International Journal of Epidemiology, 2020, 1624–1636
doi: 10.1093/ije/dyaa132
Advance Access Publication Date: 10 October 2020
Original article

Methods

Proportional multistate lifetable modelling of preventive interventions: concepts, code and worked examples

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Editorial decision 27 April 2020; Accepted 14 July 2020

Abstract

Burden of Disease studies—such as the Global Burden of Disease (GBD) Study—quantify health loss in disability-adjusted life-years. However, these studies stop short of quantifying the future impact of interventions that shift risk factor distributions, allowing for trends and time lags. This methodology paper explains how proportional multistate lifetable (PMSLT) modelling quantifies intervention impacts, using comparisons between three tobacco control case studies [eradication of tobacco, tobacco-free generation i.e. the age at which tobacco can be legally purchased is lifted by 1 year of age for each calendar year) and tobacco tax]. We also illustrate the importance of epidemiological specification of business-as-usual in the comparator arm that the intervention acts on, by demonstrating variations in simulated health gains when incorrectly: (i) assuming no decreasing trend in tobacco prevalence; and (ii) not including time lags from quitting tobacco to changing disease incidence. In conjunction with increasing availability of baseline and forecast demographic and epidemiological data, PMSLT modelling is well suited to future multiple country comparisons to better inform national, regional and global prioritization of preventive interventions. To facilitate use of PMSLT, we introduce a Python-based modelling framework and associated tools that facilitate the construction, calibration and analysis of PMSLT models.

Key words: Health-adjusted life years, macrosimulation, proportional multistate lifetable, tobacco

Key Messages

- A key role of epidemiology is to inform prevention policy, which requires comparable quantification of health impacts of interventions.
- The prospective or future-orientated quantification of intervention impacts, using simulation modelling, is seldom undertaken by epidemiologists.
- Proportional multistate lifetable simulation modelling is one type of macro-simulation available to epidemiologists to estimate the health (and cost) impacts of preventive interventions.
- Proportional multistate lifetable modeling uses disease incidence and case fatality rates, all-cause mortality and morbidity rates, intervention effects sizes, risk factor distributions and potential impact fractions—concepts familiar to epidemiologists.

Introduction

If epidemiology is to inform prevention policy, then it must quantify the health impacts of interventions. Relative risks for exposure-outcome associations alone will not suffice—information is also needed on the number of people affected and the future impacts of interventions on morbidity and mortality. Health economics—through the well-established sub-discipline of cost-effectiveness analysis[1,2]—combines information on quality-adjusted life-years (QALYs) gained or disability-adjusted life-years (DALYs) averted, together with incremental health costs, to produce estimates of the cost-effectiveness of interventions.

In epidemiology, emerging from the potential outcome approach and G methods,[3,4] there has been an increasing interest in using G computation to quantify intervention impacts.[5–7] Here one uses existing (and therefore historical) data, estimates each individual's potential outcomes under counterfactual exposure or covariate assignment and quantifies the impact of an intervention. For example, Garcia-Aymerich *et al.* estimated that the risk of asthma among nurses would decrease from 1.5% to 1.3% if: those with a body mass index (BMI) >23 decreased their weight by 5%; and moderate to vigorous physical activity was lifted to at least 3.5 h per week for all nurses—over the 10-year period 1988 to 1998. But this is not prospective; what we might really want to estimate is the future risk of asthma under intervention scenarios, allowing for projected future trends in risk factors and disease rates. This future-orientated estimation requires simulation models.

From another perspective, burden of disease studies[8,9] and the Global Burden of Disease (GBD) Study[10] take two steps along the path to comparably and systematically informing decisions about which preventive interventions are best. First, they quantify the gap between a current population's health and an external ideal in DALYs. Second, they use comparative risk assessment to determine how much of this current burden is due to non-ideal past risk factor distributions (e.g. GBD 2016 Risk Factors Collaboration[11]) However, it is less common for this work to progress to comparably estimating the future avoidable health (and cost) impacts of actual interventions, allowing for factors such as intervention coverage, uptake and adherence, and time lags from intervention to changing disease. Murray *et al.* outline a theoretical framework from attributable to avoidable measures of impact; for policy making, the avoidable impact is more important.[12]

One notable example of modelling future avoidable impacts from actual interventions is the Assessing Cost Effectiveness of Prevention (ACE-Prevention) body of work in Australia. It has used national burden of disease outputs as starting points to parameterize proportional multistate lifetable (PMSLT) simulation models of public health interventions applied to the Australian 2003 population, to estimate DALYs averted over the remainder of their lifetime.[13] A subsequent body of New Zealand work extended the same approach (e.g. for tobacco interventions[14,15]).

The same PMSLT approach has also been picked up in other countries (e.g. the UK,[16,17] Vietnam[18] and Tanzania[19]). The Netherlands has led the development of health impact assessment methods using simulation modelling, including the DYNAMO model that uses Markov modelling to quantify preventive intervention impacts on population health metrics such as (disability-free) life expectancy, prevalence and mortality rates.[20–22] The World Health Organization's CHOICE initiative,[23,24] previously very active in this area including developing epidemiological models,[25] is updating a range of tools and costing databases that provide standardized methods for conducting country-based and regional cost effectiveness analyses of a range of health interventions,[26,27] such as those carried out to inform decision making regarding intervention strategies against non-communicable diseases in Mexico.[28]

High-level overviews of the modelling approaches used in these bodies of work, including adaptations of a comparative risk assessment approach, Markov modelling, discrete event simulation and multistate lifetable models, can be found elsewhere.[17,29–37] The focus of this paper is on the PMSLT method for estimating preventive intervention impacts on life-years (LYs) and health-adjusted life-years gained (HALYs, a term we define to encompass both DALYs averted and QALYs gained), and life expectancy and health-adjusted life expectancy (HALE) gained.

Barendregt *et al.* first described the PMSLT as a means to overcome a restriction in standard Markov and (non-proportional) multistate lifetables, namely state explosion.[31] This restriction means that for a model with—say—five diseases, there are 32 possible combinations of disease states (one healthy, five single disease, 10 combinations each of two or three diseases, five combinations of four diseases, and one with all five diseases; i.e. $\sum_{r=0}^{5} \frac{5!}{r!(5-r)!}$ where r = number of diseases). This state explosion results in large model structures, with consequent computational and parameterization costs. The PMSLT rests on the assumption of disease independence. It models proportions of a cohort in each disease state, where proportions of the cohort also reside simultaneously in multiple states given the prevalence probabilities. For example, if disease A has a prevalence of 10%, and disease B a prevalence of 5%, these two diseases are modelled in parallel lifetables as these proportions of the cohort—implicitly assuming that 10% × 5% = 0.5% of the cohort had both diseases together. Within the lifetables, Markov model assumptions apply.[30,38]

Lifetables and Markov models are commonly used in epidemiology and health economics, yet not commonly taught in epidemiological courses. The purpose of this paper is to provide an overview of PMSLT models for epidemiologists. Wider adoption of modelling approaches such as PMSLT could assist epidemiologists better inform prioritization of population interventions for decision makers.

This paper has four objectives:

i. to describe the concept and methodology of lifetable and PMSLT simulation;
ii. to demonstrate the capabilities of a PMSLT using a comparison of three tobacco control interventions in a single high-income country (New Zealand) as a case study;
iii. to demonstrate how specification of the PMSLT model changes the magnitude of estimates on a spectrum between attributable and avoidable impacts;
iv. to introduce a publicly available framework for building and analysing PMSLT models in Python code.

Basic concept and lifetable method

We step through two basic examples:

i. a lifetable for one cohort (50–54-year-old New Zealand non-Māori males alive in 2011), under both business-as-usual (BAU) and a simple intervention of a 5% lowering of the all-cause mortality rate at every year of age into the future;
ii. the addition of a single coronary heart disease lifetable, in addition to the 'main' lifetable, under both BAU and an intervention scenario of a 5% lowering of the coronary heart disease incidence rate at every year of age into the future, and how that is then collated back to changes in the main lifetable.

Example 1: one main lifetable

Lifetables usually refer to 'period' lifetables that are commonly provided by government statistical agencies to produce estimates of metrics such as life expectancy. These period lifetables assume that a hypothetical group of individuals are exposed, over their hypothetical life course, to those mortality rates seen in 1 calendar year, i.e. that a 52-year-old experiences the actual observed mortality rate of a current 52-year-old this year, the observed mortality rate of a current 53-year-old next year and so on. In simulation modelling, we take a cohort perspective, using projected future mortality rates.

Table 1 shows excerpts of a cohort lifetable for 50–54-year-old New Zealand non-Māori males alive in 2011; we do not show all ages into the future, but just the first and last two annual steps (any survivors at age 110 are set to have a mortality risk of 1). Under BAU, the mortality rates, m_x, increase with age. The mortality rates are converted to mortality risks (q_x), then multiplied into the starting population in base-year and surviving population each year thereafter (l_x) to calculate deaths each year (d_x). The number of person-life-years lived to halfway through each annual time step (L_x) is assumed as the average of l_x in the current and future time step. The life expectancy (e_x) is given by the sum of all future time step L_x's (4 301 727 in Table 1), divided by the starting population size (129 850)—in this example, 33.13 years of expected remaining life from the age of 52 in 2011.

To add morbidity to the BAU, we use 'prevalent years of life lived with disability' (pYLD). The numerator for the pYLD is the total number of YLDs for the same demographic by age group from a local/national burden of disease study or (say) from the GBD estimates for each country, and the denominator is the estimated number of people in that population. Due to increasing morbidity with age, the pYLD goes up with age—in this example

Table 1 Excerpts of cohort lifetables for 50–54-year-old non-Māori NZ males in 2011 (centred on age 52) under: business-as-usual (BAU); a hypothetical 5% reduction in mortality rate at all ages; and a hypothetical 5% reduction in coronary heart disease incidence rate at all ages (see coronary heart disease lifetable in Supplementary Table 1, available as Supplementary data at *IJE* online)

Age	Average mortality rate at age x m_x	Probability of dying between age x and x + 1 $q_x = 1 - \exp(-m_x)$	No. of survivors at age x $l_x = l_{x-1} - d_{x-1}$	No. who die between age x and x + 1 $d_x = q_x \times l_x$	No. of person-years lived by cohort to age x + ½ $L_x = (l_x + l_{x+1})/2 L_{110} = (l_{110} + (l_{110} - d_{110}))/2$	Life expectancy $e_x = \Sigma_x^{110}(L_x)/l_x$	PYLD rate from all causes w_x	Health-adjusted life-years (HALYs) $Lw_x = L_x (1 - w_x)$	Health-adjusted life expectancy (HALE) $ew_x = \Sigma_x^{110}(Lw_x)/l_x$
BAU									
52 in 2011	0.0030	0.0030	129 850	390	129 655	33.13	0.1122	115 103	26.00
53 in 2012	0.0032	0.0032	129 460	413	129 254	32.23	0.1122	114 747	25.18
….	…	…	…	…	…	…	…	…	…
109 in 2068	0.4811	0.3819	136	52	110	1.31	0.3578	71	0.84
110 in 2069	0.4812	0.3820	84	32	68	0.81	0.3578	44	0.52
Total					4 301 727			3 375 530	
5% reduction in all-cause mortality rate at all ages									
52	0.0029	0.0029	129 850	370	129 665	33.58	0.1122	115 112	26.30
53	0.0030	0.0030	129 480	393	129 283	32.67	0.1122	114 773	25.49
….	…	…	…	…	…	…	…	…	…
109	0.4570	0.3668	192	71	157	1.33	0.3578	101	0.86
110	0.4571	0.3669	122	45	99	0.82	0.3578	64	0.52
Total					4 360 240			3 415 589	
Change cf. BAU					58,512	0.45†		40 059	0.31†
5% reduction in coronary heart disease incidence									
52	0.0030	0.0030	129 850	390	129 655	33.19	0.1122	115 103	26.06
53	0.0032	0.0032	129 460	413	129 254	32.29	0.1122	114 748	25.25
….	…	…	…	…	…	…	…	…	…
109	0.4788	0.3805	144	55	117	1.31	0.3571	75	0.84
110	0.4790	0.3806	89	34	72	0.81	0.3572	47	0.52
Total					4 310 348			3 383 567	
Change cf. BAU					8621	0.07[a]		8036	0.06[a]

Underlined figures in the table are from external data, but all other figures are 'produced' within the lifetable as per the equations in column headers and explained in the text. BAU, business-as-usual; PYLD, prevalent years lived with disability, divided by the number of people in that stratum (source: Naimi *et al.*[3]).

[a]Differences between intervention scenario and BAU for health-adjusted life expectancy (HALE) and life expectancy at 52 years of age.

from 0.1122 at age 52 to 0.3578 at age 110 years. One minus the pYLD at each age is then multiplied by the life-years, giving HALYs and health-adjusted life expectancy (HALE; 26.00 for 52-year olds, or 78.5% of the life expectancy).

The second panel illustrates the simplistic intervention of a 5% reduction in mortality rate at every year of age. The life-years and HALYs lived over the remainder of this cohort's lifespan increase by 58 512 (1.36%) and 40 059 (1.19%), respectively, compared with BAU—less than the 5% reduction in mortality rate due to the exponentially increasing mortality rates with age that mathematically limit survivorship. The life expectancy and HALE increase by 0.45 and 0.31 years, respectively.

Example 2: a main lifetable and one subsidiary coronary heart disease lifetable

Consider an intervention that reduces coronary heart disease incidence by 5% at every age. A parallel coronary heart disease lifetable is constructed for BAU and this intervention where the incidence rates are reduced by 5%. (Supplementary Table 1, available as Supplementary data at *IJE* online, shows an abridged lifetable for this.) BAU inputs to the disease lifetable include incidence rates (e.g. from registry data) and case fatality or excess mortality rates, for the base-year and each year into the future. Base-year disease prevalence is inputted but is calculated for subsequent years within the disease lifetable as a function of annual cycle incidence and case fatality rates. As such, prevalence provides a useful output in model calibration to ensure that its trends into the future are consistent with a priori expectation. For example, diabetes incidence, prevalence and mortality rates are rapidly changing in most countries, and estimates of these parameters are often poor, leading to concerns about parametrizing the BAU model for diabetes (see later sections). If independent forecasts or expert expectations of future diabetes prevalence trends exist, these can be compared with model outputs as a form of model validation.[39]Disease-specific disability rates are the disease-specific YLDs from a burden of disease study divided by the total population. The starting number of people in this disease lifetable does not matter, for two reasons: we are only interested in differences in rates between BAU and intervention, to then link back to the main lifetable; and we assume diseases are independent, nullifying the need for actual numbers of people in each disease state to model comorbidity. Figure 1 shows the incidence rate inputs and mortality rate and prevalence outputs for this example.

Proportional multistate lifetable modelling

Figure 2 shows a conceptual diagram of intervention modelling through a PMSLT, broken down into five modules.

Module I: multiple data sources

Epidemiological parameters for each disease can come from a range of sources, with a likely candidate source being a burden of disease study or the GBD (especially for low- and middle-income countries without rich national data), with checks using a version of the DISMOD tool that ensures incidence, prevalence, mortality, case fatality and remission rates are coherent (these parameters are mathematically related).[40,41]

Module II: intervention models

Quantifying the impact of an intervention requires careful conceptualization and modelling in its own right. For example, tobacco taxes require conversion to price rises, then to purchasing changes, all on top of BAU trends in tobacco consumption (Supplementary Figure 1, available as Supplementary data at *IJE* online). A dietary counselling intervention will require modelling a cascade of target population, population reached, population completing the programme, initial changes in diet and then maintenance of any intervention effect. One common last component of the intervention modelling—if the intervention changes disease incidence—is the use of potential impact fractions (PIFs) that blend the risk factor distribution shift relative to BAU with the effect size rate ratios (RRs) to give a change in disease incidence, for a given risk factor, i.e.

$$PIF_{itd} = \frac{\sum_k (P_{kit}^{BAU} \times RR_{kid}) - \sum_k (P_{kit}^{Int} \times RR_{kid})}{\sum_k (P_{kit}^{BAU} \times RR_{kid})}$$

where: P is the prevalence of the risk factor (e.g. tobacco smoking) for smoker category k (e.g. current, never, and (in our model) 20 states for each of the 20 years since quitting), i indexes each sex by age (and possibly other heterogeneity covariates) and t indexes for time step; RR is the incidence rate ratio by level k of the risk factor for disease d by heterogeneity I; the superscripts 'BAU' and 'Int' are for business-as-usual and intervention scenarios, respectively.

If the PMSLT includes two or more risk factors affected by an intervention, the combined PIF is:

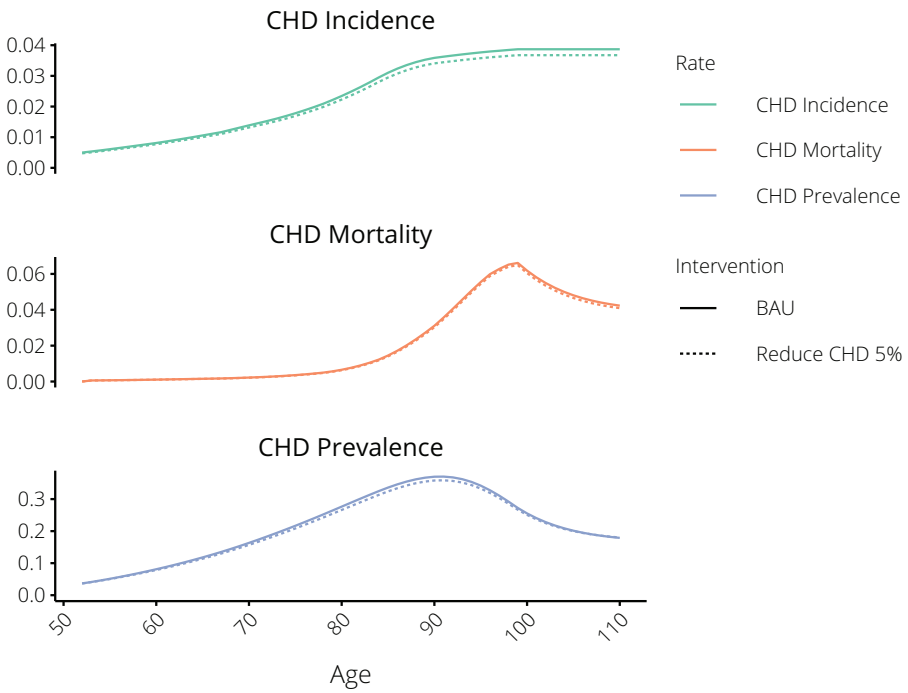

Figure 1 Business-as-usual (BAU)and intervention (5% reduction in coronary heart disease incidence) outputs of coronary heart disease mortality rates and morbidity rates (per person) and coronary heart disease prevalence, for the 50–54-year-old non-Māori male cohort in 2011 over the remainder of their lives. CHD, coronary heart disease

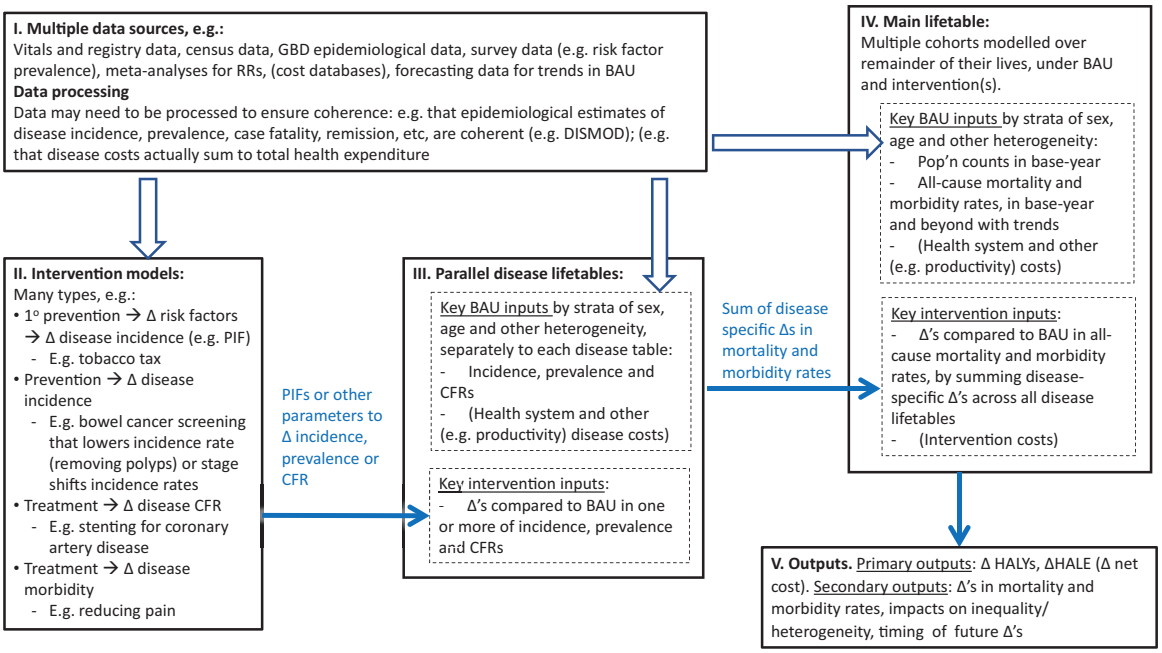

Figure 2 Conceptual diagram of intervention modelling with a proportional multistate lifetable model, showing five modules: I. Data sources; II. Intervention models; III. Parallel disease lifetables; IV. Main lifetable; and V. Outputs. GBD, Global Burden of Disease; PIF, potential impact fraction; BAU, business-as-usual; Δ, change; CFR, case fatality rate; HALY, health-adjusted life-year; HALE, health-adjusted life expectancy

$$PIF_{itd\bar{r}} = 1 - \prod_r (1 - PIF_{itd})$$

where r indexes each risk factor, and $\bar{r}$ denotes combined over risk factors.

Modules III and IV: parallel disease lifetables and main lifetable

A multiple-disease, multicohort PMSLT is an extension in the following dimensions. First, more independent diseases

are added to the model. All disease-specific mortality and morbidity rate changes are added up across diseases, then subtracted from the all-cause mortality and morbidity rates in the main lifetable. Second, multiple cohorts (i.e. not just 50–54-year-old non-Māori males as in the examples above) are run independently through the same model structure, with life-years and HALYs summed up across all sex by age cohorts. The HALYs in BAU are:

$$HALYs^{BAU} = \sum_i \sum_t \left(N_{it}^{BAU} \times \exp(-mort_{it}^{BAU}) \times (1 - morb_{it}^{BAU}) \right)$$

where: i indexes each sex by age (and possibly other heterogeneity covariates) cohort, and t indexes year (0 for base-year); N_{it}^{BAU} is the number of individuals alive at the beginning of each annual cycle ($N_{it=0}^{BAU}$ is the number in each cohort in the base-year); $mort_{it}^{BAU}$ and $morb_{it}^{BAU}$ are the projected all-cause mortality and morbidity rates for each cohort i by cycle t into the future.

Under intervention, the values of $mort_{it}^{Int}$ and $morb_{it}^{Int}$ differ (presumably less), whereby:

$$mort_{it}^{Int} = mort_{it}^{BAU} + \sum_d (mort_{itd}^{Int} - mort_{itd}^{BAU})$$

and:

$$morb_{it}^{Int} = morb_{it}^{BAU} + \sum_d (morb_{itd}^{Int} - morb_{itd}^{BAU})$$

where: d is subscript for all parallel diseases including in the model; $mort_{itd}^{BAU}$ is the BAU cause-specific mortality rate for cohort i at time t for disease d (that is the result of the inputted disease-specific incidence, case fatality and prevalence rates to each disease lifetable in module III); $mort_{itd}^{Int}$ is the intervention scenario cause-specific mortality rate (that is a result of an intervention effect on the cause-specific incidence rates); $morb_{itd}^{BAU}$ is the BAU morbidity rate (i.e. the product of BAU disease-specific prevalence and the disability rate for having disease d); and $morb_{itd}^{Int}$ is the intervention scenario morbidity rate [i.e. the product of intervention disease-specific prevalence (usually less than BAU prevalence due to lower incidence rates) and the (same as BAU) disability rate].

Module V: outputs

Differences between BAU and the intervention scenario in HALYs are the most commonly used output, but it is possible to output many other metrics (e.g. life-years, HALE and life expectancy, all-cause and cause-specific disease mortality and morbidity rates). It is feasible to extend the PMSLT to also model health system costs, allowing for cost-effectiveness estimates (cost inputs in parentheses in Figure 2).

Case studies: tobacco control interventions through a proportional multistate lifetable model

We modelled three tobacco control case studies: (i) eradication, whereby all current smokers became ex-smokers in 2011 and there was no further initiation of smoking; (ii) 10% per annum excise tax on tobacco from 2011 to 2031; and (iii) a tobacco-free generation whereby there was not further initiation of tobacco smoking after 2011 due to annual increases in the minimum legal age for purchasing tobacco.

We present results for the total New Zealand population alive in 2011, and also non-Māori males and Māori females, to give the reader a sense of heterogeneity and intervention impacts on health inequalities. (Māori—females in particular—have high smoking rates and high smoking-related disease rates.) Below we describe the aspects relevant to the model structure demonstrations (Incidence rate ratios associating tobacco to disease incidence are shown in Supplementary Table 2, available as Supplementary data at *IJE* online; further details on the New Zealand tobacco PMSLT are described elsewhere[14,15]).

Methods

Future BAU smoking prevalence

Future smoking prevalence is not explicitly incorporated into the lifetables, but rather influences intervention impact during the PIF calculations. Imagine two BAU scenarios with different future smoking prevalence: 30% and 10%. An intervention that decreases smoking prevalence by 10% will result in different future prevalence (i.e. to 27% and 9%, respectively). The three versus one percentage point difference in smoking prevalence will mean that the PIF is greater (and thence greater disease incidence reductions and greater HALYs gained) for the former compared with the latter BAU scenario.

In our default tobacco model, at the juncture of modules I and II in Figure 2, is a Markov model projecting future tobacco prevalence[42]—assuming that past annual net cessation trends and annual changes (declines) in initiation persist into the future. Thus, any interventions we model are on top of an already declining tobacco smoking prevalence (shown in Supplementary Figure 2, available as Supplementary data at *IJE* online), following an avoidable (as opposed to attributable; see Introduction above)

approach that is more policy-relevant.[12] To illustrate model structure variation, we specify a scenario of zero net cessation rates into the future (meaning tobacco prevalence for each age cohort only falls modestly due to differential mortality between current, ex-and never smokers, compared with the steeper falls in BAU shown in Supplementary Figure 2, due to cessation).

Time lags

In our default tobacco model, again approximating an avoidable as opposed to attributable approach,[12] we allow for attenuation of tobacco-related harms over 20 years since quitting, using disease-varying (and sometimes sex- and age-varying) equations from Hoogenveen *et al.*[43] (Supplementary Table 2, available as Supplementary data at *IJE* online). This is operationalized through a 20-year-long tunnel state for quitters in the above parallel tobacco prevalence Markov model. As a demonstrative scenario analysis for this paper, we also specify a no-time-lag scenario where quitters immediately receive the disease incidence rates of never smokers.

Analyses

All input parameters had parametric uncertainty intervals, allowing Monte Carlo simulation (2000 iterations) to generate 95% uncertainty intervals about all of the above outputs. Python code used in this paper is described in more detail in the last section of the Methods.

Case study results

Default model

Table 2 shows the BAU outputs and the incremental differences from BAU for each of the three interventions. For the total population alive in 2011, they are expected to have 212 million remaining life-years of which 173 million are healthy. With tobacco eradication, the life-years and HALYs increase by 1.50 and 1.57 million, respectively, or an increase of 0.70% and 0.91% over BAU, respectively. Note that the HALYs increase more than life-years, meaning there is a compression of morbidity under tobacco eradication. The tobacco tax and tobacco-free generation interventions gain 291 000 and 479 000 HALYs over BAU—or about 20% and one- third, respectively, of all potential health gain realizable from tobacco eradication.

Also shown in Table 2 are mortality and morbidity rate outputs 20- and 40-years post-intervention, as selected examples of possible outputs. There are marked reductions in age-standardized all-cause mortality rates for Māori females, and lesser percentage reductions in age-standardized morbidity rates.

An advantage of simulation modelling is the ability to extract and examine how benefits are distributed by demographic group and time into the future. Figure 3 shows one example—the ratio of HALYs to life-years gained with a tobacco tax, by cohort age in 2011 for each 5-year interval of follow-up into the future. Scanning across the figure horizontally captures the experience of each age cohort in 2011, over the reminder of their lives. Scanning down a diagonal captures the experience for the same age group into the future; we have highlighted in yellow the diagonal of people aged 75–79 (centred on 77-years-olds) by 5-year interval years into the future. The HALY gains among 75–79-year-old Māori females are a little less than the life-year gains (ratios around 0.9), but for 75–79-year-old non-Māori males, the HALY gains are a little greater (ratios about 1.25 to 1.5). The reasons for different patterns of health gains are a combination of smoking rates, disease rates and background or competing morbidity and mortality rates—a detailed analysis of which is beyond the scope of this paper that seeks more to illustrate types of output that can be generated.

Model structure scenarios

Here we demonstrate the impact of two model structure variations (Figure 4). Not allowing for decreasing smoking prevalence in BAU increases the apparent HALYs gained by over 2-fold for each of the three intervention scenarios. The reason here is fairly straightforward; if future expected reductions in tobacco prevalence (for reasons other than the intervention being modelled) are not allowed for, one will incorrectly overestimate the health gains from tobacco control in the future.

Not allowing for time lags is more nuanced, overestimating health gains for tobacco eradication but underestimating health gains for a tobacco-free generation. Regarding the latter, in a BAU without time lags new generations of smokers are not getting as much health harm as in our best model with time lags—because they enjoy instantaneous return to normal health on quitting at some age in the future. Thus, when one runs an intervention simulation of no more initiation (a tobacco-free generation), the reversed health harm is less—so HALY gains are less. But for the eradication scenario with no time lags, one has an offsetting much larger health gain among the older current smokers as they get larger than plausible health gains on quitting. Hence the no-time-lag scenario overestimates health gains for eradication, and underestimates for a tobacco-free generation. These examples

Table 2 Incremental health gains compared with BAU for three tobacco control intervention case studies [% change compared with business-as-usual (BAU)]

				Incremental compared with BAU					
Output	Demographic group	Age and calendar year	BAU	Tobacco eradication		Tobacco tax		Tobacco-free generation	
LYs	Total population		212 268 038	1 495 633	(0.70%)	276 980	(0.13%)	434 724	(0.20%)
	Māori female		18 367 339	376 362	(2.05%)	86 566	(0.47%)	146 441	(0.80%)
	Non-Māori male		85 908 173	480 672	(0.56%)	73 085	(0.09%)	104 102	(0.12%)
HALYs	Total population		173 177 807	1 568 586	(0.91%)	291 345	(0.17%)	478 989	(0.28%)
	Māori female		14 423 064	342 415	(2.38%)	80 032	(0.56%)	139 510	(0.97%)
	Non-Māori male		71 553 323	548 459	(0.77%)	86 755	(0.12%)	132 787	(0.19%)
All-cause	Māori female	62-year-olds, in 2041	1022	−273	(−26.67%)	−37	(−3.61%)	0	(0.00%)
mortality rate	Māori female	62-year-olds, in 2061	994	−195	(−19.64%)	−76	(−7.63%)	−195	(−19.64%)
(per 100 000)	Non-Māori male	62-year-olds, in 2041	549	−40	(−7.30%)	−4	(−0.79%)	0	(0.00%)
	Non-Māori male	62-year-olds, in 2061	592	−25	(−4.25%)	−8	(−1.44%)	−25	(−4.25%)
All-cause	Māori female	62-year-olds, in 2041	0.2268	−0.0106	(−4.70%)	−0.0012	(−0.55%)	0	(0%)
morbidity	Māori female	62-year-olds, in 2061	0.2268	−0.0091	(−3.97%)	−0.0034	(−1.50%)	−0.0091	(−3.97%)
rate (per 1)	Non-Māori male	62-year-olds, in 2041	0.1571	−0.0036	(−2.30%)	−0.0004	(−0.23%)	0	(0%)
	Non-Māori male	62-year-olds, in 2061	0.1571	−0.0028	(−1.75%)	−0.0009	(−0.58%)	−0.0028	(−1.75%)

Compared with previous BODE3 publications,[14,15] the outputs for tobacco eradication and the tobacco-free generation vary slightly due to: beginning of cycle and end of cycle processing varying slightly in the previous Excel models and Python; use of derived equations in Barendregt *et al.* (2003) for non-cancers as well as cancers[40]; slight modification to the calculations at age 110; and slight variations due to rounding.

95% uncertainty intervals are shown in Supplementary Table 3, available as Supplementary data at *IJE* online.

BAU, business-as-usual; LYs, life-years; HALYs, health-adjusted life-years.

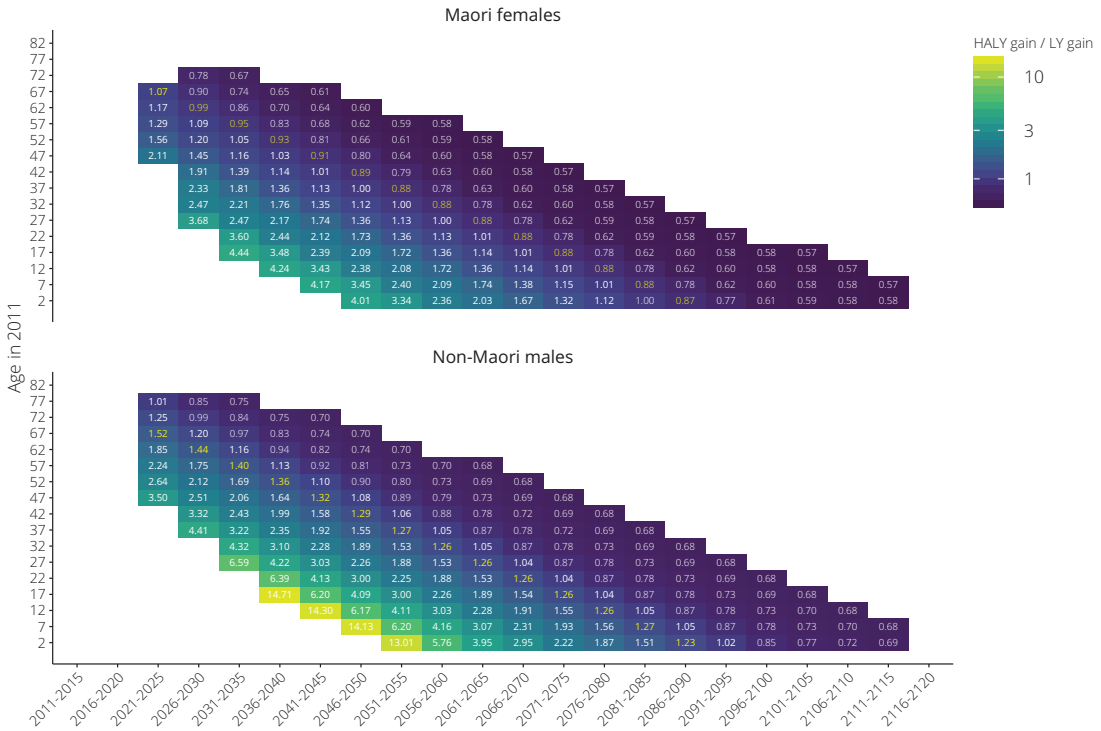

Figure 3 Ratio of health-adjusted life-years (HALYs) to life-years gained among Māori females and non-Māori males, for the tobacco tax intervention: y-axis = mid-point of 5-year age cohorts in 2011; x-axis = calendar years; yellow diagonal depicts same age group in future calendar years. The HALYs and life-years used to calculate these ratios are shown in Supplementary Figure 2, available as Supplementary data at *IJE* online. Estimates only shown if both HALYs and life-years gained for each 5-year cohort by 5-year calendar period was greater than 5.0

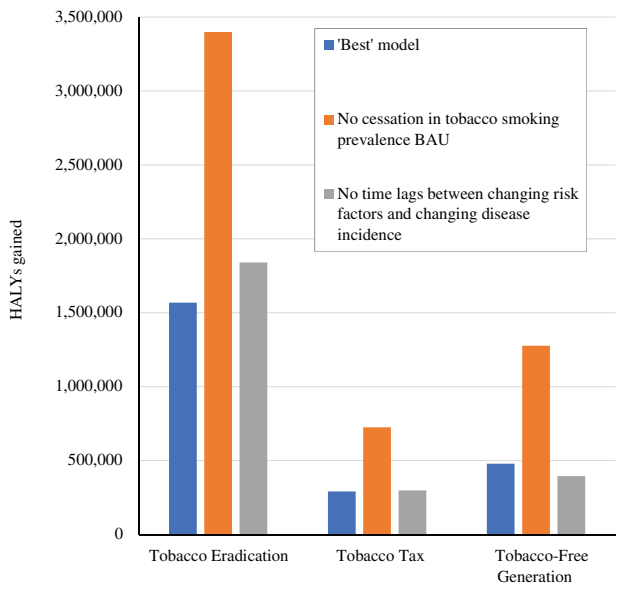

Figure 4 Health gain (in HALYs) for three tobacco control interventions, for: 'best' model structure specification; zero net cessation in future business-as-usual (BAU) smoking prevalence trends; no time lags between changes in smoking and disease incidence. HALYs, health-adjusted life-years; BAU, business-as-usual

shown in Figure 4 demonstrate the need to understand and specify model structure as correctly and transparently as possible.

A Python-based framework for PMSLT models

PMSLT models have typically been developed as Excel spreadsheets, given the intuitively 'spreadsheet nature' of lifetables and the desire to make models accessible to a variety of prospective users. Whereas spreadsheet models have the merits of accessibility and ease of use, they also have obvious limitations. Identifying data and formula errors can be difficult as they typically involve many spreadsheet cells. Spreadsheet models also have less flexibility for model adaptations and re-usability and are usually slower at running Monte Carlo simulation (where each input parameter is drawn from a probability distribution reflecting its uncertainty) compared with models programmed in computing code.

To address these limitations, we have built a general purpose PMSLT modelling toolkit within the existing Python-based Vivarium simulation framework[44]—and used it to generate the above outputs. Input data can be extracted from existing repositories (such as the GBD), further reducing the risk of errors introduced via manual handling. Separating models and data also makes it straightforward to re-use a single model across multiple countries, or to extend a model to consider multiple subpopulations within a country. Furthermore, the modular

approach facilitates re-use at the level of individual diseases, risk factors and interventions, decreasing the time required to construct new models. Finally, more efficient implementation reduces the computational time required to run large numbers of simulations and offers the opportunity of shifting to parallel computation on large-scale computing facilities.

The generic Vivarium PMSLT tools for modelling public health interventions are available from github [https://github.com/ihmeuw/vivarium_public_health], as is the specific archive of code used in this paper [https://github.com/population-interventions/vivarium_unimelb_tobacco_intervention_comparison].

Conclusion

Comparing and selecting between different combinations of preventive interventions requires comparable estimates of each intervention's health and cost impacts. Simulation modelling can provide such estimates but is under-used in epidemiology and public health more generally. Here we have demonstrated the application of one such method—PMSLT modelling—to compare tobacco control interventions.

The principal strength of PMSLT is that it allows the inclusion of multiple diseases (that the intervention causally effects), without state explosion. It is well suited to preventive interventions that work through changing risk factors, and then disease incidence, but it can also be used for interventions acting through changes in case fatality and morbidity. With the growing availability of comprehensive datasets on demographic and epidemiological parameters for all countries—and forecasts of future trends[45,46]—there is great potential to quantify future health gains from preventive interventions in a comparable manner using PMSLT.

This flexibility derives from the assumption of independence between diseases. Exploratory modelling has shown this assumption to have limited impact in most settings on overall estimates, as over- and underestimates tend to cancel each other out.[31,47] When dependencies between diseases are substantial, this can be captured in PMSLT by treating a disease as both a disease in its own right and also a risk factor for other disease conditions. For example, diabetes can be modelled as both a disease and a risk factor for stroke and coronary heart disease.

We have demonstrated how social group heterogeneity (sex and ethnicity) can be incorporated in PMSLT models. In current work we are extending our simulation framework to enable automatic disaggregation of PMSLT by population strata, given user-supplied inputs on sub-population variation in disease incidence and case fatality rates, and all-cause morbidity and mortality rates. As the number of dimensions of heterogeneity that are of interest increases, stratifying cohorts may become unwieldy, and microsimulation may be a more appropriate approach. However, although microsimulation offers the ability to model combinations of sub-populations at extremely high resolution, and correlated risk factors and diseases, it is also demanding in terms of data requirements (e.g. correlation of risk factors within individuals) and computation.

PMSLT offers an attractive compromise, providing the ability to model interventions affecting multiple diseases, and combinations of preventive interventions, across heterogeneous populations in a manner that is flexible and scaleable.

Supplementary data

Supplementary data are available at *IJE* online.

Conflict of interest

None declared.

References

1. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. *Methods for the Economic Evaluation of Health Care Programmes*. 3rd edn. Oxford, UK: Oxford University Press, 2005.
2. Sanders GD, Neumann PJ, Basu A *et al.* Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second panel on cost-effectiveness in health and medicine. *JAMA* 2016;**316**:1093–103.
3. Naimi AI, Cole SR, Kennedy EH. An introduction to G methods. *Int J Epidemiol* 2017;**46**:756–62.
4. Blakely T, Lynch J, Simons K, Bentley R, Rose S. Reflection on modern methods: when worlds collide—prediction, machine learning and causal inference. *Int J Epidemiol* 2019, Jul 11. doi: 10.1093/ije/dyz132. Online ahead of print.
5. Snowden JM, Rose S, Mortimer KM. Implementation of G-computation on a simulated dataset: demonstration of a causal inference technique. *Am J Epidemiol* 2011;**173**:731–38.
6. Keil AP, Edwards JK, Richardson DB, Naimi AI, Cole SR. The parametric g-formula for time-to-event data: intuition and a worked example. *Epidemiology* 2014;**25**:889–97.
7. Garcia-Aymerich J, Varraso R, Danaei G, Camargo CA Jr, Hernan MA. Incidence of adult-onset asthma after hypothetical interventions on body mass index and physical activity: an application of the parametric g-formula. *Am J Epidemiol* 2014;**179**:20–26.
8. Ministry of Health. *Health Loss in New Zealand 1990–2013: A Report from the New Zealand Burden of Diseases, Injuries and Risk Factors Study*. Wellington: Ministry of Health, 2016.
9. Australian Institute of Health and Welfare. *Australian Burden of Disease Study: Impact and Causes of Illness and Death in Australia 2011*. Canberra: AIHW, 2016.

10. Murray CJL, Lopez AD. Measuring global health: motivation and evolution of the Global Burden of Disease Study. *Lancet* 2017;**390**:1460–64.
11. GBD 2016 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017;**390**:1345–422.
12. Murray CJ, Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S. Comparative quantification of health risks: Conceptual framework and methodological issues. *Popul Health Metr* 2003;**1**:**1.**
13. Vos T, Carter R, Barendregt J. *Assessing Cost-Effectiveness in the Prevention (Ace-Prevention): Final Report*: School of Public Health, University of Queensland and Deakin University, 2010.
14. Van der Deen FS, Wilson N, Cleghorn C *et al.* Impact of five tobacco endgame strategies on future smoking prevalence, population health and health system costs: two modelling studies to inform the tobacco endgame. *Tob Control* 2018;**27**:278–86.
15. Blakely T, Cobiac LJ, Cleghorn CL *et al.* Health, health inequality, and cost impacts of annual increases in tobacco tax: multistate life table modeling in New Zealand. *PLoS Med* 2015;**12**: e1001856.
16. Mytton OT, Tainio M, Ogilvie D, Panter J, Cobiac L, Woodcock J. The modelled impact of increases in physical activity: the effect of both increased survival and reduced incidence of disease. *Eur J Epidemiol* 2017;**32**:235–50.
17. Briggs ADM, Cobiac LJ, Wolstenholme J, Scarborough P. PRIMEtime CE: a multistate life table model for estimating the cost-effectiveness of interventions affecting diet and physical activity. *BMC Health Serv Res* 2019;**19**:485.
18. Higashi H, Barendregt J. Cost-effectiveness of tobacco control policies in Vietnam: the case of personal smoking cessation support. *Addiction* 2012;**107**:658–70.
19. Ngalesoni F, Ruhago G, Mayige M *et al.* Cost-effectiveness analysis of population-based tobacco control strategies in the prevention of cardiovascular diseases in Tanzania. *PLoS One* 2017;**12**:e0182113.
20. Boshuizen HC, Lhachimi SK, van Baal PH *et al.* The DYNAMO-HIA model: an efficient implementation of a risk factor/chronic disease Markov model for use in Health Impact Assessment (HIA). *Demography* 2012;**49**:1259–83.
21. Kulik MC, Nusselder WJ, Boshuizen HC *et al.* Comparison of tobacco control scenarios: quantifying estimates of long-term health impact using the DYNAMO-HIA modeling tool. *PLoS One* 2012;**7**:e32363.
22. Lhachimi SK, Nusselder WJ, Smit HA *et al.* DYNAMO-HIA - a Dynamic Modeling tool for generic Health Impact Assessments. *PLoS One* 2012;**7**:e33317.
23. Tan-Torres Edejer T, Baltussen R, Adam T *et al. Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis*. Geneva: World Health Organization, 2003.
24. Hutubessy R, Chisholm D, Edejer TT, Who C. Generalized cost-effectiveness analysis for national-level priority-setting in the health sector. *Cost Eff Resour Alloc* 2003;**I**:8.
25. Lauer JA, Röhrich K, Wirth H, Charette C, Gribble S, Murray C. PopMod: a longitudinal population model with two interacting disease states. *Cost Eff Resour Alloc* 2003;**1**:6.
26. Bertram MY, Stenberg K, Brindley C *et al.* Disease control programme support costs: an update of WHO-CHOICE methodology, price databases and quantity assumptions. *Cost Eff Resour Alloc* 2017;**15**:21.
27. Stenberg K, Lauer JA, Gkountouras G, Fitzpatrick C, Stanciole A. Econometric estimation of WHO-CHOICE country-specific costs for inpatient and outpatient health service delivery. *Cost Eff Resour Alloc* 2018;**16**:11.
28. Salomon JA, Carvalho N, Gutierrez-Delgado C *et al.* Intervention strategies to reduce the burden of non-communicable diseases in Mexico: cost effectiveness analysis. *BMJ* 2012;**344**:e355.
29. Sun X, Faunce T. Decision-analytical modelling in health-care economic evaluations. *Eur J Health Econ* 2008;**9**:313–23.
30. Briggs A, Sculpher M. An introduction to markov modelling for economic evaluation. *Pharmacoeconomics* 1998;**13**: 397–409.
31. Barendregt JJ, Van Oortmarssen GJ, Van Hout BA, Van Den Bosch JM, Bonneux L. Coping with multiple morbidity in a life table. *Math Popul Stud* 1998;**7**:29–49.
32. Briggs ADM, Wolstenholme J, Blakely T, Scarborough P. Choosing an epidemiological model structure for the economic evaluation of non-communicable disease public health interventions. *Popul Health Metr* 2016;**14**: 17.
33. Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling Good Research Practices—overview: a report of the ISPOR-SMDM modeling good research practices task force-1. *Value Health* 2012;**15**:796–803.
34. Karnon J, Stahl J, Brennan A, Caro JJ, Mar J, Möller J. Modeling using discrete event simulation: a report of the ISPOR-SMDM modeling good research practices task force-4. *Value Health* 2012;**15**:821–27.
35. Siebert U, Alagoz O, Bayoumi AM *et al.* State-transition modeling: a report of the ISPOR-SMDM modeling good research practices task force-3. *Value Health* 2012;**15**:812–20.
36. Basu S. *Modeling Pubic Health and Healthcare Systems*. Oxford, UK: Oxford University Press, 2018.
37. Miller BG, Hurley JF. Life table methods for quantitative impact assessments in chronic mortality. *J Epidemiol Community Health* 2003;**57**:200–06.
38. Briggs A, Sculpher M, Claxton K. *Decision Modelling for Health Economic Evaluation*. New York, NY: Oxford University Press, 2006.
39. Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB. Model transparency and validation: A report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. *Value Health* 2012;**15**:843–50.
40. Barendregt J, Oortmarssen GJ, Vos T, Murray C. A generic model for the assessment of disease epidemiology: the computational basis of DisMod II. *Popul Health Metr* 2003;**1**:4.
41. Flaxman AD, Vos T, Murray C, eds A. *Integrative Metaregression Framework for Descriptive Epidemiology*. Seattle, WA: Institute for Health Metrics and Evaluation, 2015.
42. Cobiac L, Ikeda T, Nghiem N, Blakely T, Wilson N. Modelling the implications of regular increases in tobacco taxes as a tobacco endgame strategy. *Tob Control* 2015;**24**:e154–56.
43. Hoogenveen R, van Baal P, Boshuizen H, Feenstra T. Dynamic effects of smoking cessation on disease incidence, mortality and

quality of life: the role of time since cessation. *Cost Eff Resour Alloc* 2008;**6**:1–15.

44. Collins J , Mumford JE, Deason AW *et al.* Vivarium microsimulation tools used to model diseases and interventions. https://zenodo.org/record/2539177#.XEf-KM1xU2w. ihmeuw/vivarium_public_health v0.8.13 ed: Zenodo; 14 Jan 2019 (23 July 2020, date last accessed). Vivarium software code.
45. Foreman KJ, Marquez N, Dolgert A *et al.* Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. *Lancet* 2018;**392**:2052–90.
46. Blakely T. Major strides in forecasting future health. *Lancet* 2018;**392**:e14–15.
47. Hoogenveen RT, Boshuizen HC, Engelfriet PM, van Baal PH. You only die once: accounting for multi-attributable mortality risks in multi-disease models for health-economic analyses. *Med Decis Mak* 2017;**37**:403–14.