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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.

References

[1] House of Lords. Ready for Ageing? London: House of Lords Select Committee on Public Service and Demographic Change; 2013.

[2] Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. The Lancet. 2012; 380(9836):37-43.

[3] Li J, Green M, Kearns B, Holding E, Smith C, Haywood A, et al. Patterns of multimorbidity and their association with health outcomes within Yorkshire, England: baseline results from the Yorkshire Health Study. BMC Public Health. 2016; 16(1):649.

[4] Department of Health. Long Term Conditions Compendium of Information: Third Edition. In: Team LTC, ed. Leeds, UK: Department of Health 2012.

[5] The King's Fund. Long-term conditions and multi-morbidity. Future Trends 2017 [cited 2017 05 April]Available from: https://www.kingsfund.org.uk/time-to-think-differently/trends/disease-and-disability/long-term-conditions-multi-morbidity

[6] The National Center for Health Statistics. The 2010 National Survey of Residential Care Facilities. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES 2010.

[7] Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: A systematic review of the literature. Ageing Research Reviews. 2011:10 (4) (pp 430-9).

[8] Fortin M, Lapointe L, Hudon C, Vanasse A, Ntetu AL, Maltais D. Multimorbidity and quality of life in primary care: a systematic review. Health and quality of life outcomes. 2004; 2:51.

[9] France EF, Wyke S, Gunn JM, Mair FS, McLean G, Mercer SW. Multimorbidity in primary care: a systematic review of prospective cohort studies. The British journal of general practice : the journal of the Royal College of General Practitioners. 2012; 62(597):e297-307.

[10] Guthrie B, Payne K, Alderson P, McMurdo MET, Mercer SW. Adapting clinical guidelines to take account of multimorbidity. BMJ : British Medical Journal. 2012; 345.

[11] Guthrie B, Thompson A, Dumbreck S, Flynn A, Alderson P, Nairn M, et al. Better guidelines for better care: accounting for multimorbidity in clinical guidelines. UK2015.

[12] Habl C, Antony K, Arts D, Entleitner M, Fröschl B, Leopold C, et al. Surveying, Assessing and Analysing the Pharmaceutical Sector in the 25 EU Member States. 2006: Österreichisches Bundesinstitut für Gesundheitswesen

[13] Fleurette F, Banta D. Health technology assessment in France. Int J Technol Assess Health Care. 2000; 16(2):400-11.

[14] Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical Practice Guidelines and Quality of Care for Older Patients With Multiple Comorbid DiseasesImplications for Pay for Performance. JAMA. 2005; 294(6):716-24.

[15] Farmer C, Fenu E, O'Flynn N, Guthrie B. Clinical assessment and management of multimorbidity: summary of NICE guidance. BMJ. 2016; 354.
[16] National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. UK: National Institute for Health and Care Excellence 2014.
[17] Morton A, Adler AI, Bell D, Briggs A, Brouwer W, Claxton K, et al. Unrelated Future Costs and Unrelated Future Benefits: Reflections on NICE Guide to the Methods of Technology Appraisal. Health Economics. 2016; 25(8):933-8.
[18] Boyd CM, Fortin M. Future of Multimorbidity Research: How Should Understanding of Multimorbidity Inform Health System Design? Public Health Reviews. 2010; 32(2):451-74.
[19] Ward S, Lloyd-Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al. Statins for the Prevention of Coronary Events: The University of Sheffield; 2006.
[20] Bond M, Rogers G, Peters J, Anderson R, Hoyle M. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model. Health Technology Assessment. 2012; 16(21):469.
[21] Stevenson M, Lloyd-Jones M, Papaioannou D. Vitamin K to prevent fractures in older women: systematic review and economic evaluation. Health technology assessment (Winchester, England). 2009; 13(45):iii-xi, 1-134.
[22] National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. London: NICE; 2013. Report No.: PMG9.
[23] Office for National Statistics. Population Estimates for UK, England and Wales, Scotland and Northern Ireland, Mid-2012 United Kingdom: Office for National Statistics 2013.
[24] Briggs A, Sculpher M, Claxton K. Decision Modelling for Health Economic Evaluation Oxford (UK): Oxford University Press 2006.
[25] Ara R, Brazier J. Estimating Health State Utility Values for Comorbidities. PharmacoEconomics. 2017.
[26] Office for National Statistics. Interim Life Tables, England and Wales, 2009-2011. London: Office for National Statistics; 2013.
[27] Stampfer MJ. Cardiovascular disease and Alzheimer's disease: common links. Journal of Internal Medicine. 2006; 260(3):211-23.
[28] Warburton DER, Nicol CW, Gatto SN, Bredin SSD. Cardiovascular disease and osteoporosis: Balancing risk management. Vascular Health and Risk Management. 2007; 3(5):673-89.
[29] Baker NL, Cook MN, Arrighi HM, Bullock R. Hip fracture risk and subsequent mortality among Alzheimer's disease patients in the United Kingdom, 1988–2007. Age and Ageing. 2011; 40(1):49-54.
[30] Tankó LB, Christiansen C, Cox DA, Geiger MJ, McNabb MA, Cummings SR. Relationship Between Osteoporosis and Cardiovascular Disease in Postmenopausal Women. Journal of Bone and Mineral Research. 2005; 20(11):1912-20.
[31] Gerber Y, Joseph Melton L, Weston SA, Roger VL. Association Between Myocardial Infarction and Fractures: An Emerging Phenomenon. Circulation. 2011; 124(3):297-303.
[32] Tan Z, Seshadri S, Beiser A, et al. Bone mineral density and the risk of alzheimer disease. Archives of Neurology. 2005; 62(1):107-11.
[33] Efron B. The Jackknife, the Bootstrap, and Other Resampling Plans: Society for Industrial and Applied Mathematics 1982.
[34] National Institute for Health And Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification. In: NICE, ed. UK2014.
[35] NICE. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease. In: Excellence NIfHaC, ed. London: UK2011.
[36] Hyde C, Peters J, Bond M, Rogers G, Hoyle M, Anderson R, et al. Evolution of the evidence on the effectiveness and cost-effectiveness of acetylcholinesterase inhibitors and memantine for Alzheimer's disease: systematic review and economic model†. Age and Ageing. 2013; 42(1):14-20.
[37] Lohr SL. Sampling: Design and Analysis. 2nd Ed. ed. Boston, USA: Cengage Learning 2009.

[38] The Academy of Medical Sciences. Multimorbidity: a priority for global health research2018.
[39] Guthrie B, Thompson A, Dumbreck S, Flynn A, Alderson P, Nairn M, et al. Better guidelines for better care: accounting for multimorbidity in clinical guidelines - structured examination of exemplar guidelines and health economic modelling. Southampton (UK): NIHR Journals Library 2017.
[40] Thompson A, Sutton M, Payne K. Estimating Joint Health Condition Utility Values. Value in Health. 2018; (Accepted/In Press).
[41] Claxton K, Sculpher M, McCabe C, Briggs A, Akehurst R, Buxton M, et al. Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. Health Econ. 2005; 14(4):339-47.
[42] Stevenson MD, Oakley J, Chilcott JB. Gaussian process modeling in conjunction with individual patient simulation modeling: a case study describing the calculation of cost-effectiveness ratios for the treatment of established osteoporosis. Medical decision making : an international journal of the Society for Medical Decision Making. 2004; 24(1):89-100.