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Estimating the effect of differing assumptions on the population health impact of introducing a Reduced Risk Tobacco Product in the USA

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ABSTRACT

We use Population Health Impact Modelling to assess effects on tobacco prevalence and mortality of introducing a Reduced Risk Tobacco Product (RRP). Simulated samples start in 1990 with a US-representative smoking prevalence. Individual tobacco histories are updated annually until 2010 using estimated probabilities of switching between never/current/former smoking where the RRP is not introduced, with current users subdivided into cigarette/RRP/dual users where it is. RRP-related mortality reductions from lung cancer, IHD, stroke and COPD are derived from the histories and the assumed relative risks of the RRP.

A basic analysis assumes a hypothetical RRP reduces effective dose 80% in users and 40% in dual users, with an uptake rate generating ~10% RRP and ~6% dual users among current users after 10 years. Sensitivity study changes in tobacco prevalence and mortality from varying effective doses, current smoking risks, quitting half-lives and rates of initiation, switching, re-initiation and cessation. They also study extreme situations (e.g. everyone using RRP), and investigate assumptions which might eliminate the RRP-related mortality reduction. The mortality reduction is proportional to the dose reduction, increasing rapidly with time of follow-up. Plausible increases in re-initiation or dual users' consumption, or decreased quitting by smokers would not eliminate the drop.

1. Introduction

We have described (Weitkunat et al., 2015) an approach for assessing the population health impact of introducing a Reduced Risk Tobacco Product (RRP). As described there, the model involves two stages. The first stage starts with a defined group of individuals of a given sex and age range with a known initial distribution of conventional cigarette (CC) smoking habits that is representative of the population at a given time point. The population is then followed over a number of discrete time intervals under two Scenarios. In the Null Scenario, RRPs are not introduced and the smoking status of each individual (never, current, former) is updated at each interval based on a set of tobacco transition probabilities (TTPs) appropriate for CC use. In the RRP Scenario, RRPs are introduced and the status of each individual (never, current CC, current RRP, current dual use, former) is updated at each interval based on a set of TTPs assumed to be appropriate for this scenario. Note that "current CC smokers" and "current RRP users" refer to those who predominantly use the relevant product, with "dual users" being those with a substantial use of both products. Note also that the term "tobacco use" as used relates only to CC smoking and/or RRP use. At the end of this stage, each individual thus has a complete tobacco product use history over the follow-up period.

In the second stage, the tobacco histories are used to estimate relative risks (RR), compared to never tobacco users, of the four major smoking-related diseases - lung cancer, ischaemic heart

Abbreviations: CC, Conventional cigarette; COPD, chronic obstructive pulmonary disease; D, number of deaths; ED, equivalent dose; H, half-life; IHD, ischaemic heart disease; P, proportion of deaths attributed to tobacco; RE, relative exposure; RED, RE for dual use; REM, RE for RRP use; RR, relative risk; RRP, Reduced Risk Tobacco Product; S, population size; SAD, smoking attributable deaths; TTP, tobacco use transition probability; VNP, vaporized nicotine products.

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disease (IHD), stroke, and chronic obstructive pulmonary disease (COPD) - under the two Scenarios. For each individual, and for each period of follow-up, the RR is estimated using the negative exponential model. The model was originally used to describe the decline in excess relative risk (= RR−1) by time quit, and it has been shown to provide a good fit to data for the four smoking-related diseases (Fry et al., 2013; Lee et al., 2014a, 2012b, 2014b). These publications provided estimates for each disease of the half-life (H) of the excess relative risk, that is the time after quitting when it reaches half that for continuing smokers. Quitting may be regarded as switching from a relative exposure (RE) of 1 unit to 0 units, and a simple adaptation of the negative exponential model allows the excess relative risk to be estimated for switching to a reduced exposure, and has been shown (Lee et al., 2015) to adequately describe reductions in risk of lung cancer following reductions in amount smoked (Lee, 2013). In this paper we describe a further extension of the negative exponential model allowing more generally for multiple changes in effective dose that may result from initiation, quitting, re-initiation, and upward or downward switching of exposure.

The average RRs for each disease for individuals of a given sex and age group under each Scenario are then calculated for each follow-up year, from which the proportions of tobacco-attributable deaths from each of the four diseases are then derived. Using national estimates of numbers of deaths by disease for that sex, age group and year, numbers attributable to tobacco use are also derived. Differences in numbers and proportions between Scenarios then quantify the changes resulting from introducing the RRP. As noted elsewhere (Weitkunat et al., 2015), these estimates can be corrected for differing survival under the two Scenarios.

The work described here aims at understanding the sensitivity of the prevalence of tobacco use and mortality from smoking-associated diseases to the various parameters and assumptions used. To predict the population health impact of introducing a specific product, the model requires product-specific information. This includes population- and disease-specific mortality rates by sex, age and year, as well as estimates of the effective dose of the product relative to CCs and of the rate of product uptake. It should be noted that none of these estimates are intended to reflect likely effective doses and uptake rates for any specific RRP.

2. Methods

2.1. Population at baseline

The comparisons are based on counterfactual analyses. Representative samples of the US population in 1990 are generated, and then followed assuming either that the RRP had not been introduced in that year (Null Scenario) or that it had been (RRP Scenario). Thus the Null Scenario describes the factual situation, and the RRP Scenario the counterfactual situation. Analyses are carried out for males and females, the population followed up being initially aged 10–79 years. Each member of the sample is randomly allocated at baseline to a year of age, based on the age distribution of the population of the given sex for that time point as given in the United Nations website (United Nations, 2013). Given age and sex, each member is then randomly assigned to be a never, current or former smoker, based on published data on their relative frequencies (Forey et al., 2002; Forey and Lee, 2002; Lee et al., 2009). For former smokers, the age of quitting is then randomly allocated, assuming it cannot be less than 18 years, based on National Health Interview Survey data for 2006 (www.cdc.gov/nchs/nhis.htm). Table 1 presents the age-specific distributions of population and of smoking habits used to assign the initial status of each member of the simulated populations.

In the basic analysis and in all of the sensitivity analyses described below, the populations followed up of each sex, under both the Null and RRP Scenarios, are initially identical and of size 10,000. Exceptionally, in one analysis, in order to give insight into the magnitude of variation between simulations, 10 different populations of 10,000 of each sex were studied.

2.2. Estimation of histories of tobacco use

Under each Scenario, the tobacco use status of each member of the simulated population is estimated at each year of follow-up until the year 2010 (or age 79 if that came earlier).

Under the Null Scenario, the same set of TTPs, shown in Table 2, is used in all the analyses conducted. They are defined by the probabilities P_{NC} (initiation, from Never to Current smoking), P_{CF} (quitting, from Current to Former smoking) and P_{FC} (re-initiation, from Former to Current smoking). It is assumed that in each year of follow-up only one change of state can occur. The probabilities (expressed per million to assist readability) were derived initially from educated guesses which produced not unreasonable estimates of current and former smoking during follow-up. Comparison with rates calculated from data presented recently for a follow-up of a representative US sample (Weinberger et al., 2014) suggested that the initiation and quitting rates were reasonable, but the re-initiation rates had to be increased to those given in Table 2. TTPs are assumed to be independent of period of follow-up and of sex. Initiation rates are assumed to be zero at age 35+ years. Based on the US sample (Weinberger et al., 2014), re-initiation rates are assumed to be 48% of quitting rates. Note that the TTP for quitting, P_{CF}, is multiplied by TTP factor 2 (taken as 2 in the basic analysis) if the individual has previously quit. Also the TTP for re-initiation, P_{FC}, is multiplied by TTP factor 3 (taken as 2 in the basic analysis) if the individual is a short-term quitter (taken as up to 2 years in the basic analysis).

Under the RRP Scenario, there are 15 TTPs due to the additional possible states M (current RRP use) and D (current dual use). Three TTPs refer to initiation (P_{NC}, P_{NM}, P_{ND}), three to quitting (P_{CF}, P_{MF}, P_{DF}), three to re-initiation (P_{FC}, P_{FM}, P_{FD}) and six to switching product use (P_{CM}, P_{CD}, P_{MC}, P_{MD}, P_{DC}, P_{DM}). The TTPs were developed so that, 10 years after RRP introduction, approximately 84% of current product users would be CC smokers, 10% RRP users, and 6% dual users. The TTPs were also designed to reflect the fact that younger people may be less likely than older people to switch to RRP, because of cost. These TTPs were designed to study the effects of not implausible uptake rates for a hypothetical RRP. They may not apply, of course, to any specific RRP.

To ensure comparability with the TTPs in Table 2, various constraints were applied: the sum of the three TTPs for initiation should be equal to that for P_{NC} in the Null Scenario; the sum of the three TTPs for re-initiation should be equal to that for P_{FC} in the Null Scenario; and the three TTPs for quitting should each be equal to that for P_{CF} in the Null Scenario.

In the RRP Scenario TTP factors 2 and 3, as defined above, also apply to, respectively, all three quitting rates and all three re-initiation rates. However, two other TTP Factors are also relevant. The TTP associated with the switch P_{MC} is multiplied by TTP Factor 1 (taken as 2 in the basic analysis) if the individual has previously used CCs, except as noted below. The TTPs associated with the switches P_{MC} and P_{MD} are multiplied by TTP Factor 4 (taken as 0 in the basic analysis) if the individual has used RRP continuously for more than a defined period (taken as 2 years in the basic analysis). Note that if TTP Factor 4 is set to a value and an individual uses RRP continuously for more than the defined period, TTP Factor 1 is not applied. However, the user can choose to ignore (not set) TTP Factor 4, in which case TTP Factor 1 is relevant regardless of how long RRP

Table 1
US sex- and age-specific data on population and smoking habits for 1990.[a]

Sex	Age	Population (hundreds)	% current smokers	% former smokers	Distribution of time of quit (years)[b]					
					0	1–2	3–5	6–10	11–20	21+
Males	10–14	90413	0.0	0.0	–	–	–	–	–	–
	15–19	93115	20.0	4.4	69.4	30.6	–	–	–	–
	20–24	99492	30.7	9.1	30.2	40.3	29.5	–	–	–
	25–29	107776	35.1	14.4	27.3	30.2	21.1	21.4	–	–
	30–34	111413	34.7	19.7	20.3	15.4	36.7	23.7	3.9	–
	35–39	101077	33.0	24.8	10.2	11.3	18.5	29.6	30.4	–
	40–44	89185	31.9	30.5	8.8	5.1	13.5	15.9	56.7	–
	45–49	68739	32.0	36.6	7.2	6.3	10.6	17.5	35.8	22.6
	50–54	57142	30.1	42.2	8.6	6.8	11.0	8.7	33.4	31.5
	55–59	51965	28.5	46.9	7.7	6.5	12.9	17.4	22.2	33.3
	60–64	50602	25.8	51.5	2.5	3.6	7.7	13.0	30.9	42.3
	65–69	45859	21.6	56.1	1.8	4.6	8.7	12.9	28.3	43.7
	70–74	34917	18.6	60.6	0.6	1.5	14.8	8.7	27.2	47.2
	75–79	24601	15.2	55.7	1.8	4.9	2.8	6.3	29.7	54.5
Females	10–14	86055	0.0	0.0	–	–	–	–	–	–
	15–19	88397	18.5	5.0	60.2	39.8	–	–	–	–
	20–24	96369	26.9	12.8	34.1	34.0	31.9	–	–	–
	25–29	107257	29.2	15.9	17.3	19.9	31.1	31.7	–	–
	30–34	112405	29.5	18.8	20.1	22.8	19.7	26.7	10.7	–
	35–39	102936	26.6	21.5	10.0	12.6	20.3	24.2	32.9	–
	40–44	92403	26.4	22.1	10.7	16.7	19.9	20.6	32.1	–
	45–49	71777	26.7	23.2	9.1	7.8	11.1	20.2	32.9	19.0
	50–54	60079	25.5	24.8	5.6	9.8	9.9	20.9	26.2	27.6
	55–59	55797	22.4	26.7	4.5	5.6	8.4	11.2	28.9	41.4
	60–64	57949	20.4	28.5	2.7	5.0	9.1	11.6	33.2	38.4
	65–69	56485	15.8	30.3	4.1	3.2	7.9	12.8	22.5	49.5
	70–74	46881	14.1	32.1	0.5	3.4	2.6	11.8	25.8	55.9
	75–79	38036	10.0	19.6	1.2	1.9	3.1	6.3	28.3	39.4

[a] Sources used: Population - United Nations, 2013; Prevalence of current and former smoking - Forey et al., 2002; Forey and Lee, 2002; Lee et al., 2009; Time of quitting - www.cdc.gov/nchs/nhis.htm. See section 2.1 for further detail.
[b] The full available dataset separated 1–2 years into 1 and 2 years, 11–20 years into 11–15 and 16–20 years, and 21+ years into 21–30, 31–40 and 41–50 years.

Table 2
Monthly smoking transition probabilities (per million) under the Null Scenario.

Age	Initiation	Quitting	Re-initiation
	P_{NC}	P_{CF}	P_{FC}
10–14	2000	500	240
15–19	3500	1500	720
20–24	2000	2000	960
25–29	1000	2000	960
30–34	500	2000	960
35–54	0	2000	960
55–64	0	2500	1200
65–69	0	3000	1440
70–74	0	3500	1680
75–79	0	4000	1920

The probabilities of transition between the three states N = never, C = current and F = former, are described by P followed by two subscripts, the first representing the state changed from, and the second the state changed to.
P_{CF} is multiplied by TTP Factor 2 = 2 if the individual has previously quit.
P_{FC} is multiplied by TTP Factor 3 = 2 if the individual has quit for 2 years or less.

has been used.

The TTPs shown in Table 3 (initiation, quitting and re-initiation) and Table 4 (switching), again expressed per million, are those derived for use in the basic analysis, intended to be a suitable starting point for evaluating the effect of changes in specific parameters on estimates of deaths associated with the introduction of an RRP. A number of the sensitivity analyses described later vary these TTPs.

The methods described above build up a history of tobacco use for each individual from the age they were in 1990 to the age they would become at the end of the 20 year follow-up period. To extend these to a full lifetime history, it is further assumed that those initially classified as current smokers in 1990 started smoking at age 16 (or at age 15 if they were 15 in 1990), with no previous periods of quitting and re-initiation. For those initially classified as former smokers in 1990, where the age of quitting had been estimated, the age of starting to smoke was similarly allocated.

2.3. Estimating relative risks based on tobacco use histories

In each year of follow-up, an individual may be a non-smoker (never or former smoker), a current CC smoker, a current RRP user or a dual user. Relative exposure (RE) is defined as 0 for a non-smoker, 1 for a current CC smoker, and taken as 0.2 for RRP users and 0.6 for dual users in the basic analysis, values intended to be not implausible relative exposure estimates for a hypothetical RRP. The method of estimating the RR (relative to a non-smoker) by age for each disease depends on first calculating what is termed an equivalent dose (ED) at each age, and then multiplying this by the excess relative risk for a continuing CC smoker of that age. ED will start at 0, as no individual uses tobacco at birth. As soon as a switch occurs, ED will gradually increase towards the RE value for the product switched to. Subsequently, when RE increased (or decreases) at a further switch, ED gradually increases (or decreases) towards the new RE value.

Formally, the method can be defined as follows. Assume that, at each year of age, a, the individual's relative exposure is RE(a) and the half-life is H(a). First, calculate the negative exponential factor for a single year as $N(a) = \exp(-\log_e(2)/H(a))$. ED (1) is taken as 0, with subsequent of ED values then calculated by the formula $ED(a) = N(a)\ ED\ (a-1)+(1-N(a))\ RE(a)$.

Thus, ED is calculated based on the estimate of ED for the previous year, and the effective exposure in the current year. Note that, though the values of H(a) are derived from data on quitting, where

Table 3
Monthly tobacco use transition probabilities (per million) under the basic RRP Scenario – (a) Initiation, quitting and re-initiation rates.

Months of follow-up	Age	Initiation			Quitting			Re-initiation		
		P_{NC}	P_{NM}	P_{ND}	P_{CF}	P_{MF}	P_{DF}	P_{FC}	P_{FM}	P_{FD}
1–24	10–14	1840	80	80	500	500	500	144	48	48
	15–19	2940	280	280	1500	1500	1500	432	144	144
	20–24	1520	240	240	2000	2000	2000	576	192	192
	25–29	680	160	160	2000	2000	2000	576	192	192
	30–34	300	100	100	2000	2000	2000	576	192	192
	35–39	0	0	0	2000	2000	2000	576	192	192
	40–44	0	0	0	2000	2000	2000	576	192	192
	45–49	0	0	0	2000	2000	2000	576	192	192
	50–54	0	0	0	2000	2000	2000	576	192	192
	55–59	0	0	0	2500	2500	2500	720	240	240
	60–64	0	0	0	2500	2500	2500	720	240	240
	65–69	0	0	0	3000	3000	3000	864	288	288
	70–74	0	0	0	3500	3500	3500	1008	336	336
	75–79	0	0	0	4000	4000	4000	1152	384	384
25+	10–14	1680	160	160	500	500	500	96	96	48
	15–19	2380	560	560	1500	1500	1500	288	288	144
	20–24	1040	480	480	2000	2000	2000	384	384	192
	25–29	360	320	320	2000	2000	2000	384	384	192
	30–34	100	200	200	2000	2000	2000	384	384	192
	35–39	0	0	0	2000	2000	2000	384	384	192
	40–44	0	0	0	2000	2000	2000	384	384	192
	45–49	0	0	0	2000	2000	2000	384	384	192
	50–54	0	0	0	2000	2000	2000	384	384	192
	55–59	0	0	0	2500	2500	2500	480	480	240
	60–64	0	0	0	2500	2500	2500	480	480	240
	65–69	0	0	0	3000	3000	3000	576	576	288
	70–74	0	0	0	3500	3500	3500	672	672	336
	75–79	0	0	0	4000	4000	4000	768	768	384

Abbreviations used: CC = conventional cigarette; RRP = reduced risk tobacco product.
The probabilities of transition between the five states N = never, C = current CC, M = current RRP, D = current dual, and F = former, are described by P followed by two subscripts, the first representing the state changed from, and the second the state changed to.
P_{CF}, P_{MF} and P_{DF} are multiplied by TTP factor 2 = 2 if the individual has previously quit.
P_{FC}, P_{FM} and P_{FD} are multiplied by TTP factor 3 = 2 if the individual has quit for 2 years or less.

Table 4
Monthly tobacco use transition probabilities (per million) under the basic RRP Scenario – (b) Switching rates.

Months of follow-up	Age	Switching within current smoking groups					
		P_{CM}	P_{CD}	P_{MC}	P_{MD}	P_{DC}	P_{DM}
Any	10–14	150	30	400	400	400	400
	15–19	200	40	400	400	400	400
	20–24	300	60	400	400	400	400
	25–29	450	90	400	400	400	400
	30–34	450	90	400	400	400	400
	35–39	450	90	400	400	400	400
	40–44	450	90	400	400	400	400
	45–49	450	90	400	400	400	400
	50–54	450	90	400	400	400	400
	55–59	450	90	400	400	400	400
	60–64	450	90	400	400	400	400
	65–69	450	90	400	400	400	400
	70–74	450	90	400	400	400	400
	75–79	450	90	400	400	400	400

Abbreviations used: CC = conventional cigarette; RRP = reduced risk tobacco product.
The probabilities of transition between the five states N = never, C = current CC, M = current RRP, D = current dual, and F = former, are described by P followed by two subscripts, the first representing the state changed from, and the second the state changed to.
If the individual has used RRP continuously for more than 2 years P_{MC} and P_{MD} are multiplied by TTP factor 4 = 0.
If not, and the individual has previously used CCs P_{MC} is multiplied by TTP factor 1 = 2.

the change in RE is from 1 to 0, H(a) is used more generally in relation to any change in RE, including initiation, re-initiation, and upward or downward switching of exposure.

Table 5 shows the assumed values of the RR for continued CC smoking and of the quitting half-life, H, by disease, and age. These estimates are all derived from meta-analyses of published data, the sources being described in the footnote to the Table and in Supplementary File 1. Age-dependent estimates are included only where there is strong evidence of variation with age. There is little evidence of variation by sex, so the estimates are taken as applicable to both sexes. Figs. 1 and 2 illustrate how the estimated RRs for each disease vary with age for individuals with defined tobacco

Table 5
Assumed values of relative risks for continued CC smoking (RR) and quitting half-life (H) by disease.

	Age	Disease			
		Lung Cancer	IHD	Stroke	COPD
Relative risks	Any	11.68			4.56
	to 54		3.38	2.48	
	55 to 64		2.32	2.13	
	65 to 74		1.70	1.39	
	75 to 79		1.27	1.06	
Half-life	Any			4.78	13.32
	to 49	6.98	1.47		
	50 to 59	10.39	5.32		
	60 to 69	10.60	7.48		
	70 to 79	12.99	13.77		

Sources for relative risks: Lung cancer: Lee et al., 2012a Table 8; COPD: Forey et al., 2011 Table 7; IHD and Stroke: Supplementary file 1 Table 2.
Sources for half lives: Lung cancer: Fry et al., 2013 Table 6; COPD: Lee et al., 2014a Table 4; IHD: Lee et al., 2012b Table 5; Stroke: Lee et al., 2014b Table 5.

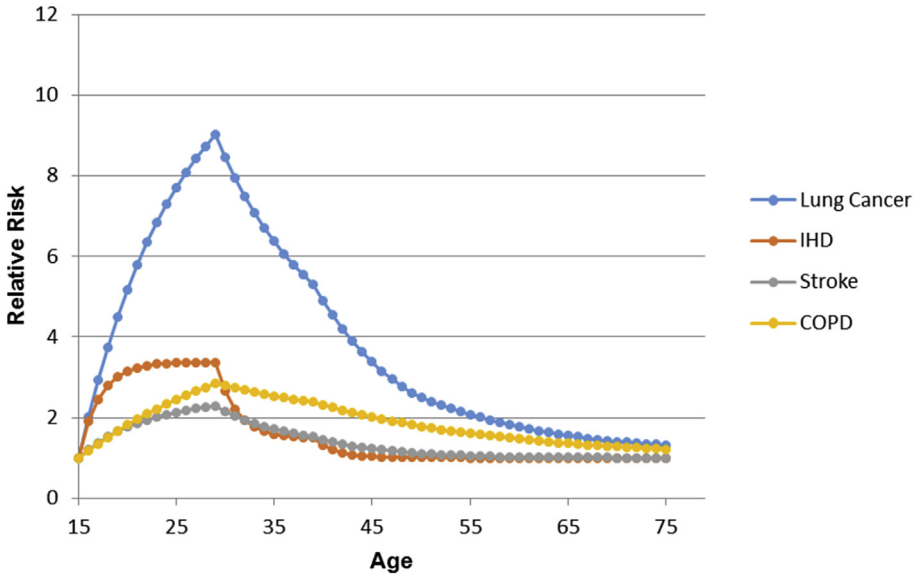


Fig. 1. Variation by age of estimated relative risks for each disease for an individual starting CC at age 16, switching to RRP use at age 30, and then quitting at age 40.

use patterns. In Fig. 1, the individual starts smoking CCs at age 16, switches to RRPs at age 30, and then quits at age 40. In Fig. 2, the individual starts smoking CCs at age 16, becomes a dual user at age 25, an RRP user at age 35, quits at age 40, and then re-initiates with CC smoking at age 50.

2.4. Estimating the number of deaths and increase in death rates associated with tobacco use

Under the Null Scenario we have, for each sex and year of follow-up, estimates (from the United Nations) for each age group of the population size (S), estimates (from the WHO) for each age group and disease of the number of deaths (D), together with the mean RR ($\overline{RR}$), as derived above. The proportion of deaths attributable to smoking (attributable risk proportion, ARP) is then calculated by ARP $= (\overline{RR}-1)/\overline{RR}$, and the number attributable to smoking (NA) calculated by NA $=$ S x ARP. Estimates of NA and of D can then be summed over age and/or year of follow-up, and a combined estimate of the proportion of deaths attributable to smoking can be estimated by dividing $\sum$NA by $\sum$D.

Corresponding estimates of numbers and proportions attributable to tobacco use are then derived using the same estimates of S and D from the same source files, but differing estimates of $\overline{RR}$ due to the scenario. The difference between the estimates for the two Scenarios quantifies the change associated with MTRP introduction.

In some analyses, adjustments are made for the change in population size associated with RRP introduction, using a method described previously (Weitkunat et al., 2015).

2.5. The basic analysis

Table 6 describes the 27 parameters used in the basic analysis. Of those listed, parameters 1–7, 16 and 18–22 do not vary in any analysis. Parameter 17, the number of simulations, is increased to the value 10 in an analysis aimed at assessing variability of the estimates used, while parameter 27 is set to be "Yes" in an analysis aimed at estimating the effect of adjustment for population size. Parameters 8–15 and 23–26 are varied as described below in section 2.6.

The appropriateness of the basic analysis Null Scenario assumptions was tested by comparison of International Smoking Statistics smoking prevalences for 1995, 2000, 2005 and 2010 with those predicted in the basic analysis. It was also tested by comparing published estimates of the population of deaths by cause attributable to smoking with those estimated in the basic analysis, as described in section 3.2. below.

2.6. Sensitivity analyses

The following sensitivity analyses were carried out, varying one parameter at a time from the values shown in Table 6.

Relative exposure for RRP use (REM): 0, 0.05, 0.1, 0.15, 0.25, 0.3, 0.35, 0.4, 0.5, 0.6 and 0.7 with the relative exposure (RE) for dual use either held at 0.6, or taken as (1+REM)/2, where REM is the relative exposure for RRP use

Relative exposure for dual use (RED): 0.4, 0.8, 1, 1.2, 1.5 and 2

TTP Factors 1, 2 and 3: 1, 1.5, 2.5 and 3

Definition of short-term quitting: 1, 3 years

TTP Factor 4: 0.5, 1 and "ignore"

Definition of short-term use of RRP: 1, 3 and 4 years

Relative risks: Excess relative risks based on the RRs given in Table 5 are multiplied by 0.8 or by 1.2. Also alternative RRs (US Surgeon General, 2014) are used (see Table 7).

Half-lives: The values given in Table 5 are multiplied by 0.8 or by 1.2.

Other sensitivity analyses varied the TTP values for the RRP Scenario shown in Tables 3 and 4

Relative frequency of initiation rates: P_{NM} and P_{ND} are either halved or multiplied by 1.5, with P_{NC} altered so that the sum of the three TTPs equals that in the Null Scenario. Exceptionally, for age 30–34 for follow-up 25+ months, where multiplying P_{NM} and P_{ND} by 1.5 would make P_{NC} become negative, P_{NM} and P_{ND} are set to 250 (per million) with P_{NC} set to 0.

Relative frequency of re-initiation rates: P_{FM} and P_{FD} are either halved or multiplied by 1.5, with P_{FC} altered so that the sum of the three TTPs equals that in the Null Scenario.

Initiation rates: In the first three analyses, P_{NM} and P_{ND} are multiplied by 1.5, 2 or 3 with P_{NC} unchanged. In the next five, all three TTPs are multiplied by 1.5, 2, 3, 4 or 8.

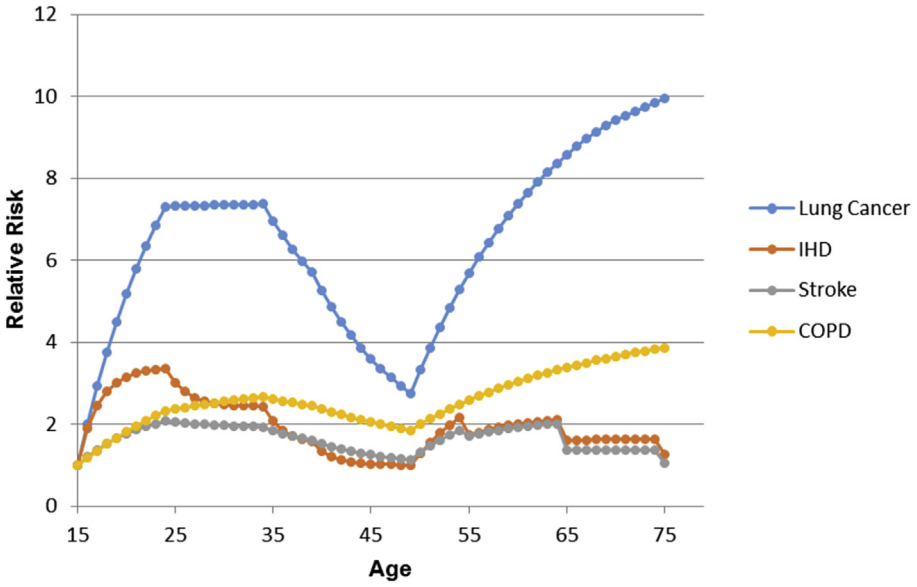


Fig. 2. Variation by age of estimated relative risks for each disease for an individual starting CC smoking at age 16, switching to dual use at age 25, becoming an RRP user at age 35, quitting at age 40, then re-initiating CC smoking at age 50.

Table 6
Assumptions and data used in the basic analysis.

Analysis No.	Variable Parameter	Values
1	Country	USA
2	Sex	males, females in separate analysis
3	Year of start	1990
4	Months of follow-up	240
5	Follow-up interval length (months)	12
6	Lower age for risk estimation	10
7	Upper age for risk estimation	79
8	Relative exposure for RRP use	0.2
9	Relative exposure for dual use	0.6
10	TTP factor 1[a]	2
11	TTP factor 2[a]	2
12	TTP factor 3[a]	2
13	Definition of short-term quitting (years)	2
14	TTP factor 4[a]	0
15	Definition of short-term use (years)	2
16	Number in population simulated	10000
17	Number of simulations	1
18	Source for population data	UN[b] (see Table 1 for 1990 data)
19	Source for current smoking prevalence data	ISS[c] (see Table 1 for 1990 data)
20	Source for former smoking prevalence data	ISS[c] (see Table 1 for 1990 data)
21	Source for quit-time distribution data	NHIS[d] (see Table 1 for data used)
22	Source for deaths by cause	WHO[e]
23	Source for relative risks	See Table 5
24	Source for half-lives	See Table 5
25	TTPs in Null Scenario	See Table 2
26	TTPs in RRP Scenario	See Tables 3 and 4
27	Adjustment for population size	None

Abbreviations used: CC = conventional cigarette; RRP = reduced risk tobacco product.
The probabilities of transition between the five states N = never, C = current CC, M = current RRP, D = current dual, and F = former, are described by P followed by two subscripts, the first representing the state changed from, and the second the state changed to.

[a] The TTP P_{MC} is multiplied by TTP Factor 1 if the individual has previously used CCs, except as noted below.The TTP P_{CF} in the Null Scenario and the TTPs P_{CF}, P_{MF} and P_{DF} in the RRP Scenario are multiplied by TTP Factor 2 if the individual has previously quit.The TTP P_{FC} in the Null Scenario and the TTPs P_{FC}, P_{FM} and P_{FD} in the RRP Scenario are multiplied by TTP Factor 3 if the individual is a short-term quitter.The TTPs P_{MC} and P_{MD} are multiplied by TTP Factor 4 if the individual has used RRP continuously for more than a defined period.Note that if TTP Factor 4 is set to a value and an individual uses RRP continuously for more than the defined period, TTP Factor 1 is not applied. However, the user can ignore (not set) TTP Factor 4, in which case TTP Factor 1 is relevant however long RRP has been used.

[b] The United Nations website (United Nations, 2013).

[c] ISS = International Smoking Statistics.

[d] National Health Interview Survey for 2006 (www.cdc.gov/nchs/nhis.htm).

[e] World Health Organization data downloaded on December 2014 (World Health Organization, 2013).

Re-initiation rates: In the first two analyses P_{FM} and P_{FD} are multiplied by 1.5 or 2, with P_{FC} unchanged. In the next four, all three TTPs are multiplied by 1.5, 2, 5 or 10.

Quitting rates: In the first four analyses, P_{MF} and P_{DF} are

Table 7
Current smoker relative risks (RRs) reported by the US Surgeon General.

Sex	Age	Lung Cancer	IHD	Stroke	COPD
Males	<55	14.33	3.88		
	55–64	19.03	2.99		
	65–74	28.29	2.76		
	75+	22.51	1.98		
	75			2.17	29.69
	75+			1.48	23.31
Females	<55	13.30	4.98		
	55–64	18.95	3.25		
	65–74	23.65	3.29		
	75+	23.08	2.25		
	75			2.27	38.89
	75+			1.30	20.96

Note that these estimates are applied to age 35+ years, while the basic estimates are restricted to ages up to 89 years.
The COPD RRs were taken as the mean of RRs for bronchitis/emphysema and for airways obstruction.
Source: US Surgeon General, 2014.

multiplied by 0.5, 0.75, 1.5 or 2 with P_{NM} and P_{CF} unchanged. In the next three, P_{CF} is multiplied by 0, 0.25 or 0.5 with P_{MF} and P_{DF} unchanged. In the final three, P_{CF} is multiplied by 0.9, 0.8 or 0.7, with P_{MF} and P_{DF} multiplied by the corresponding factors 1.5, 2.0 and 2.5. These three analyses aim to keep the overall quitting rate approximately constant.

Switching rates between current smokers: The first 18 analyses are six sets of three, each involving rates multiplied by 0.5, 5 or 10. The six sets vary in turn P_{CM} and P_{DM}, P_{CD} and P_{MD}, P_{MC} and P_{DC}, P_{CM} and P_{CD}, P_{MC} and P_{MD}, and P_{DC} and P_{DM}. In analyses 19 to 22, P_{MC} and P_{DC} are multiplied by 20, 50, 100 and 150.

Note that, in some of the analyses described above, some of the values of the factors tested are aimed at gaining information on when the estimated benefit associated with RRP introduction seen in the basic analysis is lost (see "zero benefit" analyses below).

2.7. Extreme situations

To bring the results of the basic and sensitivity analyses into context, analyses were run in four extreme situations, each affecting only the RRP Scenario.

1. All current smokers quit immediately, with no further initiation or re-initiation.
2. CC smoking is totally replaced by RRP use. Initiation rates for CC and dual use are added to that for RRP and then set to zero. The same applies to re-initiation rates. All switches are to RRP.
3. The whole population takes up RRP use at the start of follow-up, with no further CC smoking, dual use or quitting.
4. Current smokers who would otherwise have switched to RRP or dual use quit instead. Thus, the rates for CC smokers switching are added to the quitting rate and then set to zero.

2.8. Varying combinations of parameters

Each of the 16 possible combinations of two alternatives for four parameters are tested, the parameters being selected as those having a major effect on the drop in mortality associated with RRP introduction. The alternatives are:

1. REM 0.1 or 0.5, with RED varying concomitantly as 0.55 or 0.75.
2. Switching rates to RRP, PCM and PDM, 0.5 or 10 times the basic values.
3. Switching rates to CC, PMC and PDC, 0.5 or 10 times the basic values.
4. Quitting rates from RRP or dual use, P_{MF} and P_{DF}, 0.5 or 2 times the basic values.

A further similar analysis involved the same four parameters, but, for each parameter, fixed ratios of half and twice their basic value are considered, to allow more direct comparison of their effects.

2.9. Zero benefit analysis

Five parameters were initially considered which might individually, or in combination, reduce the effect of RRP introduction: dual users increasing their relative exposure by increasing their consumption; increasing initiation rates; increasing re-initiation rates; decreasing quit rates of CC smokers; and increasing switching rates to CC. In practice, it was found that two of the parameters had little effect on the estimated drop in deaths; increasing initiation rates, as initiation only affected younger ages, and increasing switching rates to CC, as this required the individual to have changed smoking status twice in the period studied. The analyses were therefore restricted to the other three parameters. For these three, a sequence of five alternative values (V_1, V_2, …V_5) was chosen which successively reduced the expected drop in deaths, the first analysis using all the V_1 values, the second all the V_2 values, and so on. The values of V_1 to V_5 for each of the three parameters were estimated as equal to the basic value plus 10%, 20%, 30%, 40% or 50% of the difference between the "elimination value" and the basic value, the elimination value being that value which, in an analysis varying only that parameter, led to the drop in deaths being approximately zero.

3. Results

Full details of all the analyses conducted are available in Supplementary File 2, and in particular in its Appendix 20, which summarizes results for mortality, and its Appendix 22, which summarizes results for tobacco prevalence. The main findings are referred to below. Statements made in the text below that are not directly supported by the material presented in this paper are supported by results in that Supplementary File.

3.1. The basic analysis

Fig. 3 (males) and Fig. 4 (females) show the prevalences of tobacco use predicted by the Null and RRP Scenarios by sex and time of follow-up for selected age groups (30–34, 50–54 and 70–74).

In males, the prevalence of never tobacco use decreases with age and, for each age group, increases with time of follow-up (since earlier born cohorts smoked less). The pattern is essentially the same for each Scenario, as overall initiation rates do not differ between them. Also, the prevalence of former use increases with age, and decreases with time of follow-up within age for both Scenarios. The overall prevalence of current use reduces somewhat with age, but varies little by time of follow-up within age. As expected, the prevalence of current CC smokers falls over time in the RRP Scenario, with RRP and dual users making up the rest, RRP users generally exceeding dual users.

In females, the pattern is less clear, with an increase in never users and a decrease in former users with time of follow-up only being clearly seen at age 30–34. The overall proportion of current users declines with age, but within age only shows a clear decrease over time at younger ages. As for males, the prevalence of current RRP and dual users rises over time, with RRP users outnumbering

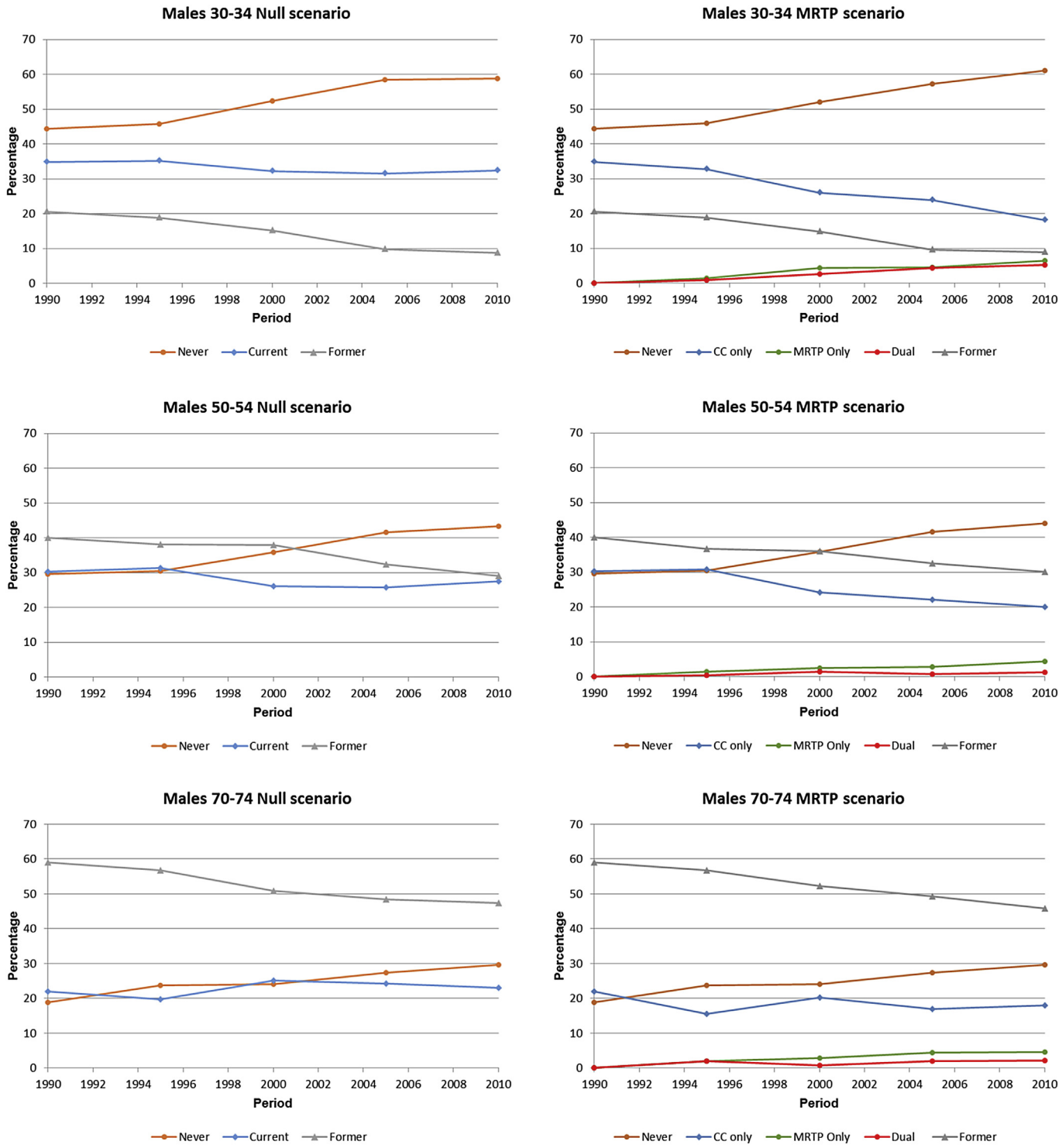


Fig. 3. Prevalences of tobacco use for males for the basic analysis by year of follow-up and age.

dual users.

Table 8 summarizes the main results for the drop in mortality associated with RRP introduction by sex, disease, period and age. For the four diseases combined and the whole 20 year follow-up, RRP introduction is associated with a drop of 35,206 deaths in males and 16,403 in females. These represent, respectively, 0.606% in males and 0.421% in females of all deaths and 1.549% in males and 1.260% in females of all deaths attributable to tobacco. In both sexes, drops in numbers of deaths are greatest for IHD, and least for stroke. However (see footnotes to Table 8), as a percentage of attributable deaths, drops are clearly greater for IHD and stroke than for lung cancer and COPD, reflecting the shorter H values for the vascular diseases. Percentage drops in total deaths are much more similar by disease.

Effects of RRP introduction, however measured, clearly increase by year of follow-up, reflecting the increase over time in the

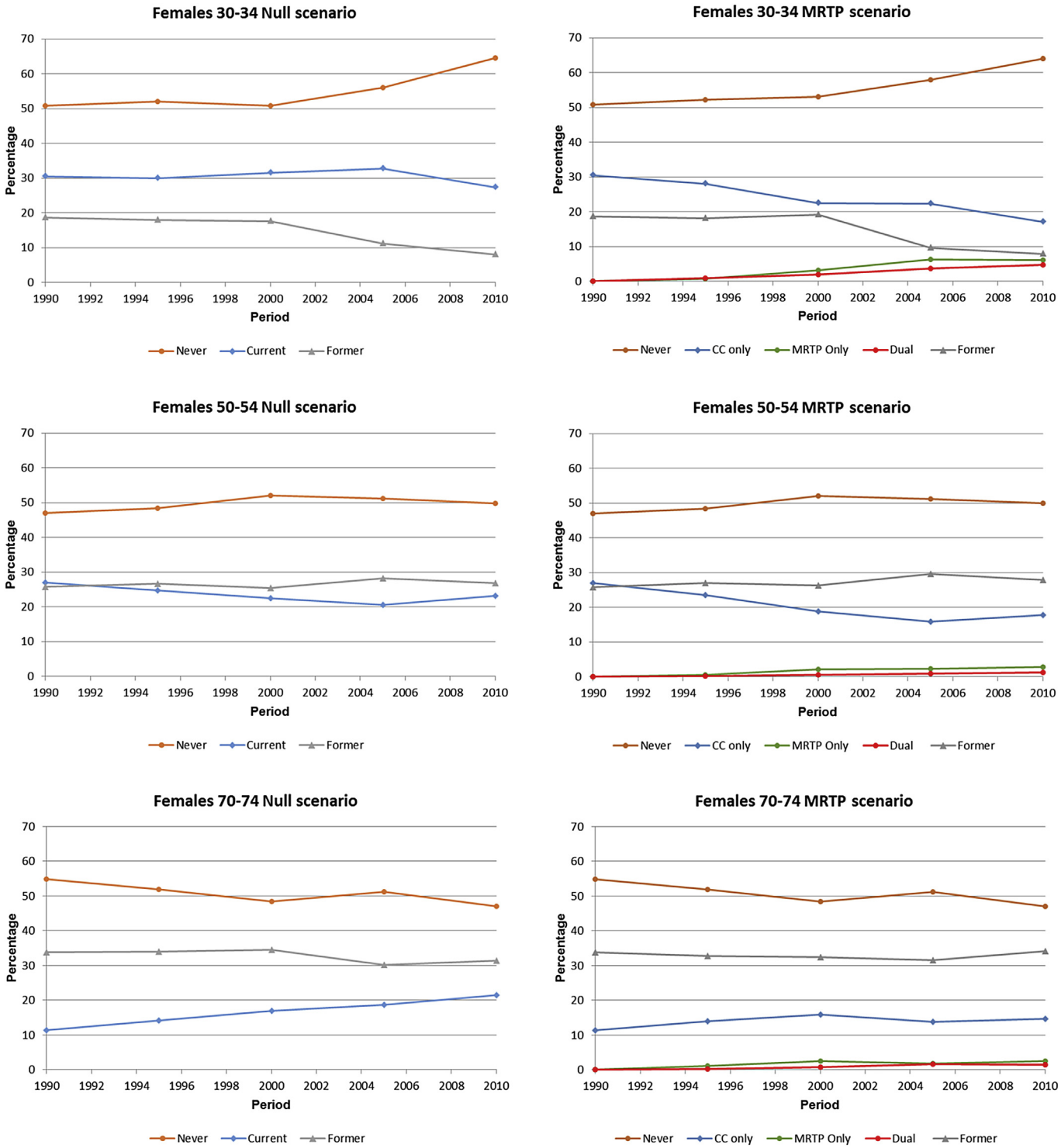


Fig. 4. Prevalences of tobacco use for females for the basic analysis by year of follow-up and age.

prevalence of current RRP users. This is true for each disease, but the patterns of the drop by age vary by disease and sex, reflecting the relative frequency of overall deaths by age for the different diseases, the differing H values by disease, and the age-dependence of RRs for IHD and stroke. Fig. 5 illustrates how the % drop in attributable deaths varies by time, for the four diseases separately and combined. Clearly, had the follow-up period been longer than 20 years, the % drop associated with RRP introduction would have increased substantially.

3.2. Appropriateness of the estimates from the Null Scenario

Fig. 6 (males) and Fig. 7 (females) compare the Null Scenario and International Smoking Statistics estimates of current and former smoking prevalence for ages 30–34, 50–54 and 70–74 and for years 1990, 1995, 2000, 2005 and 2010. For the years 1990 and 1995 the two estimates agree quite well, though for later years the correspondence is less good. The correspondence is also clearly better for ages 30–34 and 50–54 than for ages 70–74 years. Exact

Table 8
Drop in mortality associated with RRP introduction in basic analysis.

Year	Age	D	D	D	D	D	% D	% DA
		Lung cancer	IHD	Stroke	COPD	Four diseases	Four diseases	Four diseases
Males								
1990–2009	30–79	7688	19189	3064	5266	35206	0.606[a]	1.549[b]
1995	30–79	154	434	82	86	756	0.249	0.637
2000	30–79	446	1083	174	327	2031	0.668	1.766
2005	30–79	641	1653	231	460	2896	1.063	2.689
2009	30–79	844	2024	317	575	3759	1.481	3.708
1990–2009	45–49					2375	1.061	2.160
1990–2009	55–59					2686	0.510	1.123
1990–2009	65–69					5110	0.506	1.273
1990–2009	75–79					6972	0.473	1.679
Females								
1990–2009	30–79	4508	6963	2219	2714	16403	0.421[c]	1.260[d]
1995	30–79	22	66	21	11	120	0.060	0.190
2000	30–79	104	278	87	45	512	0.246	0.751
2005	30–79	405	641	209	243	1498	0.803	2.207
2009	30–79	890	1003	328	641	2862	1.656	4.295
1990–2009	45–49					1373	1.259	2.581
1990–2009	55–59					2528	0.918	2.023
1990–2009	65–69					2826	0.443	1.188
1990–2009	75–79					567	0.045	0.213

Abbreviations used: D = drop in deaths; % D = % drop in deaths; % DA = % drop in attributable deaths.
[a] %D for males for 1990–2009 were 0.521, 0.640, 0.488 and 0.739 for respectively, lung cancer, IHD, stroke and COPD.
[b] %DA for males for 1990–2009 were 0.663, 3.006, 3.625 and 1.349 for respectively, lung cancer, IHD, stroke and COPD.
[c] %D for females for 1990–2009 were 0.460, 0.422, 0.356 and 0.420 for respectively, lung cancer, IHD, stroke and COPD.
[d] %DA for females for 1990–2009 were 0.633, 2.995, 3.620 and 0.915 for respectively, lung cancer, IHD, stroke and COPD.

correspondence is not to be expected for various reasons. These include variation due to the simulation process, inaccuracies in the International Smoking Statistics estimates, and estimates for the USA not being available past 2005 at the time the calculations were conducted, estimates for later years being taken to be the same as in 2005. Also the modelling assumes that the initial sample survives throughout follow-up, with no account taken of differential mortality by smoking habit, or of immigration or emigration. While it would have been possible to modify the set of TTPs used to improve the fit, for example by allowing the TTPs to vary by time, it seems unlikely that this would have affected the main conclusions from the sensitivity analyses.

Table 9 compares estimates of smoking attributable deaths (SADs), expressed both as percentages of total deaths from the cause and as percentages of the SAD for the four diseases combined, between those estimated in the Null Scenario for 1990, 2005 and 2009 and those estimated from two other sources. One is a set of estimates (US Surgeon General, 2014) relating to the age group 35 years or older and the period 2005–2009. The other is calculated from data in Morbidity and Mortality Weekly Report (Centers for Disease Control and Prevention (CDC), 1993) for 1990 for age 35 years or older. Comparing SAD as a percentage of total deaths from the cause, the results for most diseases seem quite similar between PHIM and the published data, especially when compared with the Surgeon General estimates. However, there is a striking difference for COPD, with the Null Scenario estimates much lower in both sexes. This difference mainly arises due to the much lower current smoking RRs assumed in our analyses. While (see Table 5) we assumed a value of 4.56 for both sexes, the other estimates were higher, particularly for 2005–2009. Thus the estimates for 1990 (Centers for Disease Control and Prevention (CDC), 1993) were 9.7 for males and 10.5 for females, while those for 2005–2009 (US Surgeon General, 2014) were 29.69 at age 65–74 and 23.01 at age 75+ for males, and 38.89 at age 65–74 and 20.96 at age 75+ for females. Given that our estimate was based on a published meta-analysis (Forey et al., 2011) involving 39 North American studies, with the 95% confidence interval for our estimate as narrow as 3.69 to 5.62, it seems likely that the Surgeon General's RR estimates is far too high. While the meta-analysis (Forey et al., 2011) we used was based on studies published up to 2008, and incorporation of more recent data may somewhat modify the estimate of 4.56, it still seems unlikely that the Surgeon General's estimate would be appropriate.

3.3. Simulation analysis

While the basic analysis involved only a single run of 10,000 individuals per sex, the simulation analysis involved 10 runs per sex, the first run being the same as in the basic analysis. As shown in Supplementary File 2, standard errors of tobacco use prevalences were generally small. For example, for males aged 50–54 for the year 2010, mean percentages (standard errors) in the Null Scenario were 26.37 (0.34) for current smokers and 29.57 (0.38) for former smokers, while in the RRP Scenario they were 21.03 (0.48) for current CC smokers, 3.99 (0.16) for current RRP users, 1.29 (0.08) for current dual users and 29.40 (0.29) for former users. Standard errors were similarly low for females, other age groups and at other time points.

Standard errors, expressed as a percentage of the mean, were somewhat greater for the estimated drop in numbers of deaths associated with RRP introduction. Thus for the whole follow-up period and age 30–79, means (standard errors) for males were 7,274 (342) for lung cancer, 20,329 (977) for IHD, 3,195 (158) for stroke, 4,676 (187) for COPD, and 35,473 (1,627) for the four diseases combined. For females they were 5,249 (458) for lung cancer, 7,084 (492) for IHD, 2,207 (136) for stroke, 3,940 (425) for COPD, and 18,479 (1,478) for the four diseases combined.

While clearly carrying out 10 simulations provides greater precision, at the cost of increased computing time, use of a single simulation in the sensitivity analyses should nonetheless allow good understanding of the relative importance of the different parameters.

3.4. Sensitivity analyses

3.4.1. Adjustment for population size

This adjustment only affects the estimates of risk, reducing the

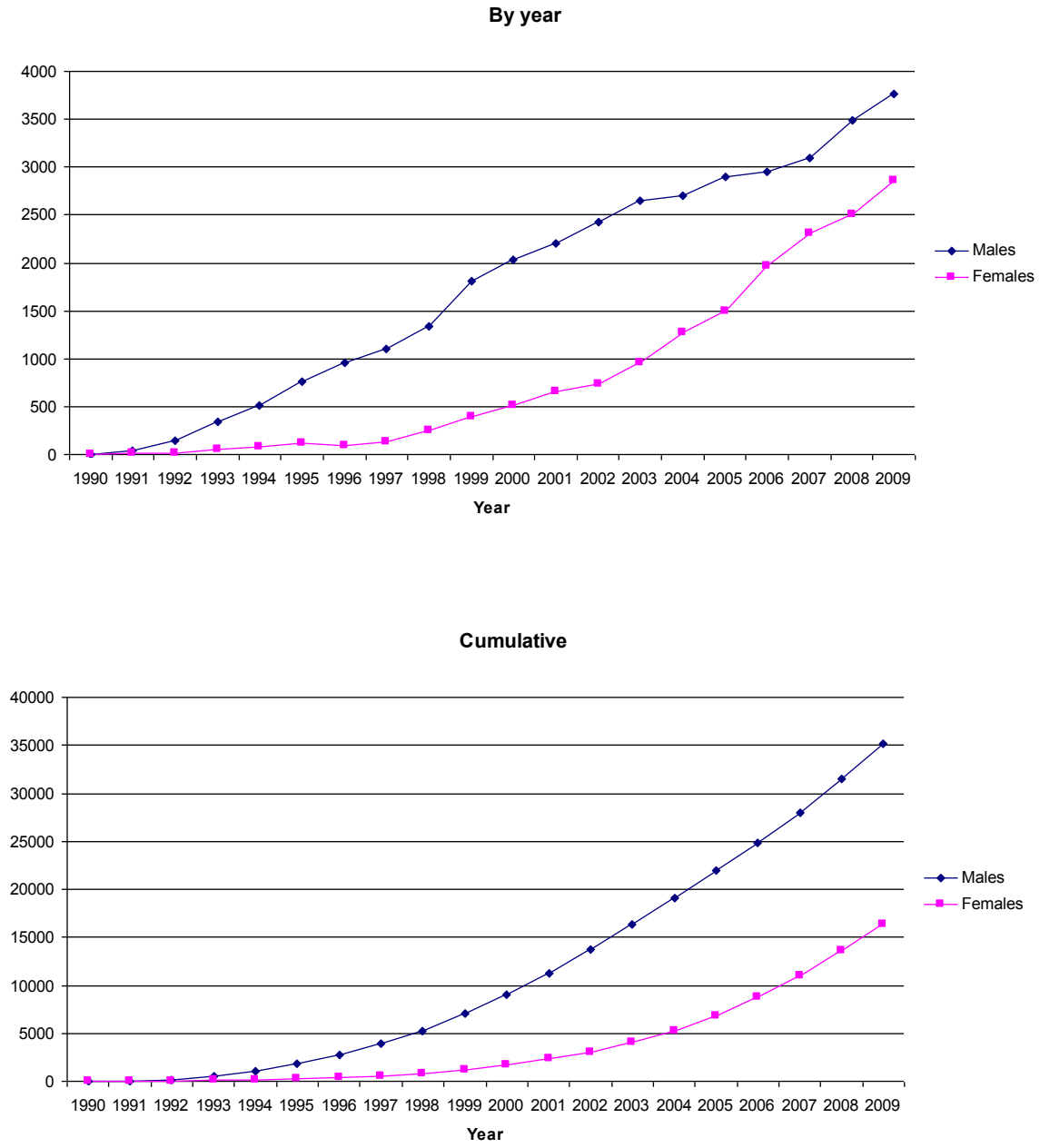


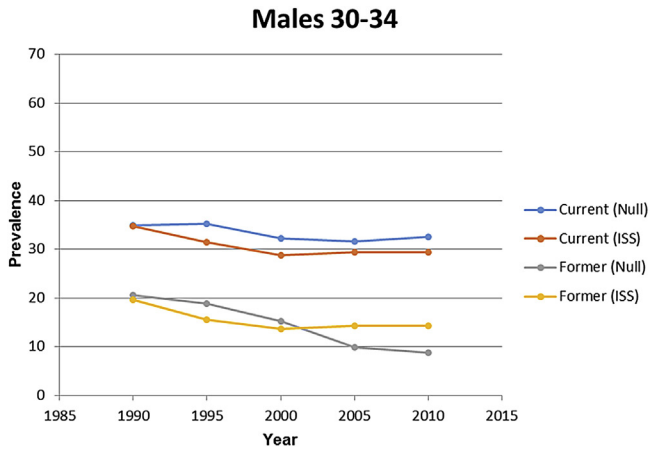
Fig. 5. Effect of length of follow-up on the estimated drop in deaths at ages 30–79 associated with RRP introduction, by year and cumulative.

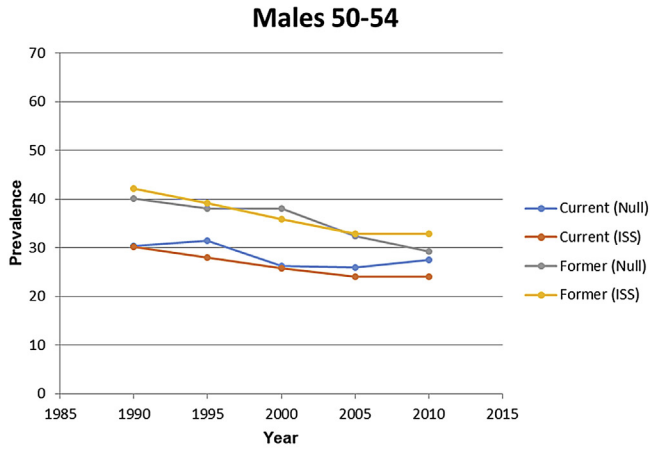
drop in mortality associated with the introduction of RRP. The effects were quite modest, very small indeed for IHD and stroke, and still not large for lung cancer and COPD. For males, for the whole follow-up period and age 30–79, adjustment changed the percentage drop in attributable deaths from 0.663 to 0.625 for lung cancer, 3.006 to 2.983 for IHD, 3.628 to 3.607 for stroke, 1.349 to 1.303 for COPD, and from 1.549 to 1.514 for the four diseases combined. For females, they were less than this, with adjustment reducing the drop by less than 1% in all cases. It is clear that inferences drawn from the following sensitivity analyses, which are based on unadjusted data, would not have been materially affected had they been based on adjusted data.

3.4.2. *Varying parameters that do not affect the TTPs*

Among the sensitivity analyses shown in section 2.6, four do not affect estimates of tobacco use prevalence, the REs for RRP and dual use, and the RR and H values. Table 10 shows how the drop in the number of deaths associated with RRP introduction for the whole follow-up period varies with these factors. Compared with the basic analysis, the drop in numbers of deaths declines as expected for both REs, whether considered on their own or in combination. As also shown in Fig. 8, this is most clearly evident when the REs are set to vary concomitantly, with dual users having the average value for CC and RRP. Here the drop declines quite linearly. This allows two conclusions. Firstly, it would extrapolate to approximately zero if exposure were identical for CC and RRP. Second, even if switching to the RRP were equivalent, as regards risk, to quitting smoking, the RE being 0 (a 100% reduction in exposure), the estimated drop in deaths would only be about 25% greater than if the RE were, as in the basic analysis, assumed to be 0.2 (an 80% reduction in exposure).

Note that values of RED can only exceed 1 if it is assumed that





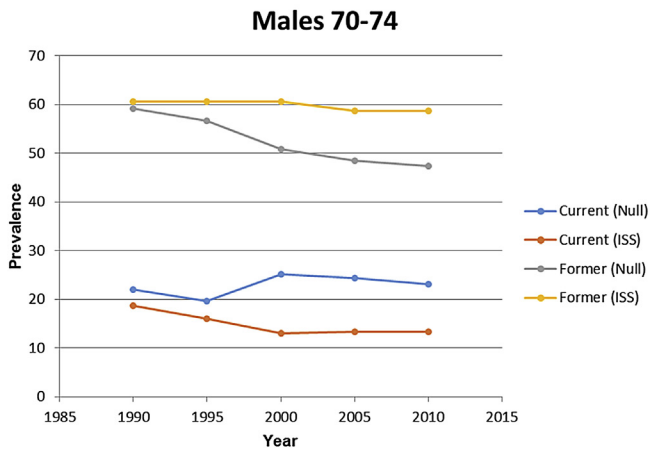
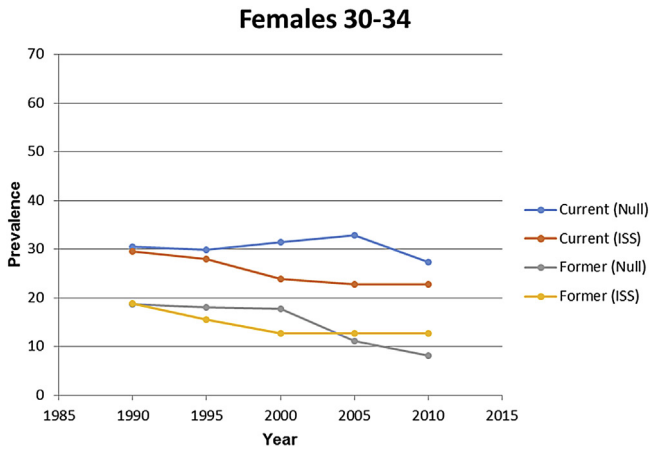
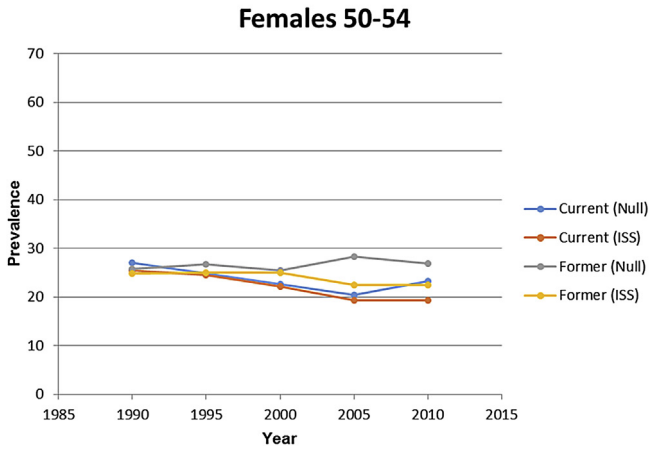


Fig. 6. Comparison of Null Scenario and International Smoking Statistics estimates of male current and former smoking prevalences by year of follow-up and age.





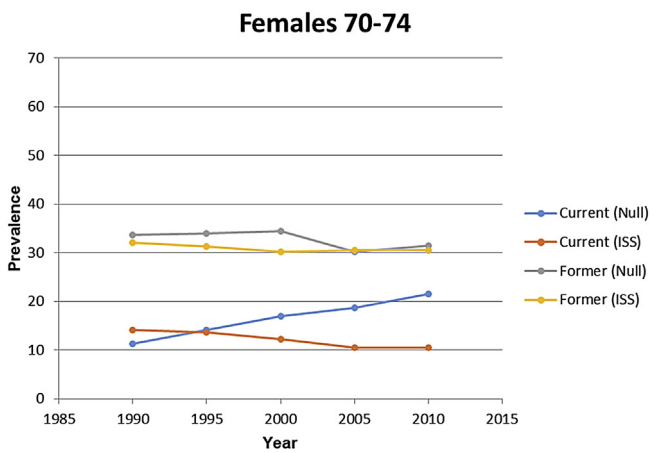


Fig. 7. Comparison of Null Scenario and International Smoking Statistics estimates of female current and former smoking prevalences by year of follow-up and age.

such users increase their overall consumption. Thus, a value of 1.2 would be equivalent to a 20 a day CC smoker using 20 of each product a day on becoming a dual user (among other possibilities). The value of 2.0 tested would indicate even greater consumption (e.g. 32 CCs and 40 RRPs a day) and was only included to see whether an increase in consumption could eliminate the drop in deaths. Clearly it could not, unless exposure from the RRP was only slightly reduced from that for CC smoking and introduction of the RRP increased consumption.

The overall estimated drop in number of deaths resulting from RRP introduction was increased by increasing the RR estimate, particularly in males where the estimate based on US Surgeon General RR values was increased to 40,091 from the basic analysis estimate of 35,206. Increases were also seen for IHD and stroke, but not for lung cancer and COPD where the relationship was in the opposite direction. Note that modifying RR values affects the estimated mortality in both the Null and RRP Scenario, implying that for lung cancer and COPD the rise in attributable deaths as RR

Table 9
Comparison of smoking attributable deaths (SAD) between basic analysis (Null Scenario) and other published estimates.

Sex	Source/year[a]	Lung cancer	IHD	Stroke	COPD	Four diseases
SAD as % of deaths from cause[b]						
Males	MMWR 1990	89.3	26.0	26.8	81.5	45.0
	Null 1990	80.5	22.4	14.0	57.1	39.7
	Null 2005	77.5	21.4	13.7	53.5	39.5
	Null 2009	76.8	21.5	14.1	52.5	39.9
	USSURG 2005-09	83.7	28.2	15.3	82.0	46.1
Females	MMWR 1990	71.4	14.2	9.6	66.4	24.9
	Null 1990	71.8	12.8	9.5	43.7	28.7
	Null 2005	72.9	15.2	10.5	46.8	36.4
	Null 2009	72.7	15.9	10.9	46.7	38.6
	USSURG 2005-09	80.7	19.4	8.7	75.7	36.8
SAD as % of SAD from four diseases						
Males	MMWR 1990	40.3	32.5	7.4	19.7	100.0
	Null 1990	50.4	30.5	3.6	15.4	100.0
	Null 2005	51.0	27.0	3.7	18.3	100.0
	Null 2009	51.1	26.0	3.8	19.1	100.0
	USSURG 2005-09	38.2	31.7	4.2	25.9	100.0
Females	MMWR 1990	35.1	33.0	8.2	23.7	100.0
	Null 1990	53.5	22.0	5.6	18.9	100.0
	Null 2005	55.3	16.0	4.3	24.2	100.0
	Null 2009	55.8	14.2	4.1	25.9	100.0
	USSURG 2005-09	37.3	24.8	4.7	33.2	100.0

[a] PHIM data are from base case scenario and for age 30–79 (see Appendix 1 of Supplementary file 2).Morbidity and Mortality Weekly Report (MMWR) data are from Centers for Disease Control and Prevention (CDC) (1993) and for age 35+. ICD-9 codes used are: lung cancer 162, IHD 410–414, stroke 430–438, COPD 491–492, 496. US Surgeon General (USSURG) data are from US Surgeon General, 2014 and also for age 35+. ICD-10 codes are used: lung cancer C33-C34, IHD I20-I25, Stroke I60-I69, COPD J40- J44.
[b] Total numbers of deaths by cause for age 35+ were not given, so, in order to calculate the percentage SAD formed of all deaths, WHO data were used. For lung cancer, IHD and stroke, the definitions of the diseases were exactly as used in MMWR, but for COPD the definition used differed (ICD9 490–493, 495, 496) somewhat.

Table 10
Effect of varying relative exposures, relative risks and half-lives on the drop in number of deaths associated with RRP introduction for 1990–2009 for age 30-79.

Factor varied	Value	D	D	D	D	D	% D	% AD
		Lung cancer	IHD	Stroke	COPD	Four diseases	Four diseases	Four diseases
Males								
None	Basic	7688	19189	3064	5266	35206	0.606	1.549
REM (RED = 0.6)	0	9065	23042	3655	6126	41888	0.720	1.843
	0.7	4329	9712	1603	3149	18792	0.323	0.827
REM (RED=(REM)/2)	0	9417	23983	3801	6353	43554	0.749	1.916
	0.7	3493	7439	1247	2598	14776	0.254	0.650
RED (REM = 0.2)	0.4	8384	21056	3354	5717	38512	0.662	1.694
	1.2	5626	13636	2200	3923	25385	0.437	1.117
	2.0	2942	6346	1058	2159	12505	0.215	0.550
Relative risk (RR)	Basic × 0.8	8597	17054	2643	5269	33562	0.577	1.626
	Basic × 1.2	6925	20897	3428	5168	36418	0.626	1.488
	USSURG	4833	27414	5763	2081	40091	0.690	1.295
Half-life (H)	Basic × 0.8	9845	21672	3456	6454	41427	0.713	1.852
	Basic × 1.2	6292	17236	2746	4509	30782	0.529	1.338
Females								
None	Basic	4508	6963	2219	2714	16403	0.421	1.260
REM (RED = 0.6)	0	5571	8362	2644	3491	20068	0.515	1.541
	0.7	1906	3510	1165	714	7375	0.189	0.566
REM (RED=(REM)/2)	0	5796	8667	2738	3653	20854	0.535	1.601
	0.7	1371	2771	935	401	5477	0.140	0.421
RED (REM = 0.2)	0.4	4952	7569	2406	3035	17962	0.461	1.379
	1.2	3189	5162	1660	1756	11767	0.302	0.904
	2.0	1467	2793	923	493	5675	0.146	0.436
Relative risk (RR)	Basic × 0.8	4936	6186	1929	2638	15690	0.402	1.337
	Basic × 1.2	4124	7578	2461	2727	16890	0.433	1.198
	USSURG	3363	9500	3065	1024	16953	0.435	0.857
Half-life (H)	Basic × 0.8	5534	7619	2482	3232	18866	0.484	1.471
	Basic × 1.2	3825	6419	2003	2376	14623	0.375	1.112

Abbreviations used: D = drop in deaths; % D = % drop in deaths; % DA = % drop in attributable deaths. REM = relative exposure for RRP; RED = relative exposure for dual use; USSURG = US Surgeon-General relative risk estimates (see Table 7).

increases is less than for the Null Scenario.

Lengthening H reduced the estimated deaths saved by RRP introduction, consistently seen in both sexes and for all diseases.

Changes in TTP factors 1 and 4 (and the definition of a short-term user) did not affect the distribution of tobacco use in the Null Scenario, and only had a very small effect in the RRP Scenario. Consequently they only had a very small effect on the estimated drop in deaths associated with RRP introduction (See Table 6

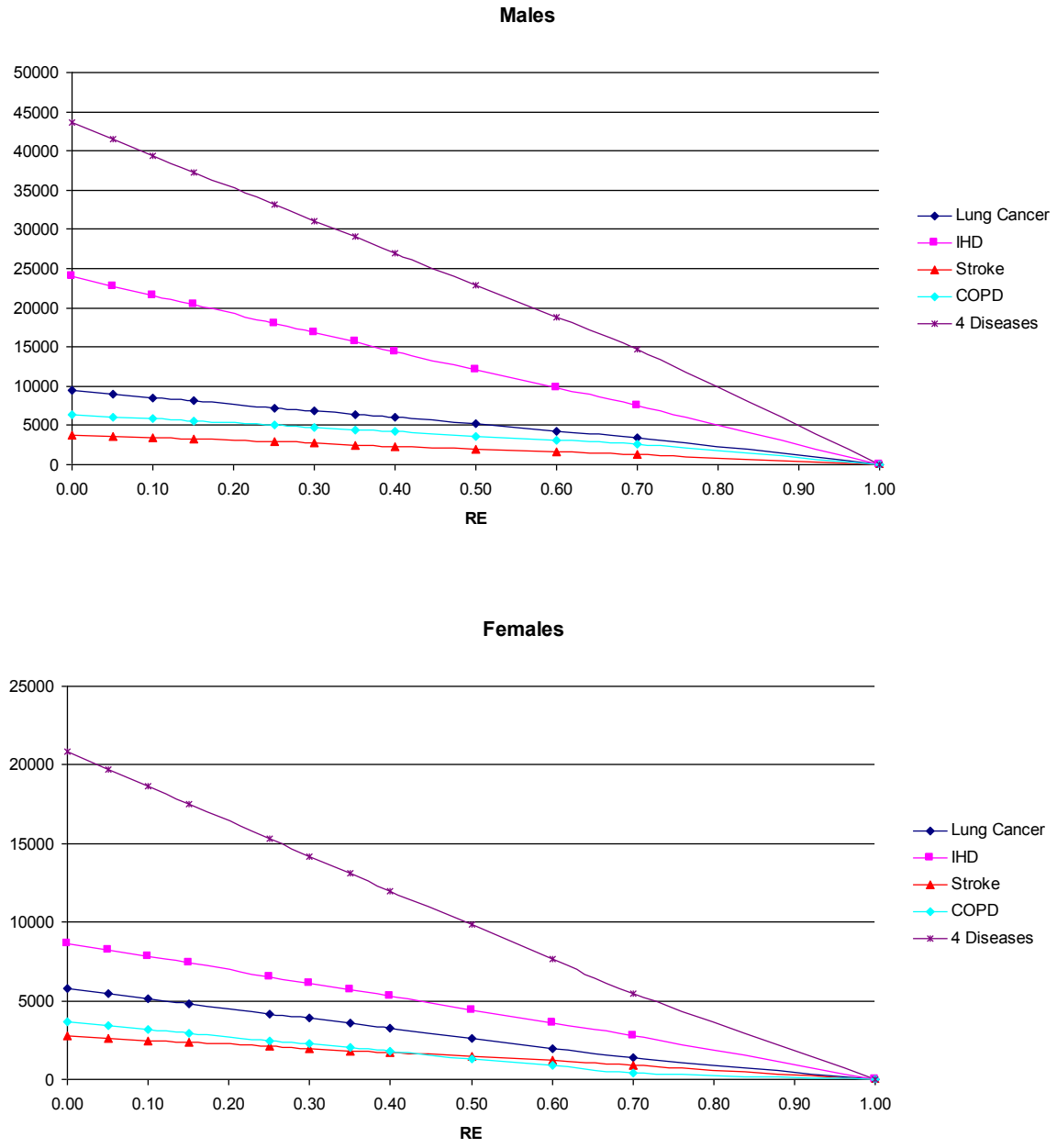


Fig. 8. Effect of varying the effective dose (RE) for RRP only users on the estimated drop in deaths associated with RRP introduction for age 30–79 years and the period 1990–2009. The effective dose for dual users is taken as (1+RE)/2.

footnotes for the definition of the TTP factors.).

Changes in TTP factors 2 and 3 (and the definition of a short-term quitter) do affect tobacco use in both Scenarios. However, the effect is very small in relation to TTP factor 3, as they require a relatively rare event, re-initiation by a short-term quitter. The effects of TTP factor 2 are clearer, increasing the percentage of quitters at the expense of current users, but are very small at younger ages and quite modest at older ages. For example, in males of age 70–74, increasing TTP factor 2 from 1 to 3 only increased the percentage of former users from 45.23% to 48.85% in the Null Scenario and from 43.51% to 47.52% in the RRP Scenario. This increase was associated with a decrease in the drop in deaths from 36,958 to 32,882 for the four diseases combined, with the corresponding decrease for females being from 17,044 to 16,022.

3.4.3. Varying the TTPs

Table 11 shows the effect of varying TTPs in the RRP Scenario on estimated tobacco use. Illustrative results are shown for the age 50–54, and for 25 variations from the basic analysis. Table 12 shows the effect of these variations on the estimated drop in mortality associated with RRP introduction for the whole follow-up period and age 30–79. From these results, and the additional results shown in Supplementary File 2, various conclusions can be drawn.

3.4.3.1. Initiation. Initiation is assumed only to occur up to age 30–34, so variation in initiation rates has no effect at all, within the 20-year follow-up, on smoking prevalence at age 70–74. It also has only a small effect at age 50–54, so that even as much as an eight-fold increase in each of the three initiation rates only increases the estimated overall percentage of current users in 2010 to 29.1% in

Table 11
Effect of varying TTPs in the RRP Scenario on the estimated prevalence of tobacco use in 2010 at age 50-54.

Analysis No.	Factor varied	Value	Never	CC	RRP	Dual	Former
Male							
1	None	Basic	44.14	20.34	4.43	1.29	30.10
2	Initiation	P_{NM}, $P_{ND} \times 0.5$[a]	44.14	20.13	4.25	1.29	30.19
3		P_{NM}, $P_{ND} \times 1.5$[a]	44.14	19.94	4.52	1.29	30.10
4	Re-initiation	P_{FM}, $P_{FD} \times 0.5$[b]	44.14	21.61	3.23	0.92	30.10
5		P_{FM}, $P_{FD} \times 1.5$[b]	44.14	19.11	5.17	1.57	30.01
6	Initiation	P_{NM}, $P_{ND} \times 3$[c]	42.94	20.04	4.89	1.85	30.29
7		P_{NC}, P_{NM}, $P_{ND} \times 8$	39.43	21.24	5.72	2.12	31.49
8	Re-initiation	P_{FM}, $P_{FD} \times 2$[d]	44.14	20.04	6.19	2.22	27.42
9		P_{FM}, $P_{FD,}$ $P_{FC} \times 10$	44.14	26.87	13.11	4.16	11.73
10	Quitting	P_{MF}, $P_{DF} \times 0.5$[e]	44.14	20.04	4.89	1.29	29.64
11		P_{MF}, $P_{DF} \times 2$[e]	44.14	20.13	3.32	0.83	31.58
12		$P_{CF} \times 0.0$[f]	44.14	31.12	4.99	1.29	18.47
13		$P_{CF} \times 0.7$ and P_{MF}, $P_{DF} \times 2.5$	44.14	22.62	3.14	0.74	29.36
14	Switching	P_{CM}, $P_{DM} \times 0.5$	44.14	21.24	3.14	1.02	30.47
15		P_{CM}, $P_{DM} \times 10$	44.14	7.94	17.91	0.55	29.46
16		P_{CD}, $P_{MD} \times 0.5$	44.14	20.31	4.43	0.92	30.19
17		P_{CD}, $P_{MD} \times 10$	44.14	17.45	4.16	5.54	28.72
18		P_{MC}, $P_{DC} \times 0.5$	44.14	19.94	4.43	1.29	30.19
19		P_{MC}, $P_{DC} \times 10$	44.14	20.59	3.51	0.92	30.84
20		P_{MC}, $P_{DC} \times 150$[g]	44.14	24.28	1.39	0.00	30.19
21		P_{CM}, $P_{CD} \times 0.5$	44.14	21.51	3.23	0.83	30.29
22		P_{CM}, $P_{CD} \times 10$	44.14	6.46	16.34	3.23	29.82
23		P_{MC}, $P_{MD} \times 0.5$	44.14	20.04	4.43	1.39	30.01
24		P_{MC}, $P_{MD} \times 10$	44.14	20.50	3.42	1.85	30.10
25		P_{DC}, $P_{DM} \times 0.5$	44.14	19.94	4.34	1.29	30.29
26		P_{DC}, $P_{DM} \times 10$	44.14	20.13	4.80	0.46	30.47
Female							
1	None	Basic	50.00	17.83	2.94	1.25	27.99
2	Initiation	P_{NM}, $P_{ND} \times 0.5$[a]	50.00	18.09	2.67	1.25	27.99
3		P_{NM}, $P_{ND} \times 1.5$[a]	50.00	17.65	3.03	1.34	27.95
4	Re-initiation	P_{FM}, $P_{FD} \times 0.5$[b]	50.00	18.72	2.67	0.71	27.90
5		P_{FM}, $P_{FD} \times 1.5$[b]	50.00	16.76	3.83	1.43	27.99
6	Initiation	P_{NM}, $P_{ND} \times 3$[c]	48.66	17.83	3.30	1.87	28.34
7		P_{NC}, P_{NM}, $P_{ND} \times 8$	42.78	19.88	4.01	2.94	30.69
8	Re-initiation	P_{FM}, $P_{FD} \times 2$[d]	50.00	17.83	4.37	1.60	26.20
9		P_{FM}, $P_{FD,}$ $P_{FC} \times 10$	50.00	25.76	9.80	4.46	9.98
10	Quitting	P_{MF}, $P_{DF} \times 0.5$[e]	50.00	17.74	3.39	1.60	27.27
11		P_{MF}, $P_{DF} \times 2$[e]	50.00	17.83	2.32	0.62	29.23
12		$P_{CF} \times 0.0$[f]	50.00	28.97	2.85	0.89	17.26
13		$P_{CF} \times 0.7$ and P_{MF}, $P_{DF} \times 2.5$	50.00	20.86	1.69	0.53	26.92
14	Switching	P_{CM}, $P_{DM} \times 0.5$	50.00	18.45	2.41	1.16	27.99
15		P_{CM}, $P_{DM} \times 10$	50.00	7.31	13.90	0.45	28.34
16		P_{CD}, $P_{MD} \times 0.5$	50.00	18.00	3.03	1.07	27.90
17		P_{CD}, $P_{MD} \times 10$	50.00	14.44	2.76	4.10	28.70
18		P_{MC}, $P_{DC} \times 0.5$	50.00	17.83	2.94	1.34	27.90
19		P_{MC}, $P_{DC} \times 10$	50.00	18.89	1.96	0.71	27.43
20		P_{MC}, $P_{DC} \times 150$[g]	50.00	21.84	0.80	0.27	27.09
21		P_{CM}, $P_{CD} \times 0.5$	50.00	18.72	2.41	0.98	27.90
22		P_{CM}, $P_{CD} \times 10$	50.00	6.51	13.37	2.67	27.45
23		P_{MC}, $P_{MD} \times 0.5$	50.00	17.91	2.94	1.25	27.90
24		P_{MC}, $P_{MD} \times 10$	50.00	18.18	1.78	2.23	27.81
25		P_{DC}, $P_{DM} \times 0.5$	50.00	17.83	2.85	1.34	27.99
26		P_{DC}, $P_{DM} \times 10$	50.00	18.45	3.30	0.53	27.72

Abbreviations used: CC = conventional cigarette; RRP = reduced risk tobacco product.
The probabilities of transition between the five states N = never, C = current CC, M = current RRP, D = current dual, and F = former, are described by P followed by two subscripts, the first representing the state changed from, and the second the state changed to.
[a] With initiation rate P_{NC} altered so that the sum of the three initiation rates equals that for the Null Scenario.
[b] With re-initiation rate P_{FC} altered so that the sum of the three re-initiation rates equals that for the Null Scenario.
[c] With initiation rate P_{NC} unchanged.
[d] With re-initiation rate P_{FC} unchanged.
[e] With quitting rate P_{CF} unchanged.
[f] With quitting rates P_{MF}, P_{DF} unchanged.
[g] With TTP factor 1 set as 1.

males and 26.8% in females from the basic analysis estimates of 26.1% and 22.0%. However, at age 30–34, the effect is much larger, with the eight-fold increase almost eliminating never users in 2010 (basic 61.1% becoming 2.6% in males, and basic 64.1% becoming 3.0% in females), and increasing the percentages of current users (30.0% becoming 70.0% in males and 28.1% becoming 72.3% in females), and of former users (8.9% becoming 27.5% in males and 7.9% becoming 24.7% in females). The distribution of tobacco use also clearly differs from that in 1990, where in males, for example, there were, at age 30–34, 44.5% never, 34.9% current and 20.8% former users.

As death rates are relatively low at age 30–34, effects of varying

Table 12
Effect of varying TTPs in the RRP Scenario on the estimated drop in mortality associated with RRP introduction for 1990–2009 for age 30-79.

Analysis No.	Factor Varied	Value	Drop in deaths	% drop in deaths	% drop in attrib. deaths
Males					
1	None	Basic	35206	0.606	1.549
2	Initiation	P_{NM}, $P_{ND} \times 0.5$[a]	34594	0.595	1.522
3		P_{NM}, $P_{ND} \times 1.5$[a]	35673	0.641	1.569
4	Re-initiation	P_{FM}, $P_{FD} \times 0.5$[b]	29223	0.503	1.286
5		P_{FM}, $P_{FD} \times 1.5$[b]	45004	0.774	1.980
6	Initiation	P_{NM}, $P_{ND} \times 3$[c]	33623	0.578	1.479
7		P_{NC}, P_{NM}, $P_{ND} \times 8$	24541	0.422	1.080
8	Re-initiation	P_{FM}, $P_{FD} \times 2$[d]	25301	0.435	1.113
9		P_{FM}, $P_{FD,}$ $P_{FC} \times 10$	−146376	−2.518	−6.439
10	Quitting	P_{MF}, $P_{DF} \times 0.5$[e]	33671	0.579	1.481
11		P_{MF}, $P_{DF} \times 2$[e]	37769	0.650	1.661
12		$P_{CF} \times 0.0$[f]	−49319	−0.848	−2.170
13		$P_{CF} \times 0.7$ and P_{MF}, $P_{DF} \times 2.5$	14636	0.252	0.644
14	Switching	P_{CM}, $P_{DM} \times 0.5$	29535	0.508	1.299
15		P_{CM}, $P_{DM} \times 10$	134620	2.315	5.922
16		P_{CD}, $P_{MD} \times 0.5$	34784	0.598	1.530
17		P_{CD}, $P_{MD} \times 10$	46878	0.806	2.062
18		P_{MC}, $P_{DC} \times 0.5$	35574	0.612	1.565
19		P_{MC}, $P_{DC} \times 10$	30574	0.526	1.345
20		P_{MC}, $P_{DC} \times 150$[g]	13264	0.228	0.583
21		P_{CM}, $P_{CD} \times 0.5$	29495	0.507	1.298
22		P_{CM}, $P_{CD} \times 10$	136878	2.354	6.021
23		P_{MC}, $P_{MD} \times 0.5$	35520	0.611	1.563
24		P_{MC}, $P_{MD} \times 10$	30778	0.529	1.354
25		P_{DC}, $P_{DM} \times 0.5$	35385	0.609	1.557
26		P_{DC}, $P_{DM} \times 10$	35889	0.617	1.579
Females					
1	None	Basic	16403	0.421	1.260
2	Initiation	P_{NM}, $P_{ND} \times 0.5$[a]	15982	0.410	1.227
3		P_{NM}, $P_{ND} \times 1.5$[a]	16737	0.429	1.285
4	Re-initiation	P_{FM}, $P_{FD} \times 0.5$[b]	11539	0.296	0.886
5		P_{FM}, $P_{FD} \times 1.5$[b]	21250	0.545	1.632
6	Initiation	P_{NM}, $P_{ND} \times 3$[c]	15541	0.398	1.193
7		P_{NC}, P_{NM}, $P_{ND} \times 8$	9537	0.245	0.732
8	Re-initiation	P_{FM}, $P_{FD} \times 2$[d]	11730	0.301	0.901
9		P_{FM}, $P_{FD,}$ $P_{FC} \times 10$	−85005	−2.179	−6.527
10	Quitting	P_{MF}, $P_{DF} \times 0.5$[e]	15654	0.401	1.202
11		P_{MF}, $P_{DF} \times 2$[e]	17588	0.451	1.351
12		$P_{CF} \times 0.0$[f]	−36006	−0.923	−2.765
13		$P_{CF} \times 0.7$ and P_{MF}, $P_{DF} \times 2.5$	1375	0.035	0.106
14	Switching	P_{CM}, $P_{DM} \times 0.5$	11735	0.301	0.901
15		P_{CM}, $P_{DM} \times 10$	72973	1.871	5.603
16		P_{CD}, $P_{MD} \times 0.5$	16390	0.420	1.259
17		P_{CD}, $P_{MD} \times 10$	21883	0.561	1.680
18		P_{MC}, $P_{DC} \times 0.5$	16599	0.426	1.275
19		P_{MC}, $P_{DC} \times 10$	13905	0.356	1.068
20		P_{MC}, $P_{DC} \times 150$[g]	4727	0.121	0.363
21		P_{CM}, $P_{CD} \times 0.5$	10785	0.277	0.828
22		P_{CM}, $P_{CD} \times 10$	75001	1.923	5.759
23		P_{MC}, $P_{MD} \times 0.5$	16516	0.423	1.268
24		P_{MC}, $P_{MD} \times 10$	13693	0.351	1.051
25		P_{DC}, $P_{DM} \times 0.5$	16433	0.421	1.262
26		P_{DC}, $P_{DM} \times 10$	16386	0.420	1.258

Abbreviations used: CC = conventional cigarette; RRP = reduced risk tobacco product; TTP = tobacco transition probability.
The probabilities of transition between the five states N = never, C = current CC, M = current RRP, D = current dual, and F = former, are described by P followed by two subscripts, the first representing the state changed from, and the second the state changed to.
[a] With initiation rate P_{NC} altered so that the sum of the three initiation rates equals that for the Null Scenario.
[b] With re-initiation rate P_{FC} altered so that the sum of the three re-initiation rates equals that for the Null Scenario.
[c] With initiation rate P_{NC} unchanged.
[d] With re-initiation rate P_{FC} unchanged.
[e] With quitting rate P_{CF} unchanged.
[f] With quitting rates P_{MF}, P_{DF} unchanged.
[g] With TTP factor 1 set as 1.

initiation rates on the total estimated drop in deaths associated with RRP introduction were quite small. Even for the eight-fold increase in all the initiation rates, the drop only reduced in males from 35,206 (basic analysis) to 24,541 deaths, and in females from 16,403 to 9,507 deaths. Note that while increasing initiation rates has little effect on mortality (given the 20 year follow-up period assumed) it is important to understand its impact on prevalence.

3.4.3.2. Re-initiation. Effects of varying re-initiation rates on tobacco use are scarcely evident in 30–34 year olds who have little time to both quit and then re-initiate. They are more evident in older age groups, as indicated by the results in Table 11 for age

50–54. Thus, in analyses 4 and 5, where overall re-initiation rates in the RRP Scenario are held equal to that in the Null Scenario, the proportions of current RRP and dual users increase at the expense of current CC smokers as the values of P_{FM} and P_{FD} increase. Increasing the value of P_{FM} and P_{FD} while holding P_{FC} unchanged (analysis 8) increases the proportions of current RRP and dual users at the expense of former smokers. Increasing all the re-initiation rates ten-fold (analysis 9) has a marked effect, reducing the prevalence of former users markedly, with increases occurring in all the current user groups.

The effects on the drop in deaths associated with RRP introduction correspond to these changes in prevalence. While increasing the re-initiation rates P_{FM} and P_{FD} while keeping overall re-initiation rates constant (Analysis 5) increases the estimated drop in deaths by almost 30% in each sex from that in the basic value, increasing P_{FM} and P_{FD} while leaving P_{FC} unaltered has a similar reverse effect. In Analysis 9, where all the re-initiation rates are increased 10-fold, RRP introduction is estimated to cause a large increase in deaths. Based on the range of factors studied in the full analyses, slightly more than a 2-fold increase in re-initiation rates in males and slightly less than a 2-fold increase in females would produce an estimated benefit of RRP introduction of zero.

3.4.3.3. Quitting. Halving or doubling (in analyses 10 and 11) the quitting rates for RRP and dual users (with quitting rates for CC smokers unchanged) had little effect on the prevalence of tobacco use. However, reducing the quitting rate for CC smokers had more effect. Thus, in analysis 12, where quitting rates for CC smokers are held at zero, the prevalence of current CC smokers clearly rises from that in the basic analysis with that of former users decreasing, as shown in Table 11 for age 50–54 in 2010. In the final set of quitting analyses, illustrated in analysis 13, P_{CF} decreases and P_{MF} and P_{DF} increase, with the overall quit rate approximately unchanged from that in the Null Scenario. Here, the prevalence of current CC smokers increases somewhat, at the expense of small decreases in the other current use groups.

As shown in Table 12 in analyses 10 and 11, changing only P_{MF} and P_{DF} has very little effect on the estimated drop in deaths associated with RRP introduction. Reducing the quit rate for current smokers, P_{CF}, has much more effect, reducing the rate to zero making the estimated drop go negative. Based on the range of values tested, it appears that reducing the overall quit rate by about 43% in males and about 29% in females would approximately eliminate the benefit. Most of the benefit is also lost in analysis 13, where the basic value of P_{CF} is reduced by 30%, with P_{MF} and P_{DF} each increased 150%.

3.4.3.4. Switching. Analyses 14 to 26 involve six different types of switching, to each of the three individual categories, and from each of the categories. In all these analyses the prevalences of never and former users remain very similar, but the distribution in the three current tobacco use groups varies. As shown in Table 11, the most striking changes in prevalence occur in analysis 15, where switching rates P_{CM} and P_{DM} are multiplied by 10, and in analysis 22, where switching rates P_{CM} and P_{CD} are multiplied by 10. Here, the prevalence of CC smoking decreases by more than half, and the prevalence of RRP use increases about four-fold, the low prevalence of dual use decreasing in analysis 15 and increasing in analysis 22. It should be noted that the switchers P_{MC}, P_{MD}, P_{DC} and P_{DM} all involve individuals making two switches, each of quite low probability, in the follow-up period, so changes in these would not be expected to have much effect. This is illustrated in analyses 19 and 20 where it takes a huge change (150-fold in analysis 20) to have much noticeable effect on the prevalences of RRP and dual use. Given also that switching from CC to dual is assumed to be five times less likely than switching from CC to RRP, it is clear why changes in P_{CM} have the largest effect.

Increasing switching 10-fold to RRP (analysis 15) or from CC (analysis 22) both cause a huge increase in the drop in deaths, to somewhat over 130,000 deaths in males and over 70,000 deaths in females (both reductions representing about a 6% reduction in attributable deaths), the next most substantial increase (analysis 17) being to about 47,000 deaths in males and 22,000 in females following a 10-fold increase in switching to dual use. Other switches have much less effect. A concern is that the introduction of RRP might lead to increased later switching from RRP or dual use to CC smoking. However, the huge increase in the rates P_{MC} and P_{DC} by a factor of 150 in analysis 20 did not eliminate the drop in deaths associated with RRP introduction, though it did reduce it to about 13,000 deaths in males and about 5,000 in females.

3.5. Extreme situations

To bring our results into context, Table 13 compares the estimated drops in deaths associated with RRP introductions from the basic analysis with that calculated under four alternative extreme situations. The largest estimates are where all smokers quit immediately, so that in the RRP Scenario the whole population consists of never and former smokers, with the prevalence of each remaining constant over time within birth cohort. For the four diseases combined, the drop in deaths, as compared to the basic analysis (whether expressed in numbers or as a percentage), is about 17.2 times higher in males and 20.3 times higher in females. The big difference is not so much because switching to the RRP involves (in the basic analysis) an 80% reduction in exposure, whereas quitting involves a 100% reduction, but because the rate of uptake of the RRP assumed in the basic analysis is much smaller and more gradual than the rate of quitting in the first extreme situation. Also, while initiation and re-initiation occurs in the basic analysis it does not in the first extreme situation.

The first extreme situation clearly illustrates the maximum benefit that one might see in 20 years given any change in tobacco use. However, over 70% of this benefit can be achieved in the second extreme situation, where CC smoking is totally replaced by RRP use. Here, all baseline CC smokers switch at once to RRP, and initiation and re-initiation is all to RRP.

In the third extreme situation, it is assumed that the whole population became current RRP users immediately after baseline, with no further CC smoking, dual use or quitting. Here the estimated drop in deaths is far lower than in extreme situations 1 or 2, though it is still substantially greater for males than in the basic analysis. For females the drop is relatively small and becomes negative for COPD. Note that the third extreme situation balances advantages of reductions in exposure for continuing users, as against increasing exposure for those who otherwise would have stayed as never or former smokers.

In the fourth extreme situation, current CC smokers who would otherwise have switched to RRP or dual use quit instead. The drops in deaths here are a substantial proportion (about 64% in each sex) of those in the first extreme situation.

3.6. Varying combinations of parameters

Table 14 summarizes effects on mortality for 16 alternatives in which each of four parameters were varied between two possibilities, half or double the values used in the basic analysis, the parameters being selected as those having a major effect on the drop in mortality associated with RRP reduction. In the Table, L indicates the parameter value which is expected to produce the larger drop in deaths, while S indicates the value expected to produce the

Table 13
Estimated drops in mortality associated with RRP introduction for 1990–2009 for age 30–79 in four extreme situations.

Analysis	D	D	D	D	D	% D	% AD
	Lung cancer	IHD	Stroke	COPD	Four diseases	Four diseases	Four diseases
Males							
Basic	7688	19189	3064	5266	35206	0.606	1.549
1. All smokers quit immediately, no further initiation or re-initiation	143456	350437	46291	65137	605321	10.412	26.563
2. CC totally replaced by RRP	99890	259044	35418	49275	443627	7.630	19.467
3. Whole population becomes current RRP users	23388	75601	10684	11585	121258	2.086	5.338
4. Current smokers who would have switched to RRP or dual use quit instead	84021	230610	31033	41251	386915	6.655	17.020
Females							
Basic	4508	6963	2219	2714	16403	0.421	1.260
1. All smokers quit immediately, no further initiation or re-initiation	113985	123016	34481	61545	333027	8.538	25.525
2. CC totally replaced by RRP	79471	92533	26458	46152	244615	6.272	18.748
3. Whole population becomes current RRP users	2090	7059	2515	−1164	10500	0.269	0.807
4. Current smokers who would have switched to RRP or dual use quit instead	68128	81691	23409	39321	212548	5.449	16.321

Abbreviations usedCC = conventional cigarettes; D = drop in deaths; RRP = reduced risk tobacco product; % D = % drop in deaths; % DA = % drop in attributable deaths.

smaller drop. Thus, larger drops in deaths are associated with lower REs for RRP (and dual use) and lower switching rates to CC, and with higher switching rates to RRP and rates of quitting from RRP or dual use. None of the alternatives affect the prevalence of never use.

Alternative 1 (all values L) is characterized by a relatively high percentage of RRP users and quitters, and a relatively low percentage of CC smokers, while alternative 16 (all values S) is characterized by a relatively high percentage of CC smokers and a low

Table 14
Effect of varying four parameters simultaneously on the drop in deaths from the four diseases combined in 1990–2009 at age 30–79 which is associated with RRP introduction.

Alternative	Parameters varied[a]						
	REM[b]	Switch to RRP[c]	Switch to CC[d]	Quit from RRP/dual[e]	Drop in deaths	% drop in deaths	% drop in attrib. deaths
Males							
1	L	L	L	L	53802	0.925	2.367
2	L	L	L	S	50299	0.865	2.213
3	L	L	S	L	52668	0.906	2.317
4	L	L	S	S	48936	0.842	2.153
5	L	S	L	L	31680	0.545	1.394
6	L	S	L	S	29078	0.500	1.279
7	L	S	S	L	31153	0.536	1.370
8	L	S	S	S	28292	0.487	1.245
9	S	L	L	L	38550	0.663	1.696
10	S	L	L	S	31489	0.542	1.385
11	S	L	S	L	37722	0.649	1.659
12	S	L	S	S	30347	0.522	1.335
13	S	S	L	L	23010	0.396	1.012
14	S	S	L	S	18120	0.312	0.797
15	S	S	S	L	22666	0.390	0.997
16	S	S	S	S	17439	0.300	0.767
Females							
1	L	L	L	L	26445	0.678	2.031
2	L	L	L	S	24678	0.633	1.895
3	L	L	S	L	25554	0.655	1.962
4	L	L	S	S	23751	0.609	1.824
5	L	S	L	L	13100	0.336	1.006
6	L	S	L	S	11296	0.290	0.867
7	L	S	S	L	12641	0.324	0.971
8	L	S	S	S	10835	0.278	0.832
9	S	L	L	L	17707	0.454	1.360
10	S	L	L	S	13885	0.356	1.066
11	S	L	S	L	16987	0.436	1.304
12	S	L	S	S	13135	0.337	1.009
13	S	S	L	L	8176	0.210	0.628
14	S	S	L	S	5003	0.128	0.384
15	S	S	S	L	7906	0.203	0.607
16	S	S	S	S	4685	0.120	0.360

Abbreviations used: CC = conventional cigarette; RRP = reduced risk tobacco product.
The probabilities of transition between the five states N = never, C = current CC, M = current RRP, D = current dual, and F = former, are described by P followed by two subscripts, the first representing the state changed from, and the second the state changed to.; Abbreviations used: REM = relative exposure for RRP use; RED = relative exposure for dual use.

[a] For each parameter, L is the alternative producing the largest drop in deaths, while S is the alternative producing the smallest drop in deaths.
[b] For L REM = 0.1, for S REM = 0.4. RED is varied concomitantly at 0.55 and 0.7.
[c] For L P_{CM} and P_{DM} in Table 4 are doubled, for S they are halved.
[d] For L P_{MC} and P_{DC} in Table 4 are halved, for S they are doubled.
[e] For L P_{MF} and P_{DF} in Table 3 are doubled, for S they are halved.

percentage of RRP users. Compared to alternative 16, alternative 1 is associated with a greater drop in deaths which is about 3.1 times greater in males, and 5.6 times greater in females. The percentage drops in attributable deaths range from 0.767% in males and 0.360% in females for alternative 16 to 2.367% in males and 2.031% in females for alternative 1.

It is possible to assess the relative importance of the four parameters by considering pairs of alternatives in which only the parameter of interest varies. Thus, for judging the effect of varying REM, one can calculate the ratio of drops for alternatives 1 and 9, 2 and 10, 3 and 11 and so on, up to alternatives 8 and 16, and take the geometric mean of the ratios. Similarly, for judging the effect of switching to RRP, one can calculate the ratio of drops for 1 and 5, 2 and 6, 3 and 7, and so on up to alternatives 12 and 16. These ratios are reasonably consistent, illustrating that inferences about variation in one parameter are little affected by variation in the others. For both sexes, the largest ratios are for variation in REM (geometric means of 1.49 in males and 1.77 in females), and for variation in the rate of switching to RRP (1.71 in males and 2.27 in females). The geometric means are substantially lower for variation in quitting than RRP or dual use (1.17 in males and 1.28 in females), and for variation in switching to CC (1.03 in males and 1.04 in females).

The results described in the previous paragraph are from the second set of analyses referred to in the methods which vary combinations of parameters. The conclusion from the first set of analyses regarding inferences about variation in one parameter being little altered by variation in the others was essentially the same. It was also clear that variations in quitting from RRP or dual use and in switching to CC were less important than variations in REM and in switching to RRP.

3.7. Zero benefit analysis

This was aimed at determining which parameter variations in combination might eliminate the drop in deaths associated with RRP introduction. Those parameters were selected (dual users increasing consumption, increasing re-initiation rates, and decreasing quit rates of CC smokers) variation in which, on their own, could eliminate the drop. For each of the three parameters considered the values selected in the five alternative analyses (see Table 15) represent, respectively, 10%, 20%, 30%, 40% and 50% of the change in value required for the parameter on its own to approximately eliminate the drop in deaths. Thus, for dual users increasing consumption (i.e. increasing RED), the results in Table 10 suggest that a value of 2.8 might on its own eliminate the drop, so the values tested are derived from interpolation between the basic value of 0.6 and 2.8. Similarly, “elimination values” of 2.0 for re-initiation and 0.64 for quitting from CC have been used, based on the results in Table 12.

The results in Table 15 show that the estimated drops in deaths associated with RRP introduction reduce successively for the five alternatives, becoming negative for alternatives 4 and 5 in both sexes. Interpolation suggests that for males the zero benefit point is about 60% of the way between alternatives 3 and 4, while for females it is about 40% of the way between alternatives 2 and 3. For the sexes combined, alternative 3 is clearly closest to the zero benefit point.

While it is clear that in theory the effects of RRP introduction might be eliminated in some situations, it seems doubtful whether such a possibility is likely to occur in practice. Thus, alternative 3 involves all of the following: increasing all the re-initiation rates by 30%, decreasing the quit rate of CC smokers by 10.8%, and increasing RED from 0.6 to 1.26. This last change is equivalent to a 20 a day CC smoker who becomes a dual user consuming 21 CCs and 21 RRPs a day, as compared to the 10 CCs and 10 RRPs assumed in the basic analysis.

4. Discussion and conclusions

The model described above differs slightly from that described initially (Weitkunat et al., 2015). Thus, in the RRP Scenario, we now allow for five categories of tobacco use, not four, by also considering dual use. We also now refer to the transition probabilities as TTPs rather than STPs, as RRPs (which may not involve combustion) may not necessarily be smoked. While the method of estimating RRs from a history of tobacco use, involving use of the negative exponential model, is identical to that described earlier in simpler applications such as quitting and reduction in dose, it differs somewhat for multiple changes in exposure from that described in another publication (Lee et al., 2015), which proved to produce rather implausible patterns of change in RR in some situations. Though the predictions of the model we used here should ideally be tested based on data from a large study involving extensive information on changes in tobacco use over time, such data are currently not available to us.

The software used to conduct the analyses we describe, which is available on request, is flexible in many ways. Thus, it can be used to study effects of introducing various different RRPs or indeed of introducing other interventions such as nicotine replacement therapy. As illustrated in this paper, the user can readily vary the effective “doses” for RRP and dual use relative to that for smoking, and the various TTPs and TTP factors, as well as whether adjustment for population size is required. Also variable are the number in the simulated population (up to 100,000), the year of start and finish of follow-up (between 1980 and 2012), the follow-up interval length (3, 6 or 12 months), the sexes studied, the age range considered (from 10 to 79), the country (US, Canada, Japan, or one of nine European countries), and the cause of death (lung cancer, IHD, COPD or stroke). The data sources used can also be varied, as illustrated in Table 6 analyses 18 to 24). While it would be relatively easy to modify the software to allow some restrictions, such as length of follow-up, and numbers of countries and diseases considered, others would be more difficult, such as allowing for more than one RRP.

Some features of the modelling approach we have used, a number discussed in more detail earlier, deserve additional comment. First, we assume that tobacco-associated exposure results only from smoking CCs and/or using the RRP of interest. Thus, ignoring exposure from forms of tobacco use such as smokeless tobacco or nicotine replacement therapy does not seem important as these products are believed to have little or no effect on risk of the diseases studied. Note that we are not saying that smokers who switch to nicotine replacement therapy will not obtain health benefits. Rather that it is not inappropriate to regard the exposure in those switchers as equivalent to that in those who quit smoking, i.e. zero. Similarly, ignoring exposure from e-cigarettes may also not be important, if claims (Nutt et al., 2014) that any health effects are less than 5% of those from CCs are correct.

Our current methodology does not allow us to study directly the effect of introducing multiple RRPs. Clearly, the impact could be substantially greater if a much greater percentage of cigarette smokers switch to one or other of the alternative RRPs. For products introduced at about the same time, and with a known average reduction in effective dose, our methodology should be able to estimate the reduction in mortality approximately, given this average effective dose and TTPs which reflect the combined uptake rate of RRPs.

Ignoring exposure from cigar and pipe smoking may seem more relevant. Our methods effectively assume that cigar and pipe smoking carry the same risk as CC smoking, as the initial smoking

Table 15
Effect of varying three parameters on the drop in deaths from the four diseases combined in 1990–2009 at age 30–79 which is associated with RRP introduction.

Alternative	Parameters varied			Drop in deaths	% drop in deaths	% drop in attrib. deaths
	RED[a]	Re-initiation[b]	Quit from CC[c]			
Males						
Basic	0.60	Basic	Basic	35206	0.606	1.549
1	0.82	×1.1	×0.964	27486	0.473	1.209
2	1.04	×1.2	×0.928	18402	0.317	0.810
3	1.26	×1.3	×0.892	7984	0.137	0.351
4	1.48	×1.4	×0.856	−5838	−0.100	−0.257
5	1.70	×1.5	×0.820	−14022	−0.241	−0.617
Females						
Basic	0.60	Basic	Basic	16403	0.421	0.260
1	0.82	×1.1	×0.964	8303	0.213	0.638
2	1.04	×1.2	×0.928	2123	0.054	0.163
3	1.26	×1.3	×0.892	−3433	−0.088	−0.264
4	1.48	×1.4	×0.856	−8284	−0.212	−0.636
5	1.70	×1.5	×0.820	−13139	−0.337	−1.009

Abbreviations usedCC = conventional cigarette; RRP = reduced risk tobacco product; REM = relative exposure from RRP use; RED = relative exposure from dual use.
The probabilities of transition between the five states N = never, C = current CC, M = current RRP, D = current dual, and F = former, are described by P followed by two subscripts, the first representing the state changed from, and the second the state changed to.
[a] RED increased from basic value. REM unchanged.
[b] P_{FC}, P_{FM} and P_{FD} increased from basic values in Table 3.
[c] P_{CF} reduced from basic values in Table 3.

status of the populations followed is based on the prevalence of smoking any product (i.e. CCs, cigars and/or pipes) rather than just CCs. Had we allocated initial smoking status based on estimates of prevalence of CC smoking, we would instead have effectively assumed that cigar and pipe smokers have the same risk as never smokers, which would clearly be a less appropriate assumption. The problem, of course, is that extending the tobacco groups to include pipe and cigar smokers (and possibly also CC smokers with differing consumption levels) could lead to a huge number of TTPs, which would be difficult or impossible to estimate reliably. In the context of the USA, our treatment of pipe and cigar smoking is probably unimportant, as CC smokers form the great majority of all smokers.

Also probably unimportant is our failure to take environmental tobacco smoke exposure into account, where we showed earlier (Weitkunat et al., 2015) that, whether or not the RRP reduces the risk from ETS exposure would have little effect on the estimated drop in mortality associated with RRP introduction.

In the absence of reliable available estimates on RRs and half-lives for all the diseases associated with smoking, we have limited attention to the four major smoking-associated diseases. We estimated earlier (Weitkunat et al., 2015) that overall estimates of deaths saved by an RRP would have to be increased about 50% to give an estimate for all smoking-related diseases combined.

As we also noted earlier, our estimates of deaths saved may be in error if those who switch from CCs to RRPs tend to be atypical in some ways (e.g. having a duration of smoking markedly different from those who do not switch) or change their distribution of other risk factors (e.g. their degree of alcohol consumption). Probably more relevant is that our analyses have so far limited attention to 20 years follow-up, particularly if introduction of an RRP has an effect on initiation of tobacco use by adolescents and young men and women. As the rate of uptake is gradual, and as time is needed for a CC smoker's risk to decline following a switch to RRP, the estimated drop in deaths would increase substantially with longer follow-up. This is illustrated by the fact that, in the basic analysis, the drop in deaths that occurred in the first 10 years was only 19.9% in males and 6.9% in females of that which occurred over the full 20 year follow-up period.

Despite these reservations we believe that the results summarized here provide some useful insight into the extent to which RRP introduction might affect the distribution of tobacco use and the number of deaths associated with tobacco, as well as the assumptions which are most critical to the predictions.

One conclusion from our results is that the predictions from the Null Scenario seem reasonably consistent with what has been observed in the USA, as regards both estimated smoking prevalences over the period from 1990 to 2010, and the estimated percentage of deaths attributable to smoking. While there are differences from estimates for other published sources (see Figs. 3 and 4 for smoking prevalences, and Table 9 for attributable deaths), these may in part be due to weaknesses in these data and to lack of representativeness in a simulated population followed for 20 years and assumed not to die. While no doubt the Null Scenario TTPs that we used could be modified slightly to better predict smoking prevalences (e.g. by varying estimates by follow-up period), and the RRs used may be somewhat inaccurate (though based on extensive meta-analyses), it seems unlikely that this would materially have affected the further conclusions listed below.

Another conclusion is that repeating our sensitivity analyses using a larger sample than the 10,000 we used per sex would have only quite a small effect on the conclusions or the accuracy of the predictions for the basic analysis.

The results of the sensitivity analyses allow various conclusions. First, effects on prevalence of tobacco use in the RRP Scenario were very much as one would have expected *a priori*. Thus, increasing initiation rates had the most effect at younger age groups, while increasing re-initiation rates tended to have more effect at older age groups. Also varying the TTP factors 1 to 4 tended to have quite a modest effect on the distribution of tobacco use habits as these all involved multiple changes of smoking status, so occurred less frequently. Varying quitting rates and rates of switching between products had a larger effect on tobacco use distributions in the RRP Scenario.

As regards effects of varying parameters on predicted reductions in mortality in the RRP Scenario, it was clear that varying any of the four TTP factors or the definitions of short-term quitting or short-term use had quite a small effect. Indeed, for TTP factor 3, the effect of a 3-fold variation in the factor value caused variations that

were small and non-monotonic, with the underlying "signal", such as it was, not clearly outweighing the "noise" from the Monte Carlo nature of the process. For the range of alternative values tested, the largest variations in reductions in deaths resulted from varying REM, particularly if RED varied in line with it. Variation in RED also had a moderate effect. Switching to RRP (from the other current tobacco use groups), switching to CC (again from the other current tobacco use groups), re-initiation and quitting also had large effects, the results being generally consistent with the notion that the greatest drops in deaths come from getting CC smokers off their high exposure product, either by quitting or switching to the lower exposure RRP. Effects of initiation, and of other switches between current tobacco use groups were less, though clearly seen, except for switching from dual use. Effects of varying RR and H to within a range of ±20% of the basic values (which seemed reasonable from the confidence limits of the meta-analysis derived estimates) were also clearly evident. Increasing the RRs to values consistent with the USSURG estimates produced quite similar estimated reductions in mortality to those given by the basic analysis for the four diseases combined, but clear differences were seen for individual diseases.

Generally, effects of varying parameters on reductions in deaths were in the same direction for each of the four diseases studied separately and combined. An exception was for varying RR values, where increasing them always decreased the percentage reduction in attributable deaths, but increased the reduction in deaths (total and percent) for IHD, stroke and all four diseases combined.

"Zero benefit" analyses were conducted to determine changes in parameter values that might eliminate the estimated reduction in deaths associated with RRP introduction. While clearly no reduction would be seen if the RRP did not reduce the effective dose ($F = 1$) or if there was no uptake of RRP, there were some situations where even where RRP was introduced and reduced the effective dose, the estimated reduction in deaths might be reduced or eliminated. Elimination of the effect could in theory occur in three situations – firstly if dual users increased consumption, second if re-initiation rates were increased, and third if quitting rates of CC smokers were decreased. However, the increases required seem large. Thus elimination of the effect by increasing consumption would require an effective dose for dual users (G) of about 2.8 (consistent with smokers of 20 cigs/day of CCs before RRP introduction consuming about 47 CCs and 47 RRPs a day after introduction), while elimination of the effect by increasing all the re-initiation rates would require as much as a 2-fold increase in the rate, and elimination by decreasing quitting rates of CC smokers would require about a 35% reduction in the rates. Some reduction of the effect could occur if RRP introduction resulted in increased rates of initiation of smoking but, as initiation is assumed only to occur in those aged up to 34 years, this would only have a minor effect. Increasing rates of switching to CC smoking could also reduce the effect, but as this only affects those making multiple transitions during follow-up could not eliminate it.

In the basic analysis (which used estimates of effective dose and of uptake considered not unreasonable for a hypothetical RRP, but which were not intended to apply to any specific one), RRP introduction was associated with a reduction in deaths from the four diseases combined over the 20 year follow-up period of 35,206 in males and 16,403 in females in the basic analysis considered. These reductions can be compared with 605,321 in males and 333,027 in females in an extreme situation where all smokers quit immediately and no initiation or re-initiation occurs, and with 443,627 in males and 244,615 in females in a second extreme situation where CC smoking is totally replaced by RRP use following the introduction of RRP. While the reductions in these extreme situations are much larger, the situations themselves are clearly less plausible. The same is true for another extreme situation where current CC smokers who would otherwise have switched to RRP or to dual use quit instead, the estimated reductions in deaths then being 386,915 in males and 212,548 in females.

That RRP introduction is unlikely to be associated with an overall adverse effect on risk is demonstrated by results for a situation where the whole population (regardless of smoking habit) became RRP users immediately on RRP introduction. Here, the overall effect on mortality was to reduce deaths by 121,258 in males and by 10,500 in females. Where everyone becomes RRP users, reduced risk in current users and short-term former users is balanced against increased risk in never smokers and long-term former smokers. The balance is more favourable for males who have fewer never smokers and more current users than females, where the overall 10,500 reduction in deaths from the four diseases conceals a 1,164 increase in COPD.

The FDA Modified Risk Tobacco Product Draft Guidance (Food and Drug Administration, 2012) highlights seven population segments and exposure patterns that should be considered when submitting an application for a new RRP. Our model considers all but two of these. One segment not considered relates to environmental tobacco smoke exposure, already discussed above. The other relates to use of the RRP rather than an FDA approved cessation medication. This is not considered as the model does not consider switching to products other than the RRP of interest. Though one could in theory use the model with the RRP Scenario replaced by a tobacco cessation medication scenario, we note that a recent publication (Stanley and Massey, 2016) suggests that nicotine replacement therapy may be ineffective as a smoking cessation aid.

The results described here do, however, relate to the other five FDA segments. Thus switching from CCs to RRPs relates to the FDA's segment 1, switching to or back to CCs having previously used RRPs relates to their segment 2, initiation with RRP relates to their segment 5, and dual use to their segment 6. Also the fourth extreme situation, which concerns use of RRP rather than quitting, relates to their segment 3.

Overall, it is clear that CC smokers who continue to use tobacco (CC and/or RRP) following RRP introduction will have a reduced average effective dose, and hence a reduced risk of disease unless the risk of dual users exceeds that of current CC smokers. The lower the effective dose of RRP users, the greater will the effective dose of dual users need to be to cancel the benefit of RRP introduction. An increased risk of dual users compared to CC smokers is only likely to be achieved in practice if dual users smoke substantially more than they did initially.

Given a reduction in average effective dose to the population, RRP introduction will reduce risk, a reduction which will increase with increasing uptake of the product. This reduction in risk to the whole population will also occur unless, rather implausibly, the introduction of the RRP leads to a substantial increase in re-initiation rates or decrease in quit rates of continuing CC smokers. The flexibility of the model allows ready assessment of the effect on prevalence of tobacco use, and on risk from tobacco-related diseases under a wide range of alternative possibilities.

A recent publication (Levy et al., 2016) estimated that introducing vaporized nicotine products (VNPs) into the US market would reduce smoking-attributable deaths by 21%. Their approach had similarities with ours, following a cohort with a known initial distribution of CC smoking habits over time, and comparing risks in a "No-VNP Scenario" with those in a "VNP Scenario" in which individuals could transition into and out of VNP use. One feature of their approach is that they divided never smokers into those who would and would not have initiated smoking in the absence of VNPs, similarly dividing current smokers into those who would or would not have quit and former smokers into those who would or

would not have relapsed. Whereas we followed individuals aged up to 79 over a 20 year period (1990–2009) in the past, Levy et al. followed individuals initially aged 15 over a much longer period (2012–2083), mainly in the future. Though they assumed a greater reduction in relative exposure for users of the VNP than we did for RRP in our basic analysis (95% vs 80%), they assumed a smaller reduction for dual users (30% vs 40%). There seem to be two main reasons why their estimated reduction in smoking-attributable deaths (21%) was so much greater than ours (1.549% for males and 1.260% for females). One was the much longer follow-up period they considered. The other was that they assumed that about 50% of current users would use VNPs (either as single or dual users) throughout the follow-up period, we assumed that only about 16% of current users would use the RRP, and even then this level of uptake would take time to achieve.

Software

The software used to generate the analyses described in this paper is available on request from the corresponding author.

Declaration of interest

Z.S-W, G.B. and R.W. are employees of Philip Morris International. P.N.L, director of P.N.Lee Statistics and Computing Ltd., is an independent consultant in statistics and an advisor in the fields of epidemiology and toxicology to a number of tobacco, pharmaceutical, and chemical companies. J.S.F. and J.F.H. are employees of P.N.Lee Statistics and Computing Ltd.

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Appendix A. Supplementary data

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Transparency document

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