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Title: Computer simulation of dementia care demand heterogeneity using hybrid simulation methods: improving population-level modelling with individual-level decline trajectories

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Abstract: Objectives: To model dementia prevalence and outcomes within an ageing population using a novel hybrid simulation model that simultaneously takes population-level and patient-level perspectives to better inform dementia care service planning, taking into account severity progression variability.

Study Design: Simulation study

Methods: We developed a hybrid computer simulation combining different methods to best represent population and individual dementia dynamics. Individual patient outcomes are aggregated into three progression rate types to report the effects of severity progression variability and intervention benefits.

Results: Fast progression of dementia severity is associated with higher annual care cost and short overall survival duration. Those patients are more likely to be develop moderate to severe symptoms more quickly, highlighting a need for more urgent provision of appropriate care services. Slower severity progression is associated with lower annual care costs, but longer survival requires higher overall financial provision. Although lifestyle interventions reduce overall care costs, treatment and lifestyle intervention benefits are modest at the population level.

Conclusions: Individual variation of dementia decline is an important factor to include in planning adequate levels of care services, and to ensure timely and appropriate service availability. Hybrid simulation models provide useful insights at the population and individual level, supporting effective decision making.

***Title page**

Computer simulation of dementia care demand heterogeneity using hybrid simulation methods: improving population-level modelling with individual-level decline trajectories

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*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Contributors
The research was conceived by SB, BW, PR and DE. DE conducted the research, data analysis, and developed the simulation model. All others contributed to data interpretation and writing of the paper. The project supervisors were SB, PR, and BW. Expert clinical knowledge was provided by CK.

***Highlights**

Public Health Journal highlights

- Provides better information to support dementia service planning in ageing populations
- Existing models do not easily allow for heterogeneity of the patient group
- Hybrid simulation model accounts for different trajectories of decline as well as severity
- Lifestyle has most impact on service use
- Drug intervention benefits can be outweighed by longer periods of care need

Title

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Introduction

In the healthcare domain, Operational Research (OR) methods are used to support service commissioners, health planners, and service provider organisations. OR often uses computer simulation to better understand the behaviours of complex systems and the interactions between system elements, allowing exploration of the impact of different policy options and service scenarios. OR has been used to understand, evaluate, and plan interventions and service delivery in a number of healthcare domains[1]. This paper describes the application of OR simulation methods to support planning of care services for people with dementia, by informing decision-makers about the variability of dementia severity progression.

In ageing populations, healthcare policy-makers and provider organisations face many challenges to meet the increasing need for care services for older people with dementia; increasing dementia prevalence will be an important driver for demand for care services. Care needs are complex, individual, and progressively more intensive depending on age at onset, comorbidities, different pathologies and risk factors underlying dementia,[2,3] eventually resulting in considerable and profound dependence on care providers.

Currently available medical and clinical interventions for dementia rely on symptomatic treatments. These are licensed only for Alzheimer's and Parkinson's disease,[4] and there is currently no known dementia cure or preventative treatment.[5] Nevertheless, clinical benefits are widely regarded as modest, inconsistent, and short-term.[6–9] In comparison, a healthy lifestyle is reported to improve outcomes, with delayed onset and fewer years with dementia.[10–13] The computer simulation model reported here allows benefit comparisons to be explored over time, capturing the interplay of competing risks and benefits.

Review of modelling studies

Previous modelling work has addressed various aspects of dementia care service planning. This includes modelling treatment effects in a simulated RCT,[14–18] strategic planning based on dementia prevalence,[19,20] diagnosis,[21] risk factors,[22] and impact on long-term care provision.[23–25] State-based models stratify care needs based on severity 'compartments', but this approach assumes homogeneity within health states and cannot address individual variability in progression. More recently, microsimulation models[26–30] have attempted to overcome these issues, however, this approach can be computationally intensive and do not include potential interventions.

We therefore modelled individualised decline trajectories for people with dementia in our computer simulation, and assessed intervention benefits in the presence of individual decline variability. We describe the results from

a computer simulation model using population-level ageing, incidence, and mortality in a hypothetical age cohort, hybridised with individual-level variability in onset, progressive decline, lifestyle, and treatment effects. The results were used to assess the likely impacts on survival and total costs (health, social, and unpaid care) at the population level over a 45-year cohort lifetime.

Methods

Model architecture and outputs

Our hybrid computer model was developed in AnyLogic[31] (a multi-method simulation software tool) using two different and complementary modelling methods. **Error! Reference source not found.** shows how a deterministic population-level System Dynamics (SD) model simulates ageing, dementia onset, and mortality, while an Agent-Based (AB) model simulates individual survival, dementia severity progression, and outcomes stochastically.

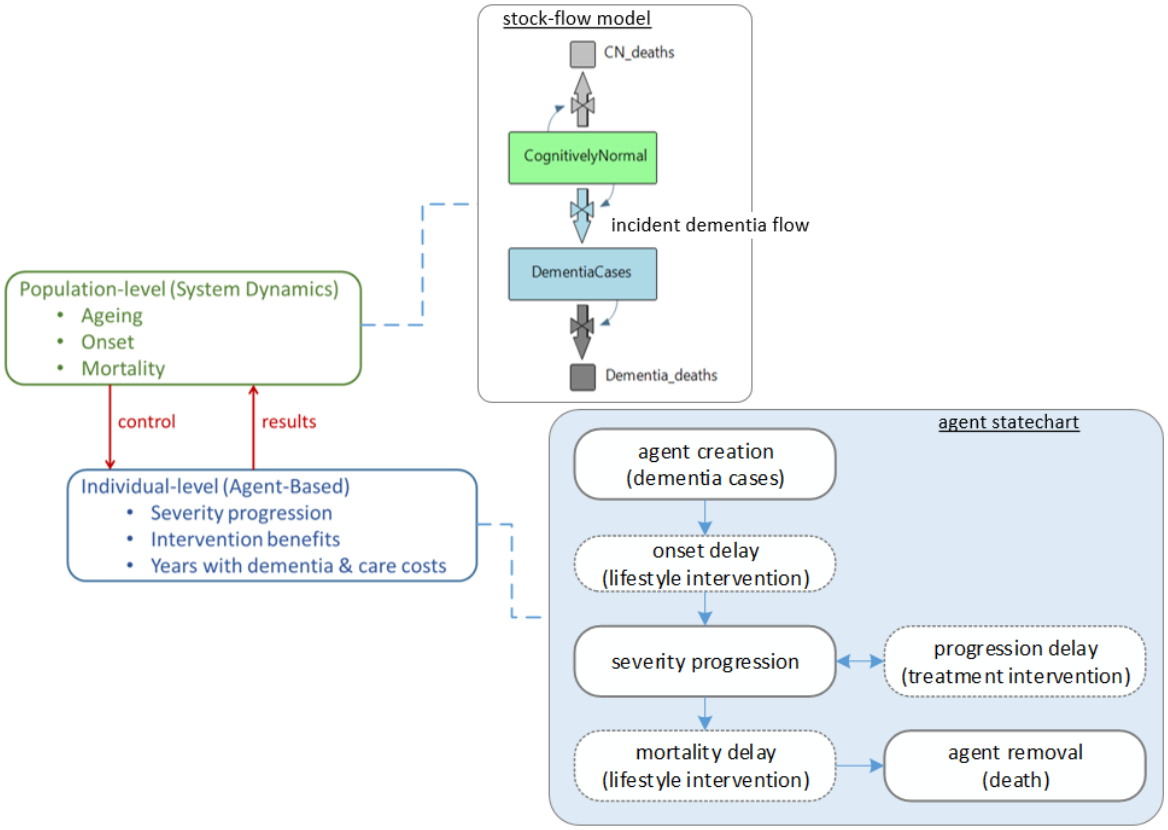

Figure 1 Simulation overview showing hybrid SD and AB model functional partitioning

Population dynamics are modelled through cognitively normal deaths (removed progressively from the cognitively normal cohort); incident dementia (removed progressively from the cognitively normal cohort); and deaths with dementia (removed progressively from the 'dementia' cohort). Within a 5-year age group this process is modelled using the stock-flow SD model shown in **Error! Reference source not found.**, where stocks are numbers of individuals in each state over time. These stock-flow models are cascaded to cover the 60 to 105 age range. To simulate ageing, every 5 years of model time, survivors are transferred to the next age group.

The SD part of the model links with the Agent-Based (AB) part, where agents (as a technical modelling term), can be equated to individual patients or people with dementia. The AB part creates and removes agents from the stocks within the SD component of the model, equivalent to individual dementia onset and death. The AB part also simulates dementia severity progression, updates individual attributes of age and years with dementia (YWD), and calculates monthly and accumulated care costs for each individual agent.

These calculations are done in the agent's statechart, also shown in Figure 1. An agent is created when the SD model simulates an onset case. In addition to an age group attribute, agents are assigned a progression rate type (slow, intermediate, or fast), and positive or neutral responses to interventions. These are drawn from probability

distribution models in the simulation. Further details of the model construction, parameterisation, and validation are published elsewhere[32] and given in the supplement to this paper.

Simulation scenarios and analysis methods

As our focus was on late onset dementia, a 'pre-dementia' cognitively normal (CN) age cohort starts at age 60. We assume no dementia onset in the starting 60-65 age group stock, only CN mortality rates. Dementia onset is modelled from the 65-70 age group up to the 100-105 age group.

The model starts with a hypothetical cohort of 35,000 cognitively normal people. This is typical of the number of 60 to 65 year old people in a large geographic health services commissioning area in the UK. The simulation then calculates the projected number of dementia cases for those aged 65 and older, over a 45-year follow-up.

Individual results were collected for years with dementia (YWD) and care costs. Mean and median results were calculated for YWD, and also reported for 90th and 95th percentiles to account for positive skew.

In the baseline simulation, agents move directly to the *severity progression* state, where severity, age, duration with dementia, and care costs are calculated. When the SD model simulates a death, an agent is selected and removed based on age group and dementia severity. Individual outcomes generated in the AB part are aggregated for summary reporting for years with dementia (YWD) and care cost outcomes.

We also conducted simulations to explore the impact of two intervention scenarios; medication and lifestyle. For the medication treatment intervention, agents with a positive intervention response move into the *progression delay* state, after progression has started. This state temporarily pauses dementia severity progression, but while still accumulating care costs. In the case of the lifestyle intervention, agents reside initially in the *onset delay* state and then later in the *mortality delay* state. Results are summarised with and without treatment and lifestyle interventions within patient progression groups.

Patient-level interventions were modelled as two years delayed onset and one year delayed mortality resulting from the lifestyle intervention based on physical activity, exercise, diet, smoking cessation and moderate alcohol consumption,[10–13] or one year delayed progression as a result of Acetylcholinesterase Inhibitor medications (a range of symptomatic treatments).[7,33]

Interventions were compared with the baseline simulation using statistical tests for mean differences in nominal costs. Individual YWD data were combined and analysed using Cox Proportional Hazards, with survival differences tabulated as Hazard Ratios (HRs).

Results

This section describes baseline simulation results for a population without interventions, and for comparison the results for the two modelled intervention scenarios. Graphical and tabulated results summaries are shown.

Figure 2 shows results from the SD part of the model, the vertical axes shows proportions of the starting cohort (the upper pane showing age-related prevalence). Results from the AB part of the model are presented as Kaplan-Meier survival curves in Figure 3, showing years with dementia (YWD) for the modelled agent survival. The agent population is treated in the same way as a real time-to-event survival analysis, comparing mean and median survival times.

Validation of the simulation outputs is an important consideration in developing computer simulation models. This is given in the supplementary material along with additional simulation results. Further details can be found elsewhere.[32]

Onset and mortality

Up to age 85 the number of onset cases is larger than those dying with dementia (i.e. grey bar values larger than solid bars in Figure 2), and it is only from age 90 to 95 the number of deaths with dementia (solid bars) exceeds both onset (grey bars) and cognitively normal deaths (light bars). The simulation therefore illustrates the rising population prevalence and associated health care burden associated with dementia, despite higher death rates in people with dementia.

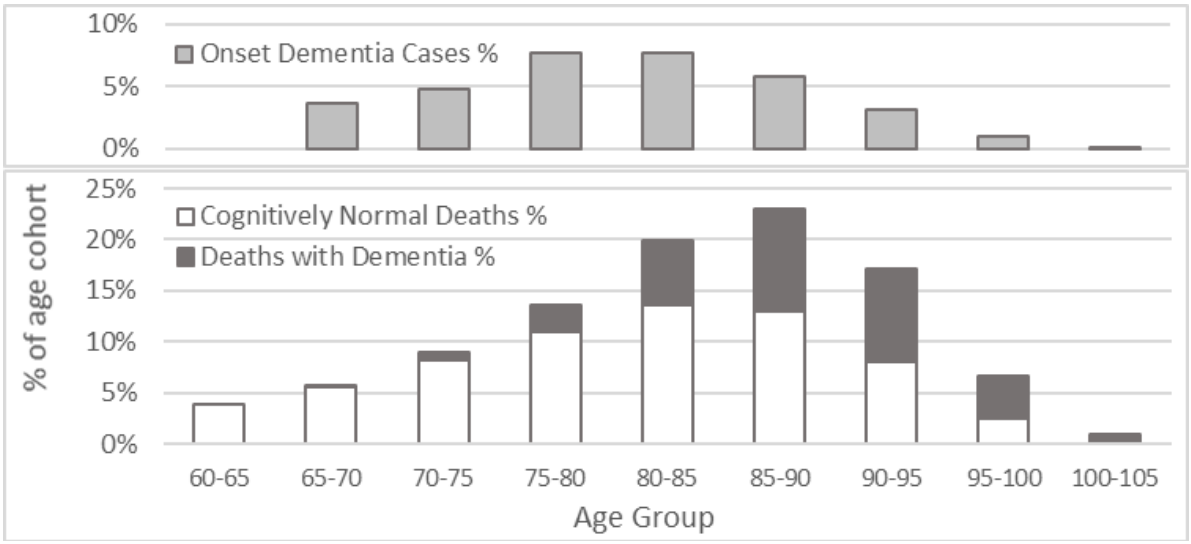

Figure 2 Onset cases and deaths as percentages of the age cohort

Baseline costs

Average accumulated care costs are £219k for slow progression types spread over 9 years or so. Fast progression types incur significantly lower overall costs, but due to the shorter survival time of 3 years 7 months, annual costs at £44·5k are nearly double the costs for slow progression types.

Intervention results

Delaying dementia onset improves incidence rates whereas delayed progression reduces mortality rate. Successfully treated patients survive with dementia on average nearly 9 months longer than those not responding to treatment. This is somewhat less than the intervention benefit duration (12 months), as it is moderated by mortality at the population level.

Costs per progression type generally do not differ statistically (95% significance) or practically for this intervention. Generally, the cost benefits of this treatment intervention are lost due to longer survival, as reduced annual care costs are incurred over an increased duration. The results for the fast progression types are an exception, as a temporarily paused fast progression prevents care costs accelerating over the short term.

The change in YWD for the lifestyle intervention suggests an overall reduction at the population level of 15 weeks. The YWD reductions are statistically significant in all cases, although the benefits are lower for fast progression types because of greater mortality (due to becoming severe earlier).

Survival with dementia

Figure 3 summarises these results as three Kaplan-Meier survival curve 'triples'. Each triple shows fast, intermediate, and slow progression type survival time (from left to right). The time axis shows years with dementia. Within each triple the middle trace is the baseline case. The left-hand traces show YWD under the lifestyle intervention, i.e. with shorter durations with dementia (reflecting a reduced duration of dementia care demand). The right hand traces within each triple show the effect of the treatment intervention, which increases the duration with dementia. The features before one year are artefacts of the delayed onset in the lifestyle intervention.

The plotting artefacts in the first year result from the lifestyle intervention's one year delayed mortality, following which survivors are subject to the higher mortality rates in older age groups due to delayed onset. This combination realises compression of morbidity[34] and the associated lower care costs.

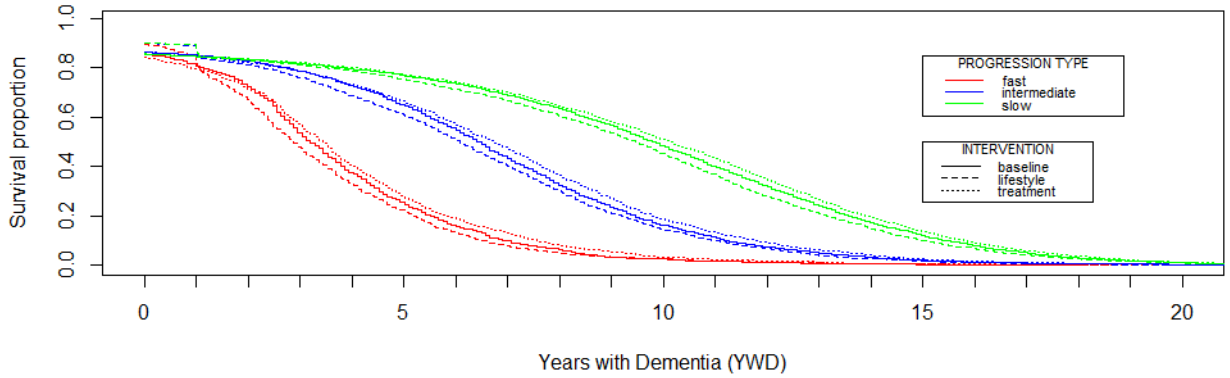

Figure 3 Years with Dementia (YWD) survival curves by progression type

The simulation results in Figure 3 show that median survival for people with dementia with slow progression is around 10 years, with 10% surviving beyond 15 years and 5% beyond 17 years, whereas median survival for fast progressors is only three-and-a-half years after onset and 5% of those beyond 8 years.

Mean and median YWD survival durations are broadly similar within each progression type, except that the fast progression type has a positive skew. Results for the 95th percentiles reveal 1·74 times median duration for the slow progression type, increasing to 2·58 times median duration for the fast types. Despite the shorter mean and median survival durations with fast progression types, there is more fractional variation in survival duration.

Overall outcomes

Table 1 shows that the treatment intervention increases the duration that patients have dementia. This is because mortality rates are typically lower for those with the temporary pause in symptomatic decline associated with the intervention. Additional time with dementia between onset and death is equivalent to a reduced Hazard Ratio compared with the baseline simulation.

Table 1 Comparison of medication intervention with baseline

	progression rate patient type			
	Slow	**Intermediate**	**fast**	**overall**
Years with Dementia – baseline				
Mean YWD ± CI	9·050 ± 0·126	6·302 ± 0·131	3·550 ± 0·155	7·660 ± 0·092
Years with Dementia – medication intervention				
Mean YWD ± CI	9·299 ± 0·129	6·550 ± 0·136	3·748 ± 0·168	7·887 ± 0·094
Years with Dementia – mean difference vs intervention				
YWD increase	0·249	0·248	0·198	0·227
YWD increase	13 weeks longer	13 weeks longer	10 weeks longer	11 weeks longer
p-value	0·0034	0·0051	0·0450	0·0006
Years with Dementia - Cox PH				
YWD Hazard Ratio	0·9399	0·9269	0·9160	0.9440
p-value	0·0003	0·0013	0·0343	<0.0001
Dementia Care Cost – change				
Mean cost increase	£1k	£4k less	£14k	£3k
p-value	0·3635 ns	0·1505 ns	0·0052	0·0815 ns

Table 2 shows the change in survival as negative values. There is a reduced duration between onset and death and so shorter times with dementia, with an overall reduction of 15 weeks at the population level. The YWD reductions are statistically significant in all cases, but the benefits are smaller for the fast progression types. This is because of greater likelihood of mortality for those who become severe earlier.

Table 2 Comparison of lifestyle benefit with baseline

	progression rate patient type			
	Slow	**Intermediate**	**fast**	**overall**
Years with Dementia – baseline				
Mean YWD ± CI	9·050 ± 0·126	6·302 ± 0·131	3·550 ± 0·155	7·660 ± 0·092
Years with Dementia – lifestyle intervention				
Mean YWD ± CI	8·740 ± 0·121	6·027 ± 0·128	3·318 ± 0·149	7·378 ± 0·089
Years with Dementia – mean difference vs intervention				
YWD change	-0·310	-0·275	-0·232	-0·282
YWD reduction	16 weeks	14 weeks	12 weeks	15 weeks
p-value	0·0003	0·0022	0·0186	<0·0001
Years with Dementia – Cox PH				
YWD Hazard Ratio	1·0796	1·0711	1·0945	1·0656
p-value	<0·0001	0·0039	0·0296	<0·0001
Dementia Care Cost – change				
Cost reduction	£14k	£16k	£13k	£15k
p-value	<0·0001	<0·0001	0.0059	<0·0001

Those who benefit from the lifestyle intervention have fewer years with dementia between onset and death, so in fact have an increased Hazard Ratio compared with the baseline case. As previously these are population-level results, so also include those not benefitting from the intervention.

Our analysis revealed higher annual costs for fast progression types albeit over a relatively short period. Although average accumulated care costs for a fast progression type are 73% of care costs (£158k versus £216k) for all people with dementia, the shorter accumulation period means that average annual care costs are 158% (£44·5k versus £28·2k). Similarly, average annual care costs for a slow progression type are 86% of the overall average annual care costs, but the longer accumulation period and the large proportion of slow progression types, means that average total care costs are close to the overall accumulated care costs (£216k).

Discussion

By highlighting the important differences between patient progression rate types, more appropriate consideration can be given to commissioning the variety of care services at the intensity level and duration needed to support people with dementia.

The originality of our study emerges from hybridising computer simulation methods to estimate key outcomes for older people with dementia including individual patient trajectories of cognitive and functional decline, driven by population level dynamics of ageing, dementia incidence, and mortality. The effect of symptomatic treatment and lifestyle interventions are also applied and modelled individually, to better capture real-world heterogeneity.

Symptomatic medication treatment has the potential to increase care costs for those that survive longer in a poor health state. Lifestyle interventions have potential for greater benefit at population level, but raise long-term adherence challenges. It is evident that the need for adequate long-term service planning with considerable resources is not ‘managed away’ by the putative intervention benefits.

We report survival duration – between onset and death – as years with dementia (YWD) with total care costs accumulated over that period. Individual results are aggregated and reported according to slow, intermediate, and fast progression type groups. Categorising patients by progression groups have been suggested[35–37] to support *inter alia* better informed patient prognosis and family counselling support, and these results demonstrate their potential for long-term service planning. While our overall survival duration results compare well with previous results, partitioning by progression type provides better information to service providers.

Intervention benefits are compared with the baseline case to reveal worthwhile but relatively modest effects for each progression type at the population level. Interventions can be worthwhile individually for people with dementia – or for those likely to develop it – however the results here suggest they are unlikely to make large reductions in population-level demand for care services.

Perhaps counter-intuitively, symptomatic treatment increases the duration of years with dementia as survival is improved due to lower mortality associated with lower severity. Any care cost reductions as a result of this are

generally lost with increased survival. As lifestyle interventions delay onset, before care costs are incurred the beneficial effects are larger. Although mortality is also delayed with this intervention, overall compression of morbidity means fewer years with dementia and saving in care costs.

Context and other studies

Previous simulation studies have demonstrated the major challenges to be met in care services provision for people with dementia.[29,38] This study is consistent with prior simulation models in highlighting the need to consider the variability and complexity of heath conditions in old age to inform policy and resource allocation decisions. This paper specifically highlights the importance of considering heterogeneity of severity progression for those with dementia – thus complementing and extending the recommendations from previous work.

Limitations

Higher dementia incidence rates have been reported[39–41] than those used here, but different methods for cohort retention, under-detection adjustment, and assumptions about dementia among decedents makes direct comparison difficult. These differences are greater for the incidence rates among the oldest old,[42,43] but there are relatively few people affected. This moderating assumption may become invalid in the future however, as longevity increases. Nevertheless, prevalence estimates can be used to provide validation against empirical data.

Progression characteristics are based on a data set from the ADNI clinical trial, so some caution is needed in generalising the trajectory characteristics. However, the purpose is to characterise the variability of progression, rather than to characterise a specific group. Progression types were identified using cognitive, functional, and global metrics (in this case MMSE, CDRSB, ADAS13, and FAQ) to cluster the patient trajectories. Different cluster allocations could emerge using different metrics, and therefore different mixed effects regression coefficients could be obtained. Reassuringly, model validation for a range of results show good consistency with a number of sources and published studies, particularly with average MMSE decline and survival.

Despite clustering using multiple domains, the need to map decline to care costs necessitated the use of an MMSE-based regression model. There are many published sources that allow MMSE score to be mapped to care costs, so although it would have been possible to produce a variety of severity progression models, there would have been less scope for mapping this to care costs. This cost modelling approach could be a source of uncertainty, but overall results compare well with independent research.[44]

Reflections on computer simulation in healthcare

Computer simulation is a flexible approach that can be used in a wide range of healthcare applications to develop better intuition of cause and effect relationships. Not only can the results be useful to evaluate and compare interventions and service models on a consistent basis, but the effect of underlying assumptions can be explored without the considerable investment required for ‘real-world’ reorganisation.

Evidence may be incorporated and evaluated from a wide range of sources, and is not limited by survey methods. Simulation results nevertheless require validation, and this can be supported using results from published studies. Where there is uncertainty or unclear trends, for example about incidence rate variation,[45,46] this can be explored in ‘what-if’ computer simulation scenarios.

While summary results are reported here by the patient’s progression type, the underlying simulation captures individuals with their inherent severity progression variability, and this is important where dementia severity has dependent effects such as differing risks of mortality. This is one of the benefits of hybrid agent-based modelling: one is potentially closer to real people than perhaps other, more abstracted simulation methods. Nevertheless, onset and death of the individual agents themselves are ultimately controlled by the more familiar population-level epidemiological model.

While long term trials to investigate lifestyle effects would be prohibitively difficult and expensive, as well as raising ethical issues, this can be readily explored in simulation modelling. An advantage of simulation is that model inputs and outputs can be tailored for specific contexts. Initial conditions and population characteristics such as starting age distributions, longevity, and incidence rates can be easily modified to be generalisable to non-UK population address, and adapted to additional research questions.

10 Author's declaration

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Ethical approval: Not required. This paper describes the results of a computer simulation modelling study. Model parameters were derived from anonymised public domain data sources and published literature.

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Supplementary material

Computer simulation of dementia care demand heterogeneity using hybrid simulation methods: improving population-level modelling with individual-level decline trajectories

Computer simulation model design

The computer model design is described in the main paper. This supplement section focusses on the parameter values used and tabulating the simulation results.

Model parameters

The computer simulation model was parameterised using values from published studies. Results from secondary data analysis was used to supplement this information.

The key input parameters controlling top-level simulation model behaviour were cohort size, age-related dementia incidence, and mortality rates for the cognitively normal and for those with dementia. The number of cognitively normal survivors at each time point determined the size of the 'at risk' pool for new dementia cases. Incidence rates were used to determine the number of onset dementia cases over time, with survival determined by age-related mortality rates for people with dementia. Population growth and life expectancy were based on national statistics projections and life tables.

Mortality for the modelled cognitively normal population was derived from overall population mortality rate.[1] To avoid double counting, mortality rates were adjusted to account for estimated dementia prevalence.[2] Dementia incidence rates were taken from a review of UK and international sources[3–11], in conjunction with a recent study providing age-related incidence rates over the complete age range by five-year age group.[12] Directly useable dementia mortality rates were found to be relatively scarce,[13–16] with figures for only AD or by age categories rather than by 5-year age group. For sources using recorded cause,[17,18] reported deaths 'from dementia' somewhat underestimates death rates 'with dementia'. Taking all this evidence together, the model was configured (with user selectable options) to use dementia mortality rates 1.5 times and 2.0 times that of the cognitively normal mortality rates, with modelling outcomes validated against published estimates of dementia prevalence, as this outcome combines mortality and incidence.

To parameterise individual trajectories of decline, patient records from an Alzheimer's Disease trial[19] were analysed. This ADNI dataset provided a variety of clinical assessments taken at intervals over 8 years for a range of patient types. For this analysis the MMSE, CDR-SB, ADAS13, and FAQ records of 1731 patients represented cognitive, functional, and global decline. Patient trajectories were partitioned using a multi-dimensional longitudinal clustering technique.[20] For consistency with previous work,[21] the resulting partitioned patient cluster groups were labelled slow, intermediate, and fast. To allocate proportions to these groups, expert judgement was sought (as the data used are subject to trial selection biases) for the likely ratios of progression types observed in the population to supplement published information.[21–23] Sensitivity analysis explored these values, and the proportions reported here are 60% slow, 30% intermediate, and 10% fast.

Each partitioned cluster was fitted with a fixed and random effects regression model, where the clustered subset is the categorical variable i. The mixed-effects regression equation account for the within-group variability of severity progression for subject j. The fixed effects regression coefficients therefore provide the average decline for that cluster, while the random effect coefficients provide intercept and slope offsets representing individual variability. Coefficients were sampled and allocated to each simulated patient. The equation result is updated for each agent during run time in the simulation.

$$MMSE_{ij}(month) = \left[\mu_{0,i} + N\left(0, \sigma^2_{0,i,j}\right)\right] + \left[\mu_{1,i} + N\left(0, \sigma^2_{1,i,j}\right)\right].month + \mu_{2,i}.month^2$$

For example, an average 10 MMSE point decline occurs after 9.5 years for slow progression, after 5 years for intermediate progression, and after 2 years for fast progression, with adjustments for intercept (σ_0) and slope (σ_1) applied individually in the computer simulation. Nevertheless, the average effects compared well with published studies.[22,23]

The outcomes reported here assume 30% of those with dementia respond positively to the interventions (based on expert opinion). Stress-testing of the computer simulation varied this parameter from 20% to 40%.

Care costs were related to dementia severity using calculated MMSE based on a linear fit to published data for overall economic impact, including healthcare, social care and unpaid care in the UK.[2] The cost equation was

$$Monthly\ Cost\ (£s)\ =\ 6568\ -\ 188.MMSE$$

Costs were calculated over the range $10 \leq MMSE \leq 26$ covering severe to mild dementia. Costs were not discounted over time.

Per-agent data output from the computer simulation were extracted to Excel to calculate mean differences, confidence intervals, and p-values. Medians and IQRs were also calculated in Excel. R was used to provide Median CIs and the *survival* package in R was used for hazard ratio analysis.

ADNI attribution

The owners of the data source[19] used for dementia severity progression parameters require the following attribution.

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

Computer simulation results

This section describes validation approach and baseline results for a population without interventions. The results for the two modelled interventions are then described.

Simulation validation

To validate the population dynamics component of the model, simulation results were compared to published values[7,9,24–26] of dementia prevalence and lifetime risk of dementia.

Results for dementia severity at death were in line with published results,[27] with 18% mild, 51% moderate and 32% severe in the model versus 22%, 50% and 27% respectively. Other aspects of simulation model validation along with model sensitivity analysis are reported elsewhere.[28]

The overall survival time distribution is a composite of slow, intermediate, and fast progression types comparing well with published results.[29] Overall annual costs at £28·2k compare well with published estimates at £29·3k.[2,30]

Baseline results

The simulation results shown in Table 1~~Table 1~~ for the baseline case correspond to the N=35,000 starting cohort. Of that starting cohort n=11,624 (33%) are projected to develop dementia. These n=11,624 agents are partitioned into 6922 slow (59.5%), 3553 intermediate (30.5%), and 1149 fast (9.9%) progression types, in the 60/30/10 nominal proportions defined in the simulation settings. Slight differences are due to simulation sampling.

Baseline results show clear distinctions between progression rate types, i.e. with non-overlapping confidence intervals. Distributions are all positive-valued, so median values with IQR are shown with 90th and 95th percentiles for the results for years with dementia. Table 1~~Table 1~~ shows that people with dementia (PWD) with slow progression live for an average of nine years, with 10% surviving beyond 15 years and 5% beyond 17 years, whereas PWD with fast progression survive for an average of only three-and-a-half years after onset and 5% of those beyond 8 years. The overall survival time distribution is a composite of slow, intermediate, and fast progression types although its characteristics are somewhat dominated by the large size of the slow progression group. These results compare well with published survival figures.[29]

Table 1 Baseline results summary

	progression rate patient type			
	slow	**intermediate**	**fast**	**overall**
Years with Dementia				
Mean YWD ± CI	9·050 ± 0·126	6·302 ± 0·131	3·550 ± 0·155	7·660 ± 0·092
(SD)	(5·353)	(3·989)	(2.682)	(5·102)
Mean years months	9 years 1 month	6 years 4 months	3 years 7 months	7 years 8 months
Years with Dementia				
Median YWD	9·78	6·41	3·205	7·808
[IQR]	[7·315]	[5·096]	[3·123]	[7·726]
YWD 90th percentile	15·45	11·18	6·98	14·3
YWD 95th percentile	17·01	12·98	8·30	16·0
Median years months	9 years 9 month	6 years 5 months	3 years 2 months	7 years 10 months
Dementia Care Costs				
Mean Costs ± CI	£219k ± £3·9k	£228k ± £5·3k	£158k ± £7·2k	£216k ± £2·9k
(SD)	(£168k)	(£162k	(£126k)	(£164k)
Mean Annual costs	£24·2k	£36·2k	£44·5k	£28·2k
Mean/Median values ± half-range confidence interval				

Medication intervention results

Table 2~~Table 2~~ shows the summary results for the treatment intervention associated with the results comparison in Table 1 of the main text.

Table 2 Medication intervention results summary

	progression rate patient type			
	slow	**intermediate**	**fast**	**overall**
Years with Dementia				
Mean YWD ± CI	9·299 ± 0·129	6·55 ± 0·136	3·748 ± 0·168	7·887 ± 0·094
(SD)	(5·469)	(4·167)	(2·958)	(5·223)
Mean years months	9 years 4 months	6 years 6 months	3 years 9 months	7 years 11 months
Years with Dementia				
Median YWD	10·110	6·740	3·452	8·055
[IQR]	[7·479]	[5·507]	[3·534]	[7·890]
90%-ile	15·781	11·753	7·562	14·712
95%-ile	17·260	13·562	9·205	16·356
Median years months	10 years 1 month	6 years 9 months	3 years 5 months	8 years 1 month
Dementia Care Costs				
Mean Costs ± CI	£220k ± £3·9k	£232k ± £5·4k	£172k ± £8·1k	£219k ± £3·0k
(SD)	(£169k)	(£165k	(£138k)	(£164k)
Mean annual costs	£23·7k	£35·5k	£45·9k	£27·7k
Mean/Median values ± half-range confidence interval				

These results apply at population level and so are ‘diluted’ by those who do not respond or adhere to treatment. Nevertheless, successfully treated patients survive with dementia on average nearly 9 months longer than those not responding to treatment (not shown in tables).

Costs per progression type generally do not differ statistically (at 95% significance) or practically for this intervention. Generally, cost benefits of this treatment intervention are lost due to longer survival, as any reduction in care costs is incurred over an increased duration. The results for the fast progression types are an exception, as a temporarily paused fast progression prevents care costs accelerating over the short term.

Lifestyle intervention results

Table 3~~Table 4~~ shows the summary results for the lifestyle intervention for the results comparison shown in Table 2 in the main text.

Table 34 Lifestyle intervention results summary

	progression rate patient type			
	slow	**intermediate**	**fast**	**overall**
Years with Dementia				
Mean YWD ± CI	8·74 ± 0·121	6·027 ± 0·128	3·318 ± 0·149	7·378 ± 0·089
(SD)	(5·162)	(3·883)	(2·618)	(4·949)
Mean years months	8 years 9 month	6 years	3 years 4 months	7 years 5 months
Years with Dementia				
Median YWD	9·452	6·082	2·876	7·346
[IQR]	[7·315]	[5·274]	[3·288]	[7·726]
YWD 90th percentile	14·98	10·99	6·43	13·93
YWD 95th percentile	16·52	12·57	7·91	15·53
Median years months	9 years 5 months	6 years 1 months	2 years 11 months	7 years 4 months
Dementia Care Costs				
Mean Costs ± CI	£205k ± £3·8k	£212k ± £5·2k	£145k ± £7·0k	£201k ± £2·9k
(SD)	(£164k)	(£156k	(£123k)	(£159k)
Annual Costs	£23·5k	£35·2k	£43·7k	£27·2k
Mean/Median values ± half-range confidence interval				

Supplementary References

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