ECONOMIC EVALUATION

Model-Based Economic Evaluation in Alzheimer's Disease: A Review of the Methods Available to Model Alzheimer’s Disease Progression

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A B S T R A C T

Objective: To consider the methods available to model Alzheimer’s disease (AD) progression over time to inform on the structure and development of model-based evaluations, and the future direction of modelling methods in AD. Methods: A systematic search of the health care literature was undertaken to identify methods to model disease progression in AD. Modelling methods are presented in a descriptive review. Results: The literature search identified 42 studies presenting methods or applications of methods to model AD progression over time. The review identified 10 general modelling frameworks available to empirically model the progression of AD as part of a model-based evaluation. Seven of these general models are statistical models predicting progression of AD using a measure of cognitive function. The main concerns with models are on model structure, around the limited characterization of disease progression, and on the use of a limited number of health states to capture events related to disease progression over time. None of the available models have been able to present a comprehensive model of the natural history of AD. Conclusions: Although helpful, there are serious limitations in the methods available to model progression of AD over time. Advances are needed to better model the progression of AD and the effects of the disease on peoples’ lives. Recent evidence supports the need for a multivariable approach to the modelling of AD progression, and indicates that a latent variable analytic approach to characterising AD progression is a promising avenue for advances in the statistical development of modelling methods.

Keywords: Alzheimer’s disease, cost-effectiveness analysis, health technology assessment, modelling methods.

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Introduction

Alzheimer’s disease (AD) is the most common cause of dementia. It is a chronic progressive neurodegenerative condition that represents an increasingly significant health care burden on individuals and health care systems [1]. Decision makers are faced with challenging questions about the development of health care services, and also over the funding of future research in the area of AD. These issues demand an understanding of the social and economic influence of AD on people’s lives, and an understanding of the effects of health care interventions.

Providing a greater understanding on these areas can be supported, in part, through the use of economic and statistical methods available to model the progression, influence, and costs associated with AD over time [2–4]. Modelling methods have been used for many years to improve our understanding of a large number of health conditions, and to inform decision making. For example, modelling methods have been used in a variety of ways and settings to predict the risk of future cardiovascular events, based on known patient-level characteristics [5,6].

The development of methods to model AD over time has been relatively slow, compared to similar research for conditions such as cancer, diabetes, and cardiovascular disease, even though the influence of AD and the size of the population affected by AD are very large. It seems that the advances in drug therapies for AD signalled the arrival of modelling methods to support claims for the cost-effectiveness of treatment; for example, cholinesterase inhibitors. Modelling studies have used a simplified representation of the underlying disease and symptom structure for AD, and there are limitations in the methods used to date to structure models for AD [7–9].

Given the growing impact of AD, and the ongoing development of new therapeutic strategies and interventions, it is important to consider the broader evidence base on the methods available to model AD over time. Previous reviews [7,9,10] have specifically discussed the use of decision-analytic models in AD. These are often cost-effectiveness analyses that synthesize the evidence from a number of different sources to compare alternative strategies (e.g., treatment options). This review reports on the current methods available to model disease progression in AD, specifically...
on the methods available to structure models, and the statistical methods and empirical data, upon which these decision-analytic models, often referred to as model-based evaluations [11], are based.

**Modelling methods and the place of model structure**

Determining model structure is central to the development of model-based evaluations that seek to address specific questions (e.g., Are cholinesterase inhibitors cost-effective?). Model structure should usually be determined by considering the relationship between the inputs (natural history of disease, treatment pathways, epidemiologic data, effectiveness data, health state values, and costs) and the resultant information output that is required by the decision maker (e.g., number of health events, outcomes, and summary of cost-effectiveness) [11]. Brennan et al. [11] have provided a detailed and clear taxonomy of model structures for use in model-based evaluations, as in the economic evaluation of health technologies, covering decision trees, Markov models, cohort models, individual level modelling methods, and methods covering both discrete and continuous time modelling.

The issue of model structure has been relatively neglected in the guidance published on the development of decision-analytic models, with this issue often limited to simple outline and summary information. Sculpher et al. [12] have advised that model structure should be as simple as possible, consistent with the stated decision problem, and a theory of the disease, and not defined by data availability. This is helpful advice, but may be seen as somewhat inconsistent with other elements of guidance, where it is accepted that data availability may affect development and choices around model structure [13,14].

In practice models are often developed around those data that are available to model the natural history of a disease. For example, by those analysts making submissions (manufacturers or independent assessment teams) to the UK National Institute of Health and Clinical Excellence (e.g., Loveman et al. [15]). When making choices over model structure there may be a number of practical considerations that shape how a model is developed. It is important that the choice of model structure is based on an understanding of the health care system, the available evidence, and the knowledge and judgment of the analyst on which model structures are available and appropriate in which circumstances [11]. Other practical considerations are factors such as the amount of time and level of resources available to develop a model.

Whilst there are many considerations in developing the overall structure of a model-based evaluation, Brennan et al. [11] have drawn attention to an important prior consideration in model development, whereby “the choice of [health] states and risk factors, and the identification of their relationship to each other should normally precede the choice of model structure [more generally]” [11]. For example, determining the statistical modelling of disease activity and progression. This key consideration draws attention to the stages of model development, and it is a particularly important consideration where models need to be developed relatively quickly using secondary evidence. Cohen and Neumann [9] captured this important prior consideration in their review of AD models, through the distinction they make between empirical and/or mechanistic models versus decision-analytic models [9]. They define empirical and mechanistic models, as a form of pre-model analyses, with these models being used to describe relationships between predictive factors and outcomes, for example statistical models using regression equations derived from observational or clinical epidemiologic studies [9]. These references to empirical and mechanistic components of model structure (i.e., statistical relationships) highlight important and distinct stages of model development, with the prior considerations on model structure (referred to by Brennan et al. [11]) being distinct from the broader specification of the structure and framework for model-based evaluations.

**Methods**

**Literature search**

A systematic search of the health care literature was undertaken to identify methods to model disease progression in AD. The search strategy (Appendix 1 found at doi:10.1016/j.jval.2010.12.008) was developed with input from an Information Specialist. Electronic databases were searched, applying the search strategy to MEDLINE and EMBASE, with search terms then adapted as necessary for searches in the Cochrane Library, PsychINFO, HTA Database, NHS EED, CEA Registry, and EconLit database. The search was limited to studies published in English, covering literature up to March 2010. References identified were reviewed by two authors (CG and JS) to identify relevant articles.

Studies were included if they reported on the use of a model to consider the progression of AD over time. These included statistical models, for example, those that developed predictive risk equations based on observational or epidemiologic data, and decision-analytic models that had been used to address specific questions or to model costs and/or consequences over time. Economic evaluations conducted alongside clinical trials were excluded unless they also modelled aspects of AD progression over time. Resulting reference lists and citations in retrieved articles were further checked to ensure that no eligible studies had been missed. Existing reviews [7,9,10] were also examined to identify relevant studies. The identified modelling studies are summarized, the approaches available to model disease progression over time are discussed in a summary descriptive review, and the review points to recommendations for the future direction of modelling of AD.

**Results**

The literature search identified 42 studies presenting methods, or applications of methods, used to model AD progression over time (summary characteristics of the identified studies are presented in Appendix 2 found at doi:10.1016/j.jval.2010.12.008). Most studies used Markov models (n = 27 out of 42) and a cohort modelling framework (n = 29 out of 42) to characterize disease progression. The majority of the identified studies (n = 25 out of 42) used measures of cognition (cognitive scores) alone to model AD progression. The review identified 10 modelling approaches that are considered to be general modelling frameworks (Table 1), either being
<table>
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<th>Model (label, reference)</th>
<th>Health outcomes/events</th>
<th>Analytical/statistical approach</th>
<th>Risk factors, determinants of disease progression</th>
<th>Baseline data source(s)</th>
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<td>Hauber et al. [52] Hauber et al. [53]</td>
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<td>CERAD-MMSE model &amp; Mendiondo et al., 2000 [29]</td>
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<td>AHEAD model &amp; Caro et al., 2001 [31]</td>
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<td>Getsios et al. [34] Green et al. [35] Caro et al. [36] Ward et al. [37] Migliaccio et al. [38] Garfield et al. [39] Caro et al. [40] Getsios et al. [33] (continued on next page)</td>
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<td>Dutch prospective longitudinal study to examine chronic disease, disability in the elderly (Rotterdam Study) recruited 1990-1993 (mean follow-up 3.4 y). Baseline AD diagnosis n = 306 New (incident) AD diagnoses n = 95</td>
<td>Mean age 84.9 AD Severity at first interview after onset: minimal 0.173/0.242; mild 0.399/0.60; moderate 0.314/0.147; severe 0.114/0.011.</td>
<td>N/A</td>
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<td>Kinosian model</td>
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<td>US National Long Term Care Survey, sample of US Medicaid beneficiaries recruited 1984-1994. n = 3254</td>
<td>69% age &gt; 75 y Suspected AD Severity not stated</td>
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<td>CERAD-SIB model</td>
<td>Time in disease (severity) stages defined by SIB (SIB mapped to MMSE, CDR). Nursing home placement conditional on cognitive functioning.</td>
<td>Regression analysis was used to predict monthly change in SIB score based on current SIB score.</td>
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<td>US validation study of SIB in moderate-severe AD (Schmitt et al. [58]) followed up semiannually for 1 year. n = 180</td>
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<td>N/A</td>
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<td>Memantine model</td>
<td>Time to dependency, institutionalisation and death</td>
<td>Markov model with transit probabilities for disease severity estimated from the placebo group in a clinical trial and from observational data. Transit probabilities for dependency, mortality and care setting based on observational data.</td>
<td>Cognitive functioning (MMSE), dependency (conditional on MMSE/severity), care setting (conditional on MMSE/severity).</td>
<td>Subset of a UK observational study of a qualitative classification of AD patients by dependency (LASER-AD). (Livingston et al. [43]) followed up for 6 mo. n = 95 Subset of placebo arm of RCT (Reisberg et al. [42]) followed for 28 wks. n = 103</td>
<td>Age not stated AD severity, moderate-severe 0.31; severe 0.69. Mean age 76 AD severity, moderate-severe 0.41; severe 0.59.</td>
<td>Gagnon et al. [44] Antonanzas et al. [45] Jönsson et al. [46] François et al. [47]</td>
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<td>Predictors ADAS-cog model</td>
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<td>Multiple regression analysis of the relationship between the annual rate of change and baseline ADAS-cog score.</td>
<td>Cognitive functioning (ADAS-Cog)</td>
<td>US prospective longitudinal study to examine AD progression (RG Stern et al. [59]) followed for mean 35 mo N = 111</td>
<td>Mean age 68.2 AD severity distribution not stated (mean score 35.1 ± 3.8).</td>
<td>Wattmo et al. [61] Fagnani et al. [62]</td>
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</table>

RCT, randomized controlled trial; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; EPS, Extrapyridonald symptoms; SIB, Severe Impairment Battery; ADAS-Cog, Alzheimer’s Disease Assessment Scale Cognitive Subscale; SPMQS, Short Portable Mental Status Questionnaire; N/A, Not applicable.
modelling frameworks applied in a number of different settings, often with some context-specific amendments, or studies that are not specific to a particular policy question (e.g., not about effectiveness or cost-effectiveness of an intervention), but could be applied in such a way. Thirty-eight of the 42 studies identified are based on these 10 general models of AD progression. These general models each present a different method to model the statistical relationship between risk factors and health states (outcomes). Table 1 presents the summary characteristics of these general models showing the majority of models based on regression analyses, with predictive risk equations derived from observational data on AD.

Summary description of general (or generalizable), approaches to the modelling of AD progression

The McDonnell model
McDonnell et al. [16] modelled AD progression using regression-based statistical methods applied to patient-level data on cognitive function (Mini Mental State Examination [MMSE] scores), care setting, and mortality. The model predicts baseline MMSE and subsequent change in MMSE score over time, using a random-effects linear regression model, with covariates for age, sex, education, and time. It is a model of MMSE progression over time, with stages of the modelling specific to both earlier and later stages of AD. The model was derived from data on a cohort of 306 prevalent and 95 incident AD patients, identified in a prospective Dutch observational study of chronic illness and disability in the elderly, with 3-year follow-up (1990–1993). The model predicted a decline of 1.71 points in MMSE at 6-month intervals for incident cases of AD, and a 0.91 point 6-month decline in prevalent cases of AD. The findings from this linear MMSE model present different rates of progression based on MMSE values declined in a non-linear fashion, and a quadratic relationship between risk factors and health states (outcomes). Those authors used a statistical modelling framework, similar to techniques of factor analysis and latent class analysis, referred to as a grade of membership technique, to explore patient-level data on cognitive impairment, and activities of daily living at baseline with data on prediction of survival, time spent in an institution, time spent with a high degree of dependence (BADL ≥ 2), total costs and hours of care, for each profile (AD health state) or broad set of patients.

The Kinosian model
Kinosian et al. [17] modelled AD progression over time using regression-based methods and latent structure modelling, to explore the relationship between multiple health indicators, and unobservable constructs of health such as AD progression. Those authors used a statistical modelling framework, similar to techniques of factor analysis and latent class analysis, referred to as a grade of membership technique, to explore patient-level data drawn from 3254 elderly (aged 65 years and older) Medicare patients in a US National Long Term Care Survey, recruited and followed between 1982 and 1994. The statistical modelling was used to estimate the care requirements in elderly people with possible AD, and to estimate costs associated with AD over the longer term (using a 10-year time horizon). Modelling identified health states (that could be used in a decision-analytic modelling framework) through simultaneously evaluating multiple variables in the data. The health states reflect profiles of AD, across six areas, with four of these based on symptoms of AD (cognitive impairment, basic activities of daily living [BADL], instrumental activities of daily living [IADL], behavior), and two contextual (whether or not living in institutional care and level of health care costs). Health states (profiles) were used, with empirical data, to allocate patients across the disease health states, to model the proportion of people with AD spread across the health states over time, and the subsequent transitions between health states over time. In this way the statistical methods provided a basis for estimating the nature of AD progression and subsequent costs. The data published by Kinosian et al. [17] provides a matrix that categorizes AD by age, sex, cognitive impairment, and activities of daily living at baseline with data on prediction of survival, time spent in an institution, time spent with a high degree of dependence (BADL ≥ 2), total costs and hours of care, for each profile (AD health state) or broad set of patients.

The Consortium to Establish a Registry in Alzheimer’s Disease-Clinical Dementia Rating (CERAD-CDR) model
Neumann et al. [18] modelled AD over time using a state transition Markov model (we refer to the CERAD-CDR model) to characterize AD progression through stages of disease severity (cognitive function) and residential settings. In summary, the CERAD-CDR model was based on annual transition probabilities, derived from the CERAD database. The CERAD database included 1145 people with AD, followed up to 8 years, with AD (severity) categorized as mild, moderate, or severe AD, based on the CDR scale, a global measure of patient functioning. Although the CDR could be described as an aggregate indicator reflecting both cognitive and functional performance, across six domains, the rating of each domain is based exclusively on cognitive ability [19]. Therefore, the CERAD-CDR model essentially relies on cognitive functioning to characterize AD progression. A survival analysis approach was used to derive transition probabilities between different stages of AD severity (mild, moderate, and severe), for transition to a nursing home setting and for the probability of death. The transition probabilities derived from the CERAD data covered staging of AD severity independent of residential setting, but the probabilities for residential setting (community or nursing home), and death were conditional on disease severity, with higher probabilities as disease severity progressed. The CERAD-CDR model transit probabilities are derived to adjust for age, sex, the presence of high or low levels of behavioral symptoms, and time spent in disease stage. The CERAD approach has been one of the most widely used of all the models and has been used to examine the effects of medications [18,20–24], behavioral interventions [25], and screening technologies [26–28] on disease progression in AD.

The CERAD-MMSE model
Mendiondo et al. [29] also used the CERAD database to present an alternative approach for the modelling of AD progression over time. These authors present a mathematical representation of decline in MMSE over time, providing a rate of change in MMSE points per year, with decline dependent on average MMSE score between the time intervals examined. Analyses and modelling are based on MMSE scores from 719 people followed between 6 months and 7 years (mean follow-up 2 years). In the modelling, MMSE values declined in a non-linear fashion, and a quadratic equation was applied to estimate the time to progress from one MMSE score to a lower MMSE score. Using regression analysis, age was found to be a significant factor (with younger patients progressing more rapidly), education was a marginally significant factor and sex was not significant in declines in MMSE. Floor and ceiling effects were noted, which might limit the sensitivity of the MMSE-based model to changes in early and late stage disease. The methods developed by Mendiondo have been applied in an evaluation by Small et al. [30].

The Assessment of Health Economics in Alzheimer’s Disease (AHEAD) model
Caro et al. [31] present a model of AD progression, the AHEAD model, which has been widely used (at times in an adapted form) in cost-effectiveness analyses. The model has been presented in
abilities are derived from the same clinical trial for more severe
tion probabilities were based on disease severity (MMSE) at the
bility for dependency and the probability for care setting. Transi-
ting the respective transition probability for severity by the proba-
states calculated in a multiplicative manner; that is, by multiply-
states are estimated using a domain specific framework (i.e., by
tivariate way, but transition probabilities between the health
setting (institution or community). The model uses transition
model is a Markov model with 13 health states (including death)
tine, a neuroprotective agent/drug that aims to preserve func-
tion, was developed to assess the cost effectiveness of meman-
ty equation for requiring nursing home placement (Caro et al. [31] refer to
FTC and death are presented as a function of patient characteris-
tics, using Cox proportional hazard models. Thereafter, Caro et al. [31] introduce the element of time-dependency to present risk
equations with time as a continuous variable. The original analys-
es presented by Stern et al. [32] are based on data from a prospec-
tive US cohort study of 236 patients (probable AD and mild demen-
tia at the first assessment) followed semiannually for up to 7 years.

The AHEAD model has been used in numerous decision ана-
lytic models, structured as Markov models using health states for
pre-FTC, FTC, and death [31,33–40], with the AHEAD risk equa-
tions, either one or both, being used to model disease progression
between these three health states over time (often over 5–10 years)
in comparisons between different cohorts of participants.

The memantine model
Jones et al. [41] modelled disease progression in moderately severe
to severe AD. The model, referred to here as the memantine model,
was developed to assess the cost effectiveness of memantine,
a neuroprotective agent/drug that aims to preserve func-
tional ability in more severely affected patients. The memantine
model is a Markov model with 13 health states (including death)
defined using severity level (moderate [MMSE score > 14], moder-
ately severe [MMSE score 10–14], and severe [MMSE score <10]),
physical dependency level (independent or dependent), and care
setting (institution or community). The model uses transition probabilities between health states, applying a 6-month model
cycle over a 2-year time frame, and it is used to estimate time to
dependency, and time to institutionalization.

Health states in the memantine model are described in a mul-
tivariate way, but transition probabilities between the health
states are estimated using a domain specific framework (i.e., by
severity, dependency, and care setting), with transitions between
states calculated in a multiplicative manner; that is, by multiply-
ing the respective transition probability for severity by the proba-
bility for dependency and the probability for care setting. Transi-
tion probabilities were based on disease severity (MMSE) at the
beginning of each model cycle, with subsequent transitions for
dependency and care setting being secondary to disease severity.
The transition probabilities for AD severity are derived from pla-
cebo group data in a clinical trial [42]. Dependency transition prob-
abilities are derived from the same clinical trial for more severe
disease stages, and from a UK epidemiologic study [43] for moder-
date disease stages. Probabilities for care setting were based on data
from both the UK cohort study [43] and a resource use study con-
ducted alongside the randomized controlled trial [42]. When in an
institutional care setting people remain in that setting. Mortality
probabilities, as a function of disease severity using the MMSE,
taken from the cohort study.

Jones et al. [41] applied this baseline model of AD progression to
evaluate the effects of memantine compared to placebo (controls),
adjusting transition probabilities in the memantine-treated co-
hort using randomized controlled trial data [42]. There have been
other applications of the memantine model [41,44–47] and its ap-
lication in cost-effectiveness analyses is discussed in some detail by Kirby et al. [48].

The Fenn and Gray model
Fenn and Gray [49] modelled AD progression using statistical
methods (survival analysis techniques) to estimate the time to
event data for changes in cognitive scores (MMSE), and to predict
the subsequent time taken for people to move from one level of AD
severity to the next, with severity based on cognitive functioning
(MMSE). The model used three health states defined using MMSE
scores: mild (21–30), moderate (11–20), and severe (≤10). The
model estimated the time (measured in days) patients are likely to
remain at their current disease stage, depending on their age and
baseline MMSE score. Mortality was not considered in the model.
Analysis was based on patient-level data from two 26-week clini-
cal trials of rivastigmine [50,51], and hazard functions were de-
ferred for movement between MMSE-defined health states. These
hazard functions were used in a Markov-type model to estimate
the progression of AD over time, and subsequent costs and out-
comes, in people treated with a cholinesterase inhibitor (rivastig-
mime) compared to those treated with placebo [49]. Differences are
estimated through the use of separate survival analyses and haz-
ard functions, based on different profiles of cognitive function (in-
formed by trial findings). There have been two other applications of the Fenn and Gray methodology [52,53].

The Kungsholmen-MMSE model
Jönsson et al. [54] modelled AD progression through estimation of
transition probabilities between four AD health states defined us-
ing cognitive (MMSE) scores (mild 30–24, mild-moderate 23–18,
moderate 17–10, and severe 9–0), plus risk of death in each of
these health states. Progression (transition probabilities) was es-
ited based on analysis of epidemiologic data on 206 partici-
pants drawn from a Swedish cohort in a prospective longitudinal
study, the Kungsholmen Project, a study of disease costs in el-
derly patients aged 75 years or older. In this subset from the
study cohort the average time between baseline and the follow-
up assessment was 3.32 ± 0.59 years). The 1-year transition probabilities between AD severity (stage-stage) and death were
calculated based on the average time between baseline and the
follow-up assessment, and reflect an assumed constant linear
relationship. The Kungsholmen-MMSE model (health states and
transition probabilities) has been applied in three published evalu-
ations [55,56,69].

The CERAD-Severe Impairment Battery (CERAD-SIB) model
Weycker et al. [57] modelled AD progression, in moderate-to-se-
vere AD (MMSE), using a statistical model to predict change in cognitive
function over time, using the SIB. The predicted level of cognitive function (SIB) was used, with data from the CERAD model [18], to
detect the risk of nursing home placement over time. In this way,
applying a two-stage approach, the model presented by Weycker et al. [57] estimates the monthly risk of nursing home placement,
conditional on predicted SIB scores. These authors argue that the
SIB was more sensitive to changes in cognitive functioning in peo-
ple with more severe AD because it permits more impaired pa-
tients to use nonverbal responses such as gestures or pointing to
answer questions. The statistical model, predicting change in SIB,
was based on data drawn from a US validation study of the SIB in
180 moderate-severe (MMSE score < 21) AD patients followed over
12 months [58]. SIB scores were mapped to MMSE or CDR severity
The Predictors Alzheimer’s Disease Assessment Scale-Cognitive Function (ADAS-cog) model

Stern et al. [59] modelled AD progression, using a mathematical model to predict changes in cognitive function (ADAS-cog score) over time. The approach, similar to that taken by Mendiondo et al. [29], found a quadratic (nonlinear) relationship between ADAS-cog and AD severity, finding deterioration of cognitive function slower in the mild and very severe stages of AD, compared to people with moderate AD. Statistical analyses were based on data from a subset of participants in an early prospective study of the natural history of AD [60], with Stern et al. [59] using a cohort of 111 patients selected where data were available on repeated observations of cognitive performance (ADAS-cog) and at least two assessments at an interval of at least 12 months. Data used had a mean follow-up of 35 months (range 12–90 months), with analyses relying solely on cognitive function as a measure/predictor of AD progression. The methods developed by Stern et al. [59] have been applied in AD progression models presented by Wattmo et al. [61] and Fagnani et al. [62].

Summary review of general approaches to the modelling of AD progression

In the empirical and mechanistic modelling methods described here, various mathematical approaches (e.g., transition probabilities, hazard ratios, and regression equations and coefficients) were used to model the progression of AD over time, across health states and events such as death and institutionalization. A range of endpoints and outcomes, and related economic effects, were considered in the ten models described here. Eight models used changes in disease severity, measured as transitions between disease severity stages (i.e., memantine model [41], Fenn and Gray model [49], CERAD-CDR model [18], Kungsholmen-MMSE model [54], and CERAD-SIB model [57]) or as changes in cognitive scale scores (i.e., Predictors ADAS-cog model [59], CERAD-MMSE model [29], and McDonnell model [16]), with all of these eight models defining disease severity in terms of cognitive function. Five of the 10 models included placement in an institution, such as a nursing home or home for the elderly as an endpoint (CERAD-CDR model [18], McDonnell model [16], Kinosian model [17], CERAD-SIB model [57], and memantine model [41]), although this has only been modelled independently of cognitive function in two of these models (Kinosian model [17] and McDonnell model [16]). Three models considered dependency or the need for full-time care, independent of care setting, as an element of the disease progression model (AHEAD model [31], Kinosian model [17], and memantine model [41]), in one case being the only outcome of interest (AHEAD model [31]).

Six of the 10 models used relatively small data sets, between 111 and 306 participants, to undertake the statistical modelling used to inform disease progression (Predictors-ADAS-cog model [59], CERAD-SIB model [57], Kungsholmen-MMSE model [54], AHEAD model [31], memantine model [41], and McDonnell model [16]). Follow-up duration in the data used for statistical analyses have also been variable across the modelling methods described, with three of the 10 models using data from clinical studies with a follow-up duration of only 26 weeks to 52 weeks (Fenn and Gray model [49], memantine model [41], and CERAD-SIB model [57]). Furthermore, in the remaining models, where follow-up data were collected between 3 and 10 years, there was a high level of attrition in the data, particularly beyond 3 years, which although reflecting the nature of the condition also affects on the robustness of the data. Another important feature, in the assessment of the statistical robustness of the models, is that generalizability of the findings from some of the statistical methods is limited due to the characteristics of the participant data used for analyses. For example, in two models (McDonnell model [16] and Kungsholmen-MMSE model [54]) there are limitations in the generalizability of data to an AD treatment-eligible population, with these studies relying on data from participants with high levels of baseline disease severity, high rates of residential care, a mean age older than age 85 years, and with mortality rates being particularly high (between 66% and 76%, over 3 years).

In only two of the models, the CERAD-CDR model [18] and the CERAD-MMSE model [29], are analyses based on a relatively large sample size with follow-up over a reasonable duration. In both of these models a further strength is the quality of the standardized clinical assessment methods that were used in the CERAD study (cohort). On the other hand, both of these models describe disease progression based on cognitive function alone.

Seven of the 10 general models described here are statistical models of cognitive function over time, reporting findings from regression-based analyses of datasets for cognitive scores reported using a range of measurement scales (e.g., MMSE, ADAS-cog, CDR, and SIB). This approach does not reflect a coherent theory of the natural history of AD, and introduces limitations in the modelling methods. It is increasingly accepted that cognition is not a good predictor of disease progression in AD, and that reliance on cognition ignores the independent effect of functioning and behavior on health care needs and costs [63–66]. Although some models have attempted to incorporate variables other than cognition when modelling disease progression (i.e., AHEAD model [31], memantine model [41], and Kinosian model [17]), none of the available models have been able to capture/present a comprehensive model of the natural history of AD, given the importance of functional ability, and behavior and mood, on the characterization of AD progression.

Discussion

The evidence base available to analysts and decision makers wishing to carry out evidence syntheses through development of models is largely restricted to the 10 general models introduced here. These general (statistical) models represent the opportunities available to structure model-based evaluations, providing an empirical and mechanistic framework to relate risk factors to health states and outcomes that are policy relevant and relevant to people with AD. When weighing up the merits of each of the approaches available, judgments are needed on the rigor and appropriateness of the alternative modelling methods, for specific applications and evaluations.

Published guidance on good practice in decision-analytic modelling is helpful in the assessment of modelling methods for specific evaluations [13,14], drawing attention to key considerations. The current methods available for modelling AD progression offer useful insights, but all have limitations. The main concerns, raised in previous reviews [7,9], are on model structure, around the limited characterization of disease progression through use of a narrow description of the natural history of AD, and on the use of a limited number of health states to capture events related to disease progression over time. A more general concern is against the evidence available [13,14].
It is inevitable that there will be trade-offs between the opportunity to develop a model that will be helpful in informing a decision and the characteristics of the model (e.g., model structure, data inputs, and level of uncertainty and consistency). However, previous reviews have not drawn specific attention to the empirical and mechanistic elements of model structure, as presented in this review. On these, specific consideration is required to assess the robustness and generalizability of the statistical relationships informing on disease progression, linking risk factors to events and/or health outcomes. This area of assessment has been characterized as ‘prior data modelling’ or ‘pre-model analyses’, in the methodologic guidance on modelling methods [13,14], and assessment of models in this area is important.

Although a detailed critical review of modelling methods is not presented here, this summary review highlights the need for analysts, reviewers, and decision makers to be aware of the trade-offs between considerations relevant for determining the structure of a decision-analytic model, and the importance of the statistical analyses upon which decision-analytic models are based. These trade-offs and considerations around model structure, as well as those more relevant to the broader requirements of model-based evaluations, will often be context specific (to the decision-making perspective and evaluation setting), and the use of published guidance on good practice for decision-analytic modelling [13,14], by both analysts and others, is recommended to inform debate when weighing up the value of a model and the potential relevance of its findings.

Advances need to be made in the methods available to model disease progression in AD [7,9], yet there are challenges for those wishing to provide robust methods to model the progression of AD. Clinical trials in AD have not provided long-term outcome data relevant to the modelling of disease progression, and relevant to economic evaluations. Epidemiologic research in AD has not placed a focus on modelling disease progression to inform health policy. There are challenges in using short-term clinical trial outcomes—such as changes in cognition, neuropsychiatric symptoms, or activities of daily living—often assessed in trials using a range of different instruments, to predict longer-term outcomes such as the need for FTC, time to institutionalization, mortality, onset of severe AD, and quality-adjusted life-years.

Although the current modelling methods do provide some assistance to those wishing to develop a better understanding of AD, and on the effectiveness and cost-effectiveness of treatments, it will be important in future years to develop new methods that take a less narrow view of AD, the effects of AD on peoples’ lives, and the influence of health technologies on the experience of AD. Recent contributions to the AD literature, exploring the underlying symptom structure for AD, have provided both support for the view that cognitive function (cognitive scores) alone is not a good way to model AD progression, and insights on a more comprehensive approach to the modelling of AD progression [67,68].

Tractenberg et al. [67] modelled the underlying structure of symptoms in AD using data on mild-to-moderate AD from two randomized controlled trials. They used latent variable analyses to explore the relationships between multiple types of health indicators and unobservable variables or construct that drive deterioration in AD. The analyses are based around the three main symptom domains of AD, covering cognition, function, and behavior, and findings support the proposition that a single symptom model (e.g., cognition alone) is a poor conceptualization of AD. Furthermore, analyses suggest that although an intervention may improve cognitive scores it can do so without altering the underlying disease process. Tractenberg et al. [67] present a more comprehensive conceptualized model of AD progression than seen to date, using the three symptom domains of cognition, behavior, and functioning as causal factors (referring to numerous methods for the potential measurement of each of these), and also referring to the role of a general neurological latent variable (representing for example synapse loss). The results are preliminary analyses based on a relatively small cross-section of AD patients enrolled in clinical trials, and they need to be extended to longitudinal data before the findings can more clearly inform on modelling of AD progression over time. The findings, however, point to potential future developments and to a more comprehensive approach to modelling AD progression.

With the use of patient-level longitudinal data, the type of statistical model suggested by Tractenberg et al. [67] may be able to distinguish underlying disease progression from the symptom structure of AD. To be practical any future developments would need to be set out against a set of health states (outcomes), with policy relevance, and would need to estimate path weights (or model coefficients) as a means of predicting transition between health states over time. It is possible to hypothesize on a potential modelling framework, constrained (in the first instance) to consideration of the symptom structure of AD, and with potential constraints on the number of possible health states (to present as feasible and practicable). Figure 1 presents such a scenario, and future statistical advances using longitudinal data on AD could present a means of populating such a model with appropriate data. The suggested model is not set out as the ideal, just a means of improving on the methods currently available to model AD over time, and to act as a spur for further debate.

Fig. 1 – Schematic/structure for proposed modelling structure for Alzheimer’s disease progression. Note: Health states using three symptom domains, each at up to three levels (state i to n; max 27 states); statistical methods needed to predict probabilities of movement between health states; and death as part of the model, but may be informed by secondary/epidemiologic data.

Conclusions

This review draws attention to the modelling methods available to empirically model the progression of AD, as a prior consideration when developing the structure of a model-based evaluation. The evidence base is sparse and undeveloped, and over recent years there have not been major advances in the modelling methods currently available. Although helpful, there are serious limitations in the currently available modelling methods. It is widely acknowledged that a single symptom, such as cognition, is not able to characterize AD progression, and that AD is heterogeneous in presentation and disease course; for example, across the main
symptoms domains of cognition, function, and behavior. Advances are needed to better model the progression of AD, and its affects on peoples’ lives. The recent evidence suggests that future modelling initiatives should incorporate a multivariable approach, and that a latent variable analytic approach to characterizing AD progression is a promising avenue for advances in the statistical development of modelling methods. The challenge is to apply these statistical techniques with longitudinal data, and to transfer findings into a relatively simple policy-relevant model that can be employed to inform on the pragmatic concerns of both clinical and health policy decision makers.

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Supplemental Materials

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