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Title: Modelling the economic impact of interventions for older populations with multimorbidity: a method of linking multiple single-disease models

Running title: Discrete Event Simulation model linkage

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Abstract

Introduction:

Individuals from older populations tend to have more than one health condition (multimorbidity). Current approaches to produce economic evidence for clinical guidelines using decision analytic models typically use a single-disease approach, which may not appropriately reflect the competing risks within a population with multimorbidity. This study aims to demonstrate a proof-of-concept method of modelling multiple conditions in a single decision-analytic model to estimate the impact of multimorbidity on the cost-effectiveness of interventions.

Methods:

Multiple conditions were modelled within a single decision-analytic model by linking multiple single-disease models. Individual Discrete Event Simulation models were developed to evaluate the cost-effectiveness of preventative interventions for a case study assuming a UK National Health Service perspective. The case study used three diseases (heart disease, Alzheimer's disease, and osteoporosis) that were combined within a single 'linked' model. The linked model, with and without correlations between diseases incorporated, simulated the general population aged 45 years and older to compare results in terms of lifetime costs and quality-adjusted life years (QALYs).

Results:

The estimated incremental costs and QALYs for healthcare interventions differed when three diseases were modelled simultaneously (£840; 0.234QALYs) compared with aggregated results from three single-disease models (£408; 0.280QALYs). With correlations between diseases additionally incorporated, both absolute and incremental costs and QALYs estimates changed in different directions, suggesting that the inclusion of correlations can alter model results.

Discussion:

Linking multiple single-disease models provides a methodological option for decision-analysts who undertake research on populations with multimorbidity. It also has potential for wider applications in informing decisions on commissioning of healthcare services and long-term priority setting across diseases and healthcare programmes through providing potentially more accurate estimations of relative cost-effectiveness of interventions.

Keywords: Discrete event simulation; multimorbidity; comorbidity; chronic diseases; economic evaluation; cost-utility analysis; health technology assessment; decision analytic modelling;

Introduction

The prevalence of long-term conditions tends to steadily increase with age [1]. This trend results in an increased prevalence of multimorbidity, defined as the co-existence of two or more long-term health conditions, in populations of older people [2-4]. The increased proportion of individuals with multimorbidity may have a significant impact on healthcare and resource allocation decision-making [5-7]. Evidence suggests that the number of conditions, rather than specific diseases, is a greater determinant of use of healthcare service resources [2]. Multimorbidity is associated with increased healthcare costs, service use, mortality, and reduced quality of life than is the case for those of single conditions [3, 8, 9]. Some commentators have suggested the need to focus on the prevention and management of multimorbidity rather than of single diseases [10].

Despite the resource and health implications of multimorbidity, most economic evaluations are conceptualised and designed to evaluate the incremental costs and benefits (relative cost-effectiveness) of interventions for single diseases [11] to recommend care and management for people with specific conditions. Decision-analytic models used to inform the Clinical Guidelines (CG) published by the National Institute for Health and Care Excellence (NICE) in England, and more widely [12-14], seldom consider people with multiple conditions [15]. Economic evidence for CG development is informed by a decision-analytic model (hereafter 'economic model') designed to appraise interventions to treat or manage adverse health events which are most likely to occur within the same (single) disease [16].

Consideration of multimorbidity in an economic model should potentially provide more reliable estimates than those from a single-disease approach. Consequently, taking account of multimorbidity should lead to improved decisions on adoption and implementation of interventions for populations with more than one conditions. Taking account of multimorbidity in a single model is likely to change the estimates of costs and quality-adjusted life years (QALYs) of treating and managing the diseases when compared with modelling separate multiple populations with single conditions [17]. Intuitively, the results from two or more separate disease models can be combined

to obtain an understanding of the overall outcomes for a multi-morbid population. However, combining recommendations produced for single conditions to take account of multimorbidity may not represent the clinically optimal or cost-effective use of healthcare resources without jointly accounting for the benefits and risks of interventions [10, 18]. Such an approach does not incorporate competing risks of death nor does it account for the modification in the risks and health-related quality of life (HRQoL) of the population with multimorbidity.

This study aimed to present a proof-of-concept approach to taking account of multimorbidity in an economic model to generate robust estimates of incremental costs and health outcomes. The main focus was to present a methodology that could address multimorbidity within a single economic model by linking multiple single-disease models and, therefore, demonstrate the feasibility of using published models to incorporate multiple conditions within a single model. The method was illustrated using a case study of three selected diseases. The paper is now presented in three main sections. Section two describes the linkage methods used and the relevant case study. Section three reports the base-case results from the linked models, including a key finding associated with interpretation of result. Section four discusses the implications and limitations of using this approach in practice.

Methods

This study demonstrates a method for linking multiple single-disease economic models using a Discrete Event Simulation (DES) constructed in SIMUL8 (©SIMUL8 Corporation). Three approaches to conceptualising and constructing an economic model were directly compared: (i) aggregating results from multiple single-disease models; (ii) modelling multiple diseases simultaneously within a single economic model; and (iii) incorporating correlations between diseases in the multi-disease economic model created in (ii).

A case study was used to illustrate the methods. Multimorbidity was captured in the case study using three example diseases: heart disease (HD), Alzheimer's disease (AD) and osteoporosis. Three diseases were selected to demonstrate the ability of the method to address any number of diseases that may co-occur. The selection of the relevant diseases to include in the case study was based on the economic, mortality and morbidity burden of each condition and the desire to cover a spectrum of conditions (see Appendix 1 for detailed selection criteria). A reference economic model to inform decisions on the structure, sources of data and key assumptions for each disease was identified from

a rapid review of recently published economic models [19-21]. Using these economic models, the current recommended treatments for the three diseases (statins for HD; donepezil for mild to moderate AD and memantine for severe AD; and alendronic acid for osteoporosis) were compared with no drug treatment. The specific details of the case study and challenges associated with the application of the method are reported in Appendices 1-8.

The analysis was undertaken from the perspective of UK National Health Service (NHS) and Personal Social Services (PSS) in line with the reference case stipulated by NICE [22]. A lifetime horizon was used to fully assess the long term effect of the interventions. Costs and health outcomes associated with a lifetime use of the interventions were presented in terms of pounds sterling (£ in 2012/13 price) and QALYs, respectively. The relevant population was defined as the UK general population aged 45 years and over with or without the diseases, rather than only the elderly, to fully capture the prevention effect of the interventions. Age and gender values were randomly sampled from the UK mid-2012 population estimates [23]. Those individuals who did not have the disease may or may not develop it before death based on the age- and gender-stratified incidence of the disease. A discount rate of 3.5% per annum was used for both costs and QALYs. The next section describes the methods used to link multiple single-disease models in reference to the conventional DES approach.

Individual patient modelling methods

A DES approach was chosen for modelling the three diseases in which individual patients are simulated to move through different disease events sampled from time-to-event distributions. The selected diseases were modelled individually and then combined within a single DES model as a linked-disease economic model (see Figure 1). Potential correlations between the diseases were additionally explored in the linked-disease economic model. Figure 2 illustrates the method for model linkage with respect to simulation time.

===== Place **Figure 1** here =====

======Place **Figure 2** here=======

Individual patient modelling was used to provide more flexibility to incorporate heterogeneity among patients when compared with cohort modelling. Whilst cohort-based models can theoretically account for different characteristics of individuals such as age, risk factors, and history of other diseases, the number of dimensions needed for the relevant health states become

exponentially large [24]. The 'time-to-event' approach used in DES provided a practical option for linking multiple diseases. Transition probabilities for pre-specified equal-length cycles as in state-transition cohort (Markov) models are not required, allowing for greater flexibility in the times when events can occur. DES models can also record more individual attributes to account for patient history than Markov models: the rate of Event 1, $r(Event\ 1)$, is updated once an individual experiences Event 2, such that $r(Event\ 1|Event\ 2) \neq r(Event\ 1)$.

Figure 2(a) represents an economic model for a disease shown as a course of changes over time in 'variables' that define the modelled system (the process of disease progression). Figure 2(a-ii) depicts a Markov model in the same format as the DES model for a selected individual from a cohort. Any occurrences that alter any set of such variables can be considered as 'events'. The variables describing the state of a disease process at a point in time include: global variables that apply to all simulated individuals (e.g. discount rates and unit costs of interventions); and individual attributes that may or may not change over time (e.g. age, sex and individual's disease history or changes in state membership if an individual from a Markov cohort is considered). The model outcomes such as lifetime costs and QALYs are based on the trajectories of these variables. Figure 2(a) shows how the DES allows for changes in the system variables to occur at any discrete point in time such that, multiple events can occur within a short period of time. The calculation of costs and QALYs is then made only when events occur, not at every cycle as in Markov models, hence allowing a large number of disease events to be incorporated in DES models.

Modelling methods for linked model: general approach

The flexibility of the DES approach means that it is possible to merge existing single-disease economic models to create a linked-economic model by combining all event-defining variables within one system (see Figure 2(b)). In the linked economic models, costs were assumed to be additive. Four approaches (additive, minimum, multiplicative and linear index methods) to combine utility values for joint health conditions are possible in the absence of actual data for a population with more than one health condition. There is no agreement on the best approach and current recommendations suggest using the multiplicative method, which was the approach adopted in this study [25].

Individuals with multiple diseases may have a higher risk of death. Multimorbidity is taken into account for disease-related death as competing risks: HD- and fracture-related deaths. The earliest

time to disease-related death was determined at the central router in the DES. Death may not be related to any of the diseases explicitly modelled. Non-disease mortality rates in the linked model were defined as all-cause mortality obtained from the UK Interim Life Tables [26] minus the death rates associated with the diseases included in the model.

Two versions of the linked-economic model were constructed which assumed (i) independence between the three diseases; or (ii) correlation between the diseases. A probabilistic analysis was conducted using the linked economic model assuming correlation. Next section describes how the linked economic model assuming independence between the three diseases was constructed. Independence assumes that the presence of one disease does not affect the risk of the others (denoted hereafter as 'independently linked model').

Linked economic model: assuming independence

All variables used in the single-disease DES models (Figure 2(b-i)) were combined to produce the independently linked economic model (Figure 2(b-ii)). This approach unifies variables, such as age and gender, commonly included in all single-disease economic models (Figure 2(b-ii)). In the linked economic model, the sequence of events is redefined to represent the times when any variables combined in the linked model are scheduled to change (Figure 2(b-ii)). Creating a linked economic model involves adding a central routing variable that directs simulated individuals to the earliest next event. This routing is done by taking a value indicating which of the diseases the identified next event is associated with (Figure 2(b-ii)). Competing risks across all individual disease models can also be compared and individuals are directed to move to the event corresponding to the earliest scheduled time to event. This linked-economic model can provide a seamless approach especially when populations at increased risks of multimorbidity are modelled and when existing models are available for the individual diseases.

Table 1 provides additional detail on the process used to update event times and routing. The table shows how to follow an individual through the DES from model entry. Individuals can have zero, one, two or three of the diseases, and enter the combined model with characteristics sampled at the entry point. These characteristics are used for the sampling of times to next event (TTNEs) and/or the calculation of aggregate costs and QALYs. Individuals enter the DES model through the central routing point where the transition to the next event is executed. Once the individuals move to the event and all relevant parameters are updated, they return to the central router to be routed to the

next event. This process is repeated until an individual has been simulated up until the point at which they die. Recording the history of previous events means that the DES can account for multimorbidity, in terms of event costs, HRQoL and influence on risks of future events. The times to all further predicted events are then either resampled based on updated parameters or reduced by the TTNE to account for the passing of time. For example, at the central routing point, TTNEs for the other diseases are subtracted by the time spent in the previous event. Other time-related variables such as time before the effect of treatments stops, and time before the end of the first year of any cardiac events or osteoporotic fractures, are then re-calculated.

===Place **Table 1** here===

Linked economic model: assuming correlations between diseases

This section describes how correlation between the three diseases was taken into account in the linked economic model. Incorporating correlations between diseases assumes that having one disease can affect the risk of other diseases and hence correlations between diseases are incorporated (denoted hereafter as 'correlated linked economic model'). The correlated linked economic model assigns disease history and event probabilities based on the status of the other diseases included in the DES model. Correlations associated with prevalence were incorporated to set the distribution of diseases at the start of the model, and correlations associated with incidence were used to dynamically change the incidence of one disease conditional on the occurrence of other disease events.

The model assumed that the occurrence of HD events affects the incidence of AD, but not vice versa due to the relatively later onset of AD compared with that of HD [27]. There is growing evidence that supports osteoporosis is correlated with both HD and AD as greater vascular dysfunction is associated with lower bone mineral density [28-30]. Excess fracture risk has been reported among patients with a diagnosis of myocardial infarction with a hazard ratio of 1.73 [95% CI, 1.32-2.27] [31]. The DES assumed that a history of HD events would increase fracture risks and those with previous fracture would be at an increased risk of stroke and AD onset [31, 32].

For demonstrating a proof-of-concept model, correlations regarding selected prevalence and incidence estimates were deemed sufficient. Five types of correlations (see Appendix 2 for detail) were incorporated in the correlated linked model: i) prevalence and ii) incidence of AD in people

with and without HD; iii) incidence of hip fracture for people with a history of MI; iv) the risk of stroke among people with a history of hip fracture; and v) incidence of AD in people with low bone mineral density. Correlations associated with prevalence were incorporated at the start of the model by setting the distribution of diseases across individuals. Correlations associated with incidence were incorporated using a more dynamic approach. For example, after an individual develops an HD event, the incidence of AD for that individual was changed from the time of that HD event. To incorporate the correlation between AD and HD, the total proportion of people who have AD was divided into the proportion of AD patients among people with HD and the proportion among people without HD. The incidence of AD for the total population was divided into that for population with HD and for population without HD, such that the sum of the incidence values equals the total incidence.

Constructing single-disease models

This section describes how the three single-disease economic models (heart disease, Alzheimer's disease and osteoporosis) were conceptualised and built for the case study (see Figure 3). A rapid review was undertaken to identify economic models published as part of the UK National Institute for Health Research (NIHR) Health Technology Assessment (HTA) monograph series (https://www.journalslibrary.nihr.ac.uk/HTA/). Two of the three identified relevant single-disease models were Markov cohort models (HD and AD). The core structure of each identified economic model for each single disease was maintained but adapted to be implemented on a DES platform. Data sources reported in the published HTA reports were also used as model input parameters (see Appendix 3). All transition probabilities reported in the published economic models were converted to rates. Event rates reflect the instantaneous likelihood of the event occurring per unit of time. For each model, the appropriate number of simulated individuals to ensure stable outcomes was identified by examining the standard error of the mean estimates of (incremental) cost and QALYs, and the mean and jackknife confidence interval for the incremental cost per QALY estimate [33]. The results from the three single-disease models were compared with those of the published models to externally validate the model.

===== Place **Figure 3** here=======

Heart disease model

The state transition cohort model developed by Ward *et al.* [19], and used to inform guidance recommended by NICE, was used as the single disease model for heart disease (HD; Figure 3a). Statins, assuming a common class effect, were the intervention used for the secondary prevention of HD in patients with angina, MI, PAD or a history of stroke, and for primary prevention in patients who are at increased risk of coronary events. High-risk patients were defined as those whose estimated 10-risk of developing CVD is greater than 20% according to NICE TA94 [19]: however, the threshold was amended to 10% in 2014 [34].

Sources of data and key assumptions reported in Ward *et al.* [19] were considered as the main reference for the model. A review of existing models suggested that the single-disease economic model for HD should be adapted to include peripheral artery disease (PAD) and that it was necessary to update some parameter estimates (see Appendix 3).

First-year events and events in subsequent years were kept distinct because of the differences in the cost of interventions and HRQoL within these time periods. No difference in event rates was assumed between the first year and subsequent years after PAD because there was no clinical evidence identified distinguishing the two periods. The DES uses continuous time which means it was possible for an individual to have multiple events, and associated utility values, within a 12-month period. It was therefore possible for one individual to incur two or more utility modifiers associated with first-year events. An event updating utility values was added to the model to ensure that changes in HRQoL were handled appropriately.

Alzheimer's disease

A DES model for Alzheimer's disease (AD) was constructed (Figure 3b) based on the Markov model published in the HTA report by Bond *et al.* [20]. After a diagnosis of AD, the model structure replicated the three-state model in Bond *et al.* [20]. In line with current NICE recommendation [35], it was assumed that patients with a Mini-Mental State Examination (MMSE) score between 10 and 26 at diagnosis (i.e. 10≤ MMSE ≤26) received donepezil. Memantine was assumed for patients with MMSE < 10.

A simulated population representative of the UK population aged 45 and over was assumed to enter the model. This analysis assumed that some individuals have AD when entering the model. Those entering the model without AD may or may not develop AD before death based on the sampled time to onset of AD. It was assumed that diagnosis of AD is not instantaneous as the development of symptoms is gradual.

Osteoporosis model

The economic model produced by Stevenson *et al.* [21] was used as a basis for osteoporosis model constructed for the case study (see Figure 3c).

Events included in the DES model for osteoporosis were defined by four index fracture sites (hip, vertebral, wrist and proximal humerus fractures) and the risks of: nursing home entry from hip fracture; death following fracture; and non-fracture related death. The events representing initiation and discontinuation of a preventative pharmacological intervention (70mg alendronate taken once weekly) were also included. The model included fractures occurring to both osteoporotic and non-osteoporotic populations [21]. It was possible to have two first year utility multipliers acting simultaneously. An event to update utility values was included in the model to reflect that utilities for the first year and subsequent years after a fracture could be different.

Results

This section presents illustrative simulation results for the UK general population aged 45 years and older from the case study. The three single-disease models produced comparable results with those from the published reference models despite the difference in model populations (see Appendix 4). Results are reported from two types of linked models: those from the independently linked model; followed by those from the correlated linked model. For all results reported in this section, stochastic variability between simulated individuals was examined to ensure stable outcomes (see Appendix 5).

Linked economic model: assuming independence

Table 2 reports the base-case results from the linked economic model assuming independence between the three diseases. Incremental cost-per-QALY estimates for the three interventions (statins, donepezil or memantine, alendronate) for the three diseases in combination (HD, AD, osteoporosis, respectively) differed between the linked economic model and the individual disease DES models. There were higher incremental costs (£840) and lower incremental QALYs (0.234) in the linked economic model compared with the sum of the three single-disease model results (£408, 0.280) (see Appendix 6). The absolute costs from the independently linked model (£14,776 for intervention arm) were slightly lower than the sum of the absolute costs from the three single-disease models (£15,520). The absolute QALYs (8.956 for intervention arm) were also lower than the minimum of the equivalent values from the three individual disease models (9.249), as utility levels were generally lower in the model including multiple diseases than in the models that consider only one disease.

=== Place **Table 2** here ======

Table 3 presents incremental cost and QALYs, and cost per QALY estimates of each intervention (statins, donepezil or memantine, alendronate) from the independently linked model based on 700,000 simulated individuals. This analysis assumed that the interventions for the other two conditions were available to individuals. The results differed from the results from the single disease

models: the linked model produced larger incremental costs and smaller incremental QALYs in absolute values than the single disease models (see Appendix 6).

This difference was most noticeable for AD intervention which produced lower QALYs with lower costs than no treatment in the linked model (incremental QALYs of -0.001; incremental cost of -£24) whilst it was dominating no treatment in the individual AD model (Appendix 6). The results in Table 3 did not have face validity because it was not considered plausible to have negative incremental QALYs associated with AD intervention: donepezil or memantine only delays cognitive impairment and the model did not capture the impact of adverse drug events. Therefore, the number of simulated individuals was increased to two million, from 700,000, individuals, and then face validity improved with the AD intervention dominating no treatment with a very small QALY gain. The small incremental values were in line with the results from the Bond et al. study [20, 36].

=== Place Table 3 here======

Impact of imbalance between the linked diseases on the interpretation of the results

Making a direct comparison between the absolute size of incremental QALYs and costs per person across the single-disease economic models (Figure 4 and Appendix 6), it is clear that the effect of HD intervention was much larger than those interventions for AD or osteoporosis. The results were shown to be stable within individual disease models. The relative cost-effectiveness of individual interventions estimated from the linked economic model could potentially be affected by the level of balance between the size of QALYs and cost outcomes from the individual diseases included in the linked economic model (regardless of whether independence or correlation was assumed). This effect was observed when the QALY gains from one disease (in the case study, HD) were much larger than those for the remainder and there were different levels of Monte Carlo sampling error between diseases. Hence, an acceptable level of sampling error in one disease for robust adoption decision for that disease could significantly impact the QALYs and cost outcomes for the other diseases.

====Place **Figure 4** here=====

The margin of error, defined as half-width of the 95% confidence interval in this study, around the mean incremental QALYs, was used to describe the amount of random sampling error in the simulation results [37]. In the individual HD model, the margin of error was estimated to be 0.0288 QALYs based on 200,000 simulated individuals. To estimate the predicted margin of error of the mean incremental QALYs with increased number of simulated individuals (N), a power regression model was used to fit a non-linear curve that decreases proportionally by $\sqrt{N}$ (R^2=0.9999). Using the fitted equation, the margin of error in incremental QALYs for HD intervention with 700,000 individuals was predicted to be 0.0155 QALYs. With 10 million individuals simulated, this value (0.0042 QALYs) was still large compared with the incremental QALYs associated with the interventions for AD (0.001 QALYs) and osteoporosis (0.008 QALYs). This shows that, where the treatment of one disease has a much larger absolute impact on cost and QALYs than the impact of treatments for other, a very large number of individuals may need to be simulated for stable results to be achieved in a linked model. Appendix 7 describes a hypothetical scenario in which a similar level of QALY gains was assumed for all three interventions, and the adoption decision within the linked model for each individual intervention was robust.

Linked economic model: assuming correlation between diseases

Table 4 reports the base-case results from the linked economic model incorporating correlations. The incremental cost-per-QALY results for the combination of the three interventions were similar to the results from the independently linked model (£3,583 per QALY gained). When the three diseases were assumed to be correlated, the absolute values of QALYs and life years increased and costs were lower. This was the result of positive correlations between diseases resulting in multimorbidity being more concentrated within a narrower population. Table 5 shows the results of running the model with two million individuals simulated to reduce the impact of the aforementioned sampling error issue. A probabilistic sensitivity analysis (PSA) using the correlated linked model was undertaken and its feasibility in the multi-disease DES context is discussed in Appendix 8. All of the 300 PSA samples showed incremental cost-per-QALY being lower than the threshold of £20,000 per QALY gained (Figure S8.1, Appendix 8). Conducting 300 PSA runs required 1.9 days of computing time for each intervention arm (Intel Core™ i7CPU 3.40GHz processor with 16GB RAM).

===Place **Table 4** here=====

==== Place Table 5 here=====

Discussion

This study aimed to demonstrate a proof-of-concept method to link multiple single-disease models using a case study involving three diseases (HD, AD and osteoporosis) managed with three interventions (statins, donepezil or memantine, alendronate). The inclusion of multiple diseases in a single DES model also enabled correlation between the diseases to be incorporated. This illustrative example showed that producing a linked economic model was feasible using DES and also allowed a PSA to be performed. The results from the three single-disease models were broadly comparable with those from the published economic models despite differences in model populations, costs and health events included (Appendix 4). The linked economic model results showed that incorporating multiple diseases and correlations between them in a model can produce different estimates of aggregate costs and QALYs for a disease when compared with those estimates derived from single-disease models. In general, the magnitude of the difference between single and linked model results increased with the proportion of the model population developing multiple diseases. These results confirm *a priori* expectations that when considering a population of individuals that are susceptible to multiple health conditions, producing an economic model that focusses on a single disease will not only misrepresent actual care pathways but seriously bias the estimated costs and QALYs. Consequently, an intervention could be mistakenly estimated to be cost-effective when it is not. This potential for bias is relevant in the context of both allocation of healthcare resources and clinical guidelines. An economic model that appropriately links multiple diseases is likely to produce different decisions on technology adoption, which in turn could alter the nature of the NHS funded treatment options made available in clinical practice [38, 39].

To be able to appropriately measure the impact of multimorbidity, it is necessary to carefully select the relevant co-existing diseases for a specified decision problem. Ideally, the use of pre-defined criteria (as exemplified in Appendix 1) should be used to guide the selection of relevant diseases. Careful consideration should be paid to how many of the relevant diseases should be included in a linked economic model. The same principles used for single-disease modelling also apply to the selection of multiple diseases: the diseases considered to alter model outcomes that are important for the population being studied and to policy makers (such as costs and QALYs) should be included. Epidemiological data that identify commonly co-existing health conditions (for example, see [10]) can be used to inform the choice of which diseases are most relevant. The assessment of marginal returns to adding more diseases in the linked model could be investigated empirically.

This proof-of-concept analysis suggested that when one disease had a much larger impact on costs and QALYs than the other diseases in a linked economic model, the sampling error around the disease with larger impact could make a significant difference to the estimated cost-effectiveness of the other individual treatments. This result could lead to lack of face validity for the diseases with smaller incremental gains. The implication is that the number of simulated patients required to stabilise the adoption decisions within linked economic models may be greater than the maximum of the numbers required for single-disease models. In circumstances where the QALY gains are similar across individual treatments, then it is likely that the proposed methods of linking single disease models produce more accurate estimates for multi-morbid populations. Further research on approaches to addressing this problem, in particular when incremental costs and QALYs are small in magnitude, would be beneficial.

The analysis showed that including correlations between diseases may potentially change the relative cost-effectiveness of interventions. When correlations were implemented, absolute QALYs were higher than when the diseases were assumed independent due to the concentration of co-morbidities onto an already diseased population, resulting in lower QALY loss from having an additional disease. Hence, adding correlations better reflects the relationship between multimorbidity and mortality. This paper demonstrated how to include correlations, based on the currently available data. Further evidence on correlations between diseases may become available in the future which would allow the model to be extended and improved.

The DES approach, as illustrated in this paper, showed how it was sufficiently flexible to allow the impact of different types of individuals in a population to be quantified. The general population was used as the entry population in the DES model, but it is possible to define more specific populations with different distributions of individual characteristics, for example, a population of individuals with prevalent HD but without osteoporosis. In turn, a particular health intervention could be evaluated for these individuals in a population, which mirrors the approach in conventional HTA analyses for interventions in single diseases.

There were some limitations to this proof-of-concept method. The use of the DES framework enabled the seamless linkage of the three disease distinct economic models, but future work could explore the application of the linkage method using methods other than DES. Also, the multiplicative method was used to combine utility values for the co-occurring health conditions. There are three other possible methods: additive, minimum and linear index methods. Each of these methods is likely to produce different utilities for any combination of health states, but the direction of the changes in the observed utility values will be the same. A future study could investigate the impact

of using different methods to combine utility values on the magnitude of the cost-effectiveness of interventions in a linked model for more than one disease [40].

In this proof-of-concept study, time-to-event distributions and random numbers were used to represent the variability among individual observations (first-order uncertainty) as reported in Appendix 5. Uncertainty around the structure of the economic model was not examined. A probabilistic sensitivity analysis (PSA) is required to understand the impact of second-order uncertainty arising from uncertainty in the model input parameters [41]. A feasibility run of PSA was undertaken that showed significant model running time would be required to conduct a large-scale PSA for this model (Appendix 8). A study designed to understand the impact of parameter and structural uncertainty in a linked economic model could be a topic for future research using parallel computing or expedited PSA with non-parametric regression modelling [42]. Also, running the model for a more narrowly defined population with specific characteristics and higher disease prevalence, rather than for the general population, would accelerate convergence to mean outcomes at each deterministic run.

In conclusion, this proof-of-concept study used DES to produce a linked economic model and demonstrated that this is a feasible approach to inform decision-making relevant to interventions for populations with multimorbidity. This study provided a modelling framework that has the potential to be modified and/or expanded to incorporate other diseases and interventions to inform the development of clinical guidelines using evidence about the relative cost-effectiveness of interventions for people with multimorbidity. This study has shown that using a linked economic model that incorporates correlations between diseases is likely to influence the potential decisions made about the allocation of healthcare resources to support interventions relevant to multi-morbid populations, increasing the health benefits experienced by those patients.

Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

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Tables

Manuscript Title:

Modelling the economic impact of interventions for older populations with multimorbidity: a method of linking multiple single-disease models

Table 1. An illustration of individual's movement through the linked model *

Simulation time	**Location (Event where updates occur)**	**Time to next disease event**
Time 0	Entry	Time to next heart disease event: Sampled to be 2.5 years Time to next Alzheimer's disease event: Sampled to be 12 years Time to next osteoporosis event: Sampled to be 4.5 years
Time 0	Central router	• Time to next event: 2.5 years (heart disease event) • Utility weight until next event: 0.85 (baseline utility)
Time 2.5	Heart disease event	Next heart disease event: Sampled to be 6.8 years
Time 2.5	Central router	Next heart disease event: 6.8 years Next Alzheimer's disease event: Updated to 9.5 (12-2.5) years Next osteoporosis event: Updated to 2 (4.5-2.5) years • Time to next event: 2 years (osteoporosis event) • Utility weight until next event: 0.595 [=0.85 (baseline utility) x 0.7 (utility multiplier for heart disease events)]
Time 4.5	Osteo event	Next osteoporosis event: Sampled to be 7.3 years
Time 4.5	Central router	Next heart disease event: Updated to 4.8 (6.8-2) years Next Alzheimer's disease event: Updated to 7.5 (9.5-2) years Next osteoporosis event: 7.3 years • Time to next event: 4.8 years (heart disease) • Utility weight until next event: 0.476 [=0.85 (baseline) x 0.7 (heart disease) x 0.8 (utility multiplier for osteoporosis events)]
Time 9.3	Heart disease event	Next heart disease event: Sampled to be 8.2 years
Time 9.3	Central router	Next heart disease event: 8.2 years Next Alzheimer's disease event: Updated to 2.7 (7.5-4.8) years Next osteoporosis event: Updated to 2.5 (7.3-4.8) years • Time to next event: 2.5 years (osteoporosis) • Utility weight until next event: 0.476 [=0.85 (baseline) x 0.7 (heart disease)† x 0.8 (osteoporosis)
		⋮ The process continues until death

*For illustration, the same utility values were assumed across all events within one disease: 0.7 for heart disease events and 0.8 for osteoporosis events. A constant baseline utility weight of 0.85 was assumed; †When the same event occurs more than once (e.g. two strokes within a year), a utility multiplier is applied only once.

Table 2. Per-capita results from the independently linked model based on n=700,000 simulated individuals

	Independently linked model			**Individual disease models**
	With all treatments*	None of the three treatments	Incremental values	Sum of incremental values across three individual models
Cost	£ 14,776	£ 13,936	£ 840	£ 408
QALYs	8.956	8.722	0.234	0.280
ICER			£ 3,582 /QALY	£ 1,458

*All the default treatments were assumed to be available.

Table 3. Cost-effectiveness of individual treatments from the all-disease linked model where diseases were assumed independent

All disease linked model	**HD treatment**		**AD treatment**		**Osteoporosis treatment**	
	No HD treatment*	Incremental values**	No AD treatment*	Incremental values**	No Osteo-porosis treatment*	Incremental values**
Based on 700,000 simulated individuals						
Cost	£ 13,815	£ 960	£ 14,800	-£ 24	£ 14,942	-£ 166
QALYs	8.720	0.236	8.957	-0.001	8.954	0.002
ICER		£ 4,068		£ 32,549†		Dominating
Based on 2,000,000 simulated individuals						
Cost	£ 13,798	£ 1,004	£ 14,819	-£ 18	£ 14,914	-£ 112
QALYs	8.717	0.240	8.958	0.000	8.952	0.005
ICER		£ 4,175		Dominating		Dominating

HD=heart disease; AD=Alzheimer's disease; *Treatments for the remaining two diseases were assumed to be available; **All incremental values are compared with the results with all three treatments available; †Treatment with lower costs and lower QALYs; Costs and QALYs discounted at 3.5% p.a.

Table 4. Base-case results from the all-disease model with correlations between diseases incorporated based on n=700,000 simulated individuals

	Linked model with correlations incorporated		
	With all three treatments*	**None of the three treatments**	**Incremental values**
Cost	£ 14,741	£ 13,894	£ 847
QALYs	8.962	8.725	0.236
ICER			£3,583 /QALY

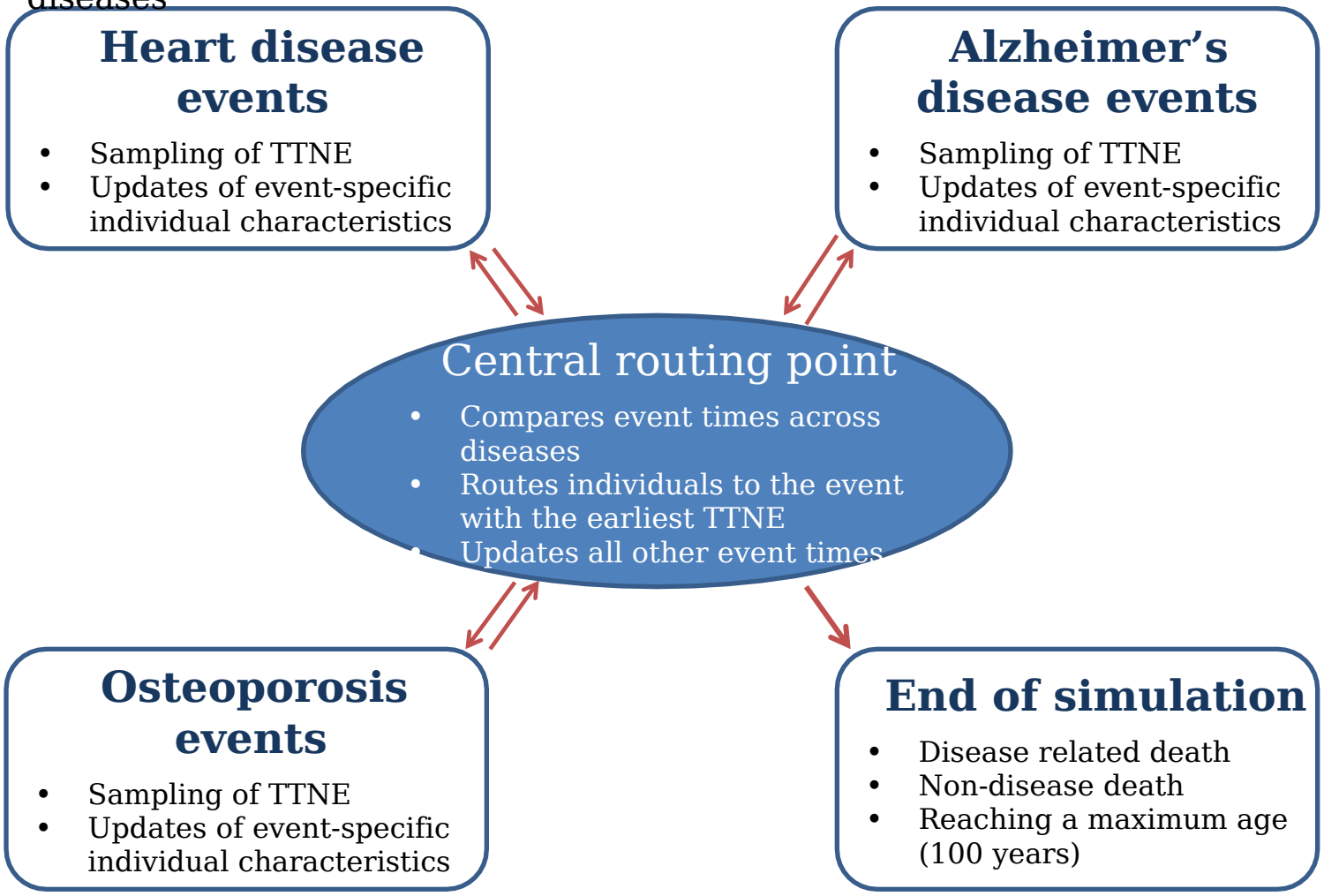
*All the default treatments were assumed to be available.

Table 5. Cost-effectiveness of individual treatments using results from the all-disease linked model with correlations incorporated, based on n=2,000,000 simulated individuals

	HD treatment		**AD treatment**		**Osteoporosis treatment**	
	No HD treatment*	**Incremental values****	**No AD treatment***	**Incremental values****	**No Osteoporosis treatment***	**Incremental values****
Cost	£ 13,791	£ 936	£ 14,742	-£ 15	£ 14,869	-£ 142
QALYs	8.730	0.235	8.963	0.002	8.961	0.004
ICER (£/QALY)		£ 3,978		Dominating		Dominating

HD=heart disease; AD=Alzheimer's disease; *Treatments for the remaining two diseases were assumed to be available; **All incremental values are compared with the results with all three treatments available.

For each simulated individual with or without any of the diseases



TTNE: time to next event

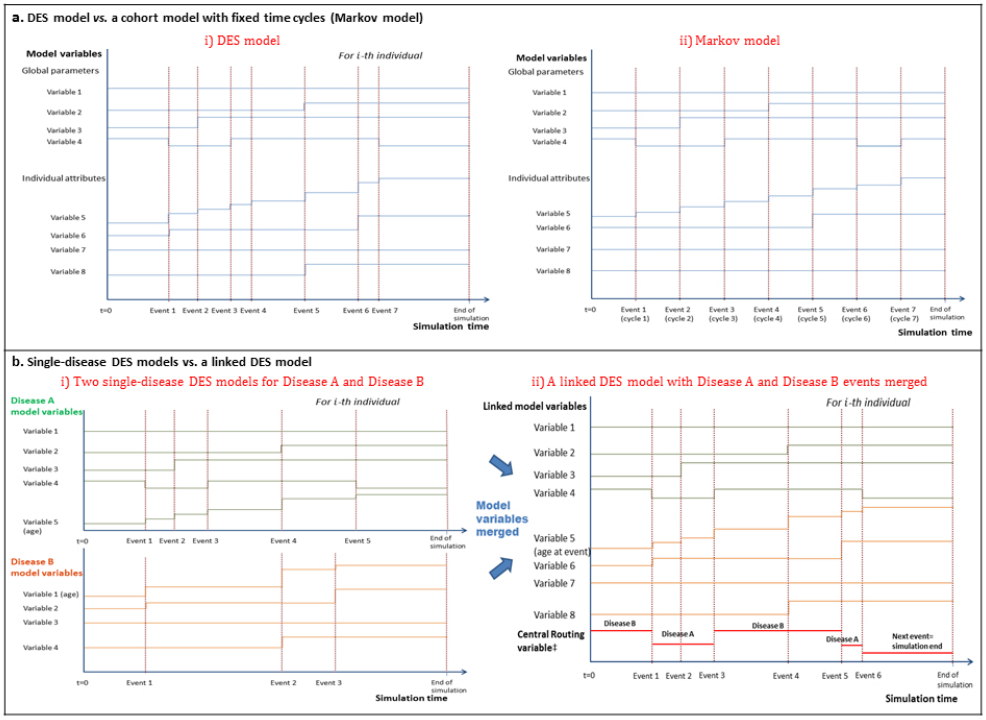


Figure 2. Discrete event simulation (DES) model with and without model linkage†

†All y-axes of the diagrams show examples of variables defining the respective models and changes in their values over simulation time (x-axes); *Global parameters: variables that apply to all simulated individuals such as discount rates, unit cost of interventions and utility associated with health events; **Individual attributes: variables that reflect changes in individual characteristics over time such as age, a previous experience of disease events and utility multipliers relevant to the individual at specific event times; ‡Central routing variable was added after combining all single-disease model variables in the linked model to indicate in which disease model the next event is scheduled to occur.

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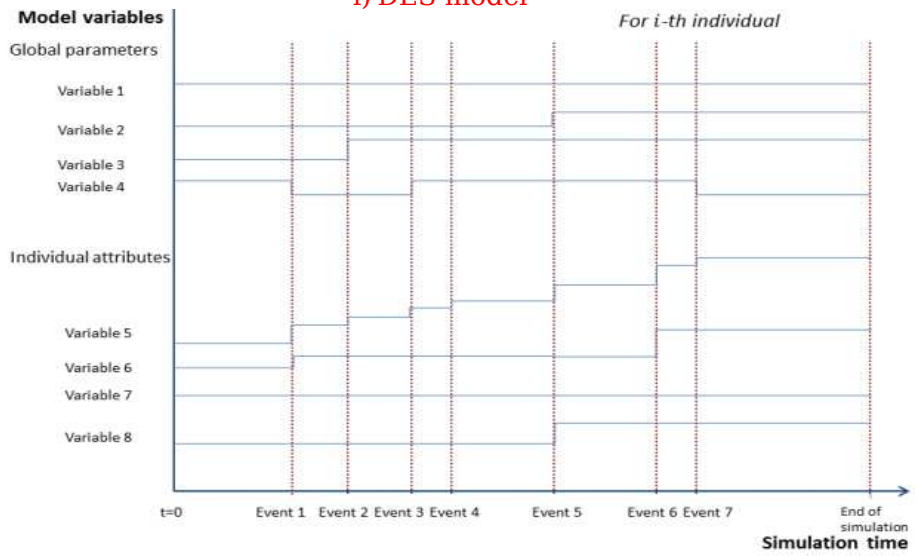
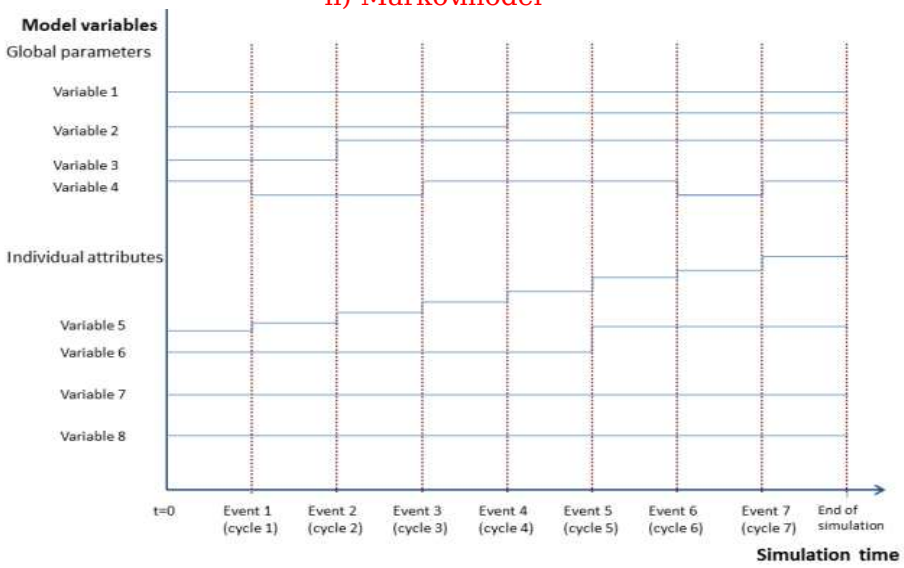
a. DES model *vs.* a cohort model with fixed time cycles (Markov model)

i) DES model

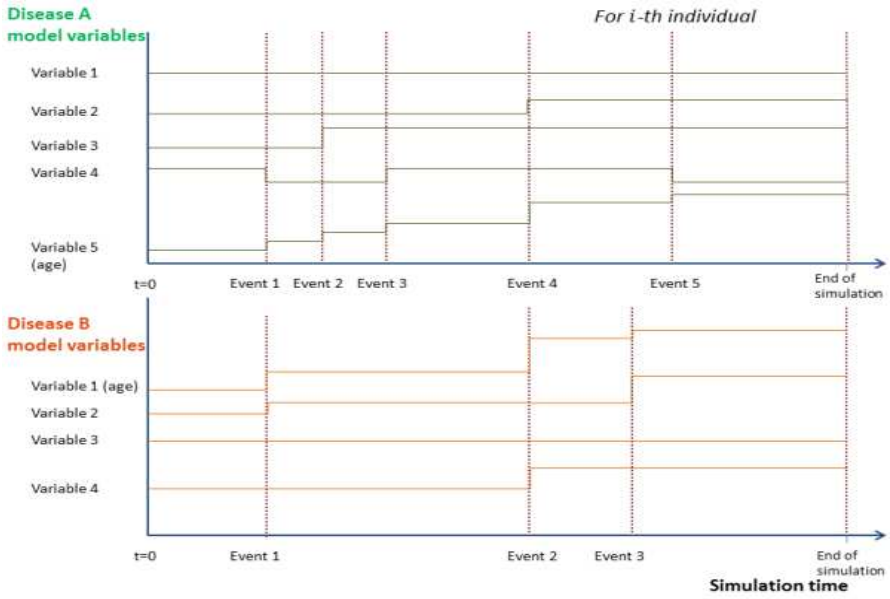


ii) Markov model



b. Single-disease DES models vs. a linked DES model

i) Two single-disease DES models for Disease A and Disease B



ii) A linked DES model with Disease A and Disease B events merged

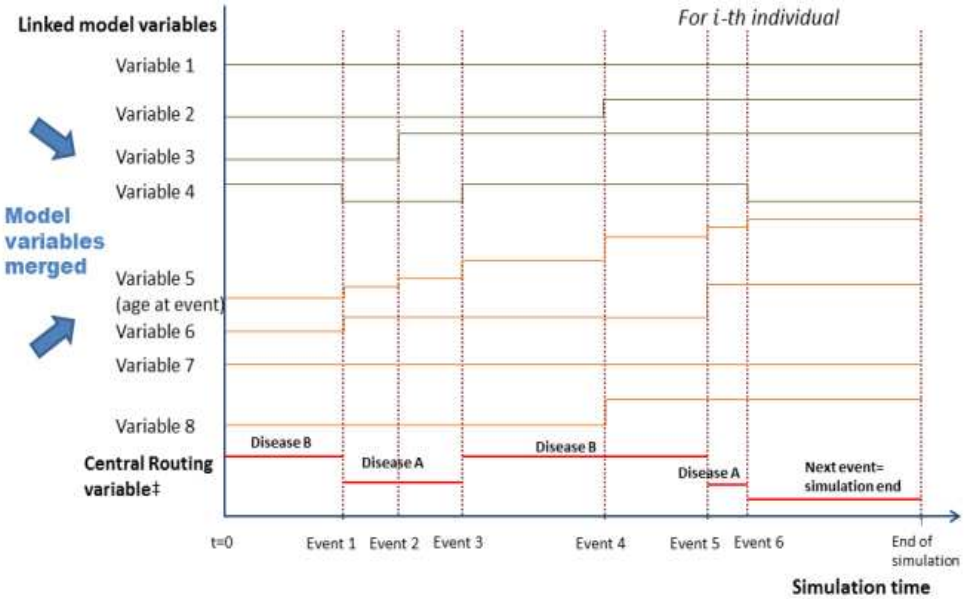


Figure 2a - i) DES model

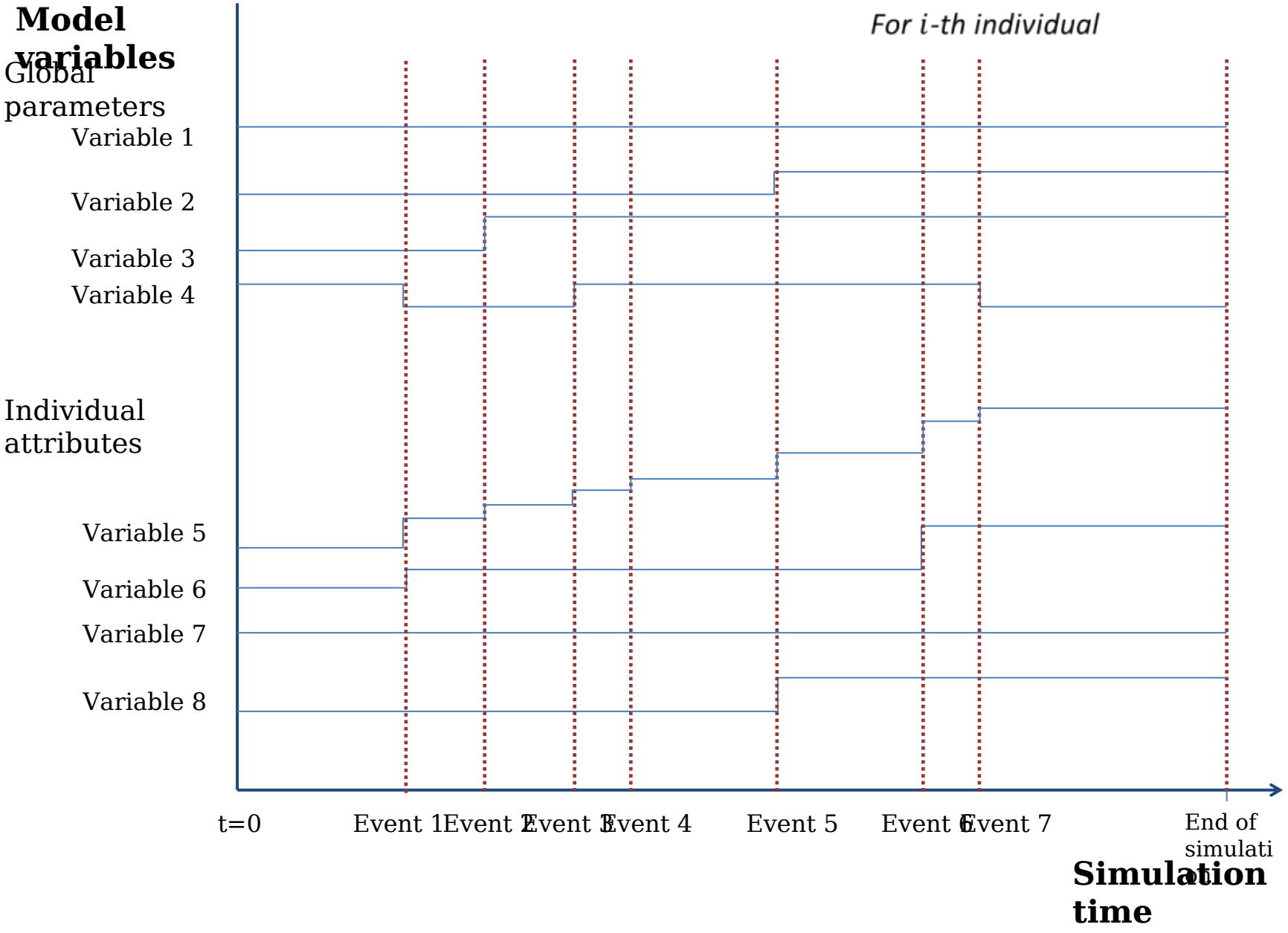


Figure 2a - ii) Markov model

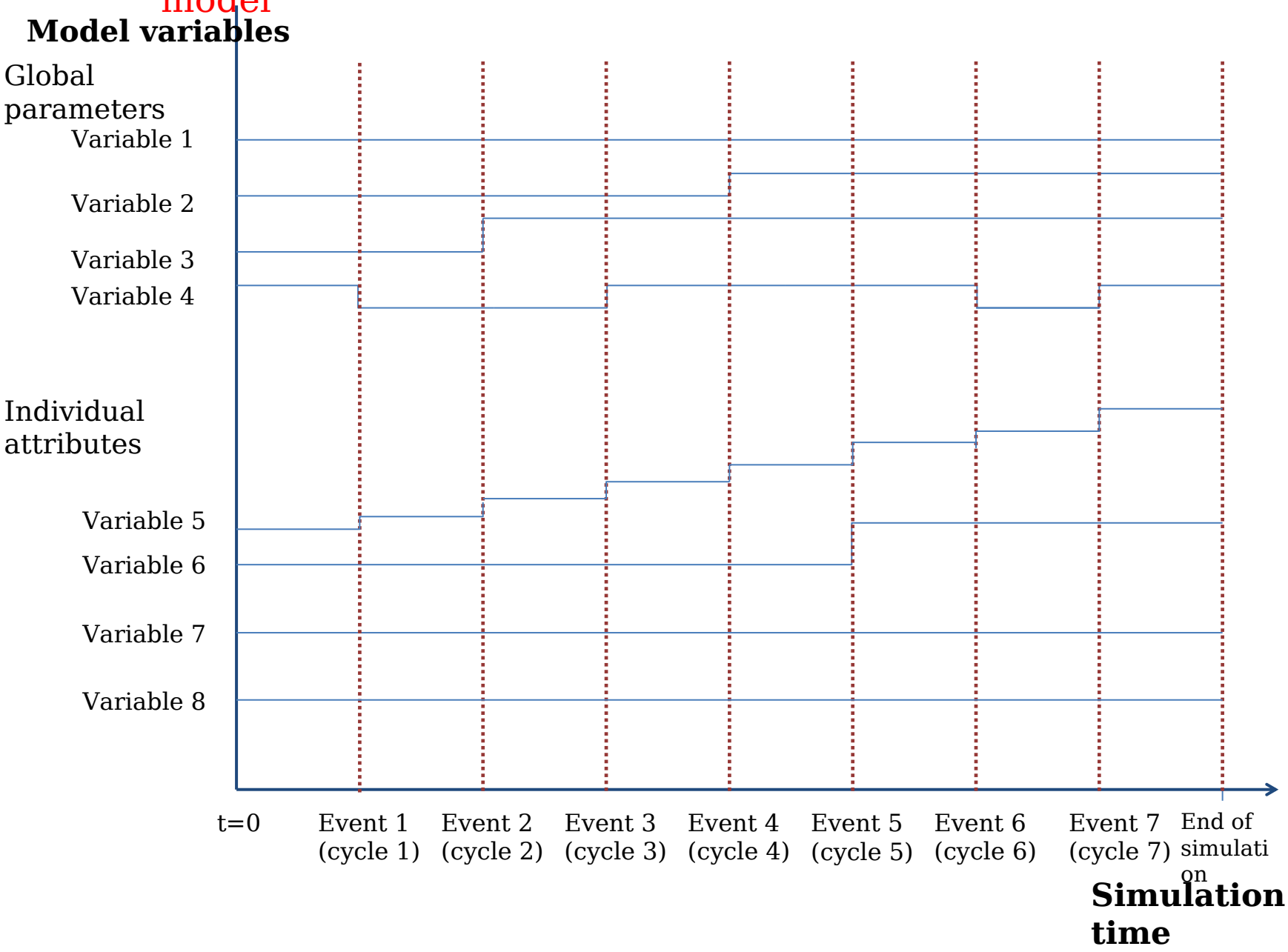


Figure 2b - i) Two Single disease DES models

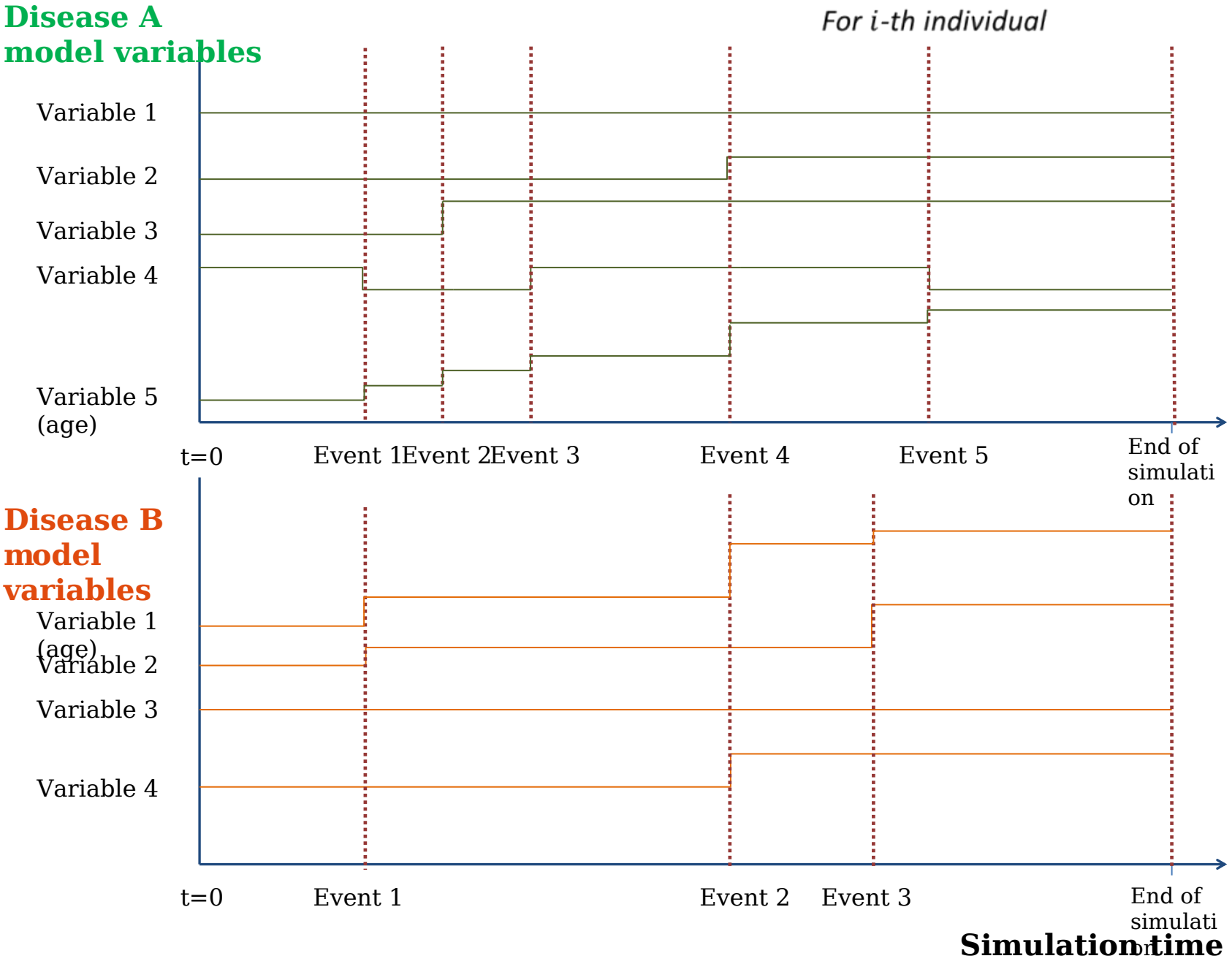
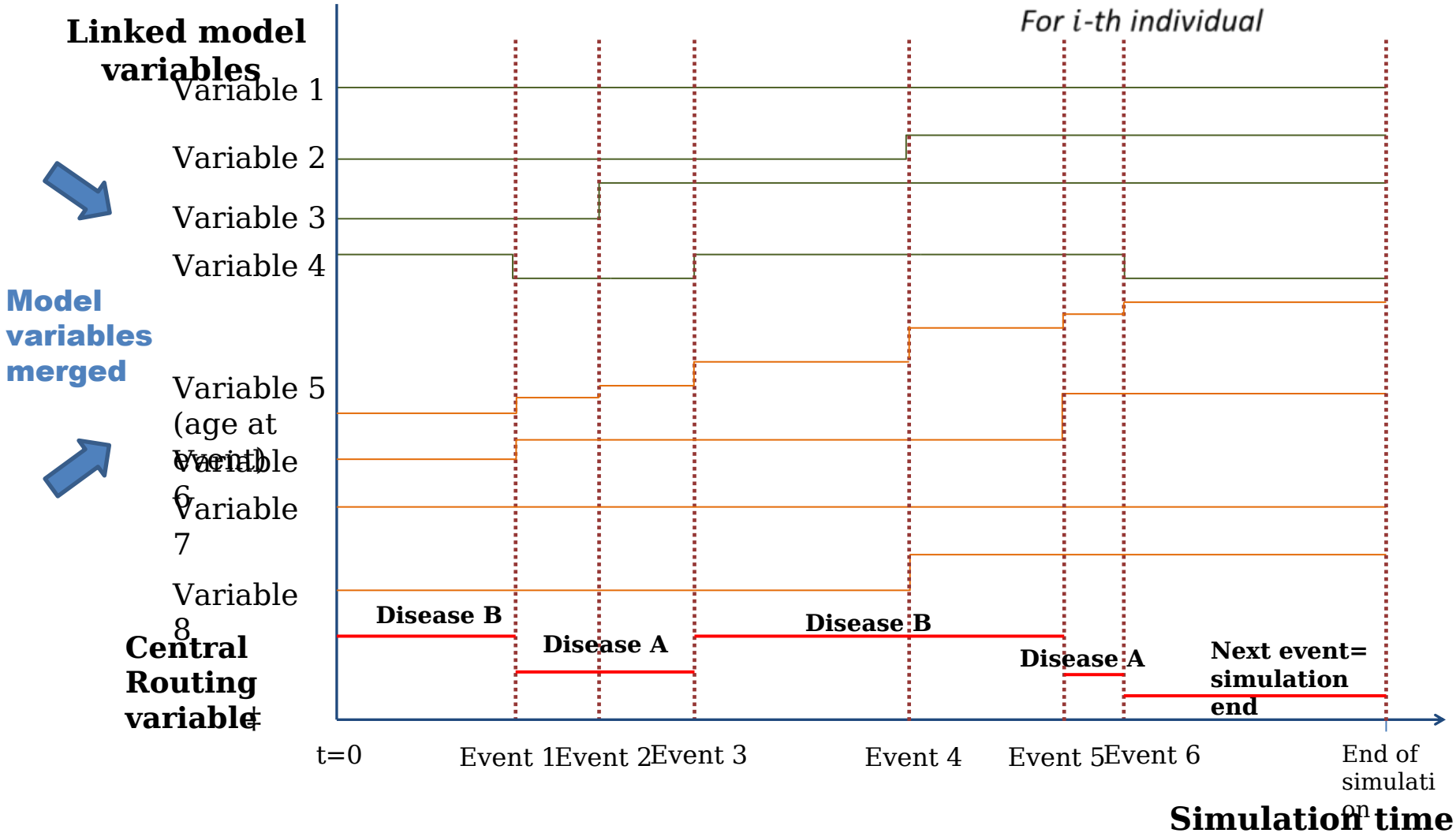
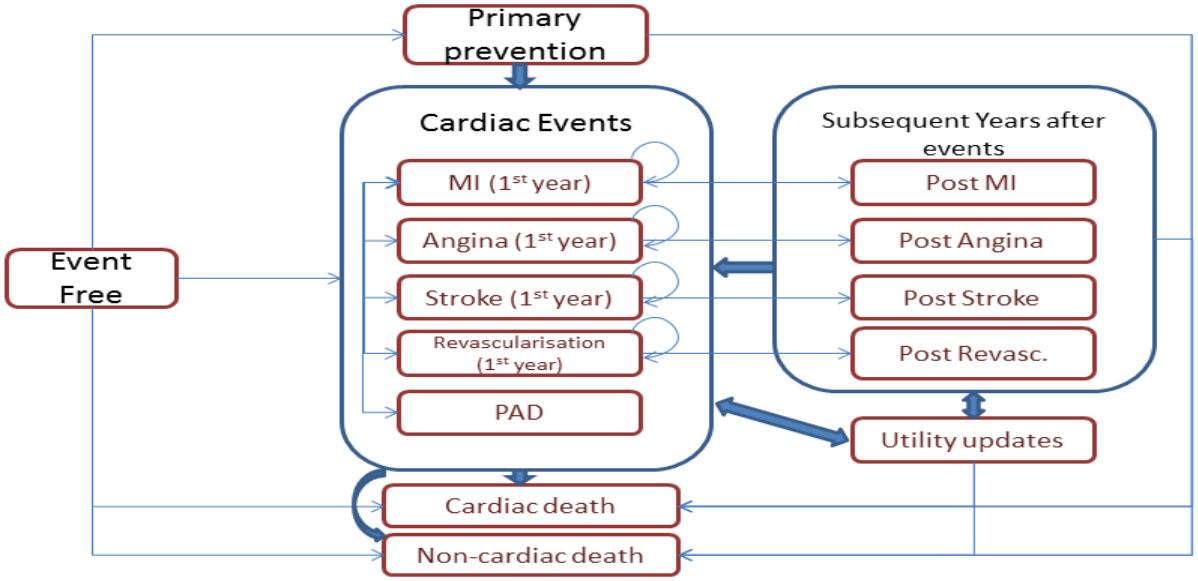


Figure 2b - ii) A Linked DES



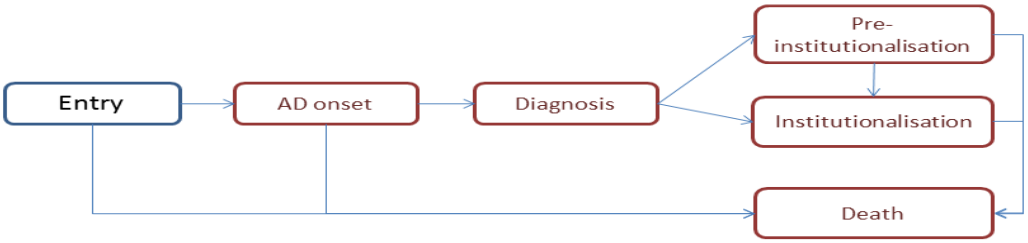
a) Heart disease model*



MI: myocardial infarction; PAD: peripheral artery disease; Revasc: revascularisation

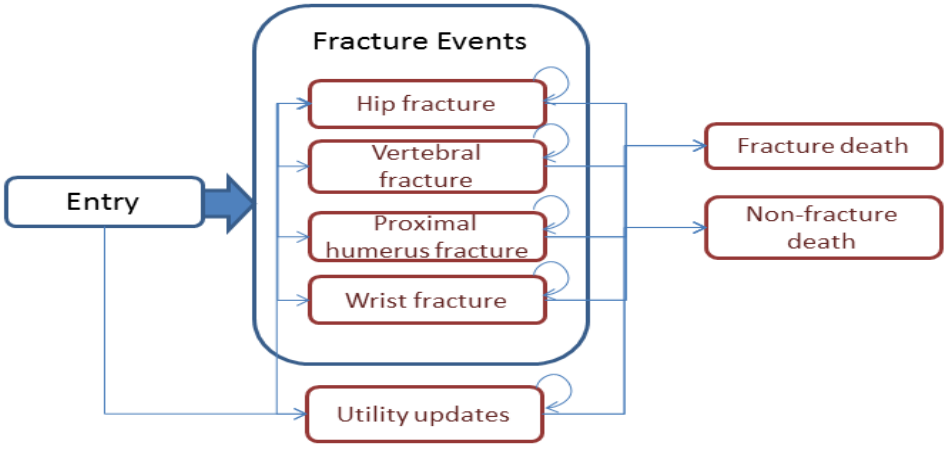
The heart disease model included MI, stroke, angina, revascularisation PAD and cardiac and non-cardiac deaths as qualifying health events. Each non-fatal cardiac event except PAD (MI, angina, stroke and revascularisation) was divided into two temporal categories: first-year and subsequent years after the event.

b) Alzheimer's disease model



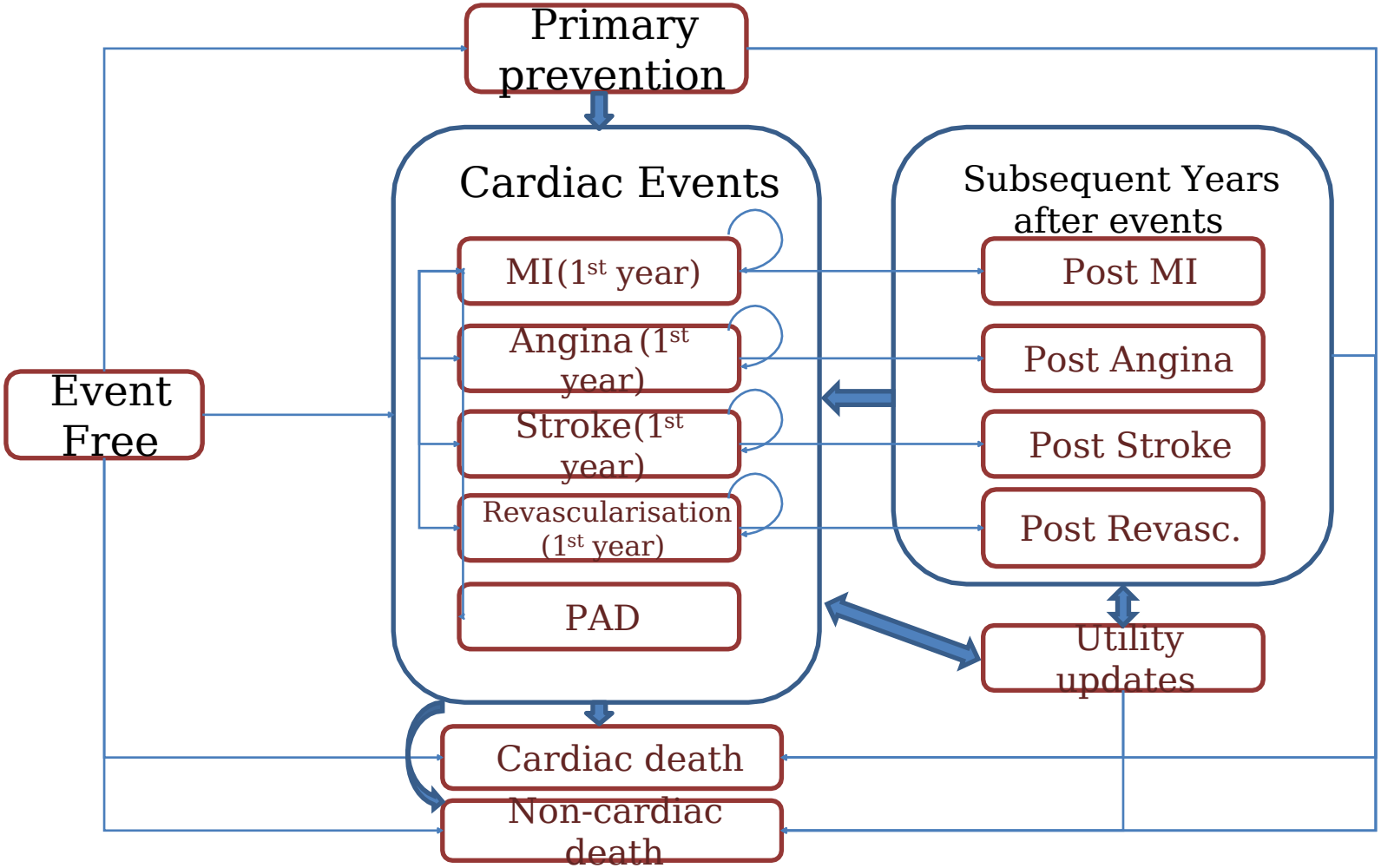
Alzheimer's disease: The onset and diagnosis of AD were added to the structure of the model by Bond et al. (2012) in order to model a general population.

c) Osteoporosis model*



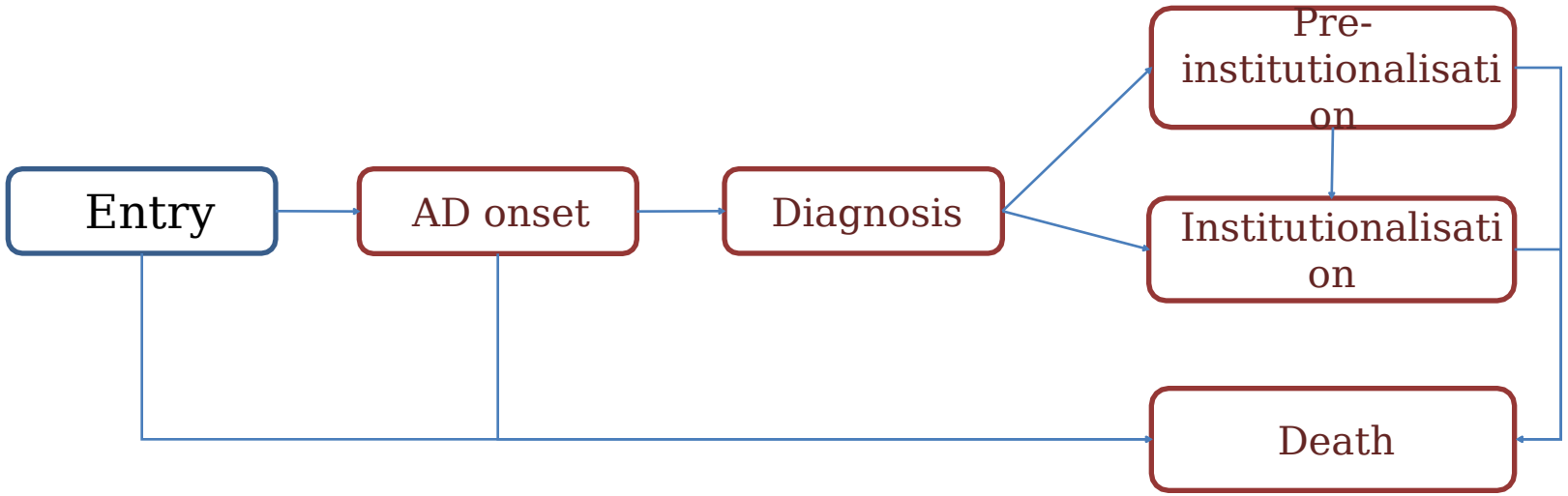
Osteoporosis model: Four fractures (hip, vertebral, wrist and proximal humerus) were included as osteoporotic fracture events. The events also included nursing home entry from hip fracture; death following fracture; and non-fracture related death (see Stevenson et al. 2009).

a) Heart Disease Model*



MI: myocardial infarction; PAD: peripheral artery disease; Revasc: revascularisation

b) Alzheimer's Disease Model



c) Osteoporosis Model*

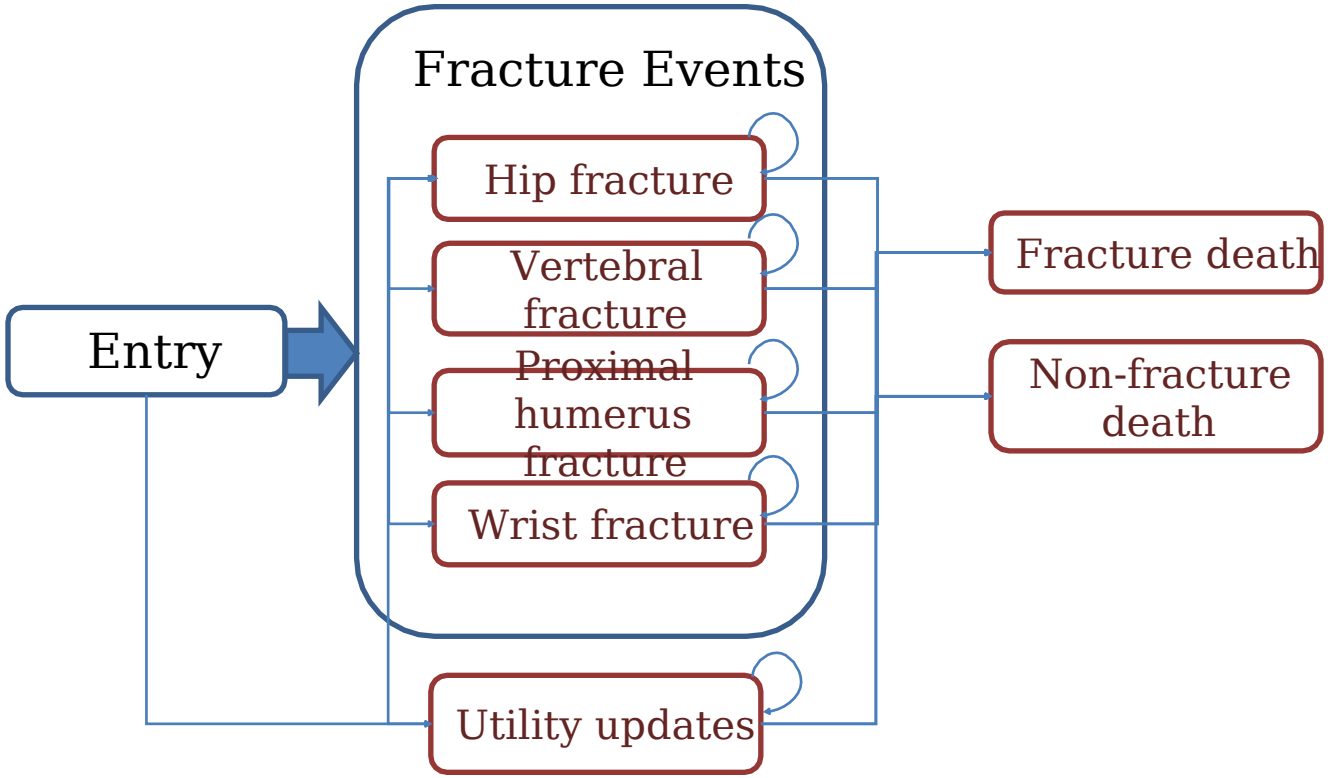
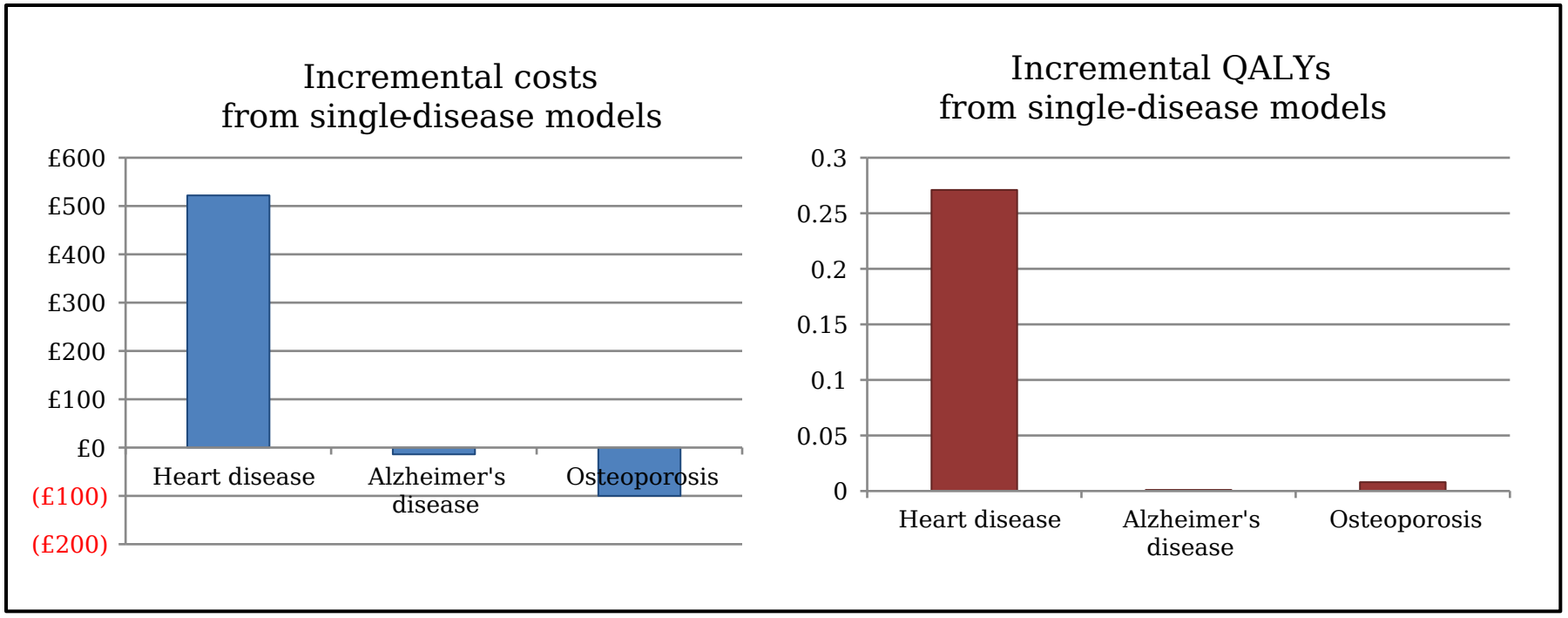


Figure 4. Comparison of incremental costs and QALYs from the three individual disease models



Supplementary Appendices

Supplementary Material for:

Modelling the economic impact of interventions for older populations with multimorbidity: a method of linking multiple single-disease models

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Appendix 1. Justification for disease selection

Appendix 2. Incorporating correlations between diseases

Appendix 3. Parameter estimates and data sources

Appendix 4. Comparison of the single-disease models in this study with the published reference models

Appendix 5. Dealing with stochastic uncertainty around the results from the linked model

Appendix 6. Summary of the results from the individual disease models for comparison

Appendix 7. Hypothetical scenario with similar levels of QALY gains assumed for all three interventions

Appendix 8. Probabilistic sensitivity analysis of the correlated linked model results

Appendix 1. Justification for disease selection

The criteria used for selecting the diseases to be modelled in the case study are summarised in Box 1.

Box 1. Criteria for selecting diseases to model

- Diseases with major cost implications: High costs to the UK NHS and Personal Social Services of treating/managing the diseases
- Diseases of the elderly: Diseases with significant mortality and morbidity burden for older population and diseases whose incidence is expected to increase as population ages.
- Establishing a balance between different disease areas in order to cover a spectrum of conditions.
- Diseases that are correlated with respect to their incidence/prevalence and thus are more likely to co-occur
- Whether there are sufficiently recent HTA reports undertaken for the disease in order that a peer-reviewed model could be replicated.
- Diseases of hard endpoints, rather than those being risk factors for other diseases themselves, such as diabetes and hypertension

Diseases with significant cost implications to the UK NHS and Personal Social Services (PSS) for an ageing population were considered for inclusion in the model. Diseases expected to become more prevalent as a population ages were given a priority.

A balance between different disease areas was also considered as one of the criteria. Including diseases from one or two areas of diseases whose mechanisms are similar may be misleading in estimating the broad impact of population ageing on healthcare expenditure and the interactions between diseases. Among diseases of significant economic, mortality and morbidity burdens, a spectrum of diseases that affect different parts of the body were included.

Diseases that are potentially correlated were considered for inclusion in the case study. Seemingly unrelated health conditions may co-occur in individuals as they often share common underlying risk factors (for further details, see Appendix 2).

Fracture risks are influenced by the presence of cardiovascular disease (CVD). In a study that was a part of the Rochester Epidemiology Project, myocardial infarction (MI) was associated with higher risk of all types of osteoporotic fracture [1]. Excess fracture risks after MI were found with the overall adjusted hazard ratio (HR) of 1.32 (95% CI 1.12-1.56) across all anatomic sites.

Further, the prevalence of heart disease (HD) among Alzheimer's disease (AD) patients was considered higher than that of HD within an age- and gender-matched general population. A number of studies have found that AD often co-exists with vascular conditions such as hypertension, hyper-cholesterolaemia, and diabetes mellitus [2-6].

Osteoporosis and stroke share several risk factors, including age, smoking, low physical activity, and hypertension. Thus, low bone mineral density (BMD) and high stroke risk can be correlated. Studies have shown that low BMD or a history of fracture has an association with the incidence of stroke [7-9]. Jørgensen et al. [9] reported that women with BMD values in the lowest quartile had a higher risk of stroke than women with BMD values in the highest quartile (odds ratio (OR)= 4.8), and a linear trend over the quartiles was statistically significant. The OR for stroke increased 1.9 per SD (0.13 g/cm^2) reduction in BMD. The association between low BMD and stroke in women remained significant when the analysis was adjusted for potential confounders. In men, however, no statistically significant difference in BMD between the stroke patients and their controls was found.

The presence of recently published (or in press) NIHR HTA reports was considered as it was deemed as evidence of the importance of the disease to major stakeholders such as decision-makers in local government, policy-makers (including the National Institute for Health and Care Excellence (NICE)), health professionals, and the general public. Further, the model structures reported in the HTA reports were largely replicated.

Diseases with hard endpoints were preferred to those which were surrogate risk factors for other diseases. It was believed that such diseases could be embedded as a risk factor, and the consequences of the diseases could be represented in the models of other diseases.

Using the selection criteria, the three diseases with significant mortality and disability burdens for the elderly – heart disease (including stroke and MI), Alzheimer's disease, and osteoporosis – were chosen for the case study.

The most expensive disease category was cardiovascular disease. Heart conditions, such as coronary heart disease (CHD) and MI, and stroke were selected for modelling as they account for the largest

proportion of mortality and prevalent cases in cardiovascular disease among older individuals [10], and impose significant economic burden on the overall healthcare system [11].

Dementia was selected for modelling considering its cost, potential association with CVD, the balance between the chosen diseases, and likely impact of population ageing. Amongst brain disorders, dementia was the most expensive category of spending [12], and affects older people in particular with the incidence positively correlated with age [13]. Only the most common form of dementia, Alzheimer's disease (AD), was modelled in this study as the current NICE guidance and relevant model-based studies (including HTA reports) focussed on AD.

It was considered appropriate to include one or more musculoskeletal disorders due to the increasing prevalence and incidence with age. Amongst the musculoskeletal conditions, osteoporosis was deemed appropriate to include in the model due to its high cost. Osteoarthritis (OA) was not selected as previous models have been built for OAs at different anatomical sites such as knees, hips, and joints of hands, which make OA more difficult to include given the aim of this paper. Furthermore, the incidence of OA is difficult to estimate as the onset is not well-defined due to the discrepancy between the symptomatic OA and OA based on the radiological changes. Rheumatoid arthritis (RA) was considered for inclusion as RA mainly affects people aged 65 years and older [14]. However, RA was not chosen for the modelling given that the cost of RA did not exceed that of OA and chronic obstructive pulmonary disease.

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Supplementary Appendices

Supplementary Material for:

Modelling the economic impact of interventions for older populations with multimorbidity: a method of linking multiple single-disease models

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Appendix 1. Justification for disease selection

Appendix 2. Incorporating correlations between diseases

Appendix 3. Parameter estimates and data sources

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Appendix 5. Dealing with stochastic uncertainty around the results from the linked model

Appendix 6. Summary of the results from the individual disease models for comparison

Appendix 7. Hypothetical scenario with similar levels of QALY gains assumed for all three interventions

Appendix 8. Probabilistic sensitivity analysis of the correlated linked model results

Appendix 2. Incorporating correlations between diseases

The following correlations were incorporated in the proof-of-concept model.

1) Prevalence of AD for people with and without HD
2) Incidence of AD for people with and without HD
3) Incidence of hip fracture for people with and without a history of MI
4) Stroke risks among people with and without a history of hip fracture
5) Incidence of AD with and without low BMD

AD=Alzheimer's disease; HD= heart disease; MI= myocardial infarction; BMD=bone mineral density

This section describes only the correlations between the prevalence of HD and AD ((1) in above table) and the incidence of osteoporotic fracture and the presence of HD ((3) in above) incorporated in the linked model and how these correlations were implemented. The correlations 1)-5) were selected due to the data availability. Different incidence and prevalence estimates were applied to two groups of people with and without the other underlying condition. Similar calculation methods to those described in this section were applied to other correlations.

Targeted literature searches in the Medline and/or EMBASE databases using a combination of the disease names were conducted to identify the required data on correlations between the modelled diseases. Wherever possible, data on the incidence and prevalence of one disease with and without the other diseases was obtained. Further details on the correlations 2), 4) and 5) can be found in Youn (2016) [1].

Correlation between Heart disease and Alzheimer's disease

Systematic searches for literature reporting the prevalence of AD and other co-existing conditions and the outcomes of intervention for patients with AD and other relevant conditions were conducted within the Medline and EMBASE databases. However, very few papers that could provide numerical data for populating the model were identified.

A small number of studies that discussed empirical data on the effect of one disease on another were identified. As Maslow [2] noted, studies mainly listed common co-existing conditions that were

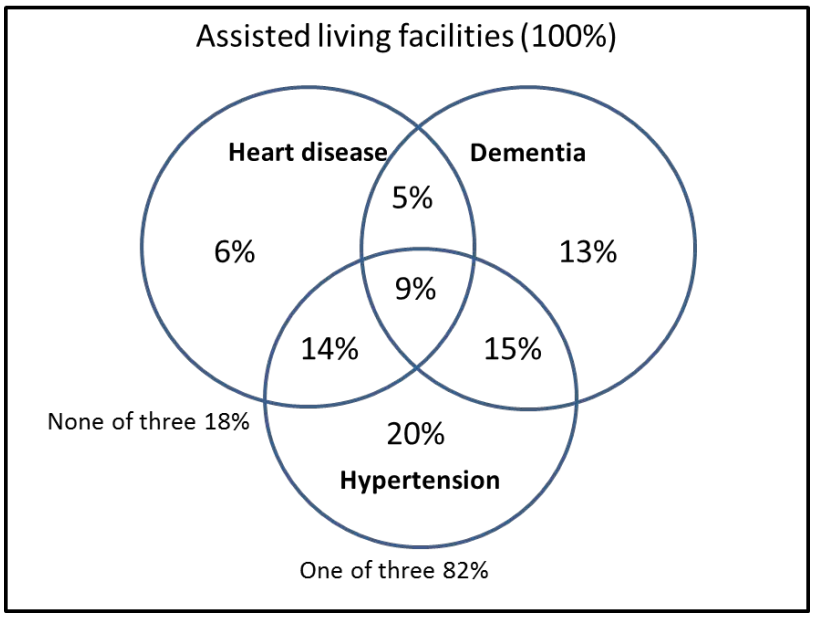
present in their study population only, or intentionally excluded people with AD who have other co-morbidities as the effect of other diseases could confound the effect of AD. Studies focussing on heart disease reported similar results.

Correlation of prevalence

The prevalence of HD among AD patients was considered higher than that of HD within an age- and gender-matched general population. A number of studies have found that AD often co-exists with vascular conditions such as hypertension, hyper-cholesterolaemia, and diabetes mellitus [2-6].

For instance, the US National Center for Health Statistics survey found that 82% of people in assisted living facilities where help is provided for daily activities such as bathing and dressing had one or more of dementia, hypertension, and heart disease (Figure S2.1) [7]. 42% of the residents had Alzheimer's disease or other forms of dementia and 34% had heart disease. 14% of people had both dementia and heart disease and 9% of them had all three of the diseases. However, as this survey was conducted in assisted living centres, the survey respondents were likely to be older than other study populations.

Figure S2.1. Co-morbidities of residents in assisted living facilities



Source: The National Center for Health Statistics, 2010 [7]

In order to incorporate the linkages between AD and HD, those with and without HD had different prevalence of AD: the total proportion of people who have AD was divided into the proportion of AD patients among people with heart disease and the proportion among people without HD.

For each age and sex group, the total prevalence of AD, $P(AD = 1)$, can be seen as a weighted average of two conditional probabilities $P(AD = 1|HD = 1)$ and $P(AD = 1|HD = 0)$ as follows;

$$P(AD = 1) = P(AD = 1|HD = 1) \cdot P(HD = 1) + P(AD = 1|HD = 0) \cdot P(HD = 0)$$

[Eq. 1]

where AD and HD are binary variables taking the value of one when the disease is present and zero otherwise. Therefore, $P(AD = 1)$ and $P(HD = 1)$ are the prevalence of AD and HD, respectively. $P(AD = 1|HD = 1)$ denotes the probability of having AD conditional on the presence of HD, or the prevalence of AD among those with HD, and $P(HD = 1|AD = 1)$ the prevalence of HD among those with AD.

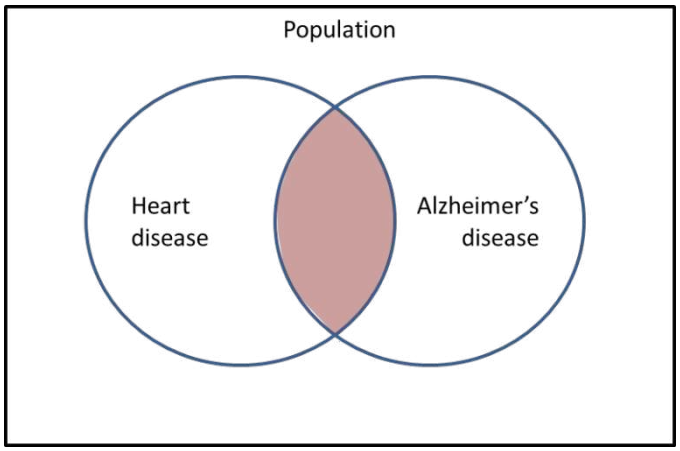
In the same way, the total prevalence of heart disease can be calculated as:

$$P(HD = 1) = P(HD = 1|AD = 1) \cdot P(AD = 1) + P(HD = 1|AD = 0) \cdot P(AD = 0)$$

[Eq. 2]

Eq. 2 expresses the total prevalence of HD in terms of $P(HD = 1|AD = 1)$ and $P(HD = 1|AD = 0)$ using the value of AD prevalence, $P(AD = 1)$. Regardless of which equation to use, the split should be the same as $P(HD = 1|AD = 1)$ and $P(AD = 1|HD = 1)$ represent the same coloured area in Figure S2.2 although the actual figures of the conditional probabilities differ depending on which disease status is assumed to be known.

Figure S2.2. Prevalence linkage between AD and heart disease



However, Eq. 2 could not be used as the total prevalence of heart disease had to be partitioned among the cardiac events included in the model and data required for using Eq. 2 were not available from the literature searches. Hence, the prevalence of AD was divided into the prevalence of AD for people with and without HD using Eq. 1.

Using Bayes' theorem, $P(AD = 1|HD = 1)$ in Eq. 1 was calculated as $P(AD = 1|HD = 1) = \frac{[P(HD=1|AD=1)\cdot P(AD=1)]}{P(HD=1)}$ **[Eq. 3]**. The relationship in Eq. 1 was used to calculate $P(AD = 1|HD = 0)$. The following sections describe the methodology and report the calculation results.

Calculation and calibration of the prevalence of Alzheimer's disease among heart disease patients

The prevalence of AD among people with HD, $P(AD = 1|HD = 1)$, was calculated by combining the results on $P(HD = 1|AD = 1)$ and $P(HD = 1)$ using Eq. 3. Subsequently, the prevalence of AD among people without HD, $P(AD = 1|HD = 0)$, was also estimated using Eq. 1.

The resulting prevalence of AD divided into $P(AD = 1|HD = 1)$ and $P(AD = 1|HD = 0)$ is shown in Table S2.1. These values were used in the linked model as the prevalence of AD in relation to the presence of heart disease. The ratio $\frac{P(AD=1|HD=1)}{P(AD=1|HD=0)}$ varied with age group and sex as the prevalence of individual diseases, $P(HD = 1)$ and $P(AD = 1)$, differ between age and sex.

Table S2.1. Prevalence of AD divided into the prevalence for people with HD and that for people without HD (before calibration)

	Prevalence of AD					
	People with HD ①		*People without HD* ②		*Ratio* (①/②)	
Age	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
<65	0	0	0	0	NA	NA
65-69	0.018267	0.044718	0.006785	0.005929	2.69	7.54
70-74	0.036962	0.05099	0.015618	0.009068	2.37	5.62
75-79	0.051255	0.091056	0.032751	0.034654	1.57	2.63
80-84	0.095646	0.180764	0.058681	0.068831	1.63	2.63
85+	0.196727	0.363585	0.108037	0.132586	1.82	2.74

The prevalence of AD before and after applying the correlations were compared using the values sampled at the model entry in order to see whether the estimation method used for splitting prevalence produced similar results. The total prevalence of AD and the prevalence for people with and without HD are compared in Table S2.2. The prevalence values of AD with and without HD were combined for comparison with the total AD prevalence before splitting using 100,000 simulated individuals for each age group (in order to have enough numbers of simulated individuals in each age group). The absolute percentage differences ranged from 0.23% to 5.09% between the total population values and the split values of prevalence. The percentage difference was the largest for female population aged 70-74 years. The differences could be due to the use of the single estimate of $P(HD = 1|AD = 1)$ in Eq. 3 for all age groups and sex, which fails to reflect variation among different populations in the estimation equation.

Although the differences could be considered small, the prevalence of AD split for people with and without HD was calibrated to match the total prevalence. Calibration was performed in order to start the model with the same population with respect to the total prevalence of AD. Based on the total prevalence values, age- and sex-specific calibration multipliers were applied to the prevalence values for people with and without HD. These were calculated as the total prevalence divided by the combined prevalence using split values. The calibrated prevalence after these multipliers were applied was used in all models for this paper where AD and heart disease were correlated.

Table S2.2. Comparison of simulated proportions of people with Alzheimer's disease (AD): between when the total prevalence of AD was used and when the prevalence of AD split into HD and non-HD groups was used

	Total prevalence of AD (before splitting)		**Combined prevalence of AD using split prevalence values***		**% Difference (compared with the total prevalence AD)**	
Age	Men	Women	Men	Women	Men	Women
<65	0	0	0	0	0	0
65-69	0.0101	0.0108	**0.0098**	**0.0104**	-3.01%	-3.98%
70-74	0.0223	0.0158	**0.0232**	**0.0166**	3.88%	5.09%
75-79	0.0403	0.0511	**0.0387**	**0.0503**	-3.94%	-1.52%
80-84	0.0734	0.1015	**0.0732**	**0.1020**	-0.38%	0.44%
85+	0.1411	0.1980	**0.1451**	**0.1985**	2.79%	0.23%

*Based on the results of 100,000 simulated individuals for each age group.

In order to examine the effect of the calibration at the population level, the numbers of people with AD across all age groups in the models before and after calibration were compared in Table S2.3 when 200,000 individuals aged 65 years and over were simulated for each model (the age distribution for people aged 65 and over was adapted from the ONS mid-2012 UK population estimates). The total numbers of people with AD among 200,000 simulated individuals from models with and without calibrated prevalence values were compared with that from the model where heart disease and AD were independently linked. The calibration reduced the difference between when the total AD prevalence was applied and when the split prevalence values were used from 0.50% to 0.24% for male population and from 1.89% to 1.18% for females.

There still existed differences in the number of people with AD after calibration due to Monte Carlo sampling error. Perfect calibration would have been possible if the calibration factors were calculated using the model results with the infinite number of runs for each age and sex group. In addition, if the infinite number of individuals were simulated in the perfectly calibrated model and the independently linked model for figures in Table S2.3, the differences would have been eliminated.

Table S2.3. Number of individuals with Alzheimer's disease (AD) before and after calibration compared with when total prevalence without correlations was applied

Number with AD when Total AD prevalence was used**		**Number with AD when split prevalence values were used* (difference (n; %))**			
Men	Women	Men	Women	Men	Women
		Before calibration		**After calibration**	
3378	6292	3395 (+17; +0.50%)	6411 (+119; 1.89%)	3386 (+8; 0.24%)	6366 (+74; +1.18%)

*Among 200,000 simulated individuals aged 65 years and older; **Results from the model where heart disease and AD were linked with independence between diseases assumed.

Correlation between Heart disease and Osteoporosis

The model in this study focussed specifically on correlations regarding hip fracture, and MI and stroke as these events are associated with the highest costs and utility effects. This section describes the correlation between hip fracture and a history of MI. Similar calculation was performed for the correlation between the risk of stroke and a history of hip fracture.

Incidence of hip fracture and prevalent cardiovascular disease

Fracture risks are influenced by the presence of CVD. In a study by Gerber and colleagues [8], MI was associated with higher risk of all types of osteoporotic fracture. Excess fracture risks after MI were found with the overall adjusted hazard ratio (HR) of 1.32 (95% CI 1.12-1.56) across all anatomic sites. Trends of the fracture incidence rates for three time-periods (1979-1989; 1990-1999; 2000-2006) were tested and an increase in fracture rates over time was found among MI patients. An HR of 1.66 for both men and women for hip fracture was used in the model, which was for the most recent time period (2000-2006). Data reported in Gerber et al. [8] was used in the model as this study was based on a large sample size and similar ethnic group to that of the UK, and provided relatively recent data in the format suitable to be applied to the time-to-event distributions used in the model. Only a transient increase of fracture risks after MI was identified in the study. In the Gerber et al. (2011) study, as the mean follow-up time was only 4 years and the association between and MI and 5-year risk of osteoporotic fracture was reported, HR was applied for five years after MI.

The incidence of hip fracture was split between that for those with MI and that for those without. Using the prevalence estimates of MI used to populate the individual heart disease model, the total incidence of hip fracture was split between the incidence of hip fracture for patient who had an MI within 5 years and that for patients who did not have MI for the last 5 years. These were reported in Table S2.4 for those on no treatment (A) and on drug treatment for osteoporosis (B) where an RR of 72% for hip fracture was applied [9]. Due to the low prevalence of MI among younger age groups, the baseline incidence for those without MI was similar to the total incidence including both groups with and without MI.

Table S2.4. Hip fracture incidence split between rates for those with MI and without MI

A. Hip fracture incidence with and without MI – No drug treatment

	Total incidence of hip fracture		Baseline rate r (without MI)		Rate for patients with MI	
Age	Men	Women	Men	Women	Men	Women
45-50	0.00030	0.00020	0.00030	0.00020	0.00049	0.00033
50-55	0.00030	0.00020	0.00030	0.00020	0.00049	0.00033
55-60	0.00070	0.00050	0.00067	0.00049	0.00112	0.00082
60-65	0.00030	0.00080	0.00029	0.00079	0.00048	0.00131
65-70	0.00080	0.00130	0.00073	0.00127	0.00121	0.00211
70-75	0.00110	0.00210	0.00100	0.00206	0.00167	0.00341
75-80	0.00200	0.00420	0.00180	0.00396	0.00299	0.00658
80-85	0.0068	0.0097	0.00613	0.00915	0.01017	0.01519
85+	0.0099	0.0217	0.00892	0.02047	0.01481	0.03398

B. Hip fracture incidence with and without MI – For individuals on drug treatment for osteoporosis

	Total incidence of hip fracture – on drug treatment		Baseline rate r (without MI)		Rate for patients with MI	
Age	Men	Women	Men	Women	Men	Women
45-50	0.00025	0.00018	0.00025	0.00017	0.00041	0.00029
50-55	0.00024	0.00017	0.00024	0.00017	0.00040	0.00028
55-60	0.00050	0.00033	0.00048	0.00032	0.00080	0.00054
60-65	0.00020	0.00055	0.00019	0.00054	0.00032	0.00090
65-70	0.00060	0.00092	0.00054	0.00090	0.00090	0.00149
70-75	0.00081	0.00150	0.00074	0.00147	0.00123	0.00244
75-80	0.00145	0.00303	0.00131	0.00286	0.00217	0.00475
80-85	0.00490	0.00695	0.00442	0.00656	0.00733	0.01088
85+	0.00713	0.01557	0.00643	0.01469	0.01067	0.02439

The incidence rates of hip fracture with and without a recent MI reported in Table S2.4 were used as the baseline event rates for hip fracture for the first 5 year period after MI. The relative risks associated with factors that can influence the event rates, such as low BMD and previous fracture, were applied onto these baseline rates. When sampling time to next hip fracture, these baseline incidence rates of hip fracture were updated when the sampled time to event was longer than the time before a change in age band, or the time left to a change in the drug efficacy due to the

treatment fall time after discontinuation. Hence, all three time intervals for which different event rates are applied – time to 5 years after MI, time to next age band, and time to next efficacy change due to the fall time of treatment effect – were continuously compared with the sampled time to event (TTE) value. When the sampled TTE value is longer than any of the three, the baseline incidence rates were changed accordingly and TTE was resampled.

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Event Rates

This section describes the event rates used for the base-case model only for HD due to the addition of PAD and updated parameters. Parameter estimates used in the AD and osteoporosis models were based on the data reported in the HTA reports [1, 2] and are detailed in Youn [3]. The data sources were identified from the six UK-based studies [4-9]. The most appropriate parameter estimates reported for similar populations and contexts in the six studies and their sources of data were used for the model in this research. UK-sourced data were used wherever possible, and age-dependent time-variant rates of transitions between health events were preferred.

All included HD disease states except PAD were split into two temporal categories – first year and subsequent years after the event – due to the difference in the rates for transitions to other events, costs, and/or utility weights between the first year of the event and thereafter. Various sources for cardiac death rates were used dependent on the 'from' state of the transition. The rate of transition to cardiac death varied with the age group and the temporal period (first year or subsequent years after the event), and time to cardiac death was sampled from an exponential distribution, the parameter of which produced the appropriate rate.

The event rates used in the model are summarised in the next sections by the origin of transitions, with each section followed by a summary table of the estimates. In addition, rates of transitions to fatal stroke and PAD were described in separate sections as they applied regardless of the origin of transitions.

Transitions from event-free state (at model initiation)

Event rates differed depending on whether an individual is on primary or secondary prevention interventions, or is untreated. Rates of transitions from the event-free state are summarised in Table S3.1.

Table S3.1. Baseline annual rates of transition from event-free state

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimates**	**Sources**
Event free	MI	Rate for men = 0.01624; Rate for women = 0.01123	WOSCOPS (Shepherd et al. 1995 [10]) and Framingham studies (D'Agostino et al. 2008 [11])
	Stroke	Exponential mean of Exp(9.218 + (-0.064)*age at event + (-0.176)*gender) for time to event distribution $T \sim Exp(\hat{\lambda})$. Then, the prob of stroke being fatal applied. P(fatal stroke)=e^xb/[1+e^xb] where xb= -4.874 + 0.043*age – 0.074*gender.	Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) trial results [8]
	Angina	Rate = 0.0027 per patient-year.	ASCOT-LLA data [12]
	Revascularisation	For only primary and secondary prevention populations, Exponential mean of Exp(5.250 + (-0.013)*age at event + (0.479)*gender) for time to event distribution $T \sim Exp(\hat{\lambda})$. Otherwise, the national average rate of revascularisation was used.	ASCOT trial [8] National Audit of PCI [13]
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study [14]
	CVD death	For individuals not receiving any interventions, Males (females): 45-54 years 0.000639 (0.000178); 55-64 years 0.001711 (0.000573); 65-74 years 0.004275 (0.001994); 75-84 years 0.013182 (0.008621); 85 years and over 0.040947 (0.035576). For only primary and secondary prevention populations, Exponential mean of Exp(6.576 + (-0.035)*age at event + (0.437)*gender) for time to event distribution $T \sim Exp(\hat{\lambda})$.	Mortality Statistics: Deaths registered in 2012 [15] ASCOT trial [8]

Transitions from MI

Table S3.2. Baseline annual rates of transitions from myocardial infarction

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimate**	**Sources**
MI	MI	For age groups 1-5: First (subsequent) year(s) rates: 0.13697 (0.01633), 0.12239 (0.01806), 0.10747 (0.01867), 0.09146 (0.0180), 0.07375 (0.01613).	NICE TA94 Table 52 [16]; Nottingham Heart Attack Register (NHAR) [17].
	Stroke	For age groups 1-5: First (subsequent) year(s) rates: Group 1 (< 55): 0.00150 (0.0004), Group 2 (55-65): 0.00321 (0.00100), Group 3 (65-75): 0.00682 (0.00220), Group 4 (75-85): 0.01420 (0.00471), Group 5 (> 85): 0.02819 (0.00914).	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR);
	Angina	Exponential rate = 0.05975	Ara et al. 2009. Table 8 [9]; Fox et al. 2005 [18]
	Revascularisation	First year rate = 0.504347	TNT trial [6]
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study (Leng et al. 1996)
	CVD death	For age groups 1-5: First (subsequent) year(s) rates: Group 1 (< 55): 0.01755 (0.00541), Group 2 (55-65): 0.03387 (0.00955), Group 3 (65-75): 0.06465 (0.01603), Group 4 (75-85): 0.12059 (0.02482), Group 5 (> 85): 0.21791 (0.03615).	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR) [17].

Transitions from Stroke

Table S3.3. Baseline annual rates of transitions from Stroke

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimate**	**Sources**
Stroke	MI	Rates by age group: Group 1 (< 55): 0.00160, Group 2 (55-65): 0.00310, Group 3 (65-75): 0.00552, Group 4 (75-85): 0.00803, Group 5 (> 85): 0.01045.	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR) [17].
	Stroke (Stroke recurrence)	Baseline rates for 0-1, 1-5, 5-10 years for individuals aged <65: 0-1 year rate= 0.06401 (mean = 15.6237); 1-5 year rate= 0.02694; 5-10 year rate= 0.01887. Then, probability of stroke being fatal= e^xb/[1+e^xb], where xb= -4.874 + 0.043*age – 0.074*gender, was applied.	Mohan et al. 2009 [19] – Stroke recurrence; ASCOT trial [8]
	Angina	Rate = 0.0027	Assumed the same as the rate of transition from event free to angina state (NICE TA 94 Table 52)
	Revascularisation	Rate= 0.01056	TNT trial [6]
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study [14]
	CVD death	For age groups 1-5: First (subsequent) year(s) rates: Group 1 (< 55): 0.00924 (0.00421), Group 2 (55-65): 0.02245 (0.00985), Group 3 (65-75): 0.05340 (0.02102), Group 4 (75-85): 0.12466 (0.04207), Group 5 (> 85): 0.27839 (0.07796).	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR) [17]

Transitions to Fatal Stroke

If the reported data did not explicitly state that the event probabilities were for non-fatal stroke only, then a proportion of the patients who experience a stroke was assumed to die due to the stroke. The proportion of fatal stroke among all stroke events was estimated using the logistic regression equation reported in the ASCOT trial results [8] with an exception of transitions from revascularisation state where a 50% probability of stroke being fatal was assumed as in Ara et al. (2009). Thus, the transitions to stroke from event free, stroke, angina and revascularisation states included a subset of patients having a fatal event and subsequently moving to cardiac death state.

Transitions from Angina

Rates of transitions from angina are given in Table S3.4. Individuals were assumed to have stable angina first and then progress to unstable angina, which requires more intense medical treatments. Once unstable angina was developed, it was assumed that patients could not improve to stable angina.

Table S3.4. Baseline annual rates of transitions from angina

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimates**	**Sources**
Angina	MI	1) From Stable angina: Rate = 0.01520; 2) Unstable angina 5%, 4.9%, 4.7%, 4.3% from 1st year event. 3.5%, 6.3%, 11.2%, 18.5% from subsequent yrs event for those aged <55, 55-65, 65-75, 75-85 yrs, respectively.	Juul-Moller, Edvardsson [20]; Ara, Pandor [9], Table 8; Gray and Hampton [17];
	Stroke	1) From Stable angina: Rate = 0.00791; Then, the prob of stroke being fatal applied, probability = e^xb/[1+e^xb], where xb= -4.874 + 0.043*age – 0.074*gender. 2) From Unstable angina: For age groups of <65, <75, <85, >85 years, [1st year rate] To non-fatal stroke: 0.2%, 0.5%, 1%, 2%; To fatal stroke: 2.6%, 4.3%, 7%, 10.3%; [subsequent yrs rate] To non-fatal stroke: 0.1%, 0.1%, 0.3%, 0.7%; → Fatal stroke: 0.4%, 0.5%, 0.6%, 0.7%.	1) Juul-Moller, Edvardsson [20]; NICE [16]; Lindgren, Buxton [8] 2) Ara et al. 2009 (HTA) Table 8.; Gray and Hampton [17]
	Angina (unstable)	Annual probability from stable angina to unstable angina: Group 1 (< 55): 0.0013, Group 2 (55-65): 0.0029, Group 3 (65-75): 0.0060, Group 4 (75-85): 0.0091, Group 5 (> 85): 0.0122.	NICE TA 94: Table 52.
	Revascularisation	Rate=0.00269	Assumed the same as the minimum revascularisation rate from PAD state. (Leng et al. 1996)
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study (Leng et al. 1996)
	CVD death	1) If no history of angina= Group 1 (< 55): 0.009, Group 2 (55-65): 0.0035, Group 3 (65-75): 0.007, Group 4 (75-85): 0.007, Group 5 (> 85): 0.007. 2) From unstable angina = (CHD and CVD death rates combined for 1st and subsequent years.	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR).

Transitions from Revascularisation

Table S3.5. Baseline annual rates of transitions from revascularisation

Individuals not receiving statin treatment			
From State	**To State**	**Estimate**	**Sources**
Revascularisation	MI	Rate= 0.03874	Fox, Poole-Wilson [18]; Ara et al. (2009) [9]
	Stroke	Rate=0.002 with 50% of stroke being assumed to be fatal.	Henderson, Pocock [21]; Ara et al. (2009) [9]
	Angina	Rate = 0.032523	Henderson et al. (2003); Ara et al. (2009) [9]
	Revascularisation	First-year rate of having a 2nd revascularisation= 0.14491	TNT trial [6]
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study [14]
	CVD death	Rate = 0.005785	RITA-2 trial [21]

Transitions from PAD

Table S3.6. Baseline rates of transitions from peripheral arterial disease

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimate**	**Sources**
PAD	MI	Rate = 0.01711	Edinburgh Artery Study [14]
	Stroke	Rate= 0.01408	Edinburgh Artery Study [14]
	Angina	Rate= 0.02019	Edinburgh Artery Study [14]
	Revascularisation	Rate=0.00269	Edinburgh Artery Study [14]
	PAD	Rate=0	Assumed
	CVD death	Exponential mean of Exp(6.576 + (-0.035)*age at event + (0.437)*gender) for time to event distribution $T \sim Exp(\tilde{\lambda})$.	The same rate as the transition from event free to CVD death: ASCOT trial [8]

Transitions to PAD

The incidence of PAD reported in the Edinburgh Artery Study was used for the estimation of transition rates to PAD. The incidence of symptomatic PAD (i.e. with intermittent claudication, IC) in general population aged 55 and over was used for all transitions to PAD event due to the lack of published evidence [14]. Age dependent incidence was not included as it was not statistically significant in the Edinburgh Artery Study [14]. However, there was some evidence of an increase with age in earlier longitudinal studies [22, 23].

Among patients with PAD, approximately 20% progress to develop severe symptoms with critical limb ischaemia (CLI) over a 5-year period and 1-2% undergo amputation over a lifetime [24]. In the model, 20% of people with IC were randomly sampled to develop CLI at the time of developing PAD for simplicity, to whom higher costs and lower utility weights were applied.

Effectiveness of statin treatments

Statin interventions was assumed to reduce the risks of coronary events (MI, angina, and fatal CHD events) and stroke. The model assumes that a proportion of individuals entering the model are receiving a statin intervention for primary and secondary prevention of CVD events. The relative risks (RRs) of events associated with statin use were applied to the baseline risks converted from the event rates reported in Tables S3.1-S3.6, and are shown in Table S3.7.

Table S3.7. Relative risks associated with statin use compared with placebo

Transitions to	Relative Risk	Source
MI	0.656	Ward et al. (2006) [4]
Non fatal stroke	0.754	Ara et al. (2009): Simvastatin 40mg/day
Fatal stroke (from Angina state)	0.876	Ara et al. (2009): Simvastatin 40mg/day
Stable Angina (from event free state)	0.59	Ward et al. (2006) [4]
To Fatal CHD event (CVD death)	0.74	Ward et al. (2006) [4]
Non CVD death (from event free state)	0.656	Ward et al. (2006) [4]

Non-disease mortality

Non-cardiac mortality rates used to construct distribution profiles for time to non-disease death were calculated by subtracting cardiac mortality rates from the all-cause death probability profiles. Cardiac mortality rates were estimated by combining the rates reported for heart disease (ICD-10 code I00-I52) and stroke (I64) using data obtained from the Mortality Statistics: Deaths registered in 2012 [15]. Cardiac mortality rates used to calculate the non-disease mortality are shown in Table S3.8. These were the same rates used for transitions to cardiac death from event-free state.

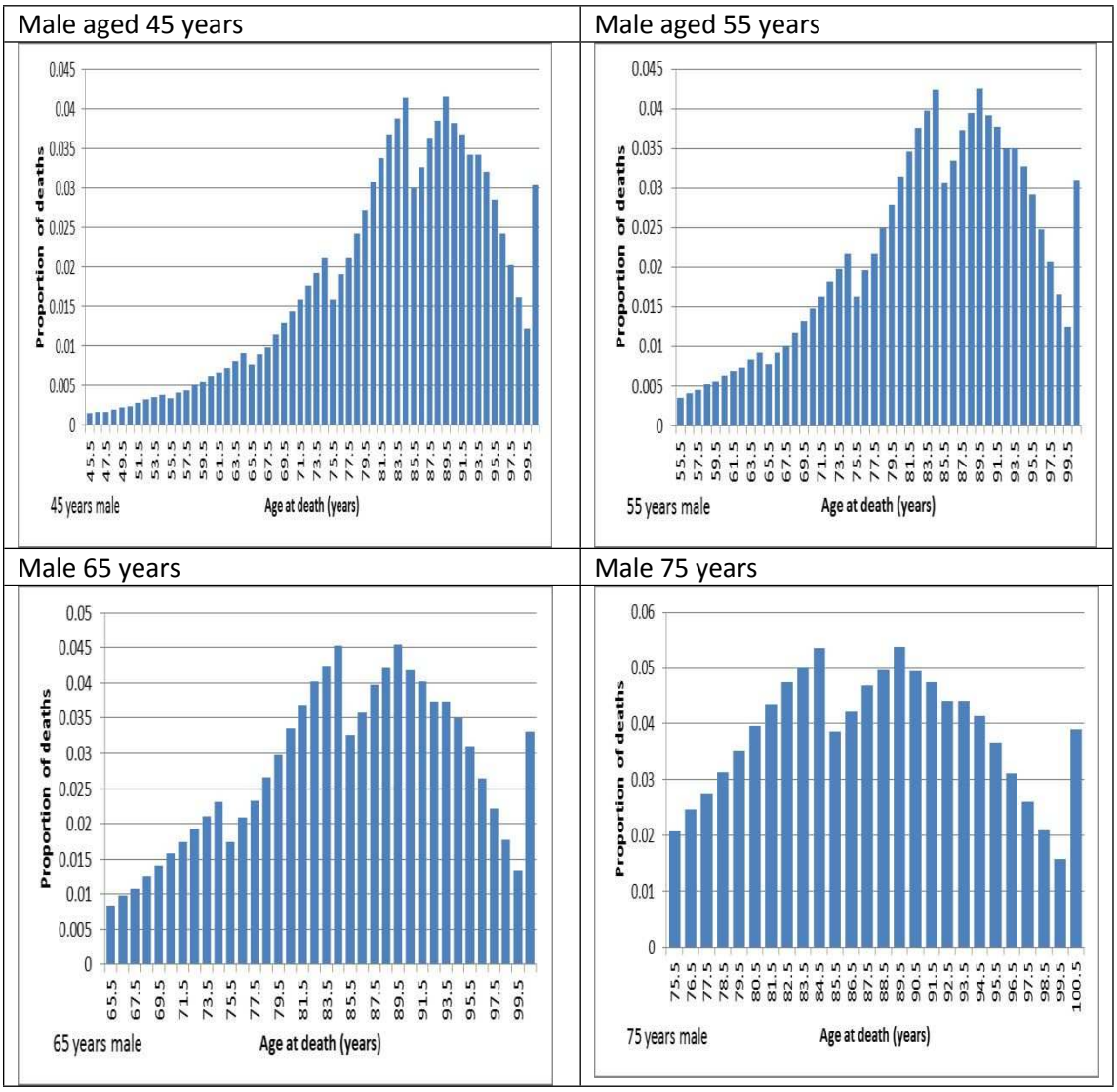
Figure S3.1 shows distributions for time to non-cardiac death for a few selected age groups. As the cardiac death rates were assumed constant across the 10-year age bands whilst the all-cause mortality rates were specified at every age x between 45 and 100 years, the probability profiles created were not smooth, but had a few stepped decreases at the age cut off values.

Table S3.8. Cardiac death rates used to estimate non-cardiac mortality rates*

	Age group				
Sex	45-54	55-64	65-74	75-84	85 and over
Male	**0.000639**	**0.001711**	**0.004275**	**0.013182**	**0.040947**
Female	**0.000178**	**0.000573**	**0.001994**	**0.008621**	**0.035576**

*Adapted from Table 8 in Deaths registered in England and Wales, 2012 [15]

Figure S3.1. Illustration of distributions for time to non-cardiac death



Costs

Table S3.9. Cost estimates used in the base-case model

Event	Data within source	Price year	Estimates [25] (2011/2012 price)	Original Source
MI - 1st year	£3,996	2007	£ 4,519.10	Ara et al. (2009) estimated using British National Formulary (2008) [26]
MI - subsequent year	£171	2004	£ 214.89	NICE TA 94 (GP contacts + medication costs)
Stroke - 1st year	£8,066	2007	£ 9,121.88	Ward, Lloyd-Jones [4]
Stroke - subsequent yr	£2,266	2007	£ 2,562.63	Ward, Lloyd-Jones [4]
Stable angina	£171	2004	£ 214.89	NICE TA 94 (GP contacts + medication costs)
Documented angina	£ 587.07	2005	£ 713.94	Taylor et al. (2009)
Revascularisation - 1st yr	£ 5,857	2007	£ 6,623.71	Taylor et al. (2009); HRG
PAD (IC)	£180	2009-2010	£189.31	Kearns, Michaels [27]
PAD (CLI)	£624	2009-2010	£656.29	Kearns, Michaels [27]; National Clinical Guideline Centre [24]
Statin treatment	£144.12	2014	£144.12	British National Formulary (2014); Estimated using the method by Ward et al. (2006)

Utilities

Baseline utility values by age and gender in the UK general population were estimated from a statistical model reported in Ara and Brazier [28].

The utility values associated with the health states included in the model were obtained from NICE TA94 and the HTA report by Ara et al. (2009). Table S3.10 describes the original sources of these

values. All the utilities were estimated using the EQ-5D, and were assumed to be multiplicative. Utility multiplier values were assumed to increase by 10% after the first year of the event as assumed in Ara et al. (2009). It was assumed that the history of revascularisation procedure did not affect the utility level, and the utility decrement for stable angina was used for individuals with history of angina. As a base-case, deterministic values for utility multipliers were used.

Alongside the current event, the history of the other health events was incorporated in the utility multiplier. For example, if a man aged 65 years who has just had a stroke has a history of MI, then the utility decrements for both stroke (first year multiplier for stroke: 0.629) and that for MI (subsequent-year multiplier: 0.836) were applied to the baseline utility (0.815); the utility weight for this person is thus 0.429 (i.e. 0.815*0.629*0.836).

When more than one cardiac event occurs within one year, the first-year periods of those events overlap. For the time periods overlapping, utility multipliers associated with the events were applied multiplicatively. For instance, if an individual experiences an MI at time=2.3 years and subsequently a stroke at time=2.7 years, then for time between 2.3 and 2.7 years, only the utility multiplier for the first year of MI would be applied (0.760) whilst for time between 2.7 and 3.3 years, utility multipliers associated with both first-year MI and first-year stroke would be applied (0.760*0.629=0.478). In the same way, for time between 3.3 and 3.7 years, utilities associated with subsequent years of MI and first year of stroke are used (0.836*0.629=0.526) In the model for this paper, whenever individuals reach these time points, they are directed to the 'utility cut off point' event in order to update variables related to utility multiplier.

Table S3.10. Utility multipliers by health state

State	First year - Mean (S.E.)	Subsequent years -	Original Sources
MI	0.760 (0.018)	0.836 (10% increase)	Goodacre, Nicholl [29]
Stroke	0.629 (0.04)	0.692 (10% increase)	Tengs and Lin [30]
(Stable) angina	0.808	0.889 (10% increase)	Melsop, Boothroyd [31]
Unstable angina	0.77	0.847 (10% increase)	Goodacre, Nicholl [29]
Revascularisation	0.78	0.858 (10% increase)	Serruys, Unger [32]
PAD IC	0.70	0.70	Kearns, Michaels [27]
PAD CLI	0.35	0.35	[Kearns, Michaels [27]]

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Supplementary Appendices

Supplementary Material for:

Modelling the economic impact of interventions for older populations with multimorbidity: a method of linking multiple single-disease models

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Appendix 1. Justification for disease selection

Appendix 2. Incorporating correlations between diseases

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Study	Model type (software)	Base-case Population	Intervention	Comparator(s)	Outcomes	Perspective	Time horizon/ price year	Health events included (e.g. Markov health states)	Stratified results (Yes/No)	Base-case ICER	Parameters driving ICER
Heart disease (HD)											
HD single-disease model in this paper	Discrete event simulation (Simul8)	General population aged 45 years and over	Statins	No statins	QALYs	NHS	Lifetime	MI, stable angina, unstable angina, stroke, revascularisation, PAD, CVD death, and non-CVD death	Yes – Base-case reported for the total population; and by age and gender, by prevention type	1) Secondary prevention - £1.5k – 4.0k/QALY vary by age and gender 2) Primary prevention - £2.2k-2.8k varied by age and gender	Reduced cost of statins (updated to 2012 values); Population age and sex distribution at model entry; Added event of PAD could lower ICERs compared to the results from Ward et al. (2006)
HD reference model by Ward et al. (2006) [1]	Markov model	A population with CHD or at increased risk of CHD events (annual CHD risk of 0.5%-3%)	Statins as a group	No statins	QALYs	NHS	Lifetime/ 2004 Discount rates of 6% for costs and 1.5% for health benefits	MI, stable angina, unstable angina, CHD death, TIA, stroke, and CVD death or non-CVD death	Yes – Base-case reported by prevention level, age and sex, and predicted annual CHD risk levels	Multiple base-case values 1) Secondary prevention - £10k-£17k /QALY 2) Primary prevention – at annual CHD risk of 3%, £10k-37k /QALY for men and £14k-48k /QALY for women	Results were most sensitive to the cost of statins, discount rates and the timeframe of the model; Larger incremental costs than the model in this study; ICERs sharply increased with age of the population

Alzheimer's disease (AD)											
AD model in this paper	Discrete event simulation (Simul8)	General population aged 45 years and over	Donepezil and memantine	BSC	QALYs	NHS and PSS	Lifetime	AD onset; diagnosis; pre-institutionalisation; institutionalisation; and death	Yes – results reported for two age groups aged >45 and >65 years	Donepezil and memantine therapy dominated BSC (cost saving £14 with 0.001 QALY gain)	The model results were generally comparable with those from Bond et al. (2012). Incremental QALYs from the model for this study were smaller than those from Bond et al. (2012) as the general population was modelled with the added events of the onset and diagnosis of AD.
AD reference model by Bond et al. (2012) [2]	Markov model (Microsoft Excel)	People with mild, moderate or severe AD	donepezil, galantamine, rivastigmine, for mild-to-moderate AD, and memantine, for moderate-to-severe AD	BSC	QALYs	NHS and PSS	20 years / 2009 price	pre-institutionalisation; institutionalisation; and death	Yes – by disease severity	Donepezil for mild-to-moderate AD dominated BSC; Memantime for moderate-to-severe AD: £32.1K/ QALY (increC=£405; increQ =0.013)	Results sensitive to assumptions on discontinuation rates; Costs of institutionalisation
Osteoporosis											
Osteoporosis model in this paper	Discrete event simulation (Simul8)	General population aged 45 years and	70mg alendronate taken once	No alendronate treatmen	QALYs	NHS and PSS	Lifetime	Hip fracture; vertebral fracture, wrist	Yes – by age and gender, BMD level, status of	Alendronate dominated no treatment for 75-year-old	Age, BMD level and history of previous fracture altered the incremental costs

		over	weekly	t				fracture; proximal humerus fracture; fracture-related death; non-fracture death	previous fracture	women with T-score of -3 SDs and -2.5 SDs with no previous fracture	and QALYs. However, regardless of the willingness-to-pay threshold per QALY, the alendronate is likely to be a cost-effective option for fracture prevention.
Osteoporosis reference model by Stevenson et al. (2009) [3]	Patient-level Markov model (Microsoft Excel)	Postmenopausal women aged 50 years and over	Vitamin K; alendronate; risedronate; strontium ranelate	No alendronate; next cost-effective treatment options	QALYs	NHS and PSS	10 years (the results subsequently adjusted to account for treatment benefits beyond the initial 10 years)	Hip fracture; vertebral fracture, wrist fracture; proximal humerus fracture; nursing home entry from hip fracture; breast cancer; and coronary heart disease; and non-fracture related death	Yes – by age, BMD level, and status of previous fracture	Alendronate dominated no treatment for 75-year-old women with T-score of -3 SDs with no previous fracture; £1,226/QALY for 75-year-old women with T-score of -2.5 SDs.	Age, fracture risks, BMD and history of previous fracture could alter the ICER estimates.

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Background : Uncertainty around DES model outputs can be represented by both first-order uncertainty, defined as stochastic variability between simulated observations assuming identical parameter values, and second-order uncertainty, defined as uncertainty in the parameters of the economic model [1].

Aim: The degree of first order uncertainty in the linked model was examined in order to identify the appropriate number of simulated individuals to ensure stable model results. Stability was defined as an adoption decision being robust with sufficiently small random errors.

Method: Incremental values were computed in comparison with no treatments for all three of the diseases (heart disease, Alzheimer's disease and osteoporosis). The first-order uncertainty around the mean incremental cost and QALYs, incremental net monetary benefit (NMB) and cost per QALY gained (CPQ) was quantified for the results from the correlated linked model for the population aged 45 years and older.

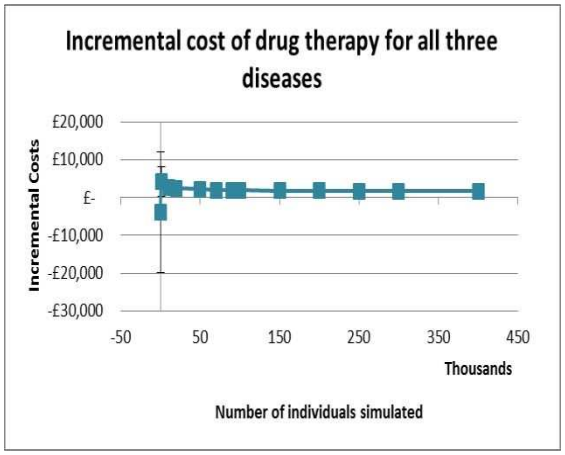
The jackknife approach was used to estimate a confidence interval for the mean cost per QALY with a reduced level of bias associated with the classical estimation of non-linear statistics [2, 3]. The standard errors of the mean results were estimated having varied the numbers of simulated individuals ranging from 1,000 to 700,000. The jackknife 95% confidence interval for the mean CPQ and the NMB results with more than 400,000 simulated individuals were derived using R programming language (R version 3.2.1, © The R Foundation) due to limited capacity of the spreadsheet software. Jackknifing execution time for the data from 700,000 simulated individuals was 4.69 hours on an Intel ® Core ™ i5 CPU 2.30 GHz processor with 4.00 GB of RAM (3.54 hours for 600,000 data points).

Results: Figure S5.1 shows that the incremental cost and QALYs stabilised when more than 200,000 individuals were simulated. The standard errors of the mean NMB and CPQ started to stabilise after running more than 500,000 simulated individuals. The chosen number of individuals to simulate was 700,000 for the base-case all-disease linked models (with and without correlations) in order to further reduce the variability of the results.

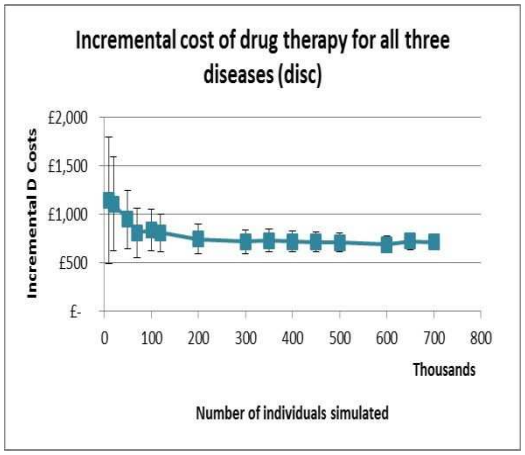
Figure S5.1. First order uncertainty in relation to the number of patients simulated in the all-disease linked model with correlations (base-year population aged 45 years and over)

1) Incremental cost (compared with none of the three treatments)

Undiscounted

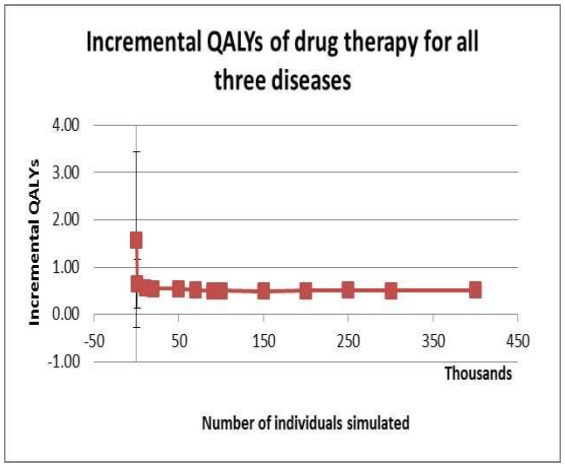


Discounted

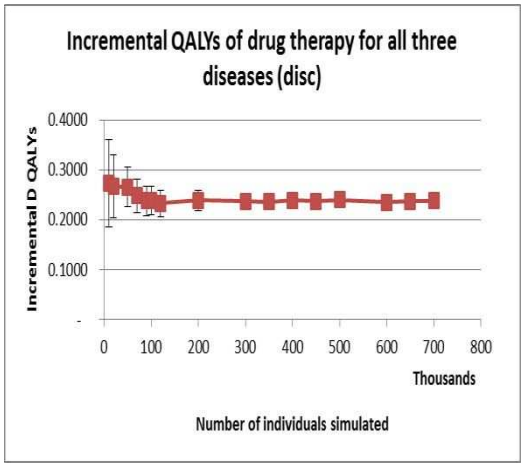


2) Incremental QALYs (compared with none of the treatments for the three diseases)

Undiscounted

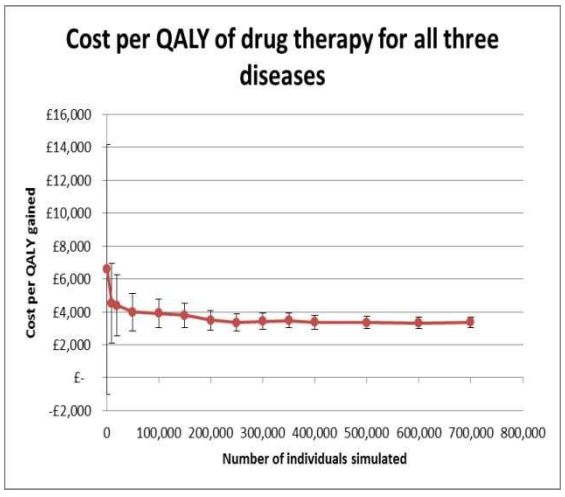


Discounted

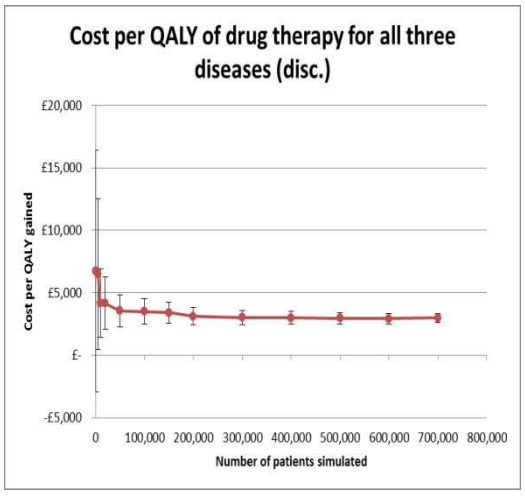


3) Cost per QALYs (95% jackknife confidence interval)

Undiscounted

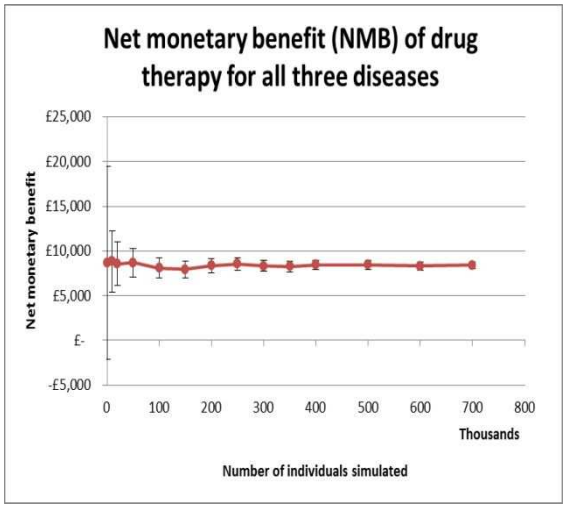


Discounted

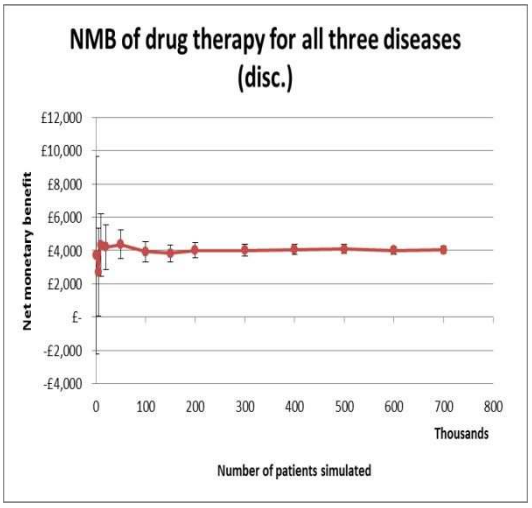


4) Net monetary benefit (£20,000 threshold)

Undiscounted



Discounted



Each figure includes error bars showing the standard error in the mean estimates of (incremental) cost and QALYs.

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[1] Briggs AH, Weinstein MC, Fenwick EAL, Karnon J, Sculpher MJ, Paltiel AD. Model Parameter Estimation and Uncertainty: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-6. Value in Health. 2012; 15(6):835-42.

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[3] Iglehart DL. Simulating stable stochastic systems, V: Comparison of ratio estimators. Naval Research Logistics Quarterly. 1975; 22(3):553-65.

Supplementary Appendices

Supplementary Material for:

Modelling the economic impact of interventions for older populations with multimorbidity: a method of linking multiple single-disease models

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Appendix 6. Summary of the results from the individual disease models for comparison

	1) Heart disease only model			2) Alzheimer's disease only model			3) Osteoporosis only model			4) Sum of incremental values across 1)-3)
	Treatment	No treatment	Incremental values (A)	Treatment	No treatment	Incremental values (B)	Treatment	No treatment	Incremental values (C)	(A)+(B)+(C)
Cost - Discounted	£ 8,091	£ 7,569	£ 522	£4,582	£4,596	-£ 14	£ 2,847	£ 2,947	-£ 100	£ 408
QALYs - Discounted	9.249	8.978	0.271	10.642	10.641	0.001	11.191	11.184	0.008	0.280
Cost	£ 14,224	£ 13,197	£ 1,027	£8,845	£8,869	-£ 23	£ 6,151	£ 6,324	-£ 173	£ 831
QALYs	13.843	13.257	0.586	16.548	16.545	0.003	17.759	17.751	0.009	0.597
Life years lived	21.319	20.319	1.000	21.653	21.650	0.003	23.530	23.525	0.004	1.007
ICER – Discounted			£ 1,926 /QALY			Dominating			Dominating	£ 1,458 /QALY
ICER			£ 1,754 / QALY			Dominating			Dominating	£ 1,391 / QALY

HD: based on n=200,000; AD n=200,000; Osteoporosis n=400,000

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In order to examine the effect of sampling error when all three treatments have a similar level of QALY gains, the scenarios in Table S7.1 were assumed: these are not meant to provide accurate evaluations of current treatments but to show that the results would have face validity when QALY gains are comparable. For all three individual diseases, populations aged 65 years and older were simulated. Scenarios for larger QALY gains for AD and osteoporosis and reduced QALY gain for HD were explored. Table S7.1 shows the scenario assumptions applied to each of the three disease models in comparison with the base-case assumptions.

Table S7.1. Comparison of scenario assumptions and base-case assumptions

Base-case assumptions	Scenario assumptions
1. Heart disease model	
Relative risks were assumed to be 0.656, 0.754, 0.876, 0.59, 0.74, and 0.656 for MI, non-fatal stroke, fatal stroke, stable angina, fatal CHD, and non-cardiac death, respectively.	Relative risks of 0.98 for statin treatment were assumed for all events.
Utility values for MI, stroke and revascularisation were set to 0.76, 0.629, and 0.78, respectively.	Utility values for MI, stroke, and revascularisation were reduced to 0.5.
2. Alzheimer's disease model	
4% of monthly treatment discontinuation rate was assumed.	Lifetime treatment: No treatment discontinuation was assumed
6 months duration of treatment effect was assumed.	Lifetime treatment effect was assumed.
Utility value for institutionalised individuals was 0.33.	Utility value for those institutionalised was reduced to 0.1
The average annual improvements in MMSE score were 2.48 for donepezil and 1.4 for memantine per year.	Double treatment effect on MMSE score: the average improvements in MMSE score were set to 4.96 for donepezil and 2.8 for memantine per year.
Some individuals are institutionalised at model entry, and some patients are institutionalised immediately after diagnosis.	No individuals start at the institutionalisation state at model entry, nor get institutionalised immediately after the diagnosis (i.e. No individuals move to the

	institutionalisation event from the diagnosis event with zero time passed.)
3. Osteoporosis model	
Relative risks of fracture for alendronate treatment were set to 0.72, 0.58, and 0.82 for hip, vertebral, and other fractures, respectively.	Relative risks were assumed to be 0.33 for all fracture types.
5 years of treatment duration was assumed.	Lifetime treatment duration was assumed.

Table S7.2 compares incremental outcomes from the three individual disease models with those for each of the individual treatments from the linked model where the diseases were assumed to be independent. Under the hypothetical scenarios, a comparable magnitude of QALY gains across all three individual disease models (Table S7.2 Column a) was achieved. The margins of error around incremental costs and QALYs at 95% confidence level are shown in brackets.

Table S7.2 reports results under the scenarios in Table S7.1, assuming the diseases were independent. When none of the treatments have much larger impact on QALYs gained the linked model produced similar results to those from the individual disease models. This shows the robustness of the adoption decision within the linked model for individual treatments.

Table S7.2. Cost-effectiveness results under larger QALY gain scenarios for individual treatments from the individual disease models and the independently linked model

1. Heart disease				
	a. Individual heart disease model†	**b. Independently linked model (n=700,000)**		
	Incremental values (Margin of error) ‡	All treatments	No HD treatment*	Incremental values
DCost	£ 683 (£ 66)	£ 11,001	£ 10,201	£ 800
DQALYs	**0.0539 (0.0179)**	4.9232	4.8784	0.0448
TCost	£ 913 (£ 94)	£ 15,499	£ 14,380	£ 1,119
TQALYs	0.0875 (0.0267)	6.2589	6.1861	0.0728
ICER (disc.)	£ 12,665			£ 17,878
ICER	£ 10,433			£ 15,360
2. Alzheimer's disease (AD)				
	a. Individual AD model†	**b. Independently linked model (n=700,000)**		
	Incremental values (Margin of error) ‡	All treatments	No AD treatment*	Incremental values
DCost	-£ 4,551 (£ 93)	£ 11,001	£ 15,413	-£ 4,412
DQALYs	**0.0508 (0.0020)**	4.9232	4.8855	0.0377
TCost	-£ 6,319 (£ 130)	£ 15,499	£ 21,582	-£ 6,083
TQALYs	0.0688 (0.0028)	6.2589	6.2089	0.0500
ICER (disc.)	Dominating			Dominating
ICER	Dominating			Dominating
3. Osteoporosis				
	a. Individual osteoporosis model†	**b. Independently linked model (n=700,000)**		
	Incremental values (Margin of error) ‡	All treatments	No osteoporosis treatment*	Incremental values
DCost	-£ 1,186 (£ 74)	£ 11,001	£ 11,983	-£ 982
DQALYs	**0.0545 (0.0128)**	4.9232	4.8918	0.0314
TCost	-£ 1,856 (£ 123)	£ 15,499	£ 16,970	-£ 1,471
TQALYs	0.0900 (0.0204)	6.2589	6.2090	0.0499
ICER (disc.)	Dominating			Dominating
ICER	Dominating			Dominating

† Based on n=200,000 for HD and AD models; and n=400,000 for osteoporosis model, as in the base-case; ‡ Margin of error at 95% confidence level; *The other two default treatments were assumed to be available; D=discounted.

When all the individual disease models produce similar QALY gains (without any disease with a significantly larger impact) the impact of Monte Carlo error for one disease on the incremental outcomes and cost-effectiveness of the other diseases can be much less influential. None of the margin of error estimates in Table S7.2 (0.0179, 0.0020, and 0.0128 for HD, AD, and osteoporosis models, respectively) will have a significant effect that changes the +/- signs of the values on the incremental QALY results from the linked model (0.0448, 0.0377, and 0.0314 for HD, AD, and osteoporosis treatments, respectively). Hence, when QALY gains are similar across all diseases, the results are less susceptible to sampling error from the other diseases. The base-case estimated very small QALY gains for AD and osteoporosis treatments which could fluctuate between positive and non-positive values due to the sampling error associated with the treatment for HD. In cases where QALY gains are similar, however, the proposed methods of linking individual disease models are likely to produce more accurate cost-effectiveness estimates for individual treatments.

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The correlated linked model for the three diseases (HD, AD and osteoporosis) was built probabilistically to take account of the uncertainty around input parameter point estimates. This section provides probabilistic results in order to show the feasibility of probabilistic sensitivity analysis (PSA) using the linked model described in this paper.

A probability distribution was defined for selected input parameters. The selection of parametric distributions was based on the nature of the data. For example, utilities were assumed beta-distributed as the data were assumed to be bounded by zero and one. Wherever possible, probabilistic distributions reported in the original publications of the reference models [1-3] were used. Where this was not possible, the distribution was parameterised using estimates of the error around mean or assumed standard errors for the purpose of this feasibility run of PSA. Table S8.1 shows the PSA input parameters and their distributional properties.

Table S8.1. Variables and distributions used in the probabilistic sensitivity analysis (PSA)

PSA Variable	Point estimate*	Distribution	Distributional properties
Clinical effectiveness			
RR of statin treatment for MI	0.656	Lognormal	Lognormal(logmean=-0.4219, logSE=0.0233)
RR of statin treatment for stroke	0.754	Lognormal	Lognormal(logmean=-0.2826, logSE=0.0203)
Change in MMSE when using Donepezil 10mg	1.24**	Normal	Normal(1.24, 0.22)
Change in MMSE when using Memantine 20mg	0.70**	Normal	Normal(0.70, 0.35)
Proportion of patients compliant to medication	0.75	Beta	Beta(13.31, 4.44)
Utilities of health states			
Stable angina	0.808	Beta	Beta(86.00, 20.44)
Unstable angina	0.77	Beta	Beta(93.67, 27.98)
MI	0.76	Beta	Beta(427.09, 134.87)
Stroke	0.628	Beta	Beta(91.07, 53.94)
MMSE: 0-9	0.33	Beta	Beta(36.59, 74.28)
MMSE: 10-14	0.49	Beta	Beta(78.04, 81.22)
MMSE: 15-20	0.5	Beta	Beta(856.27, 856.27)
MMSE: 21-25	0.64	Beta	Beta(1137.19, 639.67)
MMSE: 26-30	0.69	Beta	Beta(282.51, 126.92)
Institutionalised	0.33	Beta	Assumed the same as the utility

			value for MMSE:0-9
Vertebral fracture – 1st year	0.626	Beta	Beta(14.03, 8.38)
Vertebral fracture – subsequent year	0.909	Beta	Beta(6.61, 0.66)
Hip fracture – 1st year	0.792	Beta	Beta(12.26, 3.22)
Hip fracture – subsequent year	0.813	Beta	Beta(11.55, 2.66)
Costs			
Cost of institutionalisation	£2941	Normal	Normal(2941, 108)
Cost of death from hip fracture	£9525.86	Gamma	Gamma(scale=67.19, shape=141.78)***

MMSE: mini mental score examination; *mean values used in base-case analysis; **6month estimate; ***calculated from assumed standard error of 800.

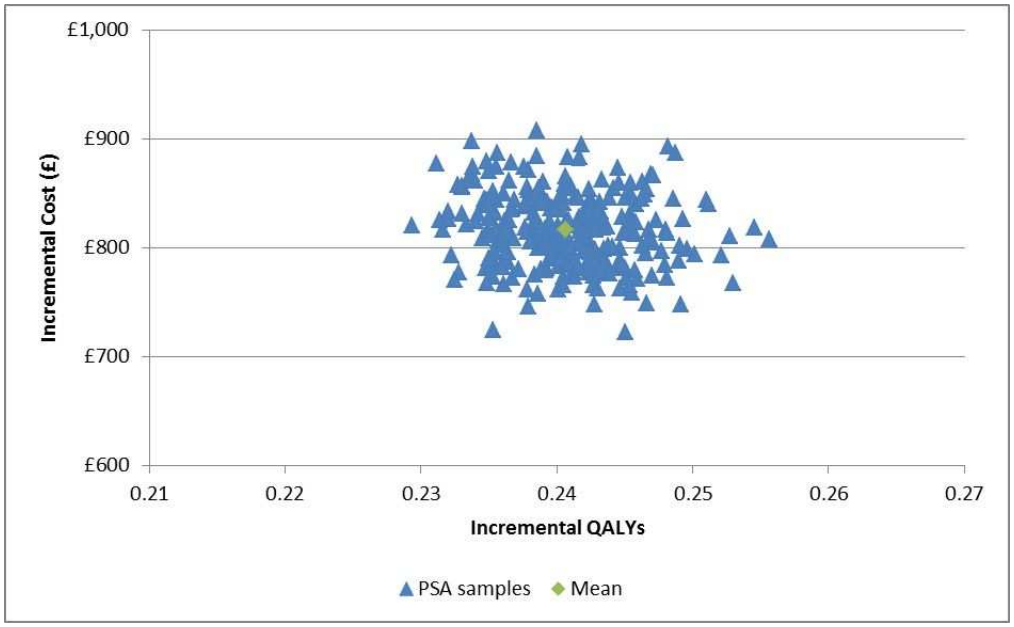
The probabilistic model results are shown in Table S8.2 based on 300 PSA runs in each of which 700,000 individuals were simulated. The mean cost and QALYs of the PSA results in Table S8.2 showed comparable results with the base-deterministic results from the correlated linked model albeit not identical. All of the PSA samples in Figure S8.1 showed cost per QALY being lower than the threshold of £20,000 per QALY gained.

Table S8.2. Comparison of probabilistic model results with the base-case deterministic results*

All-disease linked model with correlations	Deterministic results			Probabilistic results		
	All three treatments assumed	None of the three treatments assumed	Incremental values	All three treatments assumed	None of the three treatments assumed	Incremental values
Mean cost	£14,741	£13,894	£847	£14,392	£13,575	£816
Mean QALYs	8.962	8.725	0.236	8.972	8.731	0.241
ICER			£3,583/QALY			£3,391/QALY**

*Based on 300 PSA runs; each deterministic run is based on 700,000 simulated individuals;
**Jackknife 95% C.I. £3,360-£3,423.

Figure S8.1. Probabilistic sensitivity analysis scatterplot of incremental costs and QALYs



*Based on 300 PSA runs

The results show that the adoption decision is robust when assuming the willingness-to-pay threshold of £20,000 per QALY gained. Each deterministic run of 700,000 individuals took approximately 15 minutes to run and hence, conducting 300 PSA runs for each intervention arm took 1.9 days of computing time (Intel Core™ i7CPU 3.40GHz processor with 16GB RAM). Such time scales indicate it is feasible to conduct PSA using the multi-disease linked model. The probabilistic analysis of discrete event simulation model will become more achievable by using a computer with more processing power or parallel computing. The number of runs required would be affected by the homogeneity of the population studied. Hence, the use of a more narrowly defined population with specific characteristics and higher disease prevalence, than the general population adopted in the current analysis, would accelerate convergence due to higher number of disease events simulated and more homogeneous parameter values.

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Figures

Manuscript Title:

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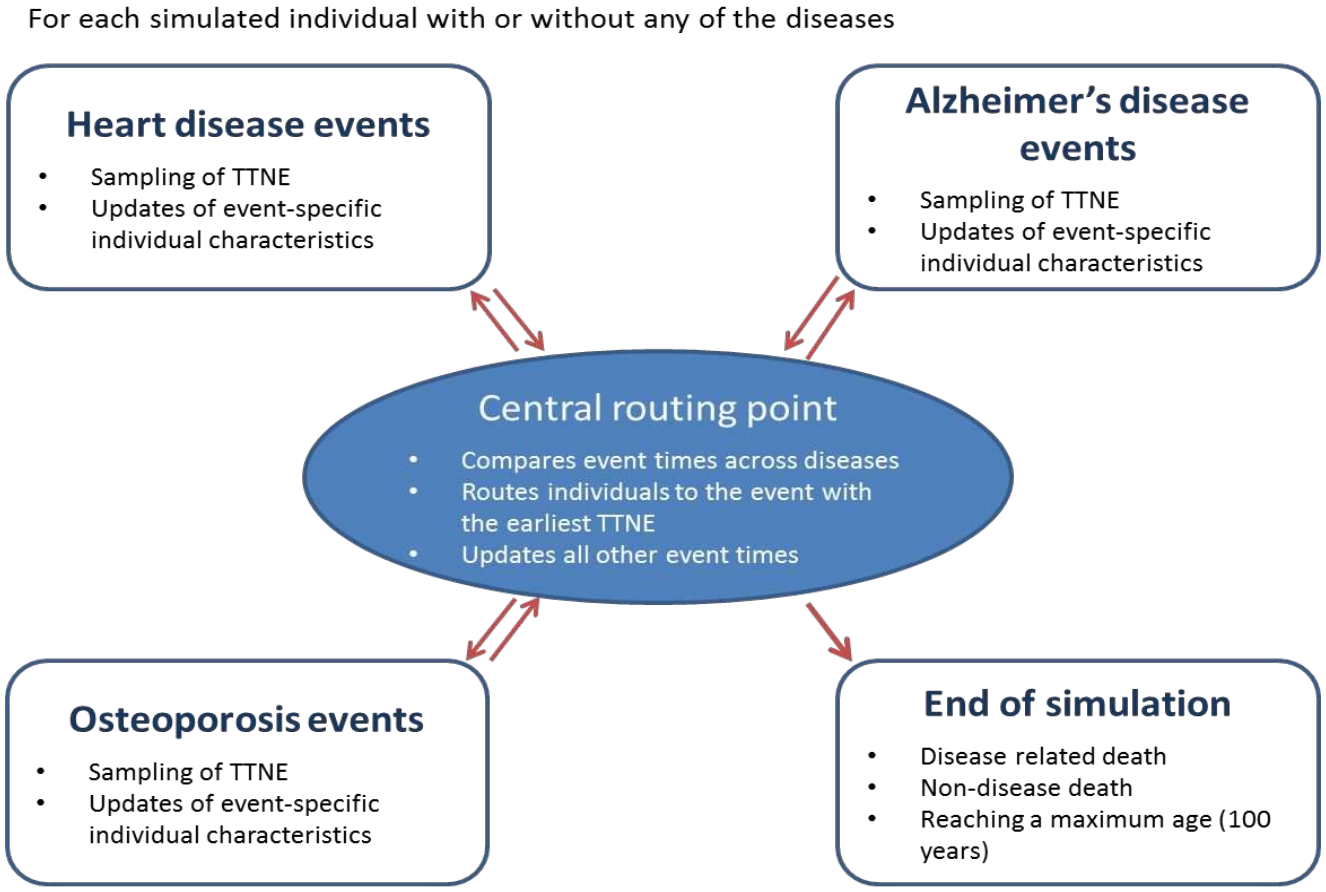
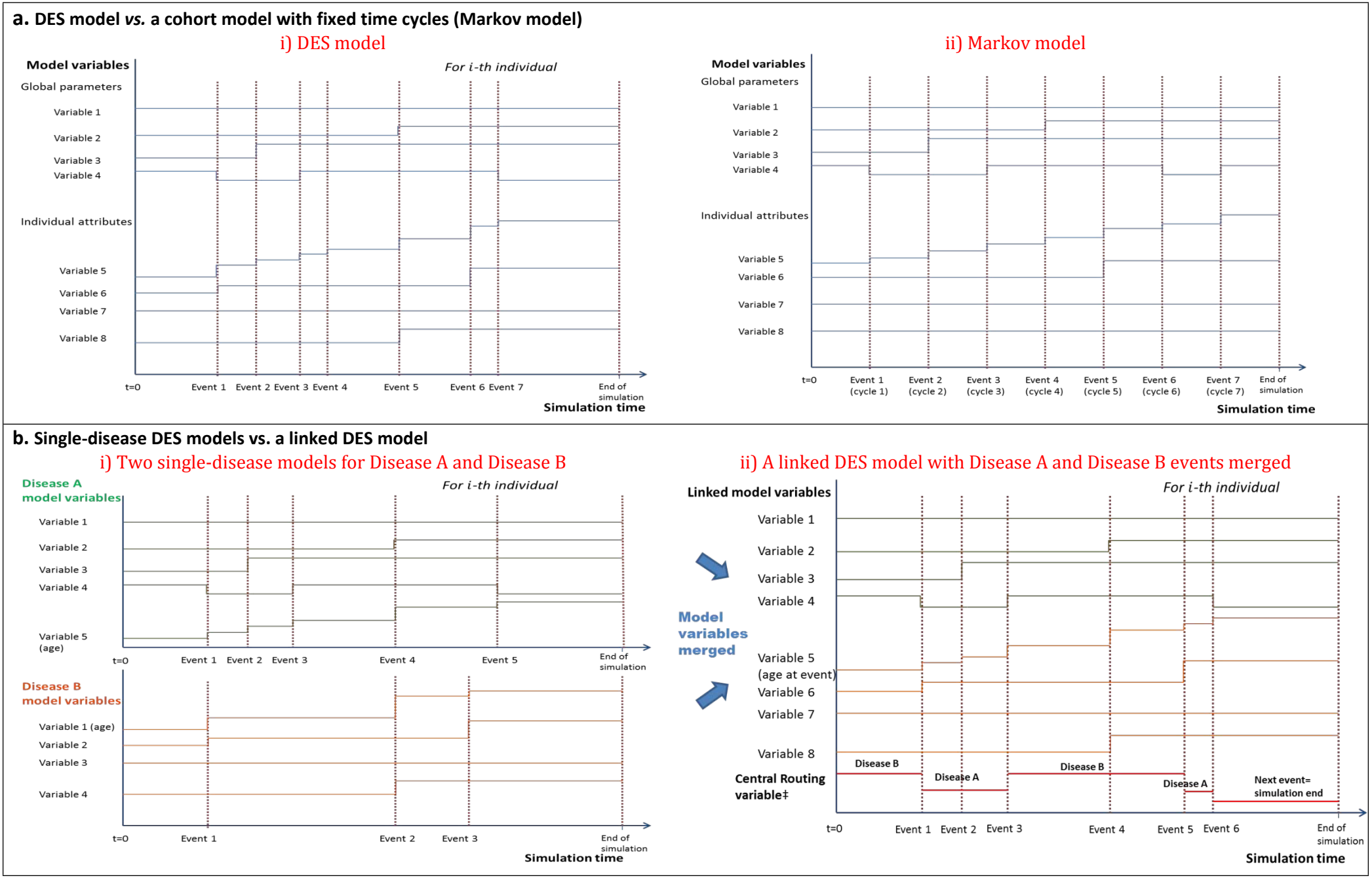
Figure 1. A schematic diagram of the linked disease model



TTNE: time to next event

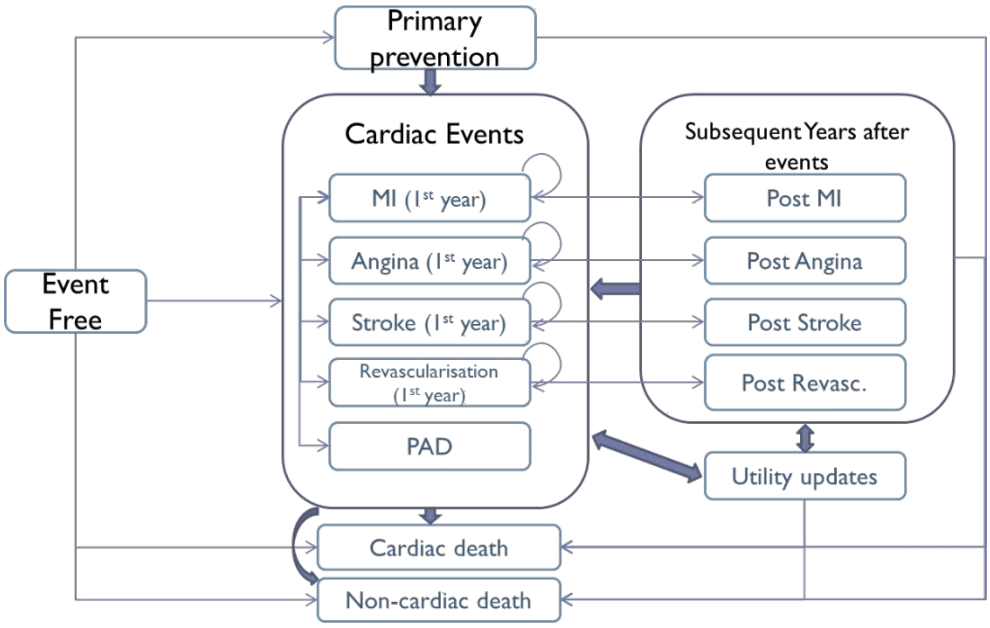
Figure 2. Discrete event simulation (DES) model with and without model linkage†



†All y-axes of the diagrams show examples of variables defining the respective models and changes in their values over simulation time (x-axes); *Global parameters: variables that apply to all simulated individuals such as discount rates, unit cost of interventions and utility associated with health events; **Individual attributes: variables that reflect changes in individual characteristics over time such as age, a previous experience of disease events and utility multipliers relevant to the individual at specific event times; ‡Central routing variable was added after combining all single-disease model variables in the linked model to indicate in which disease model the next event is scheduled to occur.

Figure 3. The structure of the individual disease models

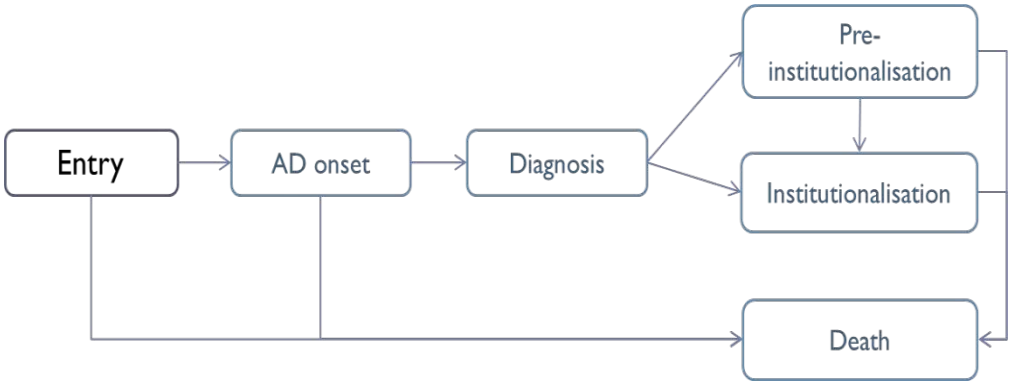
a) Heart disease model*



MI: myocardial infarction; PAD: peripheral artery disease; Revasc: revascularisation;

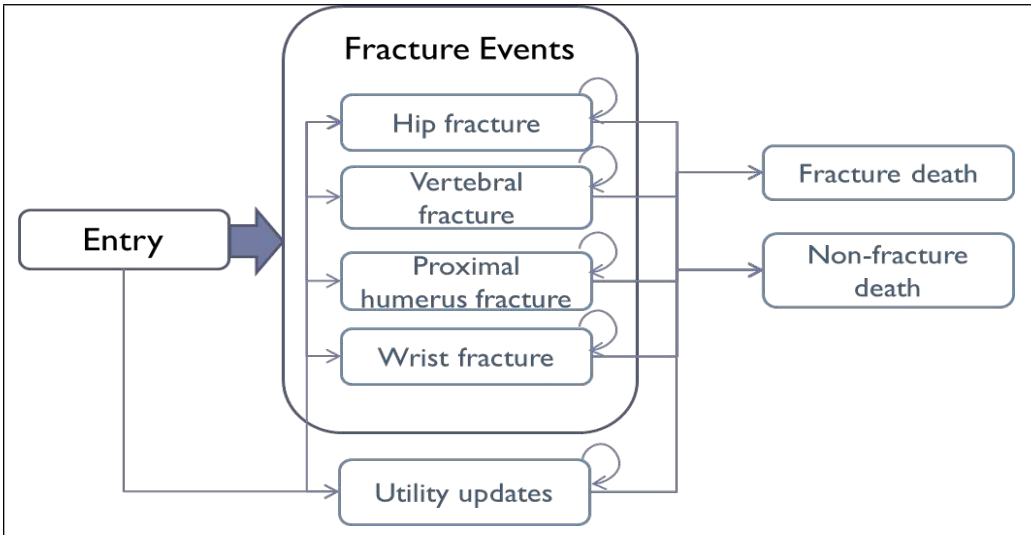
The heart disease model included MI, stroke, angina, revascularisation PAD and cardiac and non-cardiac deaths as qualifying health events. Each non-fatal cardiac event except PAD (MI, angina, stroke and revascularisation) was divided into two temporal categories: first-year and subsequent years after the event.

b) Alzheimer's disease model



Alzheimer's disease: The onset and diagnosis of AD were added to the structure of the model by Bond et al. (2012) in order to model a general population.

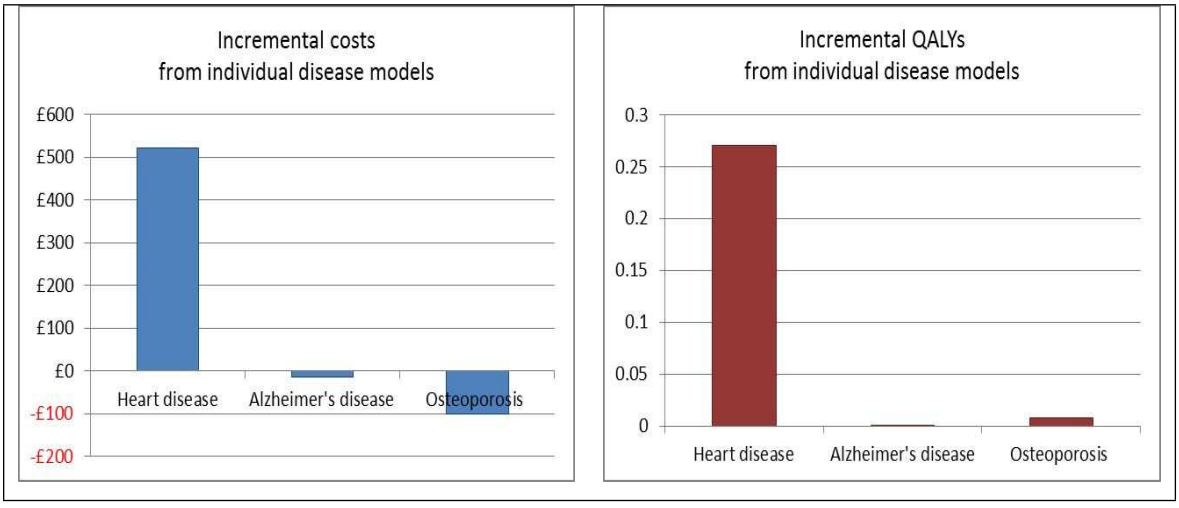
c) Osteoporosis model*



Osteoporosis model: Four fractures (hip, vertebral, wrist and proximal humerus) were included as osteoporotic fracture events. The events also included nursing home entry from hip fracture; death following fracture; and non-fracture related death (see Stevenson et al. 2009).

*The 'utility updates' event was included in Figure 2a and 2c in order to reflect the differences in costs and utilities for the first year and subsequent years after each event. This event activated a transient utility state where a different utility value is applied when there is no actual disease event but there is a change in utilities and costs.

Figure 4. Comparison of incremental costs and QALYs from the three individual disease models



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Appendix 1. Justification for disease selection

The criteria used for selecting the diseases to be modelled in the case study are summarised in Box 1.

Box 1. Criteria for selecting diseases to model

- Diseases with major cost implications: High costs to the UK NHS and Personal Social Services of treating/managing the diseases
- Diseases of the elderly: Diseases with significant mortality and morbidity burden for older population and diseases whose incidence is expected to increase as population ages.
- Establishing a balance between different disease areas in order to cover a spectrum of conditions.
- Diseases that are correlated with respect to their incidence/prevalence and thus are more likely to co-occur
- Whether there are sufficiently recent HTA reports undertaken for the disease in order that a peer-reviewed model could be replicated.
- Diseases of hard endpoints, rather than those being risk factors for other diseases themselves, such as diabetes and hypertension

Diseases with significant cost implications to the UK NHS and Personal Social Services (PSS) for an ageing population were considered for inclusion in the model. Diseases expected to become more prevalent as a population ages were given a priority.

A balance between different disease areas was also considered as one of the criteria. Including diseases from one or two areas of diseases whose mechanisms are similar may be misleading in estimating the broad impact of population ageing on healthcare expenditure and the interactions between diseases. Among diseases of significant economic, mortality and morbidity burdens, a spectrum of diseases that affect different parts of the body were included.

Diseases that are potentially correlated were considered for inclusion in the case study. Seemingly unrelated health conditions may co-occur in individuals as they often share common underlying risk factors (for further details, see Appendix 2).

Fracture risks are influenced by the presence of cardiovascular disease (CVD). In a study that was a part of the Rochester Epidemiology Project, myocardial infarction (MI) was associated with higher risk of all types of osteoporotic fracture [1]. Excess fracture risks after MI were found with the overall adjusted hazard ratio (HR) of 1.32 (95% CI 1.12-1.56) across all anatomic sites.

Further, the prevalence of heart disease (HD) among Alzheimer's disease (AD) patients was considered higher than that of HD within an age- and gender-matched general population. A number of studies have found that AD often co-exists with vascular conditions such as hypertension, hyper-cholesterolaemia, and diabetes mellitus [2-6].

Osteoporosis and stroke share several risk factors, including age, smoking, low physical activity, and hypertension. Thus, low bone mineral density (BMD) and high stroke risk can be correlated. Studies have shown that low BMD or a history of fracture has an association with the incidence of stroke [7-9]. Jørgensen et al. [9] reported that women with BMD values in the lowest quartile had a higher risk of stroke than women with BMD values in the highest quartile (odds ratio (OR)= 4.8), and a linear trend over the quartiles was statistically significant. The OR for stroke increased 1.9 per SD (0.13 g/cm^2) reduction in BMD. The association between low BMD and stroke in women remained significant when the analysis was adjusted for potential confounders. In men, however, no statistically significant difference in BMD between the stroke patients and their controls was found.

The presence of recently published (or in press) NIHR HTA reports was considered as it was deemed as evidence of the importance of the disease to major stakeholders such as decision-makers in local government, policy-makers (including the National Institute for Health and Care Excellence (NICE)), health professionals, and the general public. Further, the model structures reported in the HTA reports were largely replicated.

Diseases with hard endpoints were preferred to those which were surrogate risk factors for other diseases. It was believed that such diseases could be embedded as a risk factor, and the consequences of the diseases could be represented in the models of other diseases.

Using the selection criteria, the three diseases with significant mortality and disability burdens for the elderly – heart disease (including stroke and MI), Alzheimer's disease, and osteoporosis – were chosen for the case study.

The most expensive disease category was cardiovascular disease. Heart conditions, such as coronary heart disease (CHD) and MI, and stroke were selected for modelling as they account for the largest

proportion of mortality and prevalent cases in cardiovascular disease among older individuals [10], and impose significant economic burden on the overall healthcare system [11].

Dementia was selected for modelling considering its cost, potential association with CVD, the balance between the chosen diseases, and likely impact of population ageing. Amongst brain disorders, dementia was the most expensive category of spending [12], and affects older people in particular with the incidence positively correlated with age [13]. Only the most common form of dementia, Alzheimer's disease (AD), was modelled in this study as the current NICE guidance and relevant model-based studies (including HTA reports) focussed on AD.

It was considered appropriate to include one or more musculoskeletal disorders due to the increasing prevalence and incidence with age. Amongst the musculoskeletal conditions, osteoporosis was deemed appropriate to include in the model due to its high cost. Osteoarthritis (OA) was not selected as previous models have been built for OAs at different anatomical sites such as knees, hips, and joints of hands, which make OA more difficult to include given the aim of this paper. Furthermore, the incidence of OA is difficult to estimate as the onset is not well-defined due to the discrepancy between the symptomatic OA and OA based on the radiological changes. Rheumatoid arthritis (RA) was considered for inclusion as RA mainly affects people aged 65 years and older [14]. However, RA was not chosen for the modelling given that the cost of RA did not exceed that of OA and chronic obstructive pulmonary disease.

Appendix 2. Incorporating correlations between diseases

The following correlations were incorporated in the proof-of-concept model.

1) Prevalence of AD for people with and without HD
2) Incidence of AD for people with and without HD
3) Incidence of hip fracture for people with and without a history of MI
4) Stroke risks among people with and without a history of hip fracture
5) Incidence of AD with and without low BMD

AD=Alzheimer's disease; HD= heart disease; MI= myocardial infarction; BMD=bone mineral density

This section describes only the correlations between the prevalence of HD and AD ((1) in above table) and the incidence of osteoporotic fracture and the presence of HD ((3) in above) incorporated in the linked model and how these correlations were implemented. The correlations 1)-5) were selected due to the data availability. Different incidence and prevalence estimates were applied to two groups of people with and without the other underlying condition. Similar calculation methods to those described in this section were applied to other correlations.

Targeted literature searches in the Medline and/or EMBASE databases using a combination of the disease names were conducted to identify the required data on correlations between the modelled diseases. Wherever possible, data on the incidence and prevalence of one disease with and without the other diseases was obtained. Further details on the correlations 2), 4) and 5) can be found in Youn (2016) [15].

Correlation between Heart disease and Alzheimer's disease

Systematic searches for literature reporting the prevalence of AD and other co-existing conditions and the outcomes of intervention for patients with AD and other relevant conditions were conducted within the Medline and EMBASE databases. However, very few papers that could provide numerical data for populating the model were identified.

A small number of studies that discussed empirical data on the effect of one disease on another were identified. As Maslow [2] noted, studies mainly listed common co-existing conditions that were

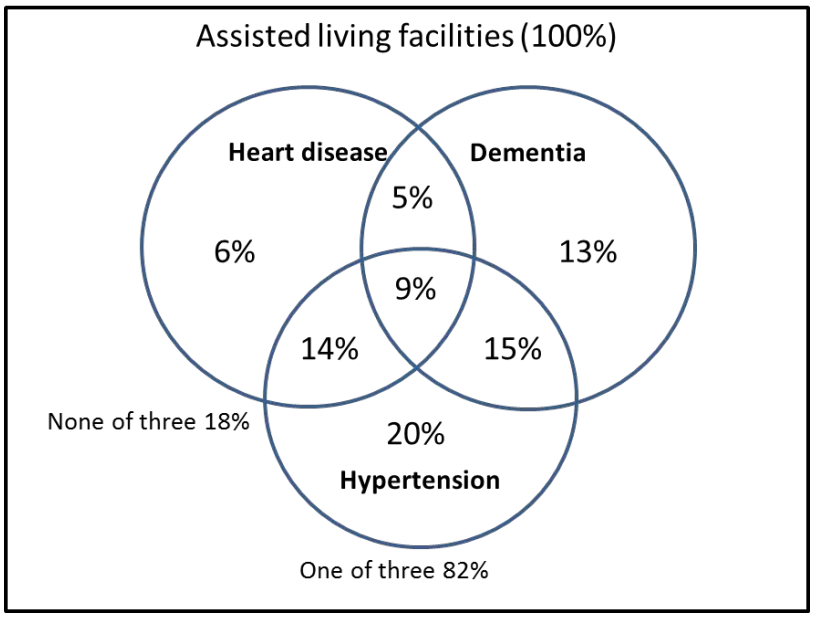
present in their study population only, or intentionally excluded people with AD who have other co-morbidities as the effect of other diseases could confound the effect of AD. Studies focussing on heart disease reported similar results.

Correlation of prevalence

The prevalence of HD among AD patients was considered higher than that of HD within an age- and gender-matched general population. A number of studies have found that AD often co-exists with vascular conditions such as hypertension, hyper-cholesterolaemia, and diabetes mellitus [2-6].

For instance, the US National Center for Health Statistics survey found that 82% of people in assisted living facilities where help is provided for daily activities such as bathing and dressing had one or more of dementia, hypertension, and heart disease (Figure S2.1) [16]. 42% of the residents had Alzheimer's disease or other forms of dementia and 34% had heart disease. 14% of people had both dementia and heart disease and 9% of them had all three of the diseases. However, as this survey was conducted in assisted living centres, the survey respondents were likely to be older than other study populations.

Figure S2.1. Co-morbidities of residents in assisted living facilities



Source: The National Center for Health Statistics, 2010 [16]

In order to incorporate the linkages between AD and HD, those with and without HD had different prevalence of AD: the total proportion of people who have AD was divided into the proportion of AD patients among people with heart disease and the proportion among people without HD.

For each age and sex group, the total prevalence of AD, $P(AD = 1)$, can be seen as a weighted average of two conditional probabilities $P(AD = 1|HD = 1)$ and $P(AD = 1|HD = 0)$ as follows;

$$P(AD = 1) = P(AD = 1|HD = 1) \cdot P(HD = 1) + P(AD = 1|HD = 0) \cdot P(HD = 0)$$

[Eq. 1]

where AD and HD are binary variables taking the value of one when the disease is present and zero otherwise. Therefore, $P(AD = 1)$ and $P(HD = 1)$ are the prevalence of AD and HD, respectively. $P(AD = 1|HD = 1)$ denotes the probability of having AD conditional on the presence of HD, or the prevalence of AD among those with HD, and $P(HD = 1|AD = 1)$ the prevalence of HD among those with AD.

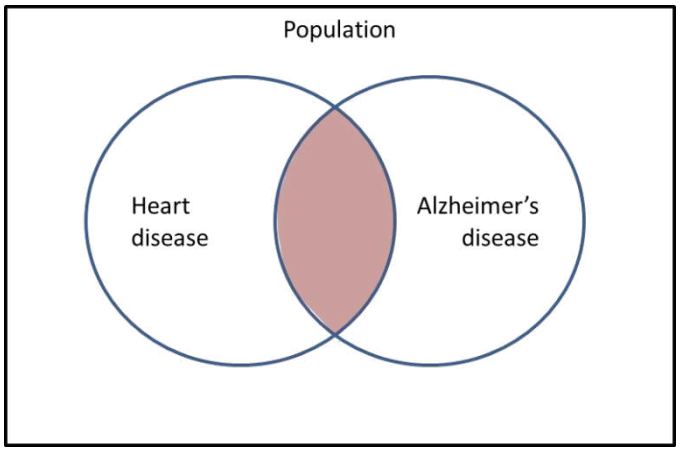
In the same way, the total prevalence of heart disease can be calculated as:

$$P(HD = 1) = P(HD = 1|AD = 1) \cdot P(AD = 1) + P(HD = 1|AD = 0) \cdot P(AD = 0)$$

[Eq. 2]

Eq. 2 expresses the total prevalence of HD in terms of $P(HD = 1|AD = 1)$ and $P(HD = 1|AD = 0)$ using the value of AD prevalence, $P(AD = 1)$. Regardless of which equation to use, the split should be the same as $P(HD = 1|AD = 1)$ and $P(AD = 1|HD = 1)$ represent the same coloured area in Figure S2.2 although the actual figures of the conditional probabilities differ depending on which disease status is assumed to be known.

Figure S2.2. Prevalence linkage between AD and heart disease



However, Eq. 2 could not be used as the total prevalence of heart disease had to be partitioned among the cardiac events included in the model and data required for using Eq. 2 were not available from the literature searches. Hence, the prevalence of AD was divided into the prevalence of AD for people with and without HD using Eq. 1.

Using Bayes' theorem, $P(AD = 1|HD = 1)$ in Eq. 1 was calculated as $P(AD = 1|HD = 1) = \frac{[P(HD=1|AD=1) \cdot P(AD=1)]}{P(HD=1)}$ **[Eq. 3]**. The relationship in Eq. 1 was used to calculate $P(AD = 1|HD = 0)$. The following sections describe the methodology and report the calculation results.

Calculation and calibration of the prevalence of Alzheimer's disease among heart disease patients

The prevalence of AD among people with HD, $P(AD = 1|HD = 1)$, was calculated by combining the results on $P(HD = 1|AD = 1)$ and $P(HD = 1)$ using Eq. 3. Subsequently, the prevalence of AD among people without HD, $P(AD = 1|HD = 0)$, was also estimated using Eq. 1.

The resulting prevalence of AD divided into $P(AD = 1|HD = 1)$ and $P(AD = 1|HD = 0)$ is shown in Table S2.1. These values were used in the linked model as the prevalence of AD in relation to the presence of heart disease. The ratio $\frac{P(AD=1|HD=1)}{P(AD=1|HD=0)}$ varied with age group and sex as the prevalence of individual diseases, $P(HD = 1)$ and $P(AD = 1)$, differ between age and sex.

Table S2.1. Prevalence of AD divided into the prevalence for people with HD and that for people without HD (before calibration)

	Prevalence of AD					
	People with HD ①		*People without HD* ②		*Ratio* (①/②)	
Age	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
<65	0	0	0	0	NA	NA
65-69	0.018267	0.044718	0.006785	0.005929	2.69	7.54
70-74	0.036962	0.05099	0.015618	0.009068	2.37	5.62
75-79	0.051255	0.091056	0.032751	0.034654	1.57	2.63
80-84	0.095646	0.180764	0.058681	0.068831	1.63	2.63
85+	0.196727	0.363585	0.108037	0.132586	1.82	2.74

The prevalence of AD before and after applying the correlations were compared using the values sampled at the model entry in order to see whether the estimation method used for splitting prevalence produced similar results. The total prevalence of AD and the prevalence for people with and without HD are compared in Table S2.2. The prevalence values of AD with and without HD were combined for comparison with the total AD prevalence before splitting using 100,000 simulated individuals for each age group (in order to have enough numbers of simulated individuals in each age group). The absolute percentage differences ranged from 0.23% to 5.09% between the total population values and the split values of prevalence. The percentage difference was the largest for female population aged 70-74 years. The differences could be due to the use of the single estimate of $P(HD = 1|AD = 1)$ in Eq. 3 for all age groups and sex, which fails to reflect variation among different populations in the estimation equation.

Although the differences could be considered small, the prevalence of AD split for people with and without HD was calibrated to match the total prevalence. Calibration was performed in order to start the model with the same population with respect to the total prevalence of AD. Based on the total prevalence values, age- and sex-specific calibration multipliers were applied to the prevalence values for people with and without HD. These were calculated as the total prevalence divided by the combined prevalence using split values. The calibrated prevalence after these multipliers were applied was used in all models for this paper where AD and heart disease were correlated.

Table S2.2. Comparison of simulated proportions of people with Alzheimer's disease (AD): between when the total prevalence of AD was used and when the prevalence of AD split into HD and non-HD groups was used

	Total prevalence of AD (before splitting)		**Combined prevalence of AD using split prevalence values***		**% Difference (compared with the total prevalence AD)**	
Age	Men	Women	Men	Women	Men	Women
<65	0	0	0	0	0	0
65-69	0.0101	0.0108	**0.0098**	**0.0104**	-3.01%	-3.98%
70-74	0.0223	0.0158	**0.0232**	**0.0166**	3.88%	5.09%
75-79	0.0403	0.0511	**0.0387**	**0.0503**	-3.94%	-1.52%
80-84	0.0734	0.1015	**0.0732**	**0.1020**	-0.38%	0.44%
85+	0.1411	0.1980	**0.1451**	**0.1985**	2.79%	0.23%

*Based on the results of 100,000 simulated individuals for each age group.

In order to examine the effect of the calibration at the population level, the numbers of people with AD across all age groups in the models before and after calibration were compared in Table S2.3 when 200,000 individuals aged 65 years and over were simulated for each model (the age distribution for people aged 65 and over was adapted from the ONS mid-2012 UK population estimates). The total numbers of people with AD among 200,000 simulated individuals from models with and without calibrated prevalence values were compared with that from the model where heart disease and AD were independently linked. The calibration reduced the difference between when the total AD prevalence was applied and when the split prevalence values were used from 0.50% to 0.24% for male population and from 1.89% to 1.18% for females.

There still existed differences in the number of people with AD after calibration due to Monte Carlo sampling error. Perfect calibration would have been possible if the calibration factors were calculated using the model results with the infinite number of runs for each age and sex group. In addition, if the infinite number of individuals were simulated in the perfectly calibrated model and the independently linked model for figures in Table S2.3, the differences would have been eliminated.

Table S2.3. Number of individuals with Alzheimer's disease (AD) before and after calibration compared with when total prevalence without correlations was applied

Number with AD when Total AD prevalence was used**		**Number with AD when split prevalence values were used* (difference (n; %))**			
Men	Women	Men	Women	Men	Women
		Before calibration		**After calibration**	
3378	6292	3395 (+17; +0.50%)	6411 (+119; 1.89%)	3386 (+8; 0.24%)	6366 (+74; +1.18%)

*Among 200,000 simulated individuals aged 65 years and older; **Results from the model where heart disease and AD were linked with independence between diseases assumed.

Correlation between Heart disease and Osteoporosis

The model in this study focussed specifically on correlations regarding hip fracture, and MI and stroke as these events are associated with the highest costs and utility effects. This section describes the correlation between hip fracture and a history of MI. Similar calculation was performed for the correlation between the risk of stroke and a history of hip fracture.

Incidence of hip fracture and prevalent cardiovascular disease

Fracture risks are influenced by the presence of CVD. In a study by Gerber and colleagues [1], MI was associated with higher risk of all types of osteoporotic fracture. Excess fracture risks after MI were found with the overall adjusted hazard ratio (HR) of 1.32 (95% CI 1.12-1.56) across all anatomic sites. Trends of the fracture incidence rates for three time-periods (1979-1989; 1990-1999; 2000-2006) were tested and an increase in fracture rates over time was found among MI patients. An HR of 1.66 for both men and women for hip fracture was used in the model, which was for the most recent time period (2000-2006). Data reported in Gerber et al. [1] was used in the model as this study was based on a large sample size and similar ethnic group to that of the UK, and provided relatively recent data in the format suitable to be applied to the time-to-event distributions used in the model. Only a transient increase of fracture risks after MI was identified in the study. In the Gerber et al. (2011) study, as the mean follow-up time was only 4 years and the association between and MI and 5-year risk of osteoporotic fracture was reported, HR was applied for five years after MI.

The incidence of hip fracture was split between that for those with MI and that for those without. Using the prevalence estimates of MI used to populate the individual heart disease model, the total incidence of hip fracture was split between the incidence of hip fracture for patient who had an MI within 5 years and that for patients who did not have MI for the last 5 years. These were reported in Table S2.4 for those on no treatment (A) and on drug treatment for osteoporosis (B) where an RR of 72% for hip fracture was applied [17]. Due to the low prevalence of MI among younger age groups, the baseline incidence for those without MI was similar to the total incidence including both groups with and without MI.

Table S2.4. Hip fracture incidence split between rates for those with MI and without MI

A. Hip fracture incidence with and without MI – No drug treatment

	Total incidence of hip fracture		Baseline rate r (without MI)		Rate for patients with MI	
Age	Men	Women	Men	Women	Men	Women
45-50	0.00030	0.00020	0.00030	0.00020	0.00049	0.00033
50-55	0.00030	0.00020	0.00030	0.00020	0.00049	0.00033
55-60	0.00070	0.00050	0.00067	0.00049	0.00112	0.00082
60-65	0.00030	0.00080	0.00029	0.00079	0.00048	0.00131
65-70	0.00080	0.00130	0.00073	0.00127	0.00121	0.00211
70-75	0.00110	0.00210	0.00100	0.00206	0.00167	0.00341
75-80	0.00200	0.00420	0.00180	0.00396	0.00299	0.00658
80-85	0.0068	0.0097	0.00613	0.00915	0.01017	0.01519
85+	0.0099	0.0217	0.00892	0.02047	0.01481	0.03398

B. Hip fracture incidence with and without MI – For individuals on drug treatment for osteoporosis

	Total incidence of hip fracture – on drug treatment		Baseline rate r (without MI)		Rate for patients with MI	
Age	Men	Women	Men	Women	Men	Women
45-50	0.00025	0.00018	0.00025	0.00017	0.00041	0.00029
50-55	0.00024	0.00017	0.00024	0.00017	0.00040	0.00028
55-60	0.00050	0.00033	0.00048	0.00032	0.00080	0.00054
60-65	0.00020	0.00055	0.00019	0.00054	0.00032	0.00090
65-70	0.00060	0.00092	0.00054	0.00090	0.00090	0.00149
70-75	0.00081	0.00150	0.00074	0.00147	0.00123	0.00244
75-80	0.00145	0.00303	0.00131	0.00286	0.00217	0.00475
80-85	0.00490	0.00695	0.00442	0.00656	0.00733	0.01088
85+	0.00713	0.01557	0.00643	0.01469	0.01067	0.02439

The incidence rates of hip fracture with and without a recent MI reported in Table S2.4 were used as the baseline event rates for hip fracture for the first 5 year period after MI. The relative risks associated with factors that can influence the event rates, such as low BMD and previous fracture, were applied onto these baseline rates. When sampling time to next hip fracture, these baseline incidence rates of hip fracture were updated when the sampled time to event was longer than the time before a change in age band, or the time left to a change in the drug efficacy due to the

treatment fall time after discontinuation. Hence, all three time intervals for which different event rates are applied – time to 5 years after MI, time to next age band, and time to next efficacy change due to the fall time of treatment effect – were continuously compared with the sampled time to event (TTE) value. When the sampled TTE value is longer than any of the three, the baseline incidence rates were changed accordingly and TTE was resampled.

Appendix 3. Parameter estimates and data sources

Event Rates

This section describes the event rates used for the base-case model only for HD due to the addition of PAD and updated parameters. Parameter estimates used in the AD and osteoporosis models were based on the data reported in the HTA reports [13, 17] and are detailed in Youn [15]. The data sources were identified from the six UK-based studies [18-23]. The most appropriate parameter estimates reported for similar populations and contexts in the six studies and their sources of data were used for the model in this research. UK-sourced data were used wherever possible, and age-dependent time-variant rates of transitions between health events were preferred.

All included HD disease states except PAD were split into two temporal categories – first year and subsequent years after the event – due to the difference in the rates for transitions to other events, costs, and/or utility weights between the first year of the event and thereafter. Various sources for cardiac death rates were used dependent on the 'from' state of the transition. The rate of transition to cardiac death varied with the age group and the temporal period (first year or subsequent years after the event), and time to cardiac death was sampled from an exponential distribution, the parameter of which produced the appropriate rate.

The event rates used in the model are summarised in the next sections by the origin of transitions, with each section followed by a summary table of the estimates. In addition, rates of transitions to fatal stroke and PAD were described in separate sections as they applied regardless of the origin of transitions.

Transitions from event-free state (at model initiation)

Event rates differed depending on whether an individual is on primary or secondary prevention interventions, or is untreated. Rates of transitions from the event-free state are summarised in Table S3.1.

Table S3.1. Baseline annual rates of transition from event-free state

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimates**	**Sources**
Event free	MI	Rate for men = 0.01624; Rate for women = 0.01123	WOSCOPS (Shepherd et al. 1995 [24]) and Framingham studies (D'Agostino et al. 2008 [25])
	Stroke	Exponential mean of Exp(9.218 + (-0.064)*age at event + (-0.176)*gender) for time to event distribution $T \sim Exp(\hat{\lambda})$. Then, the prob of stroke being fatal applied. P(fatal stroke)=e^xb/[1+e^xb] where xb= -4.874 + 0.043*age – 0.074*gender.	Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) trial results [22]
	Angina	Rate = 0.0027 per patient-year.	ASCOT-LLA data [26]
	Revascularisation	For only primary and secondary prevention populations, Exponential mean of Exp(5.250 + (-0.013)*age at event + (0.479)*gender) for time to event distribution $T \sim Exp(\hat{\lambda})$. Otherwise, the national average rate of revascularisation was used.	ASCOT trial [22] National Audit of PCI [27]
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study [28]
	CVD death	For individuals not receiving any interventions, Males (females): 45-54 years 0.000639 (0.000178); 55-64 years 0.001711 (0.000573); 65-74 years 0.004275 (0.001994); 75-84 years 0.013182 (0.008621); 85 years and over 0.040947 (0.035576). For only primary and secondary prevention populations, Exponential mean of Exp(6.576 + (-0.035)*age at event + (0.437)*gender) for time to event distribution $T \sim Exp(\hat{\lambda})$.	Mortality Statistics: Deaths registered in 2012 [29] ASCOT trial [22]

Transitions from MI

Table S3.2. Baseline annual rates of transitions from myocardial infarction

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimate**	**Sources**
MI	MI	For age groups 1-5: First (subsequent) year(s) rates: 0.13697 (0.01633), 0.12239 (0.01806), 0.10747 (0.01867), 0.09146 (0.0180), 0.07375 (0.01613).	NICE TA94 Table 52 [30]; Nottingham Heart Attack Register (NHAR) [31].
	Stroke	For age groups 1-5: First (subsequent) year(s) rates: Group 1 (< 55): 0.00150 (0.0004), Group 2 (55-65): 0.00321 (0.00100), Group 3 (65-75): 0.00682 (0.00220), Group 4 (75-85): 0.01420 (0.00471), Group 5 (> 85): 0.02819 (0.00914).	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR);
	Angina	Exponential rate = 0.05975	Ara et al. 2009. Table 8 [23]; Fox et al. 2005 [32]
	Revascularisation	First year rate = 0.504347	TNT trial [20]
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study (Leng et al. 1996)
	CVD death	For age groups 1-5: First (subsequent) year(s) rates: Group 1 (< 55): 0.01755 (0.00541), Group 2 (55-65): 0.03387 (0.00955), Group 3 (65-75): 0.06465 (0.01603), Group 4 (75-85): 0.12059 (0.02482), Group 5 (> 85): 0.21791 (0.03615).	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR) [31].

Transitions from Stroke

Table S3.3. Baseline annual rates of transitions from Stroke

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimate**	**Sources**
Stroke	MI	Rates by age group: Group 1 (< 55): 0.00160, Group 2 (55-65): 0.00310, Group 3 (65-75): 0.00552, Group 4 (75-85): 0.00803, Group 5 (> 85): 0.01045.	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR) [31].
	Stroke (Stroke recurrence)	Baseline rates for 0-1, 1-5, 5-10 years for individuals aged <65: 0-1 year rate= 0.06401 (mean = 15.6237); 1-5 year rate= 0.02694; 5-10 year rate= 0.01887. Then, probability of stroke being fatal= e^xb/[1+e^xb], where xb= -4.874 + 0.043*age – 0.074*gender, was applied.	Mohan et al. 2009 [33] – Stroke recurrence; ASCOT trial [22]
	Angina	Rate = 0.0027	Assumed the same as the rate of transition from event free to angina state (NICE TA 94 Table 52)
	Revascularisation	Rate= 0.01056	TNT trial [20]
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study [28]
	CVD death	For age groups 1-5: First (subsequent) year(s) rates: Group 1 (< 55): 0.00924 (0.00421), Group 2 (55-65): 0.02245 (0.00985), Group 3 (65-75): 0.05340 (0.02102), Group 4 (75-85): 0.12466 (0.04207), Group 5 (> 85): 0.27839 (0.07796).	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR) [31]

Transitions to Fatal Stroke

If the reported data did not explicitly state that the event probabilities were for non-fatal stroke only, then a proportion of the patients who experience a stroke was assumed to die due to the stroke. The proportion of fatal stroke among all stroke events was estimated using the logistic regression equation reported in the ASCOT trial results [22] with an exception of transitions from revascularisation state where a 50% probability of stroke being fatal was assumed as in Ara et al. (2009). Thus, the transitions to stroke from event free, stroke, angina and revascularisation states included a subset of patients having a fatal event and subsequently moving to cardiac death state.

Transitions from Angina

Rates of transitions from angina are given in Table S3.4. Individuals were assumed to have stable angina first and then progress to unstable angina, which requires more intense medical treatments. Once unstable angina was developed, it was assumed that patients could not improve to stable angina.

Table S3.4. Baseline annual rates of transitions from angina

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimates**	**Sources**
Angina	MI	1) From Stable angina: Rate = 0.01520; 2) Unstable angina 5%, 4.9%, 4.7%, 4.3% from 1st year event. 3.5%, 6.3%, 11.2%, 18.5% from subsequent yrs event for those aged <55, 55-65, 65-75, 75-85 yrs, respectively.	Juul-Moller, Edvardsson [34]; Ara, Pandor [23], Table 8; Gray and Hampton [31];
	Stroke	1) From Stable angina: Rate = 0.00791; Then, the prob of stroke being fatal applied, probability = e^xb/[1+e^xb], where xb= -4.874 + 0.043*age – 0.074*gender. 2) From Unstable angina: For age groups of <65, <75, <85, >85 years, [1st year rate] To non-fatal stroke: 0.2%, 0.5%, 1%, 2%; To fatal stroke: 2.6%, 4.3%, 7%, 10.3%; [subsequent yrs rate] To non-fatal stroke: 0.1%, 0.1%, 0.3%, 0.7%; → Fatal stroke: 0.4%, 0.5%, 0.6%, 0.7%.	1) Juul-Moller, Edvardsson [34]; NICE [30]; Lindgren, Buxton [22] 2) Ara et al. 2009 (HTA) Table 8.; Gray and Hampton [31]
	Angina (unstable)	Annual probability from stable angina to unstable angina: Group 1 (< 55): 0.0013, Group 2 (55-65): 0.0029, Group 3 (65-75): 0.0060, Group 4 (75-85): 0.0091, Group 5 (> 85): 0.0122.	NICE TA 94: Table 52.
	Revascularisation	Rate=0.00269	Assumed the same as the minimum revascularisation rate from PAD state. (Leng et al. 1996)
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study (Leng et al. 1996)
	CVD death	1) If no history of angina= Group 1 (< 55): 0.009, Group 2 (55-65): 0.0035, Group 3 (65-75): 0.007, Group 4 (75-85): 0.007, Group 5 (> 85): 0.007. 2) From unstable angina = (CHD and CVD death rates combined for 1st and subsequent years.	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR).

Transitions from Revascularisation

Table S3.5. Baseline annual rates of transitions from revascularisation

Individuals not receiving statin treatment			
From State	**To State**	**Estimate**	**Sources**
Revascularisation	MI	Rate= 0.03874	Fox, Poole-Wilson [32]; Ara et al. (2009) [23]
	Stroke	Rate=0.002 with 50% of stroke being assumed to be fatal.	Henderson, Pocock [35]; Ara et al. (2009) [23]
	Angina	Rate = 0.032523	Henderson et al. (2003); Ara et al. (2009) [23]
	Revascularisation	First-year rate of having a 2nd revascularisation= 0.14491	TNT trial [20]
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study [28]
	CVD death	Rate = 0.005785	RITA-2 trial [35]

Transitions from PAD

Table S3.6. Baseline rates of transitions from peripheral arterial disease

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimate**	**Sources**
PAD	MI	Rate = 0.01711	Edinburgh Artery Study [28]
	Stroke	Rate= 0.01408	Edinburgh Artery Study [28]
	Angina	Rate= 0.02019	Edinburgh Artery Study [28]
	Revascularisation	Rate=0.00269	Edinburgh Artery Study [28]
	PAD	Rate=0	Assumed
	CVD death	Exponential mean of Exp(6.576 + (-0.035)*age at event + (0.437)*gender) for time to event distribution $T \sim Exp(\tilde{\lambda})$.	The same rate as the transition from event free to CVD death: ASCOT trial [22]

Transitions to PAD

The incidence of PAD reported in the Edinburgh Artery Study was used for the estimation of transition rates to PAD. The incidence of symptomatic PAD (i.e. with intermittent claudication, IC) in general population aged 55 and over was used for all transitions to PAD event due to the lack of published evidence [28]. Age dependent incidence was not included as it was not statistically significant in the Edinburgh Artery Study [28]. However, there was some evidence of an increase with age in earlier longitudinal studies [36, 37].

Among patients with PAD, approximately 20% progress to develop severe symptoms with critical limb ischaemia (CLI) over a 5-year period and 1-2% undergo amputation over a lifetime [38]. In the model, 20% of people with IC were randomly sampled to develop CLI at the time of developing PAD for simplicity, to whom higher costs and lower utility weights were applied.

Effectiveness of statin treatments

Statin interventions was assumed to reduce the risks of coronary events (MI, angina, and fatal CHD events) and stroke. The model assumes that a proportion of individuals entering the model are receiving a statin intervention for primary and secondary prevention of CVD events. The relative risks (RRs) of events associated with statin use were applied to the baseline risks converted from the event rates reported in Tables S3.1-S3.6, and are shown in Table S3.7.

Table S3.7. Relative risks associated with statin use compared with placebo

Transitions to	Relative Risk	Source
MI	0.656	Ward et al. (2006) [18]
Non fatal stroke	0.754	Ara et al. (2009): Simvastatin 40mg/day
Fatal stroke (from Angina state)	0.876	Ara et al. (2009): Simvastatin 40mg/day
Stable Angina (from event free state)	0.59	Ward et al. (2006) [18]
To Fatal CHD event (CVD death)	0.74	Ward et al. (2006) [18]
Non CVD death (from event free state)	0.656	Ward et al. (2006) [18]

Non-disease mortality

Non-cardiac mortality rates used to construct distribution profiles for time to non-disease death were calculated by subtracting cardiac mortality rates from the all-cause death probability profiles. Cardiac mortality rates were estimated by combining the rates reported for heart disease (ICD-10 code I00-I52) and stroke (I64) using data obtained from the Mortality Statistics: Deaths registered in 2012 [29]. Cardiac mortality rates used to calculate the non-disease mortality are shown in Table S3.8. These were the same rates used for transitions to cardiac death from event-free state.

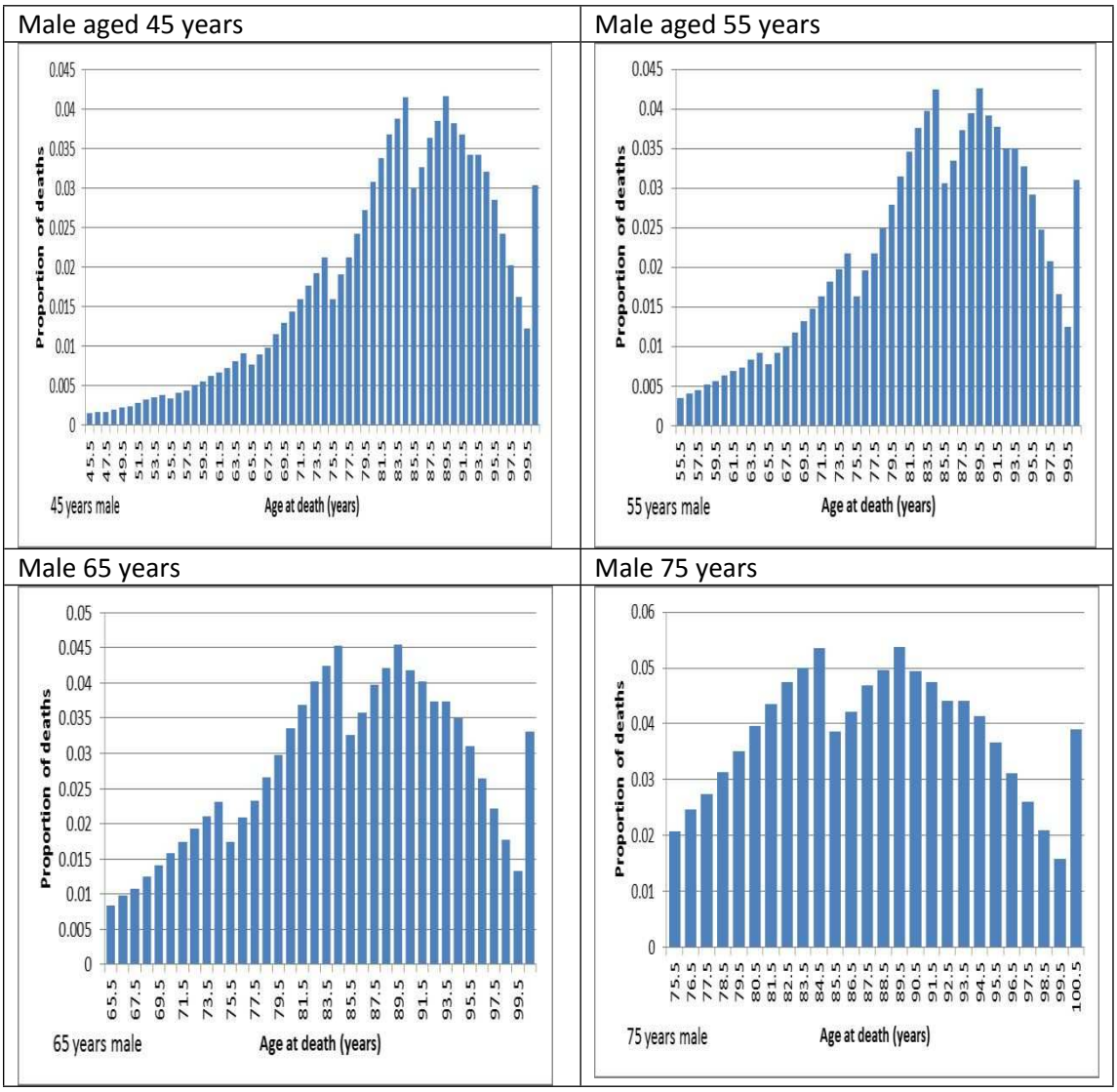
Figure S3.1 shows distributions for time to non-cardiac death for a few selected age groups. As the cardiac death rates were assumed constant across the 10-year age bands whilst the all-cause mortality rates were specified at every age x between 45 and 100 years, the probability profiles created were not smooth, but had a few stepped decreases at the age cut off values.

Table S3.8. Cardiac death rates used to estimate non-cardiac mortality rates*

	Age group				
Sex	45-54	55-64	65-74	75-84	85 and over
Male	**0.000639**	**0.001711**	**0.004275**	**0.013182**	**0.040947**
Female	**0.000178**	**0.000573**	**0.001994**	**0.008621**	**0.035576**

*Adapted from Table 8 in Deaths registered in England and Wales, 2012 [29]

Figure S3.1. Illustration of distributions for time to non-cardiac death



Costs

Table S3.9. Cost estimates used in the base-case model

Event	Data within source	Price year	Estimates [39] (2011/2012 price)	Original Source
MI - 1st year	£3,996	2007	£ 4,519.10	Ara et al. (2009) estimated using British National Formulary (2008) [40]
MI - subsequent year	£171	2004	£ 214.89	NICE TA 94 (GP contacts + medication costs)
Stroke - 1st year	£8,066	2007	£ 9,121.88	Ward, Lloyd-Jones [18]
Stroke - subsequent yr	£2,266	2007	£ 2,562.63	Ward, Lloyd-Jones [18]
Stable angina	£171	2004	£ 214.89	NICE TA 94 (GP contacts + medication costs)
Documented angina	£ 587.07	2005	£ 713.94	Taylor et al. (2009)
Revascularisation - 1st yr	£ 5,857	2007	£ 6,623.71	Taylor et al. (2009); HRG
PAD (IC)	£180	2009-2010	£189.31	Kearns, Michaels [41]
PAD (CLI)	£624	2009-2010	£656.29	Kearns, Michaels [41]; National Clinical Guideline Centre [38]
Statin treatment	£144.12	2014	£144.12	British National Formulary (2014); Estimated using the method by Ward et al. (2006)

Utilities

Baseline utility values by age and gender in the UK general population were estimated from a statistical model reported in Ara and Brazier [42].

The utility values associated with the health states included in the model were obtained from NICE TA94 and the HTA report by Ara et al. (2009). Table S3.10 describes the original sources of these

values. All the utilities were estimated using the EQ-5D, and were assumed to be multiplicative. Utility multiplier values were assumed to increase by 10% after the first year of the event as assumed in Ara et al. (2009). It was assumed that the history of revascularisation procedure did not affect the utility level, and the utility decrement for stable angina was used for individuals with history of angina. As a base-case, deterministic values for utility multipliers were used.

Alongside the current event, the history of the other health events was incorporated in the utility multiplier. For example, if a man aged 65 years who has just had a stroke has a history of MI, then the utility decrements for both stroke (first year multiplier for stroke: 0.629) and that for MI (subsequent-year multiplier: 0.836) were applied to the baseline utility (0.815); the utility weight for this person is thus 0.429 (i.e. 0.815*0.629*0.836).

When more than one cardiac event occurs within one year, the first-year periods of those events overlap. For the time periods overlapping, utility multipliers associated with the events were applied multiplicatively. For instance, if an individual experiences an MI at time=2.3 years and subsequently a stroke at time=2.7 years, then for time between 2.3 and 2.7 years, only the utility multiplier for the first year of MI would be applied (0.760) whilst for time between 2.7 and 3.3 years, utility multipliers associated with both first-year MI and first-year stroke would be applied (0.760*0.629=0.478). In the same way, for time between 3.3 and 3.7 years, utilities associated with subsequent years of MI and first year of stroke are used (0.836*0.629=0.526) In the model for this paper, whenever individuals reach these time points, they are directed to the 'utility cut off point' event in order to update variables related to utility multiplier.

Table S3.10. Utility multipliers by health state

State	First year - Mean (S.E.)	Subsequent years -	Original Sources
MI	0.760 (0.018)	0.836 (10% increase)	Goodacre, Nicholl [43]
Stroke	0.629 (0.04)	0.692 (10% increase)	Tengs and Lin [44]
(Stable) angina	0.808	0.889 (10% increase)	Melsop, Boothroyd [45]
Unstable angina	0.77	0.847 (10% increase)	Goodacre, Nicholl [43]
Revascularisation	0.78	0.858 (10% increase)	Serruys, Unger [46]
PAD IC	0.70	0.70	Kearns, Michaels [41]
PAD CLI	0.35	0.35	[Kearns, Michaels [41]]

Appendix 4. Comparison of the single-disease models in this study with the published reference models

Study	Model type (software)	Base-case Population	Intervention	Comparator(s)	Outcomes	Perspective	Time horizon/ price year	Health events included (e.g. Markov health states)	Stratified results (Yes/No)	Base-case ICER	Parameters driving ICER
Heart disease (HD)											
HD single-disease model in this paper	Discrete event simulation (Simul8)	General population aged 45 years and over	Statins	No statins	QALYs	NHS	Lifetime	MI, stable angina, unstable angina, stroke, revascularisation, PAD, CVD death, and non-CVD death	Yes – Base-case reported for the total population; and by age and gender, by prevention type	1) Secondary prevention - £1.5k – 4.0k/QALY vary by age and gender 2) Primary prevention - £2.2k-2.8k varied by age and gender	Reduced cost of statins (updated to 2012 values); Population age and sex distribution at model entry; Added event of PAD could lower ICERs compared to the results from Ward et al. (2006)
HD reference model by Ward et al. (2006) [18]	Markov model	A population with CHD or at increased risk of CHD events (annual CHD risk of 0.5%-3%)	Statins as a group	No statins	QALYs	NHS	Lifetime/ 2004 Discount rates of 6% for costs and 1.5% for health benefits	MI, stable angina, unstable angina, CHD death, TIA, stroke, and CVD death or non-CVD death	Yes – Base-case reported by prevention level, age and sex, and predicted annual CHD risk levels	Multiple base-case values 1) Secondary prevention - £10k-£17k /QALY 2) Primary prevention – at annual CHD risk of 3%, £10k-37k /QALY for men and £14k-48k /QALY for women	Results were most sensitive to the cost of statins, discount rates and the timeframe of the model; Larger incremental costs than the model in this study; ICERs sharply increased with age of the population

Alzheimer's disease (AD)											
AD model in this paper	Discrete event simulation (Simul8)	General population aged 45 years and over	Donepezil and memantine	BSC	QALYs	NHS and PSS	Lifetime	AD onset; diagnosis; pre-institutionalisation; institutionalisation; and death	Yes – results reported for two age groups aged >45 and >65 years	Donepezil and memantine therapy dominated BSC (cost saving £14 with 0.001 QALY gain)	The model results were generally comparable with those from Bond et al. (2012). Incremental QALYs from the model for this study were smaller than those from Bond et al. (2012) as the general population was modelled with the added events of the onset and diagnosis of AD.
AD reference model by Bond et al. (2012) [13]	Markov model (Microsoft Excel)	People with mild, moderate or severe AD	donepezil, galantamine, rivastigmine, for mild-to-moderate AD, and memantine, for moderate-to-severe AD	BSC	QALYs	NHS and PSS	20 years / 2009 price	pre-institutionalisation; institutionalisation; and death	Yes – by disease severity	Donepezil for mild-to-moderate AD dominated BSC; Memantime for moderate-to-severe AD: £32.1K/ QALY (increC=£405; increQ =0.013)	Results sensitive to assumptions on discontinuation rates; Costs of institutionalisation
Osteoporosis											
Osteoporosis model in this paper	Discrete event simulation (Simul8)	General population aged 45 years and	70mg alendronate taken once	No alendronate treatmen	QALYs	NHS and PSS	Lifetime	Hip fracture; vertebral fracture, wrist	Yes – by age and gender, BMD level, status of	Alendronate dominated no treatment for 75-year-old	Age, BMD level and history of previous fracture altered the incremental costs

		over	weekly	t				fracture; proximal humerus fracture; fracture-related death; non-fracture death	previous fracture	women with T-score of -3 SDs and -2.5 SDs with no previous fracture	and QALYs. However, regardless of the willingness-to-pay threshold per QALY, the alendronate is likely to be a cost-effective option for fracture prevention.
Osteoporosis reference model by Stevenson et al. (2009) [17]	Patient-level Markov model (Microsoft Excel)	Postmenopausal women aged 50 years and over	Vitamin K; alendronate; risedronate; strontium ranelate	No alendronate; next cost-effective treatment options	QALYs	NHS and PSS	10 years (the results subsequently adjusted to account for treatment benefits beyond the initial 10 years)	Hip fracture; vertebral fracture, wrist fracture; proximal humerus fracture; nursing home entry from hip fracture; breast cancer; and coronary heart disease; and non-fracture related death	Yes – by age, BMD level, and status of previous fracture	Alendronate dominated no treatment for 75-year-old women with T-score of -3 SDs with no previous fracture; £1,226/QALY for 75-year-old women with T-score of -2.5 SDs.	Age, fracture risks, BMD and history of previous fracture could alter the ICER estimates.

Appendix 5. Dealing with stochastic uncertainty around the results from the linked model

Background : Uncertainty around DES model outputs can be represented by both first-order uncertainty, defined as stochastic variability between simulated observations assuming identical parameter values, and second-order uncertainty, defined as uncertainty in the parameters of the economic model [47].

Aim: The degree of first order uncertainty in the linked model was examined in order to identify the appropriate number of simulated individuals to ensure stable model results. Stability was defined as an adoption decision being robust with sufficiently small random errors.

Method: Incremental values were computed in comparison with no treatments for all three of the diseases (heart disease, Alzheimer's disease and osteoporosis). The first-order uncertainty around the mean incremental cost and QALYs, incremental net monetary benefit (NMB) and cost per QALY gained (CPQ) was quantified for the results from the correlated linked model for the population aged 45 years and older.

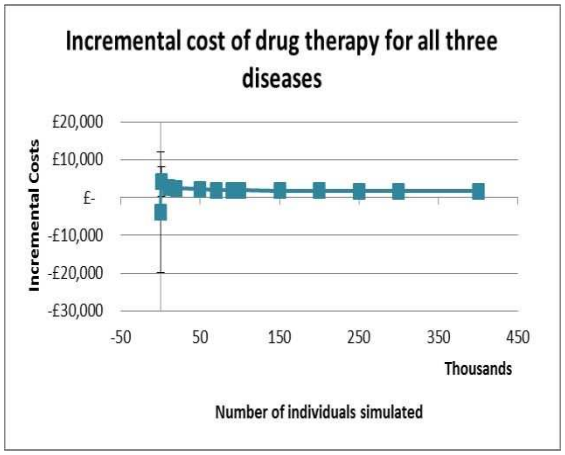
The jackknife approach was used to estimate a confidence interval for the mean cost per QALY with a reduced level of bias associated with the classical estimation of non-linear statistics [48, 49]. The standard errors of the mean results were estimated having varied the numbers of simulated individuals ranging from 1,000 to 700,000. The jackknife 95% confidence interval for the mean CPQ and the NMB results with more than 400,000 simulated individuals were derived using R programming language (R version 3.2.1, © The R Foundation) due to limited capacity of the spreadsheet software. Jackknifing execution time for the data from 700,000 simulated individuals was 4.69 hours on an Intel ® Core ™ i5 CPU 2.30 GHz processor with 4.00 GB of RAM (3.54 hours for 600,000 data points).

Results: Figure S5.1 shows that the incremental cost and QALYs stabilised when more than 200,000 individuals were simulated. The standard errors of the mean NMB and CPQ started to stabilise after running more than 500,000 simulated individuals. The chosen number of individuals to simulate was 700,000 for the base-case all-disease linked models (with and without correlations) in order to further reduce the variability of the results.

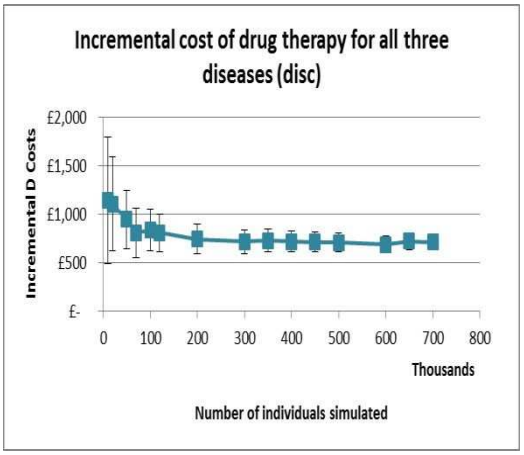
Figure S5.1. First order uncertainty in relation to the number of patients simulated in the all-disease linked model with correlations (base-year population aged 45 years and over)

1) Incremental cost (compared with none of the three treatments)

Undiscounted

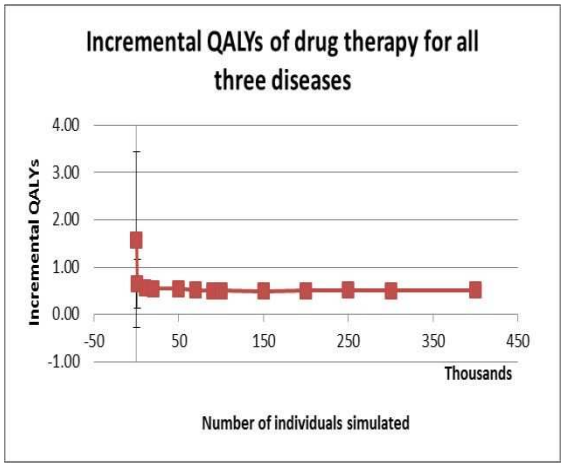


Discounted



2) Incremental QALYs (compared with none of the treatments for the three diseases)

Undiscounted



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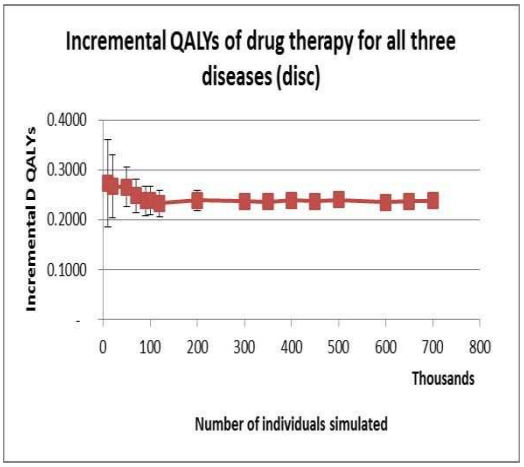
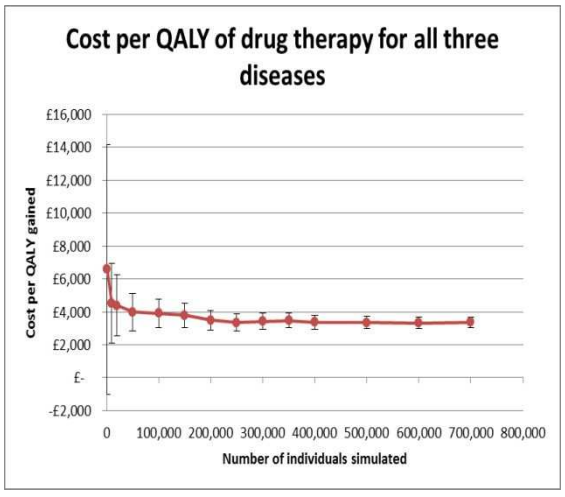
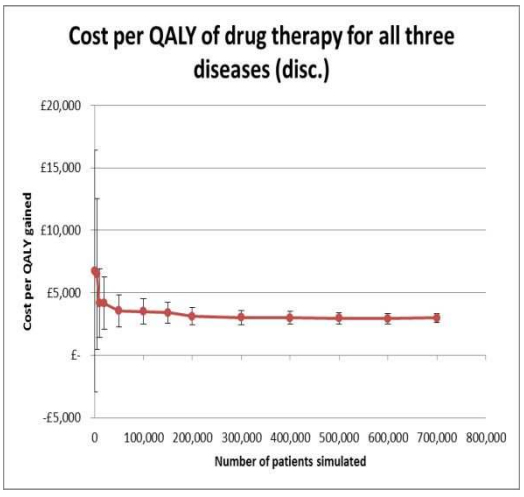


3) Cost per QALYs (95% jackknife confidence interval)

Undiscounted

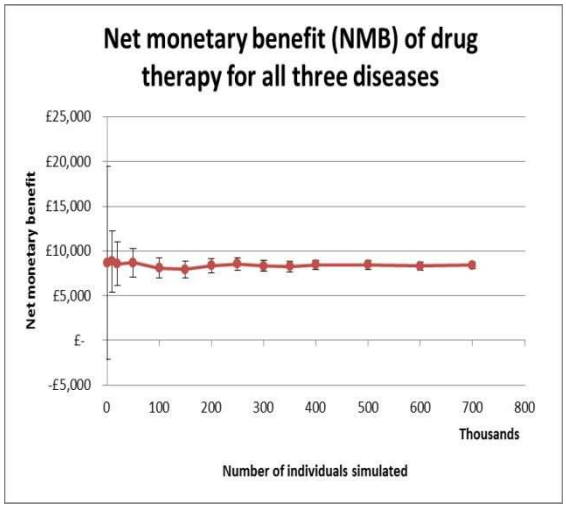


Discounted

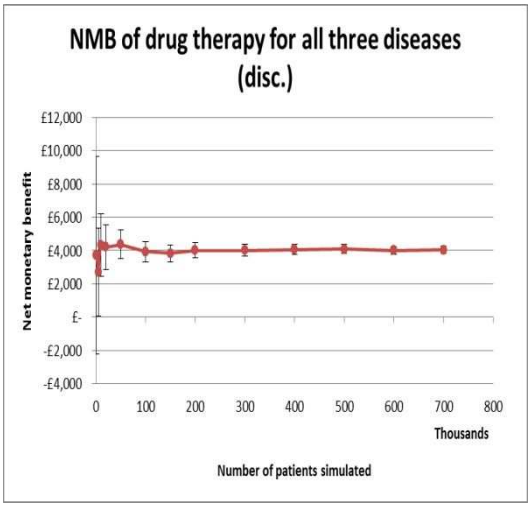


4) Net monetary benefit (£20,000 threshold)

Undiscounted



Discounted



Each figure includes error bars showing the standard error in the mean estimates of (incremental) cost and QALYs.

Appendix 6. Summary of the results from the individual disease models for comparison

	1) Heart disease only model			2) Alzheimer's disease only model			3) Osteoporosis only model			4) Sum of incremental values across 1)-3)
	Treatment	No treatment	Incremental values (A)	Treatment	No treatment	Incremental values (B)	Treatment	No treatment	Incremental values (C)	(A)+(B)+(C)
Cost - Discounted	£ 8,091	£ 7,569	£ 522	£4,582	£4,596	-£ 14	£ 2,847	£ 2,947	-£ 100	£ 408
QALYs - Discounted	9.249	8.978	0.271	10.642	10.641	0.001	11.191	11.184	0.008	0.280
Cost	£ 14,224	£ 13,197	£ 1,027	£8,845	£8,869	-£ 23	£ 6,151	£ 6,324	-£ 173	£ 831
QALYs	13.843	13.257	0.586	16.548	16.545	0.003	17.759	17.751	0.009	0.597
Life years lived	21.319	20.319	1.000	21.653	21.650	0.003	23.530	23.525	0.004	1.007
ICER – Discounted			£ 1,926 /QALY			Dominating			Dominating	£ 1,458 /QALY
ICER			£ 1,754 / QALY			Dominating			Dominating	£ 1,391 / QALY

HD: based on n=200,000; AD n=200,000; Osteoporosis n=400,000

Appendix 7. Hypothetical scenario with similar levels of QALY gains assumed for all three interventions

In order to examine the effect of sampling error when all three treatments have a similar level of QALY gains, the scenarios in Table S7.1 were assumed: these are not meant to provide accurate evaluations of current treatments but to show that the results would have face validity when QALY gains are comparable. For all three individual diseases, populations aged 65 years and older were simulated. Scenarios for larger QALY gains for AD and osteoporosis and reduced QALY gain for HD were explored. Table S7.1 shows the scenario assumptions applied to each of the three disease models in comparison with the base-case assumptions.

Table S7.1. Comparison of scenario assumptions and base-case assumptions

Base-case assumptions	Scenario assumptions
1. Heart disease model	
Relative risks were assumed to be 0.656, 0.754, 0.876, 0.59, 0.74, and 0.656 for MI, non-fatal stroke, fatal stroke, stable angina, fatal CHD, and non-cardiac death, respectively.	Relative risks of 0.98 for statin treatment were assumed for all events.
Utility values for MI, stroke and revascularisation were set to 0.76, 0.629, and 0.78, respectively.	Utility values for MI, stroke, and revascularisation were reduced to 0.5.
2. Alzheimer's disease model	
4% of monthly treatment discontinuation rate was assumed.	Lifetime treatment: No treatment discontinuation was assumed
6 months duration of treatment effect was assumed.	Lifetime treatment effect was assumed.
Utility value for institutionalised individuals was 0.33.	Utility value for those institutionalised was reduced to 0.1
The average annual improvements in MMSE score were 2.48 for donepezil and 1.4 for memantine per year.	Double treatment effect on MMSE score: the average improvements in MMSE score were set to 4.96 for donepezil and 2.8 for memantine per year.
Some individuals are institutionalised at model entry, and some patients are institutionalised immediately after diagnosis.	No individuals start at the institutionalisation state at model entry, nor get institutionalised immediately after the diagnosis (i.e. No individuals move to the

	institutionalisation event from the diagnosis event with zero time passed.)
3. Osteoporosis model	
Relative risks of fracture for alendronate treatment were set to 0.72, 0.58, and 0.82 for hip, vertebral, and other fractures, respectively.	Relative risks were assumed to be 0.33 for all fracture types.
5 years of treatment duration was assumed.	Lifetime treatment duration was assumed.

Table S7.2 compares incremental outcomes from the three individual disease models with those for each of the individual treatments from the linked model where the diseases were assumed to be independent. Under the hypothetical scenarios, a comparable magnitude of QALY gains across all three individual disease models (Table S7.2 Column a) was achieved. The margins of error around incremental costs and QALYs at 95% confidence level are shown in brackets.

Table S7.2 reports results under the scenarios in Table S7.1, assuming the diseases were independent. When none of the treatments have much larger impact on QALYs gained the linked model produced similar results to those from the individual disease models. This shows the robustness of the adoption decision within the linked model for individual treatments.

Table S7.2. Cost-effectiveness results under larger QALY gain scenarios for individual treatments from the individual disease models and the independently linked model

1. Heart disease				
	a. Individual heart disease model†	**b. Independently linked model (n=700,000)**		
	Incremental values (Margin of error) ‡	All treatments	No HD treatment*	Incremental values
DCost	£ 683 (£ 66)	£ 11,001	£ 10,201	£ 800
DQALYs	**0.0539 (0.0179)**	4.9232	4.8784	0.0448
TCost	£ 913 (£ 94)	£ 15,499	£ 14,380	£ 1,119
TQALYs	0.0875 (0.0267)	6.2589	6.1861	0.0728
ICER (disc.)	£ 12,665			£ 17,878
ICER	£ 10,433			£ 15,360
2. Alzheimer's disease (AD)				
	a. Individual AD model†	**b. Independently linked model (n=700,000)**		
	Incremental values (Margin of error) ‡	All treatments	No AD treatment*	Incremental values
DCost	-£ 4,551 (£ 93)	£ 11,001	£ 15,413	-£ 4,412
DQALYs	**0.0508 (0.0020)**	4.9232	4.8855	0.0377
TCost	-£ 6,319 (£ 130)	£ 15,499	£ 21,582	-£ 6,083
TQALYs	0.0688 (0.0028)	6.2589	6.2089	0.0500
ICER (disc.)	Dominating			Dominating
ICER	Dominating			Dominating
3. Osteoporosis				
	a. Individual osteoporosis model†	**b. Independently linked model (n=700,000)**		
	Incremental values (Margin of error) ‡	All treatments	No osteoporosis treatment*	Incremental values
DCost	-£ 1,186 (£ 74)	£ 11,001	£ 11,983	-£ 982
DQALYs	**0.0545 (0.0128)**	4.9232	4.8918	0.0314
TCost	-£ 1,856 (£ 123)	£ 15,499	£ 16,970	-£ 1,471
TQALYs	0.0900 (0.0204)	6.2589	6.2090	0.0499
ICER (disc.)	Dominating			Dominating
ICER	Dominating			Dominating

† Based on n=200,000 for HD and AD models; and n=400,000 for osteoporosis model, as in the base-case; **‡** Margin of error at 95% confidence level; *****The other two default treatments were assumed to be available; D=discounted.

When all the individual disease models produce similar QALY gains (without any disease with a significantly larger impact) the impact of Monte Carlo error for one disease on the incremental outcomes and cost-effectiveness of the other diseases can be much less influential. None of the margin of error estimates in Table S7.2 (0.0179, 0.0020, and 0.0128 for HD, AD, and osteoporosis models, respectively) will have a significant effect that changes the +/- signs of the values on the incremental QALY results from the linked model (0.0448, 0.0377, and 0.0314 for HD, AD, and osteoporosis treatments, respectively). Hence, when QALY gains are similar across all diseases, the results are less susceptible to sampling error from the other diseases. The base-case estimated very small QALY gains for AD and osteoporosis treatments which could fluctuate between positive and non-positive values due to the sampling error associated with the treatment for HD. In cases where QALY gains are similar, however, the proposed methods of linking individual disease models are likely to produce more accurate cost-effectiveness estimates for individual treatments.

Appendix 8. Probabilistic sensitivity analysis of the correlated linked model results

The correlated linked model for the three diseases (HD, AD and osteoporosis) was built probabilistically to take account of the uncertainty around input parameter point estimates. This section provides probabilistic results in order to show the feasibility of probabilistic sensitivity analysis (PSA) using the linked model described in this paper.

A probability distribution was defined for selected input parameters. The selection of parametric distributions was based on the nature of the data. For example, utilities were assumed beta-distributed as the data were assumed to be bounded by zero and one. Wherever possible, probabilistic distributions reported in the original publications of the reference models [13, 17, 18] were used. Where this was not possible, the distribution was parameterised using estimates of the error around mean or assumed standard errors for the purpose of this feasibility run of PSA. Table S8.1 shows the PSA input parameters and their distributional properties.

Table S8.1. Variables and distributions used in the probabilistic sensitivity analysis (PSA)

PSA Variable	Point estimate*	Distribution	Distributional properties
Clinical effectiveness			
RR of statin treatment for MI	0.656	Lognormal	Lognormal(logmean=-0.4219, logSE=0.0233)
RR of statin treatment for stroke	0.754	Lognormal	Lognormal(logmean=-0.2826, logSE=0.0203)
Change in MMSE when using Donepezil 10mg	1.24**	Normal	Normal(1.24, 0.22)
Change in MMSE when using Memantine 20mg	0.70**	Normal	Normal(0.70, 0.35)
Proportion of patients compliant to medication	0.75	Beta	Beta(13.31, 4.44)
Utilities of health states			
Stable angina	0.808	Beta	Beta(86.00, 20.44)
Unstable angina	0.77	Beta	Beta(93.67, 27.98)
MI	0.76	Beta	Beta(427.09, 134.87)
Stroke	0.628	Beta	Beta(91.07, 53.94)
MMSE: 0-9	0.33	Beta	Beta(36.59, 74.28)
MMSE: 10-14	0.49	Beta	Beta(78.04, 81.22)
MMSE: 15-20	0.5	Beta	Beta(856.27, 856.27)
MMSE: 21-25	0.64	Beta	Beta(1137.19, 639.67)
MMSE: 26-30	0.69	Beta	Beta(282.51, 126.92)
Institutionalised	0.33	Beta	Assumed the same as the utility

			value for MMSE:0-9
Vertebral fracture – 1st year	0.626	Beta	Beta(14.03, 8.38)
Vertebral fracture – subsequent year	0.909	Beta	Beta(6.61, 0.66)
Hip fracture – 1st year	0.792	Beta	Beta(12.26, 3.22)
Hip fracture – subsequent year	0.813	Beta	Beta(11.55, 2.66)
Costs			
Cost of institutionalisation	£2941	Normal	Normal(2941, 108)
Cost of death from hip fracture	£9525.86	Gamma	Gamma(scale=67.19, shape=141.78)***

MMSE: mini mental score examination; *mean values used in base-case analysis; **6month estimate; ***calculated from assumed standard error of 800.

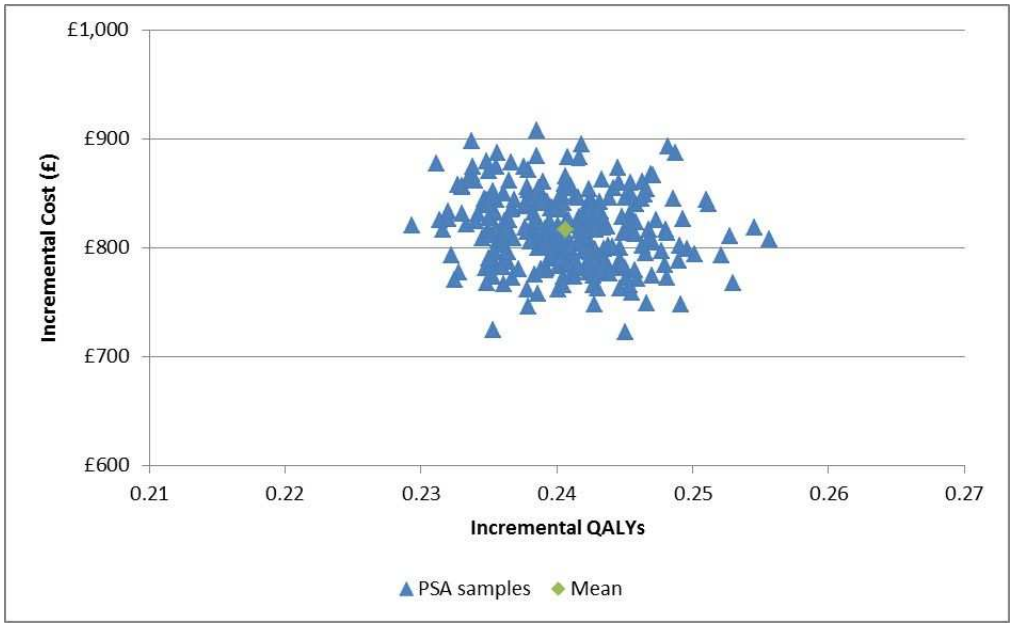
The probabilistic model results are shown in Table S8.2 based on 300 PSA runs in each of which 700,000 individuals were simulated. The mean cost and QALYs of the PSA results in Table S8.2 showed comparable results with the base-deterministic results from the correlated linked model albeit not identical. All of the PSA samples in Figure S8.1 showed cost per QALY being lower than the threshold of £20,000 per QALY gained.

Table S8.2. Comparison of probabilistic model results with the base-case deterministic results*

All-disease linked model with correlations	Deterministic results			Probabilistic results		
	All three treatments assumed	None of the three treatments assumed	Incremental values	All three treatments assumed	None of the three treatments assumed	Incremental values
Mean cost	£14,741	£13,894	£847	£14,392	£13,575	£816
Mean QALYs	8.962	8.725	0.236	8.972	8.731	0.241
ICER			£3,583/QALY			£3,391/QALY**

*Based on 300 PSA runs; each deterministic run is based on 700,000 simulated individuals;
**Jackknife 95% C.I. £3,360-£3,423.

Figure S8.1. Probabilistic sensitivity analysis scatterplot of incremental costs and QALYs



*Based on 300 PSA runs

The results show that the adoption decision is robust when assuming the willingness-to-pay threshold of £20,000 per QALY gained. Each deterministic run of 700,000 individuals took approximately 15 minutes to run and hence, conducting 300 PSA runs for each intervention arm took 1.9 days of computing time (Intel Core™ i7CPU 3.40GHz processor with 16GB RAM). Such time scales indicate it is feasible to conduct PSA using the multi-disease linked model. The probabilistic analysis of discrete event simulation model will become more achievable by using a computer with more processing power or parallel computing. The number of runs required would be affected by the homogeneity of the population studied. Hence, the use of a more narrowly defined population with specific characteristics and higher disease prevalence, than the general population adopted in the current analysis, would accelerate convergence due to higher number of disease events simulated and more homogeneous parameter values.

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