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# Understanding and predicting the longitudinal course of dementia

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## Purpose of review

To date, most research in dementia has focused either on the identification of dementia risk prediction or on understanding changes and predictors experienced by individuals before diagnosis. Despite little is known about how individuals change after dementia diagnosis, there is agreement that changes occur over different time scales and are multidomain. In this study, we present an overview of the literature regarding the longitudinal course of dementia.

## Recent findings

Our review suggests the evidence is scarce and findings reported are often inconsistent. We identified large heterogeneity in dementia trajectories, risk factors considered and modelling approaches employed. The heterogeneity of dementia trajectories also varies across outcomes and domains investigated.

## Summary

It became clear that dementia progresses very differently, both between and within individuals. This implies an average trajectory is not informative to individual persons and this needs to be taken into account when communicating prognosis in clinical care. As persons with dementia change in many more ways during their patient journey, heterogeneous disease progressions are the result of disease and patient characteristics. Prognostic models would benefit from including variables across a number of domains. International coordination of replication and standardization of the research approach is recommended.

## Keywords

dementia, disease progression, prognosis

## INTRODUCTION

Dementia is a syndrome with a variable disease course. The progression of dementia is the result of complex mechanisms interacting across multiple spatial and temporal scales that go from molecular to societal scales and from dynamics that take seconds to a lifetime to evolve [1]. To understand the longitudinal course of dementia, it is essential to recognize this hierarchy exists. This also required for an accurate prediction of the patient journey. In this, two remarks are noteworthy. First, over time not only the dementia will progress but persons with dementia (PWD), who are often older, may also experience concomitant changes during their patient journeys induced by other co-existing diseases or syndromes. Second, that ageing and dementia, which develops over 15–25 years from preclinical to end stage and usually starts during the second half of the lifespan, are closely intertwined and jointly impact on multiple life domains.

This explains why predictor research has focused on so many aspects in the progression of dementia. At the same time, each of these aspects is a field of study in itself that a single review cannot do justice to. Therefore, we do not strive for

comprehensiveness of our review at the level of the individual processes involved in the progression of dementia. They do serve, however, as ‘place holders’ to outline the multiscale processes involved in the progression of dementia. Consequently, we reviewed the latest evidence (2017–2018) on:

- (1) The heterogeneity in the multidimensional longitudinal course of dementia from diagnosis

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## KEY POINTS

- Dementia progression is heterogeneous within and between persons with dementia and originates from disease characteristics and characteristics of persons with dementia.
- This heterogeneity is perhaps best explained by a multiscale mixture of long and short-time trends included in polyfactor prediction models.
- Data sharing, coordination and standardization of explanatory and prognostic research of the patient journey of persons with dementia is merited.
- Possible risk factors should not only be evaluated as baseline (at diagnosis) exposures but also as (lagged) time-varying exposures. Also longitudinal changes in exposures can be evaluated against longitudinal changes in outcomes. This requires the assessment of risk factors at baseline and at the follow-ups.

onwards and whether clinically meaningful clustering in growth curves can be identified.

- (2) Baseline (static, between PWD) and time-varying (dynamic, within PWD) factors associated with the heterogeneity in the longitudinal course of dementia at multiple scales (disease and patient and sociodemographics).
- (3) The possibility to predict longitudinal course of dementia, institutionalization and survival.

A description of the methodology and yield of this result can be found in the Supplement, <http://links.lww.com/YCO/A46>.

## RECENT FINDINGS: HETEROGENEITY IN THE MULTIDIMENSIONAL LONGITUDINAL COURSE OF DEMENTIA

The studies reviewed confirm the earlier observation that ‘the course of dementia is unpredictable and varies greatly between individuals’ [2]. Researchers took roughly three different approaches to study this heterogeneity. First, PWD were categorized as either fast or slower decliners based on their (initial) change in outcomes [3]. Second, studies used individual growth models applying linear mixed modelling to model the heterogeneity through random intercepts and slopes [4]. Mostly, these studies focused on trajectories in one phenotypical outcome at a time [5<sup>11</sup>]. Third, researchers identified grouping in growth trajectories applying latent class growth curve analysis or growth mixture modelling (GMM) [6]. Multivariate GMM models simultaneously estimated trajectories of multiple outcomes (mostly global cognition and daily functioning) in a

so-called ‘parallel process GMM’. The outcomes most frequently involved are global cognition (Mini Mental State Examination; MMSE) and dementia severity (Clinical Dementia Rating scale – Sum of the Boxes; CDR-SB) [7<sup>11</sup>]. To a lesser extent, studies modelled activities of daily living (ADL) and instrumental activities of daily, cognitive testing and neuropsychiatric symptoms measures (NPS). Few studies were identified that modelled (time-to) relevant dichotomous outcomes such as institutionalization and death, yet no studies combining trajectories on continuous and dichotomous outcomes in a single analysis (through so-called joint modelling) were identified recently [8].

When focusing on dementia or Alzheimer’s dementia showing a rapidly progressing trajectory, the lack of consistent definitions of disease stages and PWD populations hampers the opportunity to draw precise conclusions. Yet, there is large heterogeneity with considerable proportions of the samples analyzed showing rapid declines, but often the majority shows slower decline [3,9–11]. Finally, probabilities for increasing Alzheimer’s dementia severity, institutionalization and mortality were calculated and ranged much depending on age and dementia stage [12<sup>13</sup>].

Regarding the multidimensionality of dementia disease course, a strong correlation between MMSE and CDR-SB trajectories was found in a clinical sample of persons with incident dementia [7<sup>11</sup>], which replicated the high correlations between these measures’ trajectories reported earlier [14]. A Dutch cohort of persons with new dementia diagnosis at a memory clinic (The Clinical Course of Cognition and Comorbidity in Mild Cognitive Impairment and Dementia Study; 4C study [15]) also showed that daily functioning (Disability Assessment for Dementia; DAD) and cognition (MMSE) correlate, but the correlation with neuropsychiatry symptoms was attenuated (NPS, measured with Neuropsychiatric Inventory; NPI) [16<sup>17</sup>]. This indicates within person heterogeneity, where NPS outcomes over time do not follow the trajectory of global cognitive decline. Although more coordinated approaches and further replication of results are needed [17], results to date indicate that the trajectory of a single outcome fails to capture disease progression comprehensively.

## Clustering in longitudinal course of dementia

Several recent studies tried to understand the heterogeneity in dementia disease course through the application of (parallel process) GMM. Growth classes were sought for MMSE (six classes) [18<sup>19</sup>], depressive symptoms (three classes) [19<sup>20</sup>] and quality of life

(three classes mainly characterized by baseline differences, rather than slopes) [20<sup>\*</sup>]. One study sought to replicate the four classes of parallel growth in MMSE and CDR-SB from a population-based sample of incident Alzheimer's dementia patients [14] in the National Alzheimer's Coordinating Center (NACC) clinical sample of recently diagnosed Alzheimer's dementia patients using MMSE and CDR-SB [7<sup>\*\*</sup>]. Replication was partly possible: three instead of four classes were identified, although class distribution was comparable in the sense that most individuals were members of a class with stable or slow progression. Comparison to the six growth classes for MMSE in the UK sample shows that some of their classes had a much lower MMSE already at baseline [18<sup>\*</sup>] than classes identified in Cache County Dementia Progression Study [14], NACC and 4C [7<sup>\*\*</sup>]. Perhaps this reflects that the UK study did not synchronize trajectories on the basis of dementia onset. As dementia has an insidious onset, it is very difficult to identify a single point in the patient journey to synchronize all trajectories on [21]. Compared to cases identified systematically in a cohort at risk for dementia, trajectory analysis in clinical samples is especially sensitive to this heterogeneity that occurs, amongst other reasons, because not everybody is referred for diagnosis at the same disease stage.

The results of each of these clustering exercises are relevant in that they redirect the attention from the average trajectory to the heterogeneity both between and within the PWD's journey. All consistently show that there is an – often large – group of dementia patients who follow a slower trajectory than typically reported based on the average decline, and this can help to communicate accurately with patients and caregivers about their prognosis. Moreover, deciphering slow progression mechanisms may point at new preventive and therapeutic options.

Beyond this, the purpose of GMM is to uncover distinct (but a priori unknown, thus latent) subpopulations showing different trajectories of change. From the studies reviewed here it is clear that clustering can be identified, but to which extent these clusters of trajectories are meaningful remains to be elucidated. A direct comparison of results is hampered because of different analytical choices. Hence, a consistent replication of the subpopulations across multiple datasets is crucial and lacking.

If no latent grouping of trajectories is apparent from these replications, this may essentially mean that the heterogeneity in the data does not arise from the presence of subpopulations of patients exhibiting typical trajectories, but – at the level of the whole group – behaves in a seemingly random

fashion (adequately described with random intercepts and slopes [6]) around a single mean growth curve.

## RECENT FINDINGS: BASELINE AND TIME-VARYING PREDICTORS OF LONGITUDINAL COURSE OF DEMENTIA

A large number of studies have looked into possible predictors for a range of outcome trajectories. Although some studies evaluated characteristics of the dementia, others focused on the person with the dementia, and a few both. Mostly, baseline exposure levels of predictors were evaluated, but some studies also evaluated the association with time-varying exposures.

### Disease level

At disease level, the syndrome diagnosis was an important target, where these were either compared for their impact on outcomes over time or were evaluated – in those persons receiving multiple syndrome diagnoses – for how the co-occurrence of dementia syndromes interact. A comparison of Alzheimer's dementia and Lewy Body Dementia (LBD) patients found little support for a faster decline in neuropsychological outcomes in LBD patients over four year after diagnosis [22]. Yet, when persons have both Alzheimer's dementia and LBD, this resulted in faster decline than each apart [23]. Comparably, when LBD patients had a CSF Alzheimer's dementia profile, this also resulted in a more severe manifestation of the disease and a higher risk of institutionalization and mortality [24].

Another study found that patients with a behavioural variant frontotemporal dementia worsened in frontal symptoms such as disinhibition and apathy, whereas these symptoms were rather stable in other neurodegenerative disorders and even improved in primary psychiatric disorders [25]. In contrast, a comparison of Alzheimer's dementia and behavioural variant frontotemporal dementia patients showed strongly overlapping longitudinal trajectories in executive functioning, memory and orientation measures [26]. Finally, a specific sample of young onset dementia patients showed that on the Global Deterioration Scale, Alzheimer's dementia patients progressed faster than patients with VaD and frontotemporal dementia [27].

### Neuropsychological assessments

Performance on neuropsychological assessments (NPA) also was an important disease characteristic evaluated as a predictor of dementia progression. In Alzheimer's dementia patients, free recall and

category fluency at diagnosis were the most predictive of rapid cognitive [28], as was a low MMSE [11,29], high CDR [30] and worse Trail Making B [3]. In another study, patients with a non-memory impairments profile showed faster disease progression and higher risk of mortality than patients with most prominently memory impairment [31]. More novel neuropsychological assessments targets may be 'selective attention toward novel stimuli,' or 'novelty preference,' which was associated with a greater decline in cognition [32], and the semantic memory processes which predicted global cognition at one year in Alzheimer's dementia patients [33]. Finally, (Instrumental)ADLs were over time correlated with time-varying measures of executive function and visuoconstructive skills in Alzheimer's dementia patients [34] and NPS changes were explained by MMSE [5].

### **Neuropsychiatric symptoms**

Three recent studies suggested that baseline neuropsychiatric symptom burden may be related to aggravated decline in dementia [11,27,29].

### **Blood-based biomarkers**

Regarding blood-based biomarkers, only one recent study was identified, which suggested higher plasma clusterin levels were associated to rate of cognitive decline in Alzheimer's dementia patients, whereas plasma A $\beta$  in ApoE4-positive Alzheimer's dementia patients could predict long-term agitation/aggression symptoms [35]. As such, this study adds to the emerging field of neurochemical biomarkers for dementia and Alzheimer's dementia [36].

### **Imaging biomarkers**

Imaging biomarkers are an established and active field of study, though traditionally more focused on dementia onset prediction than dementia progression. Imaging, however, has the continued interest of the field to serve as a proxy outcome in clinical trials in dementia and Alzheimer's dementia. Several studies looked at structural MRI brain atrophy patterns and white matter changes to reveal patterns related to faster progression [37–39]. Similarly, arterial spin labelling measured cerebral blood flow acted as a marker of MMSE decline [40]. Finally, PET imaging biomarkers  $\tau$  and amyloid- $\beta$  burden and microglial activation were related to dementia progression [41,42].

### **Patient level**

At patient level studies continue to be added to the literature regarding the age at presentation and speed of decline, often explicitly defined as early

vs. late onset dementia or early onset Alzheimer's disease (EOAD) vs. late onset Alzheimer's disease (LOAD). These studies showed faster progression with younger age [43,44] and higher mortality risk in EOAD [45]. However, findings also contradict each other suggesting virtually no effect of age [46] or higher age being related to faster decline [5,30]. Related is the finding that earlier diagnosed Alzheimer's dementia patients experienced similar progression in MMSE, but slower progression in CDR [47].

### **Genetic factors and family history**

As there are a number of genetic risk factors for Alzheimer's dementia [48], interest is also raised for their involvement in the progression of dementia and Alzheimer's dementia. This ranges from known genes [30,49] and polymorphisms [50] to polygenic risk scores [51] and a positive family history [11].

### **Comorbidity**

A systematic review into the impact of comorbidity on late onset Alzheimer's dementia suggested a dynamic relation between medical comorbidity and Alzheimer's dementia decline, because time-varying comorbidity burden more than baseline comorbidity burden was associated with cognitive decline [52]. The possibility that medical comorbidities may impact progression was supported by the finding that dementia patients in primary care die younger when having more comorbidities [53]. The observation that comorbidity changed over time and had predictive value for institutionalization and mortality in the short but not in the long term, may support the suggested hypothesis of a dynamic relation between dementia progression and comorbidity [54]. As separate conditions, mainly cardiovascular comorbidities were tested and found to be related to dementia progression in including NPS [5,55,56]. However, other studies found no or only modest relations of vascular risk factors and vascular diseases with progression in Alzheimer's dementia [57] and LBD [58].

### **Frailty and accelerated aging biomarkers**

Like comorbidities, frailty levels are likely to change during dementia progression, and perhaps also have predictive value in the short but not in the long term [54]. Further support for an influence of frailty biomarkers came from a study identifying an association between baseline gait speed and cognition [59] and between malnutrition and rapid decline [11]. A longitudinal association between advanced glycation end products – which may signal accelerated aging – and ADL and mobility declines could

not be evidenced in persons with Alzheimer's dementia or mixed dementia [60].

### Physical activity

Several recent studies suggested less and decreasing physical activity is associated with faster decline and mortality [61,62].

### Sociodemographics

Sociodemographic factors such as geographic area of residence in the United States and being community dwelling were found to be related to dementia progression [5<sup>\*\*\*</sup>], but another study suggested their impact may disappear with increasing severity [63<sup>\*</sup>]. Therefore, the results implied 'that the potential for extending community living for people with dementia is likely to be difficult through modification of their socio-demographic and economic environments' [63<sup>\*</sup>].

### RECENT FINDINGS: PREDICTION MODELS

Despite a rich, though sometimes conflicting, literature on dementia progression predictors and the importance of adequate prognostic information for patients [2], the body of evidence for prediction models for dementia progression is still sparse, even with the latest studies added [7<sup>\*\*\*</sup>,64,65<sup>\*\*\*</sup>]. The approaches to their development were heterogeneous and involved very different risk factors. The risk factors focused either on clinical attributes and patient characteristics [7<sup>\*\*\*</sup>], imaging biomarkers in a machine learning framework [64] and an approach combining both fixed and time-varying covariates covering multiple domains including cognitive, functional, behavioural and other symptoms/signs [65<sup>\*\*\*</sup>]. We suggest that more coordination in their development and evaluation is merited, in which a promising approach may be to combine baseline as well as time-varying predictors across multiple scales in one model as has been suggested by a number of authors [52<sup>\*\*\*</sup>,65<sup>\*\*\*</sup>].

### CONCLUSION

Though clustering of dementia time course is revealed, its relevance needs to be verified and findings replicated across multiple studies with comparable approaches to the analysis, for example, coordinated analysis [17], before we can really draw robust inferences. At this point the relevance of clustering exercises is that they point at the heterogeneity and spread in the longitudinal course of dementia that is not fully described by the average. It was also seen that this heterogeneity is perhaps best explained by a mixture of long and short-time

trends: for example, the presence of EOAD has in comparison to LOAD a sustained effect on speed of decline, but on top of that the time course is shaped by co-existing syndromes such as frailty that are more variable in their presence across the patient journey and thus have predictive value in the short, but not in the long run. Exposures which are bound to change over the course of dementia may still have relevance to predict outcome in the short run, but require frequent updates of predictor exposures and prediction models that allow for updates.

Multiple differences in the methodology, including different psychometric properties of the outcomes analyzed, became also apparent and this hampers their comparison. Polyfactor prediction models combining relevant predictors at different hierarchical (spatial and time scales) may provide further insight in the natural progression of dementia.

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### Conflicts of interest

*There are no conflicts of interest.*

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- of special interest
- of outstanding interest

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This study used longitudinal data from PWD from NACC to show that growth classes identified earlier could be partially replicated. Although an important technique to understand heterogeneity in disease course, the data-driven nature of GMM urges for replication studies. The study replicated the underappreciated finding that the majority of PWD showed a decline slower than typically reported for the average decline.

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- Despite the importance of valid prognostic information across the patient journey, this information is scarcely available. This is one of the few exercises to build a prognostic model for dementia progression.