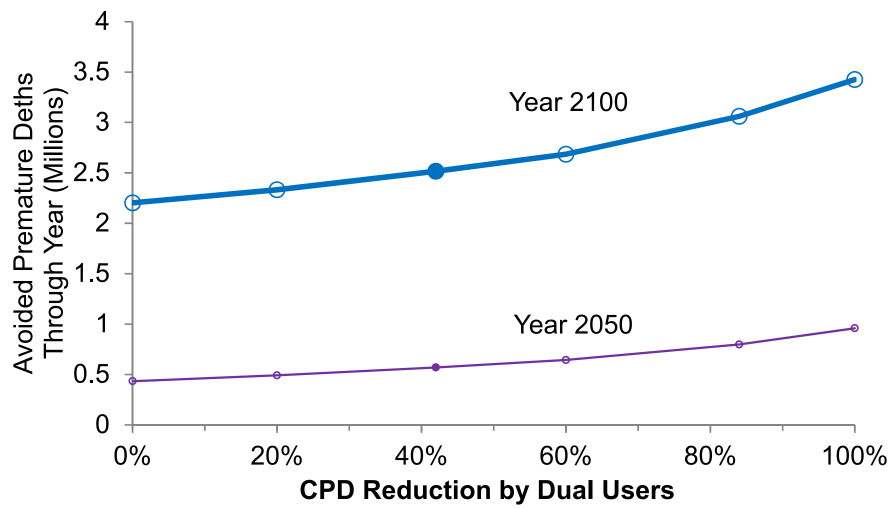
Outputs also include life-years gained and sensitivities to ERR (remarkably linear, allowing quick approximation of break-even) and to CPD.









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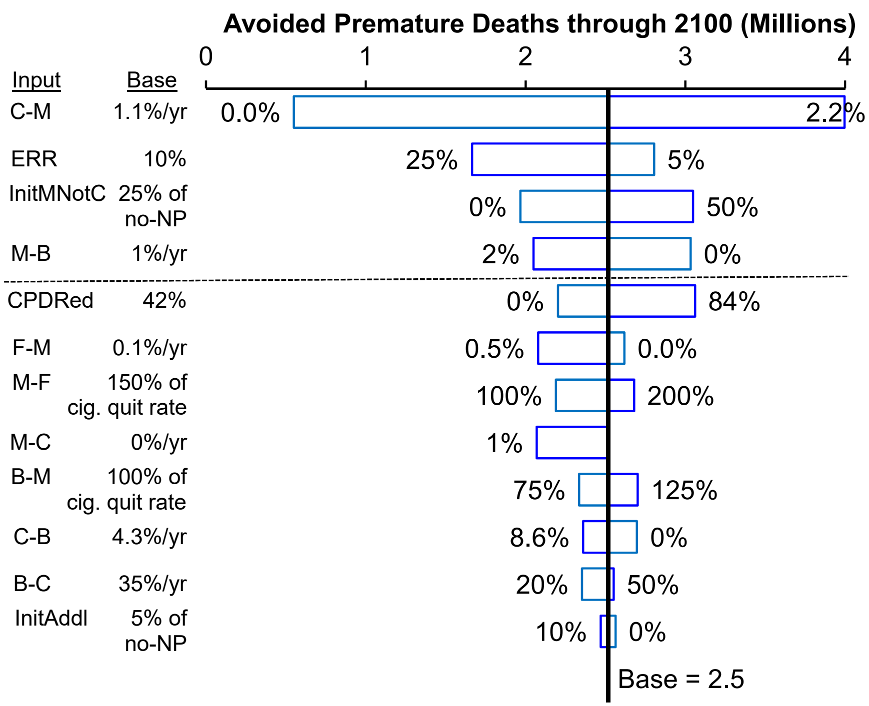
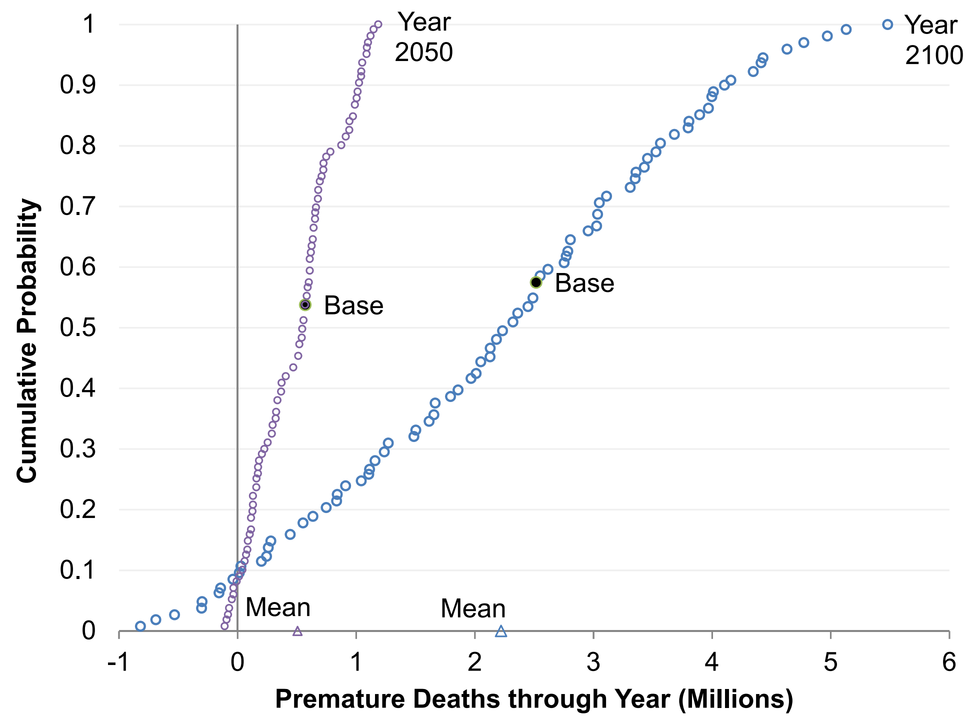
A tornado chart highlights the most sensitive inputs. In scenario analysis, key inputs are varied simultaneously.



Bars show effect of varying each input one-at-a-time between low and high cases; base line shows output with all inputs at base values.



Circles use a tree of 3^4 = 81 combinations of low (p=0.3), base (p=0.4), and high (p=0.3) values of **top 4** tornado inputs.

Poland B, Larroque S. Probabilistic Analysis of the Effects of a Modified Risk Tobacco Product on Population Health. SRNT Annual Meeting, Baltimore, MD, Feb. 21-24, 2018, Abstract POS4-134.
https://www.jt-science.com/sites/default/files/2018-04/2018-p1-jti.pdf

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Recent cost and mortality estimates give a smoking-attributable morbidity cost per smoking-attributable death.

- Measure morbidity by the smoking-attributable fraction of US healthcare expenditures, which the 2014 SG report estimated at $170 billion in year 2010 (in 2010 $).*
  - The report includes two other estimates. One is almost identical and the other, while lower, was thought to be an underestimation due to outdated attributable fractions.
  - For another approach see Lightwood J & Glantz SA 2016** which which finds a $63 billion next-year cost reduction for only a 10% reduction in smoking *prevalence* and CPD.
- This becomes $250 billion in 2019 $, when inflated at the 4.4% average increase in healthcare expenditures predicted by the Centers for Medicare and Medicaid Services.***
- The same SG report estimated 480,000 deaths from smoking and second-hand smoke in 2010 (based on analysis of 2005-2009).
- Therefore the smoking-attributable cost per smoking-attributable death (in 2019 $) is $250 billion / 480,000 = **$521,000**.

* USDHHS 2014. *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.
For details see Xu X, Bishop EE, Kennedy SM, et al. Annual healthcare spending attributable to cigarette smoking: an update. *Am J Prev Med.* 2015 Mar;48(3):326-33. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4603661/pdf/nihms725583.pdf
** Lightwood J & Glantz SA 2016. Smoking Behavior and Healthcare Expenditure in the United States, 1992– 2009: Panel Data Estimates. PLoS Med. 2016 May 10;13(5):e1002020. https://journals.plos.org/plosmedicine/article/file?id=10.1371/journal.pmed.1002020&type=printable
*** NHE Historical and Projections 1960-2027. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/NHE60-27.zip

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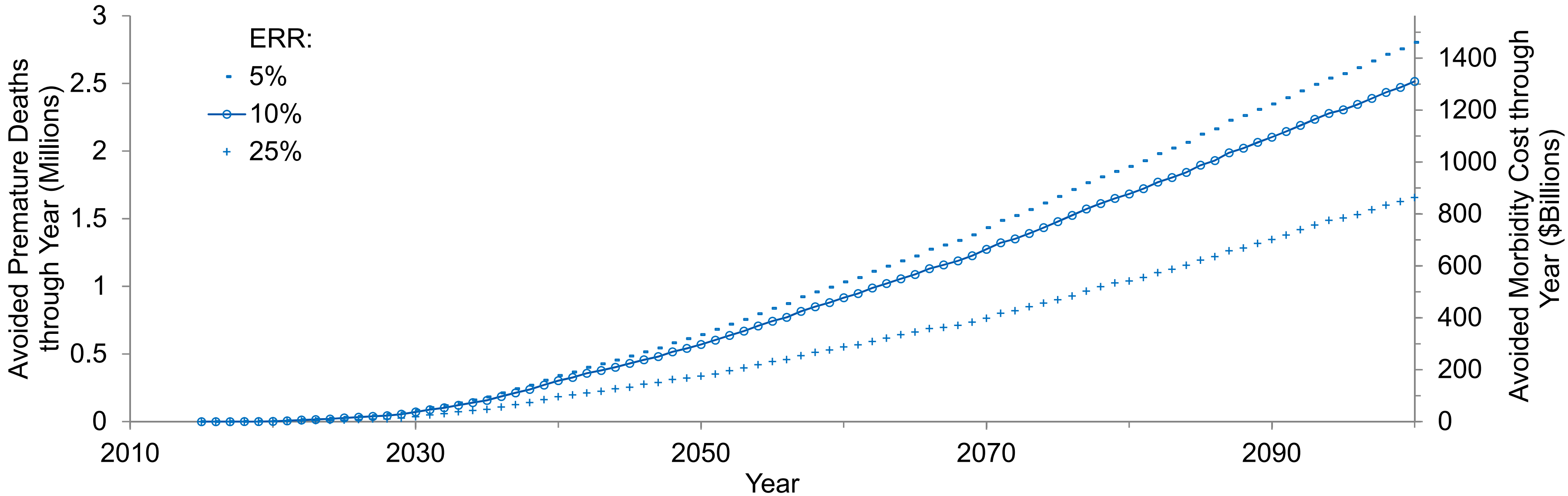
Assuming morbidity cost is proportional to mortality, we approximate avoided morbidity cost as this cost/death times APD.

- Suppose we estimate 2.5 million APD by 2100.
- Multiply this by $521,000 per death.
- Result is $1.3 trillion avoided morbidity cost by 2100.
  - Average annual APD = 29,800 and avoided morbidity cost = **$15.5 billion/year.**



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Key assumptions in this calculation:

- Smoking-attributable morbidity cost is proportional to smoking-attributable mortality.
  - Lightwood & Glantz 2016 assumed proportionality to smoking *prevalence*, but smoking-attributable mortality should better reflect the slow development of smoking-related diseases such as cancers.
- We exclude added health care costs from diseases resulting from living longer. Possibly, reducing smoking could *increase* health care costs by allowing more people to survive into old age.
- We omit lost *productivity* due to premature death and exposure to secondhand smoke, estimated at $156 billion in year 2010 in the 2014 SG Report.
  - This may more than balance the long-term health care costs of those who survive into old age*
- Healthcare spending estimates omit spending related to secondhand smoke, infant and maternal health, and dental services.
- Healthcare spending estimates are based on the civilian non-institutionalized US population.
  - 2006-2010 Medical Expenditure Panel Survey (MEPS), linked to 2004-2009 National Health Interview Survey (NHIS) for smoking history data.

* Hall & Doran 2016. How much can the USA reduce health care costs by reducing smoking? PLoS Med. 2016 May; 13(5): e1002021. https://journals.plos.org/plosmedicine/article/file?id=10.1371/journal.pmed.1002021&type=printable.

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Appendix: Abstract
Predicted Impacts of E-Cigarettes on US Mortality and Health Care Costs

- **Introduction**: The US FDA seeks to ensure that new tobacco products are appropriate for the protection of the public health and recommends assessment of tobacco-related morbidity as well as mortality. A simulation model that predicts the effect of e-cigarettes on tobacco use and mortality was extended to approximate effects on morbidity, as measured by US health care costs.
- **Methods**: The US adult population was simulated through year 2100, using randomly generated tobacco product use histories including initiation, cessation, and switching between products. Smokers and e-cigarette users also transitioned to and from dual use, which affected average cigarettes smoked per day and cigarette quit rates. The model predicted premature deaths avoided by e-cigarettes. Although e-cigarettes may benefit smokers who switch completely to them, benefits are less certain for other groups. The net effect depends on uncertain transition rates and the Excess Relative Risk (ERR) experienced by e-cigarette users relative to cigarette smokers. Sensitivity to each input was tested systematically, and a hypothetical “break-even” ERR, which would reduce a product’s net population benefit to zero in terms of avoided premature deaths, was calculated. Tobacco-attributable morbidity costs were assumed proportional to tobacco-attributable mortality and were scaled from recent US estimates.
- **Results**: Simulations suggested that e-cigarettes would avoid 2.5 million premature deaths and an average of $15.6 billion/year health care costs in the US population through 2100 in a base scenario, and provide a net benefit in all except extreme scenarios. The base-case break-even ERR was over 50% relative to cigarettes.
- **Conclusions**: These simulations show that e-cigarettes would very likely benefit the overall health and health care costs of US adults, despite uncertainties in ERR and other inputs.

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