**Title:**

Current issues and future research priorities for health economic modelling across the full continuum of Alzheimer's disease

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**Declaration of interest:**

AG and SL are employees of Quantify Research and provide consultancy services to pharmaceutical companies and other private and public organisations and institutions. DS & FdRdV are employees of Novartis Pharma AG, Basel, Switzerland. NA is a paid employee of Novartis Pharmaceuticals UK Ltd, Camberley, UK. SB is an employee of Novartis Healthcare Private Limited, India. CG has received honoraria from numerous manufacturers of AD treatments for input to methodological advisory meetings/boards, unrelated to the current manuscript. AG, CG, RwJ, HF and AW were remunerated for their work on this manuscript.

**Funding source:**

This research was funded by Novartis Pharma AG.

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**IMRAD abstract**

INTRODUCTION: Available data and models for the health-economic evaluation of treatment in Alzheimer's disease (AD) have limitations causing uncertainty to decision makers. Forthcoming treatment strategies in pre-clinical or early AD warrant an update on the challenges associated with their economic evaluation.

METHODS: The perspectives of the co-authors were complemented with a targeted review of literature discussing methodological issues and data gaps in AD health-economic modelling.

RESULTS: The methods and data available to translate treatment efficacy in early disease into long-term outcomes of relevance to policy-makers and payers are limited. Current long-term large-scale data accurately representing the continuous, multi-faceted and heterogeneous disease process are missing. The potential impact of disease-modifying treatment on key long-term outcomes such as institutionalisation and death is uncertain but may have great impact on cost-effectiveness.

DISCUSSION: Future research should give priority to collaborative efforts to access better data on the natural progression of AD and its association with key long-term outcomes.

**Key words:**

Alzheimer's disease, Dementia, pre-clinical, disease modification, economic evaluation, modelling, disease progression, health-care decision-making, outcomes, cost-effectiveness

## 1. Introduction

Dementia and its most common cause, Alzheimer's disease (AD) accounting for an estimated 60-80 percent of cases [1], present one of the largest global challenges in health care today. Worldwide, 47 million people are estimated to have dementia with costs estimated at 818 billion USD in 2015 [2]. These numbers and costs are expected to increase dramatically over the coming decades and new therapies are therefore urgently needed [2]. Drug development for AD over the last decade has been a disappointment. Only five drugs have been approved for the symptomatic treatment of AD (tacrine, donepezil, rivastigmine, galantamine and memantine) and the magnitude of their effectiveness is generally considered to be modest although debated [3]. No new therapy has been approved since 2003, and a recent review identified more than 200 compounds failing in clinical development (phases 1 through 3) since then [4].

Yet, the pipeline for new AD drug treatments remains active and is today focused on treatments that may prevent, stop or slow down disease progression, so called disease-modifying treatments (DMT). In parallel, there is a shift towards investigating treatment of subjects in earlier stages of the disease, e.g. the A4 [5], TOMMORROW [6] and API [7] trials. The study subjects in these trials may either be cognitively normal individuals at risk for AD (often with genetic risk factors), or subjects in pre-dementia stages of AD. The pre-dementia stages include mild cognitive impairment (MCI) due to AD (also referred to as prodromal AD), and preclinical AD (i.e. subjects with pathologic evidence of AD but without the clinical phenotype of AD) [8].

Licensing/regulatory approval of future DMTs will not automatically translate into patient access with their availability depending on their incremental value from a health policy and payer perspective. Policy makers and payers will require evidence on how the clinical outcomes assessed in trial (e.g. cognitive function and conversion to dementia) translate across outcomes of greater relevance to patients, care providers and society as a whole (e.g. quality of life, independence, mortality and costs). Clinical trials are generally underpowered and too short to assess such outcomes [9], to which

end health economic models combining trial data with real world evidence are useful [10]. With the advancement of treatment in earlier stages of disease, including pre-dementia and at risk populations, such models and modelling methodologies will be even more important because benefits are primarily expected to accrue in the long-term, beyond the timeline of a clinical trial.

The available health economic models, and data they are commonly based on, have important limitations causing uncertainty in both the model outcomes and the conclusions drawn from model simulations [3, 11, 12]. Here we identify and discuss the key issues in health economic modelling in AD with a particular focus on modelling the full continuum of the disease (from at risk populations through to late stage dementia) and on setting out some suggestions for future research priorities.

## 2. Methods

This paper is mainly based on the co-authors perspectives of this topic. However, to complement and update our understanding and to reduce the risk of us missing important issues, a short review of the published literature was performed. This was not a comprehensive systematic review and there may therefore be issues and opinions that others find important that we have not considered in this paper.

We identified systematic review papers published in peer-reviewed scientific journals and health technology assessment reports and reviewed these to identify commonly discussed methodological issues and data gaps in AD health economic modelling. Bibliographic databases PubMed, EMBASE and Cochrane library were searched using combinations of the following search terms including relevant permutations: Alzheimer, dementia, modelling, cost-effectiveness, cost-utility and economic evaluation. An additional search was performed in local databases on health technology assessments as identified through http://vortal.htai.org/. The search was performed in June 2015 and included publications published between January 2003 and May 2015.

Publications were included if they presented a review or discussion on methods or data in relation to the modelling of Alzheimer disease progression, or methods on the economic evaluation or cost-effectiveness analysis of any intervention type (e.g. pharmacological, psychosocial support, service delivery) in the diagnosis and/or treatment of AD and/or dementia. Publications only reporting individual outcomes (e.g. costs, utilities and caregiver burden) in a population without putting them into the context of a decision-analytic model were excluded. Commentaries, letters and non-English publications were also excluded. The identification of relevant articles was conducted by SL and uncertain cases were discussed with AG.

Figure 1 summarizes the review results. The search identified 14 relevant review papers [3, 12-24] and 5 HTA reports [25-29]. Two additional review papers [11, 30] were added after review of citations. A total of 21 publications form the basis of this analysis.

<Insert Figure 1 here>

AG reviewed all identified articles and summarized issues and data gaps discussed in these. The material was shared and discussed with all co-authors which jointly and in consensus selected those they considered most important and categorized them into five key issues, each described under a separate heading in the following results section.

## 3. Results - key issues identified in systematic review papers

### 3.1. Currently available models oversimplify the natural progression of AD

The disease models underpinning the economic evaluation of symptomatic treatments in AD have generally been thought to oversimplify the natural progression of the disease [3]. Many models rely on single domains such as cognition, without consideration of other relevant symptoms including functional ability and behaviour/mood. Models that include a broader range of symptoms have commonly not considered or described their interdependence adequately [12]. Models often simplify the representation of the disease process by stratifying patients into a small number of discrete health states (e.g. mild, moderate and severe dementia) with arbitrary cut-offs of limited relevance to patients [11]. Some models only consider the event of institutionalisation or the related construct "need for full time care" in their representation of the disease process [11]. These simplifications may, depending on the context of the economic evaluation, neglect the impact of the continuous and heterogeneous progression of the disease.

### 3.2. Many influential models are based on small or outdated data sets

The available models have been limited by the lack of natural progression data, and many of the most influential models, at a policy level, are based either on very small or outdated samples. For instance, the most recent technology appraisal of cholinesterase inhibitors and memantine conducted by the National Institute for Health and Care Excellence (NICE) in the UK was mainly

informed by a decision analytic model based on a UK sample of 92 subjects [3]. A larger sample of over 700 subjects was used for the donepezil industry submission for this appraisal but these data originated from the 1980s [31]. Recent evidence of a decline in age-specific incidence and prevalence of dementia [32], at least in developed countries, suggests that the natural progression of AD may be different today compared to 30 years ago. More recent data are therefore needed for models, and preferably on large and diverse samples of subjects, which are expected to better represent the heterogeneity of the disease (e.g. with regard to ethnicity/race, age, income, education, genetic profile, pathologic evidence etc.).

### 3.3. Long-term cost-effectiveness is uncertain when extrapolating from short-term clinical trial data

Evidence of the cost-effectiveness of currently marketed AD drugs has been criticized due to the use of prediction models with their inherent uncertainty [17]. While this may be inevitable given the potential long-term benefits of treatment, there is often a lack of supporting evidence even for central model assumptions [22]. For example, in several analyses the cost-effectiveness of the drugs has relied on outcomes such as reduced institutionalization/full-time care rates [33] or delay to onset of severe disease states [34] although no direct effects on such outcomes have been shown in clinical trials. Instead, these effects have been modelled via intermediate outcomes given some critical assumptions on their relationship with the outcomes of interest [26]. Nevertheless, the effect on institutionalization appears difficult to validate as shown in the AD2000 study [35, 36]. Differences in the availability of institutions across countries further increases the complexity of this outcome, as the relationship between dementia symptoms and institutionalization therefore likely varies across countries and contexts.

Another central assumption when extrapolating from trial data is the duration of treatment effectiveness including the potential “waning” of treatment effects or residual effectiveness (i.e. whether treated patients follow an altered disease trajectory or if they converge with controls) after

end of follow-up and after treatment discontinuation. One approach is to assume a parallel disease trajectory of treated patients and controls after end of trial, until the event of treatment discontinuation where after patients are assumed to converge to the trajectory of controls [37]. Others have assumed a parallel trajectory irrespective of whether patients discontinue on treatment or not, with reference to lack of convincing data on either alternative [3]. Future, emerging evidence of a truly disease modifying effect may support assumptions of residual effectiveness. Specific designs have been proposed to help identify such effects in clinical trials, including staggered start and delayed withdrawal [38].

### 3.4. Uncertain mortality effects of treatment may have large impact on long-term cost-effectiveness

The potential effect of a treatment on mortality shares some challenges with the effect on institutionalisation; they are both important long-term outcomes that are difficult to assess in a clinical trial. Economic evaluations of symptomatic drugs have generally assumed no treatment effect on mortality, e.g. evaluations by NICE [22]. This assumption is supported by the lack of evidence of such an effect from relatively short term clinical trials (although some studies show a long-term mortality effect [39-41], and also consistent with the assertion that the symptomatic therapies have no impact on the underlying disease process [30]. Conversely, because epidemiological data indicate that dementia shortens life [42], with evidence growing of increasing mortality rates as the disease progresses to more severe states, DMTs – when modelled over time - are expected to increase survival i.e. reduce exposures to increased risk of death, although to what extent is highly uncertain. It may not be feasible to detect a potential mortality effect in clinical trials because of the restricted duration of follow-up. Instead, it is likely that mortality will need to be modelled based on patient characteristics and their expected disease progression. Available models have clearly shown that differences in assumptions can have a significant impact on results [43-45], and the nuances of modelling mortality alongside AD progression.

Preferably, additional life-years are gained before the onset or worsening of AD symptoms, when quality of life is high and costs are low. If instead additional life years are gained in later stages of AD, increased survival may be associated with perverse incentives where the additional life-years causes poorer cost-effectiveness. This because a drug becomes less cost-effective if the additional life-years increase the time in disease stages when costs are higher and quality of life lower. This is both a challenge from a modelling perspective (the challenge being to reduce uncertainty of the expected outcomes) and from a policy perspective (the ethical aspects of punishing treatment that adds life in costly disease stages). More research is needed to understand better the implications of treatment on death.

### 3.5. Consensus on choice of relevant outcomes is missing

Primary efficacy endpoints in mild to moderate AD trials tend to be similar, often including the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) [46] as the primary cognitive endpoint and a global or functional ability measure as co-primary endpoint [47]. These endpoints are however less accepted by policy makers and payers because their scores are not well understood and have unclear relevance to the patients' perceived value of the treatment [10]. Instead, the efficacy endpoints are typically incorporated as intermediate outcomes in models to simulate disease progression and the impact of a potential treatment thereon. The resulting patient trajectories (i.e. representations of disease progression over time) can then be linked to relevant outcomes such as quality of life and costs [10]. This can be done from cross-sectional data e.g. by estimating mean outcomes in each relevant disease state or by estimating statistical functions with each outcome as the dependent variable and the intermediate outcomes as explanatory variables. The dependence scale, which measures the patient's care need, has been suggested to be a valuable tool to bridge between patients' abilities to perform activities of daily living (ADL) and what care is actually provided to them [48].

However, these payer relevant outcomes also have significant limitations associated with the lack of acceptance of their use. The validity of measures of quality of life in subjects with dementia are questionable given their limited capacity to assess and report on their situation [49]. Proxy-ratings by a primary caregiver (or informed health care professional) may be used instead although inconsistencies between their reports and those of patients are well-recognized [3]. Another uncertainty is the valuation of caregiver burden and the provision of informal care. The potential impact of a treatment on primary caregivers may both be considered from a cost perspective (informal care provision) and from a quality of life perspective (health-related impact of caregiver burden) [50]. The above are only examples of a wider discussion on what are the relevant outcomes in Alzheimer therapy and management.

## 4. Discussion - elaboration on additional issues for modelling the full continuum of AD

The methods for economic evaluation of interventions in pre-dementia stages of AD are less established compared to those in dementia stages [30]. This is also mirrored by the issues discussed in the reviews identified which generally do not focus on the potential challenges for health economic modelling of early interventions in AD. Instead, we allude here some of the key expected challenges.

### 4.1. Role of health economic models

It is clear that health economic models will be needed to evaluate future prevention and treatment strategies in AD. Payers may consider prevention strategies to be particularly expensive when given to relatively healthy subjects with low health care costs. However, the main consequences of these strategies are expected in the long-term beyond the duration of clinical trials, and possibly decades after treatment is initiated. Potentially large investments in prevention and treatment may only pay back many years ahead, and furthermore, the benefits may accrue in different payer lines of business or segments, from the one bearing the initial treatment cost. Both the temporal and segments are critical policy issues where models can be used to guide decisions. The treatment cost is only one factor in this analysis, albeit an important one as shown in a recent analysis of a hypothetical DMT [44]. Indeed, delaying the onset of dementia is expected to have a long term impact for individuals and their families if they can live independent lives for longer. Similarly, society would benefit from lower prevalence and care costs assuming that delayed onset also leads to a reduction in disease duration.

### 4.2. Modelling conversion to dementia

The few available models starting in pre-dementia stages of AD commonly assume a relative risk reduction of conversion to dementia in subjects on treatment, followed by a simulation model of disease progression throughout the dementia stages [44, 51-53]. However, conversion to both MCI and dementia are uncertain and highly dependent on the study methods. For instance, differences in diagnostic criteria and frequency of follow-up visits between studies may result in different findings. Moreover, separating early decline in cognition and function into a binary variable for MCI or dementia diagnosis may imply that important data on subtle differences between subjects and within subjects over time are overlooked, thereby further increasing the uncertainty of models. It may therefore be preferable to assess changes in early symptoms of AD (e.g. early cognitive decline) and explore the correlation between such changes and long-term outcomes in longitudinal cohort studies. However, such a framework will require robust statistical analyses and data before it can be used in decision making.

### 4.3. Instruments in different stages of disease

Where studies require assessment over the full continuum of AD, it is important to consider the relevance of different instruments at different disease stages. As noted above, ADAS-cog is usually the preferred primary cognitive endpoint in clinical trials in mild to moderate AD [47] but it has ceiling and floor effects making it less suitable in early and late stages of AD [35]. In moderate to severe AD, the Severe Impairment Battery (SIB) [54] may be better suited, whereas in early AD, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [55] has been suggested [35]. The availability of data have caused many models to use the screening tool Mini-Mental State Examination (MMSE) [56] to represent cognitive decline. MMSE may provide a less granular representation of the disease, but it is unclear whether this has any impact on the modelling results. The Montreal Cognitive Assessment (MoCA) is another screening instrument which is

suggested to be more sensitive than MMSE in detecting MCI [57] and may therefore be explored in pre-dementia stages of AD.

It will be important to set out and support the use of different instruments over different stages of AD, given that specific tests in early disease may be useful for predicting the scores of other tests in later stages of disease. Again, such frameworks put high demand on data and the analysis thereof.

### 4.4. Need for longitudinal data on natural progression

Updated disease progression data on the full continuum of AD would help to understand the relationship between symptoms in the different stages. Data would preferably need to be available on subjects identified prior to the onset of MCI and then followed until their death, while conducting frequent assessments of their dementia symptoms, biomarkers and outcomes over time with instruments that are relevant for each stage of their disease. However, such a study would need to be conducted over many years in order to capture the long-term events. There are many examples of ongoing population-based longitudinal aging cohorts which may provide some of this data with follow-up in the range of 15-20 years, e.g. the English Longitudinal Study on Aging (ELSA) [58], Swedish National Aging Cohort (SNAC) [59], the Rotterdam study [60] in the Netherlands and the Aging Demographics and Memory Study (ADAMS) [61] in the US. However, these cohorts generally have different objectives and scope limiting the selection of outcomes, frequency of assessments and sample size. Quality of care registries such as the Swedish SveDem (currently with about 62,000 dementia cases) may provide long term follow-up of large samples, but again with a limited range of assessments [62]. Claims data are generally insufficient to describe dementia progression because of the lack of events, health care visits or treatments defining the relevant progression of disease. In contrast to other disease areas, for example cardiovascular disease, where both relevant events and risk factors can often be identified via diagnosis or procedure codes in administrative databases, dementia is not easily studied in real-world data.

Alzheimer specific studies with both adequate detail of data and long follow-up may therefore be unrealistic or at least very rare. Again, modelling may help to overcome this problem by bridging data from cohorts at different stages of the disease, which can be followed in parallel in shorter term studies. Such approaches to study the full continuum of AD in shorter studies are further explored in Figures 1-3.

Up-to-date resource use data are also needed for modelling and can be assessed in cross-sectional studies assessing the resource use (together with outcomes such as quality of life and caregiver burden) in different stages of the disease. These data can then be linked to different disease trajectories in simulation models to predict outcomes over time.

### 4.5. Model predictions of mortality

The potential impact of a future DMT on mortality will most likely need to be modelled. Many of the available models have used simplistic approaches where the risk of death is simply a function of the current disease stage. Applied in a context where a DMT causes a delay in onset or slower rate of decline, this naïve assumption may have significant impact on the results by reducing the estimated value of the DMT. This needs to be studied further but in Figure 4 we offer an elaboration on why it is important to consider the age- and comorbidity related mortality in future models.

### 4.6. Organisational, economic and ethical challenges related to diagnosis

Early prevention in AD is dependent on the feasibility of identifying subjects at risk of developing dementia or of progression to dementia. Depending on indication, novel interventions may therefore need to be accompanied by the use of biological markers, e.g. assessed with positron emission tomography (PET) and cerebrospinal fluid (CSF), which currently are not widely used in clinical

practice. This may create a need for organisational changes and significant costs as health care systems adapt to new diagnostic requirements.

In the absence of any effective preventive treatment, it has been argued that early testing may not be ethically justified because of negative factors such as the risk of misdiagnosis, particularly false positive cases [63], and the distress a diagnosis may cause those affected and their families [64]. Such negative consequences need to be weighed against any positive factors such as facilitating more informed health decisions and planning for the future. Indeed, a US survey showed that individuals may value a predictive test even if it does not have immediate treatment implications [65].

These aspects of early diagnosis should be considered in the economic evaluation of treatment in early AD as well. More data are therefore needed on the costs and consequences of early diagnosis.

## 5. Conclusions

Producing new data on disease progression across the full continuum of Alzheimer's disease is a priority for future research. This would help in addressing many of the identified shortcomings of the currently available health economic models in AD as well as the challenges facing the economic evaluation of forthcoming treatment in pre-dementia stages of AD. Indeed, most of the limitations of currently available health economic models have their origin in limitations of the underlying data, and as such the challenge is rather to improve on the data and then further develop modelling techniques. The studies should preferably follow large cohorts of subjects from at-risk populations throughout the dementia stages of the disease. Assessments should be conducted for all key symptom domains, with instruments of relevance for each specific stage of the disease. Their relationship over time should be investigated for use in long-term simulation models of Alzheimer disease progression. Specifically, better data for the prediction of key long-term outcomes such as conversion to dementia, institutionalization and mortality are needed. This analysis should also consider the influence of co-variates such as age and comorbidity on the risk of such events.

When developing models, consideration of model validity is of prime importance, together with transparency to support peer-review and reproducibility. Therefore model assumptions for extrapolating short-term efficacy data to long-term outcomes should at best be validated using appropriate methods and data. In absence of such data, sensitivity analyses can be conducted to highlight the uncertainty associated with key assumptions and this may be specifically important for industry sponsored research. The credibility of the work of individual research groups would generally increase if scrutinized and validated by independent researchers. We suggest a wider collaboration, including academia, manufacturers and other research institutions, may enable pooling of resources to enable more robust data and evidence to better inform models.

One option is the development of a collaboration to introduce an open-access model of the natural progression of disease in AD. One

**Figure 1. PRISMA chart on targeted literature search**

**Figure 2. Hypothetical example of data linking early and late symptoms in Alzheimer's disease**. (NB. The figure is for illustrative purposes.)

Assume we are interested in a relationship between two variables A and B, e.g. because A is something we have assessed in clinical trial and B is a long-term outcome of interest to inform decision-makers. Assume A and B are uncorrelated at each point in time because they are sensitive in different stages of the disease. However, values of A in early stages of disease may still be correlated with values of B in later stages of disease, thereby making it possible to predict values of B given the trajectory of A. This relationship would best be assessed in a longitudinal study on subjects collecting data throughout their disease process.

**Figure 3. Hypothetical example of data linking early and late symptoms in Alzheimer's disease**. (NB. The figure is for illustrative purposes.)

A second best option could be to develop a step-wise model where a third variable C is used as an intermediate between A and B. Variable C needs to vary both with A and B although not necessarily in the same stages of the disease. Two different cohorts can be studied to assess the relationship between C and A (cohort 1) and C and B (cohort 2) respectively.

**Figure 4. Hypothetical example of data linking early and late symptoms in Alzheimer's disease**. (NB. The figure is for illustrative purposes.)

Another option may be to assess a longitudinal relationship between A and B by studying several cohorts that stem from the same underlying population but are followed over different stages of their disease. Assuming subjects in cohort 1 can be matched to subjects in cohort 2 (and

subsequently to subjects in cohort 3), these can together form a longitudinal representation throughout the disease process, including eliciting the relationship between A and B.

**Figure 5. Hypothetical example of the expected impact of disease modifying treatment (DMT) on mortality and cumulative costs (excluding treatment costs), based on different assumptions of risks of death. (**NB. The figure is based on hypothetical data for illustrative purposes.)

Panel A. Delay in onset, mortality independent of age/comorbidity

A DMT is assumed to cause a delay in onset of disease where after subjects on DMT experience a parallel decline in function compared to controls. Assuming that the risk of death is only dependent on functional decline, the event of death is expected to be equally postponed as onset of disease. This implies that the DMT will not have any impact on the duration of disease. Likewise, costs are expected to be equal, although postponed in subjects on DMT.

Panel B. Delay in onset, mortality dependent on age/comorbidity

In comparison to Panel A, we now consider that subjects on DMT, at disease onset, will be older and potentially have additional morbidity compared to controls. Therefore, subjects on DMT are expected to have increased risk of death that cannot be attributed to their cognitive and functional decline. Subjects on DMT are therefore expected to experience a shorter duration of disease, which consequently may reduce their cumulative costs (excluding costs of treatment) in comparison to controls.

Panel C. Slower decline, mortality independent of age/comorbidity

Another DMT is assumed to cause a slower decline in function compared to controls, while the onset is unaffected by treatment. Assuming that the risk of death is only dependent on functional decline, the duration of disease in subjects on DMT is expected to be longer compared to controls. This may

lead to higher cumulative costs (even when excluding costs of treatment) for subjects on DMT compared to controls.

Panel D. Slower decline, mortality dependent on age/comorbidity

In comparison to Panel C, we now consider that subjects on DMT will be older once they reach the same level of function as their controls. Therefore, subjects on DMT are expected to have increased risk of death that cannot be attributed to their functional decline. Subjects on DMT are therefore expected to die at a higher level of function on average, which consequently may reduce their cumulative costs (excluding costs of treatment) in comparison to controls.

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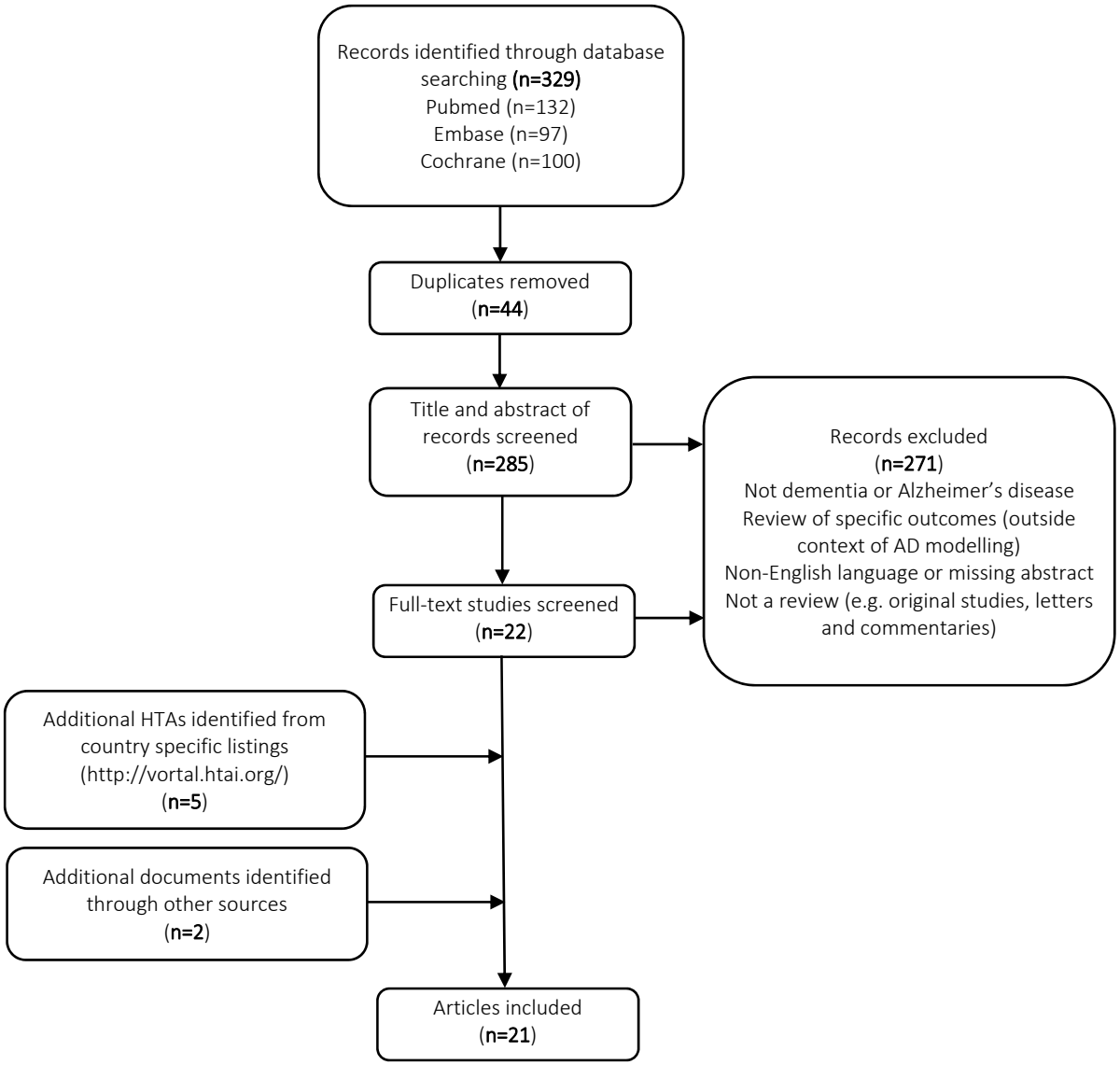

Records identified through database searching (n=329)
Pubmed (n=132)
Embase (n=97)
Cochrane (n=100)
Duplicates removed (n=44)
Title and abstract of records screened (n=285)
Records excluded (n=271)
Not dementia or Alzheimer's disease
Review of specific outcomes (outside context of AD modelling)
Non-English language or missing abstract
Not a review (e.g. original studies, letters and commentaries)
Full-text studies screened (n=22)
Additional HTAs identified from country specific listings (http://vortal.htai.org/) (n=5)
Additional documents identified through other sources (n=2)
Articles included (n=21)

# Figure 2

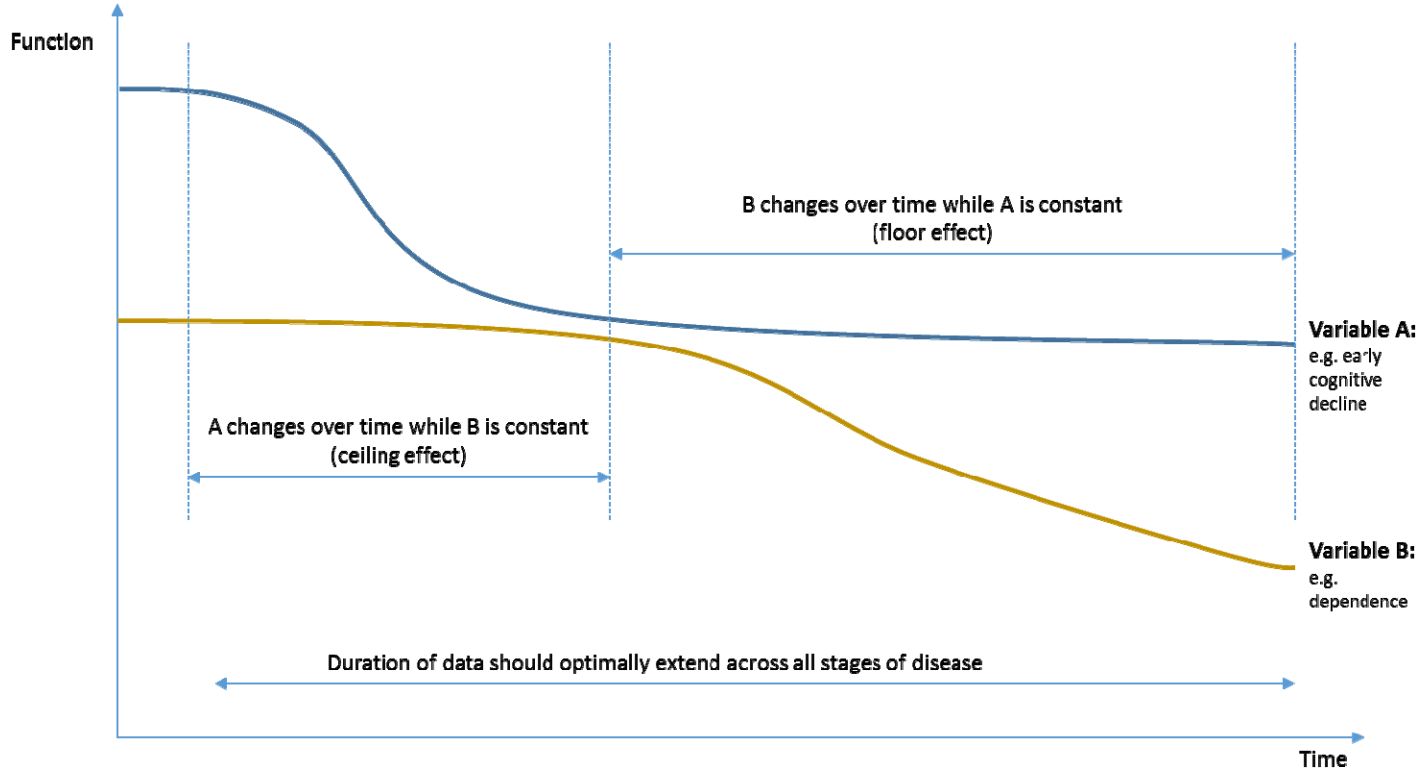

Function
B changes over time while A is constant
(floor effect)
Variable A:
e.g. early
cognitive
decline
A changes over time while B is constant
(ceiling effect)
Variable B:
e.g.
dependence
Duration of data should optimally extend across all stages of disease
Time

Figure 3

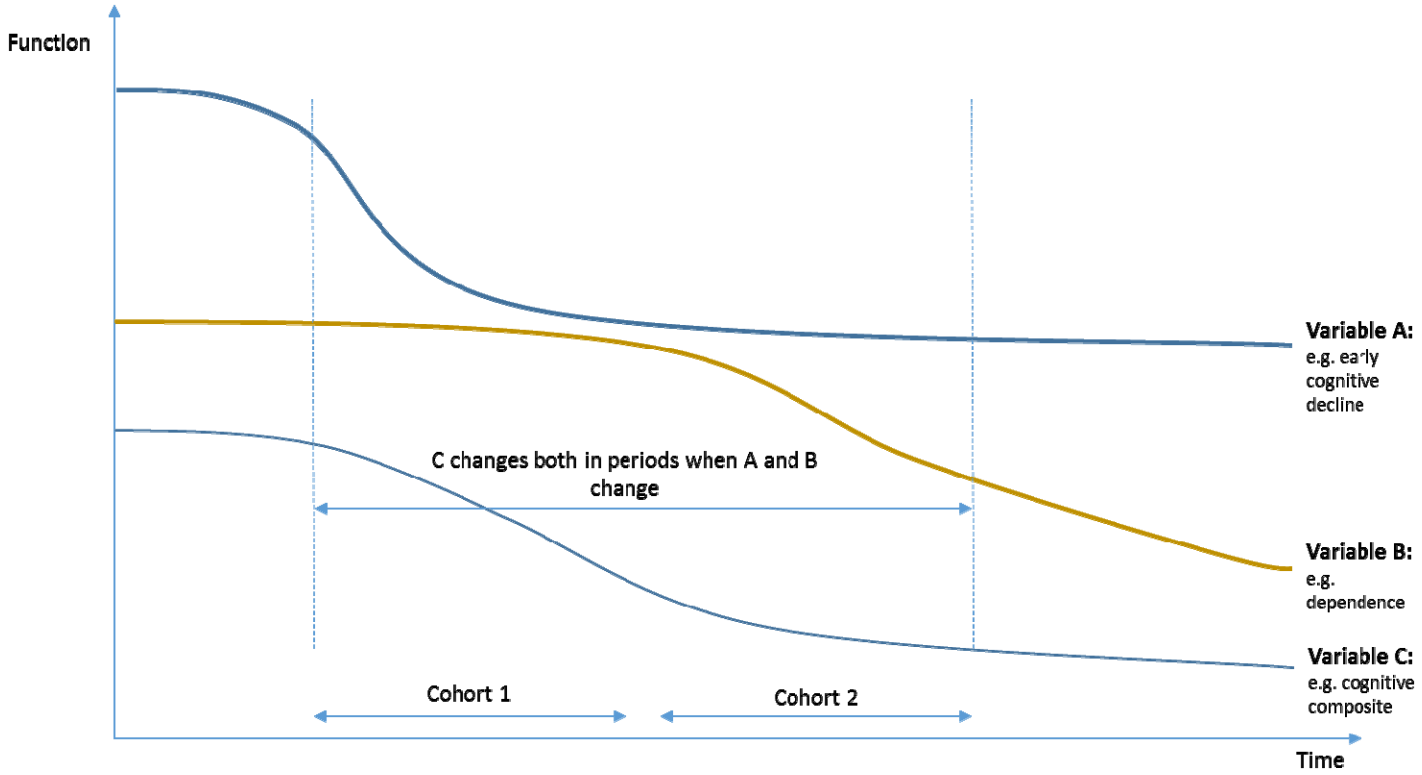
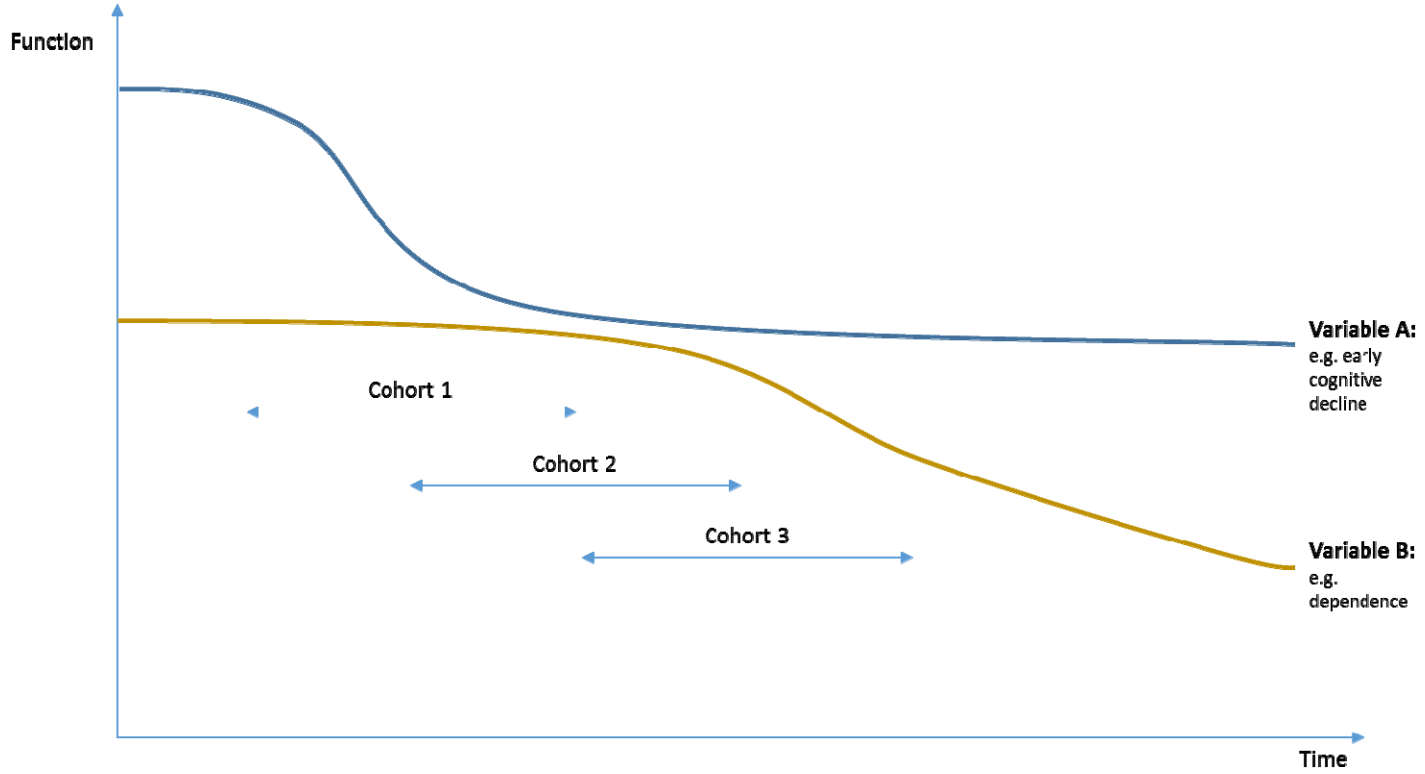
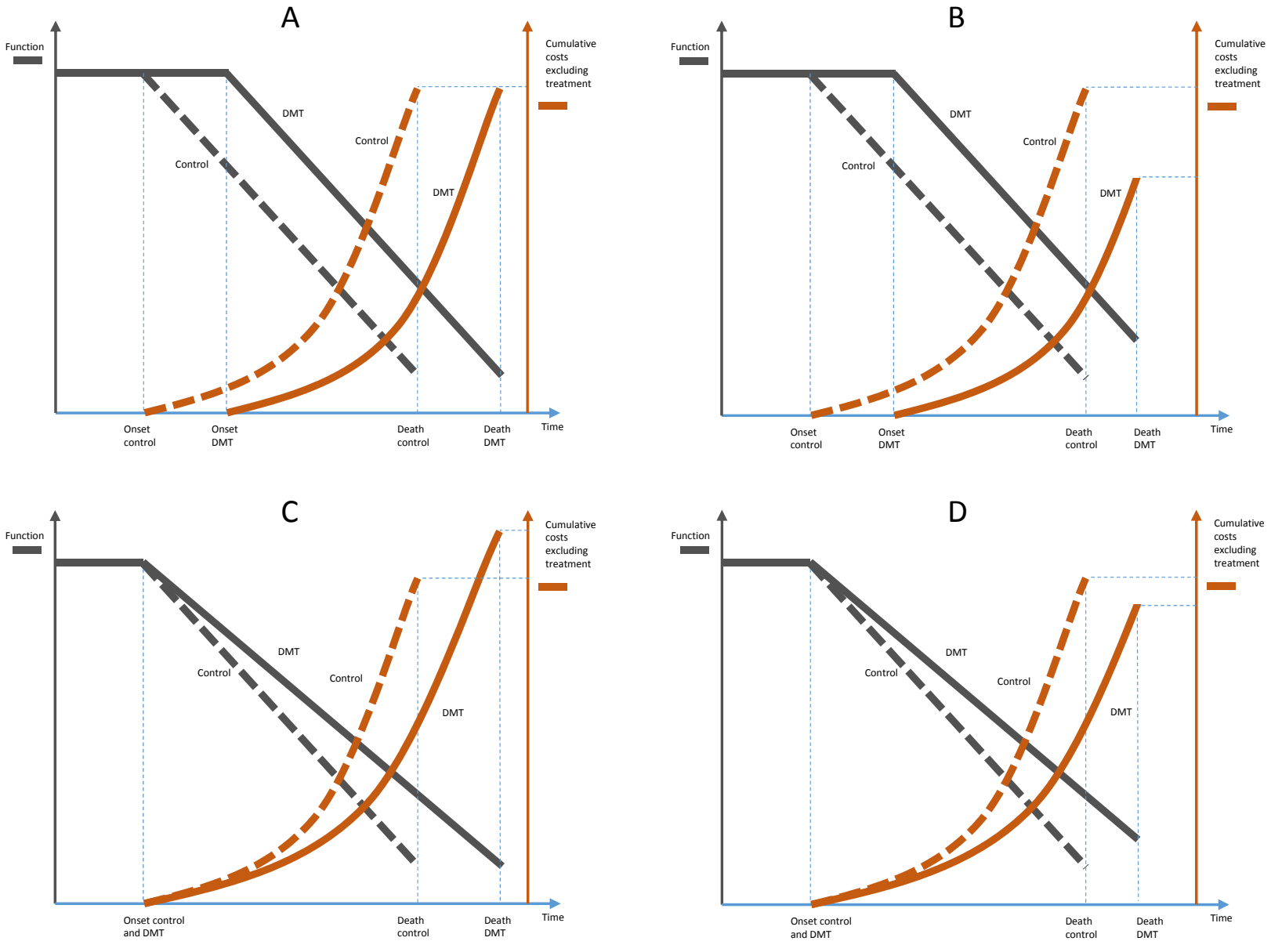

Function
Variable A:
e.g. early
cognitive
decline
C changes both in periods when A and B
change
Variable B:
e.g.
dependence
Variable C:
e.g. cognitive
composite
Cohort 1
Cohort 2
Time

Figure 4


Function
Variable A:
e.g. early
cognitive
decline
Cohort 1
Cohort 2
Cohort 3
Variable B:
e.g.
dependence
Time


A
Function
Cumulative costs excluding treatment
DMT
Control
Control
DMT
Onset control
Onset DMT
Death control
Death DMT
Time
B
Function
Cumulative costs excluding treatment
DMT
Control
Control
DMT
Onset control
Onset DMT
Death control
Death DMT
Time
C
Function
Cumulative costs excluding treatment
DMT
Control
Control
DMT
Onset control and DMT
Death control
Death DMT
Time
D
Function
Cumulative costs excluding treatment
DMT
Control
Control
DMT
Onset control and DMT
Death control
Death DMT
Time