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A comparison of two approaches for modeling dementia progression in a changing patient context

Nina Wubben[1] | Miriam Haaksma[2] | Inez H. G. B. Ramakers[3] | Wiesje M. van der Flier[4] | Frans R. J. Verhey[3] | Marcel G. M. Olde Rikkert[5] | René J. F. Melis[1]

[1]Department of Geriatric Medicine & Radboudumc Alzheimer Center, Radboud Institute for Health Sciences, Radboud University Medical Centre, Nijmegen, The Netherlands

[2]Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, the Netherlands

[3]Department of Psychiatry and Neuropsychology, Maastricht University, School for Mental Health and Neuroscience, Alzheimer Centre Limburg, Maastricht, The Netherlands

[4]Department of Neurology I Amsterdam Neuroscience, Alzheimer Center Amsterdam, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, Netherlands

[5]Department of Geriatric Medicine, Donders Institute for Brain, Cognition and Behaviour, Radboudumc Alzheimer Center, Radboud University Medical Centre, Nijmegen, The Netherlands

Correspondence
René J. F. Melis, Department of Geriatrics / Radboudumc Alzheimer Center, Radboud Institute for Health Sciences, Radboud University Medical Center, Internal postal code 925, PO Box 9101, NL-6500 HB Nijmegen, The Netherlands.
Email: rene.melis@radboudumc.nl

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Abstract

Objectives: To explain the heterogeneity in dementia disease trajectory, we studied the influence of changing patient characteristics on disease course by comparing the association of dementia progression with baseline comorbidity and frailty, and with time-varying comorbidity and frailty.

Methods: We used individual growth models to study baseline and time-varying associations in newly diagnosed dementia patients ($n = 331$) followed for 3 years. We measured cognition using the Mini-Mental State Examination (MMSE), daily functioning using the Disability Assessment for Dementia (DAD), frailty using the Fried criteria and comorbidity using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G).

Results: Although baseline comorbidity and frailty were associated with decreased daily functioning at diagnosis, their effects clearly diminished over time. In contrast, when incorporating comorbidity and frailty as time-varying covariates, comorbidity was associated with lower daily functioning, and frailty with both lower cognition and daily functioning. Being frail was associated with a 0.9-point lower MMSE score ($p = 0.03$) and a 14.9-point lower DAD score ($p < 0.01$). A 1-point increase in CIRS-G score was associated with a 1.1-point lower DAD score ($p < 0.01$).

Conclusions: Time-varying comorbidity and frailty were more consistently associated with dementia disease course than baseline comorbidity and frailty. Therefore, modeling only baseline predictors is insufficient for understanding the course of dementia in a changing patient context.

KEYWORDS
Alzheimer, comorbidity, comorbidity, dementia, disease trajectory, frailty, mixed models

Key points

- Changes in personal characteristics such as comorbidity and frailty during follow-up explain, in part, the observed heterogeneity in trajectories of dementia progression.

- As comorbidity and frailty fluctuate over time and often increase with age, baseline measurements might not suffice when modelling their relationship with disease progression measurements.
- Our results show that unlike at-diagnosis (i.e., baseline) levels of frailty and comorbidity, time-varying levels are more consistently associated with changes in the course of dementia.

1 | INTRODUCTION

Much remains unknown about dementia and its burden to patients, their loved ones and society. Alzheimer's disease accounts for 60%–80% of dementia cases. There are no therapies available that can counter disease progression, and knowledge advancement is slow. One of the challenges is the significant heterogeneity that is seen in dementia disease trajectories.[1–5] This heterogeneity complicates the forecasting of an accurate disease prognosis. It is one of the barriers that clinicians encounter in advanced care planning,[6,7] and stands in the way of personalized care provision. But it may also provide avenues for better care, if we could understand why some people show milder and slower decline than others.

Part of the heterogeneity may be explained by disease-related factors, such as sub-type of dementia. Other factors are patient related and more contextual to the disease itself.[8] Among these are frailty and comorbidity, both common in people with dementia. Few studies so far have focused on exploring the role of patient factors in dementia disease progression as most research is focused on disease-related factors.[9] The studies that have focused on the influence of patient factors on disease course have yielded inconsistent results.[10–13]

This inconclusiveness may be aggravated by the fact that some of studies have overlooked important aspects of clinical manifestation by defining dementia disease progression predominantly in terms of cognitive decline.[9,14] As dementia is characterised by changes in daily functioning as well, a multidimensional definition of disease progression is recommended.[1,13,14] Moreover, previous studies[1,12] generally failed to consider the impact of other health variables that fluctuate during follow-up on disease progression. Especially in elderly people, both comorbidity and frailty status can vary, contributing to a dynamic relationship with disease progression.[7,13,15,16] The changing nature of such patient characteristics should be considered when analysing their association with disease progression, for instance, by incorporating them as time-varying variables in multilevel models of change.[17] Previous research has demonstrated a time-varying association between comorbidity and Alzheimer's progression, while finding none between progression and baseline comorbidity. This means that disease severity at a particular time-point was associated with comorbidity burden at that same time-point.[7]

In light of this, the present study aims to investigate the associations of both baseline and time-varying comorbidity and frailty with dementia progression, measured through daily functioning and cognition. Given that patient factors also change during the progression of dementia, we hypothesise that baseline comorbidity and frailty are likely less associated with disease progression, as compared to time-varying comorbidity and frailty.

2 | MATERIALS AND METHODS

2.1 | Participants

Data from the longitudinal, prospective Clinical Course of Cognition and Comorbidity in Dementia (4C) study were used.[8] Inclusion criteria for the cohort were objective cognitive impairments, fulfilment of the DSM-IV diagnosis criteria for dementia,[18] a Clinical Dementia Rating higher than 0.5, and a Mini-Mental State Examination (MMSE) score equal to or higher than 10. No constraints were put on age or comorbidity.[19] The dataset contains the records of 331 patients who were included in the study upon a clinical diagnosis of mild to moderate dementia in 2009–2011[18] in the Alzheimer Centres of Amsterdam, Maastricht and Nijmegen, the Netherlands. Following inclusion, all participants were contacted once a year for three consecutive years. Three local ethics committees approved the study.[8]

2.2 | Outcomes

The main outcome of this study is disease progression, measured multidimensionally as cognition and daily functioning. Cognition was measured using the MMSE[20] (range: 0–30). A higher score equals better cognitive functioning. Daily functioning was quantified using the Disability Assessment for Dementia (DAD) score[21] (range: 0–100), which assesses both basic and instrumental activities of daily living (ADL and iADL). The total score was the percentage of all of the activities considered that a patient was able to perform. A higher score equals better daily functioning.

2.3 | Independent variables of interest

To quantify comorbidity, the Cumulative Illness Rating Scale for Geriatrics (CIRS-G)[22] was used. The CIRS-G measures severity of chronic morbidity in 14 disease categories. Every category is scored from 0 to 4 to represent the disease burden. A higher score represents a higher burden of morbidity. For this study, the disease category 'psychiatric' was excluded in order to prevent overlap with the outcome measures of dementia progression (range: 0–52).

TABLE 1 Baseline and follow-up characteristics

	Baseline	12 months	24 months	36 months
N	331			
Female sex; N (%)	181 (54.7)			
Age (years); mean (SD)	74.9 (10.2)			
Follow up (years); mean (SD)	1.8 (1.3)			
Low education; N (%)	74 (22.4)			
Dementia type; N (%)				
- Alzheimer's disease	216 (65)			
- Vascular dementia	71 (21)			
- Other	44 (13)			
	Baseline	12 months	24 months	36 months
CIRS-G score; mean (SD)	7.5 (4.9)	6.1 (4.5)	5.9 (4.1)	7.0 (4.8)
N with comorbidity (%)	269 (81.3)	153 (46.2)	120 (36.3)	116 (35.0)
- 1 comorbidity; N (%)	69 (25.7)	52 (34.0)	41 (34.2)	37 (31.9)
- 2 comorbidities; N (%)	55 (20.4)	32 (20.9)	32 (26.7)	24 (20.7)
- ≥3 comorbidities; N (%)	145 (53.9)	69 (45.1)	47 (39.2)	55 (47.4)
Fried frailty; mean (SD)	1.2 (1.2)	1.0 (1.0)	1.2 (1.0)	1.2 (1.1)
N with Fried frailty (%)	325 (98.2)	212 (64.0)	150 (45.3)	107 (32.3)
- ≤1; N (%)	224 (68.9)	151 (71.2)	104 (69.3)	75 (70.0)
- 2; N (%)	55 (16.9)	41 (19.3)	28 (18.7)	16 (15.0)
- ≥3; N (%)	46 (14.2)	20 (9.4)	18 (12.0)	16 (15.0)
Frailty index; mean (SD)	0.31 (0.2)	0.31 (0.1)	0.23 (0.1)	0.30 (0.2)
N with FI calculated (%)	331 (100)	222 (67.1)	158 (47.7)	145 (43.8)
- ≤0.08; N (%)	13 (3.9)	4 (1.8)	15 (9.5)	13 (9.0)
- 0.08–0.25; N (%);	108 (32.6)	78 (35.1)	75 (47.5)	54 (37.2)
- ≥0.25; N (%)	210 (63.5)	140 (63.1)	68 (43.0)	78 (53.8)
MMSE; mean (SD)	21.9 (3.7)	21.0 (5.1)	19.1 (5.8)	18.3 (5.9)
N with MMSE (%)	331 (100)	218 (65.9)	150 (45.3)	112 (33.8)
DAD; mean (SD)	70.8 (24.1)	68.6 (24.5)	59.1 (27.4)	48.2 (27.0)
N with DAD (%)	326 (98.5)	219 (66.2)	154 (46.5)	141 (42.6)

Note: CIRS-G, Cumulative Illness Rating Scale for Geriatrics (range: 0–52); Frailty Index (range 0–1); MMSE = Mini-Mental State Examination (range: 0–30); DAD = Disability Assessment for Dementia (0%–100%).

Frailty was quantified using the Fried criteria[23] (frail/not frail) and a Frailty Index (FI; range: 0–1).[24,25] The Fried criteria describe frailty by scoring five different areas associated with the frailty phenotype.[23] According to the Fried criteria, a person is frail when fulfilling at least three out of five criteria.[26] The FI operationalises frailty as an accumulation of health deficits covering multiple domains. A higher score indicates more frailty.[25] In this study, the method described by Searle et al.[24] was used to develop an FI. To prevent overlap between determinants and outcomes we did not include any items from the MMSE, DAD or CIRS-G in the FI. A list of all 22 deficits used in the FI in this study can be found in supporting information S1.

2.4 | Statistical analysis

Individual growth models were used to study the effects of comorbidity and frailty on change in cognition and daily functioning. Time was measured in years from the moment of diagnosis onwards. Firstly, unconditional growth models were built to test whether linear growth or curvilinear growth best explained within-person change over time. Random terms for intercept and slope were added, as these improved model fit. Next, independent variables of interest were added to the models to assess whether they significantly ($\alpha < 0.05$) explained the between-person variance.[27]

Separate models were built for the two different outcome measurements; MMSE and DAD. Longitudinal comorbidity and Fried frailty were included as either time-invariant variables (measured at diagnosis) and their interactions with time, or as time-varying covariates, resulting in four individual growth models.

In all four models, the intercept, slope and quadratic slope were adjusted for baseline age, gender and whether a person had had a low education, defined as having finished only primary education.[28] All of the covariates were mean-centred. Mean growth curves were plotted for each of the individual growth models, representing the trajectory of an average 75-year-old patient with dementia. In addition, growth curves for the average patient with ±1 point of Fried frailty and for the average patient with ±4 points on the CIRS-G scale were added to graphically demonstrate the covariates' effects.

As an additional analysis, we also built two models (one for each of our two outcomes; MMSE and DAD), including the effects of frailty as operationalized by the FI.

SAS version 9.2 was used to perform all statistical analyses. R version 3.4.3 was used to produce the plots.

3 | RESULTS

3.1 | Baseline characteristics

Baseline characteristics of the study population can be found in Table 1. The mean age of the population was 74.9 (SD = 10.2) years. The majority of the sample was female (55%). Mean follow-up was 1.8 (SD = 1.3) years, and 22% of the sample had only finished primary education. At the last follow-up point at 36 months, around a third of the study participants had a measurement value for the CIRS-G, Fried frailty, MMSE and DAD scores. The Frailty index had a slightly higher percentage of 43.8% participants for whom a score could be calculated. The mean baseline MMSE score was 21.9 (SD = 3.7), ranging from 11 to 30, while the mean DAD score was 71% (SD = 24%), and ranged from 3% to 100%. Both of these outcomes decreased over time.

There was considerable variability in frailty and comorbidity over time within individuals, as shown in Table 1. Moreover, 81.2% of study participants reported at least one comorbidity (Table 2). Across all follow-up measurements, patients most often had three or more comorbidities, rather than one or two. Regardless of number of comorbidities, patients most often reported vascular comorbidity (N = 170).

3.2 | Individual growth models

Modelling the within-person change over time in unconditional growth models showed that the best fitting models were curvilinear, with a random intercept and random linear slope. A random quadratic slope was tested but did not improve model fit. An unconditional growth model, as well as two conditional growth models for change in MMSE, are shown in Table 3. Similarly, three models for change in DAD are reported in Table 4.

3.3 | Cognition

As can be seen from the unconditional growth model (model 1) in Table 3, cognitive function as measured by the MMSE score declined over time.

Neither baseline comorbidity nor baseline frailty showed an association with cognition (model 2). However, there was an association between time-varying frailty status and cognition (model 3).

TABLE 2 Affected organ systems in patients having either 1, 2 or ≥3 comorbidities, N (%)

	1 chronic disease (%)[a] N = 69 (20.8)	2 chronic diseases (%)[a] N = 55 (16.6)	≥3 chronic diseases (%)[a] N = 145 (43.8)	Total (%)[a] N = 269 (81.2)
Heart	2 (2.9)	13 (23.6)	75 (51.7)	90 (33.5)
Vascular	24 (34.8)	32 (58.2)	114 (78.6)	170 (63.2)
Hematopoietic	1 (1.4)	0 (0)	24 (16.6)	25 (9.3)
Respiratory	5 (7.2)	12 (21.8)	37 (25.5)	54 (20.1)
Eyes/ears/nose/throat	9 (13.0)	5 (9.1)	58 (40.0)	72 (26.8)
Upper gastrointestinal	1 (1.4)	5 (9.1)	37 (25.5)	43 (16.0)
Lower gastrointestinal	2 (2.9)	6 (10.9)	27 (18.6)	35 (13.0)
Liver	0 (0)	6 (10.9)	15 (10.3)	21 (7.8)
Renal	0 (0)	1 (1.8)	18 (12.4)	19 (7.1)
Genitourinary	7 (10.1)	7 (12.7)	61 (42.1)	75 (27.9)
Neuromuscular	5 (7.2)	9 (16.4)	56 (38.6)	70 (26.0)
Neurological	4 (5.8)	8 (14.5)	36 (24.8)	48 (17.8)
Endocrine	9 (13.0)	6 (10.9)	44 (30.3)	59 (21.9)

[a]Column percentage.

TABLE 3 Multilevel models of change in cognition (MMSE) as a function of follow-up time, age, gender, low education, comorbidity measured with the CIRS-G score and frailty status (yes/no) according to the Fried criteria

Fixed effects	Model 1: Unconditional growth model		Model 2: Effect of baseline comorbidity and frailty on MMSE[a]		Model 3: Effect of time-varying comorbidity and frailty on MMSE[a]	
	B (SE)	p-Value	B (SE)	p-Value	B (SE)	p-Value
Intercept predictors						
Intercept	22.0 (0.21)	<0.01	22.5 (0.32)	<0.01	22. 6 (0.32)	<0.01
Baseline CIRS-G			−0.02 (0.05)	0.70		
Baseline frailty according to Fried			−0.7 (0.64)	0.28		
Time-varying CIRS-G					−0.02 (0.04)	0.60
Time-varying frailty according to Fried					−0.9 (0.42)	0.03
Slope predictors						
Follow-up year	−1.2 (0.28)	<0.01	−0.8 (0.44)	0.09	−0.9 (0.45)	0.06
Baseline CIRS-G			0.1 (0.07)	0.29		
Baseline frailty according to Fried			−0.9 (1.09)	0.28		
Quadratic slope predictors						
Follow-up year	−0.3 (0.09)	0.00	−0.5 (0.13)	<0.01	−0.4 (0.14)	<0.01
Baseline CIRS-G			−0.02 (0.02)	0.38		
Baseline frailty according to Fried			0.4 (0.37)	0.32		
Random effects						
Initial MMSE	9.6 (1.15)	<0.01	9.1 (1.09)	<0.01	9.1 (1.14)	<0.01
Covariance	1.9 (0.66)	<0.01	1.9 (0.63)	<0.01	1.7 (0.68)	0.01
Rate of change	4.0 (0.69)	<0.01	3.9 (0.69)	<0.01	4.1 (0.74)	<0.01
Residual	5.1 (0.47)	<0.01	4.9 (0.45)	<0.01	5.0 (0.50)	<0.01

Abbreviations: CIRS-G, Cumulative Illness Rating Scale for Geriatrics; MMSE, Mini-Mental State Examination.

[a]Intercept, slope and quadratic slope have been corrected for baseline age, gender and low education.

Being classified as frail as opposed to not frail by the Fried criteria was associated with a 0.9 lower MMSE score at each time point ($p = 0.03$). There was no evidence for an association between time-varying comorbidity and cognitive decline.

The findings of the multilevel models of change in cognition are summarised in Figure 1. The mean growth curves represent the MMSE trajectory of an average 75-year-old patient with dementia. The MMSE models and graphs using the FI to operationalize frailty can be found in supporting information S1.

3.4 | Daily functioning

From the unconditional growth model (model 4) in Table 4, which describes change in daily functioning over time, it is apparent that daily functioning decreased over time.

In the time-invariant model (model 5), Fried frailty at baseline was associated with a 19.6% ($p < 0.01$) lower daily functioning score at baseline. Similarly, a 1-point increase in baseline CIRS-G score results in a 1.2% lower DAD score ($p < 0.01$) at baseline.

However, neither baseline frailty status nor comorbidity were associated with change in daily functioning over time in the long term. Although there initially appears to be an effect of baseline comorbidity on the linear slope of the DAD (1.1% per CIRS-G point per year, $p < 0.01$), this effect clearly diminished over time, as it was offset by a lower baseline DAD (−1.2 per point CIRS-G, $p < 0.01$) and the negative quadratic slope (−0.3 per point CIRS-G per year, $p = 0.02$).

In the time-varying model (model 6), an increase in time-varying comorbidity score and being classified as frail were both associated with lower DAD scores at each time-point (−1.1 per point CIRS- G, $p < 0.01$, and −14.9, $p < 0.01$, respectively).

These findings are summarised in mean growth curves in Figure 2. These graphs depict how using only baseline measurements attenuates the relationship between the predictors and change in daily functioning. A more consistent effect is observed when using time-varying predictors, that is, when updating covariates at each time-point (right panel). The DAD models and graphs including the FI to operationalise frailty can be found in supporting information S1.

TABLE 4 Multilevel models of change in daily functioning (DAD) as a function of follow-up time, age, gender, low education, comorbidity measured with the CIRS-G score and frailty status (yes/no) according to the Fried criteria

Fixed effects	Model 4: Unconditional growth model		Model 5: Effect of baseline comorbidity and frailty on DAD[a]		Model 6: Effect of time-varying comorbidity and frailty on DAD[a]	
	B (SE)	p-Value	B (SE)	p-Value	B (SE)	p-Value
Intercept predictors						
Intercept	71.1 (1.33)	<0.01	75.1 (1.85)	<0.01	74.3 (1.80)	<0.01
Baseline CIRS-G			−1.2 (0.29)	<0.01		
Baseline frailty according to Fried			−19.6 (3.68)	<0.01		
Time-varying CIRS-G					−1.1 (0.23)	<0.01
Time-varying frailty according to Fried					−14.9 (2.25)	<0.01
Slope predictors						
Follow-up year	−3.6 (1.51)	0.02	−3.2 (2.34)	0.17	−4.1 (2.32)	0.08
Baseline CIRS-G			1.1 (0.38)	<0.01		
Baseline frailty according to Fried			8.9 (5.52)	0.11		
Quadratic slope predictors						
Follow-up year	−2.0 (0.46)	<0.01	−2.3 (0.74)	<0.01	−1.1 (0.75)	0.16
Baseline CIRS-G			−0.3 (0.12)	0.02		
Baseline frailty according to Fried			−1.1 (1.88)	0.56		
Random effects						
Initial DAD	411.3 (45.1)	<0.01	287.8 (35.04)	<0.01	295.0 (36.19)	<0.01
Covariance	−40.8 (18.32)	0.04	−19.6 (16.08)	0.22	−21.9 (17.52)	0.21
Rate of change	68.7 (13.10)	<0.01	63.7 (12.17)	<0.01	66.5 (13.87)	<0.01
Residual	170.1 (14.60)	<0.01	163.3 (13.91)	<0.01	150.8 (14.50)	<0.01

Abbreviations: CIRS-G, Cumulative Illness Rating Scale for Geriatrics; DAD, Disability Assessment for Dementia.

[a]Intercept, slope and quadratic slope have been corrected for baseline age, gender and low education.

4 | DISCUSSION

4.1 | Interpretation of results

In this study, time-varying frailty was associated with both functional and cognitive decline, while time-varying comorbidity was associated with functional decline. At-baseline comorbidity and frailty were associated with functional decline only and mostly in the short term.

Figures 1 and 2, where we compare our baseline and time-varying approaches, show that models using baseline data differ from the time-varying models that use data at each time-point. When one only uses the exposure levels at diagnosis, the impact of the post-diagnosis fluctuations on the disease course will be left unnoticed. Our results suggest that the impact of at-diagnosis measurements of patient characteristics, such as frailty and comorbidity, on disease progression may not be sustained over time, i.e., these baseline measurement are not associated with disease outcomes in the long run. This might be due to the fact that comorbidity and frailty, like other patient-related factors, change during the progression of chronic diseases, particularly in older persons with dementia.

4.2 | Comparison with previous studies

In this study, no evidence was found for associations between at-baseline nor time-varying comorbidity and change in cognition. These results are in line with a Swedish population-based study in incident dementia cases, which found no association between baseline comorbidity and cognitive decline either.[13] Neither did another longitudinal study in incident dementia cases in the United States.[7] However, in a time-varying model, the latter study did find an increased comorbidity score to be associated with cognitive decline,[7,13] possibly due to their usage of a different comorbidity score: the General Medical Health Rating. Although in a recent systematic review seven out of 10 studies found comorbidities to be related to decreased cognitive performance,[17] we did not find such an association.
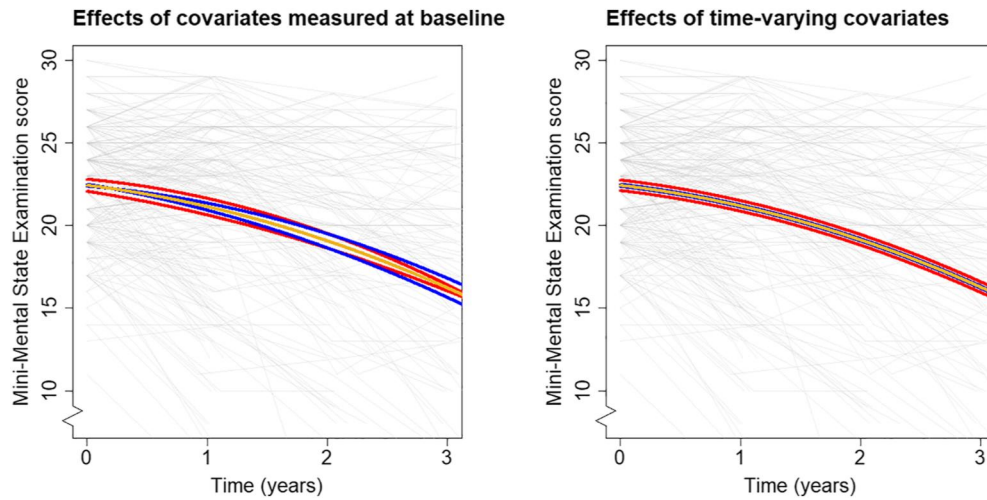
FIGURE 1 Mean growth curves (yellow) for cognitive function (Mini-Mental State Examination) over time (time = 0 representing dementia diagnosis), representing the trajectory of an average 75-year-old patient with dementia. Growth curves for the average patient with ±1 point of Fried frailty, incorporated as a continuous variable (range: 0–4) for the purpose of this graph, are shown in red. Growth curves for the average patient with ±4 points on the Cumulative Illness Rating Scale for Geriatrics scale are depicted in blue. The left panel shows the model including time-invariant (baseline) covariates; the right panel shows the model including time-varying covariates
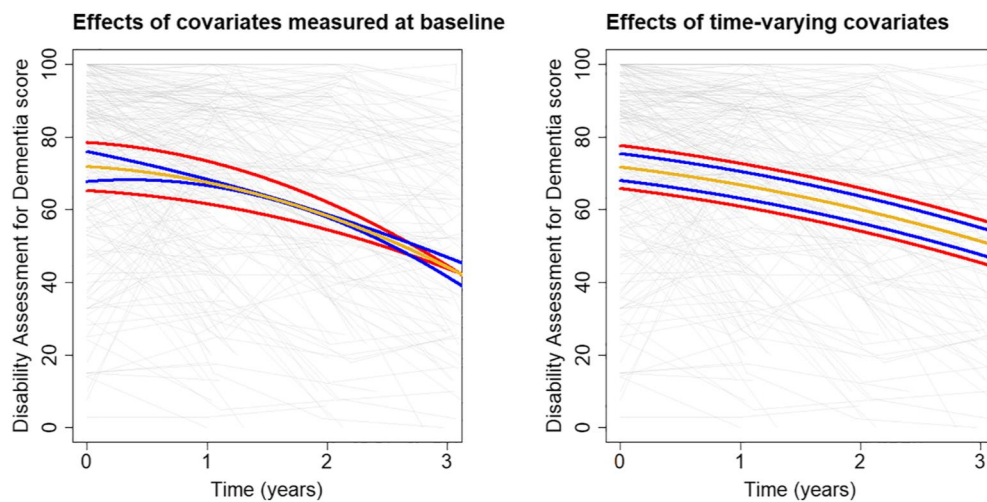
FIGURE 2 Mean growth curves (yellow) for daily functioning (Disability Assessment for Dementia) over time (time = 0 representing dementia diagnosis), representing the trajectory of an average 75-year-old patient with dementia. Growth curves for the average patient with ±1 point of Fried frailty, incorporated as a continuous variable (range: 0–4) for the purpose of this graph, are shown in red. Growth curves for the average patient with ±4 points on the Cumulative Illness Rating Scale for Geriatrics scale are depicted in blue. The left panel shows the model including time-invariant (baseline) covariates; the right panel shows the model including time-varying covariates

With regards to frailty, the present study showed an association between time-varying frailty and a decline in cognitive function, but that effect was small and probably not clinically relevant. Despite the small effect size, the fact that an association was observed in the time-varying model while it was not observed in the model using only baseline frailty, may indicate the existence of a dynamic relationship between frailty and cognitive function. In other words, our findings indicate that, over time, disease and patient factors (e.g., frailty and physical health) are mutually dependent on each other. Baseline frailty has been linked to (future) cognitive decline in reviews containing both cross-sectional and longitudinal studies,[29,30] which both

mention the scarcity of relevant studies as a limitation in their discussion of results. Our findings are in agreement with those from a small memory clinic cohort from Singapore which found time-varying frailty to be associated with cognitive deterioration in patients with mild to moderate Alzheimer's disease.[15]

Associations of frailty and comorbidity with changes in daily functioning were stronger than those with cognitive decline. An influence of physical impairments (i.e. comorbidity) on day-to-day functioning seems intuitive, and is supported by existing literature.[12,13,17,31] In our study, both baseline and time-varying comorbidity were associated with a decrease in daily functioning. In their

review, Haaksma et al. described several longitudinal studies that looked at associations between comorbidity and daily functioning.[17] Of the studies described, the Swedish study referenced earlier concluded that there was an association between baseline comorbidity and daily functioning,[13] as is in line with our present study. A population-based cohort study from the United States also found stronger associations between daily functioning and time-varying comorbidity, as compared to baseline comorbidity.[7]

We found baseline and time-varying frailty to be linked to a decrease in daily functioning at baseline and at each time-point, respectively. Frailty and decreased daily functioning have previously been linked in the general geriatric population.[32] In addition, Oosterveld et al. previously showed a cross-sectional association between baseline frailty and decreased daily functioning in our sample.[12]

In summary, the fact that we mainly observed a detrimental effect of time-varying comorbidity and frailty on cognition and daily functioning in dementia is in line with the hypothesised existence of a dynamic relationship between these characteristics and dementia progression.[7,15,17]

4.3 | Strengths and limitations

Among the strengths of this study is our large, representative sample of clinically diagnosed dementia patients, hailing from three different Alzheimer centres. Also, comorbidity and frailty assessments were performed by physicians and experienced research nurses only.[8] Moreover, considering dementia a multidimensional disease and consequently quantifying disease progression by measuring both cognition and daily functioning is another strength. As in all conditions with an insidious onset, a clinical sample of dementia patients has the limitation that a dementia diagnosis does not equal disease onset.[33] It is likely that patients were enrolled in our study at different points in their disease trajectory. This could, in part, explain the heterogeneity of dementia progression observed in our study.

As we found strong associations between comorbidity and change in daily functioning, a subsequent study with larger sample size could identify which comorbidities are related to the increased progression speed. Like-wise, it was the sample size that kept us from stratifying our results by dementia subtypes, or by age group. Notably, the loss-to-follow-up during the study period, often due to death, was large. This is not wholly unexpected, due to the advanced age of the study population. Descriptive analyses (not shown) were used to ascertain that the baseline characteristics of the lost-to-follow-up group did not differ significantly from the group who completed follow-up. Nevertheless, results should be interpreted bearing this in mind.

4.4 | Practical implications

The relevance of our findings may carry beyond studying dementia progression alone and have implications for studying the time course of chronic diseases in general. Firstly, the heterogeneous progression of chronic diseases may be better understood if not only disease characteristics such as disease types, disease severity and biomarkers are included in the analysis, but also patient factors such as frailty and other diseases the person has. In clinical care, the relevance of a biopsychosocial perspective for understanding disease is well established and models are available to guide research towards a more holistic perspective.[34,35] Secondly, it is often the case that these patient and context characteristics change during the course of a chronic disease. Therefore, future studies that endeavour to explore the role of patient factors in chronic disease progression may consider a possible time-varying relationship in addition to studying baseline (time-invariant) exposure levels. The practical consequence of this is that one has to measure repeatedly—not just outcomes, but also predictors.[36]

This study found less strong associations of baseline comorbidity and frailty measures with changes in cognition and daily functioning, than when incorporating comorbidity and frailty as time-varying covariates. Time-varying covariates were more consistently associated with dementia disease course. These results indicate that when using only the exposure levels at diagnosis, the impact of the post-diagnosis fluctuations on the disease course may be left unnoticed. In addition, these results suggest that adequate management of frailty and comorbidity across the disease course may help optimize disease management by slowing dementia-related declines in cognition and daily functioning. Future research should consider incorporating multiple repeated measurements of both predictors and outcome variables to capture the dynamic relationships between fluctuating patient characteristics and long-term outcomes of chronic disease.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

ETHICS STATEMENT

The ethical committees of the institutes Alzheimer Centre Limburg of the Maastricht University Medical Center, and Radboudumc Alzheimer Center, Radboud University Medical Center participating in this study approved the study. The 4C-Dementia cohort was approved by the CMO Arnhem-Nijmegen (CMO 0529, registration number 2010/046), respectively.

PATIENT CONSENT STATEMENT

The clinician responsible for the care during the memory clinic visit asked whether patients would be willing to consider participation in the 4C study. If so, they were provided with written study information and a visit was scheduled with a research assistant to obtain

written informed consent from the participant and an informant and to complete the baseline assessments.

DATA AVAILABILITY STATEMENT

The 4C research group actively encourages and welcomes external collaborations. Data are available for researchers with a specific research question. Interested and potential collaborators are invited to contact the study coordinators (Dr. René Melis Rene.Melis@radbou-dumc.nl or Dr. Inez Ramakers i.ramakers@maastrichtuniversity.nl).

ORCID

Nina Wubben https://orcid.org/0000-0001-6461-0068
Miriam Haaksma https://orcid.org/0000-0002-3518-9152
Inez H. G. B. Ramakers https://orcid.org/0000-0002-4747-2879
Wiesje M. van der Flier https://orcid.org/0000-0001-8766-6224
Frans R. J. Verhey https://orcid.org/0000-0002-8307-8406
Marcel G. M. Olde Rikkert https://orcid.org/0000-0003-1397-1677

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.