Estimated public health gains from German smokers switching to risk-reduced alternatives: Results from population health impact modelling

Romana Rytsar (romana.rytsar@pmi.com)
Philip Morris International Research and Development Campus Neuchatel https://orcid.org/0000-0003-1936-1300
Smilja Djurdjevic
PMI
Alexander K Nussbaum
PMI
Ashok Kaul
Saarland University
Emanuel Bennewitz
IPE Institute for Policy Evaluation
Peter N Lee
P N Lee Statistics and Computing Ltd
John S Fry
RoeLee Statistics Ltd.

Research

Keywords: Smoking, public health, modelling, lung cancer, chronic obstructive pulmonary disease, ischaemic heart disease, stroke, e-cigarettes, heat-not-burn product, Germany

DOI: https://doi.org/10.21203/rs.3.rs-135255/v1

Abstract

Background

Smoking is associated with cancer and cardiorespiratory disease mortality. Reducing smoking prevalence reduces deaths and life-years lost. Here, we estimate the impact of introducing heat-not-burn products and e-cigarettes in Germany from 1995 to 2015 on mortality from lung cancer, chronic obstructive pulmonary disease, ischaemic heart disease, and stroke in men and women aged 30–79 years.

Methods

We used the previously described population health impact model. Modelling starts with individuals of a given sex and age range with a defined cigarette smoking distribution. They are then followed under a “Null Scenario”, where reduced-risk products are never introduced, and one of seven “Alternative Scenarios”, where they are. Transition probabilities allow tobacco product use to change annually, and the individual product histories then allow estimation of risks, relative to never users, for each year and Scenario, which are then used to estimate reductions in deaths and life-years lost for each Alternative Scenario.

Results

In the Null Scenario, we estimated 852,357 deaths from cigarette smoking, with 8.61 million life-years lost. Had everyone quit in 1995, with no further use of the three products, these numbers would reduce by 216,650 and 2.88 million. The reductions would be 159,278 and 2.06 million with an immediate complete switch from cigarettes to heat-not-burn products, and 179,470 and 2.34 million with an immediate switch to 50% heat-not-burn products and 50% e-cigarettes. In four Scenarios with a more gradual switch, estimated decreases were 39,818–81,293 deaths and 0.50–1.05 million life-years, representing 17.5%-37.5% of the effect of cessation. These estimates assume switching to heat-not-burn products and e-cigarettes involves risk decreases of 80% and 95% of those from quitting. The decreases would have increased, had more diseases and a wider age range been considered, and also with a longer follow-up period, the decreases increasing markedly with time.

Conclusions

Various limitations are discussed, none affecting our conclusion that introducing these new products into Germany in 1995 could have substantially reduced mortality. Our results imply deaths from cigarette smoking could be substantially reduced, both by cessation and switching to reduced-risk products. Risk-proportionate public health campaigns and regulation might increase such switching.

Background

Smoking represents the greatest avoidable risk factor for health [1, 2]. Nevertheless, the World Health Organization (WHO) estimates that there will be 1.1 billion smokers globally in 2025 [3]. In Germany, smoking prevalence is at around 28%, with no change since 2016 [4], and the number of quit attempts is currently decreasing [5]. In 2013, an estimated 125,000 people died from smoking-related diseases in Germany [6].

Clearly, the best option for smokers is to completely quit smoking at once. In recent years, however, an increasing number of public health experts and institutions have started to embrace the concept of harm reduction as a complementary tool to existing tobacco control efforts [7–12]. Tobacco harm reduction is directed at adult smokers of cigarettes who would otherwise continue to smoke and aims to encourage them to switch completely to smoke-free alternatives such as snus, the e-cigarette (ECig), and the heat-not-burn product (HnB). These smoke-free products avoid combustion of tobacco, known to create the majority of toxicants contained in cigarette smoke. The aerosols of ECigs and HnBs have been shown to contain toxicant levels lower by an average of > 90% compared with cigarette smoke [13–15].

The proof of principle for tobacco harm reduction comes from epidemiological findings spanning decades from Swedish smokers switching to snus, with the result that smoking rates and smoking-related mortality in Sweden are the lowest in Europe today [16]. ECigs have contributed tens of thousands of additional quitters in England, with the most recent estimates ranging from 50,000 to 70,000 additional smokers abandoning cigarettes in the UK per year [17]. The effect is probably based on the superior efficacy of ECigs over nicotine replacement products [18], coupled with the high acceptance of ECigs by smokers wishing to replace cigarettes. At the same time, youth initiation continues to be low in the UK and New Zealand [19, 20], and youth vaping only rarely seems to lead to smoking [21]. As for HnBs, it is noteworthy that, in Japan, 20% of smokers have switched to such products, which is a very plausible reason for the unprecedented drop in cigarette sales observed in Japan [22]. Taken together, these facts suggest that both ECigs and HnBs could play a role in reducing smoking-attributed morbidity and mortality.

In Germany, ECigs have been available since 2007, and current users now form about 2–3% of the population aged 14 or over [http://debra-study.info/wordpress//]. HnB products only became available much later, in 2016, with the number of users estimated to have risen from about 36,000 in 2017 to about 300,000 in 2019, then forming about 0.4% of the population aged 18 or over [https://www.pmi.com/investor-relations/overview]. The two products are predominantly used by current or former smokers, and only by very few never-smokers [4]. Among 12- to 17-year-olds, use in the last 30 days, which is not necessarily a good marker for regular use, remains low at 5.1% for ECigs and 0.1% for HnBs [23].

Our main objective is to estimate the population health impact of introducing HnBs or ECigs into Germany during 1995–2015 under various assumptions about their rate of uptake. We also compare our estimates with those derived by assuming that the whole population ceased smoking cigarettes immediately.

To avoid uncertainty about the future, and to take into account the effect of exogenous factors—such as medical progress and infectious disease epidemics—on future mortality rates, we use a “hindcasting” approach, in which individuals start in 1995, with a nationally representative distribution of cigarette smoking, and are then followed until 2015 under various assumptions. This approach has previously been applied for assessing the population health impact of introducing HnBs into the US [24, 25] and Japanese [26] markets. In this study, we have considered two types of product, HnBs and ECigs. Both can be termed reduced-risk products (RRPs) — that is, products considered likely to present less risk of harm to cigarette smokers who switch to them.

The approach generates estimates of the number of smoking-related deaths (SRD) and number of years of life lost (YLL) in scenarios where RRPs are or are not introduced, the difference between the two scenarios being referred to as the drop in deaths (DD) and number of years of life saved (YLS). These are calculated separately for the four main diseases known to be related to cigarette smoking, lung cancer (LC), chronic obstructive pulmonary disease (COPD), ischaemic heart disease (IHD), and stroke. Note that, while the term SRD is normally used in reference to the additional deaths arising from the increased risk from cigarette smoking, it is here used in reference to the additional deaths arising from the increase in risk associated with the use of any of the three products considered: cigarettes, HnBs, or ECigs.

Methods

Outline of the approach used in population health impact modelling (PHIM)

The basic method used for estimating the population health impact of introducing an RRP into a country is as described earlier [27] and involves two components, the Prevalence (P-) component and the Epidemiologic (E-) component.

The P-component starts in a specified year with a group of individuals of a given sex and age range with a defined distribution of cigarette smoking. This group is then followed over discrete time intervals under both a “Null Scenario” and various “Alternative Scenarios”, by using different sets of transition probabilities (TP). In the Null Scenario, RRPs are never introduced, and each individual’s cigarette smoking status (never, current, or former) is updated at each yearly interval. In each Alternative Scenario, RRPs are introduced during follow-up, and the TPs allow for switching between six groups (never user, current exclusive cigarette smoker, current exclusive HnB user, current exclusive ECig user, current multiple product user, and former product user). “Never users” have never used cigarettes or either of the two RRPs considered. “Current multiple product users” currently use two or three of the products considered, while “former product users” have previously used at least one of the three products but do not currently use any of them. At the end of the P-component, each individual has a complete history of use of the three products over the follow-up period under each Scenario. Note that the modelling ignores products other than cigarettes, ECigs, and HnBs.

The E-component then uses the product use histories to estimate, for each individual in the predefined population, the relative risks (RR), compared to never users, of LC, COPD, IHD, and stroke for each follow-up year and Scenario. The estimation involves an extension of the negative exponential model (NEM), which allows for multiple changes in use, as fully described elsewhere [24]. The NEM requires estimates of the RR for continued smoking for each of the four diseases. It also requires estimates of the effective doses for current exclusive HnB use, exclusive ECig use, and multiple product use relative to that for current cigarette smoking (taken as one unit). The effective dose is a measure of harm, so that if cigarette smokers have excess risk (RR – 1) for a disease, the excess risk for an RRP user with an effective dose of q is q (RR – 1). The effective dose for an RRP is assumed to be the same for each disease. The NEM also requires estimates, for each of the four diseases, of the RR for continued smoking and the quitting half-life (H). H is the time from quitting when the excess relative risk (RR – 1) declines to half that for continuing smokers, the decline over time being assumed to follow a negative exponential distribution, as has been shown to be approximately true for LC [28], COPD [29], IHD [30], and stroke [31].

The estimation of the RR for an individual does not specifically take into account the amount smoked, but the effective dose for multiple product users may be set to reflect a reduced consumption of cigarettes. A discussion of how the effective dose may be quantified for an RRP is given elsewhere [27].

For each Scenario, the average RR for each of the four diseases for individuals of a given sex and age group is then calculated for each follow-up year, from which the proportions of SRD can be derived. These are then converted to numbers by using national mortality estimates by sex, age group, and year. The differences in estimated numbers and proportions among the Scenarios then quantify the effect of RRP introduction.

For a given scenario, YLL is estimated by using the method of Gardner and Sanborn [32]. YLL (N) is calculated by summing up the product of the number of deaths in each age group by the number of years life remaining up to a given age of N years, with N taken here as 75 years. Thus, for an age group of 40–44 years, where the mean age is taken as 42.5 years, the number of years remaining is taken to be 75 – 42.5 = 32.5 years. For age groups above 70–74 years, the number of years remaining is taken as zero. YLS is then calculated from the difference in YLL between the Alternative and Null Scenarios.

Although the individuals in each Alternative Scenario might have death rates different from those in the Null Scenario, estimates of DD and YLS assume that the size of the populations of risk remains the same during follow-up, with no correction for differential survival. These estimates of the effect of RRP introduction can be corrected for this possibility, if required [27].

The methodology can also compare the Null Scenario with Alternative Scenarios where RRPs are not introduced but where different sets of TPs for cigarette smoking are used.

The modelling starts with a population aged 10–79 years, with individuals dropping out of the calculations as they reach 80 years of age. This is partly because cause of death certification is unreliable at an older age and partly because our estimates of population health impact also include YLS, which is unaffected by deaths above the age of 74 years.

Common features of each simulation

Each simulation involved the follow-up of 100,000 individuals in 1-year intervals from 1995, with the product use status of each member of the simulated population being estimated at each year of follow-up until the year 2005 (or age 79, if that came earlier). For each situation described in the Methods section, separate simulations were conducted for each sex.

Population at baseline

As previously described [24], each individual in a simulation is randomly allocated at the start of the P-component to a year of age, then to a cigarette smoking group (never, current, or former), and, then, for former smokers, to an age of quitting.

The sex-specific age distributions used for Germany for 1995 are as published by the United Nations [33].

Sex- and age-specific distributions of current and former smoking prevalence for Germany for individual years from 1995 to 2015 were derived by combining data from three sources: International Smoking Statistics [34], which provides results by 5-year age groups from 1980–2015 for current smoking; a report by Forey and Lee [35], which provides results by 15-year age groups from 1980–2005 for former smoking; and the German Socioeconomic Panel [36], which provides data for 2002 and 2012 for current and former smoking. Only the estimates for 1995 are required for the baseline population.

The sex- and age-specific distribution of quit time for former smokers used for the baseline population in 1995 was taken, in the absence of alternative data, from estimates for 2002 derived from the German Socioeconomic Panel [36]. Because this source only provided data for age groups 20–24 and above, the data for younger age groups were taken from US estimates for 2006 [24].

Additional File 1 gives further details on the derivation of the data on current and former smoking prevalence and quit time. It also includes tables summarizing the age-specific distribution of the population and the data on smoking habits used to assign the initial status of each member of the simulated population in 1995.

Estimation of histories of cigarette smoking for the Null Scenario

The sex- and age-specific TPs used in the P-component for developing the histories of cigarette smoking for the Null Scenario were derived as described in Additional File 2 and are shown in Table 1. In order to test the validity of the TPs, the prevalences predicted by using these TPs were compared with the estimates for Germany derived for years up to 2015 as described in Additional File 1.

Table 1
Monthly TPs (per million) in the Null Scenario for Germany

Period		**Initiation (P_{NC})**		**Quitting (P_{CF})**		**Re-initiation (P_{FC})**	
(years)	Age	Men	Women	Men	Women	Men	Women
1–5	10–14	4,296	3,462	2,446	1,454	1,166	695
	15–19	5,767	6,728	3,931	7,159	1,866	3,366
	20–24	745	3,030	1,347	5,018	644	2,374
	25–29	560	724	2,037	3,152	972	1,499
	30–34	220	358	2,551	2,546	1,216	1,213
	35–39	0	0	2,245	807	1,070	387
	40–44	0	0	2,006	1,589	957	257
	45–49	0	0	2,297	1,617	820	130
	50–54	0	0	3,109	2,161	442	86
	55–59	0	0	3,460	2,805	243	57
	60–64	0	0	3,419	3,480	119	35
	65–69	0	0	4,712	2,245	80	22
	70–74	0	0	7,878	20,834	57	16
	75–79	0	0	7,878	20,834	57	16
6–10	10–14	3,654	2,986	2,063	2,210	985	1,054
	15–19	5,459	5,213	4,928	7,249	2,332	3,407
	20–24	516	1,981	974	5,150	466	2,435
	25–29	1,231	958	3,263	4,390	1,551	2,080
	30–34	330	472	2,975	2,472	1,416	1,178
	35–39	0	0	1,873	902	894	432
	40–44	0	0	1,760	2,185	800	259
	45–49	0	0	2,284	2,342	602	139
	50–54	0	0	3,662	2,689	432	80
	55–59	0	0	4,096	2,714	241	57
	60–64	0	0	3,954	3,334	211	35
	65–69	0	0	5,848	4,040	155	21
	70–74	0	0	4,772	16,169	114	15
	75–79	0	0	4,772	16,169	114	15
11+	10–14	2,883	2,072	1,840	3,593	879	1,706
	15–19	5,538	4,627	6,243	9,383	2,943	4,382
	20–24	323	767	578	4,563	277	2,161
	25–29	1,935	1,155	4,942	6,037	2,338	2,848
	30–34	497	567	3,601	2,098	1,710	1,001
	35–39	0	0	1,455	928	695	444

Period		Initiation (P_{NC})		Quitting (P_{CF})		Re-initiation (P_{FC})	
	40–44	0	0	1,554	3,112	598	368
	45–49	0	0	2,593	3,029	382	233
	50–54	0	0	4,187	3,004	307	181
	55–59	0	0	4,678	2,446	171	138
	60–64	0	0	4,391	2,710	163	73
	65–69	0	0	7,638	2,323	136	41
	70–74	0	0	1,575	5,489	36	31
	75–79	0	0	1,575	5,489	57	16

The first period relates to 5 years starting from 1995, the second to 5 years starting from 2000, and the third to 10 years starting from 2005.

The probabilities of transition among 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.

Note that RRPs are not introduced in the Null Scenario.

Estimation of histories of product use for the Alternative Scenarios

Seven different Alternative Scenarios were tested and are summarized in Table 2; Scenarios 1 to 3 are termed “Extreme Scenarios” and Scenarios 4 to 7 “Pragmatic” Scenarios. The Pragmatic Scenarios were designed to provide a range of possible uptake rates of HnBs and ECigs on the basis of known market data for Germany, with Scenario 6 (the “Conversion Scenario”) being regarded as perhaps the most plausible one. Converted RRP users are defined as the estimated number of Legal Age (over 18 years old) users that used the RRP for over 95% of their daily nicotine product consumption over the past 7 days. The link above also presents evidence on conversion rates.

Table 2
The Alternative Scenarios

Scenario		
Number	Name	Summary description and comments
	Extreme Scenarios	
1	Complete cessation	In 1995, all current cigarette smokers immediately stop smoking. There is no further initiation or re-initiation of cigarettes, HnB, or ECig use.
2	Complete switch to RRPs (HnBs)	In 1995, all current cigarette smokers immediately switch to HnBs. The subsequent initiation, re-initiation, and quitting rates are as in the Null Scenario, but only involve transfers in or out of HnBs.
3	Complete switch to RRPs (50% HnBs and 50% ECigs)	In 1995, all current cigarette smokers immediately switch to either HnBs or ECigs with equal probability. The subsequent rates are as in the Null Scenario, but only involve transfers involving the new products.
	Pragmatic Scenarios	
4	Conservative Scenario	HnB:The market share in 2005 is 9% of that in 1995 for cigarette smoking, with 67% exclusive users. ECig:The market share in 2005 is 27% of that in 1995 for cigarette smoking, with 40% exclusive users. The calculated target distributions for 2005 are: **Never Cig only HnB only ECig only Multiple use Former use** **Men**:35.46 24.22 2.28 4.09 7.25 26.70 **Women**:60.56 15.64 1.47 2.64 4.68 15.01 Note: Multiple (product) users currently use at least one of the three products, while former (product) users have used at least one of the products, but do not currently use any). The sum of the TPs for initiation and the sum of the TPs for re-initiation are the same as that for the Null Scenario. Each quitting TP is as for the Null Scenario. The difference between the four Pragmatic Scenarios only relates to the rates of switching among the three products.
5	Dynamic Scenario	The market shares in 2005 increase to 15.5% for HnBs and 36.4% for ECigs. The proportions of exclusive users are as in the Conservative Scenario. The calculated target distributions for 2005 are: **Never Cig only HnB only ECig only Multiple use Former use** **Men**:35.46 18.20 3.93 5.51 10.20 26.70 **Women**:60.56 11.75 2.54 3.56 6.59 15.01 The rates of switching from exclusive cigarette smoking are increased from those in the Conservative Scenario.
6	Conversion Scenario	The same as the Dynamic Scenario, except that the proportions of exclusive users rise to 84% for both RRPs. The calculated target distributions for 2005 are: **Never Cig only HnB only ECig only Multiple use Former use** **Men**:35.46 18.20 4.93 11.57 3.14 26.70 **Women**:60.56 11.75 3.18 7.47 2.03 15.01 Relative to the Dynamic Scenario, all 12 possible rates of switching vary, except those of switching from exclusive use of one RRP to exclusive use of the other.

Abbreviations used: Cig = cigarette, ECig = e-cigarette, HnB = heat-not-burn, RRP = reduced risk product, TP = transition probability

Scenario		
7	Full Conversion Scenario	The same as the Dynamic Scenario, except that the proportions of exclusive users rise to 100% for both RRPs. The calculated target distributions for 2005 are: **Never Cig only HnB only ECig only Multiple use Former use** **Men**:35.46 18.20 5.87 13.87 0.00 26.70 **Women**:60.56 11.75 3.79 8.89 0.00 15.01 The comment for the Conversion Scenario applies here as well.
Abbreviations used: Cig = cigarette, ECig = e-cigarette, HnB = heat-not-burn, RRP = reduced risk product, TP = transition probability		

No RRP is introduced in Alternative Scenario 1. For the other six Alternative Scenarios, the effective doses are assumed to be 0.2 for exclusive HnB use and 0.05 for exclusive ECig use, in contrast to an effective dose of 1 for exclusive cigarette smoking. The value for HnBs was conservatively based on biomarkers and clinical findings [37], and that for ECigs was based on a published expert opinion [38]. For multiple product use, the effective dose is assumed to be the mean of the three effective doses (i.e., 0.42).

The TPs used in the P-component for developing usage histories in the Alternative Scenario are presented in Additional File 3. Note that, for each Alternative Scenario, the sum of the initiation TTPs (for a given sex, age, and follow-up period) was constrained to be equal to the corresponding initiation TP for the Null Scenario. The same constraint was applied to the re-initiation TPs. Each cessation TP in the Alternative Scenario was also constrained to be equal to the cessation TP in the Null Scenario. These constraints were applied so that the various Alternative Scenarios considered only the effect of the RRPs introduced on the distribution of current smoking habits, without any effect on overall initiation, cessation, or re-initiation rates.

Estimating relative risks on the basis of product use histories

For each disease, the estimates of the RR for continued cigarette smoking and of H were derived from meta-analyses of published data. The estimates and sources used are given in Table 3.

Table 3
Assumed values for Germany of the relative risk for continued cigarette smoking (RR) and quitting half-life (H) by disease

	Age (years)	LC	COPD	Stroke	IHD
Relative risk	Any	8.68	3.31		
	to 54			2.48	3.38
	55–64			2.13	2.32
	65–74			1.39	1.70
	75–79			1.06	1.27
Half-life	Any		13.32	4.78	
	to 49	6.98			1.47
	50–59	10.39			5.22
	60–69	10.60			7.48
	70–79	12.99			13.77
Sources for RRs: LC [39]; COPD [40]; IHD, and Stroke [24].					
Sources for H: LC [28]; COPD [29]; IHD [30], and Stroke [31].					

The sex- and age-specific data on national population size for Germany for the years 1995 to 2015 are as published by the United Nations Department of Economic and Social Affairs Population Division [33].

The data on numbers of deaths in Germany from LC, COPD, IHD, and stroke come from the World Health Organization [41]. The data on population size and numbers of deaths for Germany for the years 1995 to 2015 are presented in Additional File 4, which gives full details on sources and disease definitions.

The method of estimating the number of deaths and increase in death rates associated with tobacco is as described earlier [24]. Unless indicated, the results are presented without adjustment for changes in population size associated with each Alternative Scenario.

Results

Full results of the analyses are available in Additional File 5. Figure 1 compares never, current, and former smoking prevalence estimates for Germany by sex for age groups 30–34, 50–54, and 70–74 years as simulated in the Null Scenario (broken lines) with those derived as described in the Methods section (solid lines). The fit is generally very good, though there is some tendency for the Null Scenario current smoking estimates to be lower than the derived estimates at age 70–74 years.

Figure 2 presents the simulated estimates of product usage in the Conversion Scenario by sex, age (30–34, 50–54, and 70–74 years), and year (1995, 2000, 2005, 2010, and 2015). In 1995, the estimates for current, never and former product use are identical, as expected, to those for cigarette smoking in the Null Scenario shown in Fig. 1. The proportions of never and former product users in Fig. 1 and Fig. 2 remain very similar over the whole time period. While in the Null Scenario, the current product users all smoke cigarettes, in the Conversion Scenario, they fall into four groups. Over the first 15 years, there is a large decline in exclusive cigarette smoking and a corresponding increase in the other three current product use categories. This pattern flattens out between 2010 and 2015, with some decline in some of the groups. Further details for the Conversion Scenario as well as other Pragmatic Scenarios are shown in Additional File 5.

Additional File 6 summarizes the current product use distributions in 2005 for all the Scenarios. With regard to the distributions in 2005, after 10 years follow-up, there were, as expected, no current product users at all in Scenario 1, with all HnB users in Scenario 2 and half HnB and half ECig users in Scenario 3. In the Pragmatic Scenarios, the proportions of exclusive cigarette smokers decrease and those of exclusive HnB and ECig users increase from Scenarios 4 to 7. Relative to Scenario 5, the proportions of multiple product users decline in Scenarios 6 and 7. In 2010 (and also at other time points) the overall prevalence of current product users is essentially the same in each of Scenarios 2 to 7. This represents a drop of about 25% in men and 12% in women relative to the proportions in 1995.

As estimated by the P-Component of PHIM, 852,357 deaths were attributed to cigarette smoking over the whole follow-up period in the Null Scenario. 77.9% of these were in males, with the percentages by disease being 54.6% for LC, 26.4% for IHD, 13.4% for COPD and 5.7% for stroke.

Table 4 presents the estimated DDs at age 30–79 years over the whole follow-up period for all seven Scenarios. These are shown for each disease separately and combined. The results are expressed both as numbers and percentages of all SRDs.

Table 4
Drops in deaths over the whole follow-up period associated with the seven Alternative Scenarios in Germany

		Drop in deaths					% drop in deaths				
	Sex/Scenario	LC	IHD	Stroke	COPD	All four diseases	LC	IHD	Stroke	COPD	All four diseases
	MEN										
1	Complete cessation	48,092	83,798	15,429	14,166	161,485	13.38	45.26	46.06	16.48	24.32
2	Complete switch to RRPs (HnBs)	34,148	61,591	11,783	10,820	118,342	9.50	33.27	35.17	12.59	17.82
3	Complete switch to RRPs (50% HnBs; 50% ECigs)	38,967	69,431	13,111	12,038	133,547	10.84	37.50	39.14	14.01	20.11
4	Conservative Scenario	8,316	16,144	3,286	2,969	30,714	2.31	8.72	9.81	3.46	4.63
5	Dynamic Scenario	13,437	25,533	5,136	4,680	48,785	3.74	13.79	15.33	5.44	7.35
6	Conversion Scenario	15,950	30,276	6,004	5,425	57,655	4.44	16.35	17.92	6.31	8.68
7	Full Conversion Scenario	17,210	32,734	6,431	5,777	62,153	4.79	17.68	19.20	6.72	9.36
	WOMEN										
1	Complete cessation	23,231	18,101	7,345	6,487	55,165	22.01	45.20	50.02	23.22	29.31
2	Complete switch to RRPs (HnBs)	16,617	13,670	5,649	5,000	40,936	15.74	34.14	38.47	17.89	21.75
3	Complete switch to RRPs (50% HnBs; 50% ECigs)	18,882	15,245	6,261	5,534	45,923	17.89	38.07	42.64	19.81	24.40
4	Conservative Scenario	3,476	3,089	1,369	1,169	9,104	3.29	7.71	9.32	4.19	4.84
5	Dynamic Scenario	5,605	4,934	2,141	1,859	14,540	5.31	12.32	14.58	6.66	7.72
6	Conversion Scenario	7,014	6,035	2,616	2,277	17,942	6.64	15.07	17.81	8.15	9.53
7	Full Conversion Scenario	7,530	6,404	2,783	2,424	19,140	7.13	15.99	18.95	8.67	10.17

Abbreviations used: COPD = chronic obstructive pulmonary disease, ECig = e-cigarette, HnB = heat-not-burn, IHD = ischaemic heart disease, LC = lung cancer

The DDs in the Conversion Scenario are also shown by disease over the whole follow-up period in Fig. 3.

As expected, the largest DD for the four diseases combined is seen in the complete cessation Scenario. Substantial DDs are also seen in the complete switch Scenarios —more so in Scenario 3 than in Scenario 2, because the assumed effective dose is lower for ECigs (0.05) than it is for HnBs (0.2). The DDs are lower in the Pragmatic Scenarios, because the transition from Cigarettes to HnBs and ECigs is less rapid. As would be predicted from the patterns of uptake by Scenario shown in Fig. 2, the greatest DDs are seen in the Full Conversion Scenario, where smokers switch gradually to the RRPs — they are about 40% of the DDs associated with Complete Cessation, where smokers quit smoking immediately in 1995.

The patterns of DDs for the individual diseases are similar to that for the four diseases combined. Among men, the largest absolute DDs are for IHD, with LC next, followed by stroke and COPD with lower and similar DDs. Among women, the DDs for LC are higher than those for IHD, reflecting the lower overall IHD rate among women. As a proportion of all SRDs, the DDs in both sexes are substantially higher for IHD and stroke than for LC and COPD, reflecting the shorter half-lives for IHD and stroke (i.e., the more rapid reduction in cardiovascular disease risk after smoking cessation or switching to RRPs).

As is shown in Fig. 3 for the Conversion Scenario, but as is also clearly evident from Additional File 5 for the other Scenarios, a clear increase in DDs is seen with time in both sexes. This is due partly to the time needed for take-up of HnBs and ECigs and partly to the time required for the resulting decline in risk. This trend clearly suggests that the DDs would have been substantially greater had the follow-up period been extended.

In the Null Scenario, 8.61 million YLL were attributed to cigarette smoking. 76.2% of these were in males, with the percentages by disease being 51.6% for LC, 31.8% for IHD, 8.4% for COPD and 8.2% for stroke. The percentages by disease, compared to those given above for attributable deaths, reflect the higher proportion of deaths at younger ages for IHD and stroke than for LC and COPD.

Table 5 and Fig. 4 summarize the results for the seven Scenarios with regard to YLS by age 75 over the whole follow-up period. The relative values for the different Scenarios are very similar to those for DD seen in Table 4. Indeed, on the basis of the results for the four diseases combined in Tables 4 and 5, the sex- and scenario-specific ratios of YLS to DD only vary between 12.5 and 13.4.

Table 5
Years of life saved (thousands) by age 75 over the whole follow-up period in the different Alternative Scenarios in Germany

		Men					**Women**				
	Scenario	LC	IHD	Stroke	COPD	All four diseases	LC	IHD	Stroke	COPD	All four diseases
1	Complete cessation	520	1,329	213	98	2,160	292	258	118	52	720
2	Complete switch to RRPs (HnBs)	357	943	160	74	1,534	203	189	89	40	521
3	Complete switch to RRPs (50% HnBs; 50% ECigs)	412	1,077	180	83	1,752	233	213	99	44	589
4	Conservative Scenario	83	241	43	20	387	42	43	21	10	116
5	Dynamic Scenario	134	379	68	31	612	67	68	33	15	183
6	Conversion Scenario	161	461	80	37	739	84	84	40	18	226
7	Full Conversion Scenario	176	506	86	39	807	90	89	43	19	241

Abbreviations used: COPD = chronic obstructive pulmonary disease, ECig = e-cigarette, HnB = heat-not-burn, IHD = ischaemic heart disease, LC = lung cancer

The analyses summarized above do not take into account the increase in population size associated with the reduced mortality in the Alternative Scenarios relative to that in the Null Scenario. As shown in the detailed results in Additional File 5, this had little effect on the estimated DD or YLS. For example, for the Conversion Scenario, where the overall unadjusted DDs were 57,655 (8.68% of all SRDs) in men and 17,942 (9.53% of SRDs) in women, the corresponding adjusted DDs were 57,026 (8.59%) and 17,892 (9.51%), respectively.

Discussion

Over a period of 20 years, from 1995 to 2015, in the absence of any switching to HnBs or ECigs and with the patterns of prevalence of cigarette smoking as existing in Germany, we estimate that there would have been 852,357 SRDs from LC, COPD, IHD, and stroke combined for both sexes, with about 8.61 million YLL.

In the work described here, we attempt to estimate how these numbers would have been affected had various alternative patterns of product use occurred. The greatest impact would clearly have occurred had all cigarette smokers quit in 1995, with no further use of cigarettes, HnBs, or ECigs (Scenario 1), resulting in a DD of 216,650 and 2.88 million YLS. However, substantial reductions would still have occurred had cigarette smoking in Germany been immediately replaced by either HnB use (Scenario 2; 159,278 DDs and 2.06 million YLS, corresponding to 74% and 71%, respectively, of Scenario 1, immediate cessation) or equally by either HnB or ECig use (Scenario 3; 179,470 DDs and 2.34 million YLS, corresponding to 83% and 81% of Scenario 1), with the greater numbers for Scenario 3 reflecting the assumed lower effective dose for ECigs compared with HnBs. These numbers would have been greater still had we included a Scenario in which cigarette smoking was immediately replaced by ECig use.

In practice, such Scenarios are rather unrealistic; more plausible are the estimates associated with the Pragmatic Scenarios in which a proportion of cigarette smokers move gradually to use HnBs and ECigs. Scenarios 4 to 7 vary in the extents to which uptake of these

RRPs occurs and to which RRP users fully convert to exclusive RRP use rather than becoming multiple users of Cigarettes and RRPs. However, each Scenario shows a relevant population health impact, with DDs varying, between Scenarios 4 and 7, from 39,818 to 81,293 and YLS varying from 0.50 to 1.05 million. The different Pragmatic Scenarios would thus have achieved 18–38% for DDs and 17–36% for YLS of the effect of immediate cessation (Scenario 1), the best albeit unrealistic scenario.

Our estimates may be regarded as conservative for three main reasons. The first reason is that we only considered deaths from the four main SRDs because of the lack of reliable data on RR and H for all diseases associated with smoking. We have noted elsewhere [27] that our estimates of deaths saved would have to be multiplied by about 1.52 to yield an estimate for all smoking-related diseases.

The second, and very important, reason is that we only considered a 20-year follow-up period. This was because we did not wish to project into the future, where disease rates might be affected by a variety of exogenous factors, such as improvements in disease treatment. It is clear from the results in Fig. 3 that the annual numbers of lives saved increase rapidly over time, particularly from LC and COPD, where quitting takes a long time to reduce risk.

The third reason is that our analyses did not take into account the possibility that cigarette smokers who take up ECigs or HnBs might be more likely to quit cigarette smoking than those who continued to exclusively smoke cigarettes. Evidence from the US shows that use of ECigs is associated with increased cessation rates [42].

Our analyses are limited by a number of factors shown in a previous work [24] to have only a modest effect on the estimates of population health impact. These include failure to consider pipe and cigar smoking, use of smokeless tobacco or nicotine replacement therapy, ignoring exposure from environmental tobacco smoke, and not allowing TPs to vary by previous product use history. Though the negative exponential model has been validated on the basis of extensive data on quitting as well as limited data on changes in the number of cigarettes smoked [43], the accuracy of its predictions on more complex changes in usage over time has not been formally tested.

Our results related to the introduction of RRPs will be affected by the choice of effective doses used. For ECigs, we have used an estimate of 0.05 on the basis of expert opinion [38], although this estimate was derived on the basis of chemistry and short-term toxicological results. For HnBs, our estimate of 0.20 was conservatively based on biomarker and clinical data [37], with results for a number of endpoints suggesting a lower effective dose. Elsewhere [24], we have demonstrated that the estimated DD is linearly related to the assumed values of the effective dose used, with DD increasing as the effective dose decreases. While the estimated effective dose is an important factor when smokers switch to RRPs like ECigs and HnBs, other factors also play a role. These include changes in the frequency of use and the extent to which cigarettes are completely abandoned.

A possible limitation of our modelling is that we considered people who simultaneously used two or three out of cigarettes, ECigs, and HnBs as multiple-product users, with their effective dose taken as the mean of 1, 0.05, and 0.20. People who are dual users of cigarettes with either ECigs or HnBs might have a higher effective dose than the mean, while those who are dual users of ECigs and HnBs might have a lower effective dose. However, because the proportion of multiple product users is quite low, particularly for the Conversion and Full Conversion Scenarios, the overall effect of this limitation on the results seems likely to be quite modest.

A further possible limitation of our modeling is that we did not consider oral tobacco products like snus, the reason being that snus is not on the market in the EU outside of Sweden. Undoubtedly, snus can have a large positive impact on public health when smokers switch to it [16]. With other forms of oral tobacco having become available in Germany over the past years, uptake of such products could thus increase the overall effect on DD and YLS in the case of smokers switching to products without tobacco combustion, as has already been modelled in Sweden [44].

The rate at which smokers switch to less harmful alternatives like ECigs and HnBs is likely to depend on product risk perception, a large body of evidence having already shown this to be the case for ECigs. For instance, accurately perceiving ECigs as less harmful than cigarettes predicted subsequent ECig use among British smokers [45] and continues to correlate with ECig use among UK smokers [46]. German smokers were more likely to use ECigs for smoking cessation if they perceived them as less harmful than Cigarettes [47]. US adult dual users of ECigs and Cigarettes who perceived ECigs as less harmful than cigarettes were more likely to switch to exclusive ECig use 1 year later [48]. However, correct risk perceptions of ECigs remain low and are getting worse over time, both internationally [45, 46] and in Germany, where more than half of the population perceives ECigs [49, 50] and HnBs [50] as at least as harmful as cigarettes. Even among ever-users of HnBs in Germany, only just over half of them accurately perceived HnBs as less harmful than cigarettes [51]. Public health experts in the UK, the US, and Germany are, therefore, calling for better access to fact-based information [9, 45, 52, 53].

Educational campaigns via trusted public health institutions are likely the most effective tool [54]. While such campaigns exist in the UK, they are virtually absent in Germany.

Intuitively, maximizing the beneficial population health impact of introducing ECigs and HnBs will require a combination of high uptake among smokers, with many ultimately becoming exclusive RRP users. Our modeling results support this notion, with the DD and YLS increasing between Scenarios 4 and 5, when uptake was increased, and between Scenarios 5 and 7, when exclusive product use was increased. As discussed above, RR perceptions for ECig/HnB vs. smoking are potential drivers for both product uptake and exclusive product use, with health policy actions like public education campaigns being a recommended tool. Other factors likely to have an impact include risk-proportionate regulation in general [55]—such as product health warnings [56]—and local smoking cessation guidelines and healthcare professional recommendations [57] as well as media headlines [58]. Moreover, fiscal policies can have an impact on relative product use. Recent US retail panel data suggest that ECig taxation increased cigarette sales [59].

Many other published papers have attempted to quantify the population health impact of introducing RRPs. These include estimates based on the methodology we have used, but applied to the USA [24, 25] or Japan [26], as well as attempts using different methodology, supported by other tobacco companies [60–65] or by public funding [66–72]. Despite methodological differences, most modelers have assumed that the risk from RRP use, relative to that from cigarette smoking, is low and have concluded as we have that introduction of RRPs is likely to have a beneficial impact. For example, Levy et al. [69] concluded that "The tobacco control community has been divided regarding the role of e-cigarettes in tobacco control. Our projections show that a strategy of replacing cigarette smoking with vaping would yield substantial life year gains, even under pessimistic assumptions regarding cessation, initiation and relative harm." Although this previous paper focused on e-cigarettes, the authors did note that "…heat-not-burn tobacco products have been introduced in some countries, and these may be a better substitute for cigarettes than e-cigarettes…"

As noted in the introduction, the number of smoking-attributable deaths estimated by Mons and Brenner to have occurred in Germany in 2013 is 125,000 [6]. In the Null Scenario, in 2013, the number of SRDs was estimated to be 39,629. There are three main reasons for this discrepancy. First, we only considered four diseases, which form only about 67.5% of the total number of smoking-related diseases [2]. Second, we only considered the deaths of people aged 30–79 years, whereas the published estimate was related to age 35 years or above. Third, the disease-specific RRs used by Mons [2] were derived from specific US studies, whereas ours were derived from detailed meta-analyses (see Table 5). While the RRs from the two studies were quite similar for both IHD and stroke, those for LC (23.26 for men and 12.69 for women vs. 11.68 for both sexes) and COPD (10.58 for men and 13.08 for women vs. 4.56 for both sexes) were markedly higher in the previous study. Had we considered more diseases, a wider age range, or higher RRs, the estimated DD and YLS would, of course, have increased.

Overall, our results provide insight into how much the introduction of the two RRPs considered might affect the distribution of usage in Germany and the mortality related to cigarette smoking. Policies and regulation can accelerate switching to these RRPs, including calling for a more risk-proportionate approach and for the best available information on RRPs to be available to adult smokers. This will help increase the perception of the harm-reduction capabilities of RRPs and encourage switching, make alternatives to cigarettes more attractive for smokers, and help maintain product standards for building consumer trust in RRPs. Rather than any single measure, an integrated tobacco control strategy is likely to be more successful in encouraging smokers to switch to RRPs and thus result in an overall public health gain.

Conclusions

On the basis of plausible estimates of the rate of uptake of two RRPs (HnBs and ECigs) in Germany and their effective dose compared with cigarettes, it is estimated that there would be a drop in SRDs from LC, COPD, IHD, and stroke of approximately 40,000 to 81,000, with 0.50 to 1.05 million YLS, corresponding to 17–38% of the effect of immediate cessation (Scenario 1). While cessation is the best option for smokers, we estimate that introducing RRPs and encouraging smokers who would otherwise continue to smoke cigarettes to switch to them will result in a substantial population health benefit, even under conservative assumptions about their relative harm and rate of uptake.

Abbreviations

COPD = chronic obstructive lung disease, DD = drop in deaths, E- component = epidemiologic component, E-cig = electronic cigarette, H = quitting half-life, HnB = heat-not-burn, IHD = ischaemic heart disease, LC = lung cancer, NEM = negative exponential model, P- component

= prevalence component, PHIM = public health impact modelling, RR = relative risk, RRP = reduced risk product, SRD = smoking-related disease, TP = transition probability, WHO = World Health Organization, YLL = years of life lost, YLS = years of life saved.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

RR and AKN are employees of Philip Morris International. SD was an employee of Philip Morris International at the time the work was carried out. AK, EB, PNL and JSF were contracted consultants for the project and paid by Philip Morris International.

Funding

The work described was wholly supported by Philip Morris Products S.A.

Authors' contributions

The work described here was conceived by RR, SD, AKN and PNL. Some of the data required was extracted by AK and EB. The analyses were run by JSF, RR and SD, and checked by PNL. The manuscript was drafted by PNL, with contributions by AKN, and developed following comments by RR, SD, EB and JSF. All authors read and approved the final manuscript.

Acknowledgements

We thank Jan and John Hamling for their assistance in running the software (which they helped develop) and for checking some of the results. We also thank Laszlo Pecze for his involvement at an early stage of the work and Yvonne Cooper and Diana Morris for typing various drafts of this report.

References

1. Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, et al. 21st-century hazards of smoking and benefits of cessation in the United States. N. Engl. J. Med. 2013;368(4):341-50. doi:10.1056/NEJMsa1211128.
2. Mons U. Tabakattributable Mortalität in Deutschland und in den deutschen Bundesländern - Berechnungen mit Daten des Mikrozensus und der Todesursachenstatistik (Tobacco-attributable mortality in Germany and in the German Federal States - calculations with data from a microcensus and mortality statistics). Gesundheitswesen 2011;73(4):238-46.(Epub 20100614): doi:10.1055/s-0030-1252039.
3. World Health Organization. WHO global report on trends in prevalence of tobacco smoking 2015. Geneva: World Health Organization; 2015. Available: https://www.who.int/tobacco/publications/surveillance/reportontrendstobaccosmoking/en/index4.html.
4. Kotz D, Bockmann M, Kastaun S. The use of tobacco, e-cigarettes, and methods to quit smoking in Germany: A representative study using 6 waves of data over 12 months (the DEBRA study). Dtsch Arztebl Int 2018;115(14):235-42. doi:10.3238/arztebl.2018.0235.

5. Kotz D, Batra A, Kastaun S. Smoking cessation attempts and common strategies employed: A Germany-wide representation survey conducted in 19 waves from 2016 to 2019 (the DEBRA Study) and analyzed by socioeconomic status. Dtsch Arztebl Int 2020;117:7-13. doi:10.3238/arztebl.2020.0007.
6. Mons U, Brenner H. Demographic ageing and the evolution of smoking-attributable mortality: the example of Germany. Tob Control 2017;26(4):455-7.(Epub 20160704): doi:10.1136/tobaccocontrol-2016-053008.
7. Chaloupka FJ, Sweanor D, Warner KE. Differential taxes for differential risks--toward reduced harm from nicotine-yielding products. N Engl J Med 2015;373(7):594-7. doi:10.1056/NEJMp1505710.
8. Royal College of Physicians. Nicotine without smoke: tobacco harm reduction. London: RCP; 2016. Available: www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction.
9. Kozlowski LT, Abrams DB. Obsolete tobacco control themes can be hazardous to public health: the need for updating views on absolute product risks and harm reduction. BMC Public Health 2016;16:432.(Epub 20160524): doi:10.1186/s12889-016-3079-9.
10. Abrams DB, Glasser AM, Villanti AC, Pearson JL, Rose S, Niaura RS. Managing nicotine without smoke to save lives now: Evidence for harm minimization. Prev Med 2018;117:88-97.(Epub 20180623): doi:10.1016/j.ypmed.2018.06.010.
11. Abrams DB, Glasser AM, Pearson JL, Villanti AC, Collins LK, Niaura RS. Harm minimization and tobacco control: reframing societal views of nicotine use to rapidly save lives. Annu Rev Public Health 2018;39:193-213.(Epub 20180111): doi:10.1146/annurev-publhealth-040617-013849.
12. Fairchild A, Healton C, Curran J, Abrams D, Bayer R. Evidence, alarm, and the debate over e-cigarettes. Science 2019;366(6471):1318-20. doi:10.1126/science.aba0032.
13. McNeill A, Brose LS, Calder R, Bauld L, Robson D. Evidence review of e-cigarettes and heated tobacco products. A report commissioned by Public Health England. London: Public Health England; 2018. Available: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/684963/Evidence_review_of_e-cigarettes_and_heated_tobacco_products_2018.pdf.
14. Schaller JP, Keller D, Poget L, Pratte P, Kaelin E, McHugh D, et al. Evaluation of the Tobacco Heating System 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. Regul Toxicol Pharmacol 2016;81(Suppl 2):S27-s47.(Epub 20161006): doi:10.1016/j.yrtph.2016.10.001.
15. Mallock N, Böss L, Burk R, Danziger M, Welsch T, Hahn H, et al. Levels of selected analytes in the emissions of "heat not burn" tobacco products that are relevant to assess human health risks. Arch Toxicol 2018;92(6):2145-9.(Epub 20180505): doi:10.1007/s00204-018-2215-y.
16. Ramström L, Wikmans T. Mortality attributable to tobacco among men in Sweden and other European countries: an analysis of data in a WHO report. Tob Induc Dis 2014;12(1):14.(Epub 20140901): doi:10.1186/1617-9625-12-14.
17. Beard E, West R, Michie S, Brown J. Association of prevalence of electronic cigarette use with smoking cessation and cigarette consumption in England: a time-series analysis between 2006 and 2017. Addiction 2019;115(5):961-74.(Epub 20191016): doi:10.1111/add.14851.
18. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. N Engl J Med 2019;380(7):629-37.(Epub 20190130): doi:10.1056/NEJMoa1808779.
19. Bauld L, MacKintosh AM, Eastwood B, Ford A, Moore G, Dockrell M, et al. Young people's use of e-cigarettes across the United Kingdom: findings from five surveys 2015-2017. Int J Environ Res Public Health 2017;14(9).(Epub 20170829): doi:10.3390/ijerph14090973.
20. Walker N, Parag V, Wong SF, Youdan B, Broughton B, Bullen C, et al. Use of e-cigarettes and smoked tobacco in youth aged 14-15 years in New Zealand: findings from repeated cross-sectional studies (2014-19). Lancet Public Health 2020;Published online ahead of print January 21, 2020 (doi: 10.1016/s2468-2667(19)30241-5).(Epub 20200121): doi:10.1016/s2468-2667(19)30241-5.
21. Levy DT, Warner KE, Cummings KM, Hammond D, Kuo C, Fong GT, et al. Examining the relationship of vaping to smoking initiation among US youth and young adults: a reality check. Tob Control 2019;28(6):629-35.(Epub 20181120): doi:10.1136/tobaccocontrol-2018-054446.
22. Stoklosa M, Cahn Z, Liber A, Nargis N, Drope J. Effect of IQOS introduction on cigarette sales: evidence of decline and replacement. Tob Control 2019;29(4):381-7.(Epub 20190617): doi:10.1136/tobaccocontrol-2019-054998.
23. Bundeszentrale für Gesundheitliche Aufklärung. Rauchen bei Jugendlichen und jungen Erwachsenen in Deutschland 2018:
24. Ergebnisse des Alkoholsurveys 2018 und Trends. Köln: Bundeszentrale für gesundheitliche Aufklärung; 2019. Available: https://www.bzga.de/fileadmin/user_upload/PDF/studien/Alkoholsurvey_2018_Bericht-Rauchen.pdf.

25. Lee PN, Fry JS, Hamling JF, Sponsiello-Wang Z, Baker G, Weitkunat R. Estimating the effect of differing assumptions on the population health impact of introducing a Reduced Risk Tobacco Product in the USA. Regul Toxicol Pharmacol 2017;88:192-213. (Epub 20170623): doi:10.1016/j.yrtph.2017.06.009.
26. Djurdjevic S, Lee PN, Weitkunat R, Sponsiello-Wang Z, Ludicke F, Baker G. Modeling the population health impact of introducing a modified risk tobacco product into the U.S. market. Healthcare (Basel) 2018;6(2):47; doi: 10.3390/healthcare6020047.(Epub 20180516): doi:10.3390/healthcare6020047.
27. Lee PN, Djurdjevic S, Weitkunat R, Baker G. Estimating the population health impact of introducing a reduced-risk tobacco product into Japan. The effect of differing assumptions, and some comparisons with the U.S. Regul Toxicol Pharmacol 2018;100:92-104. (Epub 20181024): doi:10.1016/j.yrtph.2018.10.010.
28. Weitkunat R, Lee PN, Baker G, Sponsiello-Wang Z, González-Zuloeta Ladd AM, Lüdicke F. A novel approach to assess the population health impact of introducing a modified risk tobacco product. Regulatory Toxicology and Pharmacology 2015;72:87-93. doi:10.1016/j.yrtph.2015.03.011.
29. Fry JS, Lee PN, Forey BA, Coombs KJ. How rapidly does the excess risk of lung cancer decline following quitting smoking? A quantitative review using the negative exponential model. Regul. Toxicol. Pharmacol. 2013;67:13-26. doi:10.1016/j.yrtph.2013.06.001.
30. Lee PN, Fry JS, Forey BA. Estimating the decline in excess risk of chronic obstructive pulmonary disease following quitting smoking - a systematic review based on the negative exponential model. Regulatory Toxicology and Pharmacology 2014;68(2):231-9. doi:10.1016/j.yrtph.2013.12.006.
31. Lee PN, Fry JS, Hamling JS. Using the negative exponential distribution to quantitatively review the evidence on how rapidly the excess risk of ischaemic heart disease declines following quitting smoking. Regul. Toxicol. Pharmacol. 2012;64:51-67. doi:10.1016/j.yrtph.2012.06.009.
32. Lee PN, Fry JS, Thornton A. Estimating the decline in excess risk of cerebrovascular disease following quitting smoking - A systematic review based on the negative exponential model. Regul. Toxicol. Pharmacol. 2014;68(1):85-95. doi:10.1016/j.yrtph.2013.11.013.
33. Gardner JW, Sanborn JS. Years of potential life lost (YPLL)--what does it measure? Epidemiology 1990;1(4):322-9. doi:10.1097/00001648-199007000-00012.
34. United Nations Department of Economic and Social Affairs Population Division. World population prospects: the 2015 revision. United Nations. 2015. http://esa.un.org/unpd/wpp/Download/Standard/Population/.
35. Forey B, Hamling J, Hamling J, Thornton A, Lee P. International Smoking Statistics. A collection of worldwide historical data (2006-2016). P N Lee Statistics and Computing Ltd, Sutton, Surrey. 2016. www.pnlee.co.uk/iss.htm.
36. Forey BA, Lee PN. A comparison of smoking prevalence and quitting between countries which use either Virginia or blended tobacco cigarettes. Sutton, Surrey: P N Lee Statistics and Computing Ltd; 2012. Available: www.pnlee.co.uk/Reports.htm [Download FOREY2012].
37. Bennewitz E, Kaul A. Quitting smoking in Germany: evidence from the SOEP. Saarbrücken: Saarland University, Germany; 2020. Available: https://www.uni-saarland.de/fileadmin/user_upload/Professoren/fr12_ProfKaul/Research/2020_01_29_Quitting_Smoking.pdf.
38. Martin F, Vuillaume G, Baker G, Sponsiello-Wang Z, Ricci PF, Lüdicke F, et al. Quantifying the risk-reduction potential of new Modified Risk Tobacco Products. Regul Toxicol Pharmacol 2018;92:358-69.(Epub 20171216): doi:10.1016/j.yrtph.2017.12.011.
39. Nutt DJ, Phillips LD, Balfour D, Curran HV, Dockrell M, Foulds J, et al. Estimating the harms of nicotine-containing products using the MCDA approach. Eur. Addict. Res. 2014;20(5):218-25. doi:10.1159/000360220.
40. Lee PN, Forey BA, Coombs KJ. Systematic review with meta-analysis of the epidemiological evidence in the 1900s relating smoking to lung cancer. BMC Cancer 2012;12:385. doi:10.1186/1471-2407-12-385.
41. Forey BA, Thornton AJ, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. BMC Pulmonary Medicine 2011;11:36. doi:10.1186/1471-2466-11-36.
42. World Health Organization. WHO Mortality Database. http://www.who.int/healthinfo/mortality_data/en/.
43. Zhu SH, Zhuang YL, Wong S, Cummins SE, Tedeschi GJ. E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. Bmj 2017;358:j3262.(Epub 20170726): doi:10.1136/bmj.j3262.
44. Lee PN, Hamling J, Fry J, Forey B. Using the negative exponential model to describe changes in risk of smoking-related diseases following changes in exposure to tobacco. Advances in Epidemiology 2015;Article ID 487876, 13 pages (doi:

10.1155/2015/487876). doi:10.1155/2015/487876.

45. Djurdjevic S, Pecze L, Weitkunat R, Luedicke F, Fry J, Lee P. Using data on snus use in Sweden to compare different modelling approaches to estimate the population health impact of introducing a smoke-free tobacco product. BMC Public Health 2019;19(1):1411.(Epub 20191029): doi:10.1186/s12889-019-7714-0.
46. Brose LS, Brown J, Hitchman SC, McNeill A. Perceived relative harm of electronic cigarettes over time and impact on subsequent use. A survey with 1-year and 2-year follow-ups. Drug Alcohol Depend 2015;157:106-11.(Epub 20151022): doi:10.1016/j.drugalcdep.2015.10.014.
47. (ASH) Action on Smoking and Health. Factsheet: Use of e-cigarettes (vaporisers) among adults in Great Britain, 2019. 2019. Available: https://ash.org.uk/wp-content/uploads/2019/09/Use-of-e-cigarettes-among-adults-2019.pdf.
48. Atzendorf J, Aschenbrenner AB, Gomes de Matos E, Kraus L, Kröger C, Delle S, et al. E-Zigaretten: Einschätzung von Gesundheitsgefahren und Nutzung zur Tabakentwöhnung (E-cigarettes: Perceived harmfulness and use for smoking cessation). Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2018;61(11):1415-21.(Epub 20181004): doi:10.1007/s00103-018-2822-z.
49. Persoskie A, O'Brien EK, Poonai K. Perceived relative harm of using e-cigarettes predicts future product switching among US adult cigarette and e-cigarette dual users. Addiction 2019;114(12):2197-205.(Epub 20190725): doi:10.1111/add.14730.
50. Eichler M, Blettner M, Singer S. The use of e-cigarettes - A population-based cross-sectional survey of 4002 individuals in 2016. Dtsch Arztebl Int 2016;113(50):847-54. doi:10.3238/arztebl.2016.0847.
51. VdeH (Verband des eZigarettenhandels). E-Zigaretten - die unterschätzte Chance - Was die Deutschen über E-Zigaretten wissen - und was nicht Ergebnisse der repräsentativen forsa - Befragung. (November) 2019. Available: https://vd-eh.de/wp-content/uploads/2019/11/vdeh-forsa-2019.pdf.
52. Kotz D, Kastaun S. E-Zigaretten und Tabakerhitzer: repräsentative Daten zu Konsumverhalten und assoziierten Faktoren in der deutschen Bevölkerung (die DEBRA-Studie) (E-cigarettes and heat-not-burn products: representative data on consumer behaviour and associated factors in the German population (the DEBRA study)). Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2018;61(11):1407-14.(Epub 20181004): doi:10.1007/s00103-018-2827-7.
53. Kozlowski LT, Sweanor D. Withholding differential risk information on legal consumer nicotine/tobacco products: The public health ethics of health information quarantines. Int J Drug Policy 2016;32:17-23.(Epub 20160401): doi:10.1016/j.drugpo.2016.03.014.
54. SMC (Science Media Center). Press briefing: Wie sollen E-Zigaretten künftig reguliert werden? 21 January. 2020. https://www.sciencemediacenter.de/alle-angebote/press-briefing/details/news/wie-sollen-e-zigaretten-kuenftig-reguliert-werden/.
55. Weaver SR, Jazwa A, Popova L, Slovic P, Rothenberg RB, Eriksen MP. Worldviews and trust of sources for health information on electronic nicotine delivery systems: Effects on risk perceptions and use. SSM Popul Health 2017;3:787-94.(Epub 20170929): doi:10.1016/j.ssmph.2017.09.003.
56. Levy DT, Fong GT, Cummings KM, Borland R, Abrams DB, Villanti AC, et al. The need for a comprehensive framework. Addiction 2017;112(1):22-4. doi:10.1111/add.13600.
57. Kimber C, Frings D, Cox S, Albery IP, Dawkins L. Communicating the relative health risks of E-cigarettes: An online experimental study exploring the effects of a comparative health message versus the EU nicotine addiction warnings on smokers' and non-smokers' risk perceptions and behavioural intentions. Addict Behav 2020;101:106177.(Epub 20191104): doi:10.1016/j.addbeh.2019.106177.
58. Hummel K, Nagelhout GE, Fong GT, Vardavas CI, Papadakis S, Herbeć A, et al. Quitting activity and use of cessation assistance reported by smokers in eight European countries: Findings from the EUREST-PLUS ITC Europe Surveys. Tob Induc Dis 2018;16(Suppl 2). doi:10.18332/tid/98912.
59. ZIS (Zentrum für Interdisziplinäre Suchtforschung der Universität Hamburg). Konsumgewohnheiten und Motive von E-Zigaretten-Konsumenten in Deutschland – Eine Querschnittsanalyse. Hamburg 2016. Available: https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/5_Publikationen/Drogen_und_Sucht/Berichte/161005_Anlage_5-Abschlussbericht_ZIS.pdf
60. Cotti CD, Courtemanche CJ, Maclean JC, Nesson ET, Pesko MF, Tefft N. The effects of e-cigarette taxes on e-cigarette prices and tobacco product sales: evidence from retail panel data. (Working Paper 26724). NBER Working Papers. Massachusetts, USA 2020. Available: https://www.nber.org/papers/w26724.pdf.
61. Bachand AM, Sulsky SI. A dynamic population model for estimating all-cause mortality due to lifetime exposure history. Regulatory Toxicology and Pharmacology 2013;67(2):246-51. doi:10.1016/j.yrtph.2013.08.003.

62. Bachand AM, Sulsky SI, Curtin GM. Assessing the likelihood and magnitude of a population health benefit following the market introduction of a modified-risk tobacco product: enhancements to the dynamic population modeler, DPM(+1). Risk Anal 2018;38(1):151-62.(Epub 20170424): doi:10.1111/risa.12819.
63. Black R, Murillo J, Pithawalla Y, editors. Population modeling. A practical approach to evaluate the net benefit of a new tobacco product. Tobacco Computational Modeling Meeting, NYU College of Global Public Health; July 23-24: Altria Client Services (ALCS)2018.
64. Hill A, Camacho OM. A system dynamics modelling approach to assess the impact of launching a new nicotine product on population health outcomes. Regul Toxicol Pharmacol 2017;86:265-78.(Epub 20170322): doi:10.1016/j.yrtph.2017.03.012.
65. Muhammad-Kah RS, Pithawalla YB, Boone EL, Wei L, Jones MA, Black RA, et al. A computational model for assessing the population health impact of introducing a modified risk claim on an existing smokeless tobacco product. Int J Environ Res Public Health 2019;16(7):1264.(Epub 20190409): doi:10.3390/ijerph16071264.
66. Poland B, Teischinger F. Population modeling of modified risk tobacco products accounting for smoking reduction and gradual transitions of relative risk. Nicotine Tob Res 2017;19(11):1277-83.(Epub 20170327): doi:10.1093/ntr/ntx070.
67. Apelberg BJ, Feirman SP, Salazar E, Corey CG, Ambrose BK, Paredes A, et al. Potential public health effects of reducing nicotine levels in cigarettes in the United States. N Engl J Med 2018;378(18):1725-33.(Epub 20180315): doi:10.1056/NEJMsr1714617.
68. Kalkhoran S, Glantz SA. Modeling the health effects of expanding e-cigarette sales in the United States and United Kingdom: A Monte Carlo analysis. JAMA Intern Med 2015;175(10):1671-80. doi:10.1001/jamainternmed.2015.4209.
69. Levy DT, Borland R, Villanti AC, Niaura R, Yuan Z, Zhang Y, et al. The application of a decision-theoretic model to estimate the public health impact of vaporized nicotine product initiation in the United States. Nicotine Tob Res 2017;19(2):149-59.(Epub 20160714): doi:10.1093/ntr/ntw158.
70. Levy DT, Borland R, Lindblom EN, Goniewicz ML, Meza R, Holford TR, et al. Potential deaths averted in USA by replacing cigarettes with e-cigarettes. Tob Control 2018;27(1):18-25.(Epub 20171002): doi:10.1136/tobaccocontrol-2017-053759.
71. Soneji SS, Sung HY, Primack BA, Pierce JP, Sargent JD. Quantifying population-level health benefits and harms of e-cigarette use in the United States. PLoS One 2018;13(3):e0193328.(Epub 20180314): doi:10.1371/journal.pone.0193328.
72. Vugrin ED, Rostron BL, Verzi SJ, Brodsky NS, Brown TJ, Choiniere CJ, et al. Modeling the potential effects of new tobacco products and policies: a dynamic population model for multiple product use and harm. PLoS One 2015;10(3):e0121008.(Epub 20150327): doi:10.1371/journal.pone.0121008.
73. Warner KE, Mendez D. E-cigarettes: Comparing the possible risks of increasing smoking initiation with the potential benefits of increasing smoking cessation. Nicotine Tob Res 2019;21(1):41-7.(Epub 20180329): doi:10.1093/ntr/nty062.