Costs and effects of strategies to support quitting the use of smokeless tobacco

Update information

November 2021: NICE guideline PH26 (June 2010) has been updated and replaced by NG209.

This guideline contains the evidence and committee discussion for recommendations from PH26 dated [2010] and [2010, amended 2021].

See www.nice.org.uk/guidance/NG209 for all the current recommendations and the evidence behind them.

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EXECUTIVE SUMMARY

This document summarizes an assessment of the potential health benefits and monetary savings related to therapies which aim to support people to quit the use of smokeless tobacco. It is written in support of a broader systematic review of the effectiveness of smokeless tobacco interventions for South Asians and a review of contextual factors relating to smokeless tobacco among South Asian users and health care providers

METHODS

The initial plan for the analysis was to take the interventions and their effectiveness-estimates from the systematic review and to link those with two models, 1) a short term model for analysing the cost effectiveness of a therapy in terms of costs per quitter and 2) a long term model addressing further benefits and further cost savings due to quitting the use of smokeless tobacco.

Unfortunately, no clear estimates could be obtained considering well described strategies in terms of numbers of quitters and costs per quitter. The most promising estimates concern an unpublished pilot study, carried out in London, Leicester and Bradford and financed by the department of health within the Tobacco Control Health Inequalities project (Croucher et al. 2011a -, Croucher et al. 2011b). It concerns a non-randomised community-based tobacco cessation programme combining behavioural support in the form of brief advice and encouragement with nicotine replacement therapy. A document was made available by Prof R. Croucher, in which the costs of the therapy are estimated at £100,000. The number of subjects recruited was 324, the number of quitters 161 and the costs per quitter are estimated at £624.

The long term model is best characterised as a combination of a life table that interacts with a number of Markov-chain disease models in terms of incidence, prevalence and survival rates. There are four disease models. The first model is a cardiovascular disease model which is based on earlier work defining the Dutch guidelines in 2006 (CBO, 2006). The second model is a model for oral cancer which is based on a 2006 HTA study addressing the cost effectiveness of oral cancer screening (Speight et al. 2006). The third model is a relatively simple model for pancreatic cancer. The fourth model concerns periodontal disease/tooth-decay which is based on a 2003 HTA study addressing the cost effectiveness of routine dental checks (Davenport et al, 2003).

Each model is a Markov model distinguishing patients in different health states. The cardiovascular model distinguishes patients guided by their history in terms of events (MI's and strokes). The oral cancer model distinguished individuals by the stage of their disease and the duration in that stage. The pancreatic cancer model has a breakdown according to the number of years since diagnosis. The periodontal/tooth-decay model distinguishes patients by the number of teeth with decay.

The overall model has the following input parameters:

- the UK life tables
- the incidence rates
- the transition probabilities within the disease models (including mortality)
- costs per stage
- quality of life per stage
- the effect of the use of smokeless tobacco

Estimates of the model parameters have been found for all parameters searching the literature. The results of the extensive literature search in relationship to smokeless tobacco were used as a starting point. Naturally, this search was very specific with respect to the evidence concerning treatments to help stop people using smokeless tobacco, which is naturally the most important parameter of the model. Similar searches to support all other parameters of each model were outside the scope of the project. For this purpose additionally searches within Econlit were performed using the various disease names as relevant. Additionally searches within PubMed were carried out combining the disease names in combination with "costs", "epidemiology", "incidence", "prevalence", "model", "costs" and "quality of life". The same was done by using Google. All searches were repeated by adding the term "South Asians". The most recent UK source was used if possible, unless stated otherwise.

The incidence of cardiovascular disease has been estimated age- and gender-specific using the data underlying the derivation of the QRISK score based on 4,238,309 UK person years and an average incidence of 6.57 per 1,000 person years [Hippisley-Cox 2007]. The incidence in mouth cancer is estimated on the basis of 2007 data from Cancer research UK (Cancer Research UK, 2011). The incidence in periodontal disease is estimated such that the prevalence which is predicted in the model is about 50% in line with epidemiologic data. All incidence data are British and are not specific for the Asian population.

The transition probabilities for cardiovascular disease have been estimated using an iterative process combining earlier models with data from the British Heart Foundation concerning age and gender specific event rates, case fatality rates and mortality rates (Scarborough et al., 2011a). In fine tuning the model it was assumed that transition probabilities move in an exponential fashion with age. This is with respect to the probability of having MI's, the probability of having strokes (conditional on having CHD) and the probability of other cardiovascular death as well as to the distribution between fatal and non-fatal events . It was chosen not to use South Asian specific estimates as published by the British Heart Foundation (Scarborough et al., 2011b). This was due to the rather mixed picture with respect to the epidemiology (no consistent picture indicating that CHD is more or less serious in the South Asian population was found) and the limited numbers on which the estimates would be based.

The transition probabilities for the oral cancer model are taken from the UK HTA assessment considering oral cancer screening [Speight et al, 2006]. Mortality rates are different per stage and per age group.

The transition probabilities for the periodontal disease model are based on the 2003 HTA report concerning routine dental check-ups assuming that individuals visit the dentist every 12 months [Davenport et al, 2003].

Costs per stage, with the exception of the costs before having an event, were derived from a previously published UK specific cost-effectiveness analysis [Heeg et al, 2007]. No estimates were available concerning the annual costs of being diagnosed with CHD but being event free. These have been estimated such that the total costs as predicted by the model (adding up the expected costs for an average 20 year old male and female and correcting for the size of the population) is equal to the estimate of £7.4 billion as published by the British Heart Foundation (Scarborough et al., 2011a). The estimates concerning the costs of oral cancer have been taken from the 2006 HTA report [Speight et al, 2006]. The costs of each additional tooth in decay have been estimated, rather arbitrary, at £204 similar to what one has to pay for one band 3 treatment.

The model allows for the inclusion of unrelated health care costs which have been estimated based on Dutch estimates of the costs of diseases by gender and age in 2005. This is for illustrative purposes only as the inclusion of these costs is not in accordance with NICE guidelines.

The utilities per stage are all based on the literature. Account is taken of an age specific decrement for all individuals. When individuals are in a disease model the age specific values are multiplied with factors that represent the disutility of being in the specific health states within the disease models. For the cardiovascular model these factors are based on earlier studies and for the oral cancer model, they are based on the oral cancer screening study [Speight et al, 2006].

When searching the literature for utility decrements concerning the effects for periodontal disease, results were found which seem unrealistic and it was decided to follow an indirect approach by estimating – rather arbitrary - that individuals are willing to pay £1,000 to save a tooth. With some further heroic assumptions it is estimated that the expected QALY loss due to a decayed teeth is at least 0.00125 per year.

Estimates of the costs and effects of quitting the use of smokeless tobacco are obtained by comparing the estimates of an average person with those with increased risks due to the use of smokeless tobacco for the diseases under consideration. The increased risk for cardiovascular disease is based on a meta-analysis of Swedish & US studies. The estimate of the effect of the use of smokeless tobacco on periodontal disease is also based on a western population. The increase in the risk of oral cancer was based on a study in in Asian men and women in the US and Canada.

RESULTS

When running the model for an average 20 year old male, the average additional life expectancy is estimated at 58 years, and for a 20 year old women at 63 years. Total undiscounted life time costs of cardiovascular disease are estimated at £15,199 for males and at £12,617 for females. Total undiscounted life time costs for oral cancer are estimated at £166 for men and £79 for

women, for pancreatic cancer and £42 for males and £41 for females. Total undiscounted life time costs for periodontal disease/tooth-decay are estimated at £1,099 for men and £1,238 for women.

It is estimated that when a 40 year old female who uses smokeless tobacco and quits and as such becomes an average individual, that this would save up to £467 in (discounted) life time health care costs. It would result in a 0.069 gain in (discounted) life expectancy and a gain of 0.082 (discounted) QALY's. When using a limit for the cost effectiveness of £ 30,000 per QALY, a therapy which makes people quit is "cost effective" up to a cost per quitter of £ 2,915. For a 40 year old male, this figure is £4,218.

The results differ for different age groups. The higher the age, the smaller the expected gains and the smaller the expected savings. Figure I presents for different ages and gender what the maximum cost per quitter may be such that therapy may still be called cost effective. The left figure does this when assuming a maximum limit of £ 30,000 per QALY, the right figure does this assuming a maximum limit of £ 20,000 per QALY.

Univariate sensitivity analysis (varying parameters within their uncertainty margins) is carried out, suggesting that the results are relatively robust. The biggest changes are seen when assuming that smokeless tobacco affects the whole incidence in cardiovascular disease instead of just the event rates.

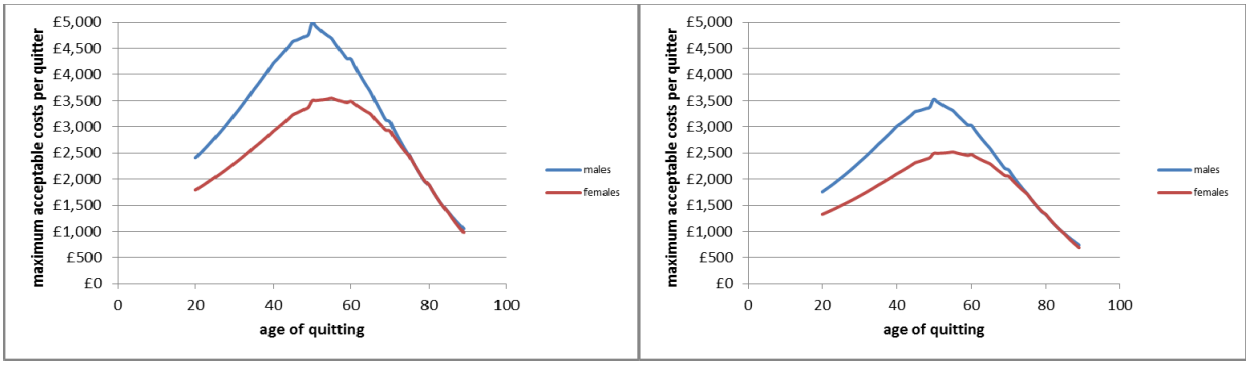

Figure I. Maximum costs per quitter for a therapy to be called acceptable using a £30,000 (left) and £20,000 (right) per QALY threshold.

DISCUSSION AND CONCLUSION

It is concluded that the maximum cost per quitter which can be considered acceptable depends on the age at which one quits and differs for males and females. Within the age range between 20 and 70 the maximum cost per quitter ranges between £1,758 and £3,525 for males and between £1,328 and £2,520 for females. That is when setting the maximum cost per QALY at £20,000. When this is £30,000, the ranges are £2,408-£4,991 for males and £1,795-£3,549 for females.

The estimates suggest that a strategy, as in the Croucher pilot study (combining behavioural support with nicotine replacement therapy), is likely to be cost effective (if one accepts the estimate of the costs per quitter). However such conclusion can only be dawn with extreme care. Lacking crucial data, it has been inevitable to make a number of heroic assumptions. For example it has been assumed that when the increased risks are removed, that this translates into immediate benefits. This may not be the reality. First, there may be lag times before the body has cleared all the risks. Second, it may be that the intervention is too late and that the damage has already been done. Both phenomena would decrease the effectiveness and would decrease the maximum amount at which a therapy that increases quitting can still be called cost effective.

While there are reasons to suggest that the current estimates may be considered too optimistic , there are also reasons to suggest that they are too conservative. The estimates concerning the effect of smokeless tobacco on the incidence in coronary heart disease and stroke are based on studies from the US and Sweden where individuals use less toxic products. Doing it this way may have underestimated the effects and it has been shown that a 10% increase in the total incidence of coronary heart disease and stroke (replacing the estimates of an increase in cardiovascular events) may more than double the maximum acceptable costs. Similarly, the doubling of periodontal disease has been estimated using US data where the population uses less toxic products than as used by South Asians in the UK.

Most of the uncertainties mentioned here are difficult to quantify without additional research and expert knowledge. So, one might say that even the uncertainty is uncertain. As such an estimate of cost effectiveness is difficult to give. When twisting ones arm one might say that a therapy such as offered by Tobacco Control Health Inequalities project is very cost effective, almost cost saving. Twisting the arm even further, one might say that it would even be cost effective with half the efficacy and that the cost per QALY of such therapy for a 40 year old female would be estimated at £9,551 per QALY and for a 40 year old male at £5,453. Naturally, one has to weigh these figures with one's own assessments of where the base line estimates have been too optimistic or too conservative. The analyses presented here offers a starting point to guide ones assessment. The data limitations are too severe to offer anything else.

ACKNOWLEDGEMENT

This report has benefited greatly from the help and insights of Dr. Lesley Owen, analysis at NICE. The responsibility for any flaws or errors remains with the author(s).

1 INTRODUCTION

The use of smokeless tobacco is associated with an increase in a number of diseases among which mouth cancer, pancreatic cancer, cardiovascular disease and periodontal disease. In the United Kingdom, the use of smokeless tobacco is especially prevalent in individuals of South Asian origin.

Initiatives to help people stop using smokeless tobacco may improve their (healthy) life expectancy and may save costs. The question is raised to what extent this happens and what the balance is between the costs to make someone quit, the savings due to less health care costs and the benefits in terms of life years and quality of life. This document aims to assess these costs and effects. It is written in support of a broader systematic review of the effectiveness of smokeless tobacco interventions for South Asians and a review of contextual factors relating to smokeless tobacco among South Asian users and health care providers.

2 SEARCHES

Searches for the cost-effectiveness/economics review were undertaken at the same time as the effectiveness searches, using population (south asian smokeless tobacco users) terms only, with the same date restrictions in NHS EED via Wiley and Econlit via OVID SP. With an almost complete absence of studies about effectiveness, it may come as no surprise that no studies were found addressing cost-effectiveness. Therefore, a fresh analysis was deemed necessary and a model is built which covers four diseases: cardiovascular disease , oral cancer, pancreatic cancer, and periodontal disease. Where additional information requirements were identified, targeted searches were undertaken for model parameters.

3 MODEL DEVELOPMENT

The initial plan for the analysis was to use two models, a short term model for analysing the cost effectiveness of a therapy in terms of costs per quitter and a long term model addressing further benefits and further cost savings due to quitting the use of smokeless tobacco.

3.1 SHORT TERM MODEL

A short term model was scheduled to address the balance between costs and effects of therapies which support people quit the use of smokeless tobacco expressing the benefits in terms of the percentage of participants who quit.

An extensive review of potential strategies and their effectiveness was carried out and the results are summarized in the main study report. In this distinction is made between behavioural interventions, educational interventions and pharmacological interventions. The strength of the evidence seems most clear when considering a combination of behavioural therapy with the use of nicotine replacement therapy.

Papers by Croucher et al. 2011a -, Croucher et al. 2011b +; Croucher et al. 2011c + and Croucher et al. 2003a + found that behavioural support in the form of brief advice and encouragement was effective in helping participants successfully quit using tobacco. Croucher et al. + (2003a) showed that of those who completed a 4-week tobacco cessation, 17% had successfully stopped using tobacco with the help of brief advice and encouragement alone. Croucher et al. (2011a) found that 88% of tobacco cessation participants chose nicotine replacement therapy (NRT) with behavioural support as the method used to quit. Croucher et al. + (2011c) showed that behavioural support plus NRT was more effective in helping participants stop using tobacco compared to behavioural support alone.

The 2011 papers by Prof Croucher hold results from a pilot study financed by the department of health within the Tobacco Control Health Inequalities project. It concerns a non-randomised community-based tobacco cessation programme combining behavioural support in the form of brief advice and encouragement with nicotine replacement therapy carried out in London, Leicester and Bradford. Concerning the same study, a document was made available by Prof R. Croucher where costs of the program are estimated at £100,000. The number of subjects recruited was 324, the number of quitters 161 (about 50%) and consequently, the costs per quitter are estimated at £624.

The main report qualifies the articles summarizing the Tobacco Control Health Inequalities project as of the highest quality. This is a relative score. The study concerns a non- randomised study, and it is unknown how many people would have quitted without the programme and how many people will relapse into their old habit. In light of the scant evidence concerning short term effectiveness attention has concentrated on the long run model trying to establish what the costs per quitter need to be such that a therapy may still be called cost effective at a cost of £20,000 or £30,000 per QALY. In doing so, the figure of £624 per quitter is used as a reference point.

3.2 LONG TERM MODEL

With respect to the long term model, no references were found which specifically address the long term costs and effects of smokeless tobacco. This may be because the problems has never been addressed in terms of costs and effects or, less likely, because of the technicality that has to take account of more than one disease at the same time. The model developed here is an extension to the structure and ideas as summarized in 1998 [Barendregt et al, 1998] and used earlier to estimate the health care costs of smoking [Barendregt et al, 1997]. The same method is used in the DISMOD models of the WHO when modelling multiple diseases. (http://www.who.int/healthinfo/global_burden_disease/tools_software/en/.)

It is best characterised as a combination of a life table that interacts with a number of Markov-chain disease models in terms of incidence, prevalence and survival rates.

A 'wish list' of what the model needs to be able to do is:

- Describe the population in terms of mortality and the incidence and prevalence of the diseases which need to be taken into account
- Build models for the various diseases at hand
- Link costs and quality of life to the models
- Analyse the effects of smokeless tobacco on the incidence and disease trajectory
- Model the effectiveness of an intervention
- Analyse the relationship between effectiveness and costs

3.3 THE OVERALL STRUCTURE OF THE MODEL

To be able to describe the population in terms of mortality the model starts with a simple standard life table with numbers of individuals per age class. This life table includes disease specific mortality rates which are derived from separate disease models. The crucial link between the life table and the disease models is made by breaking down the all-cause-death-rate from the life table into a) the disease specific death rates from the disease models and b) a rate for other causes of death. Here we are using three disease models, one for cardiovascular disease, one for oral cancer and one for periodontal disease.
The central parameters in each disease model are the incidence rates and the matrix of transition probabilities measuring the probability to go from the one state to the other, including mortality. Each disease model is a Markov model.

The life table defines the total death rate, the disease models define the disease specific death rates (as a function of the incidence rates and the transition probabilities). Together, they define the death rate for other causes. By substituting the total death rate in the disease model a dynamic link is created between the disease model and life table. Then, any assumption about changing incidences or changing transition probabilities will affect the total death rate in the life table taking account of all the competing risks.

For each scenario (including the base line model) a number of epidemiologic parameters can be calculated and presented. Disease specific mortality, as measured in probabilities and in terms of real numbers, can be calculated as well as the real and relative prevalence of each disease and the number of individuals in the various sub-stages within each disease. Moreover, given the structure of the model, and given the assumption of conditional independence, the numbers of people with more than one disease can be calculated as the simple product of the prevalence rates.

So, in order to run the epidemiologic part of the model, one only needs the following input-parameters:

- the life table estimates (D(a))
- the disease specific incidence rates (γ(a))

- the matrices of transition probabilities ($p^{j}_{ik}(a)$)

All others parameters need to be derived following the equations presented in appendix 1 which presents a more detailed discussion of the model. It is emphasized that the probability of death, as included in the Markov-chain models, should not cover all-cause-mortality but only mortality due to the disease under consideration. As such it is only the additional mortality that needs to be included in the Markov-models. Not taking this into account will lead to double counting.

Figure 1 gives a rudimentary illustration of the model. On the left hand side there is the life table, starting with a cohort of 20 year old subjects who are followed until they die. During each year they may get ill due to one of the diseases under consideration and the relative prevalence and the mortality due to those diseases is registered. Competing causes of mortality, costs and impacts on quality of life are taken into account. Each disease model runs on its own, without any direct interference with the life table except for the incidence rate. After the life table and the disease models have communicated, estimates are obtained of real numbers of individuals and of costs and quality of life.

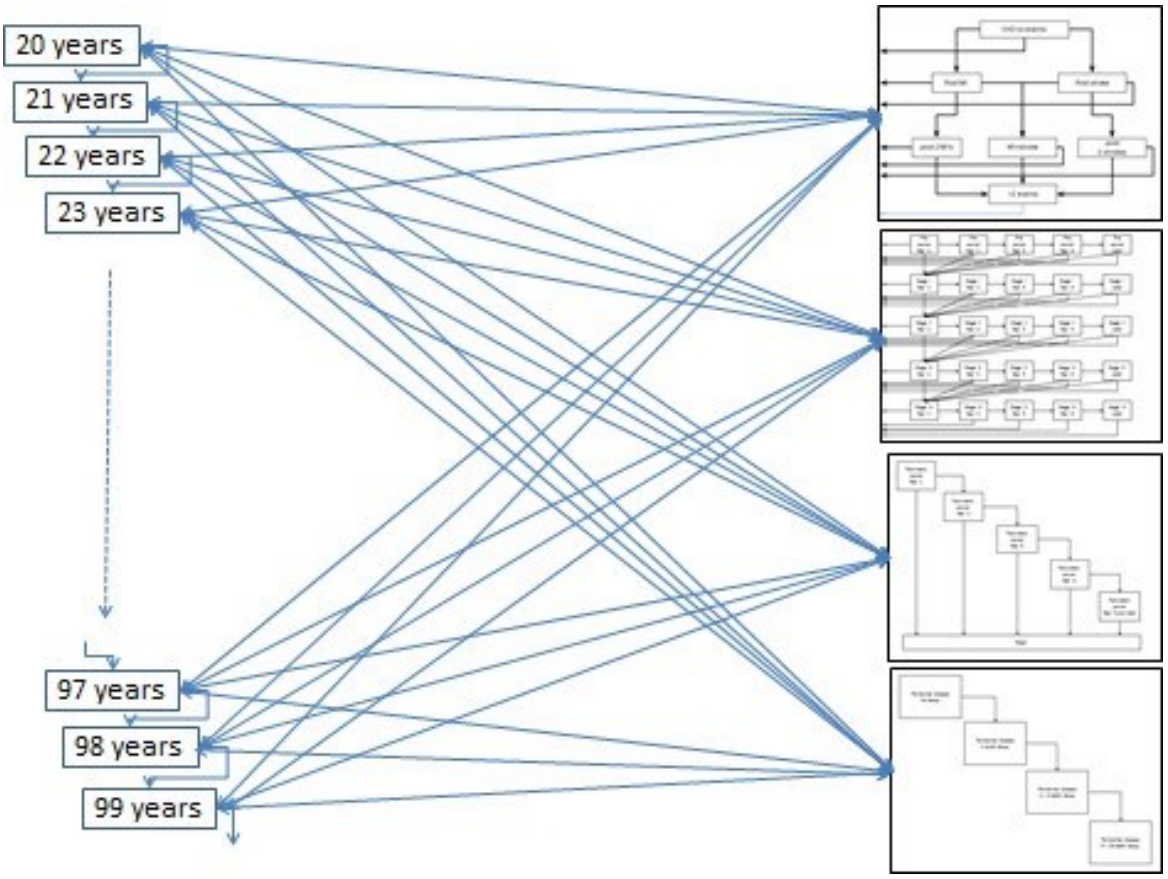

Figure 1. The life table and the disease models

3.4 THE DISEASE MODELS

There are four disease models. The first model is a cardiovascular disease model which is based on earlier work defining the Dutch guidelines [CBO, 2006] with respect to cholesterol lowering therapies and blood pressure control. Additionally it has been used to assess the cost effectiveness of clopidogrel in a variety of indications [Heeg et al 2007a, Heeg et al 2007b].

3.4.1 THE CARDIOVASCULAR MODEL

Cardiovascular disease is used here as term to capture coronary heart disease (CHD) and stroke. While the original model was developed for secondary prevention, it is adapted here for primary prevention by the inclusion of a health state for individuals who have been diagnosed with CVD but have not experienced an MI or stroke. So, within the overall model individuals may get cardiovascular disease at any age, diagnosed or not, and may enter the stage called "CHD, no events". Individuals may stay in this stage forever but may leave it by way of an MI or stroke or by cardiovascular death. Within MIs and strokes, distinction is made between fatal and non-fatal MI's. After surviving such an event an individual may have a second event (fatal or non fatalMI or stroke) or may die. After having a second event an individual may have a third event, in which case no further distinction is made between MI's and strokes. Making the distinction would complicate the model without much added value in light of the limited number of individuals entering this stage. Within each state, after an event an additional distinction is made between the first year after such event and later years.

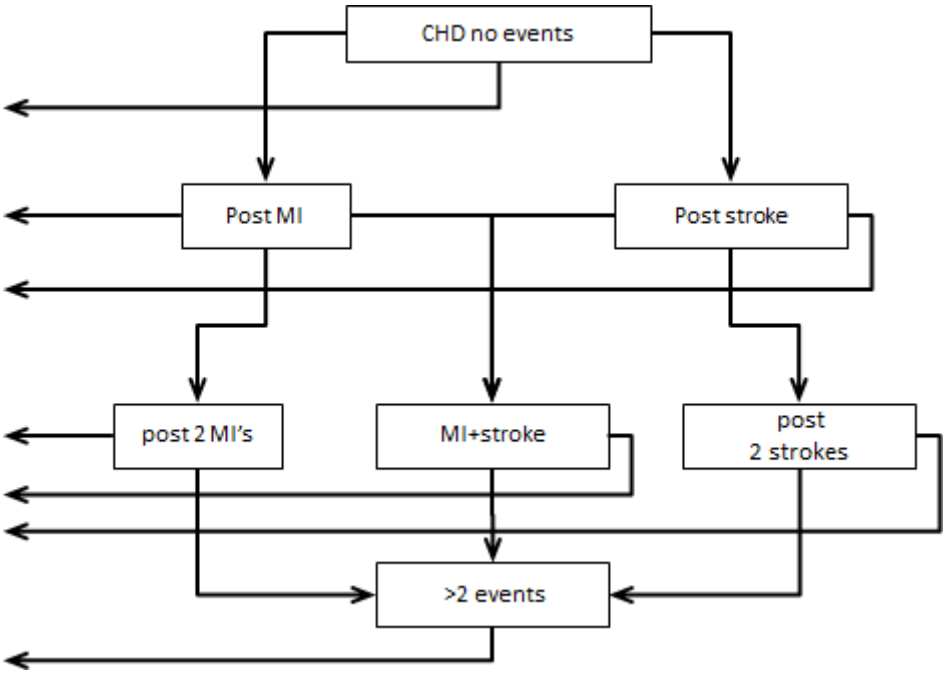

Figure 2. The cardiovascular disease model

Transition probabilities are age and gender dependent and are related to the probability of having an initial event (which is also age dependent). Probabilities of having second events and third events are directly related to the probability to have a first event. The probability of having an event increases with age. The probability to die of each event conditional on having an event (the case fatality rate) also increases with age.

3.4.3 THE ORAL CANCER MODEL

The oral cancer model is based on a relatively recent English 2006 HTA study addressing the cost effectiveness of oral cancer screening (Speight et al 2006). It categorises individuals in five stages: pre cancer and stage I to IV. Within each stage further distinction is made according to the duration of being in each state (i.e. 1, 2, 3, 4 and 5+ years). In each state an individual may die or progress. The probabilities of dying are age dependent; the probabilities of progression are not.

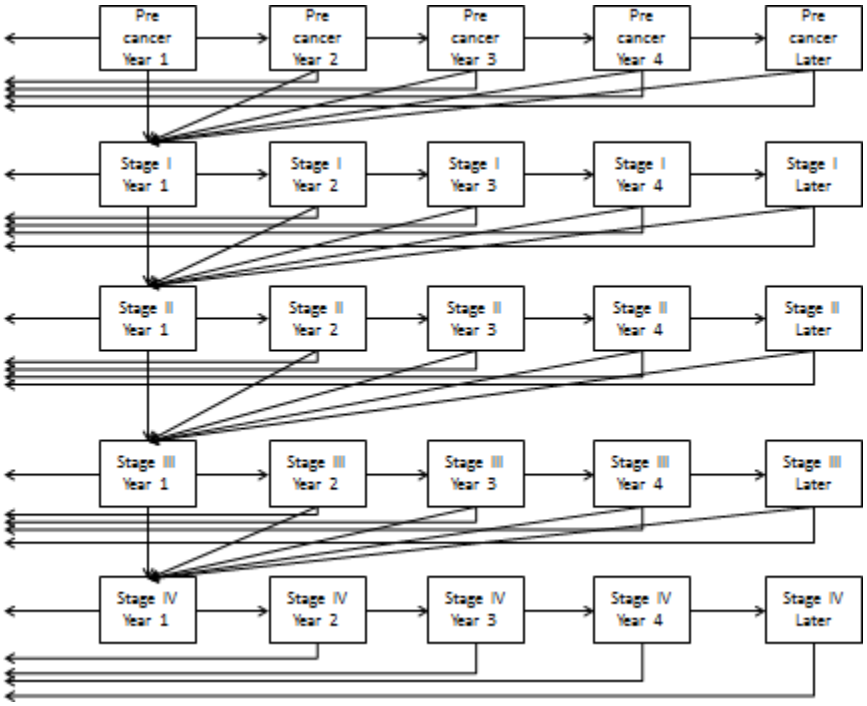

Figure 3. The oral cancer disease model

3.4.3 THE PANCREATIC CANCER MODEL

Pancreatic cancer has a bad prognosis and about 80% of patients have died within a year of having been diagnosed. A sub division in states such as made in models assessing the cost effectiveness of different therapies [Murphy et al, 2012, Aristides et al, 2003] has not been made. As the model runs in time unit of just one year, such degree of subtlety would not offer added

information. Also in light of the information about survival a simple breakdown is made according to the number of years since diagnosis. Figure 4 illustrates the model.

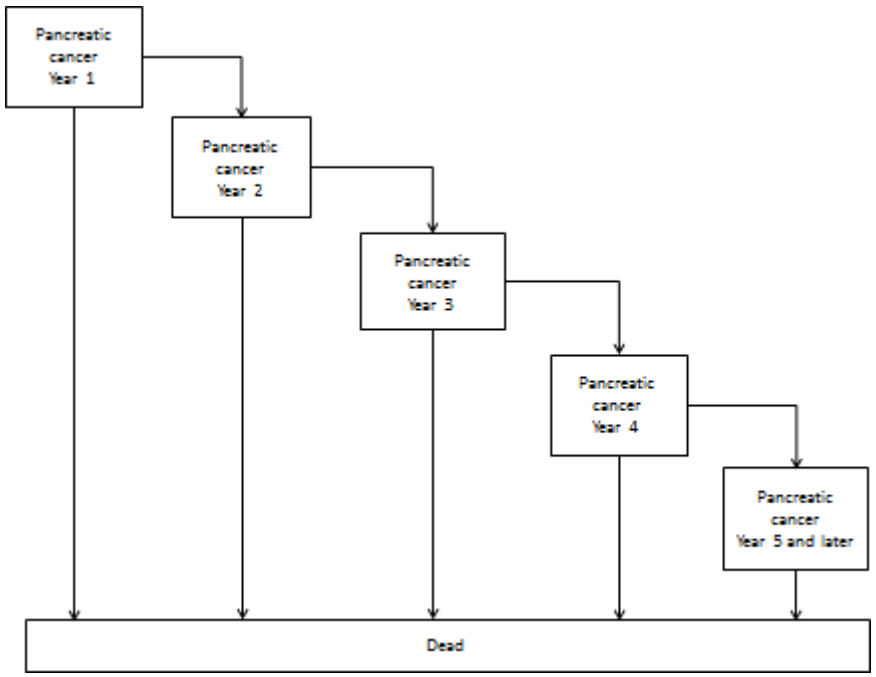

Figure 4. The pancreatic cancer disease model

3.4.4 THE PERIODONTAL DISEASE MODEL

The model for periodontal disease distinguishes between four severity states which are more related to tooth decay than to periodontal disease in a strict sense. Currently, the definition of the states is based on a 2003 HTA study addressing the cost effectiveness of routine dental checks [Davenport et al 2003]. Within this report only three states are defined: 1 tooth decayed, 2 to 4 teeth decayed and 5 to 28 teeth decayed as they mark differences in quality of life. Transition-probabilities are assumed to be one way, towards more decay. Figure 5 pictures the model.

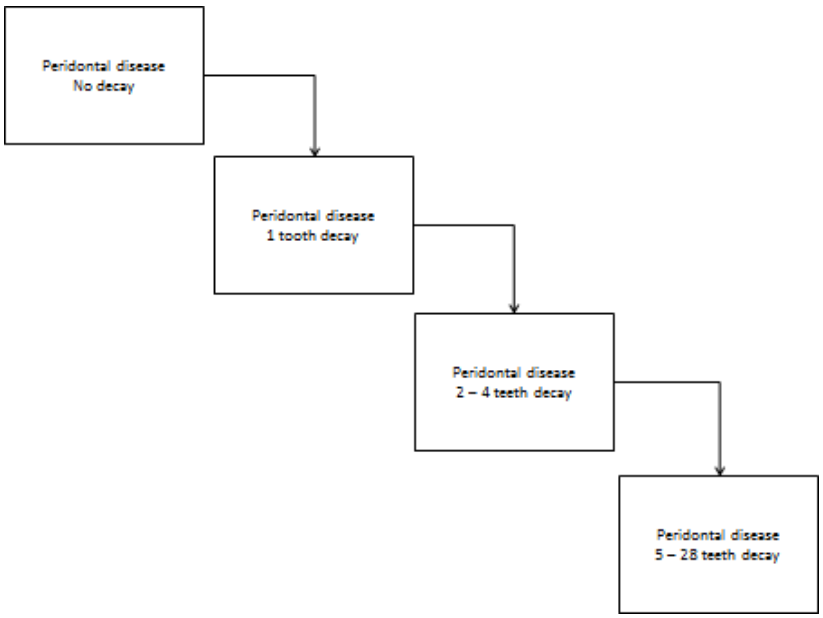

Figure 5. The periodontal disease model

4 FITTING THE MODELS

The model has the following input parameters:

- the UK life tables (§4.1)
- the incidence rates (§4.2)
- the transition probabilities within the disease models (including mortality) (§4.3)
- costs per stage (§4.4)
- quality of life per stage (§4.5)
- the estimates of the effects of using smokeless tobacco (§4.6)

Estimates of the model parameters have been found for all parameters searching the literature. The results of the extensive literature search in relationship to smokeless tobacco were used as a starting point. Naturally, this search was very specific with respect to the evidence concerning treatments to help stop people using smokeless tobacco, which is naturally the most important parameter of the model. Similar searches to support all other parameters of each model were outside the scope of the project. For this purpose additionally searches within Econlit were performed using the various disease names as relevant. Additionally searches within PubMed were carried out combining the disease names in combination with “costs”, “epidemiology”, “incidence”, “prevalence”, “model”, “costs” and “quality of life”. The same was done by using Google. All searches were repeated by adding the term “South Asians”. The most recent UK source was used if possible, unless stated otherwise.

When interpreting the estimates one may want to remember that the estimates of the cost and

effects of quitting will be derived by comparing a population with increased risk due to the use of smokeless tobacco with a population with no such risk. So, in the ideal case one would need estimates concerning South Asians who are not using smokeless tobacco. Unfortunately, the quest to find data considering the Asian population in the UK has been rather unsuccessful.
A positive exception is a report by the British Heart Foundation considering ethnic differences in cardiovascular disease (Scarborough 2011b). This report has specific figures for South Asians and non South Asians and concludes that the numbers of MI's are higher for South Asians but that the case mortality rates are lower. Additional data in this shows that when considering coronary heart disease, the age standardised death rate is lower in South Asian men than in white men (107 vs 149 per 100,000) but higher in South Asian women than in white women (85 vs 71 per 100,000). The age standardised death rate for stroke is higher in South Asian men than in white men (128 vs 105) but slightly lower in South Asian women than in white women (109 vs 111). Additionally it is reported that of the 37,223 people who died in 2008 as a result of diseases of the circulatory system, 738 were from India, 441 from Pakistan and 183 from Bangladesh. Such numbers limit the potential for strong statistical inference. The mixed results with respect to the epidemiology - not indicating a clear difference in one or the other direction– together with the small numbers supported the choice to estimate the epidemiologic parameters using data from the whole of England and Wales.

4.1 THE LIFE TABLE

While the mortality rates from the diseases which are modelled result from the disease specific models, mortality due to other reasons is also taken into account. This is estimated by subtracting the UK mortality rates for CHD, stroke and mouth cancer from the all-cause mortality rates as published by the National Bureau of Statistics [2008]. Figure 6 presents the resulting rates. The relatively small size of the mortality due to mouth and pancreatic cancer makes that these are almost unnoticeable in this graph.

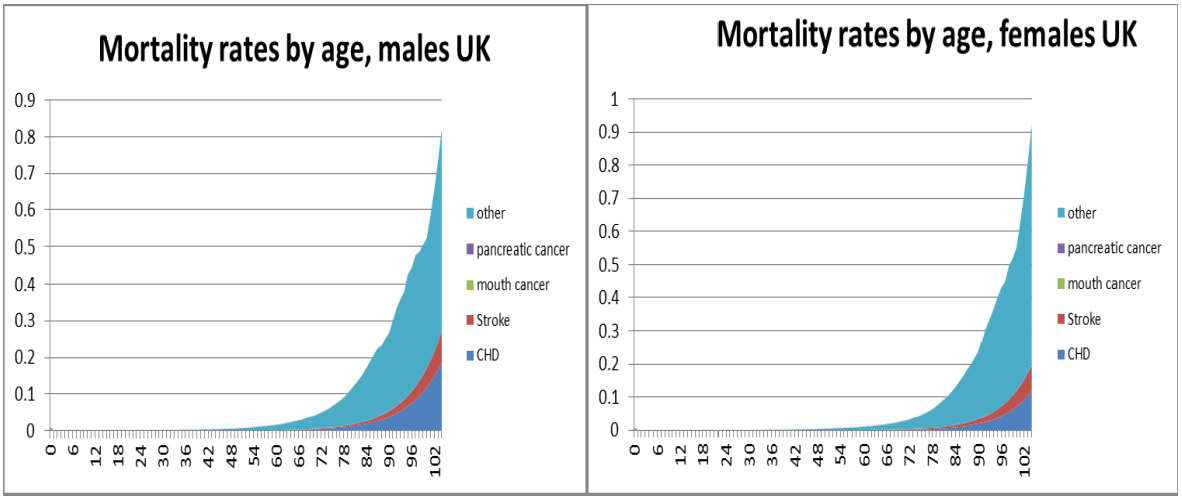

Figure 6 UK mortality rates

The mortality data concern the average UK citizens and figures concerning South Asians may differ. In the sensitivity analysis it is analysed to what extend the results change when using higher mortality figures.

4.2 THE DISEASE INCIDENCES

4.2.1 CARDIOVASCULAR DISEASE

The incidence of cardiovascular disease has been estimated using the data underlying the derivation of the QRISK score based on 4,238,309 person years and an average incidence of 6.57 per 1,000 person years (Hippisley-Cox, 2007). Data was collected between 1995 and 2007 in 160 UK GP-practices. Again, no data were found which were specific for the South Asian population in the UK.

An exponential curve was used to smooth the curve. Figure 7 presents the results.

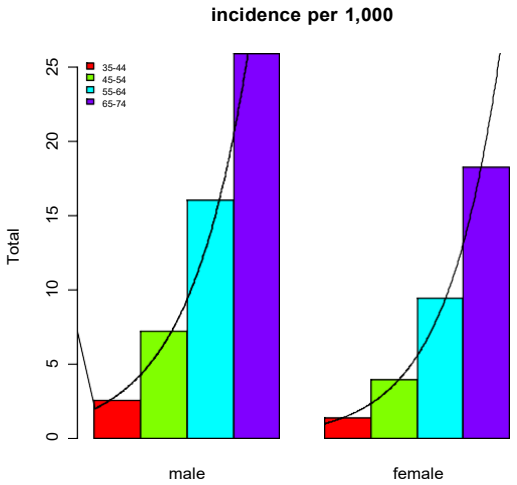

Figure 7. Cardiovascular incidence

4.2.2 MOUTH CANCER

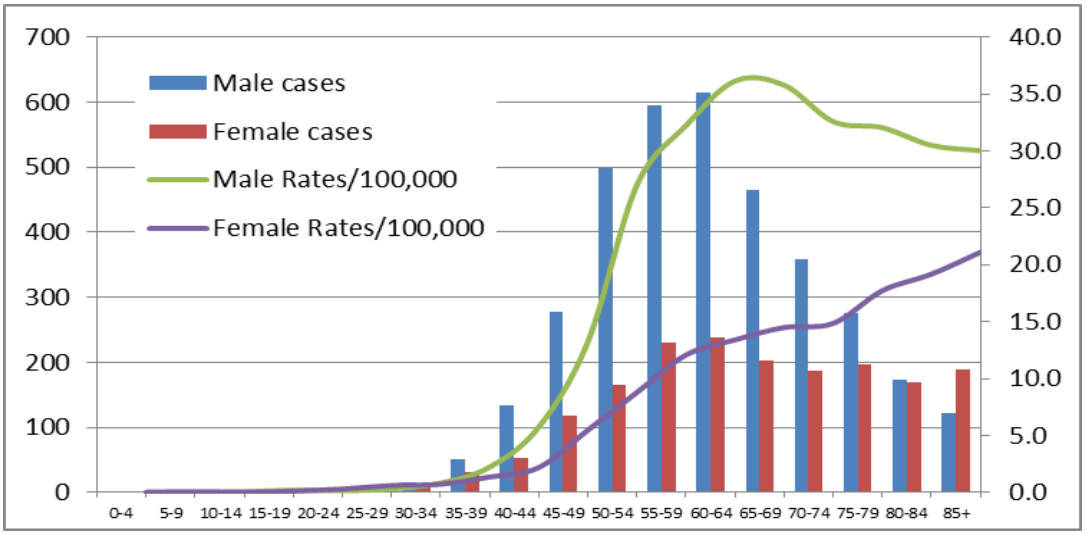

Figure 8. Incidence in oral cancer UK, 2007

Figure 8 presents the estimated incidence in mouth cancer on the basis of a publication from Cancer research UK. (http://info.cancerresearchuk.org/cancerstats/types/oral/incidence/uk-oral-cancer-incidence-statistics). The figures are not specific for South Asians nor for users and non-users of smokeless tobacco. It is noted that these incidence figures logically concern diagnosed cancer while the model includes a pre-cancerous state in which individuals may be un-diagnosed. It is assumed that all subjects continue to develop to the later stages within – on average – one year. Additionally we note that the incidence figures are per 100,000 and not per 1,000 as when considering cardiovascular disease.

4.2.3 PANCREATIC CANCER

The incidence in pancreatic cancer is estimated on the basis of a 2007 publication from Cancer research UK. The figures are not specific for South Asians nor for users and non-users of smokeless tobacco.

Figure 9 is again a copy of a published figure and the underlying numbers are available in a downloadable spread-sheet.
(http://info.cancerresearchuk.org/cancerstats/types/pancreas/incidence/)

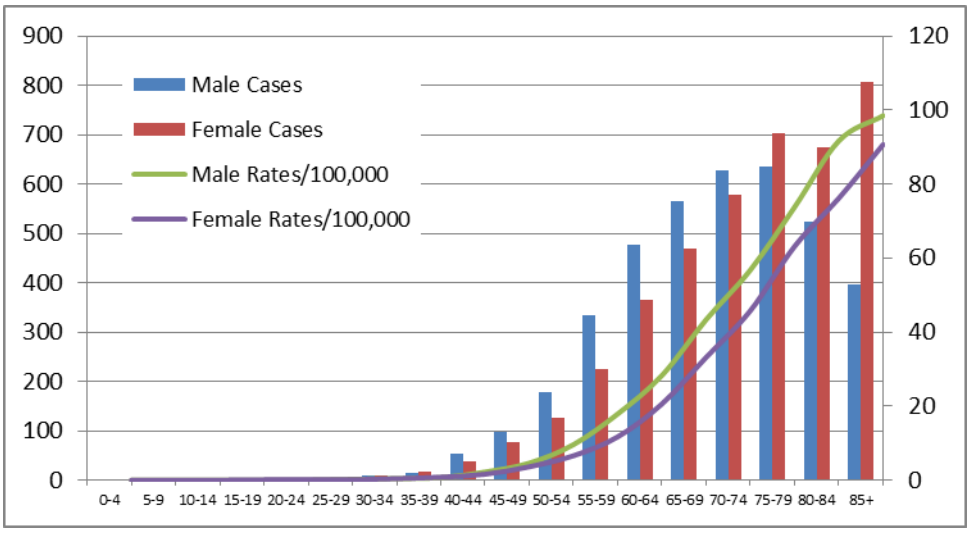

Figure 9. Incidence in pancreatic cancer UK

4.2.4 PERIODONTAL DISEASE

In the UK the annual incidence of individuals presenting with symptoms of periodontal disease in general medical practice is 6 per 10,000 people per year [Birmingham Research Unit, 2005]. These are people who are symptomatic and at the severe end of the spectrum. A survey in the UK in 1998 found that in adults with their own teeth [Office for National Statistics, 2000], plaque was visible in 72% of people. Calculus was visible in 73% of people and periodontal pocketing (indicating periodontitis)was present in 54% of people. Loss of gum attachment greater than or

equal to 4 mm (indicating moderate to severe periodontitis) was present in 43%. Loss of attachment greater than or equal to 6 mm (indicating severe periodontitis) was present in 8%.

Given the transition probabilities, and given prevalence one may estimate the incidence. Using an annual probability of additional teeth decay of 26% and an estimate of the prevalence of 50% (about halfway between the earlier mentioned 54% and 43%) an estimate of the incidence is derived of 3.41% per year. This is used as the estimate of the annual incidence.

4.3 THE TRANSITION-PROBABILITIES

Within the disease models different health states are defined and subjects may move from one health state to another. The probability that this happens defines the transition-probability. All estimates of the transition-probabilities are based on the literature, not necessarily on the basis of the same sources that were used to estimate the incidences.

4.3.1 THE CARDIOVASCULAR DISEASE MODEL

The transition probabilities for cardiovascular disease have initially been based on earlier work using epidemiologic data collected between 1985 and 1995 from a province in Canada (Saskatchewan) where a unique analysis was performed concerning survival after MI's and strokes (Caro et al [2005]). Taking this work as a starting point, the model was adapted to fit a number of UK statistics. These are: the age and gender specific mortality rates from CHD and stroke (by 10 year groups as published by the National Bureau of Statistics, 2011), the age and gender specific data about the occurrence of MI's and strokes (all ages and <75 years) and the age and gender specific case-fatality rates for MI's and strokes (all ages and <75) as published by the British Heart Foundation (Scarborough, 2011a).

In fine tuning the model it was assumed that transition-probabilities are age dependent and that they move in an exponential fashion. This is with respect to the probability of having MI's, the probability of having strokes (conditional on having CHD) and the probability of other cardiovascular death as well as to the distribution between fatal and non-fatal events (Appendix 2 presents how this is taken into account technically).

The approach of estimating the model parameters is best described as being iterative.

Figure 10 presents the event probabilities for a 20 year old male and female. It is noted that the decrease in the male MI-incidence does not imply that one would see less MI's with age. These

figures concern probabilities for those who have CHD.

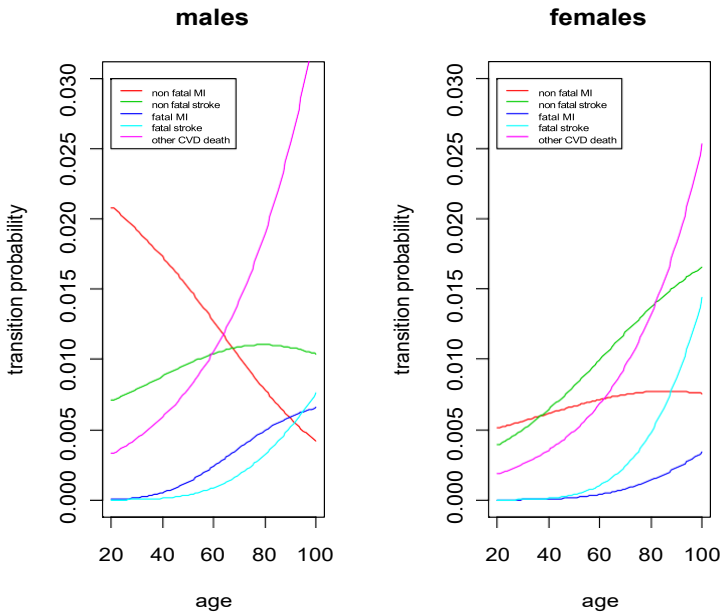

Figure 10. Event probabilities

Probabilities of having a second event are assumed to be directly related to having a first event and estimated to be increased. The degree of the increase is estimated on the basis of data from the CAPRIE-study (CAPRIE Steering Committee, 1996) containing data from 11,993 subjects with a recent MI and 11,630 subjects with a recent stroke . When comparing the results from this trial with the model estimates it was estimated that having an MI increases the probability to have another one by 5.2 times the probability of having an initial event. Having a stroke increases the probability of having another stroke by 3.7 times the probability of having an initial event. The CAPRIE data do not suggest any increased probability for the non-index events. The probability of having a third event is estimated at 4.5 times the probability of having an initial event. .

4.3.2 THE ORAL CANCER DISEASE MODEL

The transition probabilities for the oral cancer model are taken from the 2006 HTA assessment considering oral cancer screening (Speight eat al. 2006). Mortality rates are different per stage and per age group. Figure 11 presents the results for males graphically. The results for females show a similar pattern. The annual probabilities of moving from stage I to II, form II to III and II to IV are taken from the same study and estimated at 0.53, 0.59 and 0.67 respectively.

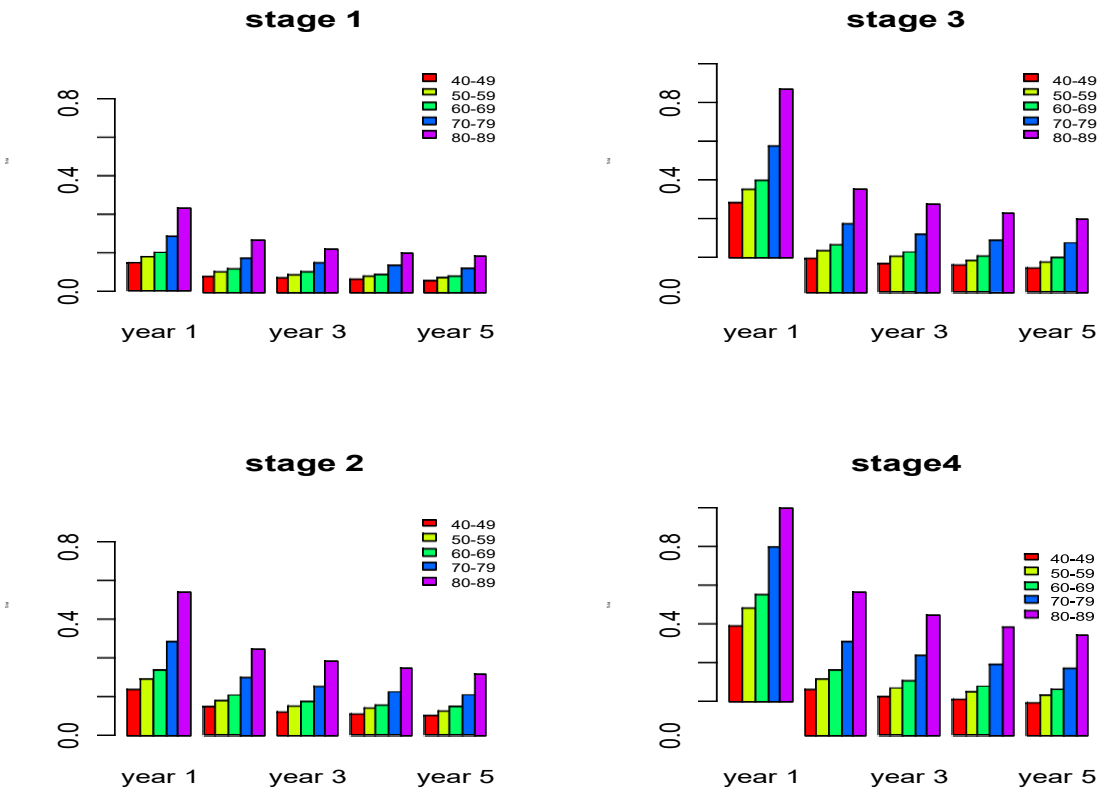

Figure 11 Mortality due to oral cancer

The HTA report is quite clear about mortality and about progression from the active stages but rather vague about the number of individuals who go from pre-cancerous to stage I and further. The UK cancer statistics indicate a total of 3594 incident males and 1816 incident females in 2008. The same source reports 1153 male patients dying of oral cancer and 669 female patients. By choosing the probabaility to progress to from pre-cancerous to stage I at 4% per year, a similar ratio between incidence and mortality is obtained.

4.3.3 THE PANCREATIC CANCER DISEASE MODEL

The most recent publications from Cancer Research UK show that 1 year survival rates have increased from 6% (males) and 7% (females)in 1971-1975 to 16%(males) and 17%(females) in 2004-2006. Five survival have increased from 2 to 3%,, 10 year survival has stayed at 2%. Within this, the introduction of more effective therapies has been most influential and more targeted and more liberal use are likely to have further improved survival. So, we estimate 1 year survival at 20% and 5 year survival at 4%. So, the probability to die during the first year is estimated at 0.8 and the probability to die in later years at 0.33. As a consequence average survival after diagnosis is estimated at 1.1 years.

4.3.4 THE PERIODONTAL DISEASE MODEL

The 2003 HTA report concerning routine dental check-ups estimates the probability of an additional tooth decay within 12 months when visiting the dentist every 12 months at 0.26. This probability is used here. So, the probability to go from 1 tooth to 2-5 teeth decayed is estimated at 0.26 and the probability to go from 2 to 4 to 6 to 28 teeth decayed at 0.095 (=1-(1-0.26)^3). It is realised that in doing so the probability of decay is overestimated during the first two years after entering the 2 to4 teeth decayed state.

4.4 COSTS PER STAGE

4.4.1 THE CARDIOVASCULAR MODEL

Costs per stage, with the exception of the costs before having an event, - were derived from a previously published cost-effectiveness analysis by Heeg et al [2007] holding UK cost figures which were inflated to 2011 prices using the UK consumer price index for health. No estimates were available concerning the annual costs of being diagnosed with CHD but being event free. That is free of MI's and strokes but potentially undergoing PTCA and by-pass surgery. These have been estimated independently such that the total costs as predicted by the model (adding up the excepted costs for an average 20 year old male and female and correcting for the size of the population) is equal to the estimate of 7.4 billion as published by the British Heart Foundation (Scarborough 2011a) . Using this approach, the costs of being event free are estimated at £1,050 per year. It is noted that this may be a high estimate when considering that South Asians seem to have much lower intervention rates (Scarborough 2011b).

Table 1: Costs per year per cardiovascular health state

State	1st year	later
Event Free,	£1,050	£1,050
After 1st or 2nd MI	£5,249	£2,099
After 1st or 2nd Stroke	£10,031	£6,065
After MI + stroke, or 3th event	£7,640	£4,082

4.4.2 THE ORAL CANCER MODEL

The estimates concerning the costs of oral cancer have been taken from the 2006 HTA report and been inflated with the consumer price index for health. Table 2 presents the results. We recognise that most of the costs are concentrated in the early years in a stage.

Table 2 Costs in oral cancer health states

	pre-cancer	stage I	stage II	stage III	stage IV
year 1	£1,310	£4,605	£8,318	£11,950	£11,541
year 2	£429	£644	£818	£989	£2,159
> year 2	£441	£483	£819	£920	£2,062

4.4.3 THE PANCREATIC CANCER MODEL

The most recent cost effectiveness analysis from the UK concerning pancreatic cancer are from 2001 (Ward et al, 2001) and 2003 (Aristides et al, 2003) , relatively recent after the introduction of gemcitabine . A most recent cost effectiveness analysis is from the US concerning modern radiotherapy techniques (Murphy, 2012). Within this, a scenario where patients are only treated with gemcitabine is estimated to costs $42,000 per patient. This is with a survival of less than a year. The 2001 HTA report mentions average costs per patient per year between £7,800 and £12,000. Here we estimate costs per year at £10,000 per year at current prices and remind ourselves that this a relatively crude estimate which needs broad confidence intervals.

4.4.4 THE PERIODONTAL MODEL

In the NHS, dental charges are broken down into three bands. Band 1 (£17) covers an examination, diagnosis (e.g. X-rays), advice on how to prevent future problems, a scale and polish if needed, and application of fluoride varnish or fissure sealant. A Band 2 course of treatment costs £47.00 and includes everything listed in Band 1 plus any further treatment such as fillings, root canal work or taking out teeth Band 3 treatment costs £204.00 and covers everything listed in Bands 1 and 2 plus crowns, dentures or bridges.

These are NHS tariffs which are just the prices being paid by the consumers. Additionally dentists receive reimbursement based on the number of NHS clients in their practice, independent of the number of treatments. Therefore, private tariffs may be a more reliable estimate of the real costs. While writing this report, the first author had private root canal treatments by a specialist for £650 which excludes the costs of the preparatory work exceeding £300.

Given this mixture between private and NHS health care, it was, rather arbitrarily, decided to estimate the costs of treatment as one band 3 treatment per decayed tooth. The probability of having a next tooth decayed is estimated at 26% per year and as such the costs per year after the first decayed tooth are estimated at £ 53.

4.4.5 OTHER COSTS

The model allows for the inclusion of unrelated health care costs which have been based on Dutch estimates of the costs of diseases by gender and age in 2005 [Kosten van Ziekten. Bilthoven: RIVM, <http://www.kostenvanziekten.nl> versie 1.1, 26 juni 2008]. This is for

illustrative purposes only as the inclusion of those costs is not according to the UK guidelines. An exchange rate was used of 1.15. Figure 12 presents the estimates.

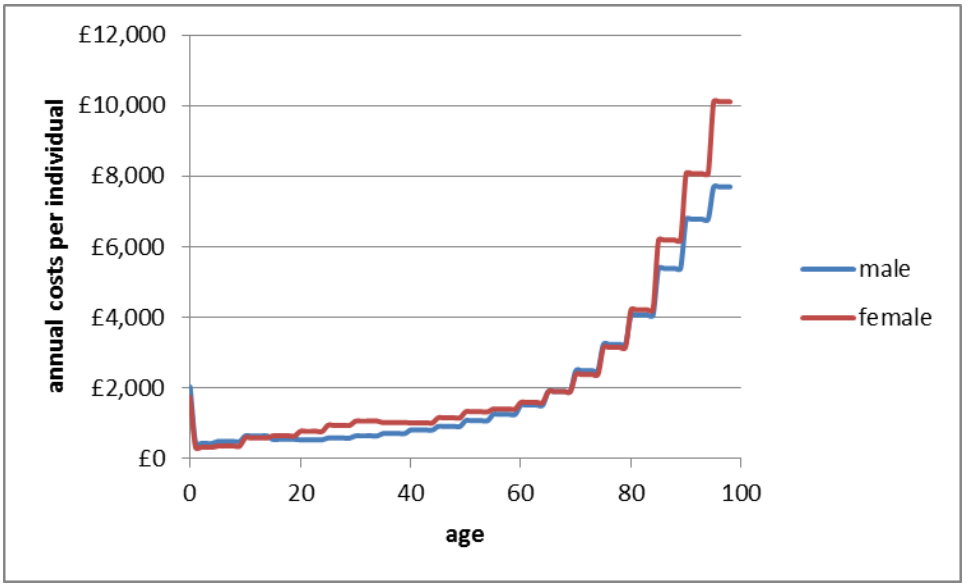

Figure 12 Costs of unrelated diseases, Dutch distribution, 2005, transferred to NHS costs 2010.

4.5 UTILITIES PER STAGE

The utilities per stage are all based on the literature. A report by Mark Oppe and colleagues in the annual EQ-5D proceedings of 2003 shows an almost perfect linear decrease in peoples self reported visual analogue scale of 0.0034 per year (Oppe, 2003). Acknowledging that part of this decrease may be related to the diseases that have been modelled here, it is estimated that the age specific decline is 0.0020 per year and starting at 1.00 at the age of 20. (This implies that we estimate the average utility of a 60 year old person at 0.92.)

4.5.1 CARDIOVASCULAR DISEASE

The age specific utility values are multiplied - for those people in the disease models – with factors which represent the disutility of being in the specific health states within the disease models. These factors are 0.91 for MI and 0.8 for stroke. Having experienced two MI's decreases the factor to 0.81 and having experienced two strokes to 0.64. Further events are assumed not to decrease the disutility any further. This implies that someone who is 60 years of age with an average utility of 0.92 will have a utility of 0.91*0.92 when having a myocardial infarction.

4.5.2 ORAL CANCER

Based on the 2006 HTA report, dis-utilities due to oral cancer are estimated at 0.92 for pre-cancer, at 0.88 for stage 1 and at 0.68 for all later stages (Speight et al 2006).

4.5.2 PANCREATIC CANCER

In a most recent cost effectiveness analysis, the utility for pancreatic cancer patients in stable disease was estimated at 0.68, for patients with local or distant progression at 0.62, and the utility of both local and distant progression was estimated at 0.56. (Murphy at al 2012). Here, we estimate the average utility over the whole course of the disease at 0.62.

4.5.3 PERIODONTAL DISEASE

When searching the literature for utility decrements concerning the effects for periodontal disease one is likely to find a very relevant publication from Fyffe and Kaye [1992] using the standard gamble technique to derive utilities for various stages of decay. Unfortunately the results seem almost silly. The utility of being in a state with a decayed and painful posterior tooth is estimated at 0.46. The utility of being in a state with a decayed and **non-painful** posterior tooth is estimated at 0.51. These are values which are below those associated with having a stroke. An alternative is to estimate that individuals are prepared to accept treatments up to 20,000 per QALY and that they are prepared to pay say £1,000 to save a tooth. This would imply that one would expect to gain at least 0.05 QALY's over a time horizon of say 40 years and that the expected QALY gain is at least 0.00125 per year with a utility estimate of 0.99875. This estimate is used here.

4.6 THE EFFECTS OF USING SMOKELESS TOBACCO

A recent meta-analysis concerning the effects of smokeless tobacco on the incidence of MI's and strokes presents different results for both manifestations of CVD. Moreover, it suggests that the effects on fatal MI's and strokes is more pronounced than on non-fatal MI's and strokes. The estimates are a risk ratio of 1.03 for all MI's and 1.16 for fatal MI's, 1.19 for all strokes and 1.40 for fatal strokes [Bofetta et al. 2009]. Unfortunately, this study is a meta-analysis of Swedish & US studies and concerns smokeless tobacco products quite unlike those used by South Asians in the UK. In this group, products are used such as paan and niswar which are different from what American and Swedish people typically use.

However, no similar estimates have been found for those products and these estimates are used as the base line estimates. Sensitivity analysis is carried out to address the uncertainty.

There are various estimates concerning the increased cancer risks of using smokeless tobacco. In a recent overview it was reported that using smokeless tobacco may increase the risk of oral cancer by a factor 5.1 in Asian men and women and by a factor of 2.6 in men in the US and Canada [Bofetta et al 2008]. Another estimate is a more than sevenfold increase from Sudan. Here, the point estimate of 5.1 is used for the Asian men and women in the US and Canada. The same study reports an increase in the incidence of pancreatic cancer of 1.8. This again concerns data from Sweden. [Bofetta et al 2008] No data were found concerning South Asians or the products they typically use.

The use of smokeless tobacco is also associated with a doubling of periodontal disease (Fisher et al, 2005). This estimate is based on the Third National Health and Nutrition Examination Survey, a population based dataset representative of the civilian, non-institutionalized US population. No distinction was made considering the type of smokeless tobacco used.

All estimates seem to be in line with an overview of Critchley et al from 2003 who presented numbers of people dying due to oral cancer (India) and cardiovascular disease (Sweden).

5 RESULTS

The model can be used to simulate what happens when we change some parameters such as of the incidence of oral cancer. First however, results are presented to check whether what the model predicts, is in line what is observed..

5.1 THE AVERAGE POPULATION

Figure 13 presents survival estimates starting with 20 year old males and females. The upper line shows what survival would be if one would only die of oral cancer. The second line shows what survival would look like if one adds pancreatic cancer and the third when one would add CHD and stroke. The lower line indicates overall survival which is line with the survival statistics.

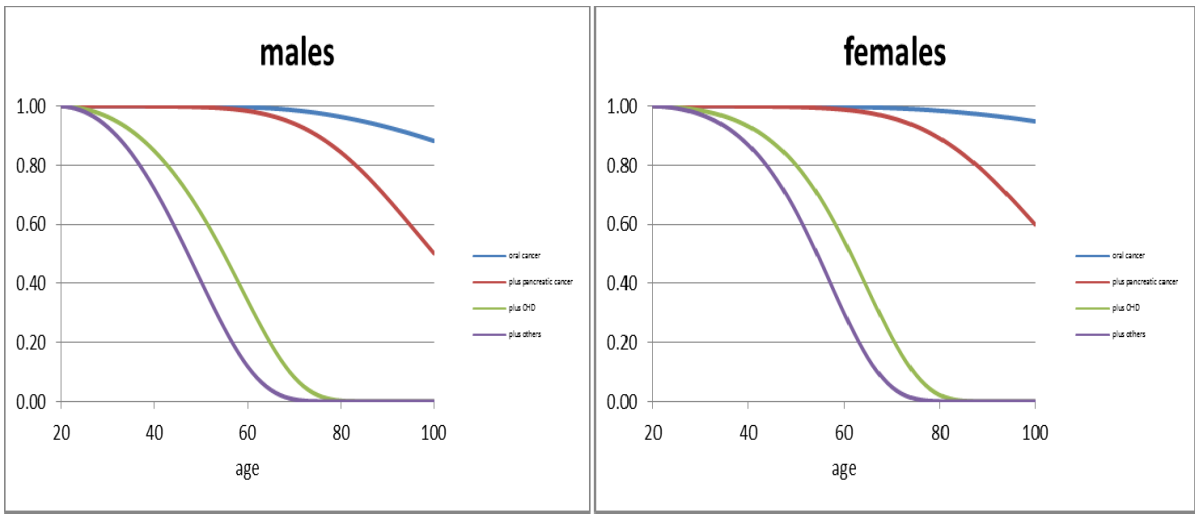

Figure 13 Cumulative survival, males and females

The life expectancy of a 20 year old male is estimated at 58 years, for a 20 year old women at 62 years. When discounted after the first year at 3.5% per annum these figures are 25.0 and 25.7 years. (When using a 3.5% discount rate, a life year 10 years from now is equivalent to 0.7 current years, a life year 30 years from now to 0.35 current years and 50 year from now as 0.18 current years.)

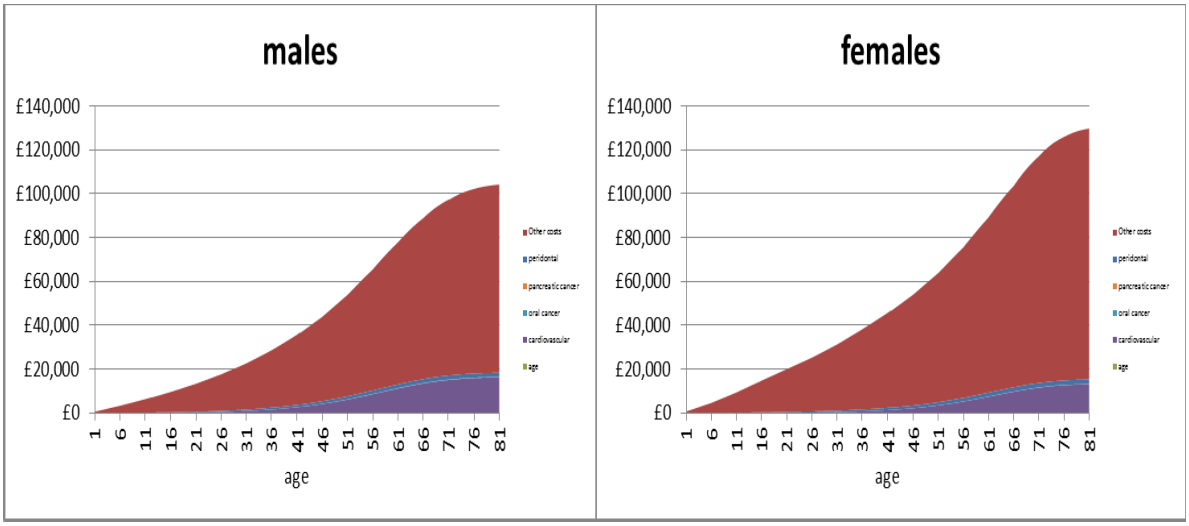

Figure 14 Cumulative cost of health care, males and females from the age of 20

Figure 14 presents estimates of the predicted health care costs per 20 year old individual. Table 3 presents some summary figures.

Table 4 and table 5 present cardiovascular disease outcomes by gender. The tables compare model results (predicted column) with results as published by the British Heart Foundation (observed column) (published in 2010, concerning 2006).

Table 3 Expected life years, QALY's and costs

	20 year old males		20 year old females	
EFFECTS	undiscounted	discounted	undiscounted	discounted
life years	58.69	25.07	62.71	25.75
QALY's	54.15	23.87	57.91	24.53
COSTS				
cardiovascular	£16,258	£2,805	£13,096	£1,989
oral cancer	£167	£31	£83	£15
pancreatic cancer	£42	£7	£42	£6
peridontal disease	£1,925	£631	£2,107	£659
other unrelated costs	£86,441	£23,561	£115,427	£31,886
TOTAL (excl other costs)	£18,393	£3,474	£15,327	£2,668

Table 4 Cardiovascular events, observed and predicted, females

Females		Events per 100000		Case fatality rates	
		predicted	observed	Predicted	Observed
MI	20<age<75	63	61	7.00%	7.40%
	all ages	158	158	15.10%	15.10%
Strokes	20<age<75	89	88	12.42%	13.10%
	all ages	280	280	24.68%	24.70%

Table 5 Cardiovascular events, observed and predicted, males

Males		Events per 100000		Case fatality rates	
		predicted	observed	predicted	observed
MI	20<age<75	180	179	5.29%	5.30%
	all ages	270	270	10.60%	10.60%
Strokes	20<age<75	126	126	10.02%	10.30%
	all ages	249	249	17.10%	17.10%

Figure 15 presents a comparison of the predicted number of subjects dying of CHD and stroke with published figures of the National Bureau of Statistics concerning 2010.

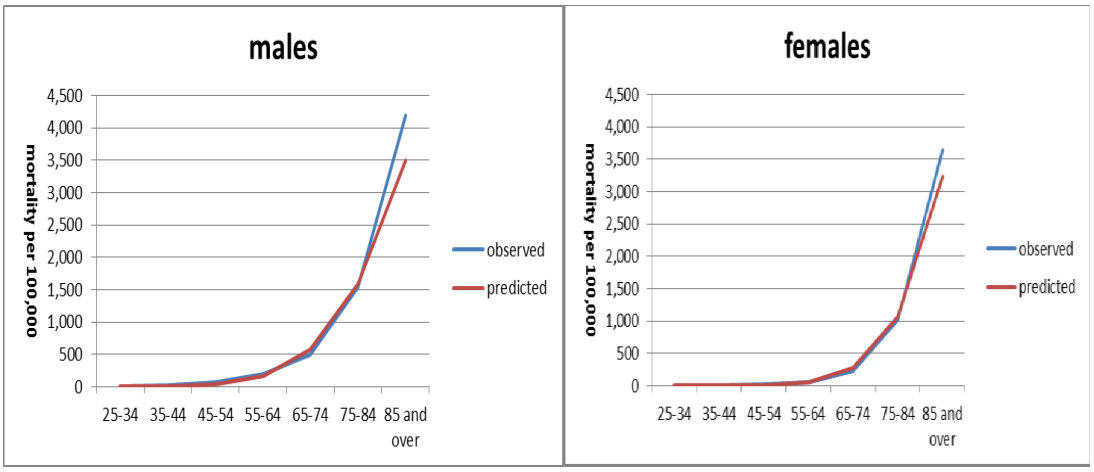

Figure 15 Mortality, observed and predicted

It may not come as suprise that the predictions are close to the data as it it exactly this data that has been used to calibrate the model.

When comparing the predictions in terms of prevalance with those as published by the National Heart Foundation concerning 2006 (data that wasn't used to calibrate the model), a less

spectacular fit is found. Table 6 presents the results. The predicted prevalence in the higher age groups is much higher than reported by the British Heart Foundation. However, the latter figures are based on a lifestyle survey, where people need to self report their diseases. The estimates underlying the model are based on registrations with GP's and hospitals.

Table 6 Prevalence, "observed" and predicted

Age group	males		females	
	predicted	observed	predicted	observed
15-44	0.88%	1.40%	0.43%	1.20%
45-64	9.70%	15.60%	5.77%	9.90%
65-74	27.08%	31.20%	18.49%	23.00%
>74	49.61%	31.10%	38.94%	32.00%

When considering the model for oral cancer the estimation of duration in pre-cancer states dominates the distribution of patients. Figure 16 illustrates this. The probabaility to progress to the later stages is estimated at 0.04. This is to ensure a similar ratio between the reported number of patients who are diagnosed with oral cancer and the number of patients dying of oral cancer. When choosing higher rates of progression one may need to estimate lower incidence rates of lower mortality rates to preserve consistency with the sources of data.

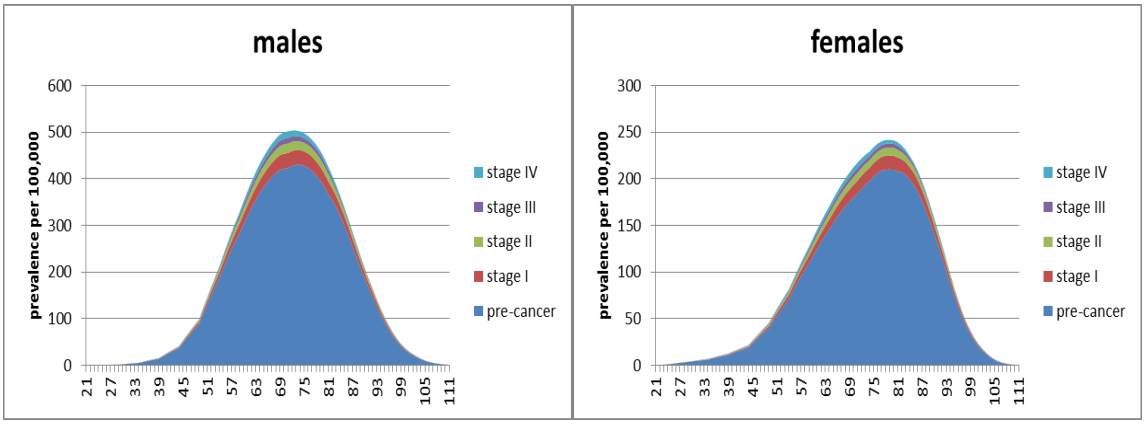

Figure 16 Predicted number of individuals with mouth cancer

The parameters for the model concerning periodontal disease are chosen such that they result in a prevalence of about 50% and such that the annual probabaility of further teeth with decay, given peridontal disease, is 26%. This is copied by the model.

5.2 THE COSTS AND EFFECTS OF QUITTING THE USE OF SMOKELESS TOBACCO

When adapting the model-parameters to the increased risks an estimate can be obtained of the expected costs, life expectancy and QALY's of smokeless tobacco users. These can subsequently be compared with a national average and the difference can be used as an estimate of the cost savings due to quitting. Table 7 presents the results for a 40 year old female. Table 8 presents similar results for a 40 year old male. The age of 40 is chosen as being representative for the age distrubution that was included in the Chroucher-pilot study.

Table 7 Costs and effects of smokeless tobacco users versus the average population, 40 year old female

	Undiscounted			**Discounted**		
EFFECTS	Average population	Smokeless tobacco users	difference	Average population	Smokeless tobacco users	difference
life years	43.19	42.93	-0.26	22.25	22.18	-0.069
QALY's	40.53	40.25	-0.29	21.29	21.21	-0.082
COSTS						
Cardiovascular	£12,617	£12,973	£356	£3,631	£3,745	£114
oral cancer	£79	£396	£317	£26	£131	£105
pancreatic cancer	£41	£75	£33	£12	£22	£10
peridontal disease	£1,238	£1,700	£462	£514	£751	£238
other costs	£97,989	£96,782	-£1,207	£37,434	£37,176	-£258
TOTAL (ex other)	£13,975	£15,143	£1,168	£4,183	£4,649	£467

The results suggest that when a 40 year old female who uses smokeless tobacco becomes an average individual by stopping using smokeless tobacco, this would save up to £496 in (discounted) health care costs related to the increased risk. Most of those costs are related to the costs of dental care. It would result in 0.032 gain in (discounted) life expectancy and a gain of 0.048 (discounted) QALY's. When using a limit for the cost effectiveness of £ 30,000 per QALY, a therapy which makes people quit is "cost effective" up to a cost per quitter of £ 2,915. For a 40 year old male, this figure is £ 3,214.

The life time results differ for different age groups. The higher the age, the smaller the expected gains and the smaller the expected savings. The left hand side of the figures 15 and 16 present the expected gain in QALY's when varying the age of the individual who quits the use of smokeless tobacco. The right hand sides present the expected cost savings when varying the age. In the latter, the additional unrelated costs are depicted under the savings=0 axis and the savings above the savings=0 axis.

Table 8 Costs and effects of smokeless tobacco users versus the average population, 40 year old male

	Undiscounted			Discounted		
EFFECTS	Average population	Smokeless tobacco users	difference	Average population	Smokeless tobacco users	difference
life years	39.69	39.35	-0.34	21.26	21.16	-0.099
QALY's	37.14	36.75	-0.39	20.30	20.18	-0.121
COSTS						
cardiovascular	£15,199	£15,476	£277	£4,879	£4,991	£112
oral cancer	£166	£825	£659	£59	£296	£237
pancreatic cancer	£42	£76	£33	£13	£24	£11
peridontal disease	£1,099	£1,524	£425	£477	£704	£226
other costs	£76,195	£74,913	-£1,281	£30,320	£30,017	-£303
TOTAL (ex other)	£16,507	£17,900	£1,394	£5,429	£6,015	£586

The figures suggest that stopping the use of smokeless tobacco is most favourable the younger an individual is. This conclusion may change when applying a discount rate for both costs and effects as is illustrated in figures 19 and 20. Later in life, with higher risks, the effects are more immediate leading to a higher value of the benefits.

Figure 17. Expected number of QALY's gained, additional unrelated costs and related savings as a function of age. Undiscounted. Males

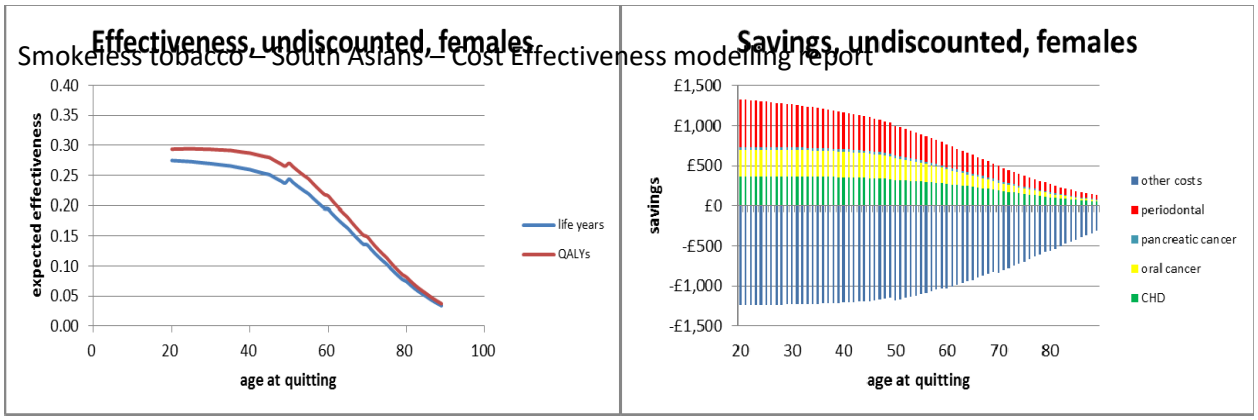

Figure 18. Expected number of QALY's gained, additional unrelated costs and related savings as a function of age. Undiscounted. Females

Figure 19. Expected number of QALY's gained, additional unrelated costs and related savings as a function of age. Discounted. Males

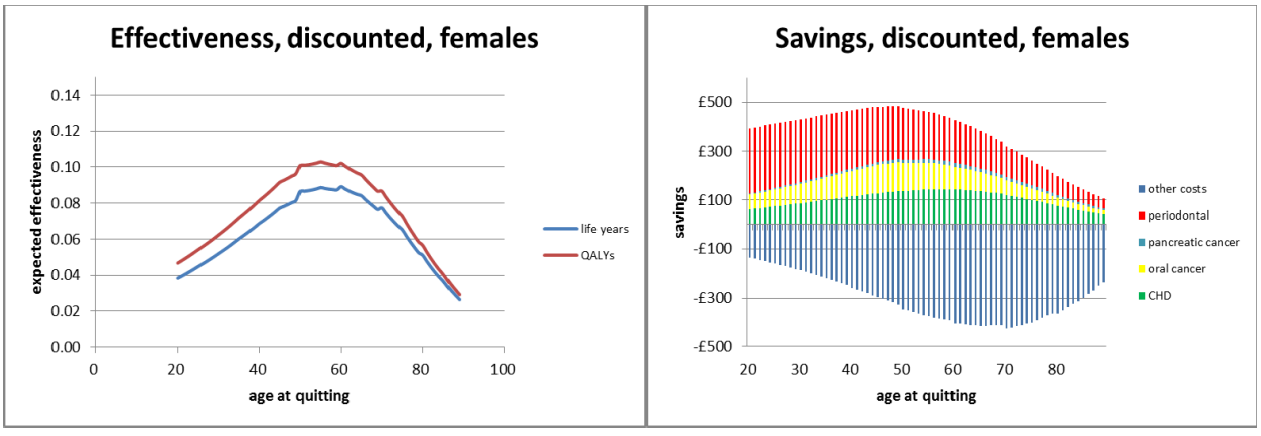

Figure 20. Expected number of QALY's gained, additional unrelated costs and related savings as a function of age. Discounted. Females

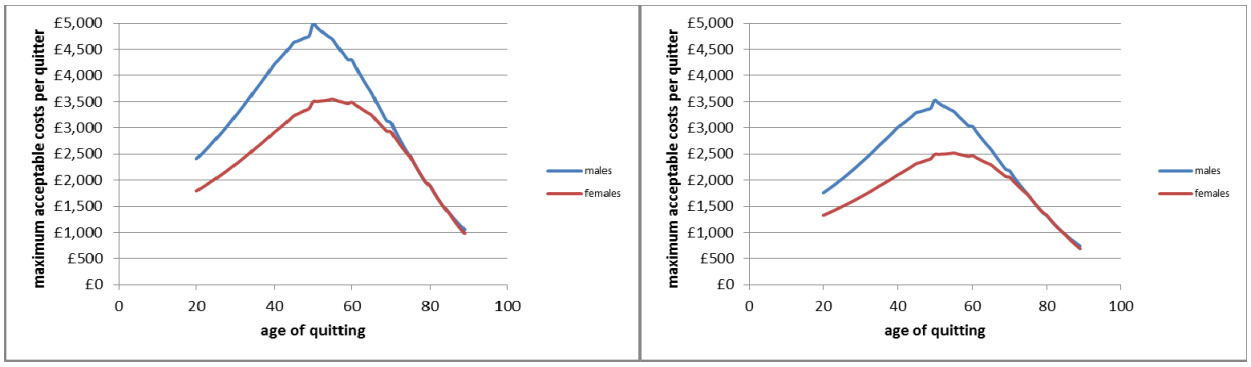

Figure 21. Maximum costs per quitter for a therapy to be called acceptable using a £30,000 (left) and £20,000 (right) per QALY threshold.

Earlier it was estimated that when using a limit for the cost effectiveness of £ 30,000 per QALY, a therapy is "cost effective" up to a cost of £ 2,915 per 40 year old quitting female. For a 40 year old male, this figure was £4,218. Figure 21presents for different ages and gender what the maximum cost per quitter may be such that therapy may still be called cost-effective. The left hand figure does this when assuming a maximum limit of £ 30,000 per QALY, the left hand figure does it assuming a maximum limit of £ 20,000 per QALY.

5.3 SENSITIVITY ANALYSIS

The results of the sensitivity analysis are presented using a 40 year old woman as a reference point which is representative for the age group in the Croucher studies.

5.3.1 EFFICACY

It is estimated that when a 40 year old female quits that she will gain 0.069 life years and that when a 40 year old man quits that he will gain 0.099 years. Table 9 presents what these estimates would have been if there would be no effect on the subsequent diseases that have been taken into account. It is found, when considering life years saved and QALY's, that the results are most sensitive to the effects on oral and pancreatic cancer. The first is due to the large effect of a 5.1 increase, the second because of the in Faust prognosis of about a year. With respect to cost savings, results are most sensitive concerning the effects on periodontal disease.

Table 9. Costa and effects disregarding the effects of smokeless tobacco

			No effect on			
		base line	CHD	oral cancer	pancreatic cancer	periodontal disease
females	life years	0.069	0.059	0.047	0.032	0.069
	QALY's	0.082	0.067	0.053	0.049	0.077
	Savings	£467	£320	£375	£481	£226
	Max acceptable cost per quitter	£2,915	£2,338	£1,957	£1,937	£2,527
males	life years	0.099	0.088	0.051	0.059	0.099
	QALY's	0.121	0.105	0.058	0.085	0.116
	Savings	£586	£412	£386	£608	£356
	Max acceptable cost per quitter	£4,218	£3,553	£2,111	£3,168	£3,848

5.3.2 COSTS

It is estimated that when a 40 year old woman who uses smokeless tobacco quits doing so, savings are expected of about £ 496 of which 51% is related to the costs of periodontal disease, 24% to the costs of cardiovascular disease, 22% to the costs of oral cancer and only 2% to the costs of pancreatic disease.

The costs of periodontal disease have been estimated as one band 3 treatment per decayed tooth. The probability of having a next tooth decayed is estimated at 26% per year and as such the costs per year after the first decayed tooth are estimated at £ 53. For a 40 year old women with a life expectancy of an additional 44 years, the average total undiscounted costs are estimated at £1,238. This is on top of normal dental care, due to periodontal disease. When it is estimated that not all decayed teeth require treatment equal to the costs of band 3 treatments, but to the costs of band 2 treatments, then the costs saving decreases from £240 to £58. The maximum cost per quitter decreases from £2,915 to £2,336.

Half of the costs of cardiovascular disease are related to subjects who have not experienced events yet. These costs are currently estimated at £1,050 which has been estimated rather high and this is to be able to reproduce the estimated total costs as estimated by the British Heart Foundation in their 2010 report (considering costs in 2006). It is speculated that the other half of the costs, those related to events and the care after events, may have been underestimated.

These estimates are mainly based on diagnosis related groups and may not account for re-hospitalisations. When, as an alternative, the costs of the early stages are multiplied by 0.5 and the cost in the later stages by 2, discounted cost savings for a 40 year old woman are estimated at £662 instead of £496 and the maximum cost per quitter increases from £2,915 to £3,110. It is noted that decreasing the early costs has hardly any effect given the assumption that smokeless tobacco affects the cardiovascular event rates, not the incidence.

The savings due to the decrease in the incidence of oral cancer are estimated at £105 per 40 year old women who quits. The underlying cost estimates were taken from the literature. In this literature, point estimates were accompanied by standard deviations as well as numbers of patients. So, standard errors around the means could be estimated assuming that all patients were followed for three years. Using the standard errors to reflect the uncertainty around each individual cost estimate and doing a partial multivariate sensitivity analysis, a standard deviation around the central estimate was estimated at £8. This estimate results after taking 1,000 random draws from all normal distribution surrounding each estimate. This means that it is possible that the one unit cost estimate underestimates the real costs and the other over-estimates the real costs. When drawing from the estimates completely dependently (using a single random number for all estimates, instead of a different random number for each estimate and implying that all unit costs are either under or over-estimated) the new estimate of the standard deviation is £17.

The savings due to the decrease in the incidence of pancreatic cancer are estimated at £10 per 40 year old women who quits. Eerlier, it was acknowledged that th estimate of the costs of pancreatic cancer were surrounded with large uncertainty. However, the results are quite insensitive to this result. A doubling of the costs would increase the estimated cost savings with just £10, increasing the expected savings from £467 to £477 and increasing the maximum cost per quitter increases from £2,915 to £2,925.

Table 10 Results univariate sensitivity analysis concerning costs

	Females		Males	
	Savings	max acceptable cost per quitter	Savings	max acceptable cost per quitter
Base line estimate	£467	-£2,915	£586	-£4,218
Cardio costs pre events *0.5 costs post events *2	£662	-£3,110	£803	-£4,435
oral cancer costs + 1*SD	£479	-£2,927	£596	-£4,228
pancreatic cancer costs * 2	£477	-£2,925	£598	-£4,230
Periodontal costs *49/204	£284	-£2,732	£412	-£4,043

5.3.3 QALY WEIGHTS

The effects of periodontal disease on quality of life are estimated at decrements of 0.00125 for all stages . When this is set at zero and the QALY gains due to periodontal disease are neglected, the total QALY gain decreases from 0.082 for a 40 year old women to 0.077. In that case the maximum acceptable cost per quitter decreases from £2,915 to £2,771. Table 11 compares these figures with what happens to the same numbers when the QALY effects on the other diseases are neglected. It is found that the disutility's which are associated with the various diseases are not the main drives behind the cost effectiveness.

Table 11 Effects of neglecting the disutility of being in a disease

			No effect on			
		base line	CHD	oral cancer	pancreatic cancer	periodontal disease
females	QALY gain	0.082	0.078	0.072	0.081	0.077
	Max acceptable cost per quitter	£2,915	£2,806	£2,640	£2,905	£2,771
males	QALY gain	0.121	0.118	0.101	0.121	0.117
	Max acceptable cost per quitter	£4,218	£4,120	£3,602	£4,207	£4,083

5.3.4 EPIDEMIOLOGY

The incidence in periodontal disease is estimated at 3.41% per year and the probability of additional decay is estimated at 0.26 per year. When doubling the incidence (but not decay after becoming incident) by using smokeless tobacco, it becomes 6.82% per year. In that case the estimated cost savings should be £440 instead of £467. One might expect an increase but this is not seen. That is because - with an annual incidence of above 6% per year - all people, users or non users, will have periodontal disease and the potential savings due to decreasing the risk gets smaller. When the incidence has been overestimated by a factor 2, the estimate of the savings decrease to £430.

The cardiovascular disease model as used here is full with estimates which have been based on a rather informal calibration process using incidence figures, event rates, case fatality rates and mortality rates, all being age and gender specific. Theoretically, when one parameter changes, other parameters also have to change and one cannot assume independence (as is usually done in multivariate sensitivity analyses). To take the dependency into account one would need to model the correlations (potentially using some covariance matrix). This requires advanced techniques which have not been applied here. Additionally, there may also be some structural uncertainty in light of the exponential growth curves in incidence, case fatality and other mortality. It is therefore that the attention with respect to the cardiovascular disease model in this sensitivity analysis is limited to the incidence. This is also the main source of uncertainty as the US and Swedish sources have been used to estimate the effects of using smokeless tobacco

on cardiovascular events. On the basis of this study, it is estimated that the use of smokeless tobacco does not affect the incidence but only the probabilities of having an event given that one has become incident. When instead estimating a 10% increase in the overall incidence of cardiovascular disease (again addressing a 40 year old women who quits the use of smokeless tobacco) , the estimate of the lifetime cardiovascular cost savings increases from £114 to £313 and the gain in QALY's from 0.121 to 0.212. For a 40 year old man cost savings increase from £112 to £636 and QALY's gained from 0.121 to 0.212. In that case, the maximum acceptable price per quitter leading to a cost effectiveness ratio of under £30,000 is £7,462. For females of 40 years, this is £5,194. It is noted that this is mainly caused by the increase in the relatively large number of individuals without cardiovascular events (with a cost per year of £1,050).

The model for oral cancer is based on a combination of population wide incidence and mortality figures, as published by the British Cancer registries, and transition-probabilities as contained in a report addressing the costs effectiveness of oral cancer screening. To be able to obtain consistent estimates it is assumed that there is rather high probability of being diagnosed in the pre-cancerous stages. When the annual probability to move from pre-cancerous to stage I is not 4% but 20%, cost savings increase from £97 to £161 and QALY's gained from 0.048 to 0.079. However this would imply that instead of estimating that 71/100,000 persons die of oral cancer (starting with 40 year old females) 1,623/100,000 do. This may, in light of the data from cancer registrations, be too high.

The average life expectancy of a 40 year old women is estimated at 43.36 years. This is based on national statistics and may not reflect the Asian focus group. When mortality for other reasons is doubled, the average life expectancy of a 40 year old women decreases to 37.75 years; QALY gains decrease to 0.036 and the maximum costs for a therapy to be cost effective at a limit of £30,000 decreases from £2,915 to £2,233.

Table 12 Results of miscellaneous univariate sensitivity analyses

	life years	QALY's	Savings	max acceptable cost per quitter	life years	QALY's	Savings	max acceptable cost per quitter
Base line	0.069	0.082	£467	£2,915	0.099	0.121	£586	£4,218
CVD incidence * 1.1	0.108	0.129	£704	£4,560	0.160	0.194	£908	£6,743
from per to stage 1 oral cancer 20% instead of 4%	0.103	0.112	£501	£3,869	0.174	0.189	£656	£6,329
panc cancer 1 year surv: 25%, 5 year surv: 10%	0.067	0.081	£483	£2,905	0.097	0.120	£604	£4,208
doubling incidence periodontal disease	0.069	0.081	£440	£2,876	0.099	0.121	£565	£4,187
doubling hazard other death	0.049	0.061	£411	£2,233	0.068	0.089	£507	£3,168
discout rate effects: 0%	0.260	0.287	£467	£9,085	0.343	0.390	£586	£12,297

Table 12 summarises some of the results from this chapter and indicates the results when a discount rate is used of 0% for effects. In that case, the costs per quitter may be extremely high and still be considered cost effective

6 DISCUSSION AND CONCLUSIONS

Firm data about the effectiveness of strategies which make individuals quit using smokeless tobacco seem to be emerging but are not in the public domain yet. Unpublished documents suggest estimates of the cost per quitter of around £623, as observed in a pilot study. This is a observational study without a control group and one may wonder how many individuals would have stopped without the intervention. Moreover, one wonders whether such results can be reproduced on a larger scale with potentially less motivated subjects. As such, the uncertainty surrounding the effectiveness goes further than just the statistical uncertainty due to the numbers of individuals in the study.

Disregarding the whole question about whether or not there is any strategy which makes people quit and what the costs of such strategy are, one may try to estimate what the long term costs and effects are given that someone stops using smokeless tobacco. The analysis as presented in this document aims to do so. It combines three disease models, for cardiovascular disease, oral cancer and periodontal disease in a single framework to estimate the cost and effects. An important outcome variable is the maximum costs per quitter that a strategy may have to still be called "cost-effective" when using a limit of £20,000 per QALY. It is found that this limit may depend on age and gender. Within the age range between 20 and 70 the maximum cost per quitter ranges between £1,758 and £3,525 for males and between £1,328 and £2,520 for females. That is when setting the maximum cost per QALY at £20,000. When this is £30,000, the ranges are £2,408-£4,991 for males and £1,795-£3,549 for females.

The estimates suggest that a strategy as in the Croucher pilot study (combining behavioural support with nicotine replacement therapy) is very likely to be cost effective. However such conclusion can only be dawn with extreme care. Lacking crucial data, it has been inevitable to make a number of heroic assumptions. For example it has been assumed that when the increased risks are removed, that this translates into immediate benefits. This may not be the reality. First, there may be lag times before the body has cleared all the risks. Second, it may be that the intervention is too late and that the damage has already been done. Both phenomena would decrease the effectiveness and would decrease the maximum amount at which a therapy that increases quitting can still be called cost effective.

One may also note that the duration of tobacco use has been neglected in this study. The longer the use, the higher the risk, the higher the potential benefits. But also, the longer the use, the higher the potential damage and the lower the potential benefits. Whether a therapy attracts short term users or long term users may well affect the balance between costs and effects but it is difficult to quantify how.

While there are reasons to suggest that the current estimates may be considered too optimistic , there are also reasons to suggest that they are too conservative. These estimates are based on US

and Swedish data, and concern types of smokeless tobacco use which may be less toxic than those used by South Asians in the UK . As such, the effect on cardiovascular disease may be underestimated and the assumption that the incidence in cardiovascular disease is not affected, only the event rates, may be "conservative". When assuming that the overall incidence is affected by 10%, much bigger savings are expected. This is mainly due to the high incidence (a 10 % increase in the size of an elephant is still a lot more that a 500% increase in a mouse) and the relatively high associated costs. And when "Asianizing" the analyses, one may want to realize that the latter may be too high. South Asians have much lower intervention rates (bypass surgery and percutaneous procedures).

Next to the uncertainty surrounding the various parameters there are concerns about the reliability of some of the registries on which the model is based or on the match between model and data. Additionally, there may be structural uncertainty, most notably concerning the various shapes of the age dependencies which have been built into the model.

Often a multivariate sensitivity analysis can be used to address such uncertainty by summarizing the results in a cost effectiveness acceptability curve. No such analysis has been carried out here. Most of the uncertainties mentioned here are difficult to quantify without additional research and expert knowledge. So, one might say that even the uncertainty is uncertain. As indicated, the data about the efficacy, often the most important variable, are only based on a non randomised pilot-study. Additionally, the model has largely been calibrated using data from different sources and there is a non quantified dependency between the estimates. The development of calibration techniques which take account of those dependencies, such that they can be included in a probabilistic sensitivity analysis, is subject of further research.

The point estimates indicate that a therapy such as offered by Tobacco Control Health Inequalities project is very cost effective, almost cost saving. It would still be cost effective with half the efficacy, either due to people who quit without therapy or due to relapse. In that case the cost per QALY of such therapy for a 40 year old female would be estimated at £9,551 per QALY. For a 40 year old male, this figure would be £5,453. Naturally, one has to weigh these figures with one's own assessments of where the base line estimates have been too optimistic or too conservative. The analyses presented here offers a starting point to guide ones assessment. The data limitations were too severe to offer anything else.

APPENDIX 1

The model starts with a simple standard life table with numbers of individuals per age class (N(a)) is used. E.g. a cohort of 1,000 women of a certain age a_0, can be summarised in the standard life table as:

$$N(0) = 1{,}000$$

$$D(a) = N(a-1) - N(a), \quad a = 1,....$$

$$d(a) = 1 - \frac{N(a)}{N(a-1)}, \quad a = 1,....$$

$$\delta(a) = -\ln(1 - d(a)), \quad a = 1,....$$

$$\Delta(a) = \sum_{age=1}^{a} \delta(a), \quad a = 1,....$$

$$N(a) = N(0).\exp(-\Delta(a)), \quad a = 1,....$$

Here (a) reflects age, measuring the difference with the age under consideration and the starting age a_0. D(a) measures the number of individuals dying during (a-1,a], d(a) the probability to die, δ(a) the all cause mortality rate during (a-1,a] and Δ(a) the cumulative all cause mortality rate at a. Estimates for all those parameters are derived from the national statistics.

The crucial link between the life table and the disease models is made by breaking down the all-cause death rate Δ(a) from the life table into a) the disease specific death rates $\Delta^j(a)$, j=1,J from the disease models and b) a rate for other causes of death $\Delta^0(a)$:

$$\Delta^0(a) = \Delta(a) - \sum_{j=1}^{J} \Delta^j(a), \quad a = 1,....$$

Here we are using three disease models, one for cardiovascular disease, one for oral cancer and one for periodontal disease.

The central parameters in each disease model j are the incidence rates $\gamma^j(a)$ during (a-1,a] and the matrix of transition probabilities $P^j(a)$ where $p^j_{ik}(a)$ measures the probability to go from state i to state k during (a-1,a]. The incidence $i^j(a)$ entering the disease model is calculated after defining the proportion of healthy individuals $h^j(a)$ as:

$$h^j(0) = 1$$

$$h^j(a) = \exp\left(\sum_{age=1}^{a} \gamma^j(age)\right), \quad a = 1,....$$

$$i^j(a) = h^j(a - 1) - h^j(a), \quad a = 1,....$$

Each disease model is a Markov model. Markov chains divide a disease process into a number of sub-states that differ with respect to costs, quality of life and survival probabilities. A typical way to characterize such a model is by:

$$\begin{bmatrix} n_1^j(a) \\ n^j(a) \\ 2 \\ . \\ . \end{bmatrix} = \begin{bmatrix} p_{1,1}^j(a) & p_{2,1}^j(a) & . & . & 0 \\ p^j(a) & p^j(a) & . & . & 0 \\ 1,2 & 2,2 & & & \\ . & . & . & . & . \\ . & . & . & . & . \end{bmatrix} \cdot \begin{bmatrix} n_1^j(a-1) \\ n^j(a-1) \\ 2 \\ . \\ . \end{bmatrix} + \begin{bmatrix} i_1^j(a) \\ i^j(a) \\ 2 \\ . \\ . \end{bmatrix}$$

$$n_N^j(a) \quad p_{1,N}^j(a) \quad p_{1,N}^j(a) \quad . \quad . \quad 1 \quad n^{N\,j}(a-1) \quad 0$$

considering N-1 health states and denoting death as the N′th health state.

More detail about the disease models is given in the next section.

The proportion dying $d^{*j}(a)$ and the corresponding death rate $\delta^j(a)$ can now be calculated by:

$$d^{*j}(a) = \frac{\sum_{i=1}^{6} p_{1,N}^j(a) \cdot n^j(a)}{\sum_{i=1}^{6} n(a)}, a = 1,..$$

$$\delta^{*j}(a) = -\ln(1 - d^{*j}(a)),\ a = 1,.....$$

Subsequently, the cumulative proportion diseased $cs^j(a)$, can be calculated as:

$$cs^j(0) = 0$$

$$cs^j(a) = cs^j(a-1).e^{\delta^{*j}(a)} + h^j(a-1).[1 - e^{-\gamma^j(a)}] - h^j(a-1).\left[\frac{\delta^{*j}(a).(1 - e^{-\gamma^j(a)}) - \gamma^j(a).(1 - e^{-\delta^{*j}(a)})}{\delta^{*j}(a) - \gamma^j(a)}\right],\ a = 1,....$$

In the right hand side of this, the first term refers to the number of patients who were already diseased at age a-1, the second term refers to those who become diseased during the interval [a-

1,a), the third term is a correction for those who become diseased during [a,a+1) and who die during the same interval. Now, the cumulative probability to die $cd^j(a)$ can be calculated as:

$$cd^{j}(0) = 0$$

$$cd^{j}(a) = cd^{j}(a-1) + cs^{j}(a-1).(1 - e^{-\delta^{*j}(a)}) + h^{j}(a-1).\left[\frac{\delta^{*j}(a).(1 - e^{-\gamma^{j}(a)}) - \gamma^{j}(a).(1 - e^{-\delta^{*j}(a)})}{\delta^{*j}(a) - \gamma^{j}(a)}\right],\ a = 1,....$$

The first term reflects the proportion that had already died before a-1; the second term reflects the proportion of the diseased that dies during [a-1,a) and the third term reflects the proportion that becomes diseased but also dies during [a-1,a).

Subsequently the cumulative death rate Δ(a), can be calculated as:

$$\Delta^{j}(0) = 0$$

$$\Delta^{j}(a) = -\ln(1 - cd^{j}(a)),\ a = 1,....$$

$$\delta^{j}(a) = \Delta^{j}(a) - \Delta^{j}(a-1),\ a = 1,....$$

The life table defines the total death rate and the disease models define the disease specific death rates (as a function of the incidence rates and the transition probabilities). Together, using the second equation, they define the death rate for other causes. By substituting the total death rate in the disease model by the sum of the death rate for other causes and the disease specific death rates, a dynamic link is created between the disease model and life table. Then, any assumption about changing incidences or changing transition probabilities will affect the total death rate in the life table taking account of all the competing risks.

And for each scenario (including the base line model) a number of epidemiologic parameters can be calculated and presented. Disease specific mortality, in probabilities $d^{j}(a)$ and real numbers $D^{j}(a)$ can be calculated per time interval [a-1,a) as:

$$d^{j}(a) = d(a).\frac{\delta^{j}(a)}{\delta(a)},\ j = 0,...J,\ a = 1,.....$$

$$D^{j}(a) = d^{j}(a).\ N_{a},\ j = 0,....J\ \ a = 1,....$$

The prevalence of each disease $pp^{j}(a)$ can now be calculated as:

$$pp^{j}(0) = 0$$

$$(1 - pp^{j}(a)) = e^{-(\gamma^{j}(a) - \delta^{j}(a))}(1 - pp^{j}(a-1)),\ a = 1,....$$

the prevalence of each disease in numbers of people as:

$$N^{j}(a) = pp^{j}(a).N(a), \quad j = 0, \ldots J, \quad a = 1,\ldots$$

and the number of patients in the various stages of each disease $N_i^j(a)$ (here, the stages corresponding with the number of years after onset of the disease) as:

$$N_i^j(a) = \frac{n_i^j(a)}{\sum_{k=1}^{K-1} n_k^j(a)} \cdot N^j(a),\ i = 1....K-1,\ a = 1.....$$

And now, given the structure of the model, and given the assumption of conditional independence, the numbers of people with more than one disease can be calculated by the simple product of the prevalence rates. This is for people with two ($N^{ij}(a)$) and three diseases ($N^{ijk}(a)$) by:

$$N^{ij}(a) = pp^j(a).\ pp^i(a).\ \left(1 - pp^j(a)\right).N(a),\quad j = 1,....J,\ i = j,....J,\ k \neq j, a = 1,....$$
$$k \neq i$$

$$N^{ijk}(a) = pp^j(a).\ pp^i(a).\ pp^k(a).N(a),\quad j = 1,... J,\ i = j,....J,\ k = i...J,\ a = 1,....$$

So, in order to run the epidemiologic part of the model only needs the following input-parameters:

- the life table estimates (D(a))
- the disease specific incidence rates ($\gamma^j(a)$)
- the matrices of transition probabilities ($p^j_{ik}(a)$)

All others parameters need to be derived following the equations presented above. It is emphasized that the probability of death, as included in the Markov-chain models, should not cover all-cause-mortality but only mortality due to the disease under consideration. As such it is only the additional mortality that needs to be included in the Markov-models. Not taking this into account will lead to double counting.

APPENDIX 2

The change in rates by age is explained for the stage "well". Within this stage an individual may get a first myocardial infarction (fatal or not),a first stroke (fatal or not) or may die of other cardiovascular causes. The probability to stay "well" is:

$$S(t) = \exp(-\lambda_{MI}(t) - \lambda_{Stroke}(t) - \lambda_{Other}(t)).$$

Now the various rates increase with a fixed percentage and:

$$S(t) = \exp\left(\lambda_{MI}(t) - \lambda_{Stroke}(t) - \lambda_{Other}(t)\right) =$$

$$\exp\left((\lambda^{S}_{MI} + \lambda^{D}_{MI})(1 + r_{MI})^{t} - (\lambda^{S}_{Stroke} + \lambda^{D}_{Stroke})(1 + r_{Stroke})^{t} - \lambda_{Other}(1 + r_{other})^{t}\right)$$

and

$$P_{MI}(t) = \frac{(\lambda^{S}_{MI} + \lambda^{D}_{MI})(1 + r_{MI})^{t}}{(\lambda^{S}_{MI} + \lambda^{D}_{MI})(1 + r_{MI})^{t} + (\lambda^{S}_{Stroke} + \lambda^{D}_{Stroke})(1 + r_{Stroke})^{t} + \lambda_{Other}(1 + r_{other})^{t}} \cdot (1 - S(t))$$

$$P_{Stroke}(t) = \frac{(\lambda^{S}_{Stroke} + \lambda^{D}_{Stroke})(1 + r_{MI})^{t}}{(\lambda^{S}_{MI} + \lambda^{D}_{MI})(1 + r_{MI})^{t} + (\lambda^{S}_{Stroke} + \lambda^{D}_{Stroke})(1 + r_{Stroke})^{t} + \lambda_{Other}(1 + r_{other})^{t}} \cdot (1 - S(t))$$

$$P_{Stroke}(t) = \frac{\lambda_{Other}(1 + r_{other})^{t}}{(\lambda^{S}_{MI} + \lambda^{D}_{MI})(1 + r_{MI})^{t} + (\lambda^{S}_{Stroke} + \lambda^{D}_{Stroke})(1 + r_{Stroke})^{t} + \lambda_{Other}(1 + r_{other})^{t}} \cdot (1 - S(t))$$

However, only the probability of having an MI is required. The probability of dying from an MI and of surviving an MI are also needed. Within this model, account has to be taken of the idea that the mix between the death and survival per event changes with age. By starting with a fixed proportion of survivors and decreasing this proportion with a fixed percentage per year the calculation of the probabilities is as follows:

$$P^{S}_{MI}(t) = \left(1 - \exp\left(\ln(1 - \frac{\lambda^{S}_{MI}}{\lambda^{S}_{MI} + \lambda^{D}_{MI}}) \cdot \frac{1}{(1 + r^{change}_{MI})^{t}}\right)\right) \cdot P_{MI}(t)$$

$$P^{D}_{MI}(t) = \exp\left(\ln(1 - \frac{\lambda^{S}_{MI}}{\lambda^{S}_{MI} + \lambda^{D}_{MI}}) \cdot \frac{1}{(1 + r^{change}_{MI})^{t}}\right) \cdot P_{MI}(t)$$

The same is done for stroke.

If an individual survives the first MI or the first stroke they may get another MI or stroke and the similar formulas apply.

After a second MI or after a second stroke, no distinction is made between subsequent events. While it may not be relevant in the transition probabilities per se, it is for the calculation of the

changes in time and therefore, it is necessary to say something about the distribution of λ^S_{MI} and λ^S_{Stroke}. If, this distribution is known, the distribution of λ^S_{MI} and λ^D_{MI}, and of λ^S_{Stroke} and λ^D_{Stroke}. is

also known. Assuming that the distribution of MI's and stokes is identical to the one for patients without any events. So define:

$$\mu = \frac{\lambda^S_{MI}}{\lambda^S_{MI} + \lambda^S_{Stroke}}$$

and

$$S(t) = \exp\left(-\left((\mu.\lambda^S + \lambda^D_{MI})(1 + r_{MI})^t - ((1-\mu).\lambda^S + \lambda^D_{Stroke})(1 + r_{Stroke})^t - \lambda_{Other}\ (1 + r_{other})^t\right)\right.$$

In that case:

$$P_{MI}(t) = \frac{(\mu.\lambda^S + \lambda^D_{MI})(1 + r_{MI})^t}{(\mu.\lambda^S + \lambda^D_{MI})(1 + r_{MI})^t + ((1-\mu).\lambda^S + \lambda^D_{Stroke})(1 + r_{Stroke})^t + \lambda_{Other}(1 + r_{other})^t}\left(1 - S(t)\right)$$

$$P_{Stroke}(t) = \frac{((1-\mu).\lambda^S + \lambda^D_{Stroke})(1 + r_{MI})^t}{(\mu.\lambda^S + \lambda^D_{MI})(1 + r_{MI})^t + ((1-\mu).\lambda^S + \lambda^D_{Stroke})(1 + r_{Stroke})^t + \lambda_{Other}(1 + r_{other})^t}\left(1 - S(t)\right)$$

and now:

$$P^S = \left(1 - \exp\left(\ln\left(1 - \frac{\mu\lambda^S}{\mu\lambda^S + \lambda^D_{MI}}\right).\frac{1}{(1 + r^{change}_{MI})^t}\right)\right).P_{MI}(t) + \left(1 - \exp\left(\ln\left(1 - \frac{(1-\mu)\lambda^S}{(1-\mu)\lambda^S + \lambda^D_{stroke}}\right).\frac{1}{(1 + r^{change}_{Stroke})^t}\right)\right).P_{Stroke}(t)$$

$$P^D_{MI}(t) = \exp\left(\ln\left(1 - \frac{\mu\lambda^S}{\mu\lambda^S + \lambda^D_{MI}}\right).\frac{1}{(1 + r^{change}_{MI})^t}\right).P_{MI}(t)$$

$$P^D_{Stroke}(t) = \exp\left(\ln\left(1 - \frac{(1-\mu)\lambda^S}{(1-\mu)\lambda^S + \lambda^D_{Stroke}}\right).\frac{1}{(1 + r^{change}_{stroke})^t}\right).P_{Stroke}(t)$$

The change in rates by age is explained for the stage "well". Within this stage an individual may get a first myocardial infarction (fatal or not),a first stroke (fatal or not) or may die of other

$= \quad -\lambda \quad -\lambda$

cardiovascular causes. The probability to stay "well" is:

$$S(t) \quad \exp(\quad _{MI}(t) \quad _{Stroke}(t) - \lambda_{Other} \quad (t)) \; .$$

+

Now the various rates increase with a fixed percentage and:

$$S(t) = \exp\left(-\lambda_{MI}(t) - \lambda_{Stroke}(t) - \lambda_{Other}(t)\right) =$$
$$\exp\left(-\left(\lambda^{S}_{MI} + \lambda^{D}_{MI}\right)(1 + r_{MI})^{t} - \left(\lambda^{S}_{Stroke} + \lambda^{D}_{Stroke}\right)(1 + r_{Stroke})^{t} - \lambda_{Other}(1 + r_{other})^{t}\right)$$

and

$$P_{MI}(t) = \frac{\left(\lambda^{S}_{MI} + \lambda^{D}_{MI}\right)(1 + r_{MI})^{t}}{\left(\lambda^{S}_{MI} + \lambda^{D}_{MI}\right)(1 + r_{MI})^{t} + \left(\lambda^{S}_{Stroke} + \lambda^{D}_{Stroke}\right)(1 + r_{Stroke})^{t} + \lambda_{Other}(1 + r_{other})^{t}} \cdot \left(1 - S(t)\right)$$

$$P_{Stroke}(t) = \frac{\left(\lambda^{S}_{Stroke} + \lambda^{D}_{Stroke}\right)(1 + r_{MI})^{t}}{\left(\lambda^{S}_{MI} + \lambda^{D}_{MI}\right)(1 + r_{MI})^{t} + \left(\lambda^{S}_{Stroke} + \lambda^{D}_{Stroke}\right)(1 + r_{Stroke})^{t} + \lambda_{Other}(1 + r_{other})^{t}} \cdot \left(1 - S(t)\right)$$

$$P_{Stroke}(t) = \frac{\lambda_{Other}(1 + r_{other})^{t}}{\left(\lambda^{S}_{MI} + \lambda^{D}_{MI}\right)(1 + r_{MI})^{t} + \left(\lambda^{S}_{Stroke} + \lambda^{D}_{Stroke}\right)(1 + r_{Stroke})^{t} + \lambda_{Other}(1 + r_{other})^{t}} \cdot \left(1 - S(t)\right)$$

However, only the probability of having an MI is required. The probability of dying from an MI and of surviving an MI are also needed. Within this model, account has to be taken of the idea that the mix between the death and survival per event changes with age. By starting with a fixed proportion of survivors and decreasing this proportion with a fixed percentage per year the calculation of the probabilities is as follows:

$$P^{S}_{MI}(t) = \left(1 - \exp\left(\ln\left(1 - \frac{\lambda^{S}_{MI}}{\lambda^{S}_{MI} + \lambda^{D}_{MI}}\right) \cdot \frac{1}{\left(1 + r^{change}_{MI}\right)^{t}}\right)\right) \cdot P_{MI}(t)$$

$$P^{D}_{MI}(t) = \exp\left(\ln\left(1 - \frac{\lambda^{S}_{MI}}{\lambda^{S}_{MI} + \lambda^{D}_{MI}}\right) \cdot \frac{1}{\left(1 + r^{change}_{MI}\right)^{t}}\right) \cdot P_{MI}(t)$$

The same is done for stroke.

If an individual survives the first MI or the first stroke they may get another MI or stroke and the similar formulas apply.

After a second MI or after a second stroke, no distinction is made between subsequent events. While it may not be relevant in the transition probabilities per se, it is for the calculation of the changes in time and therefore, it is necessary to say something about the distribution of λ^{S}_{MI} and λ^{S}_{Stroke}. If, this distribution is known, the distribution of λ^{S}_{MI} and λ^{D}_{MI}, and of λ^{S}_{Stroke} and λ^{D}_{Stroke}. is also known. Assuming that the distribution of MI's and stokes is identical to the one for patients

without any events. So define:

$$\mu = \frac{\lambda^{S}_{MI}}{\lambda^{S}_{MI} + \lambda^{S}_{Stroke}}$$

and

$$S(t) = \exp\left(-\left(\frac{(\mu.\lambda^S + \lambda^D_{MI})(1+r_{MI})^t}{\ln(2)} + \frac{((1-\mu).\lambda^S + \lambda^D_{Stroke})(1+r_{Stroke})^t}{\ln(2)} + \frac{\lambda_{Other}(1+r_{other})^t}{\ln(2)}\right)\right)$$

In that case:

$$P_{MI}(t) = \frac{(\mu.\lambda^S + \lambda^D_{MI})(1+r_{MI})^t}{(\mu.\lambda^S + \lambda^D_{MI})(1+r_{MI})^t + ((1-\mu).\lambda^S + \lambda^D_{Stroke})(1+r_{Stroke})^t + \lambda_{Other}(1+r_{other})^t}\left(1 - S(t)\right)$$

$$P_{Stroke}(t) = \frac{((1-\mu).\lambda^S + \lambda^D_{Stroke})(1+r_{MI})^t}{(\mu.\lambda^S + \lambda^D_{MI})(1+r_{MI})^t + ((1-\mu).\lambda^S + \lambda^D_{Stroke})(1+r_{Stroke})^t + \lambda_{Other}(1+r_{other})^t}\left(1 - S(t)\right)$$

and now:

$$P^S = \left(1 - \exp\left(\ln(1 - \frac{\mu\lambda^S}{\mu\lambda^S + \lambda^D_{MI}}).\frac{1}{(1+r^{change}_{MI})^t}\right)\right).P_{MI}(t) + \left(1 - \exp\left(\ln(1 - \frac{(1-\mu)\lambda^S}{(1-\mu)\lambda^S + \lambda^D_{stroke}}).\frac{1}{(1+r^{change}_{Stroke})^t}\right)\right).P_{Stroke}(t)$$

$$P^D_{MI}(t) = \exp\left(\ln(1 - \frac{\mu\lambda^S}{\mu\lambda^S + \lambda^D_{MI}}).\frac{1}{(1+r^{change}_{MI})^t}\right).P_{MI}(t)$$

$$P^D_{Stroke}(t) = \exp\left(\ln(1 - \frac{(1-\mu)\lambda^S}{(1-\mu)\lambda^S + \lambda^D_{Stroke}}).\frac{1}{(1+r^{change}_{stroke})^t}\right).P_{Stroke}(t)$$

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