The future of smoking-attributable mortality: the case of England & Wales, Denmark and the Netherlands

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ABSTRACT

AIMS
We formally estimate future smoking-attributable mortality up to 2050 for the total national populations of England & Wales, Denmark and the Netherlands, providing an update and extension of the descriptive smoking-epidemic model.

METHODS
We used smoking prevalence and population-level lung-cancer mortality data for England & Wales, Denmark and the Netherlands, covering the period 1950 to 2009. To estimate the future smoking-attributable mortality fraction (SAF) we: (1) project lung cancer mortality by extrapolating age-period-cohort trends, using the observed convergence of smoking prevalence and similarities in past lung cancer mortality between men and women as input; (2) add other causes of death attributable to smoking by applying a simplified version of the indirect Peto-Lopez method to the projected lung cancer mortality.

FINDINGS
The SAF for men in 2009 was 19% (44,872 deaths) in England & Wales, 22% (5,861 deaths) in Denmark and 25% (16,385 deaths) in the Netherlands. In our projections, these fractions decline to 6%, 12% and 14%, respectively, in 2050. The SAF for women peaked at 8% (38,883 deaths) in 2008 in England & Wales, and is expected to peak in 2028 in Denmark (22%) and in 2033 in the Netherlands (23%). By 2050, a decline to 9%, 17% and 19%, respectively, is foreseen. Different indirect estimation methods of the SAF in 2050 yield a range of 1-8% (England & Wales), 8-13% (Denmark), and 11-16% (the Netherlands) for men, and 7-16%, 12-26%, and 13-31%, for women.

CONCLUSIONS
From Northern European data we project that smoking-attributable mortality will remain important for the future, especially for women. Whereas substantial differences between countries remain, the age-specific evolution of smoking-attributable mortality stays similar across countries and between sexes.
INTRODUCTION

Smoking is a lifestyle with a considerable effect on health, mortality, and trends therein over time. Within Europe, smoking is the leading risk factor of premature mortality (1). However, smoking behaviour and, consequently, smoking-attributable mortality (i.e. the number of all deaths in a population caused by smoking) differ strongly by country and cause a major gender gap in mortality (2,3).

The smoking-epidemic model by Lopez et al in 1994 (3) described that in general men in Anglo-Saxon countries were the first to take up smoking in the early 20th century. After a rapid rise lasting two to three decades, male smoking prevalence started to decline. Smoking-attributable mortality follows the increase and subsequent decline in smoking prevalence some 30 to 40 years later. For women, the increase in smoking started about 20 years later than men, but depending on the country, this period may be shorter or longer (4). The maximum levels in female smoking prevalence would be considerably lower than for men and, consequently, female smoking-attributable mortality would be lower than that for men.

In the last stage of the original smoking-epidemic model, similar (declining) levels of smoking prevalence for men and women were put forward, suggesting that smoking-attributable mortality for men and women will convergence in the future (2,3). Smoking-attributable mortality for women, however, still increased in this last stage. Nowadays, some countries already experienced the peak in smoking-attributable mortality for women, e.g. England & Wales (4). In other countries in Northern and Western Europe, such as Denmark and the Netherlands, this peak is approaching as well, due to the past peak in smoking prevalence for women. An update of the smoking-epidemic model is therefore warranted.

A previous update of the smoking-epidemic model by Thun et al (4) in which the experience of developing countries was added, and previous projections of smoking-attributable mortality (5,6), however, only included the short-term future. Whereas Thun et al. (4), qualitatively suggested a parallel future decrease in smoking-attributable mortality for men and women and Pampel (5) also revealed equalization of smoking mortality rates for men and women, the long-term future evolution of the gap between the sexes in smoking-attributable mortality has not been formally studied before. Furthermore, in the original smoking-epidemic model and its update (4) not much information is provided on differences by age groups.
Our objective is to update and extend the smoking-epidemic model by estimating future levels of smoking-attributable mortality up to 2050 for England & Wales, Denmark, and the Netherlands, three countries that are ahead in the smoking-epidemic. We shall formally estimate the peak and subsequent decline in smoking-attributable mortality for women, and will provide information on the differences by sex and age groups for the long-term future. Our results will aid policy makers and public health professionals in setting goals for tobacco control programs and can provide important input to all-cause mortality projections.

**ESTIMATION METHODOLOGY**

We studied past trends in age- and sex-specific smoking prevalence, lung cancer mortality rates, and smoking-attributable mortality for England & Wales, Denmark and the Netherlands over the period 1950-2009.

Data on smoking prevalence by sex and age group were obtained from Cancer Research UK (7) for England & Wales for the years 1950-2009, and The Dutch Expert Centre on Tobacco Control (STIVORO) (8) for the Netherlands for the years 1958-2009. For Denmark, data on smoking prevalence among adults by sex was obtained from International Smoking Statistics WEB Edition (9), OECD Health Data (10), and the World Health Organization (WHO) (11) for the years 1950-1969, 1970-1993, and 1994-2009, respectively.

Annual lung cancer mortality deaths (ICD-9: 162; ICD-10: C33-C34) by age (40-44, 45-49, …, 80+) and sex were obtained through the WHO Statistical Information System (12) for England & Wales (1950-2009), Denmark (1951-2006), and the Netherlands (1950-2009). For Denmark, additional death numbers for the years 2007-2009 were obtained through the Nordic cancer statistics database NORDCAN (13). Rates were calculated by dividing the deaths by population exposure data from the Human Mortality Database (14).

To estimate the smoking-attributable mortality fraction (SAF), i.e. the proportion of all deaths due to smoking, an adapted and simplified version of the indirect Peto-Lopez method (15) was used. Our method, like Peto et al. (16), uses observed lung cancer mortality – controlled for background lung cancer mortality – as an indicator of the accumulated damage from smoking. That is, the observed national lung cancer mortality rates are compared with the rates of smokers and never-smokers of the ACS CPS-II study to obtain the proportion of the population...
that is exposed to smoking \((p)\) (16). We combined this indicator with relative risks \((RR)\) for all-cause mortality for smokers versus non-smokers from the ACS CPS-II study to obtain the age- and sex-specific SAF: \(SAF = p(RR-1)/(p(RR-1)+1)\) (17). The \(RRs\) were smoothed by applying a second-level polynomial and the excess risk was reduced by 30% to allow for confounding (18).

Lung cancer mortality and the SAF for all ages combined were directly age-standardised using sex- and country-specific population and death numbers, respectively, in 2009 as the standard.

To more formally summarize the past trends, age-period-cohort (APC) analysis was applied to lung cancer mortality. We chose an APC model with drift (19), defined as:

\[
y_{a,p} = N_{a,p} \exp(\delta \cdot p + \alpha_a + \beta_p + \gamma_{p-a}) + \varepsilon_{a,p}
\]

where \(y_{a,p}\) is the number of deaths in age group \(a\) in period \(p\) which follows a Poisson distribution, \(N_{a,p}\) is the number of person-years at risk in age group \(a\) in period \(p\), and \(\varepsilon_{a,p}\) is the error term. \(\delta\), \(\alpha_a\), \(\beta_p\), \(\gamma_{p-a}\) are the drift, age, (non-linear) period, and (non-linear) cohort effect, respectively. The model is applied to data by five-year age groups (45-49,…,80+) and five-year calendar periods (1950-2009). We set the first and last cohort, and first and last period to zero to ensure identifiability (19). The model is fitted in R 2.10 using the function glm.

**PAST TRENDS**

For men, smoking prevalence in the 1950s was very high: 60% in England & Wales, 80% in Denmark and 90% in the Netherlands (Figure 1). Over the period 1950-2009, smoking prevalence for men declined in all three countries, reaching a level of 30% in the Netherlands and about 20% in the other two countries. For women, smoking prevalence in the 1950s was between 30% and 40%. After reaching a maximum of around 45% between 1970 and 1980, smoking prevalence for women started to decline as well. From 1990 onwards the decline in smoking prevalence for women was parallel with the decline for men in all three countries. In 2009, smoking prevalence for women was near 20% in England & Wales and Denmark and approximately 24% in the Netherlands.
For men, lung cancer mortality and the corresponding age-standardised SAF reached its maximum around 1975 in England & Wales and nearly 10 years later in Denmark and the Netherlands (Figure 1). The SAF was 33%, 29%, and 37%, respectively. Thereafter, the SAF showed a steady decline in all three countries, leading to a level of SAF in 2009 of 19%, 22%, and 25%, respectively. For women, lung cancer mortality and the SAF increased over the whole period in all three countries and converged to the level of men. The female SAF in 2009 was 14% in England & Wales, 19% in Denmark, and 12% in the Netherlands.

For men, the age-specific lung cancer mortality rates (Figure 2) show a clear cohort-pattern in the timing of the maximum, reflecting the uptake of smoking. The maximum is followed by a more period-pattern after the peak, reflecting the quitting of smoking as a result of, for instance, tobacco control or changes in lifestyle when there is a decline in the lung cancer mortality rates at the same time for different age groups. The declines after the peak show parallel trends at the log scale for the different age groups, indicating that the age-specific patterns converge. For women, the cohort-pattern in the lung cancer mortality is less clear, but visible in the moment the lung cancer mortality starts to rise for each successive age group, and in the moment the increase for the youngest age groups ceases. For the youngest age groups we can observe that the moment the rates for women cross the rates for men, the rates start to decline at the same pace. The rates for women at higher ages show a steady increase over time. These observations also hold for the age-specific SAF’s (results not shown).

Our APC analysis shows that men with the highest lung cancer mortality are born around 1900 in England & Wales, around 1925 in Denmark, and around 1910 in the Netherlands (see Online Resource 1). The increase in lung cancer mortality among the oldest cohorts is very similar for the three countries, as well as the decline after the maximum. For women, differences in the timing of the increase in lung cancer mortality show England & Wales being the forerunner. Women in England & Wales born around 1930 experienced the highest lung cancer mortality. For Denmark and the Netherlands no such maximum occurred.
PROJECTION METHODOLOGY

Based on our study of the past trends (see previous section) we were able to formulate the basic assumptions behind our projection methodology:

- convergence of smoking prevalence and lung cancer mortality between men and women;
- a similar decline in age-specific lung cancer mortality rates for women as men after the age-specific rates for women reached the age-specific rates for men;
- a cohort approach for the increase in lung cancer mortality and a period approach for its decrease.

We projected lung cancer mortality up to 2050, making qualitative use of the predictive value that current smoking prevalence has on mortality for the next 30-40 years. We then apply indirect estimation techniques to estimate the future SAF. For our main results we use the same simplified Peto-Lopez estimation technique. In addition we performed a sensitivity analysis including four additional indirect estimation techniques (see Online Resource 3).

For men, the observed decline in lung cancer mortality for different age groups is projected to continue into the future. That is, we first estimated the maximum cohort exposed to smoking using an APC model applied to the lung cancer mortality data, and then projected the drift from the APC model applied to the lung cancer mortality data after this estimated maximum cohort (see Online Resource 1).

For women, we needed to estimate the year and level of the maximum in lung cancer mortality as well as the trend up to and after this maximum. We extrapolated the age-specific increase through an APC model with drift using the drift and non-linear cohort component. The peak years for the separate age groups were obtained by estimating the year in which the age-specific trends for women would reach the age-specific trends for men. The long-term decline after the maximum for women has been set equal to the drift from the model of men.

The limited reliability of historical smoking prevalence – mainly due to changed definitions and samples (20) – and the fact that smoking prevalence is a poor proxy of smoking intensity – mainly because it does not include dosage and age at onset (18) –, are important restrictions of incorporating smoking prevalence directly in any
projection methodology. Smoking prevalence is thus merely used to generate assumptions, i.e. the similarities in current smoking prevalence for men and women and its main effect on mortality 30 to 40 years later (3).

We project lung cancer mortality and not smoking-attributable mortality, because of the different indirect estimation techniques that exist to estimate smoking-attributable mortality, and the likely impact on the projection.

**FUTURE LEVELS OF SMOKING-ATTRIBUTABLE MORTALITY**

Figure 3 shows the projected age-standardised lung cancer mortality and SAF. For men in England & Wales, the SAF is estimated to decline from 19% in 2009 to 6% in 2050. The maximum SAF for women in England & Wales was already reached in 2008, and the SAF is estimated to decline from 14% in 2009 to 9% in 2050. The SAF for men in Denmark is estimated to drop from 22% in 2009 to 12% in 2050. The level for Danish women is estimated to first increase from 19% in 2009 to 22% in 2028 and then decline to 17% in 2050. For men in the Netherlands, the SAF is estimated to decline from 25% in 2009 to 14% in 2050. For Dutch women, the SAF is estimated to increase from 12% in 2009 to 23% in 2033 and then decline to 19%.

Figure 4 presents the future SAF by age (see Online Resource 2 for the projected lung cancer mortality by age). The results show the continuing convergence between the age groups and the (more pronounced) cohort-pattern in the trend up to the maximum for women. For each country and each age group, it is expected that the SAF in 2050 for women is higher than the SAF for men.

When we apply five different indirect estimation methods (see Online Resource 3) - including using the NHIS-LMF cohort study and the recent regression methods (21-23) - , the SAF’s for men in 2050 range from 1% to 8% (England & Wales), from 8% to 13% (Denmark), and from 11% to 16% (the Netherlands). For women the ranges are 7% to 16%, 12% to 26%, and 13% to 31%, respectively. Note that without the outliers, method 2 (NHIS-LMF cohort study) for men and the regression method 3 (21) for women, the ranges were much lower.
DISCUSSION

Summary of the results

The SAF for men in 2009 was 19% in England & Wales, 22% in Denmark and 25% in the Netherlands. In our projections, these fractions decline to 6%, 12% and 14%, respectively, in 2050. The SAF for women peaked at 14% in 2008 in England & Wales, and is expected to peak in 2028 in Denmark (22%) and in 2033 in the Netherlands (23%). By 2050, a decline to 9%, 17% and 19%, respectively, is foreseen.

Update and extension of the smoking-epidemic model

The original smoking-epidemic model assumes that, after a rapid rise, the SAF among women could be expected to peak at around 20-25% of all deaths, significantly lower than what men experienced (33%) and occurring about 20 years later. Thereafter smoking-attributable mortality for both sexes would progressively decline (3).

Our projected maximum levels of SAF for women in Denmark (22%) and the Netherlands (23%) correspond with the expected peak of SAF for women in the smoking-epidemic model. The observed maximum level for women in England & Wales (14%) is clearly lower though. The difference in the timing of the maximum level between men and women, which amounts to 20 years in the smoking-epidemic model, is much greater in England & Wales (35 years), Denmark (43 years) and the Netherlands (48 years), and supports earlier findings of differential results for different countries (4).

Our observed differences between the countries in the future level of smoking-attributable mortality and in the sex differences in the (timing of the) smoking-epidemic are clearly related to differences in historical smoking prevalence, especially for women. These differences in smoking prevalence can be related to differences in cultural, political and economic determinants that led to differences in tobacco control and lifestyle (4). For instance, in England & Wales tobacco companies begin the pursuit of female smokers after World War I (24). In other countries the government promoted traditional social roles for women that, among other things, discouraged tobacco use (25).
Our analyses also highlighted some important differences and commonalities between the different age groups. The SAF by age is characterized by a clear cohort-pattern, and starts to rise, to peak and subsequently to decline first at younger ages. The SAF for younger age groups is higher than for older age groups, but after the maximum there is convergence between the age groups. These age patterns are similar across countries and sexes.

In spite of the observed convergence in smoking prevalence and lung cancer mortality rates between men and women, the SAF’s in 2050 for women are higher than that for men. This is because of lower relative risks and lower all-cause mortality rates for women as compared to men in each age group.

**Reflection on the projection methodology**

Previous projections of smoking-attributable or smoking-related mortality mostly consisted of methods incorporating lagged smoking prevalence or different smoking scenarios (5,6). Probably because of the limited historical data on smoking prevalence, these projections were limited to a short projection period. Our methodology can be used for a longer projection period.

Previous projections of lung cancer mortality all used age-period-cohort methodologies, although in different ways (e.g. (26-29)). Most of these methods do not perform well in a situation where the past trend in lung cancer mortality does not continue in the future, as we expect to happen with the trend for women. An exception is Shibuya et al. (28), who replaced the period variable by lagged information on smoking. Their method might project changes in the trend in lung cancer mortality due to changes in smoking habits, although to obtain projections for the long run, the smoking habits themselves need to be projected. Thus, previous projection methods of lung cancer mortality were only relevant for short-term projections.

Our methodology – different from earlier studies – takes into account the expectation that future smoking-attributable mortality will first increase and then decline among women. Our assumption – and subsequent estimation – of the maximum level in lung cancer mortality for women resulted from the observed similar smoking prevalences for men and women and our assumption that this would result in similar lung cancer mortality rates 30 to 40 years later (as described by the smoking epidemic model by Lopez et al. (3) and already
observed for the youngest age groups). Applying our methodology to part of the data for England & Wales (1950-1999), our assumption and methodology proved able to predict the observed maximum in 2008, justifying the use of the trend and level in lung cancer mortality of men to determine the maximum for women.

**Reflection on the indirect estimation method**

The adapted and simplified Peto-Lopez method we used to estimate SAF, has the advantage of a low demand of data, is easy to use, and widely used (30). Furthermore, potential benefits of smoking cessation and likely effects of secondhand smoking are indirectly taking into account because of the use of lung cancer mortality. The results of the simplified method are comparable to the results of the original Peto-Lopez method (17).

A limitation of the (adapted and simplified) Peto-Lopez method is the use of the ACS CPS-II study, which may not be representative for the population under consideration, for instance, due to generally lower lung cancer mortality rates for female smokers. Furthermore, Mehta and Preston (31) show a continuing increase over time in the relative risk of death for current and former smokers. Finally, the Peto-Lopez method assumes that the temporal relationship between accumulated exposure (including cessation) and risk will be similar between lung cancer and other smoking determined risks (e.g. vascular disease, chronic respiratory disease).

In recent years additional indirect estimation methods have been developed, making use of regression analysis (21-23). These methods rely only on observed lung cancer mortality and all-cause death rates. The two most recent methods (22,23) showed large similarity with the method we used, showing the validity of the three methods. Because differences at higher age groups had the largest effect on the SAF of all ages combined, its estimation should receive special attention.

**OVERALL CONCLUSION AND IMPLICATIONS**

Our results for England & Wales, Denmark and the Netherlands clearly illustrate that smoking-attributable mortality will remain important for the future, especially for women. Substantial differences between countries are expected, both in the future level of smoking-attributable mortality and in the sex difference in the (timing of
the smoking-epidemic. However, because of similarities in smoking prevalence, the similar age-specific evolution of smoking-attributable mortality across countries and between sexes, with convergence between the age groups, is likely to occur as well for other countries currently in the fourth stage of the smoking epidemic.

Because our projection methodology requires a limited amount of data, it can easily be applied to other countries where lung cancer is dominated by smoking. The methodology would be suitable especially for countries where (i) the maximum level of lung cancer mortality for men was reached quite some time ago (e.g. Finland, Ireland, Italy, Sweden and Switzerland), and (ii) recent smoking prevalence are similar for men and women. In countries where the maximum for men was reached only recently (e.g. France, Norway, Portugal and Spain), an APC model would be more difficult to estimate and information from forerunners would be needed as well. For countries in an earlier stage of the smoking epidemic, in addition, detailed information on smoking prevalence would be necessary.

Our formal quantification of future health effects of past smoking behaviour and differences therein by age and sex can aid policy makers and public health professionals in setting goals for tobacco control programs. The effect of recent control measures, such as the WHO Framework Convention on Tobacco Control (32), is expected to have its main effect on mortality after 2050. Moreover, it is essential to take into account the non-linear development of the smoking-epidemic to correctly project all-cause mortality for the future.

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**LIST OF FIGURES**

**Fig. 1** Smoking prevalence (%), age-standardised lung cancer mortality rate (per 1000) and age-standardised smoking-attributable mortality fraction (SAF) for Denmark, England & Wales and the Netherlands between 1950 and 2009, by sex.

**Fig. 2** Lung cancer mortality rate (log-scale) for Denmark, England & Wales and the Netherlands between 1950 and 2009, by sex and age group (the ten year age groups are weighted averages of two five year age groups).

**Fig. 3** Age-standardised lung cancer rate (per 1000) and age-standardised smoking-attributable mortality fraction for Denmark, England & Wales and the Netherlands for 1950-2009 (observations), and 2010-2050 (projections), by sex.

**Fig. 4** Smoking-attributable mortality fractions for Denmark, England & Wales and the Netherlands for 1950-2009 (APC-estimates), and 2010-2050 (projected), by sex and age group (the ten year age groups are weighted averages of two five year age groups).