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## Hybrid simulation modelling for dementia care services planning

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### ABSTRACT

Dementia is an increasing problem in today's ageing society, and meeting future demand for care is a major concern for policy-makers and planners. This paper presents a novel hybrid simulation model that simultaneously takes population-level and patient-level perspectives to calculate the numbers of patients at different stages of disease severity over time, and their associated care costs. System Dynamics is used at population level to capture ageing, dementia onset, and all-cause mortality, whereas disease progression is modelled at individual patient level using Agent-Based methods. This enables the model to account for variability between patients in the rate of cognitive decline, dementia-related mortality and response to treatment interventions. Using epidemiological data from the medical literature, disease progression is modelled via a longitudinal clustering method to identify progression type, followed by mixed-effects regression to reflect each individual's rate of cognitive decline. Results are presented for population data from the south of England, and show that the currently available interventions have only modest effects at population level.

### ARTICLE HISTORY

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### KEYWORDS

Hybrid simulation;  
dementia; disease  
progression; healthcare

## 1. Background

Dementia is a long-term neurodegenerative condition associated with progressive cognitive and functional decline, often requiring ongoing and eventually high levels of care. It is mainly, but not exclusively, associated with old age, and while medication can temporarily delay symptom progression in some patients, there is currently no cure. The onset is insidious, occurring many decades before clinical symptoms appear, making protective medical interventions difficult to target. Provision of care services is therefore critically important, particularly as 36.5% of the estimated 850,000 people with dementia in the UK are reported to be living in care homes (Alzheimer's Society, 2014).


This modelling study was undertaken in collaboration with the Wessex Academic Health Science Network ([wessexahsn.org.uk](http://wessexahsn.org.uk)). Data availability was an important factor in the model design process; the model uses published data from clinical studies as well as local population data. The model estimates the number of people over 65 with dementia over time (broken down by disease severity stage) and the associated quality-adjusted life-years (QALYs), the costs of care, and the number of deaths. The

model can also be used to explore the effects of any potential treatments or interventions. Section 9 of this paper presents comparative results for two currently available interventions, medical treatment and a healthy lifestyle intervention.

## 2. Previous modelling work in dementia

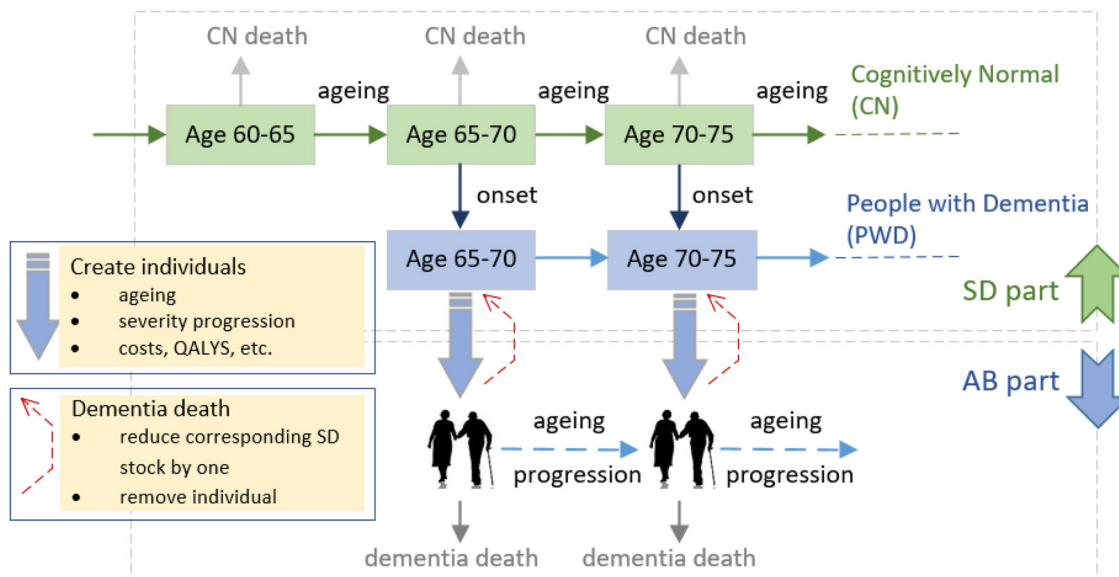
As part of the Assessment of Health Economics in Alzheimer's Disease (AHEAD) project, Guo et al. (2014) developed a discrete-event simulation model of the treatment and control arms, representing a drugs "trial" to determine intervention benefits. The dementia cohort was modelled using a fixed and random effects regression model (Getsios et al., 2010). The model depicted incremental cognitive decline, using one single set of coefficients to represent the entire dementia cohort.

System Dynamics was applied to family size trends and family living arrangements in Singapore (Ansah et al., 2013; Thompson et al., 2012, 2014). These studies considered projections for the potential demand for long-term care, and the impact on acute care services if the provision of long-term care is inadequate. Given the cultural differences in

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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](http://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](http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf)

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**Figure 1.** Conceptualisation of ageing, dementia onset, and severity progression.

family life and the important role of foreign domestic workers in Singapore, this work is difficult to generalise to the UK. Moreover, model parameters were based on limited, historical data (Reisberg et al., 1996).

A more recent study, IMPACT-BAM (Ahmadi-Abhari et al., 2017; Guzman-Castillo et al., 2017) uses Markov states to model ageing and progression of healthy 35 year olds to age 100 into several impaired health states and death. The model focusses on cardiovascular disease and cognitive impairment as drivers of life expectancy and disability. The results on dementia support other studies (Matthews et al., 2013; Wu et al., 2017) that show that the dominant factor driving the overall number of prevalent cases in future will be the ageing population.

The PACSim model (Kingston et al., 2018, 2018) uses microsimulation to predict a decrease in care need for those aged 65–74 and an increase in the number of people with high care dependencies in the over 85 s. The authors found that the prevalence of those with four or more multiple morbidities is projected to increase, with most of the anticipated life expectancy gains accompanied by disease. Their model was parameterised from three different population surveys, but dementia was not modelled explicitly and was determined as a post-simulation analysis of related factors.

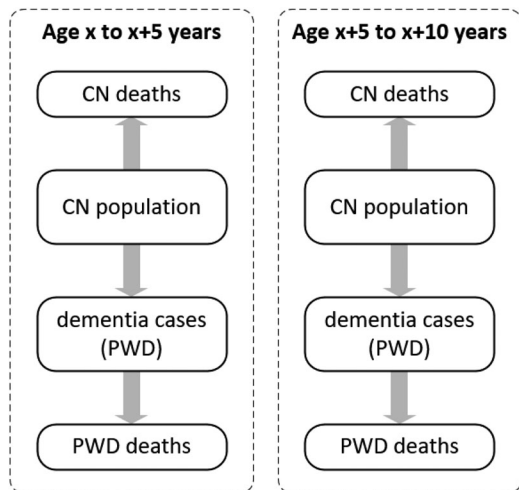
Other than these studies, to date OR techniques have not been widely applied to care service planning for people with dementia. This is particularly the case with hybrid approaches. The model presented here adds to this previous work by classifying dementia severity by progression type and by using multiple outcome measures to compare scenarios. Most importantly, the use of hybrid simulation

allows two entirely different but closely interconnected processes, population dynamics and individual disease progression dynamics, to be modelled using methods appropriate to their specific characteristics, making it possible to explore the interactions between population-level effects and individual-level effects.

### 3. Computer simulation modelling approach

The model was developed in the software AnyLogic (XJ Technologies, 2015). At the population level, ageing, dementia onset, and mortality are modelled using System Dynamics (SD). At the individual patient level, disease severity progression and the effects of any interventions are modelled using Agent-Based Modelling (ABM) to capture variability between individuals (Macal & North, 2010). Figure 1 shows the conceptual model design, combining SD stocks and flows (upper part) and agent-based severity progression and death (lower part). The interactions between the SD and AB parts, i.e. dementia onset (creating agents) and death (removing agents), are indicated in the side panels. Interfacing continuous SD and discrete ABM or DES modelling methods is a recognised challenge in hybrid simulation (Brailsford et al., 2019). In this model, agents are created and removed by monitoring and discretising the onset and mortality flows for each age group on a weekly basis, as described in Section 6.

The term “dementia death” in Figure 1 is shorthand for “death of a person with dementia,” since dementia increases the risk of dying from other conditions. Severity progression is classified as slow, intermediate, or fast (Doody et al., 2010), represented by three different mixed effects regression



**Figure 2.** Adjacent age groups  $[x, x+5]$  and  $[x+5, x+10]$  with no flows between age bands.

models, as described in Section 5. When an agent is created, the progression type and the corresponding regression parameters are randomly sampled. The use of agents to capture heterogeneity in progression and the complexities of response to interventions overcomes the assumption of homogeneity within each stock, as in standard SD modelling (Forrester, 1994; Sterman, 2000). Care costs, quality of life, and years with dementia are calculated for each individual agent and then aggregated at the population level and by progression type.

#### 4. System dynamics model architecture

The population is broken down into 5-year age groups from 65 to 105. The model excludes early-onset dementia, so people in the “entry” stock [60 to 65] are assumed to be cognitively normal (CN). As shown in Figure 1, each CN stock has two, age-related, outflows: CN deaths and incident (new) cases of dementia. Age-related mortality is also applied to each stock of people with dementia (PWD). The PWD cases and PWD deaths stock levels are monitored at weekly intervals to control agent creation and removal in the ABM component. Age-related mortality and incidence rates were estimated from published data (see Appendix A.1).

Conventional SD ageing chains contain flows between adjacent age-group stocks, as indicated in Figure 1; at each time step  $dt$ , material drains from one stock and flows into the next. The model presented here uses a new approach, and instantaneously transfers the entire remaining contents of each stock (i.e. survivors) at 5-year intervals. This is depicted in Figure 2; note the absence of horizontal flows between stocks. Ageing for both CN and PWD sub-populations is controlled by purpose-written code executed at 5-year intervals. First, the remaining contents of the penultimate stock [95 to

100] are moved to stock [100 to 105]. Next, the contents of stock [90 to 95] are moved to stock [95 to 100], and so on down the age groups until each stock has been aged and the population is subject to new mortality and incidence rates for the next five years of modelled time.

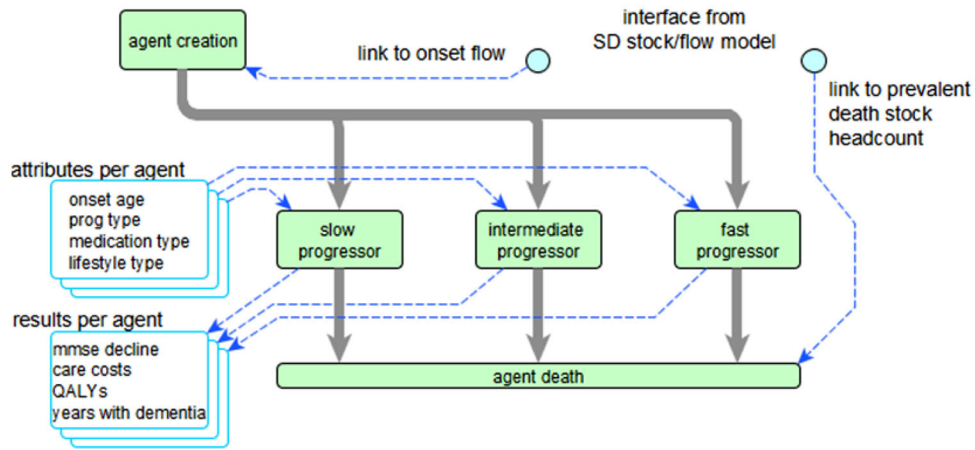
This approach assumes that the average age in each age group stock remains unchanged over the 5-year period, and hence the age-related mortality and incidence rates also remain unchanged. This relatively minor assumption significantly simplifies the standard approaches in the literature (Eberlein & Thompson, 2012, 2013; Sterman, 2000) and avoids the considerable complications of stock mixing that would otherwise arise due to differences between inflows and outflows. This was fairly straightforward to implement in the simulation model, but the corresponding analytical formulation would be very difficult to solve: see Appendices A3 and A4.

#### 5. Agent-based model architecture

Each agent has its own instantiation of a generic statechart that describes all the possible states it can be in and the transitions between them. Agents flow through the statechart under the control of transition routings and conditional logic, depicted conceptually in Figure 3.

##### 5.1. Agent creation and attribute allocation

When an agent is created, it is allocated several attributes which determine its behaviour. Each agent is allocated a unique ID number, progression type (*slow*, *intermediate*, and *fast*), individual progression rate parameters, potential response to medication (*positive* or not), and a lifestyle response (*more healthy* or not). The values of these attributes are sampled from the probability distributions described in Appendix A.6. Dementia severity is represented by the score in the mini mental state exam (MMSE), a commonly used clinical instrument to assess a person’s cognitive state (Folstein et al., 1975; Sheehan, 2012). MMSE test scores are ubiquitous in the dementia literature, and enable dementia severity to be associated with QALYs and care costs. Cognitive decline is calculated at monthly intervals, using a mixed effects regression equation to calculate an updated value of the MMSE. The underlying fixed effect parameters are the same for all agents of that progression type, but the random effects adjustments of intercept and slope are sampled for each individual agent. Other attributes are used to track and record simulation outputs, such as age of onset and accumulated care costs. Based on the agent’s



**Figure 3.** Agent-based severity progression concept.

monthly MMSE value, additional functions are called to calculate care costs based on published sources (Alzheimer’s Society, 2014) and QALYs, based on summing health utility scores. The equations relating cognitive decline to QALYs and costs are given in Appendix A.7.

## 5.2. Modelling interventions and benefits

The two interventions compared in this paper are medication and a healthy lifestyle, both of which are only effective for some patients. Medication can temporarily slow down disease progression, and a healthy lifestyle can delay the onset of dementia (and also death). These effects and the proportions of patients that benefit are shown in Table 1. The source references are given in Appendix A.1.

The effect of medication is modelled using conditional triggers that transition the agent to states where progression is temporarily decoupled from the simulation timer. After 12 months, the agent moves out of this state and their severity progression is re-synchronised with simulation time. Other time-dependent calculations (age, elapsed time with dementia, etc.) are not affected. To model the benefits of a healthier lifestyle, agents move to a delayed onset state, remain there for 24 months, and subsequently move into the severity progression states. These agents then later move to a delayed mortality state in which their “scheduled” death is delayed by 12 months. These actions occur only if the patient has a positive response attribute to that intervention.

## 6. Interaction between SD and ABM

This interaction occurs twice, at dementia onset and at death, and is one of the most innovative features of the model. Both processes originate in the SD part but require changes to be made in the AB part. In each age band, dementia onset is represented by the flow from CN to PWD, but the PWD stocks

**Table 1.** Intervention parameter values.

Intervention	Parameter	Value
Medication	Start time	Onset + 12 months
	Progression delay	12 months
	% benefitting	30%
Lifestyle	Onset delay	24 months
	Mortality delay	12 months
	% benefitting	30%

alone cannot be used to count new cases as they have outflows to PWD deaths. Therefore, in order to determine when a new agent should be created, each age group  $[x, x + 5]$  has an artificial “onset stock” with (continuous-valued) stock level  $N^{x, x+5}$  and integer-valued tracking threshold  $P^{x, x+5}$ . The inflow to each onset stock duplicates the flow from CN to PWD for that age group using shadow flows. The values of  $N^{x, x+5}$  are monitored at one week intervals in the SD part, and if  $N^{x, x+5} > P^{x, x+5}$ , then  $\lfloor N^{x, x+5} - P^{x, x+5} \rfloor$  new agents in that age band are created and  $P^{x, x+5}$  incremented to the next integer greater than  $N^{x, x+5}$ . These onset stocks are simply a modelling device to count the number of new cases; they have no outflows, and hence are not shown in Figures 1 and 2.

For agent removal, i.e. death, the process is slightly simpler as the PWD death stocks have no outflows and hence there is no need for a logical equivalent of the onset stocks. The PWD death stock levels are monitored at one week intervals, and each time the (rounded down) stock level increases, the corresponding integer number of agents whose ages fall within that age band are removed. Since increased dementia severity is associated with increased risk of mortality (Larson et al., 2004; St. John et al., 2002; Su et al., 2014), agent removal is biased preferentially to the more severe cases. This is implemented in the model by sampling an MMSE value from a uniform distribution, and selecting (at random) an agent whose MMSE value exceeds this sampled value. If the chosen agent is in the delayed mortality state, another agent is selected.

**Table 2.** Summary outcome measures.

Outcome	Comments
Years with dementia (YWD)	Calculated for all patients and also broken down by progression type
Quality adjusted life years (QALYs)	
Care costs	Calculated for each patient; costs per annum were estimated by dividing this by YWD
Number of PWD, by age group and severity	
Number of deaths of PWD by age group	

## 7. Model outputs

The main model outputs are the numbers of patients at different stages of disease severity over time, and the numbers of cognitively normal and dementia deaths by age group, also broken down by severity level. These numbers can be used to inform care service planning as well as the design of end-of-life services (Georghiou et al., 2012) (Table 2).

User-selectable options allow all-female or all-male populations to be simulated, as sex-specific incidence and mortality rates give different distributions of dementia onset age and longevity. The results presented in this paper are for a mixed population (see Appendix A.1).

## 8. Model validation

The simulation was validated by comparing the model results with independent sources where available. For example, Figure 4 compares mortality in a cohort of 5,000 persons starting at age 60, obtained by aggregating CN (green) and PWD (blue) deaths in the model (solid orange) and using reference data from the UK Office of National Statistics (dotted orange).

On average, modelled patients survived 7.761 years with dementia (see Table 5). This value is consistent with published studies, although these studies are relatively old and the ranges are very wide, for example 3.8 to 10.7 years (Xie et al., 2008) and 5.9 to 12.2 years (Waring et al., 2005). The model results for age-related prevalence were compared with published estimates (Alzheimer's Society, 2014), and the overall number of cases compared with the published lifetime risk of dementia (Brookmeyer & Abdalla, 2018; Fishman, 2017), as shown in Table 3. Given the uncertainty in the published estimates, the simulation results are reasonably consistent.

Simulated care cost outcomes were compared with other published care cost data for England (Wübker et al., 2015), not used in the model, which reported that the average annual cost per person was £27,000, rising to £44,600 per annum for people in nursing homes. The model gives an average annual cost of £28,800 per person. Costs are not broken down by progression type in the literature so further comparison is not possible, but assuming that fast progressors are more likely to require

nursing home care, these costs also compare well: the simulation gave £45,100 per person per year.

## 9. Experimentation and results

Table 4 presents the results for a no-intervention scenario, using the mortality rate and incidence parameters given in Table A3 in the Appendix, for a cohort of 10,000 persons entering the model in 2015 at age 60. To account for uncertainty, three parameters (two mortality; one incidence) were varied over  $a \pm 20\%$  range, with 10 intervals (so 11 measurement points), giving  $11^3 = 1331$  iterations and an overall total of 2,791,382 agents. This experiment took about 40 min on an i5-6600 CPU running at 3.3 GHz with 8GB RAM under Windows 10.

Table 4 shows that unsurprisingly, in the younger age groups there are more new cases than deaths from dementia, whereas the reverse is true in the older age groups. This is indicated by the inequality symbols.

Table 5 summarises the baseline results, showing distinct differences by progression type in YWD and care costs.

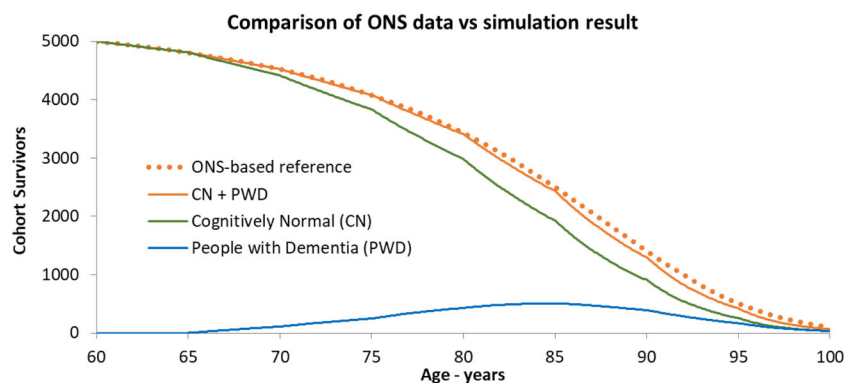
Table 6 presents the results from two further experiments for the same cohort and the two interventions described in Section 5.2.

## 10. Discussion

### 10.1. Simulation results

It can be seen from Table 6 that both interventions show a benefit in terms of increased QALYs and reduced costs. However, medication increases YWD by reducing progression rates and mortality, whereas lifestyle interventions *reduce* YWD and thus result in greater cost savings as well as a greater QALY gain compared with medication. Although medical interventions can be worthwhile at an individual level, only a minority of patients benefit and the average cost saving per patient (£3.1k) is small. On the other hand, the lifestyle intervention results in an average cost saving per patient of £15.2k, and is likely to benefit the CN population as well.

Table 6 shows that slow progressors survive about 9 years, whereas fast progressors only survive 3.4 years on average. This more rapid decline is associated with reduced quality of life and higher



**Figure 4.** Validation of modelled overall mortality.

**Table 3.** Dementia prevalence and lifetime risk (LTR) of dementia.

Age	65	70	75	80	85	90	95	LTR
Reference	1.7%	3.0%	6.0%	11.2%	18.3%	29.9%	41.1%	31.0%
Simulation	0.5%	3.2%	7.4%	14.4%	22.9%	32.3%	42.3%	26.9%

**Table 4.** Numbers of new cases and PWD deaths for a single age cohort.

Age group	CN deaths	95% CI	New cases	95% CI		PWD deaths	95% CI
60–65	380.5	±2.0	–	–	–	–	–
65–70	557.7	±2.7	230.4	±2.2	>	13.6	±0.1
70–75	836.7	±3.9	328.8	±3.0	>	71.9	±0.7
75–80	1159.9	±4.9	540.4	±4.7	>	223.6	±2.0
80–85	1496.8	±5.9	601.2	±4.8	>	529.6	±4.6
85–90	1510.0	±6.3	525.6	±4.0	<	810.4	±6.5
90–95	986.0	±6.7	322.7	±2.8	<	696.8	±5.3
95–100	337.7	±4.3	120.6	±1.5	<	292.0	±2.2
100–105	39.1	±0.5	19.0	±0.2	<	46.1	±0.5
Total	7304.4	±19.8	2688.7	±19.8		2684.0	±19.8

Notes: 95% CI values are calculated in AnyLogic as half-width values about the mean. Stock level rounding errors are <0.5%.

mortality. The annual care costs for fast progressors are higher, but they are incurred over a shorter period, resulting in lower average total care costs (£155k). Slow progressors incur higher average total costs (£233k), but over a longer period.

### 10.2. Clinical and policy implications

Prompt assessment for fast progressors is clearly important, as there is less time to get individual care plans in place and to identify the budgetary means. For a typically-sized care service planning area, with 10,000 persons aged 60–65, there will be several hundred new dementia cases within that cohort over each 5-year interval. The number of new cases within that age cohort peaks at age 80 to 85, after which the number of people dying with dementia exceeds the number of new cases. At this point, the emphasis for care services shifts from managing new cases to providing end of life care.

The scenarios in Section 9 were chosen to illustrate the simplest way that the model can be used, i.e. for one single age cohort starting at age 60, and are thus closer to the world of clinical trials than the world of care service planning. However, the model can also handle more realistic population-

based scenarios, described in Appendix A.2. These include multiple age cohorts, i.e. new arrivals aged 60–65 every five years; a “cross-sectional” initial population in each age group at time zero; and, most realistic of all, a combination of both these.

Until more effective treatments become available, medication alone is unlikely to make significant reductions in population-level demand for dementia care services. Lifestyle interventions have greater potential, and may also lead to other health benefits in addition to dementia, but require considerable planning and long-term commitment from all stakeholders to ensure that these benefits are realised. An appropriate precautionary approach would be to prepare for increased demand based on the key driver of older population growth, supporting previous recommendations (Prince et al., 2016). In addition, a deeper appreciation of differing progression rates, and their effect on service need affords better capability in matching service provision with local demand and future service growth.

### 10.3. Modelling and simulation reflections

The scientifically novel aspects of this model are the application of several modelling concepts –

**Table 5.** Summary baseline outcomes, aggregated and by progression type.

Outcome measure	Mean values and 95% CI			
	Slow	Intermediate	Fast	Total
Years with dementia (YWD) 95% confidence interval	9.181 ± 0.03	6.049 ± 0.026	3.439 ± 0.023	7.671 ± 0.027
Quality adjusted life years (QALYs) 95% confidence interval	5.661 ± 0.018	3.527 ± 0.014	1.802 ± 0.011	4.637 ± 0.016
Total care costs 95% confidence interval	£233.1k ± £994	£217.9k ± £1145	£155.2k ± £1196	£220.8k ± £1011
Annual care costs	£25.4k	£36.0k	£45.1k	£28.8k

Notes: 95% CI values are calculated in AnyLogic as half-width values about the mean. Annual costs are calculated from the stated point estimates.

**Table 6.** Intervention effects, calculated for individual PWD, and averaged over all progression types.

Outcome measure	Baseline	Medication	Lifestyle
Years with dementia (YWD) 95% confidence interval	7.671 ± 0.027	7.753 ± 0.027	7.376 ± 0.027
Quality adjusted life years (QALYs) 95% confidence interval	4.637 ± 0.016	4.707 ± 0.016	4.914 ± 0.015
Total care costs 95% confidence interval	£220.8k ± £1012	£217.7k ± £986	£205.6k ± £976
Annual care costs	£28.8k	£28.1k	£27.9k
Summary of benefits		(1 month)	3.5 months
YWD reduction (increase) over baseline		0.070 QALY	0.277 QALY
QALY improvement over baseline		Saving £3.1k	Saving £15.2k
Overall care costs			

including hybrid-modelling concepts – to the dementia use-case. These include the ageing mechanism in the SD submodel, the interfaces between SD and AB (i.e. accumulation-only stocks used for agent creation and statistical model-based agent removal processes), and individual disease progression analysis in the AB submodel. The hybrid approach exploits the complementary strengths of SD and ABM. In a healthcare context, many problems can benefit from combining a deterministic, population-level system-wide view with a detailed, stochastic, patient-level perspective (Brailsford et al., 2019). Public health campaigns in particular are typically “targeted” at very large populations, more efficiently modelled using SD, but their impact is felt by individual patients, with variable effect. The healthy lifestyle intervention in this paper exemplifies this. Any such intervention would have to be aimed at (say) all people over 50, the majority of whom will never develop dementia (although they might still benefit from taking more exercise and a more healthy diet). For those individuals who do develop dementia, the health benefits are variable. Service planners and decision-makers need to take all these aspects into account.

ABM is still relatively underused in practice (Brailsford et al., 2019), but is a very powerful approach for modelling human systems. It would enable this model to be extended to include complications and comorbidities associated with dementia (Bunn et al., 2014; Kurrle et al., 2012; Poblador-Plou et al., 2014), and also handle more complex network-based interactions, such as social engagement (Badham et al., 2018) and health service provider interactions and behaviours (Mills, 2013), assuming sufficient data were available to parameterize such a model. This model demonstrates the potential of currently underutilised OR techniques (Monks,

2016; Penn et al., 2015) to better understand the interactions between population and patient-level effects of public health interventions. The general principle of modelling macro-micro interactions extends far beyond healthcare into many other application areas.

### Disclosure statement

No potential conflict of interest was reported by the authors.

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## Appendix A

This appendix provides a more detailed description of the model, covering the following areas:

1. Parameter data sources and references
2. The population definition
3. The SD model as a system of differential equations (DEs)
4. The solution to those DEs
5. The derivation of dementia incidence and mortality rate
6. The dementia severity progression model
7. Care cost and QALY equations

### A.1. Data sources

### A.2. Population definition

The model allows various population starting scenarios, from single and multiple successive age/birth cohorts, to a cross-sectional age distribution with starting-value stock levels in all age groups for both CN and PWD stocks.

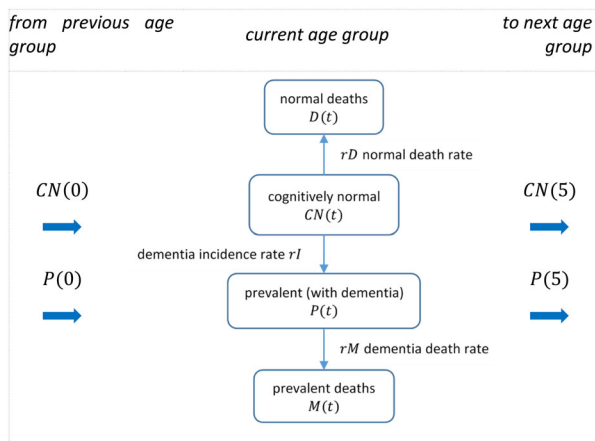
This paper focusses on the results for a single cohort approach, as this provided the most easily interpretable results. Ageing, onset, and death could be directly observed without more complicated interaction effects. Observing a single age cohort also provided clearer insights into the underlying epidemiology, and the intervention benefits for a specific age group.

**Table A1.** Input parameter data sources.

Parameter	Source details
Population mortality	National Life Tables (ONS, 2014a)
Population distribution	Estimates for mid-2016 (ONS, 2014b)
Population projections	25 year forecast by Local Authority (ONS, 2014c)
Incidence rates	(Brookmeyer & Abdalla, 2018; Corrada et al., 2010; CSHA Working Group, 2000; Edland et al., 2002; Fichter et al., 1996; Fishman, 2017; Grasset et al., 2016; Matthews et al., 2016; Miech et al., 2002; Ott et al., 1998; Rait et al., 2010; Seshadri et al., 1997)
Dementia mortality	(Agüero-Torres et al., 1999; Ganguli et al., 2005; ONS, 2019) Values interpolated to 5-year age groups
Dementia prevalence	Dementia UK: Update (Alzheimer's Society, 2014)
Severity progression	Alzheimer's Disease Neuroimaging Initiative (ADNI, 2016) Longitudinal clustering method (Genolini et al., 2015) Mixed effects regression (Bates et al., 2015)
Medication benefit	(Birks, 2006; Birks et al., 2013; 2015; Perera et al., 2014) plus expert judgement for the proportion benefitting.
Lifestyle benefit	(Elwood et al., 2013; Larson et al., 2006; Ray & Davidson, 2014; van Baal et al., 2016)
Care costs	(Alzheimer's Society, 2014; Jones et al., 2017; Kahle-Wroblewski et al., 2015)

**Table A2.** Population growth and longevity comparison.

Age	65	70	75	80	85	90	Over 65s	Parameters
Reference	1.22	1.55	1.64	1.81	1.99	2.81	1.55	(ONS, 2014c)
Case 1	1.54	1.59	1.61	1.64	1.72	1.99	1.71	2.2% and 1.2%
Case 2	1.60	1.66	1.71	1.79	1.98	2.78	1.99	2.2% and 3.0%



**Figure A1.** Age group stock-flow structure.

For multiple age cohorts, the effect of population growth can be explored by making subsequent 60–65 age groups entering the model progressively larger. The model does not attempt to reflect short-term fluctuations in real-world population growth and longevity, but simply depicts general trends. Younger cohorts entering the model are increased by a cohort inflation parameter to reflect projected population increases. Younger cohorts also live longer, and this is controlled by a mortality rate reduction parameter. The ONS-based (ONS, 2014c) reference values in Table A2 show the projected relative growth in each age band over the next 20 years: for example, in 2034 there will be 1.99 times as many 85-year-olds as there were in 2014. Simulation case 1 shows the results for annual increases of 2.2% in population growth at age 60 and a 1.2% reduction in mortality rate. Case 2 shows the results for 2.2% and 3.0% respectively.

For the cross-sectional age distribution, the cognitively normal stocks were initialised with headcounts based on published values (ONS, 2014b) of the number of people in each 5-year age group. While this approach is more

realistic, older people spend a shorter time in the model and the results are a composite of onset and mortality effects across these different age groups. While the results obtained were more comprehensive, detailed interpretation is thus more difficult, and are not reported here.

### A.3. Analytical formulation

In this section we present a continuous, analytical, formulation of the ageing process in the SD model as a set of ordinary differential equations (ODEs). The broad horizontal arrows in Figure A1 represent how stock levels are transferred at 5-year intervals between age groups. The vertical arrows show the incidence and mortality flows between stocks within an age group. For simplicity this formulation omits the age band index, but (unlike many studies in the literature) the model uses age-related incidence and mortality rates.

The stock of people with dementia  $P(t)$  has initial value  $P(0)$ , an inflow of new cases with incidence rate  $rI$ , and an outflow to the stock  $M(t)$  (dementia deaths) with dementia mortality rate  $rM$ .  $P(0)$  are the survivors with dementia transferred in from the previous age group. Similarly, the stock  $CN(t)$  of cognitively normal (CN) people, has initial value  $CN(0)$  and an outflow to the stock  $D(t)$  of CN deaths with CN mortality rate  $rD$ .

At the end of each 5-year interval, the surviving  $CN(5)$  and  $P(5)$  stocks are transferred to the next oldest age group, where they become  $CN(0)$  and  $P(0)$  for that age group. These transferred stocks therefore represent the initial conditions for the differential equations describing that process.

The rate of change of  $CN(t)$  over time  $t$  is determined by the incidence rate  $rI$  and the CN mortality rate  $rD$  :

$$dCN(t)/dt = -(rI + rD).CN(t)$$

The rate of change of  $D(t)$  is determined by  $CN(t)$  and the CN mortality rate  $rD$  :

**Table A3.** SD flow parameter values.

Age group	CN mortality rate	Incidence rate Cases per 1000 person-years	PWD mortality rate
60–65	8	–	–
65–70	12	5	18
70–75	20	8	30
75–80	34	16	51
80–85	62	25	93
85–90	112	39	168
90–95	191	63	287
95–100	308	110	462
100–105	308	150	462

**Table A4.** Severity progression type parameter values.

Type	Baseline	Intercept	Linear slope	Quadratic slope
Slow	60%	$N(26.9, 1.39^2)$	$N(0.03, 0.044^2)$	$\mu_2 = 0.00052$
Intermediate	30%	$N(25.2, 1.57^2)$	$N(0.14, 0.074^2)$	$\mu_2 = 0.00047$
Fast	10%	$N(22.5, 1.50^2)$	$N(0.38, 0.201^2)$	$\mu_2 = 0.00165$

$$dD(t)/dt = rD.CN(t)$$

The rate of change of  $P(t)$  is determined by the incidence rate  $rI$  from  $CN(t)$  and the dementia mortality rate  $rM$  :

$$dP(t)/dt = rI.CN(t) - rM.P(t)$$

Finally, the rate of change in  $M(t)$  is determined by  $P(t)$  and the dementia mortality rate  $rM$  :

$$dM(t)/dt = rM.P(t)$$

#### A.4. Solutions of the differential equations

We present solutions for these ODEs in the case where there are no survivors from the previous age group, i.e.  $P(0) = 0$ .

Number of CN people:

$$CN(t) = CN(0).exp[-t.(rI + rD)]$$

CN deaths:

$$D(t) = \frac{CN(0).rD}{rD + rI} (1 - exp[-t.(rI + rD)])$$

Number of PWD:

$$P(t) = \frac{CN(0).rI}{rD + rI - rM} (exp[-t.rM] - exp[-t.(rI + rD)]) \quad (A1)$$

Dementia deaths:

$$M(t) = \frac{CN(0).rI}{rD + rI} \cdot \left( 1 + \frac{rM}{rD + rI - rM} \cdot exp[-t.(rI + rD)] - \frac{rD + rI}{rD + rI - rM} \cdot exp[-t.rM] \right)$$

In general, survivors with dementia from the previous age group would be included as an initial condition. In this case, Equation (A1) becomes:

$$P(t) = \frac{CN(0).rI}{rD + rI - rM} \cdot (exp[-t.rM] - exp[-t.(rI + rD)]) + P(0).exp[-t.rM]$$

These ODEs are not easy to solve analytically, but are relatively straightforward to implement and solve by simulation.

#### A.5. Incidence and mortality parameter derivation

To parameterise the model, published studies were reviewed to obtain the most relevant evidence. Incidence rates – which define onset of dementia in a population were based on a review of several studies (Table A1). The availability of published data in most sources by 5-year age group informed the model's age group architecture.

Similarly, dementia mortality rates were based on a review of sources (Agüero-Torres et al., 1999; Ganguli et al., 2005; ONS, 2019). Estimated dementia mortality rates were between one-and-a-half times and twice the rates for the cognitively normal population, consistent with previous studies (e.g. Ravi, 2011). Cognitively normal age-related death rates in the model ( $rD$ ) were derived from overall population mortality rate (ONS, 2014a), corrected to account for estimated prevalence (Alzheimer's Society, 2014), where  $rO$  is the overall population mortality rate and  $prev$  is the prevalence.

$$rD = \frac{rO}{1 - prev} - rM \cdot \left( \frac{prev}{1 - prev} \right)$$

Table A3 presents the population parameters used for a mixed population. The model may also be run with values specific to female and male populations.

#### A.6. Agent based model – dementia progression parameter values

A key set of parameters were the severity progression rates for the three progression types. Cognitive and functional assessments results for 1736 patients (ADNI, 2016), obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, were partitioned using a longitudinal clustering method to identify progression type membership (Genolini et al., 2015, 2013), and then mixed-effects regression was used to estimate fixed and random effects progression coefficients. These were used to parameterise individual agent-based cognitive decline.

The mathematical formulation of the mixed-effects regression model is

$$\begin{aligned} MMSE_{ij}(month) = & [\mu_{0,i} + N(0, \sigma_{0,i,j}^2)] \\ & + [\mu_{1,i} + N(0, \sigma_{1,i,j}^2)] \cdot month \\ & + \mu_{2,i} \cdot month^2 \end{aligned}$$

Where  $N(0, \sigma_{0,i,j}^2)$  and  $N(0, \sigma_{1,i,j}^2)$  are normally distributed adjustments to take account of individual variability for the  $j^{th}$  agent in the  $i^{th}$  progression-type group, to the fixed effect intercept and slope terms  $\mu_{0i}$  and  $\mu_{1i}$ , and  $j \in \{slow, intermediate, fast\}$ . A random effects term was also explored for the quadratic term, but as model fit was not significantly improved this was not included. These values are summarised in the following table.

These values are given in Table A4 showing cognitive decline as MMSE points per month, implemented with normally distributed random effects shown as  $N(\mu_1, \sigma^2)$ . Non-linear slope coefficient values are mean changes per month squared. For example, an agent simulating intermediate progression of dementia symptoms would start with a mean MMSE score of 25.2, declining on average by 10.1 MMSE points after 5 years, but with random effects of  $\sigma_0 = 1.57$  and  $\sigma_1 = 0.074$  to that agent's intercept and linear slope.

Published studies (Table A5), which report fixed effect linear slope values, show reasonable agreement with our results. For example, 0.38 MMSE points per month (for

**Table A5.** Summary of published progression rates.

Source	Slow	Intermediate	Fast
Soto 2005* Soto 2008*			≥4 pts at 1/2 year ≥5 pts at 1 year
Carcaillon 2007*			≥3 pts/year
(Doody et al., 2010)	<2 pts/year	2–5 pts/year	≥5 pts/year
Musicco*			5 pts at 2 years
(Barocco et al., 2017)		≥5 pts at 1.5 years	≥5 pts at 1 year
(Grootoank et al., 2016)	≤3 pts at 2 years	3–6 pts at 2 years	≥6 pts at 2 years

Table summarises points on the MMSE scale.

\*indicates a secondary reference cited in Sona et al. (2013).

fast progression types in Table A4) is 4.56 MMSE points per year, comparable with the fast column in Table A5.

**A.7. Agent based model – care costs and QALYs**

Monthly costs were calculated using the following equation based on a fit to the care cost references stated in Table A1. For example, a moderate severity MMSE level = 17 equates to a £3,389 monthly care cost or £40,668 per year. This compares with £2,983 per month (Wübker et al., 2015) and £39,294 per year for moderate dementia (Alzheimer’s Society, 2014).

$$Costs (\pounds) = 6568.4 - 187.85MMSE$$

To calculate QALYs, firstly health utility scores were calculated using the following equation based on the AHEAD modelling equations (Getsios et al., 2010, Equation 6) with the same simplification used by Barnett et al. (2014, p. 3), so that:

$$Utility = 0.408 + 0.01MMSE$$

Health utility was calculated monthly, so that the QALY result is the summation of health utility values over the years with dementia (YWD):

$$QALY = \sum_{YWD} Utility/12$$