# Costs and benefits of increasing physical activity to prevent the onset of dementia: a modelling analysis

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# 1. Introduction

Many middle-aged people have one or more risk factors for chronic diseases, such as smoking, high blood pressure, raised lipid levels, a low level of physical activity and obesity. Chronic diseases are associated with substantial disability and frailty (Hoeymans et al., 2012; Majer et al., 2011; Melzer et al., 1999; Spiers et al., 2005). Preventive interventions targeted at middle-aged people such as smoking cessation in programs and interventions aimed at increasing physical activity result in health gains through the prevention of chronic diseases and therefore increase life expectancy and delay the onset of disability later in life (NICE, 2013). Data about the effects and costs of preventive interventions are needed to determine which interventions targeted at changing lifestyle behaviours are most effective and cost-effective. This information is valuable for professionals within the public health sector and beyond, both at national and local levels for evidence-based guideline development and recommendations for daily practice (NICE, 2013).

As most lifestyle interventions targeted at middle-aged people result in the prevention of chronic diseases in later life, a model is needed to translate the short-term effectiveness of the interventions into the reduction in chronic diseases over a longer time period (Buxton et al., 1997). Furthermore, a model may be necessary to calculate quality-adjusted life years (QALYs) based on intermediate outcomes as well as the long term impact on the demand for health care and social care.

Health care programs that increase life expectancy of patients may create additional consumption of medical goods and services in so-called 'added life-years'. Added years are those years that would not have been lived without the intervention. While part of this medical consumption in added years is directly related to the intervention, other costs in added years are not directly related to the interventions and are termed costs of 'unrelated medical care'. The distinction between related and unrelated future medical costs is less clear in the area of prevention than of cure, as interventions are often targeted at the general population instead of diseased populations. Moreover, as preventive interventions usually influence a variety of diseases the distinction between related and unrelated becomes even more arbitrary. Although it has been shown that ignoring costs of unrelated diseases is in conflict with the decision rules of cost effectiveness (Feenstra et al., 2008; Lee, 2008; Meltzer, 1997; Meltzer, 2008; van Baal et al., submitted), in practice, in the evaluation of public health program costs of diseases that are known to be causally related to the risk factor are included while costs of other diseases are ignored (Anokye et al., 2014; Bolin et al., 2009; Taylor et al., 2011; Trueman et al., 2010).

The general objective of the current study is to perform a model-based analysis to estimate the costs and benefits of interventions for middle-aged people to prevent or delay the onset of disability, frailty and dementia in later life. In these analyses we will investigate the influence of including future medical costs on the outcomes. In the first PHAC meetings, it was decided that in order to answer these rather broad questions the focus would be on physical activity and dementia. Therefore, the more specific objective of the study is to estimate the costs and benefits of interventions aimed at increasing physical activity in the prevention of dementia in later life.

This report is structured in the following manner. Chapter two provides an introduction to the field of dementia and gives an overview of the currently available models in the field of dementia and physical activity. Chapter three describes the model structure, the model input parameters and the data sources and methods used to estimate the model parameters. Chapter four presents the model predictions in terms of life expectancy, quality-adjusted life expectancy and costs in several scenarios. In chapter five, results of the cost-effectiveness of interventions that promote physical activity are presented. In chapter 6 we will present the results of several sensitivity analyses with the aim of exploring the robustness of our findings in chapters 4 and 5. Chapter seven describes the conclusion and recommendations for further research.

# 2. Literature review

## 2.1 Dementia

Dementia is caused by permanent damage or death of brain cells and is characterized by symptoms, such as the loss of memory, language, orientation, thinking, learning capacity and judgement. In addition, dementia is often accompanied by impairments in social behaviour and emotional control. Several diseases cause dementia. Alzheimer's disease is the major cause of dementia and is estimated to account for about 60% of dementia cases. Vascular dementia associated with stroke is the second major cause (Luengo-Fernandez et al., 2010; WHO, 2012). Because the onset of dementia is gradual, the early stage of the disease, associated with symptoms such as short-term memory loss or difficulty with communication, is often overlooked and related to older age. In the middle stage, symptoms worsen and limitations become more apparent, increasing the need for support. The final stage of the disease is associated with serious memory disturbances, resulting in nearly total dependence. As a result, dementia is one the major causes of disability in older people worldwide. No treatment is available to cure dementia. Therefore current drug treatments and non-drug interventions mainly focus on the reduction of symptoms. The three available cholinesterase inhibitors donepezil, galantamine and rivastigmine are found to be associated with a delay in disease progression up to about 3 months, but without any proven associated change in life expectancy (NICE, 2011).

The social and economic burden of dementia for society is high. Worldwide, there are more than 35 million people with dementia and each year 7.7 million new cases are diagnosed (WHO, 2012). Due to ageing, the number of people with dementia is projected to increase to 65.7 million in 2030 (WHO, 2012). In the UK, the number of people with dementia is estimated to be 820,000 and annually 163,000 new cases occur in England and Wales (Luengo-Fernandez et al., 2010). The total number of deaths annually attributable to dementia is estimated to be over 59,000 (Dementia UK, 2007). Projections of the future number of people with dementia predict an increase from 680,000 cases in 2005 to 940,000 cases in 2021 and 1,735,000 in 2051 (Dementia UK, 2007). Total societal costs for dementia in the UK in 2010 were estimated to be £23 billion, comprising £1.2 billion for health care costs, £9.1 billion for long-term care and £12.4 billion for unpaid carers and productivity losses (Luengo-Fernandez et al., 2010).

There are many risk factors that increase the risk of developing dementia. The most important risk factor is age. Other non-modifiable risk factors are gender, ethnicity and genetic factors. The most important modifiable or life style risk factors are high alcohol intake, cognitive inactivity, depression, diabetes mellitus, hyperlipidemia, obesity, physical inactivity, smoking and social isolation (Barnes et al., 2011; Chen et al., 2009; Daviglus et al., 2011; Flicker, 2010; Weih et al., 2007). Most of the associations found, however, are based on cohort studies, while evidence based on intervention studies is still limited or completely lacking, depending on the risk factor.

## 2.2 Overview of current dementia models

Several studies used a model to project future prevalence of either dementia or Alzheimer's disease over time (Dementia UK, 2007; Hebert et al., 2013; Jacqmin-Gadda et al., 2013; Jorm et al., 2005; Tobias et al., 2008). Some studies quantify the impact of hypothetical measures on the future burden of dementia (Brookmeyer et al., 1998; Jacqmin-Gadda et al., 2013; Jagger et al., 2009; Jorm

et al., 2005; Tobias et al., 2008), but these measures were mainly defined as in general terms; an x% reduction in incidence or mortality risk would result in y% fewer prevalent cases in year z or onset of dementia delayed by x years would result in y% fewer prevalent cases in year z. Jacqmin-Gadda et al evaluated the impact of public health interventions on the future dementia cases in France (Jacqmin-Gadda et al., 2013). Interventions were defined as a change in risk factor prevalence, change in hazard ratio for incidence, change in hazard ratio from no dementia to death or from dementia to death, change in high blood pressure or treatment targeting people with the APOE4 gene. Between 2010 and 2030 the total number dementia cases was projected to increase by about 75%. Reducing high blood pressure prevalence in the whole population would have a modest impact on the number of dementia cases, while treatment of people with the APOE4 gene, if feasible, would decrease prevalence by about 15-25% (Jacqmin-Gadda et al., 2013). A study of Jagger et al explored the impact of reduced dementia incidence, improved survival with dementia and reduced disability with dementia on the number of people with disability in the UK in 2026 (Jagger et al., 2009). Results showed that due to ageing, the number of people with disability would increase by 82%, while the number of people with cognitive impairment would increase by almost 50% (Jagger et al., 2009). Tobias et al projected the dementia prevalence in New Zealand to increase approximately 2.5 fold between 2006 and 2032 (from 28,000 to 70,000 cases). A reduction of incidence rates by 25% in combination with a reduction in disease progression rates by 25% could reduce this growth by up to 50% (Tobias et al., 2008). A study of Jorm et al showed that prevalence of dementia in Australia was projected to increase from 172,000 in 2000 to 588,000 in 2050. Delaying the onset of dementia by 5 years would decrease the prevalence in 2050 by 44% (Jorm et al., 2005).

Only three modelling studies have looked at the association between physical activity and the risk for developing dementia. A study of Zang et al investigated the cost-effectiveness of an intervention program reducing the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) risk score (Zhang et al., 2011). This risk score was based on seven risk factors including physical activity level. Assuming that the intervention would reduce the risk score for dementia incidence from 8-9 points (base case) to 0-5 points would result in the intervention program being dominant, resulting in more QALYs and lower costs (Zhang et al., 2011).

The other two studies estimated the impact of modifiable risk factors on the current or future prevalence of dementia. Barnes et al performed a review to summarize the evidence regarding seven potentially modifiable risk factors for Alzheimer's disease (Barnes et al., 2011). By calculating population attributable risks (PARs) the effect of risk factor reduction of 10% and 25% on the current worldwide prevalence of Alzheimer's disease and the prevalence in the USA was investigated. Worldwide about 13% of the cases of Alzheimer's disease were potentially attributable to physical inactivity making it the third largest contributor after smoking and a low education level. In the USA, physical inactivity was estimated to be the most important cause of preventable Alzheimer's disease (21%) (Barnes et al., 2011).

Nepal and colleagues (2010) evaluated the potential impact of interventions on the projections of dementia prevalence in Australia for the period 2006 to 2051 (Nepal et al., 2010). The impact of the interventions was modelled via a decrease in gender, age and risk-factor specific prevalence rates. Results showed that an increase of physical activity among inactive persons of 1% annually would reduce the dementia prevalence in 2051 by 11%, which was a larger reduction than assuming the same proportionate reduction in smoking (2%) or obesity (6%) (Nepal et al., 2010).

## 2.3 Overview of current physical activity models

At least four models have been published that have been used to model the long-term cost-effectiveness of physical activity interventions (Cobiac et al., 2009; NICE, 2006; Over et al., 2012; Roux et al., 2008). In all four models, the impact of physical activity on the incidence of four or five physical activity-related diseases was modelled: ischaemic heart disease/coronary heart disease, stroke, type 2 diabetes, colon cancer and/or breast cancer. Furthermore, in all models, physical activity was modelled in classes, for example two classes, active and sedentary, or four classes, very active, meets guidelines, irregularly active and inactive. Roux et al (2008) modelled the cost-effectiveness of seven public health interventions to promote physical activity in the US. This lifetime analysis from a societal perspective showed that all interventions were cost-effective (Roux et al., 2008). Another study investigated the cost impacts and health outcomes of six physical activity interventions over the lifetime of the Australian population. Results varied from cost saving (mass media campaigns) to AUS$79,000/DALY for GP referral to an exercise physiologist (Cobiac et al., 2009). A UK study determined the cost effectiveness of two types of interventions increasing physical activity levels: brief interventions in primary care and exercise referral. All interventions were found to be more effective and cost saving compared to usual care (NICE, 2006). The fourth model of Over et al (2012) estimated the cost-effectiveness of counselling in combination with pedometer use in increasing physical activity. Targeting this intervention to one million insufficiently active adults who visit their general practitioner in the Netherlands was found to be cost-effective, although health benefits were relatively small (Over et al., 2012).

## 2.4 Conclusions of the literature review

Although several dementia models have been published that evaluate the impact of preventive measures, most of these models use the change in future prevalence of dementia as the main outcome measure. To our knowledge, only one study has evaluated the cost-effectiveness of a preventive intervention defined as a reduction in a multi-component risk score for the incidence of dementia. With regard to the physical activity models, none of the models found included the impact of physical activity on the incidence of dementia. Because none of the studies has explicitly modelled the cost-effectiveness of physical activity interventions in the prevention of dementia up to now, the current model will be the first to model this association. In addition, the new model takes into account that physical activity has important effects on health through channels other than dementia.

# 3. The model

## 3.1 Model structure

Figure 3.1 displays the basic structure of the model employed in this study. The level of physical activity determines (besides age and gender) the risk of developing dementia. Having dementia influences quality of life, health care and social care use and mortality risk.

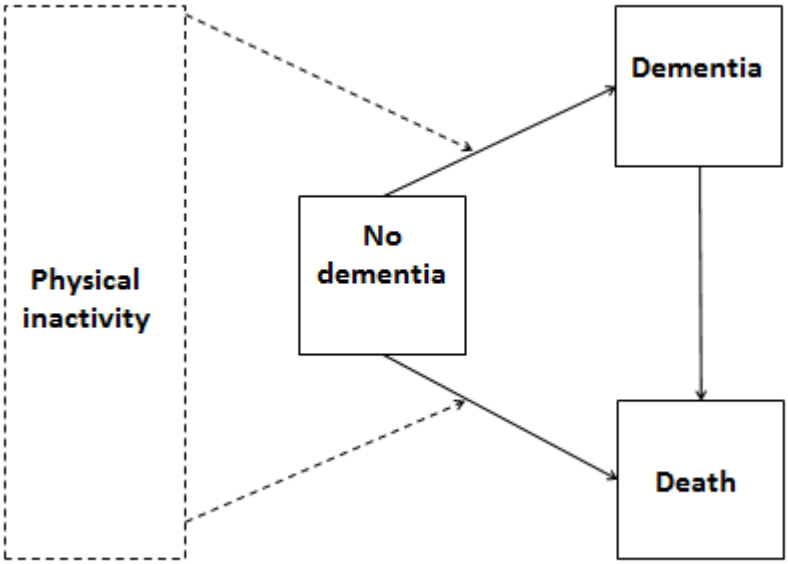


***Figure 3.1:*** *Model structure*

Physical activity has been modelled to have an impact on the incidence of dementia and indirectly on mortality, because dementia influences mortality. In addition, physical activity may also influence mortality directly. The intervention is modelled to affect physical activity which in turn influences mortality/quality of life/health care and social care consumption directly as well as indirectly through the effect on dementia. This model structure has been successfully used before with the RIVM Chronic Disease Model (Hoogenveen et al., 2008; Hoogenveen et al., 2010; van Baal et al., 2006) in the Dutch context as well as the DYNAMO-HIA model which contained data from several EU countries including the United Kingdom (Boshuizen et al., 2012). This is depicted in Figure 3.2.

***Figure 3.2*** *causal chain from physical activity to health outcomes*

The model is a Markov-type model in which we subdivided the population of the model into different groups (called states) and modelled the changes over time in the size of these groups by

allowing transitions between these states. States in the model are defined by age, gender, level of physical activity and disease status. To define physical activity classes we used the same classification as the most recently published English Health Survey from 2012 (Bridges et al., 2013). In that report physical activity was classified into the following four classes (see page 9 for a definition of these classes):

1. Meets recommendations;
2. Somewhat active;
3. Low activity;
4. Inactive.

Disease status is simply modelled by having dementia or not. So within each physical activity class there is a group with dementia and a group without dementia. Furthermore, there is the absorbing state: death. The cycle length of the model is one year, which means that transitions between states occur on an annual basis. The model has the facility to vary the time horizon from one year to lifetime, but in this paper only a lifetime horizon was used.

The starting population of the model is the population in England in 2012 specified by age, gender, physical activity level and disease status. The model then simulates the changes in the population over time due to changes in physical activity level, incidence of dementia and mortality. Output of the model consists of the distribution of the population over the different model states by age and gender over time. These estimates can then be multiplied by quality of life and cost values which are also stratified by age, gender, disease status and level of physical activity.

## 3.2 Modelling the effect of interventions

The target population of the intervention is the group of middle-aged, physically inactive people in England. To quantify the impact of interventions for this group we ran the model in two scenarios and compared the outcomes of these two scenarios. In the current practice scenario the model was run for the group of inactive people assuming that they remained inactive till they died. In the intervention scenario we assumed that part of this inactive group became active as result of the intervention. In this scenario the model was run assuming that part of the inactive people had become active. For example, if the number of middle-aged people inactive people in England is 50,000, the current practice scenario was run assuming that these 50,000 people remained inactive the rest of their life. If, due to an intervention, 20% of these inactive people became active, the intervention scenario was run assuming 40,000 people to be inactive and 10,000 people to be active. An increase in the number of active people results in a lower new incidence of dementia, lower mortality (directly and indirectly), a gain in quality of life and a reduction in dementia-related costs compared to the current practice scenario. The model can be run assuming a continuing effect of the intervention over time, i.e. people will remain active for the rest of their life, but the model can also take into account annual relapse from the active to the inactive state, which was carried out as a sensitivity analysis.

## 3.3 Data sources

This paragraph describes the data sources used to estimate all model input parameters.

*Population numbers and mortality rates*

Population numbers and mortality rates for England specified by age and gender were obtained from the UK Office for National Statistics. Population numbers were defined as the mid 2012

population numbers for England (ONS, 2013b). Mortality rates were defined as death rates per 1000 in the population for England (ONS, 2013a).

*Physical activity distribution*

The distribution of the physical activity level of the population of England was obtained from the Health Survey for England (HSE) in 2012 (Bridges et al., 2013). The HSE reported on adults' physical activity in the four weeks prior to interview by examining overall participation in activities in terms of type, frequency, duration and intensity of activity. Levels of self-reported activity were expressed in accordance with the recommendations in the UK guidelines for aerobic activity introduced in 2011: meets aerobic guidelines, some activity, low activity and inactive. 'Meeting aerobic guidelines' was defined as at least 150 minutes of moderately intensive physical activity (MPA) or 75 minutes vigorous activity (VPA) per week or an equivalent combination of these. 'Some activity' was defined as 60-149 minutes of MPA or 30-74 minutes of VPA per week. 'Low activity' was defined as 30-59 minutes of MPA or 15-29 minutes of VPA per week, while 'inactive' was defined as less than 30 minutes of MPA or less than 15 minutes of VPA per week. For the current project we used the distribution of over the four physical activity classes specified by age and gender.

*Association physical activity and all-cause mortality and dementia*

Relative risks for the different physical activity classes in relation to all-cause mortality were obtained from a meta-analysis of Samitz et al (Samitz et al., 2011). This study presented results for RR's of the highest physical activity level compared to the lowest level as well as RR's for a dose-response analysis. We used the adjusted RR for all-cause mortality per increment of 1 hour of physical activity per week for the domain leisure-time physical activity in our model, i.e. 0.94 (95% CI: 0.92-0.97). Based on the definition of the physical activity classes the number of hours of physical activity per week was estimated (Bridges et al., 2013). Compared to the inactive group, the number of hours of physical activity was estimated to be about 0.5 hours higher in the low activity group, 1.5 hours higher for the some activity group and 2.5 hours higher for the group that meets recommendations. The resulting RR's for each group physical activity group are shown in Table 1. Relative risks for physical activity classes in relation to dementia were based on a meta-analysis of Sofi et al (Sofi et al., 2011). In this study the risk ratio for the onset of cognitive decline was 0.62 (95%: 0.54-0.70) for subjects with high levels of physical activity compared to subjects being sedentary. For low-to moderate levels of activity the risk ratio was found to be 0.65 (95% CI: 0.57-0.75) compared to the sedentary group. In the model the risk ratio for high levels of physical activity was applied to the group that meets recommendations, while the risk ratio for low-to-moderate levels of activity was applied to the groups with low and some activity (Table 3.1).

***Table 3.1:*** *relative risks*

| | Inactive | Low activity | Some activity | Meets recommendations |
|---|---|---|---|---|
| RR all-cause mortality | 1 | 0.97 (0.96-0.98) | 0.91 (0.88-0.96) | 0.86 (0.81-0.93) |
| RR onset of dementia | 1 | 0.65 (0.57-0.75) | 0.65 (0.57-0.75) | 0.62 (0.54-0.70) |

*Incidence of dementia*

The incidence of dementia in England was obtained from the first Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) performed between 1990 and 1996 (Matthews et al., 2005). The MRC CFAS is a population-based study of individuals aged 65 years and over, performed at five different sites in England and Wales. A more recent study on the incidence of dementia in England based on primary care registrations (Rait et al., 2010) was judged less representative, as the incidence of dementia is usually underestimated in primary care.

*Prevalence of dementia*

The prevalence of dementia in England was obtained from the second MRC CFAS study performed between 2008 and 2011 (Matthews et al., 2013).

*Excess mortality*

Excess mortality rates as a result of having dementia were based on the study by Rait et al. who looked at survival after incidence of dementia in primary care (Rait et al., 2010). In that study it was found that mortality in the first year after diagnosis of dementia was higher than in other years. A likely explanation for this finding is that in primary care a diagnosis of dementia is more often made at a time of crisis. Therefore, we used the relative mortality risk of persons with dementia compared to persons without dementia one year after diagnosis. The values thereof centered around 2.5 which is in line with relative risk estimates from the Eurodem study which included data from the CFAS study (the Eurodem study found a value of 2.38)(Dementia UK, 2007). The big advantage of using the estimates from Rait et al. is that the confidence intervals surrounding the central estimate are much smaller due to the bigger sample size (Rait et al., 2010).

*Quality of life*

Health-related quality of life for persons without dementia was obtained from a study of Heijink et al. who reported the quality of life, i.e. EQ-5D, of the general population in the UK specified by gender and age (Heijink et al., 2011).

To make quality of life values dependent on physical activity level, a study of Anokye et al was used (Anokye et al., 2012). This study used data of the National Survey in England to estimate the relationship between subjective and objective measures of physical activity and the EQ-5D. Physically active people were found to have 0.047 (95% CI: 0.022-0.072) higher quality of life values compared to inactive people (Anokye et al., 2012).

Health-related quality of life for people with dementia was based on a UK study of Sheehan et al. in patients with dementia admitted in general hospital (Sheehan et al., 2012). Quality of life in this study was measured using the EQ-5D, which was completed by both the patient and a proxy of the patient. Several studies showed that patients with dementia value their quality of life higher than their proxies (Coucill et al., 2001; Jonsson et al., 2006; Naglie et al., 2006; Vogel et al., 2006). Because of the problems people with dementia have with cognitive function and their ability to make judgments, quality of life valued by patients themselves seems less valid (Hounsome et al., 2011). Therefore we used the utility value of the proxies in the study of Sheehan, 0.30 (95% 0.22-0.38) in the model (Sheehan et al., 2012). In sensitivity analyses (see Chapter 6) we will use patient values.

*Costs*

Costs in our model were derived from two studies. One study focused on patterns of social care and hospital care use at the end of life for different conditions (Georghiou et al., 2012) and the other study focused on health care spending patterns by age and disease for a broader set of health care providers (Kasteridis et al., 2014).

The study by Georghiou et al. linked several data sources coming from seven different local authority areas across England, comprising a total population of more than three million people (Georghiou et al., 2012). Using this data, the authors created a data set of more than 70,000 individuals which allowed them to estimate costs of health and social care services for people in the last 12 months of life. They found that there were significant differences in the use of social care at the end life between diseases and that usage levels were highest in people with dementia, falls and cerebrovascular disease.

The study by Kasteridis used data from the Symphony Project, an anonymised individual-level dataset, spanning primary, community, acute, mental health and social care (Kasteridis et al., 2014). The data set includes costs, clinical conditions, age, sex and ward of residence for the entire population of 114,874 people in 2012 from South Somerset. The study found that the average annual cost of a person with dementia is around £12,000 and that age and gender do not explain variation in costs for people with dementia. A high proportion of the costs are related to the provision of mental health, social and continuing care. South Somerset is an area that might not be representative of England (Kasteridis et al., 2014). To correct for this we used information from the 2011-12 PCT (Primary Care Trust) revenue allocations exposition book available from the Department of Health which showed that spending per head in Somerset is about 5% lower than average spending per head in England (Department of Health, 2011).

There were no studies using UK data relating PA to health care use. To model the influence of PA on health care expenditures (HCE) through diseases other than dementia we related health care expenditures to mortality risk. Empirical research has shown that most HCE is centered in the last phase of life: the closer persons are to death the more health care on average they consume per unit of time. By making a distinction between HCE in the last year of life and other years it is possible to proxy the effect that diseases have on the demand for health (de Meijer et al., 2011; Gandjour et al., 2005; van Baal et al., 2011a; van Baal et al., 2011b). As persons who are less active have a higher mortality risk they have on average higher HCE than persons who are more active independently of whether they have dementia or not.

All costs were expressed in year 2012 prices.

## 3.4 From data to input parameters

The model requires input for all possible states (e.g. the incidence of dementia among inactive people and the mortality risk for inactive persons with dementia). However, as can be seen from the data sources we only have data stratified either by risk factor or by disease but not stratified by both risk factor and disease (e.g. we have data on the incidence of dementia in the UK population

stratified by age and gender but not specified by physical activity). Here, it is described how we calculated model parameters from the data.

### 3.4.1 Notation

Let *P* denote the probability to be in a certain state *r,* an indicator variable for risk status running from 1 to 4 (1 = meets recommendations; 2= some activity; 3= low activity; 4=inactive), *d* an indicator variable for having dementia (*d* = 1) or not (*d*=0). Then $P(r = 4, d = 1)$ is the probability of being inactive and having dementia. The probability of being in state 'dead' is denoted by $P(dead)$. Note that all these probabilities can be further stratified by age and gender, but that for notational simplicity we will suppress age and gender indices.

The model is defined in continuous time, so we will define model parameters in terms of transition rates instead of transition probabilities (transition rate matrices are converted to transition probability matrices by calculating matrix exponentials). By defining the model in continuous time we can assume that only one transition can occur per infinitesimal time step (e.g. a person who is active without dementia cannot become demented and inactive in an infinitesimal time step). However, as the model uses time steps of one year, multiple transitions can occur within a year (e.g. a person can become inactive, get dementia and die within one year). Let *i(r)* denote the incidence rate of getting dementia for risk factor class *r* (the transition from $P(r, d = 0)$to $P(r, d = 1)$ and *m(r,d)* denote the mortality rate for risk factor class *r* and disease class *d* (the transition from $P(r, d)$to $P(dead)$. Transitions between risk factor classes are denoted $t(r_1, r_2, d)$ where $t(r_1=3, r_2=4, d)$ denotes the transition rate from low active to inactive. Note that values of $t(r_1, r_2, d)$ are assumed to equal zero in the current practice scenario but may have non-zero values in the intervention scenario. We denote by *p* the probability of being in a certain state conditional on being alive. Quality of life is denoted by *q* and QALYs are denoted by *Q. c* denotes annual costs for a given state while *C* denotes total costs in a given year. *y* is an indicator value which takes on value 1 (indicating the last year of life) or 0 (other years of life). *t* is an index variable denoting years. Throughout this report age and gender indices are suppressed for notational simplicity.

### 3.4.2 Incidence rates

As we only have data from CFAS I on the incidence of dementia (Matthews et al., 2005) specified by age and gender but not stratified by physical activity status, we had to back-calculate incidence rates stratified by physical activity status $i(r)$. We did this by using relative risks of disease incidence and the prevalence of physical activity:

$$i(r) = \frac{RR(r,i)}{\sum_j RR(r=j,i) \times p(r=j)} \times i \qquad (1)$$

where $RR(r, i)$ is the relative risk on the incidence of dementia (see Table3.1) and *i* the incidence rate. The assumption behind equation (1) simply is that *i* is the weighted average of the incidence of the different physical activity classes. *i* was estimated using a Poisson regression model as a function of age and gender and the number of person-years as offset. The prevalence of physical activity in the population, *p(r),* was estimated using a multinomial regression model using polynomials of age and gender (and interaction terms between age and gender).

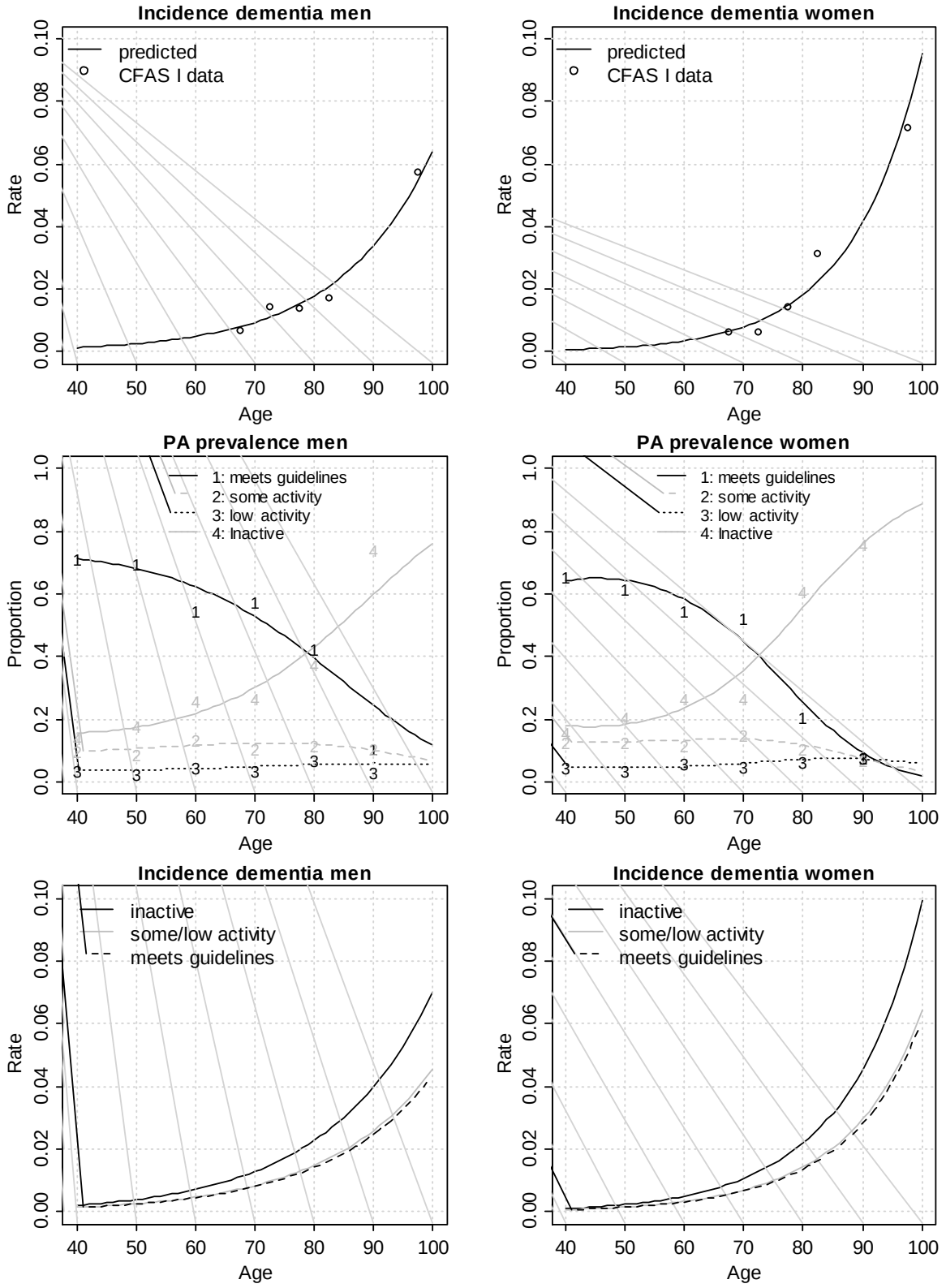


***Figure 3.3*** *Upper two panels: estimated incidence of dementia in the UK population (dots indicate data points from CFAS I). Middle two panels: physical activity (PA) prevalence by age and gender (numbers indicate data points from the Health survey England 2012 and the lines indicate predictions derived from a regression model. Lower two panels: back-calculated incidence of dementia for different PA classes.*

Figure 3.3 displays estimates of incidence in the general population based on CFAS I (upper two panels), the estimated prevalence of physical activity (middle two panels) and the back-calculated incidence for the physical activity classes. From 3.3 it can be seen that incidence in the UK increases with age and, beyond the age of 80, is higher for women. The prevalence of inactivity generally increases with age while the percentage that meets recommendations for PA decreases with age. The lower two panels indicate the back-calculated incidence for the different physical activity classes. As the relative risks on the onset of dementia are equal for the classes with low activity and some activity the incidence rate is the same for these two classes. Note that the combination of the incidence rates for the different PA classes and the prevalence of PA implies that about 20% of all cases of dementia are caused by insufficient physical activity which is in line with the study by Barnes et al (Barnes et al., 2011).

### 3.4.3 Mortality rates

To estimate mortality rates stratified by risk factor and disease status *m(r,d)* we proceeded in several steps. First, we estimated mortality rates by disease status denoted *m(d)*:

$$m(d) = \frac{RR(d,m)}{\sum_j RR(d=j,m) \times p(d=j)} \times m \qquad (2)$$

where $RR(d,m)$ is the relative risk on mortality for the different disease states (dementia or not) from the Rait study, and *m* the mortality in the overall population not stratified by risk factor class. The prevalence of dementia in the population, *p(d),* was estimated using logistic regression as a function of age and gender using data from CFAS II (Matthews et al., 2013). A crucial assumption for deriving mortality rates for all states stratified by both physical activity and disease status is that the excess mortality of dementia (denoted *em*) is the same for all risk factor classes:

$$em = m(r, d = 1) - m(r, d = 0) = m(d = 1) - m(d = 0) \qquad (3)$$

Mortality rates for persons without dementia stratified by risk factor class were calculated by using the relative risks on all-cause mortality denoted $RR(d,m)$:

$$m(d = 0) = m - p(d = 1) \times em \qquad (4)$$

$$m(r, d = 0) = \frac{RR(r,m)}{\sum_j RR(r=j,m) \times p(r=j)} \times m(d = 0) \qquad (5)$$

Figure 3.4 displays the estimated prevalence, excess mortality rates due to dementia and mortality rates for persons without dementia.

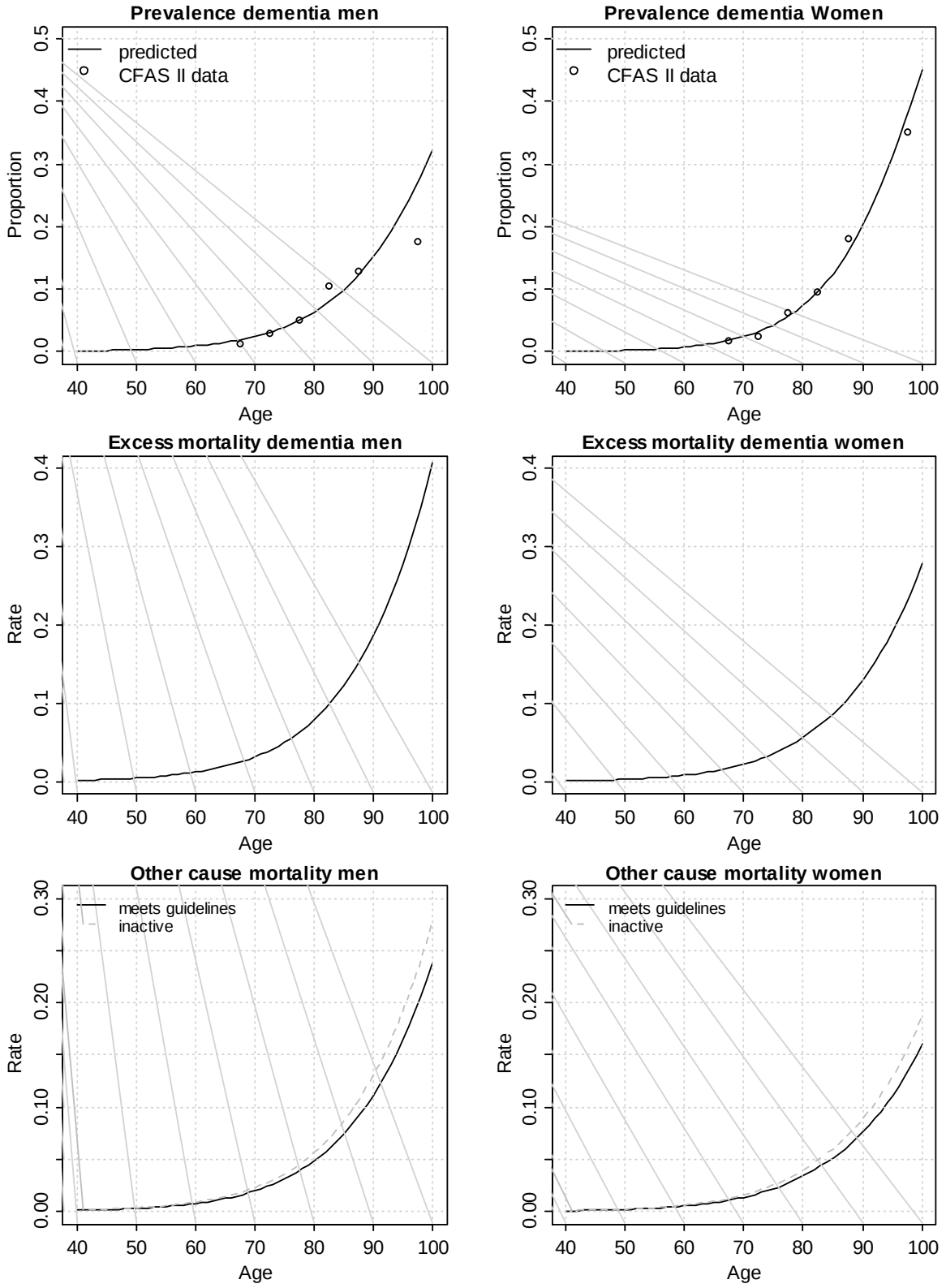


***Figure 3.4:*** *Upper two panels: estimated prevalence of dementia in the UK population used as input for the simulation model (dots indicate data points from CFAS II). Middle two panels: excess mortality rates as a result of having dementia' by age and gender. Lower two panels: back-calculated mortality rates for different PA classes not having dementia.*

### 3.4.4 Quality of life

For quality of life for persons without dementia (*q(d=0)* )we use estimates by age and gender as published by Heijink (Heijink et al., 2011). We combined these estimates with prevalence estimates of PA and losses in quality of life due to physical inactivity (denoted *eq(r)*) from the study by Anokye et al (Anokye et al., 2014):

$$q(d=0) = \sum_j p(r=j|d=0) \times [q(r=1|d=0) + eq(r)] \quad (6)$$

The study of Anokye et al reported the difference in quality of life between inactive and active persons to be 0.047 using a subjective measurement of physical activity. To estimate quality of life values for the four physical activity classes, we assumed that the estimated quality of life difference in the study of Anokye corresponded to the difference in quality between a person that meets the physical activity recommendations compared to a person that is inactive. We interpolated quality of life losses for the middle two classes assuming a linear relation between quality of life and physical activity as measured in hours per week. Using the same differences in number of hours of physical activity per week between the physical activity classes as used for the RR calculation, the quality of life of the inactive, low active and some active classes were estimated to be 0.047, 0.0282 and 0.0094 lower than the group that meets guidelines (so $eq(r=1)=0$; $eq(r=2)=0.0094$; $eq(r=3)=0.0282$; $eq(r=4)=0.047$). Figure 3.5 shows the quality of life values used for persons without dementia in the model. Figure 3.5 illustrates that quality of life decreases with age.

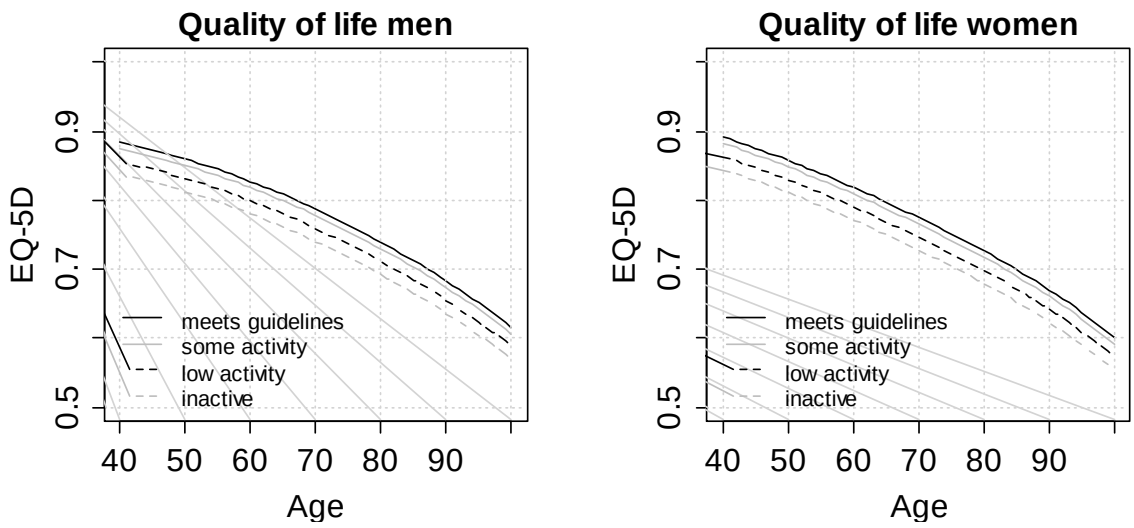


***Figure 3.5:*** *QoL by age for persons without dementia*

Mean quality of life for persons with dementia were taken from the study by Sheehan et al 2012 (Sheehan et al., 2012). We opted to use the values assessed by carers (0.30). As the study consisted mainly of moderate to severe dementia patients we used these values for the inactive persons with dementia and increased values for low active, some active and the meets guidelines persons with dementia by 0.0094, 0.0282 and 0.047 resulting in quality of life values of respectively 0.30, 0.31,0.33 and 0.35 (Anokye et al., 2012).

QALYs lived by the population simulated with the model in year $t$ can be calculated in the following manner:

$$Q(t) = \sum_j P(r = j, d = 1, t) \times q(r = j, d = 1) + P(r = j, d = 0, t) \times q(r = j, d = 0) \quad (7)$$

Estimates of the number of persons alive in the different states are produced with the model and depend on time *t,* while quality of life weights in the different states are assumed constant over time (conditional on age and gender).

### 3.4.5 Costs

In this report we make a distinction between costs for social care and cost for other health care providers publicly financed by the NHS (for notational simplicity we will not make a distinction between these cost categories). For hospital costs and social care costs we made a distinction between costs in last year of life and costs made in other years. Costs in the last year of life *c(d=1,y=1)* for people with dementia were derived from the study of Georghiou (Georghiou et al., 2012). Costs for other years were back-calculated in the following manner:

$$c(d = 1, y = 0) = \frac{c(d=1) - m(d=1) \times c(d=1, y=1)}{1 - m(d=1)} \quad (8)$$

where $c(d = 1)$ are the average costs for people with dementia derived from the study from Kasteridis (Kasteridis et al., 2014). The assumption underlying equation (8) is that average cost is the weighted average of those who are in their last year of life and those who are not. In line with the results of Kasteridis and Georghiou we assumed annual costs for the persons with dementia to be independent of age and gender. The prevalence of dementia in the studies in the studies by Kasteridis and Georghiou was a bit lower than in the data sources we used to estimate prevalence for the model. This suggests that not everybody with dementia receives formal care. Therefore, to calculate costs per patient we divided total spending on persons with dementia from the studies of Kasteridis and Georghiou not by the number of persons with dementia from those studies but rather by the number of persons with dementia used as input for the model.

As a starting point to calculate costs for other diseases, we used per capita spending summed over all diseases from the study by Kasteridis. Then we decomposed to costs in the last year of life and other years by using the results from Georghiou and corrected for the costs of dementia:

$$c(d = 0, y = 1) = \frac{c(y=1) - p(d=1|y=1) \times c(d=1, y=1)}{p(d=0|y=1)} \quad (9)$$

$$c(d = 0, y = 0) = \frac{c(y=0) - p(d=1|y=0) \times c(d=1, y=0)}{p(d=0|y=0)} \quad (10)$$

Figure 3.6 shows the resulting estimates of costs. From this graph it can be seen that costs in the last year of life are much higher than in other years. While hospital expenditures for persons without dementia decrease with advancing age, social care costs increase with age. This is especially the case for women which may be explained by the fact that a higher proportion of women at an elderly age are single than men.

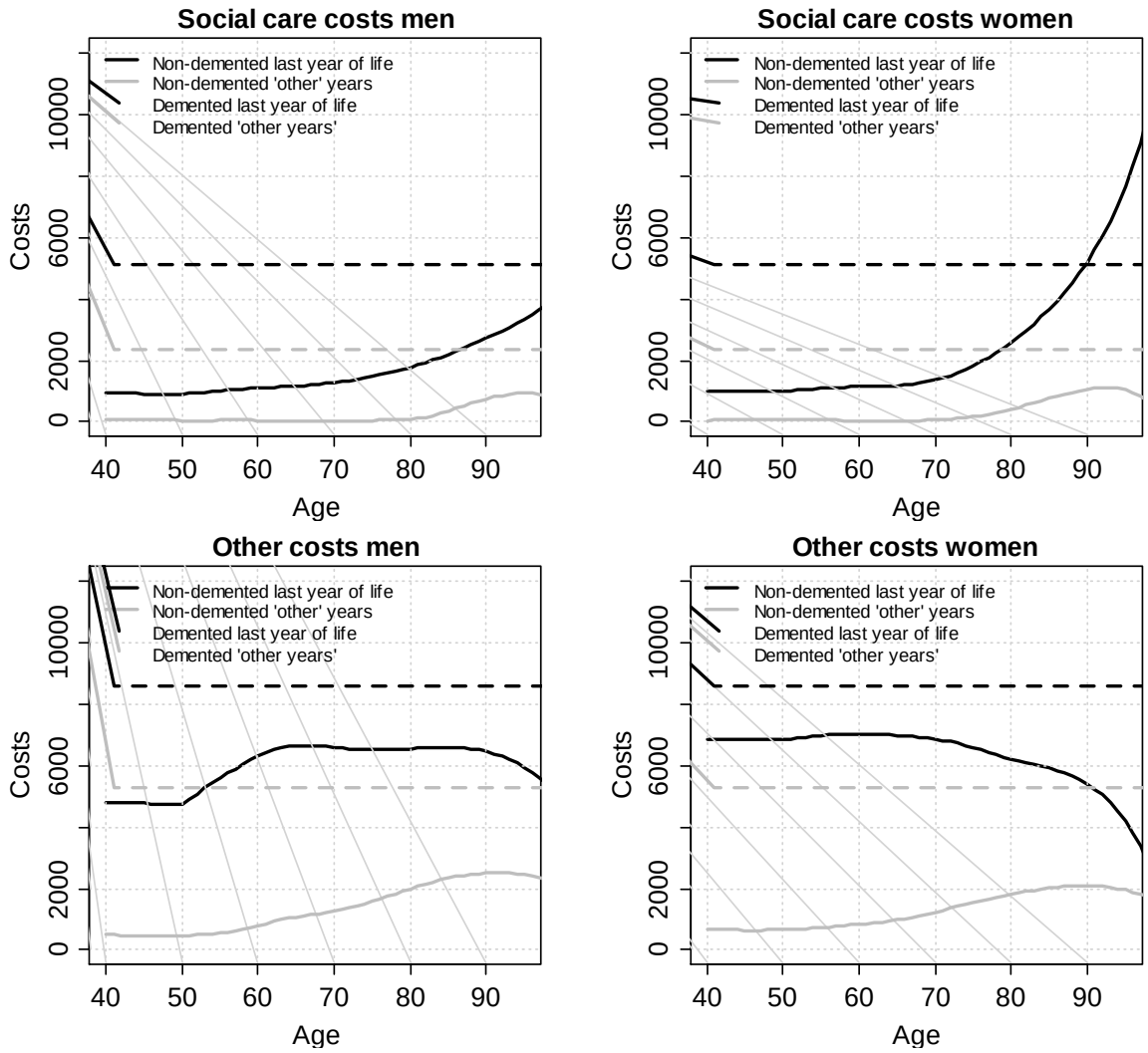


***Figure 3.6:*** *Costs by age stratified by the last year of life and 'other years' for persons with and without dementia*

Total costs in year $t$ are then calculated with the model in the following manner:

$$C(t) = P(d=1, y=0, t) \times c(d=1, y=0) + P(d=0, y=0, t) \times c(d=0, y=0) \tag{11}$$

$$+P(d=1, y=1, t) \times c(d=1, y=1) + P(d=0, y=1, t) \times c(d=0, y=1)$$

## 3.5 Quantifying uncertainty within the model

To translate uncertainty surrounding the input parameters into uncertainty around the outcomes of the model we used probabilistic sensitivity analysis (PSA). Uncertainty was available for prevalence, incidence, excess mortality, quality of life and RRs of the different physical activity classes in relation to all-cause mortality and dementia. We assumed the following parameters fixed in our analysis: population numbers, total mortality, and the initial distribution of the population over the four physical activity classes and costs.

Most importantly, values of the relative risks were varied in the PSA. Distributions for the relative risks were based on the published relative risks and their confidence intervals assuming an uninformative prior RR distribution with mean 1 and a large variance (Boshuizen et al., 2009). Uncertainty surrounding incidence, prevalence and excess mortality for dementia was based on the uncertainty of the regression coefficients of the estimated regression models. Uncertainty around the quality of life for people with dementia was obtained from the study of Sheehan et al ((Sheehan et al., 2012).

PSA was conducted by drawing random values from the parameter distributions of the input data. For each set of input data that was drawn the model input parameters were calculated as described in paragraph 3.4. After that, the model was run for each set of input parameters and results of each run were collected. The current analyses were based on 1,000 simulations.

# 4. Lifetime costs and benefits of promoting physical activity

In this chapter we present predictions of the model and discuss their implications for preventive policies targeted at promoting physical activity. These model predictions help to better understand the dynamics of preventive interventions. Firstly, the lifetime trajectories of cohorts that differ in their level of physical activity are presented in terms of health outcomes and costs. Secondly the dynamic effects of preventive interventions on health and health care use are shown. This chapter concludes with an estimate of the potential effects that preventive interventions promote physical activity might have on the health and health care use of the English population aged 40 to 65. Note that in this chapter, health benefits and health and social care costs were not discounted, while in chapter five – presenting the results of the cost-effectiveness of interventions – discounting has been applied.

## 4.1 Cohort analysis

Figure 4.1 below displays survivor curves for inactive persons, low active persons and persons that meet the recommendations for physical activity as well as dementia prevalence by age, forecast with the model for a person aged 40 at baseline. For clarity the curves for somewhat active persons are not displayed, because they are almost the same as the curves for low active persons. These graphs show that inactive persons live shorter lives than low active persons and spend a larger part of their lives with dementia. Also, quality of life varies by level of physical activity. Figure 4.1 shows clearly the influence of the relative risks used on the dementia incidence as there is a big difference in dementia prevalence between inactive and low-active persons, but a rather small difference between persons that meet the recommendations for physical activity as compared to persons that are low-active.

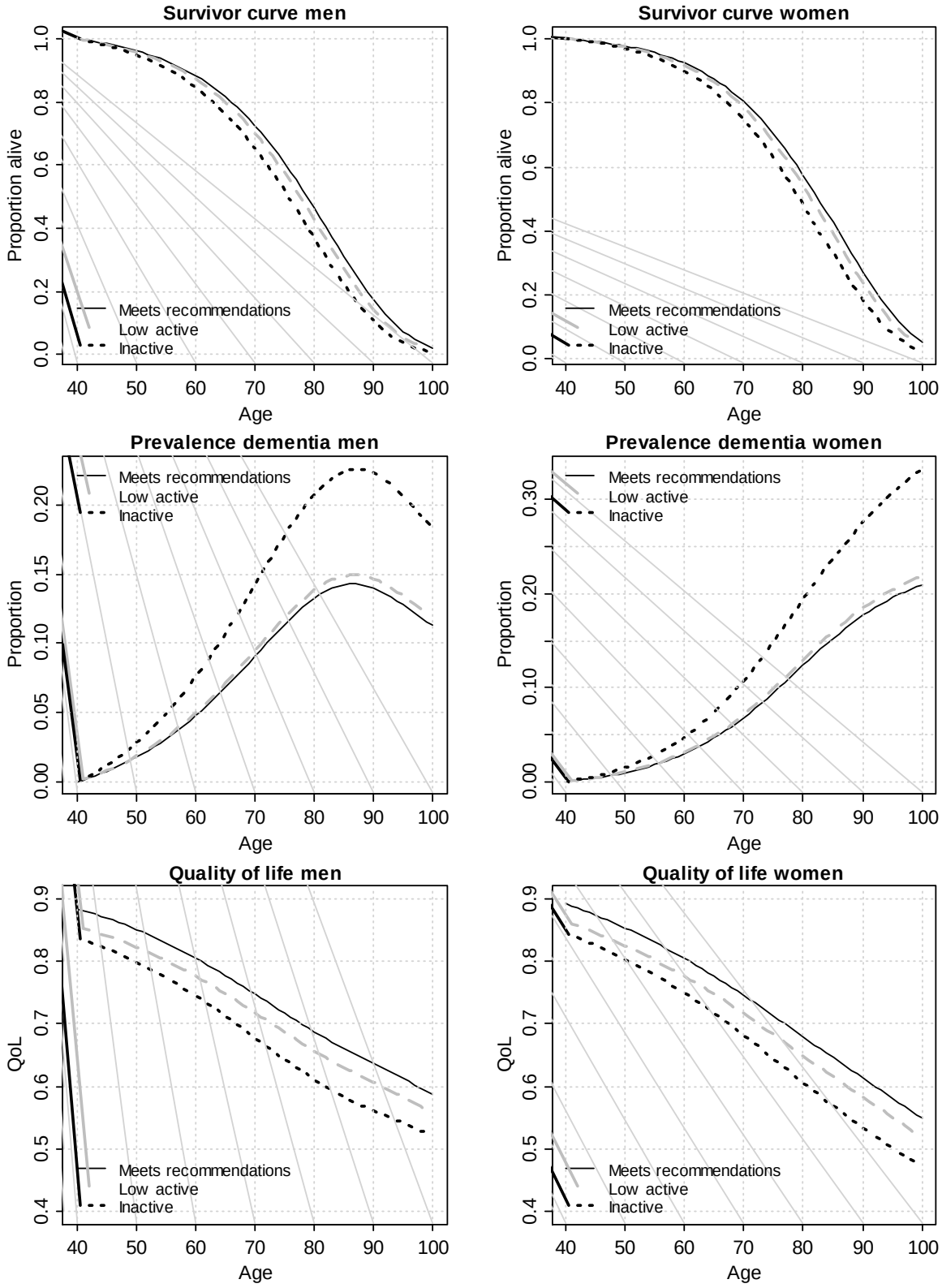


***Figure 4.1:*** *Predictions of the model over time (survival, prevalence of dementia and quality of life). Note that the prevalence of dementia is expressed as a proportion indicating the number of persons with dementia divided by the number of persons alive. Quality of life estimates illustrate average quality of life for those still alive.*

Table 4.1 displays estimates of the life expectancy (LE) and quality adjusted life expectancy (QALE) at age 40 years and the number of years spent with dementia. For example, a 40-year old inactive male was predicted to have a life expectancy of 38.1 years (3.4 years with dementia) and a quality adjusted life expectancy of 28.0 years. In a 40-year old male that meets the recommendations for physical activity these estimates were 40.1 years (2.4 with dementia) and 31.6 years, respectively. The differences between the different activity classes are the direct result of the relative risks that are used. For instance, the big difference in the life years lived with dementia between the inactive and low active persons is the result of the big difference in dementia incidence between these two groups. Note that these figures have not been discounted to reflect time into the future.

***Table 4.1:*** *Predictions of the model at the age of 40 years, mean (95% confidence interval)*

| | | Life Expectancy (age 40) | Years with dementia | Quality-Adjusted Life Expectance (age 40) |
|---|---|---|---|---|
| Men | Meets recommendations | 40.1 (39.6-40.5) | 2.4 (1.8-3.4) | 31.6 (30.8-32.3) |
| | Some activity | 39.5 (39.0-39.8) | 2.4 (1.8-3.5) | 30.8 (30.0-31.4) |
| | Low activity | 39.0 (38.5-39.3) | 2.4 (1.7-3.4) | 29.7 (28.9-30.3) |
| | Inactive | 38.1 (37.5-38.6) | 3.4 (2.5-4.8) | 28.0 (26.8-28.7) |
| Women | Meets recommendations | 43.9 (43.5-44.4) | 2.5 (2.0-3.1) | 34.2 (33.5-34.6) |
| | Some activity | 43.3 (43.0-43.7) | 2.5 (2.0-3.3) | 33.3 (32.7-33.8) |
| | Low activity | 42.8 (42.5-43.1) | 2.5 (1.9-3.2) | 32.2 (31.6-32.6) |
| | Inactive | 42.0 (41.6-42.4) | 3.5 (2.8-4.5) | 30.4 (29.7-31.0) |

Figure 4.2 shows average annual costs conditional on being alive (upper two panels) and total costs (average annual costs times the probability to be alive) of dementia and other diseases over time. This figure shows that inactive persons cost more annually than active persons because they more often have dementia and also have a higher mortality risk; more people are in the last year of their life, which is associated with higher costs than other years.

However, if we look at total costs of the cohort it not only matters how much a person costs on average conditional on being alive but also how many persons of the cohort are still alive. The middle two graphs again illustrate the importance of the relative risks on dementia incidence. The costs due to dementia are by far the highest for the inactive group. Differences between the three physical activity classes with at least low activity are negligible. Costs for other diseases are driven by differences in longevity between the different groups. As the cohort that meets recommendations for physical activity lives longest, their costs for other diseases are also highest.

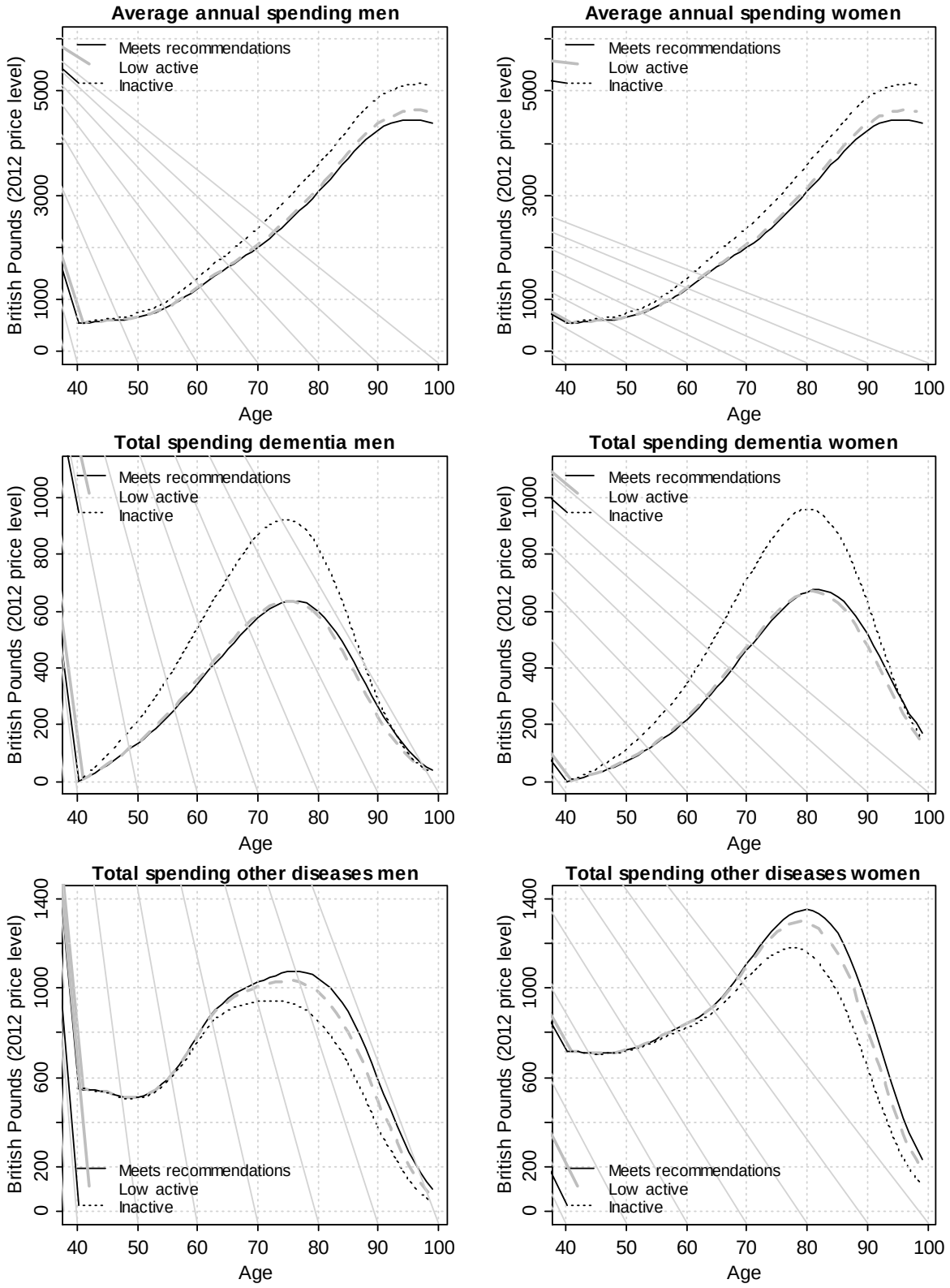


***Figure 4.2:*** *Average annual costs and total costs over time per cohort. Note that the upper two graphs indicate average annual costs conditional on being alive while the middle two and lower two graphs are not conditional on being alive (and thus also determined by the number of persons still alive).*

Table 4.2 shows the estimated lifetime costs at the age of 40, specified into costs for the NHS versus social care and costs for dementia versus costs for other diseases. The NHS costs for a 40-yr old inactive male, for example, are estimated to be 19,200 pounds for dementia and 34,100 pounds for other diseases. The social care costs are estimated to be 8,900 pounds for dementia and 3,500 pounds for other diseases. If the 40-yr old inactive male were to become low active, the NHS dementia-related costs for this person would decrease from 19,200 to 13,300 pounds, while the costs for other diseases would increase from 34,100 to 37,300 pounds. The social care costs would decrease from 8,900 to 6,200 pounds for dementia and increase from 3,500 to 4,000 pounds for other diseases. In general, life time health care expenditures were higher for women than for men due to their longer life expectancies. Costs for other diseases showed a direct relation with life expectancy; the longer you live, the greater your expenses. Again the largest difference in expenditures was found between the inactive persons and low active persons due to the relative risks on dementia incidence used.

***Table 4.2:*** *Undiscounted lifetime cost (x 1000 Pound) at the age of 40 years*

| | | Social care costs | | NHS costs | | |
|---|---|---|---|---|---|---|
| | | Other diseases | Dementia | Other diseases | Dementia | Total |
| Men | Meets recommendations | 4.3 (4.1-4.6) | 6.3 (4.7-8.7) | 39 (37-40.6) | 13.5 (10-18.8) | 63.1 (59.5-68.7) |
| | Some activity | 4.2 (3.9-4.4) | 6.4 (4.7-8.9) | 38 (35.8-39.5) | 13.7 (10.1-19.2) | 62.2 (58.6-67.9) |
| | Low activity | 4 (3.7-4.3) | 6.2 (4.6-8.7) | 37.3 (35.2-38.7) | 13.3 (9.8-18.9) | 60.8 (57.1-66.5) |
| | Inactive | 3.5 (3.2-3.8) | 8.9 (6.6-12.3) | 34.1 (31.3-36) | 19.2 (14.1-26.8) | 65.7 (60.3-66.2) |
| Women | Meets recommendations | 9.5 (8.9-10.1) | 6.6 (5.4-8.2) | 45.7 (44.2-47.0) | 14.1 (11.5-17.6) | 75.8 (73.2-79.3) |
| | Some activity | 9.1 (8.4-9.6) | 6.6 (5.2-8.6) | 44.8 (43.2-46.2) | 14.3 (11.2-18.6) | 74.8 (72.1-78.8) |
| | Low activity | 8.8 (8.2-9.3) | 6.5 (5.1-8.4) | 44.2 (42.6-45.5) | 13.8 (10.8-18.1) | 73.3 (70.5-77.3) |
| | Inactive | 7.4 (6.8-7.9) | 9.2 (7.4-11.6) | 41.2 (39.3-42.7) | 19.7 (15.9-25) | 77.5 (73.8-82.8) |

## 4.2 Prevention

To illustrate the potential impact of interventions that successfully promote physical activity we illustrated in this paragraph what happens if a cohort of 500 men and 500 women aged 40 at baseline increase their level of physical activity. We illustrated the impact of three different scenarios assuming that:

1. An inactive cohort becomes low active;
2. A low active cohort becomes somewhat active;
3. A somewhat active cohort becomes more active and meets recommendations.

Figure 4.3 show the differences in dementia prevalence, numbers of persons alive, the number of QALYs and costs for dementia and other diseases over time. The first scenario in which an inactive cohort was assumed to become low active resulted in the largest decrease in dementia cases and

dementia-related costs compared to the current practice scenario. As a result the gain in life years and QALYs was also highest for scenario one. The observed reduction in dementia-related costs is accompanied by an increase in costs for other diseases, because people live longer when they become (more) active. Comparing the results for the three scenarios showed that the biggest gain in health outcomes can be expected by motivating the inactive group to become active, which is again a direct effect of the RRs used for the incidence of dementia. As the difference in dementia incidence is rather small in scenarios 2 and 3, the difference in the prevalence of dementia is also quite small and even increases a bit because of increases in survival.

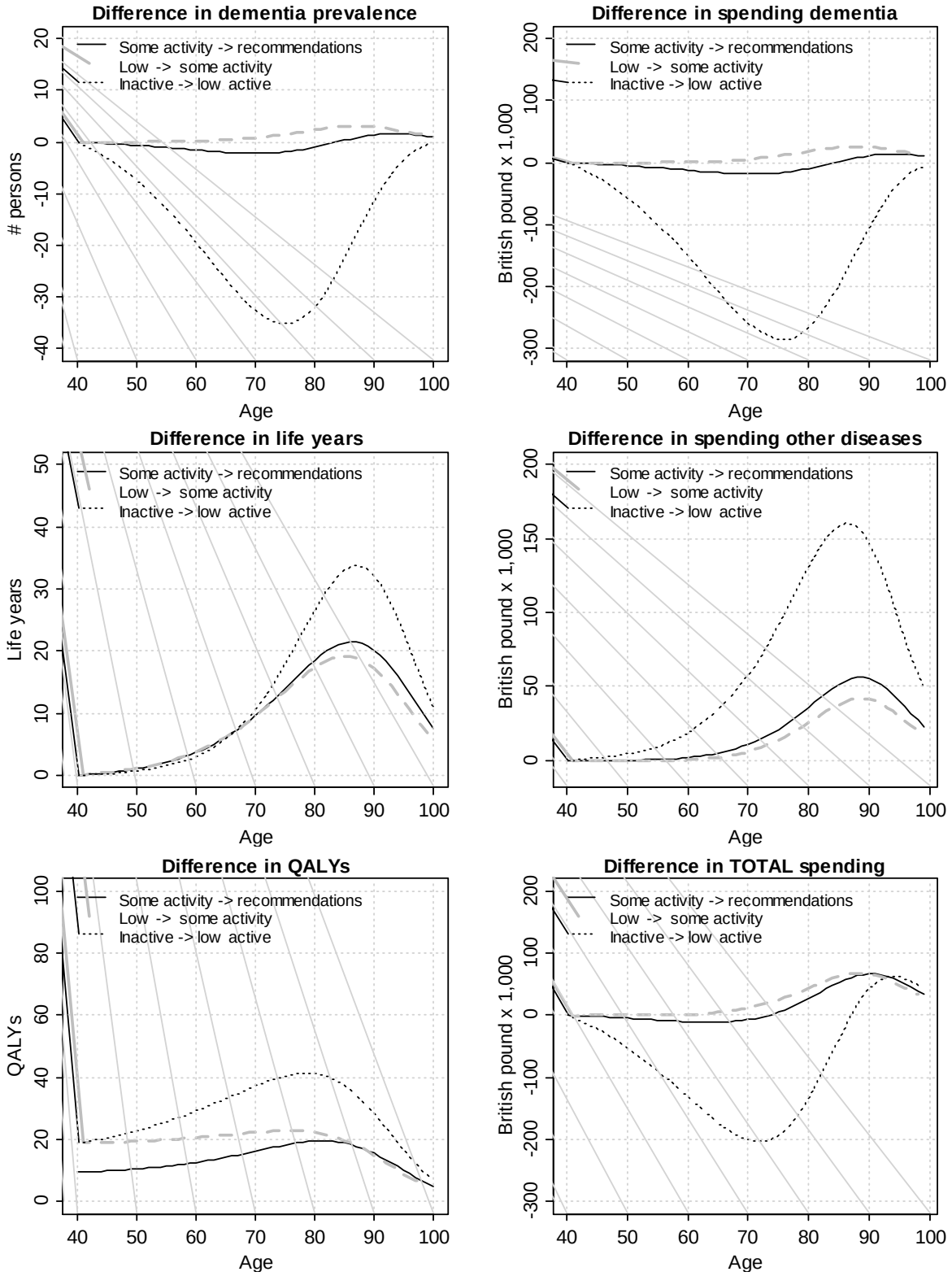


***Figure 4.3:*** *Effect of three scenarios of increase in physical activity level on the prevalence of dementia, life years, QALYs and costs for a cohort of 500 males and 500 females aged 40 years at baseline. Scenario 1: inactive cohort becomes low active; scenario 2; low active cohort becomes somewhat active; scenario 3: somewhat active cohort becomes more active and meets recommendations. Note that in all graphs displayed results are not conditional on being alive and thus also determined by the number of persons alive.*

In addition, the results of the three scenarios of increase in physical activity level were compared to the current practice scenario in which no change in physical activity level was applied. Table 4.3 presents the impact of the three scenarios in terms of life years gained, QALYs gained and costs compared to the current practice scenario. If a cohort becomes more active the risk of developing dementia decreases and the therefore the number of years with dementia decreases, while the total life expectancy and quality-adjusted life-expectancy increases. This results in a gain in life years and QALYs and a decrease in costs for dementia. The costs for other diseases, however, increase because of the longer life expectancy.
The gain in life years and QALYs was highest for the scenario assuming inactive people to become low active, 809 and 1741, respectively. Table 4.3 illustrates that for scenario one the increase in costs for other diseases due to increased life expectancy (934 + 3044 pounds) was completely compensated by the savings as a result of avoiding dementia (2665 + 5769 pounds). Note that this would not be case if an intervention causes an active person to become even more active (scenario two and three).

***Table 4.3:*** *Results for three possible scenarios of increase in physical activity level for a cohort of 1000 people (500 males and 500 females)*

| | | Scenario 1: Inactive → low active | Scenario 2: Low active → some activity | Scenario 3: Some activity → meets recommendations |
|---|---|---|---|---|
| Health | Life years gained | 812 | 530 | 582 |
| | QALYs gained | 1750 | 1122 | 826 |
| Costs | ΔSocial care costs* | -1764 | 397 | 221 |
| | - due to dementia* | -2699 | 186 | -87 |
| | - due to other causes* | 935 | 211 | 307 |
| | ΔNHS costs* | -2786 | 1052 | 735 |
| | -due to dementia* | -5847 | 396 | -193 |
| | -due to other causes* | 3061 | 656 | 928 |

***** In thousand British pounds

## 4.2 Effects at a population level

Figure 4.4 displays LE, QALE and lifetime health care expenditures by age and physical activity class for the age range in the target population. From this figure it can be seen that at all ages a higher level of physical activity results in a higher LE and QALE and that the differences between the different classes are roughly equal at most ages. Lifetime health expenditures per person at most ages are highest for the inactive group, except at higher ages at which they are similar to the group that meets recommendations.

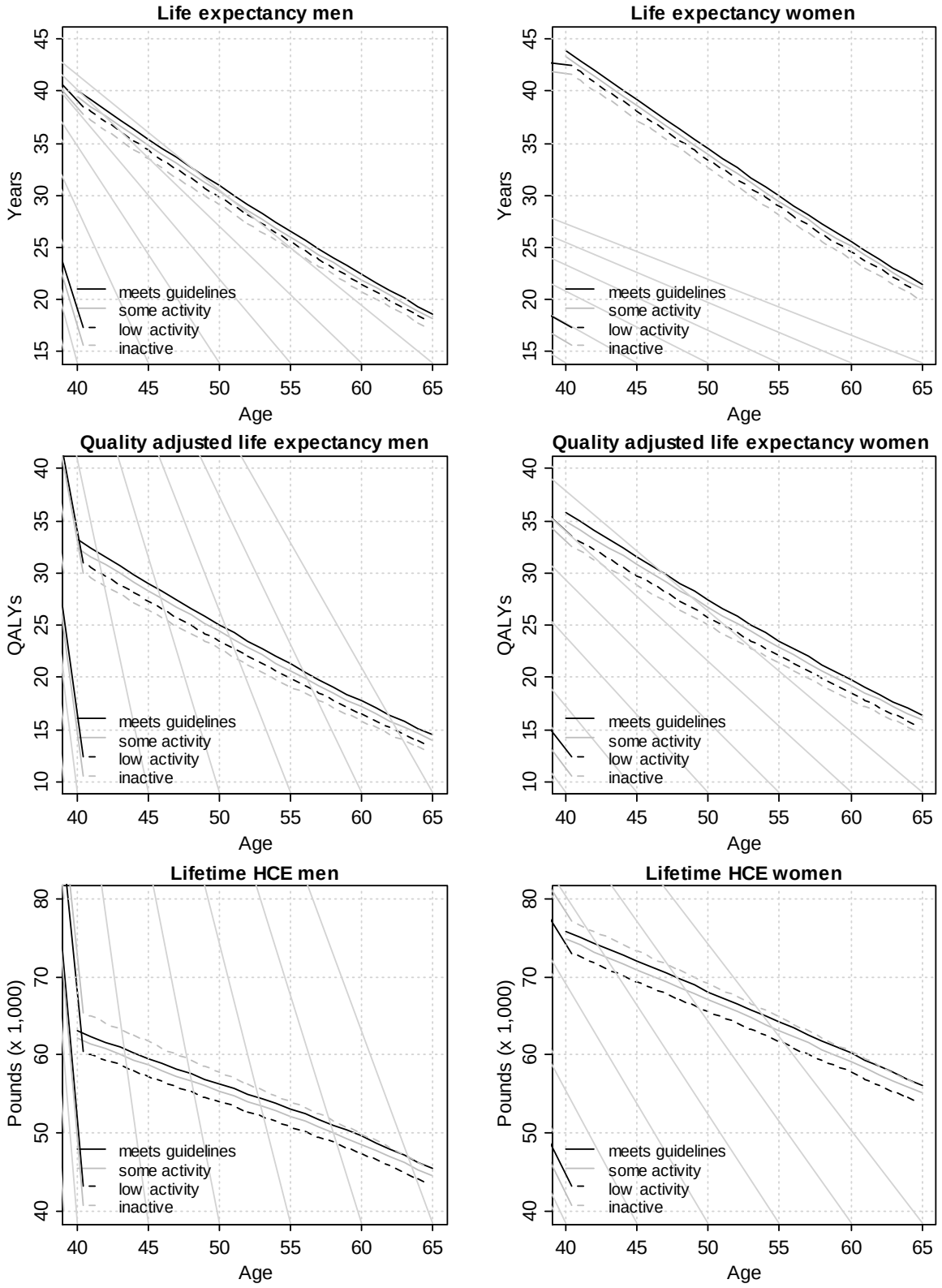


***Figure 4.4:*** *life expectancy, quality adjusted life expectancy and lifetime health care expenditures for different physical activity classes for different ages by gender*

To understand the impact of physical inactivity on the English population aged 40 to 65 we will estimates health and health and social care expenditures in three scenarios:

1. Current practice;
2. Everybody shifts a class: everybody becomes a bit more active;
3. Everybody meets recommendations.

Table 4.4 shows the results for the three scenarios modelled at population level. If all 40-65 year olds in England were to increase their activity level by one class (i.e. inactive become low active, low active become somewhat active etc.) life expectancy would increase 0.2 years per person. Lifetime expenditures would decrease by 500 pounds. If all 40-65 year olds were to increase their physical activity level to the level where they meet the recommendations the increase in life expectancy would be 0.5 year, while lifetime expenditures would remain the same.

***Table 4.4:*** *Effects at population level*

| | Scenario 1: Current practice | Scenario 2: Everybody shifts a class | Scenario 3: Everybody meets recommendations |
|---|---|---|---|
| Life expectancy | 30.9 | 31.1 | 31.3 |
| Quality-adjusted life expectancy | 24.5 | 24.8 | 25.1 |
| Lifetime health and social care expenditures* | 60.9 | 60.4 | 60.9 |
| *Difference compared to scenario 1* | | | |
| Life expectancy | - | 0.2 | 0.5 |
| Quality-adjusted life expectancy | - | 0.3 | 0.6 |
| Lifetime health and social care expenditures* | - | -0.5 | 0 |
| *Difference compared to scenario 2* | | | |
| Life expectancy | - | - | 0.2 |
| Quality-adjusted life expectancy | - | - | 0.3 |
| Lifetime health and social care expenditures* | - | - | 0.5 |

* times thousand pound

# 5. Cost effectiveness of interventions that promote physical activity

In the previous chapter the impact of different scenarios of increase in physical activity level was presented for both a cohort of 40 year old people (section 4.2) as well as for the English population aged 40-65 years (section 4.3). Results of the scenarios were expressed in terms of gain in life years and QALYs and changes in dementia-related costs and costs due to other causes. In the current chapter, the cost-effectiveness of interventions that promote physical activity are shown. Compared to chapter four, the results presented in this chapter also take into account the costs of the intervention. The effect of the intervention has been applied as a reduction in the risk factor prevalence and the model simulated the resulting change in quality of life, health care costs and mortality. The duration of the implementation depends on the type of interventions. Time horizon for the evaluation was lifetime. Outcomes were simulated for the scenario in which the intervention was assumed to be applied, the intervention scenario, and for a scenario in which no intervention was applied, the current practice scenario. Incremental cost effectiveness ratios (ICERs) were calculated as the difference in total costs between the intervention scenario and the current practice scenario divided by the difference in effects, i.e. QALYs .

$$ICER=(Total_costs_{intervention_scenario} - Total\ costs_{current_practice}) / (QALYs_{intervention_scenario} - QALY_{current\ practice})$$

Total costs for the intervention scenario were calculated as the sum of the intervention costs, dementia-related costs and costs for other causes. Total costs for the current practice scenario were calculated as the dementia-related costs plus the costs for other causes. If in the intervention scenario more people become active, the prevalence of dementia decreases resulting in lower dementia-related costs but higher costs due to other causes. The cost difference between the two scenarios then consists of the intervention costs minus the savings in dementia-related costs plus the additional costs for other causes. Unless otherwise indicated effects and costs in this chapter were discounted at 1.5% annually.

## 5.1 Description of intervention scenarios

Many interventions targeted at increasing PA are not that attractive to model as they either have a very short follow-up or are targeted at very specific groups. Therefore, rather than modelling specific interventions aimed to promote PA, we model the cost-effectiveness of two broad categories of interventions in several what-if scenarios:

- Population level campaigns
- Individual level interventions

In these what-if scenarios we varied the costs per participant, the effectiveness as well as relapse after the interventions. To make the outcomes of the what-if analyses easier to interpret we used the following two interventions as model interventions for the two categories:

1. Mass media campaigns for which effectiveness in reducing sedentary/inactive behavior was assumed to be RR=1.06 (95% CI: 0.95-1.17) (Abioye et al., 2013) corresponding to a decrease in

the probability of being inactive of about 0.01% in the English population. The RR estimated by Abioye et al. was based on a meta-analysis of three studies with a follow-up of 2-3 years. Intervention costs of mass media campaigns were taken from an Australian study and estimated to be around 10 pounds (Cobiac et al., 2009)[1].

2. Exercise referral schemes that increase the probability of becoming active by about 0.05% at a cost of about 200 pounds per participant (Trueman et al., 2013). Effectiveness in the study of Trueman et al was based on a meta-analysis of Pavey et al calculating the effectiveness of exercise referral versus usual care for studies with a follow-up of 6-12 months (Pavey et al., 2011).

Although these interventions can in no way be exactly copied to the target population in England, the costs of these interventions would be roughly transferable to similar types of interventions if these were to be implemented in England. More generally, mass media campaigns are usually characterized by low costs per person and low effectiveness, while the reverse is true for face-to-face interventions like exercise referral schemes. In the scenarios, we estimated the costs and benefits for a wide range of effectiveness estimates. Effectiveness is expressed as the increase in the probability that someone becomes more active a year after the intervention. While interventions at the individual level can be targeted at specific groups such as the inactive (and the costs also largely depend on the number of persons participating) this is less the case for mass-media campaigns. In the results section, estimates of costs and effects are shown for the situation that the interventions will cause the inactive to become low active. In contrast to this, a scenario is shown in which everybody becomes more active (the inactive become somewhat active, the low active become somewhat active and the somewhat inactive meet guidelines). Paragraph 5.2 shows the results for the cost-effectiveness in the case where the effect on physical activity is maintained throughout life, i.e. assuming no relapse. In paragraph 5.2.2 the impact of taking into account relapse was investigated. Furthermore, the role of including future unrelated medical costs was explored in paragraph 5.2.3.

## 5.2 Results

In Figure 5.1 the results are shown for the scenario that all inactive persons become low active. The left graph of Figure 5.1 shows the ICER as a function of the probability of becoming active for both population-based interventions and individual level interventions. The grey area around the curves represents the range in outcomes when intervention costs are varied from 5 to 15 pounds for population interventions and from 150 to 250 pounds for individual interventions. The black dots present the ICER when effectiveness of the population and individual level interventions was assumed to be 0.01 and 0.05, respectively. For both types of interventions this would result in an ICER well below 10,000 pound per QALY.

The right graph in Figure 5.1 shows the uncertainty around the outcomes as a result of the uncertainty around the input parameters of the model in the case where the effectiveness and costs of the individual/population intervention were respectively fixed at probabilities of 0.05/0.01 and 200/10 pounds per person. Results for the individual level interventions show that this type of intervention is more effective but there is more uncertainty around the results than for the population interventions.

[1] Given that the English population is about 2.5 times the Australian population the cost per person estimates are probably on the high end.

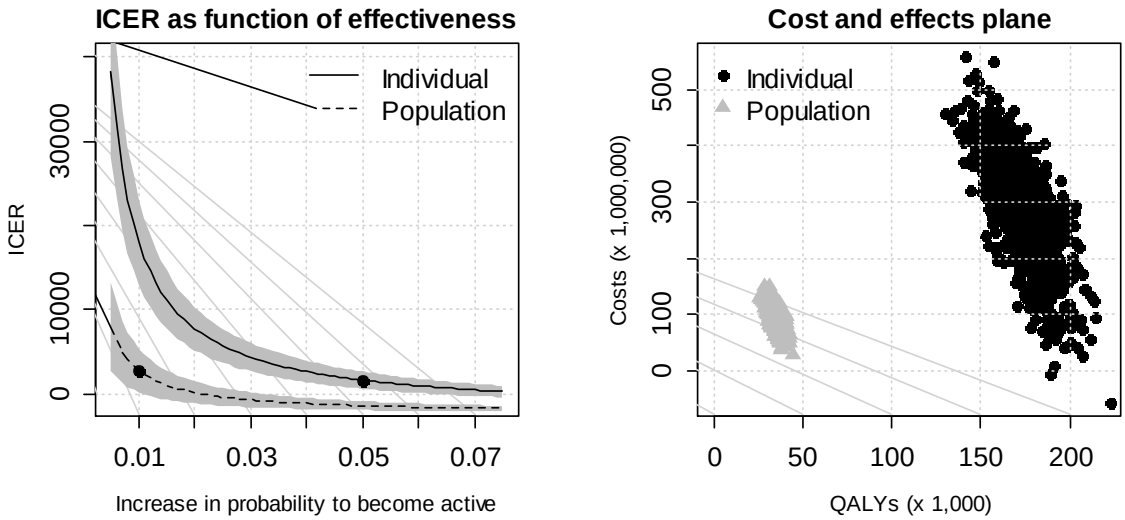


***Figure 5.1:*** *Scenario: inactive persons become low active; no relapse assumed* ***Left graph****, ICER as function of effectiveness of an intervention for both individual level interventions (200 pounds per person) and population interventions (10 pounds per person). The grey area displays the results when intervention costs are varied between 150 and 250 pounds for the individual level interventions and between 5 and 15 pounds for the population interventions.* ***Right graph,*** *uncertainty around the point estimates displays in the left graph assuming an increase in probability of 0.01of becoming active for population interventions and 0.05 for individual level interventions.*

Figure 5.2 presents the results for the scenario that the total population becomes more active and shifts one class.

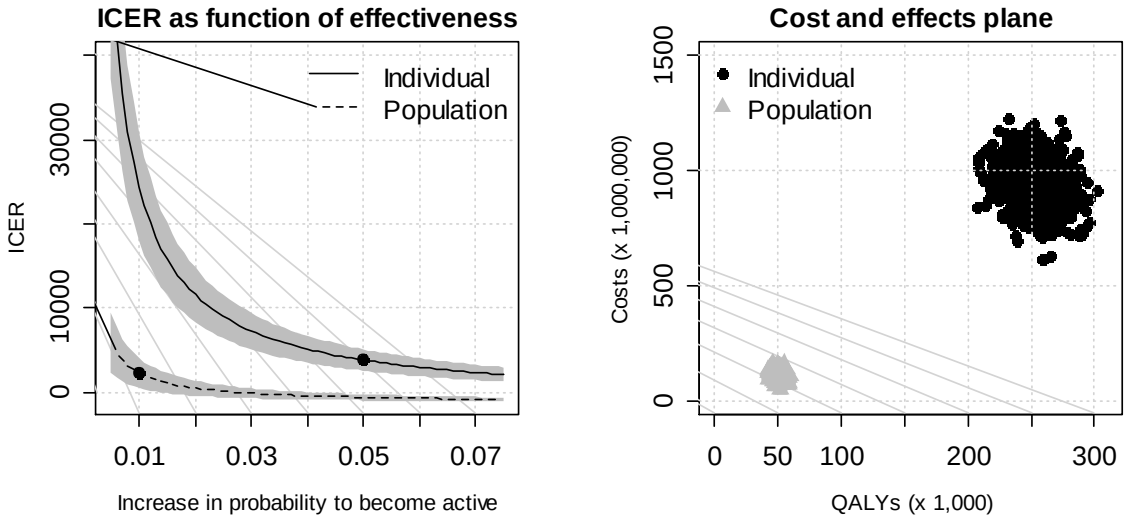


***Figure 5.2:*** *Scenario: everyone becomes more active; no relapse assumed* ***Left graph****, ICER as function of effectiveness of an intervention for both individual level interventions (200 pounds per person) and population interventions (10 pounds per person). The grey area displays the results when intervention costs are varied between 150 and 250 pounds for the individual level interventions and between 5 and 15 pound for the population interventions.* ***Right graph,*** *uncertainty around the point estimates displays in the left graph assuming an increase in probability of 0.01 of becoming active for the population interventions and 0.05 for the individual level interventions.*

Comparing the results in figure 5.1 and 5.2 showed that the target population has a substantial influence on the ICER of individual level interventions as well as health gains effects. Targeting these types of interventions to the specific subgroup of inactive people is more cost-effective. The target population has less influence on the ICER of population-based interventions. For both interventions, however, total health gains are much bigger if everybody shifts a class compared to the case in which only the inactive become low-active.

### 5.2.2 The influence of relapse

Figure 5.3 displays the impact of taking relapse into account. Relapse is defined as the percentage that returns to their pre-intervention level of activity each year. For instance, a relapse rate of 10% means that 10% of the previously inactive persons who have become somewhat active as a result of an intervention have become inactive again a year later. Another year later, only 81% is still somewhat active given a relapse rate of 10% in each of two years. Results are shown for the scenario that inactive people become low active and for four different relapse rates. Taking into account relapse increases the ICERs, but relapse rates seem to have more impact in individual interventions than in population-based interventions.

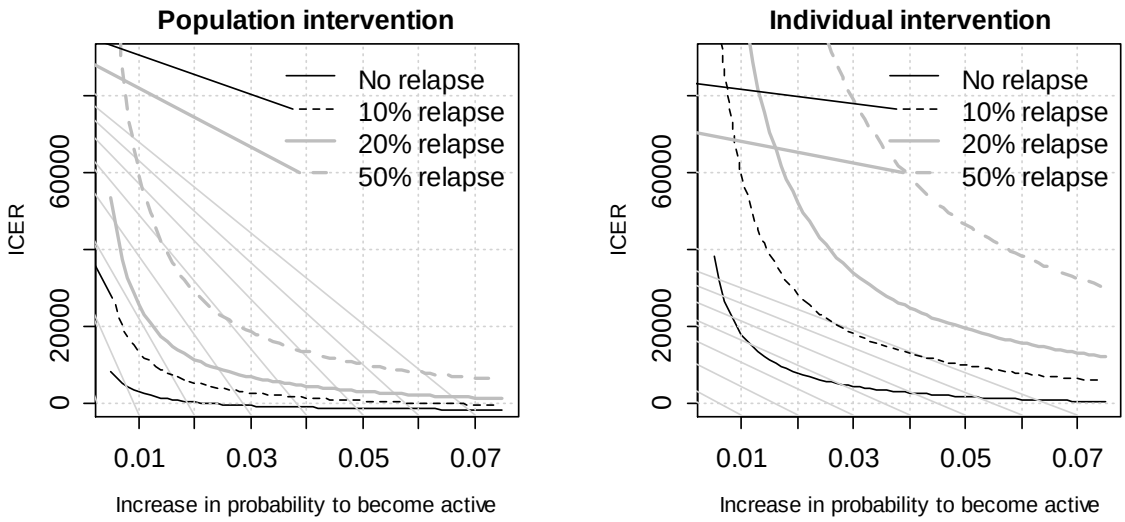


***Figure 5.3:*** *Relation between short term effectiveness, relapse and the Incremental cost-effectiveness ratio (ICER) for the scenario that inactive people become active. Intervention costs for population and individual level interventions are assumed to be 10 and 200 pounds, respectively.*

### 5.2.3 The influence of including future unrelated medical costs

The impact of including future unrelated medical costs in the analyses is shown in figure 5.4. In case no relapse is assumed, including only the costs of dementia while excluding the costs of other diseases reduces the ICER by roughly 2500 pound per QALY gained independent of the effectiveness of the interventions. When a relapse of 20% is assumed the ICER reduces by roughly 1500 pound per QALY gained if costs of unrelated medical care are excluded. Inclusion of future unrelated costs increases the ICERs, but the impact on the ICER is less than the influence of relapse.

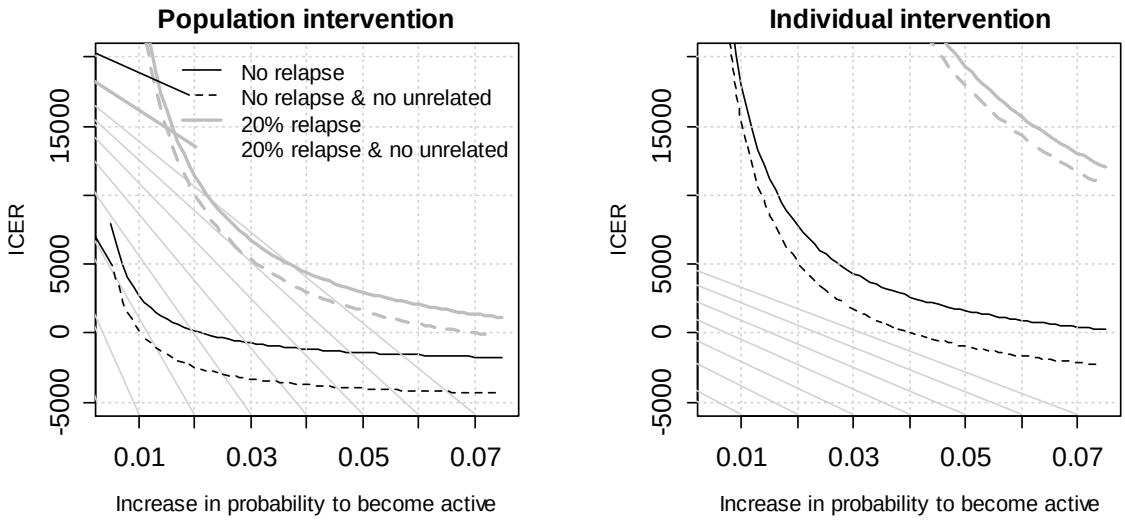


***Figure 5.4:*** *Influence of excluding costs of unrelated medical care on ICER for the scenario that inactive people become active. Intervention costs for population and individual level interventions are assumed to be 10 and 200 pounds, respectively. Please note that in the graph on the rights a legend has been omitted for clarity: lines in this graph mean the same as in the graph on the left.*

### 5.2.4 The influence of the discount rate

The impact of changing the discount rate for costs and effects is shown in figure 5.5. From this figure it can be seen that if future costs and effects are more heavily discounted the ICER increases. This is mainly due to the fact that most health gains occur in the future while most costs are made now (the costs of the intervention). Especially if the effectiveness of the intervention is low, the impact of the discount rate can be substantial. Please note that in all different scenarios shown in Figure 5.5 costs and effects are discounted at an equal rate (0%, 1.5% or 3.5% annually).

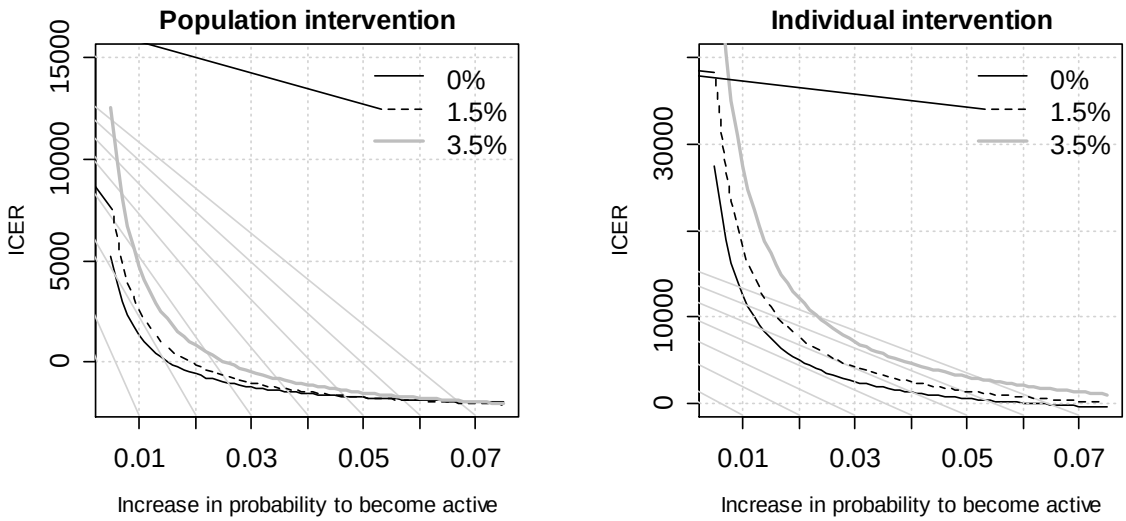


***Figure 5.5:*** *Influence of the discount rate for costs and effects on the ICER for the scenario that inactive people become active. Intervention costs for population and individual level interventions are assumed to be 10 and 200 pounds, respectively.*

# 6. Sensitivity analyses

In this chapter we investigated the robustness of the results with respect to several key assumptions. Firstly, the most important key assumptions of the model are presented. Based on these assumptions, six scenarios are described in which these key assumptions are challenged. Finally, the results of the different scenarios are presented.

As the sensitivity analysis showed that the ICERs are mainly sensitive to changes in the long term effectiveness (as shown in section 5.2.2) we do not present results in this chapter for the ICERS. Instead, in this chapter, we will focus on the results as presented in chapter four about lifetime costs and benefits of promoting physical activity.

## 6.1 Key assumptions and definition of sensitivity analysis

The key assumptions and input parameters we used to construct the model were the following (in order of importance):

A. Relative risk values used as input in the model for the association between PA and all-cause mortality and the association between PA and the onset of dementia;
B. Relative risks of PA on all-cause mortality were used to model the effect of PA through all other diseases besides dementia on mortality;
C. Quality of life values used in the model states with dementia were assessed by proxies and not by patients themselves;
D. We assumed that health care and social costs are highest in last year of life compared to 'other' years.

Based on these assumptions we formulated six different scenarios in which we varied one of the five presented assumptions. The first scenario is about the relative risks used for the association between PA and all-cause mortality. Physical activity was modelled in four classes (Meets recommendations / Somewhat active / Low activity / Inactive) and it was assumed that PA was 0.5 hours higher in the low activity group compared to the inactive, 1.5 hours higher for the some activity group and 2.5 hours for the group that meets recommendations. Using these assumptions, we could calculate relative risks on mortality for the different classes using results from a recent meta-analysis reporting the dose-response relationship between mortality and hours of PA (Samitz et al., 2011). The effect of PA on all-cause mortality using these relative risks was quite small if we compare these risks to the dose-response relationship as published by the US Physical Activity Guidelines Advisory Committee (see table 6.1) (Physical Activity Guidelines Advisory Committee, 2008). In scenario one of our sensitivity analysis we used the RRs as published in the US study.

***Table 6.1:*** *relative risks for the association between physical activity and all-cause mortality*

| | Inactive | Low activity | Some activity | Meets recommendations |
|---|---|---|---|---|
| Base case | 1 | 0.97 | 0.91 | 0.86 |
| Scenario one | 1 | 0.90 | 0.80 | 0.73 |

Scenario two is about the RRs used for the association between PA and the onset of dementia. The relative risk on the onset of dementia in the US report mentioned above (RR=0.63 (95% CI 0.50 to 0.80)) is very similar to the estimate reported by Sofi et al that was used in the base case of our model (RR=0.62-0.65 for the different PA classes) (Sofi et al., 2011). A more general problem when quantifying the relation between PA and dementia is that both the US report as well the Sofi meta-analyses do not provide detailed information on the level of physical activity. In the US report RRs are presented as the RR of subjects with a high physical activity level versus subjects with a low physical activity level without further definition of high and physical activity (Physical Activity Guidelines Advisory Committee, 2008). In the paper of Sofi et al. two risk ratios for the onset of cognitive decline were presented both compared to subjects being sedentary; one for subjects with high and one for subjects with low-to-moderate levels of physical activity (Sofi et al., 2011). Again no definition of high or low-to-moderate levels of physical activity was given. In this sense the way we used the RRs for the different classes is a bit arbitrary. In scenario two we therefore used different RRs for dementia. Instead of assuming that the RR of 0.65 applies to the low active group, we assume that it applies to the somewhat active group. We interpolated the RR for the low active group assuming a linear relation between RR and physical activity as measured in hours per week (see table 6.2).

***Table 6.2:*** *relative risks for the association between physical activity and the onset of dementia*

| | Inactive | Low activity | Some activity | Meets recommendations |
|---|---|---|---|---|
| Base case | 1 | 0.65 | 0.65 | 0.62 |
| Scenario two | 1 | 0.89 | 0.65 | 0.62 |

Scenario three is also about the relative risks used for all-cause mortality and the onset of dementia (key assumption A). In this scenario we applied the relative risks not to the entire age range, but only to ages 90 and below. The relative risks above the age of 90 were set to one.

Scenario four addressed key assumption B. For the base case we chose to apply the relative risks for the association between physical activity and all-cause mortality to the mortality due to other causes and not mortality due to dementia (equation (4 and 5)). Another option would be to calculate these in the following manner: $m(r, d = 0) = m - p(r, d = 1) \times em$. However, given the large impact dementia has on mortality at old ages, this would imply a lower 'other cause' mortality risk for the inactive at very old age (90+) than the active. In scenario four we applied this alternative assumption to calculate mortality rates for other causes stratified by PA.

Scenario five is about the assumption we made with regard to the health-related quality of life for people with dementia (assumption C). In the base case quality of life for dementia was based on a UK study of Sheehan et al. in patients with dementia admitted in general (Sheehan et al., 2012). We used the value as assessed by the proxies of the patients (0.30), because this value seems more valid. In scenario five, quality of life for dementia was based on the same study of Sheehan but now we used the value as reported by patients themselves (0.71).

In the base case analysis health care and social costs were made specified by the last year of life and 'other' years (assumption D). To model the influence of PA on health care expenditures (HCE) through diseases other than dementia we related health care expenditures to mortality risk. By making a distinction between HCE in the last year of life and other years it is possible to proxy the effect that diseases have on the demand for health. In scenario six we challenged this assumption and made costs dependent on age only.

Table 6.3 summarizes the six different scenarios that we analyzed in the sensitivity analysis.

***Table 6.3:*** *Overview of the six different scenarios that were run for the sensitivity analyses*

| Scenario | Assumption | Definition |
|---|---|---|
| 1 | A | RRs PA and all-cause mortality 1/0.9/0.8/0.73 instead of 1/0.97/0.91/0.86 |
| 2 | A | RRs PA and dementia 1/0.89/0.65/0/62 instead of 1/0.65/0.65.0.62 |
| 3 | A | RRs above age 90 were set at 1 |
| 4 | B | Alternative assumption with respect to mortality |
| 5 | C | QoL for persons with dementia based on patient ratings instead of proxies |
| 6 | D | Costs for other diseases depend on age only instead of age and last year of life |

## 6.2 Results sensitivity analyses

Table 6.4 displays estimates of the life expectancy at the age of 40 years for the base case and the six different scenarios that were run in the sensitivity analysis. Scenario one in which different RRs for the association between PA and all-cause mortality were used had the highest impact and increased differences in life expectancy between the different PA class most. For males with low activity and inactive males the life expectancy decreased from 39.0 to 38.8 and from 38.1 to 37.4 years, respectively. Using a different RR for the onset of dementia for the group that is low active (scenario two) had, as expected, the most impact on the life expectancy of the low active persons, which changed from 39.0 to 38.6 years for males and from 42.8 to 42.5 years for females. Scenario 4 in which an alternative assumption was used to calculate other cause mortality rates did not have a big impact on life expectancy estimates.

***Table 6.4:*** *Life expectancy at the age of 40 years in different sensitivity analysis**

| | | Base case | Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4 |
|---|---|---|---|---|---|---|
| Men | Recommendations | 40.1 | 40.7 | 40.1 | 40 | 40 |
| | Some activity | 39.5 | 39.8 | 39.5 | 39.5 | 39.4 |
| | Low activity | 39.0 | 38.8 | 38.6 | 38.9 | 38.8 |
| | Inactive | 38.1 | 37.4 | 38.2 | 38.2 | 38.2 |
| Women | Recommendations | 43.9 | 44.6 | 43.9 | 43.7 | 43.7 |
| | Some activity | 43.3 | 43.8 | 43.4 | 43.2 | 43.2 |
| | Low activity | 42.8 | 42.8 | 42.5 | 42.8 | 42.6 |
| | Inactive | 42.0 | 41.4 | 42 | 42 | 42.1 |

**Scenarios five and six on quality of life and costs did not change the life expectancy compared to the base case.*

Table 6.5 shows the average number of years spent with dementia at the age of 40 years for the six different scenarios. Compared to the base case the changes were minimal. Only scenario two using a different RR for the onset of dementia for the low active group had some impact. The years with dementia within this physical activity class changed from 2.4 to 3.1 for males and from 2.5 to 3.2 for females.

***Table 6.5:*** *Years with dementia at the age of 40 years in different sensitivity analysis**

| | | Base case | Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4 |
|---|---|---|---|---|---|---|
| Men | Recommendations | 2.4 | 2.5 | 2.4 | 2.4 | 2.4 |
| | Some activity | 2.4 | 2.5 | 2.4 | 2.5 | 2.4 |
| | Low activity | 2.4 | 2.4 | 3.1 | 2.4 | 2.4 |
| | Inactive | 3.4 | 3.3 | 3.4 | 3.4 | 3.4 |
| Women | Recommendations | 2.5 | 2.6 | 2.5 | 2.5 | 2.5 |
| | Some activity | 2.5 | 2.6 | 2.5 | 2.6 | 2.5 |
| | Low activity | 2.5 | 2.5 | 3.2 | 2.5 | 2.4 |
| | Inactive | 3.5 | 3.4 | 3.4 | 3.5 | 3.5 |

**Scenarios five and six on quality of life and costs did not change estimates of years with dementia compared to the base case.*

Table 6.6 displays the quality-adjusted life expectancy (QALE) at the age of 40 years for the six different scenarios. Using the quality of life value for dementia as reported by patients themselves instead of proxies (scenario five) had the highest impact on the results. In all physical activity classes the QALE increased with about one year. Scenario one on the different RRs for all-cause mortality had the second highest impact. In this scenario the QALE for persons that meet the recommendation increased with about 0.5 year, while for inactive persons the QALE decreased with 0.3-0.5 year.

***Table 6.6:*** *Quality-adjusted life expectancy (QALE) at the age of 40 years in different sensitivity analysis*

| | | Base case | Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4 | Scenario 5 |
|---|---|---|---|---|---|---|---|
| Men | Recommendations | 31.6 | 32.1 | 31.7 | 31.6 | 31.6 | 32.6 |
| | Some activity | 30.8 | 31 | 30.8 | 30.8 | 30.7 | 31.8 |
| | Low activity | 29.7 | 29.6 | 29.1 | 29.7 | 29.6 | 30.7 |
| | Inactive | 28.0 | 27.5 | 28 | 28 | 28 | 29.4 |
| Women | Recommendations | 34.2 | 34.6 | 34.2 | 34 | 34.1 | 35.2 |
| | Some activity | 33.3 | 33.6 | 33.4 | 33.3 | 33.2 | 34.4 |
| | Low activity | 32.2 | 32.2 | 31.7 | 32.2 | 32.1 | 33.2 |
| | Inactive | 30.4 | 30.1 | 30.5 | 30.5 | 30.5 | 31.9 |

**Scenario six on costs did not change the quality adjusted life expectancy compared to the base case.*

Results for the estimated lifetime total costs at the age of 40 years are presented in table 6.7. The impact of changing assumptions on the total costs was limited in all six scenarios. Making costs dependent on age only instead of age and last year of life hardly influenced the results. Using a different RR for the all-cause mortality (scenario one) had the highest impact, but lifetime costs increased or decreased by only 1000 to 2000 pounds compared to the base case. Using a different RR for the onset of dementia in the low active group (scenario two) resulted in an increase of the lifetime total costs by 4000 pounds for both low active males and females. Scenario five on quality of life did not change the estimates compared to the base case.

***Table 6.7:*** *Undiscounted lifetime total costs (x 1000 pounds) at the age of 40 years in different sensitivity analysis**

| | | Base case | Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4 | Scenario 6 |
|---|---|---|---|---|---|---|---|
| Men | Recommendations | 63 | 65 | 63 | 63 | 63 | 63 |
| | Some activity | 62 | 63 | 62 | 62 | 62 | 62 |
| | Low activity | 61 | 61 | 65 | 61 | 60 | 60 |
| | Inactive | 66 | 64 | 66 | 66 | 66 | 65 |
| Women | Recommendations | 76 | 78 | 76 | 76 | 75 | 75 |
| | Some activity | 75 | 76 | 75 | 75 | 74 | 74 |
| | Low activity | 73 | 74 | 77 | 73 | 73 | 72 |
| | Inactive | 77 | 76 | 77 | 77 | 78 | 76 |

**Scenario five on quality of life did not change estimates of lifetime total costs compared to the base case.*

In table 6.8 the results of three different scenarios of increase in physical activity level are shown. The scenarios are the same as described in paragraph 4.2: 1) an inactive cohort becomes low active, 2) a low active cohort becomes somewhat active and 3) a somewhat active cohort becomes more active and meet recommendations.

***Table 6.8:*** *Undiscounted QALY gains and incremental costs in different sensitivity analysis for the three different scenarios described in paragraph 4.2.1*

| | | Base case | Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4 | Scenario 5 | Scenario 6 |
|---|---|---|---|---|---|---|---|---|
| QALYs gained | Inactive → low active | 1750 | 2132 | 1163 | 1710 | 1595 | 1320 | |
| | Low active → some activity | 1122 | 1444 | 1702 | 1095 | 1138 | 1151 | |
| | Some activity → recommendations | 826 | 1000 | 827 | 790 | 827 | 812 | |
| ΔCosts* | Inactive → low active | -4551 | -2665 | -848 | -4511 | -5440 | | -4580 |
| | Low active → some activity | 1449 | 2777 | -2191 | 1306 | 1547 | | 1701 |
| | Some activity → recommendations | 955 | 1643 | 960 | 807 | 972 | | 1196 |

***** In thousand British pounds

For the situation that all inactive persons would become low active, the gain in QALYs dropped substantially compared to the base case when a different RR for the onset of dementia for the low active group was used (from 1741 to 1163 QALYs gained). Using different quality of life values for dementia also had a high impact on the number of QALYs gained (decrease from 1741 to 1320). However, in all sensitivity analysis scenarios the situation that all inactive persons would become low active resulted in cost savings, although the savings may decrease to only one-fifth of the total savings as observed in the base case (scenario two). For the situation that all low active persons would become somewhat active, the gain in QALYs was also mostly influenced by the assumption used on the RR for the onset of dementia in the low active group (scenario two). Using the higher RRs resulted in an increase in QALYs gained from 1123 to 1702 and cost savings. Using different RRs for all-cause mortality also had some influence on the results. The QALY gained and costs for the situation that somewhat active persons would become more active and meet the recommendations did not differ much between the different sensitivity analysis scenarios and the base case. The assumption on the RRs for all-cause mortality (scenario one) had the highest impact.

# 7. Conclusions & discussion

In this report we constructed a model that links physical activity to dementia, mortality, quality of life and health and social care expenditures. With this model we ran several analyses from which we derive the following key messages:

- Inactive persons live almost a year less than active persons and in a lower quality of life;
- In their shorter lives, inactive persons can expect to live about a year more of their lives with dementia;
- Preventing inactivity yields more health gains than increasing activity levels in those already active;
- Preventing inactivity has the potential to decrease health and social care spending as the savings due to preventing dementia outweigh the additional spending in life years gained;
- Promoting physical activity has the potential to increase (quality adjusted) life expectancy in the English middle aged population by about half a year without increasing the demand for health and social care;
- Individual level interventions are likely to be more cost-effective when targeted at inactive persons;
- The most crucial determinant for interventions to be cost-effective is whether they succeed in maintaining increased levels of physical activity in the long run;
- Interventions would be at best borderline cost-effective if each year more than 20% return to their pre-intervention level of activity;
- Including costs of unrelated medical care increases the cost effectiveness by about 2500 pound per QALY on average.

The biggest gap in evidence relates to a lack of knowledge regarding the dose-response relationship between physical activity and the onset of dementia, while results of the model were highly dependent on the RRs used for the relation between physical activity and the onset of dementia. We used the relative risks as published by Sofi et al (Sofi et al., 2011). In this study the risk ratio for the onset of cognitive decline was published for subjects with high and low-to-moderate levels of physical activity compared to subjects being sedentary. In the model, the risk ratio for high levels of physical activity was applied to the group that meets recommendations, while the risk ratio for low-to-moderate levels of activity was applied to the groups with low and some activity. As a result there was no difference in the onset of dementia between the low and some activity classes in our model in the base case analysis. In chapter six we presented the results of a sensitivity analysis scenario in which the RR for the onset of dementia in the low active group was assumed to be higher (0.89 instead of 0.65). Results showed that life expectancy and QALE of the low active group would decrease, while the number of years with dementia and lifetime total costs would increase compared to the base case scenario. Using these alternative RRs suggests that both the health benefits as well as cost savings of preventing inactivity would diminish. From the base case analysis we concluded that targeting the inactive group to become low active should be preferred. Using a higher RR for the onset of dementia for the low active group would change this conclusion as both the option of targeting the inactive group as well as targeting the low active group would be cost saving. More detailed information on the association between physical activity and dementia in terms of decreased risk per increment of hour of physical activity per week would further improve the model. The most important other assumptions that were addressed in the sensitivity analysis

(chapter six) were the use of different RRs for the association between physical activity and all-cause mortality, using quality of life values for dementia based on patients instead of proxies and making costs for other diseases dependent on age only instead of age and last year of life. The impact of all these assumptions was limited as shown in chapter six. The assumption on the RR for all-cause mortality had the highest impact on the estimates of life expectancy, the years with dementia and the total life time costs. Using different quality of life values for dementia had the highest impact on the QALE. Results for the different scenarios of increase in physical activity changed slightly but the conclusion remained unchanged.

Another important gap in information is the lack of evidence regarding the long-term effectiveness of interventions promoting physical activity. Although many interventions targeting physical activity have been evaluated most of them have a short follow-up or are targeted at very specific groups. Furthermore, effectiveness of interventions is often difficult to compare and combine. Outcomes are self-reported or based on more objective measures of cardiorespiratory fitness, outcomes are presented as percentage change in inactivity or change in hours of physical activity per week and outcomes are reported for different domains of physical activity. Because of the lack in evidence in long-term effectiveness of interventions targeting physical activity, we chose to present the cost-effectiveness of interventions as a function of the effectiveness to ensure that the results are broadly applicable.

Three other modeling studies looked at the association between physical inactivity and the risk of developing dementia (Barnes et al., 2011; Nepal et al., 2010; Zhang et al., 2011). The study of Barnes et al calculated the population attributable risks (PAR) for several risk factors on the current prevalence of Alzheimer's disease worldwide and in the US (Barnes et al., 2011). Worldwide 13% of Alzheimer cases were estimated to be potentially attributable to physical inactivity, while for the USA this estimate would be 21%. In our study about 20% of the dementia cases were attributable to physical inactivity, which is in line with the study of Barnes. Nepal and colleagues evaluated the potential impact of physical activity interventions on the projections of dementia prevalence in Australia (Nepal et al., 2010). The prevalence of physical inactivity in males was estimated to range from 30% to 55% over the different age classes (>45 years), while for females this estimate ranged from 35% in the lowest age class (45-49 years) to 75% in the highest age class (85+). Combined with the RR reported for the association between physical inactivity and dementia, this resulted in a PAR estimate varying from 17% in the lowest age class to 34% in the highest age class. Our estimate of about 20% was comparable to the PAR estimates in the study of Nepal for the age classes up to 70 years of age. The study of Zhang et al included physical inactivity as one of the seven risk factors that were combined in one overall risk score (Zhang et al., 2011). Therefore results of that study could not be compared to the results of our study.

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