OPEN

CURRENT OPINION

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▪▪]. 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▪▪]. 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▪,13▪].

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▪▪], 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▪]. 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▪], depressive symptoms (three classes) [19▪] and quality of life

(three classes mainly characterized by baseline differences, rather than slopes) [20▪]. 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▪▪]. 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▪] than classes identified in Cache County Dementia Progression Study [14], NACC and 4C [7▪▪]. 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 Aβ 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 τ and amyloid-β 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▪▪], but another study suggested their impact may disappear with increasing severity [63▪]. 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▪].

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▪▪,64,65▪▪]. 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▪▪], 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▪▪]. 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▪▪,65▪▪].

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.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

1. Fotuhi M, Hachinski V, Whitehouse PJ. Changing perspectives regarding late-life dementia. Nat Rev Neurol 2009; 5:649–658.
2. Livingston G, Sommerlad A, Orgeta V, *et al.* Dementia prevention, intervention, and care. Lancet 2017; 390:2673–2734.
3. Eldholm RS, Barca ML, Persson K, *et al.* Progression of Alzheimer's disease: a longitudinal study in Norwegian memory clinics. J Alzheimers Dis 2018; 61:1221–1232.
4. Singer JD, Willet JB. Applied longitudinal data analysis: modeling change and event occurrence. New York: Oxford University Press; 2003.
5. ▪▪ Jutkowitz E, MacLehose RF, Gaugler JE, *et al.* Risk factors associated with cognitive, functional, and behavioral trajectories of newly diagnosed dementia patients. J Gerontol A Biol Sci Med Sci 2017; 72:251–258.

This study used longitudinal data from PWD from NACC to study the predictors of multidimensional progression of dementia. Studying multiple outcomes simultaneously (in this case cognition and daily functioning) sets out this study from most other studies in the field. Also showing the impact of sociodemographic characteristics is both fairly unique and important.

6. Jung T, Wickrama KA. An introduction to latent class growth analysis and growth mixture modeling. Social Personal Psychol Compass 2008; 2: 302–317.
7. ▪▪ Haaksma ML, Calderon-Larranaga A, Olde Rikkert MG, *et al.* Cognitive and functional progression in Alzheimer disease: s prediction model of latent classes. Int J Geriatr Psychiatry 2018; 33:1057–1064.

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.

8. Terrera GM, Piccinin AM, Johansson B, *et al.* Joint modeling of longitudinal change and survival: an investigation of the association between change in memory scores and death. GeroPsych 2011; 24:177–185.
9. Barocco F, Spallazzi M, Concari L, *et al.* The progression of Alzheimer's disease: are fast decliners really fast? A four-year follow-up. J Alzheimers Dis 2017; 57:775–786.
10. Ferrari C, Lombardi G, Polito C, *et al.* Alzheimer's disease progression: factors influencing cognitive decline. J Alzheimers Dis 2018; 61:785–791.
11. Tchalla AE, Clement JP, Saulnier I, *et al.* Predictors of rapid cognitive decline in patients with mild-to-moderate Alzheimer disease: a prospective cohort study with 12-month follow-up performed in memory clinics. Dement Geriatr Cogn Disord 2018; 45:56–65.
12. ■ Davis M, O Connell T, Johnson S, *et al.* Estimating Alzheimer's disease progression rates from normal cognition through mild cognitive impairment and stages of dementia. Curr Alzheimer Res 2018; 15:777–788.

This study reported annual transitional probabilities for PWD increasing in severity, or transitioning to institutionalization or death. The probabilities were variable and depended on age. Transition probabilities from normal cognition through Alzheimer's dementia severity states are important for understanding patient progression across the Alzheimer's dementia spectrum.

13. ■ Emerson JA, Smith CY, Long KH, *et al.* Nursing home use across the spectrum of cognitive decline: merging mayo clinic study of aging with CMS MDS assessments. J Am Geriatr Soc 2017; 65:2235–2243.

Institutionalization is an important – because often dreaded – and understudied outcome in dementia.

14. Leoutsakos JM, Forrester SN, Corcoran CD, *et al.* Latent classes of course in Alzheimer's disease and predictors: the Cache County Dementia Progression Study. Int J Geriatr Psychiatry 2015; 30:824–832.
15. Liao W, Hamel RE, Olde Rikkert MG, *et al.* A profile of The Clinical Course of Cognition and Comorbidity in Mild Cognitive Impairment and Dementia Study (The 4C study): two complementary longitudinal, clinical cohorts in the Netherlands. BMC neurol 2016; 16:242.
16. ■ Haaksma ML, Leoutsakos JS, Bremer JA, *et al.* The clinical course and interrelations of dementia related symptoms. Int Psychogeriatr 2018; 30:859–866.

Dementia impacts multiple aspects of life, but the simultaneous impact of dementia across multiple outcomes is seldom studied. This study used parallel process growth modelling to evaluate how cognitive, functional and neuropsychiatric outcome trajectories correlated.

17. Hofer SM, Piccinin AM. Integrative data analysis through coordination of measurement and analysis protocol across independent longitudinal studies. Psychol methods 2009; 14:150–164.
18. ■ Baker E, Iqbal E, Johnston C, *et al.* Trajectories of dementia-related cognitive decline in a large mental health records derived patient cohort. PloS one 2017; 12:e0178562.

Dementia progression studies are sparse. This study offers a unique example how quantitative information on dementia progression such as cognitive scores can be derived from electronic health records, even from free text fields.

19. ■ Barca ML, Persson K, Eldholm R, *et al.* Trajectories of depressive symptoms and their relationship to the progression of dementia. J Affect Disord 2017; 222:146–152.

This study went beyond traditional dementia progression markers to evaluate the interaction of cognitive decline and mood. A more rapid progression of dementia was found in a group of patients with increasing depressive symptoms.

20. ■ Ydstebo AE, Bergh S, Selbaek G, *et al.* Longitudinal changes in quality of life among elderly people with and without dementia. Int Psychogeriatr 2018; 30:1607–1618.

This study went beyond traditional dementia progression markers, to evaluate the impact of dementia on quality of life, which not necessarily corresponded with deterioration in clinical outcomes.

21. Yang E, Farnum M, Lobanov V, *et al.* Quantifying the pathophysiological timeline of Alzheimer's disease. J Alzheimers Dis 2011; 26:745–753.
22. Breitve MH, Chwiszczuk LJ, Bronnick K, *et al.* A Longitudinal study of neurocognition in dementia with Lewy bodies compared to Alzheimer's disease. Front neurol 2018; 9:124.
23. Blanc F, Mahmoudi R, Jonveaux T, *et al.* Long-term cognitive outcome of Alzheimer's disease and dementia with Lewy bodies: dual disease is worse. Alzheimer's Res Ther 2017; 9:47.
24. Lemstra AW, de Beer MH, Teunissen CE, *et al.* Concomitant AD pathology affects clinical manifestation and survival in dementia with Lewy bodies. J Neurol Neurosurg Psychiatry V 88 2017; 113–118.
25. Reus LM, Vijverberg EG, Tijms BM, *et al.* Disease trajectories in behavioural variant frontotemporal dementia, primary psychiatric and other neurodegenerative disorders presenting with behavioural change. J Psychiatr Res 2018; 104:183–191.
26. Ramanan S, Bertoux M, Flanagan E, *et al.* Longitudinal executive function and episodic memory profiles in behavioral-variant frontotemporal dementia and Alzheimer's disease. J Int Neuropsychol Soc 2017; 23:34–43.
27. Gerritsen AA, Bakker C, Verhey FR, *et al.* The Progression of dementia and cognitive decline in a Dutch 2-year cohort study of people with young-onset dementia. J Alzheimers Dis 2018; 63:343–351.
28. Koskas P, Henry-Feugeas MC, Feugeas JP, *et al.* Factors of rapid cognitive decline in late onset Alzheimer's disease. Curr Aging Sci 2017; 10:129–135.
29. Hishikawa N, Fukui Y, Takemoto M, *et al.* Clinical predictors of Alzheimer's disease progression. Geriatr Gerontol Int 2018; 18:929–936.
30. Yang YH, Wu MN, Chou PS, *et al.* Longitudinal neuropsychological outcome in Taiwanese Alzheimer's disease patients treated with medication. Curr Alzheimer Res 2018; 15:474–481.
31. Scheltens NM, Tijms BM, Heymans MW, *et al.* Prominent non-memory deficits in Alzheimer's disease are associated with faster disease progression. J Alzheimers Dis 2018; 65:1029–1039.
32. Chau SA, Herrmann N, Sherman C, *et al.* Visual selective attention toward novel stimuli predicts cognitive decline in Alzheimer's disease patients. J Alzheimers Dis 2017; 55:1339–1349.
33. Tchakoute CT, Sainani KL, Henderson VW. Semantic memory in the clinical progression of Alzheimer disease. Cogn Behav Neurol 2017; 30:81–89.
34. ■ Saari T, Hallikainen I, Hanninen T, *et al.* Relationships between cognition and activities of daily living in Alzheimer's disease during a 5-year follow-up: ALSOVA Study. J Alzheimers Dis 2018; 64:269–279.

Separate cognitive domains may be differently related to dementia progression, but this is not often studied. Especially measures of executive functioning and visuoconstructive skills were associated with progression.

35. Hsu JL, Lee WJ, Liao YC, *et al.* The clinical significance of plasma clusterin and Aβ in the longitudinal follow-up of patients with Alzheimer's disease. Alzheimer's Res Ther 2017; 9:91.
36. Hampel H, Burger K, Teipel SJ, *et al.* Core candidate neurochemical and imaging biomarkers of Alzheimer's disease. Alzheimers Dement 2008; 4:38–48.
37. Poulakis K, Pereira JB, Mecocci P, *et al.* Heterogeneous patterns of brain atrophy in Alzheimer's disease. Neurobiol Aging 2018; 65:98–108.
38. Risacher SL, Anderson WH, Charil A, *et al.* Alzheimer disease brain atrophy subtypes are associated with cognition and rate of decline. Neurology 2017; 89:2176–2186.
39. Chou PS, Kao YH, Wu MN, *et al.* Effect of the interaction between hypertension and cerebral white matter changes on the progression of Alzheimer disease. Curr Alzheimer Res 2018; 15:1354–1360.
40. Benedictus MR, Leeuwis AE, Binnewijzend MA, *et al.* Lower cerebral blood flow is associated with faster cognitive decline in Alzheimer's disease. Eur Radiol 2017; 27:1169–1175.
41. Koychev I, Gunn RN, Firouzian A, *et al.* PET tau and amyloid-β burden in mild Alzheimer's disease: divergent relationship with age, cognition, and cerebrospinal fluid biomarkers. J Alzheimers Dis 2017; 60:283–293.
42. Hamelin L, Lagarde J, Dorothee G, *et al.* Distinct dynamic profiles of microglial activation are associated with progression of Alzheimer's disease. Brain 2018; 141:1855–1870.
43. Barnes J, Bartlett JW, Wolk DA, *et al.* Disease course varies according to age and symptom length in Alzheimer's disease. J Alzheimers Dis 2018; 64:631–642.
44. Wattmo C, Wallin AK. Early- versus late-onset Alzheimer's disease in clinical practice: cognitive and global outcomes over 3 years. Alzheimer's Res Ther 2017; 9:70.
45. Chang KJ, Hong CH, Lee KS, *et al.* Mortality risk after diagnosis of early-onset Alzheimer's disease versus late-onset Alzheimer's disease: a propensity score matching analysis. J Alzheimers Dis 2017; 56:1341–1348.
46. Sinforiani E, Bernini S, Picascia M. Disease progression in relation to age at onset in a population with Alzheimer's dementia. Aging Clin Exp Res 2018. [Epub ehead of print]
47. Kirson NY, Scott Andrews J, Desai U, *et al.* Patient characteristics and outcomes associated with receiving an earlier versus later diagnosis of probable Alzheimer's disease. J Alzheimers Dis 2018; 61:295–307.
48. Winblad B, Amouyel P, Andrieu S, *et al.* Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol 2016; 15:455–532.
49. Chou PS, Wu MN, Chou MC, *et al.* Angiotensin-converting enzyme insertion/deletion polymorphism and the longitudinal progression of Alzheimer's disease. Geriatr Gerontol Int 2017; 17:1544–1550.
50. Burfeind KG, Murchison CF, Westaway SK, *et al.* The effects of noncoding aquaporin-4 single-nucleotide polymorphisms on cognition and functional progression of Alzheimer's disease. Alzheimers Dement (New York, N Y) 2017; 3:348–359.
51. Del-Aguila JL, Fernandez MV, Schindler S, *et al.* Assessment of the genetic architecture of Alzheimer's disease risk in rate of memory decline. J Alzheimers Dis 2018; 62:745–756.
52. ■■ Haaksma ML, Vilela LR, Marengoni A, *et al.* Comorbidity and progression of late onset Alzheimer's disease: a systematic review. PloS one 2017; 12:e0177044.

This review provides evidence of an association between somatic comorbidities and multifaceted LOAD progression. Time-varying comorbidity burden, but much less so baseline comorbidity burden, was associated with dementia progression.

53. ■ Browne J, Edwards DA, Rhodes KM, *et al.* Association of comorbidity and health service usage among patients with dementia in the UK: a population-based study. BMJ Open 2017; 7:e012546.

This study provided evidence that comorbidity is a key factor that should be considered when allocating resources and planning care for people with dementia. It is especially important for being one of the few studies from primary care.

54. Haaksma ML, Rizzuto D, Ramakers I, *et al.* The Impact of frailty and comorbidity on institutionalization and mortality in persons with dementia: a prospective cohort study. J Am Med Dir Assoc 2018. [Epub ehead of print]
55. Xiang J. Carotid atherosclerosis promotes the progression of Alzheimer's disease: a three-year prospective study. Exp Ther Med 2017; 14: 1321–1326.
56. Bleckwenn M, Kleineidam L, Wagner M, *et al.* Impact of coronary heart disease on cognitive decline in Alzheimer's disease: a prospective longitudinal cohort study in primary care. Br J Gen Pract 2017; 67: e111–e117.
57. Eldholm RS, Persson K, Barca ML, *et al.* Association between vascular comorbidity and progression of Alzheimer's disease: a two-year observational study in Norwegian memory clinics. BMC Geriatr 2018; 18:120.
58. Bergland AK, Dalen I, Larsen AI, *et al.* Effect of vascular risk factors on the progression of mild Alzheimer's disease and Lewy body dementia. J Alzheimers Dis 2017; 56:575–584.
59. Taylor ME, Lasschuit DA, Lord SR, *et al.* Slow gait speed is associated with executive function decline in older people with mild to moderate dementia: a one year longitudinal study. Arch Gerontol Geriatr 2017; 73:148–153.
60. Drenth H, Zuidema SU, Krijnen WP, *et al.* Association between advanced glycation end-products and functional performance in Alzheimer's disease and mixed dementia. Int Psychogeriatr 2017; 29:1525–1534.
61. Soni M, Orrell M, Bandelow S, *et al.* Physical activity pre and postdementia: English longitudinal study of ageing. Aging Ment Health 2017. [Epub ehead of print]
62. Minn YK, Hye Choi S, Ju Suh Y, *et al.* Effect of physical activity on the progression of Alzheimer's disease: The Clinical Research Center for Dementia of South Korea Study. J Alzheimers Dis 2018; 66:249–261.
63. Korhonen K, Einio E, Leinonen T, *et al.* Time-varying effects of socio-demo-
■ graphic and economic factors on the use of institutional long-term care before dementia-related death: a Finnish register-based study. PloS one 2018; 13:e0199551.
During dementia progression, the patient may also change in other ways; this urges for studying features not just as baseline but also as time-varying exposures. This study showed that individuals with dementia require intensive professional care at the end of life, regardless of their sociodemographic or economic resources.
64. Tsao S, Gajawelli N, Zhou J, *et al.* Feature selective temporal prediction of Alzheimer's disease progression using hippocampus surface morphometry. Brain Behav 2017; 7:e00733.
65. Stallard E, Kinosian B, Stern Y. Personalized predictive modeling for patients
■■ with Alzheimer's disease using an extension of Sullivan's life table model. Alzheimers Res Ther 2017; 9:75.
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.

