



**HAL**  
open science

## Dynamic reciprocal relationships between cognitive and functional declines along the Alzheimer's disease continuum in the prospective COGICARE study

Sophie Carles, Bachirou O Taddé, Claudine Berr, Catherine Helmer, Hélène Jacqmin-Gadda, Isabelle Carrière, Cécile Proust-Lima

### ► To cite this version:

Sophie Carles, Bachirou O Taddé, Claudine Berr, Catherine Helmer, Hélène Jacqmin-Gadda, et al.. Dynamic reciprocal relationships between cognitive and functional declines along the Alzheimer's disease continuum in the prospective COGICARE study. *Alzheimer's Research and Therapy*, 2021, 13 (1), pp.148. 10.1186/s13195-021-00887-4 . hal-03356240

**HAL Id: hal-03356240**

**<https://hal.science/hal-03356240>**

Submitted on 27 Sep 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

# **Dynamic Reciprocal relationships between cognitive and functional declines along the Alzheimer's disease continuum in the prospective COGICARE study**

Sophie Carles<sup>1</sup>, Bachirou O.Taddé<sup>2</sup>, Claudine Berr<sup>1</sup>, Catherine Helmer<sup>2</sup>, Hélène Jacqmin-Gadda<sup>2</sup>,  
Isabelle Carrière<sup>1</sup>, Cécile Proust-Lima<sup>2\*</sup>

<sup>1</sup>Institute for Neurosciences of Montpellier INM, Univ. Montpellier, INSERM, F-34091  
Montpellier, France

<sup>2</sup>Univ. Bordeaux, INSERM, BPH, U1219, F-33000 Bordeaux, France

\*corresponding author: [cecile.proust-lima@inserm.fr](mailto:cecile.proust-lima@inserm.fr) ; ORCID: 0000-0002-9884-955X

## **DECLARATIONS**

**Ethics approval and consent to participate:** the study protocols of the 3C and COGICARE studies used in this work were approved by the Ethics Committee of the University Hospital of Bicêtre and Sud-Méditerranée III (France) and written informed consent obtained for each participant.

**Consent for publication:** not applicable

**Availability of data and material:** Anonymized data will be shared by reasonable request to the 3C scientific committee. Scripts for replicating the analyses can be sent on demand.

**Competing interests:** no conflict of interest or competing interests.

**Funding:** This study was funded by the French National Research Agency [grant ANR-15-CE37-0002 for the SMALA project, grant ANR-07-LVIE-003 for the COGICARE project] .

**Authors' contributions:** All authors contributed to the study conception and design. Acquisition of the data was performed by Catherine Helmer and Claudine Berr. Statistical analyses were performed by Sophie Carles, Bachirou Taddé and Cécile Proust-Lima. All the authors contributed to the interpretation of the results. The first draft of the manuscript was written by Sophie Carles and Cécile Proust-Lima, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Acknowledgement:** Computer time was provided by the computing facilities MCIA (Mésocentre de Calcul Intensif Aquitain) at the Université de Bordeaux and the Université de Pau et des Pays de l'Adour.

**Authors' information:** not applicable

## **ABSTRACT**

**Background:** Thoroughly understanding the temporal associations between cognitive and functional dimensions along the dementia process is fundamental to define preventive measures likely to delay the disease's onset. This work aimed to finely describe the trajectories of cognitive and functional declines, and assess their dynamic bidirectional relationships among subjects at different stages of the dementia process.

**Methods:** We leveraged extensive repeated data of cognition and functional dependency from the French prospective COGICARE study, designed to better characterize the natural history of cognitive and functional declines around dementia diagnosis. Cognition was measured by the Mini Mental State Examination, the Isaacs Set Test for verbal fluency, the Benton Visual Retention Test for visuo-spatial memory and Trail Making Test Part B for executive functioning. Functional dependency was measured by basic and instrumental activities of daily living. The study included 102 cognitively normal, 123 mildly cognitively impaired and 72 dementia cases with a median of 5 repeated visits over up to 57 months. We used a dynamic causal model which addresses the two essential issues in temporal associations assessment: focusing on intra-individual change and accounting for time.

**Results:** Better cognitive abilities were associated with lower subsequent decline of the functional level among the three clinical stages with an intensification over time but no reciprocity of the association whatever the clinical status.

**Conclusion:** This work confirms that the progressive functional dependency could be induced by cognitive impairment. Subjects identified as early as possible with clinically significant cognitive impairments could benefit from preventive measures before the deterioration of activities of daily living and the appearance of dementia clinical signs.

**KEYWORDS:** Activities of daily Living; Cognitive aging; Mini-Mental State Examination; Temporal Association; Causality; Dementia

## **BACKGROUND**

There is now evidence that the pathophysiological process of Alzheimer's Disease (AD) begins decades before the appearance of clinical signs of dementia [1–4]. AD's preclinical stages may constitute a critical window to define and implement early preventive measures likely to delay the disease's onset or magnitudes of symptoms. Thoroughly describing the multiple dimensions, mainly cognitive and functional ones, all along the complex AD process, is consequently fundamental. However, longitudinal studies in this field were mainly limited to one dimension at a time ignoring the possible inter-relationships with others. Yet, investigating how the different dimensions interplay over time at distinct clinical stages could be a key to better understand the AD pathological cascade and prioritize interventions.

Uncertainties remain in particular on the temporal relationships between cognitive and functional declines. Subjects with initial clinical presentation of AD have been described with cognitive deficits and no evident limitations in activities of daily living (ADL) that seem to appear later in the disease process [5]. Correlation between cognition and function has been shown to increase as AD patients progressed from preclinical to moderate dementia [6]. Few studies formally assessed the temporal relationships between patterns of cognitive and functional declines and potential differences in their joint evolution along the AD continuum [7–9]. These results suggest that cognitive decline precedes and predicts subsequent functional impairment assessed notably, in mild cognitive impairment (MCI), by the ability to perform ADL. Functional decline has also been suggested as a predictor of both cognitive decline (but only intermittently and not in incident AD cases) [10], and conversion from MCI to AD [11].

Since longitudinal processes are likely to vary between individuals and to change over time, two major aspects have to be taken into account when investigating temporal relationships [12]. First, time is central and association assessment should be unrelated to the visit

schedule. Second, the interest should be in the intra-individual change rather than the inter-individual differences. Indeed, from a causal perspective, the goal is to understand how the system changes as time goes on, and what factors influence the future individual change [13]. By relying on autoregressive and cross-lagged models (ARCL), the rare studies investigating reciprocal temporal dependencies between cognition and functional dimensions over time [7,9,10] did not account for these two major elements [12]. They considered inter-individual differences between successive levels of variables at observed visit times, thus not targeting intra-individual changes, limiting the interpretation to the visit schedule of the study, and possibly inducing spurious associations if sparse [14]. With cognitive and functional dimensions being measured by scores with ceiling/floor effects or unequal interval scaling [15], a third aspect to take into account is the departure from normality which can induce biased estimates if not properly taken into account [16].

In the current study, we aimed to finely describe the trajectories of both cognitive and functional declines, and assess their dynamic bidirectional relationships among subjects with normal aging, MCI or AD participating in a French cohort study, the natural history of COGNitive decline and need of CARE in the elderly (COGICARE) Study. We applied for that a dynamic multivariate causal model [17] that overcomes the major methodological requisites to assess temporal associations.

## **METHODS**

### **The COGICARE study**

The current study analyses the data from COGICARE which is a sub-study of the Three-City (3C) study in Montpellier and Bordeaux centers. COGICARE was designed to better characterize the natural history of cognitive and functional declines around dementia diagnosis through an extensive follow-up of subjects at three different stages: AD, MCI or cognitively normal (CN). The study protocols of the 3C and COGICARE studies were approved by the Ethics Committee of the University Hospital of Bicêtre and Sud-Méditerranée III (France) and written informed consent obtained for each participant.

The 3C study is a community-living cohort of 9,294 elders ( $\geq 65$  years of age) randomly recruited from the electoral rolls of three French cities (Bordeaux, Dijon and Montpellier) between 1999 and 2001 [18]. Standardized examinations including face-to-face interviews and cognitive and functional assessments (in a medical center or at home) took place at inclusion and then every 2-3 years (i.e., after 2, 4, 7, 10, 12 and 14 years of follow-up). AD incident cases diagnosis was based on an examination by a neurologist of all participants in Montpellier and of participants suspected of having a dementia (based mainly on their clinical, cognitive or functional assessments) in Bordeaux. An adjudication panel of independent neurologists reviewed all the existing information to confirm the diagnosis of dementia according to the Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition (DSM-IV) [19], and its etiology. AD was classified according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria [20]. MCI was defined as (details in Web appendix 1) (i) an alteration of verbal episodic memory (i.e. a free recall score  $<17$  and a total recall score  $<40$ ) [21] on the Free and Cued Selective Reminding Test (FCSRT) [22] and (ii) partial or total

limitation in their abilities to perform at least two of four Instrumental Activities of Daily Living (IADL) [23].

Were eligible to enter the COGICARE sub-study: 1/ AD incident cases from Bordeaux and Montpellier centers diagnosed at the 3C 7- or 9-year follow-up and non-demented at the last visit preceding the AD diagnosis. Each incident AD case was theoretically matched to one control considered as cognitively normal (CN) from the pool of participants free of both dementia and MCI according to sex, age (+/-2.5 years) and examination date (within the interval of 45 days before or after the diagnosis date of their matched AD case); 2/participants who fulfilled criteria for MCI at the 3C 9-year follow-up.

Of the 4,363 participants included in the Bordeaux's and Montpellier's centers, 2,751 and 2,409 were still followed at the 3C 7- and 9-year follow-up, respectively. Among all incident AD cases at the 7- (n=133) and 9-year (n=114) follow-up, 176 were included in COGICARE (participation rate: 71%). Furthermore, 166 MCI identified at the 3C 9-year follow-up were included. A total of 125 matched CN controls were included. The 467 COGICARE participants (AD, MCI or CN), underwent cognitive and functional assessments every 6 months from the 3C 9-year follow-up (thereafter considered as baseline) and during 18-24 months, and then underwent their planned 3C follow-ups.

### **Cognitive and functional assessments**

Three cognitive tests were intensively administered during COGICARE follow-up. The global cognitive function was assessed using the face-to-face 30-item Mini-Mental-State-Examination (MMSE) [24] for AD and MCI, and the telephonic 25-item MMSE for CN. Telephonic 25-item MMSE scores were rescaled so that all MMSE scores ranged from 0 (severe impairment) to 30 (no impairment). The verbal fluency was assessed by the Isaacs Set Test (IST) truncated at 30

seconds [25] which was either administered in face-to-face for AD and MCI or by telephone for the CN. Its range was 0 to 82. The visuo-spatial memory was assessed by the Benton Visual Retention Test (BVRT) [26] (range 0-15) during face-to-face interviews for AD and MCI. In addition, we considered the Trail Making Test Part B (TMT-B) [27] administered only during the 3C visits (twice during this study period) in order to include a measure of executive functioning to the cognitive level definition. The score was the number of correct moves per minute.

Functional dependency was assessed by the limitation in basic ADL (BADL) scale [28] and Instrumental ADL (IADL) scale [23] during face-to-face (for AD and MCI) and telephonic interviews (for CN). A total of 5 BADL (bathing, dressing, toileting, eating and transferring) and 4 IADL (telephone use, transportation, self-administration of medication, finances) were considered [29], each one on a 3-point scale as having no limitation, partial limitation, or total limitation (coded 0, 1, and 2 respectively) in performing the task. Following a previous work that showed a continuum in IADL and BADL [30], we considered the total sumscore of IADL and BADL which ranged from 0 to 18.

### **Study sample within COGICARE**

From the 467 participants of COGICARE study, we excluded the individuals with no repeated cognitive or functional measures during the 57 months of follow-up considered for the present study, and with incomplete information on potential confounders (Flowchart in Web Figure 1). Potential confounders were age at baseline (3C 9-year follow-up) in 5 categories chosen at the quintiles of the distribution ( $\leq 79.1$  as the reference class, ]79.1-82.0], ]82.0-84.5], ]84.5-87.7],  $\geq 87.7$ ), sex, binary educational level (lower/equal to primary school versus higher than primary school), and Apolipoprotein E (apoE)  $\epsilon 4$  status (at least one  $\epsilon 4$  allele versus none). The final study sample included 297 individuals.

## Statistical analysis

Trajectories of cognitive and functional declines and their temporal reciprocal relationships according to the clinical status (AD, MCI, CN) were assessed using a multivariate latent process model [17]. The theoretical graph of the model is specified in Figure 1.

The model describes the trajectories and inter-dependencies over time of the cognitive functioning and functional dependency, defined as two latent processes. Cognitive process was measured by MMSE, IST, BVRT and TMT-B while functional process was measured by the BADL-IADL sum score. In order to correct for its departure from normality and ceiling/floor effect, each observed marker was linked to its underlying latent process using a marker-specific parameterized link function approximated by quadratic I-splines with two internal knots chosen at the quartiles for the MMSE, IST, BVRT and TMT-B, and one internal knot at the median for the limitation score [31]. The latent processes were standardized (mean 0, standard deviation 1) at baseline in the reference category (CN men with a higher educational level and less than 79.1 years old at baseline). Thus, in the results section, a one-unit change of cognition or functional dependency always corresponds to the residual standard deviation of the dimension at baseline after adjustment for age, sex, age and clinical stage.

The longitudinal model for the cognitive and functional latent trajectories was split in two parts to exhibit the temporal relationships. Both parts accounted for intra-individual correlation and missing at random mechanism (as based on the mixed model theory [32]):

- the initial levels of cognitive ability and functional dependency were regressed on the stage of the disease, age, apoE4 status, gender, education, the interaction between education and stage, and an individual random intercept;
- the changes over time of cognitive ability and functional dependency were described over a finely discretized time of 3 months unrelated to the visit process. The change between  $t$  and

t+3 months was regressed on the same covariates as initial levels, an individual random effect, and the level of cognitive ability and functional dependency at time t. The effect of the level of cognitive ability and functional dependency on each other was different by stage and could vary over time to precisely explore their inter-relations, and especially potential changes in these relationships over time. Further details on the dynamic model specification are given in Web Appendix 2.

Statistical analyses were done with R software and the dynamic model was fitted using CInLPN R package available at <https://github.com/bachirtadde/CInLPN>. Reported *P* values are from two-sided Wald tests.

## **RESULTS**

### **Sample description**

The study sample included 102 CN(34.3%), 123 were MCI (41.4%) and 72 were AD (24.3%). AD subjects (median age 84.4 years) were slightly older than MCI (82.0 years) and CN (83.4 years) at inclusion (Table 1). Two third of the sample were women with slight differences over groups (65.3%, 59.5% and 67.6% for AD, MCI and CN, respectively). MCI and AD subjects had a lower educational level compared to CN. Subjects with AD were more frequently APOE ε4 carriers than CN (36.1% vs 14.7%). The percentage of individuals with no IADL and BADL limitations at baseline gradually decreased between CN, MCI and AD, and MCI and AD had lower cognitive scores than CN.

The 170 excluded subjects (see flowchart in Web Figure 1) were more likely AD (61.2% AD, 13.5% MCI, 25.3% CN). They were slightly older (median age: 86.5) and more likely to be women (72.9%) than included subjects but comparable regarding their education level and APOE ε4 status.

The sample comprised a total of 3974 and 1388 repeated measures of cognition (through the 4 scores) and function, respectively. The median number of visits per participant was 5 for all groups. Web Tables 1 and Web Figure 2 further describe the number of measurements available by clinical stage and 3-month steps, and the observed individual marker trajectories.

### **Cognitive and Functional trajectories**

The mean predicted trajectories of cognition and function showed a gradual progression from normal to AD stage with differences according to education (Figure 2). Estimations from the dynamic model for cognitive and functional trajectories are reported in Table 2 for the baseline levels and in Table 3 for the rates of change, and further described below. The association between observed markers and the underlying dimensions highlighted the curvilinear nature of the markers and notably confirmed the ceiling effect of MMSE and floor effect of TMT-B (See Web Figure 3). The adequacy of the model to the data was very good (see Web Figure 4 for the comparison of predictions with observations).

#### *Association with baseline cognitive and functional levels*

A gradient in baseline cognitive and functional abilities was observed according to clinical stage after adjustment for other potential confounding factors, with slight differences according to education. Participants with an educational level higher than primary school had systematically a higher cognitive level in mean compared to low educated participants with no substantial differences across groups (Mean difference in the latent dimension scale (MD)=-0.868, 95% Confidence Interval (95%CI)=-1.308,-0.429,  $P=0.00011$  for CN; MD=-0.649, 95%CI=-1.013,-0.285,  $P=0.0005$  for MCI; and MD=-0.695, 95%CI=-1.178,-0.211,  $P=0.005$  for AD). For functional dependency, differences according to education were only observed among AD subjects, lower educated AD subjects having higher limitations than higher

educated AD subjects (MD=0.838, 95%CI=0.237,1.439,  $P=0.006$ ). Adjusted for clinical stage and other potential confounding factors, there was not differences in cognition according to APOE  $\epsilon 4$  status ( $p=0.954$ ) and gender ( $p=0.903$ ). However, APOE  $\epsilon 4$  carriers tended to have a better functional ability (MD=-0.355, 95%CI=-0.741,0.0310,  $P=0.072$ ) at baseline compared to non-carriers, and so did men (MD=-0.316, 95%CI=-0.650,0.017,  $P=0.0631$ ). Older individuals were more cognitively and functionally impaired adjusted for the other factors.

#### *Association with cognitive and functional rates of change*

Adjusted for confounding factors, the functional level at any time  $t$  was not significantly associated with the subsequent rate of change in cognitive dimension in any group (all  $p>0.320$ ). In contrast, whatever the clinical stage, the cognitive level significantly affected the subsequent rate of change of functional dependency after adjustment on potential confounding factors (in all groups:  $p<0.045$  at baseline,  $p<0.009$  at 2 years,  $p<0.012$  at 4 years). As illustrated in Figure 3, higher cognitive abilities at any given time were systematically associated with a lower subsequent change in functional limitations with an intensification of the association over time for CN subjects and to a lesser extent for MCI (and even lesser extent for AD). This means that the benefit of better cognitive abilities on the change of limitation was larger and larger as the time spent in the cohort increased. The annual change in functional limitations was reduced by 0.403 (95%CI=0.023,0.783,  $P=0.037$ ), 0.966 (95%CI=0.355,1.576,  $P=0.002$ ), and 1.529 (95%CI=0.591,2.466,  $P=0.001$ ) for a one-unit increase of current cognition in CN subjects after 0, 2, and 4 years in the cohort, respectively. It was reduced by 0.307 (95%CI=0.006,0.609,  $P=0.045$ ), 0.738 (95%CI=0.184,1.293,  $P=0.009$ ), and 1.169 (95%CI=0.255,2.084,  $P=0.012$ ) for a one-unit increase of current cognition in MCI subjects after 0, 2, and 4 years, respectively. It was reduced by 0.342 (95%CI=0.083,0.601,  $P=0.010$ ), 0.427 (95%CI=0.118,0.736,  $P=0.007$ ), and 0.512 (95%CI=0.126,0.899,  $P=0.009$ ) for

a one-unit increase of current cognition in AD subjects after 0, 2, and 4 years in the cohort, respectively.

The size of these temporal associations can be compared with others. For instance, for the same current cognitive level, and the same other confounding factors, the annual change of functional limitations was reduced by 1.105 (95%CI=0.267,1.943,  $p=0.010$ ), 0.643 (95%CI=0.038,1.247,  $p=0.037$ ), and 0.877 (95%CI=0.269,1.484,  $p=0.005$ ) for a one-unit increase of current functional limitation in CN, MCI and AD, respectively. The annual increase in functional limitations was also less pronounced for low educated subjects compared to higher educated subjects with a constant mean difference of -0.471 (95%CI=-0.828,-0.114,  $P=0.010$ ).

Adjusted for current cognitive and functional levels and other confounding factors, there was no residual association with annual change of cognition or limitation for gender, APOE  $\epsilon 4$ , and age except for the oldest (>88.3 years old) who had a higher increase of functional dependency than younger participants. There was also a residual association of clinical status with functional change, AD individuals having a much higher functional annual change (MD=2.166, 95%CI=0.784,3.549,  $P<0.002$ ) than CN and MCI.

## **DISCUSSION**

Leveraging longitudinal cohort data and exploiting a dynamic statistical model dedicated to the evaluation of temporal associations, this work allows understanding the cognitive and functional trajectories over time along AD continuum, from normal cognitive aging to MCI and AD, and assesses the temporal relationships between cognitive and functional dimensions. Our study showed that better cognitive abilities were associated with lower subsequent decline of the functional level among CN, MCI and AD, but with no reciprocity whatever the

clinical stage. We adjusted on main confounders identified in cognitive aging studies but cannot exclude residual confounding in these relationships.

Our results are consistent with part of the few studies that explored the potential reciprocal causal-effect between cognitive decline and functional impairment and showed that in MCI subjects or non-demented community dwelling older persons the cognitive impairment preceded and predicted subsequent functional decline but functional impairment did not predict cognitive decline [7–9,33,34]. Although Zahodne et al.[10] also concluded to a main causal effect of the cognitive impairment on the functional decline, they reported more mixed findings with a causal effect of the functional decline on the cognitive impairment also observed at a few times in non-demented elders and prevalent AD but not in incident AD. Several other studies have not formally explored the dynamic bi-directional association, but rather described the trajectories of cognitive and functional abilities and compared the shape of the declines in the pre-dementia phase. They identified that the decline in cognitive performances (observed first in measures of semantic memory and conceptual formation, and then in more global cognitive functioning) preceded the increase in dependency in IADL and in BADL [1,35].

From a methodological point of view, differences in the literature results could first be attributable to heterogeneity in the scales used to assess cognitive and functional dimensions, some functional scales including for instance a social dimension. Second, previous works used ARCL models which focus on (i) determinants of inter-individual differences over time rather than determinants of intra-individual changes [12,13], and (ii) differences between observed visits in the study rather than differences in continuous [12–14] or finely discretized [17] time which are yet necessary for causal interpretations. The use of ARCL models makes previous results strongly depend on the visit schedule, possibly too sparse for causal interpretation, and different from one study to the other so that comparisons are challenging. It also assumes

that processes do not substantial change over time at the individual level which is very unlikely. In our work we circumvented these limits by exploring associations with the subsequent individual rate of change of each dimension, and retrieving association over a 3-month period which is unrelated to the visit schedule and very small compared to the AD process timescale. By relying on the mixed model theory, the method naturally handled intermittent and monotonic missing data under the missing at random mechanism [36]. We also considered that the temporal relationships may evolve between CN, MCI and AD, and over time within each group, thus allowing the identification of specific time windows where the cognitive/functional dimensions could have a more important influence on the evolution of the other. We underlined that the cognitive latent dimension influenced the functional change at each stage of the disease and at each time window of interest. However the influence of high cognitive abilities in maintaining the functional abilities increased over time, particularly in cognitively normal and MCI subjects.

A major strength of this work is the repeated longitudinal data collected in COGICARE study. Exploring subtle changes in the dynamic of cognitive and functional dimensions was made possible by the regular follow-up of elders along the disease process. In this study, the MCI and AD groups were precisely defined. Subjects with AD were identified through an active screening and confirmed by an independent experts committee. The potential of a misclassification bias is thus minimized. The threshold used to identify MCI has also been shown to discriminate MCI who will develop AD from MCI non-converters [21]. Targeting these subjects offered the opportunity to better characterize the prodromal period of AD. When exploring temporal relationships, the number of repeated measures is also a critical issue. The median number of visits per subject in our study was 5 in all groups both for the cognitive and functional dimension. It is particularly valuable for AD as the disease is often closely associated with attrition that can potentially introduce bias in the results and lower

the possibility to assess the dynamic of processes. Finally, the cognitive dimension was defined from an extensive battery of cognitive tests including global functioning, visuo-spatial memory, verbal fluency and executive functioning, domains particularly central in cerebral aging. The definition of a general latent cognitive factor using these specific domains had been previously validated by the authors [37].

## **LIMITATIONS**

This study has some limitations. First, some psychometric tests (BVRT for CN and TMT-B for all groups) were only assessed during the 3C interviews. Considering TMT-B substantially reduced the size of the sample (112 participants did not have any TMT-B evaluation). However, it was critical that the cognitive dimension included an assessment of executive functioning given the robust relationship between instrumental activities of daily living and tests of executive function repeatedly identified in the literature (e.g. [38]).

Second, at COGICARE visits, MMSE and IST scores resulted from telephonic interviews among controls and from face-to-face interviews in MCI and AD subjects. However it has been shown that telephonic version of MMSE provides reliable results [39]. In addition, the shape of the latent cognitive process trajectories over time among controls seems coherent with previous studies [1,40]. Functional dependency was assessed through a summary score of 4 instrumental activities of daily living and 5 basic activities of daily living following previous works that showed a continuum of degradation in these items [29,30]. However, by focusing on (instrumental) activities of daily living, we might have missed very early changes in functional dependency. Finally, we considered that data were missing at random and we did not take into account the possible changes of status over time. Yet, by the end of the follow-up, 26 of the 123 MCI had become AD, and 24/8 of the 102 controls had become MCI/AD. Therefore results must be interpreted for groups of subjects initially healthy, MCI or AD.

## **CONCLUSION**

The approach we used provides valuable information on the dynamic co-evolution of the cognitive and function dimensions along the AD continuum. This work supports the hypothesis that cognitive performances contribute to maintain functional abilities whether subjects are cognitively normal or in the pathological process of cognitive decline. As stated in a recent FDA report [41], such a result is an essential argument to reinforce persuasiveness of the clinical trials identifying treatment effect on cognitive functioning. We highlighted that the benefit of cognitive performances in maintaining functional abilities increased over time when subjects were cognitively normal or at the beginning of the pathological process (MCI) but not at later stages (AD) when the severity of the disease is probably so high that function cannot be maintained. In the absence of a cure for AD, a pivotal challenge is to maintain a good quality of life for future AD as long as possible without overwhelming functional abilities. Identifying subjects with significant cognitive impairments as early as possible is consequently crucial so that they can benefit from preventive measures before the appearance of AD clinical signs.

## REFERENCES

1. Amieva H, Le Goff M, Millet X, Orgogozo JM, Pérès K, Barberger-Gateau P, et al. Prodromal Alzheimer's disease: successive emergence of the clinical symptoms. *Ann Neurol*. 2008;64:492–8.
2. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J Neuropathol Exp Neurol*. 2011;70:960–9.
3. Dartigues JF, Gagnon M, Barberger-Gateau P, Letenneur L, Commenges D, Sauvel C, et al. The Paquid epidemiological program on brain ageing. *Neuroepidemiology*. 1992;11 Suppl 1:14–8.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* [Internet]. Fifth Edition. Arlington (VA): American Psychiatric Association; 2013. Available from: <https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596>
5. Knopman DS. Alzheimer's Disease and Other Dementias. *Goldman's Cecil Medicine: Twenty Fourth Edition* [Internet]. Elsevier Inc.; 2011 [cited 2020 Sep 17];2274–83. Available from: <https://mayoclinic.pure.elsevier.com/en/publications/alzheimers-disease-and-other-dementias-3>
6. Liu-Seifert H, Siemers E, Selzler K, Sundell K, Aisen P, Cummings J, et al. Correlation between Cognition and Function across the Spectrum of Alzheimer's Disease. *J Prev Alzheimers Dis*. 2016;3:138–44.
7. Liu-Seifert H, Siemers E, Sundell K, Mynderse M, Cummings J, Mohs R, et al. Analysis of the Relationship of Cognitive Impairment and Functional Impairment in Mild Alzheimer's Disease in EXPEDITION 3. *J Prev Alzheimers Dis* [Internet]. 2018 [cited 2020 Sep 17];5:184–7. Available from: <https://doi.org/10.14283/jpad.2018.22>
8. Liu-Seifert H, Siemers E, Sundell K, Price K, Han B, Selzler K, et al. Cognitive and functional decline and their relationship in patients with mild Alzheimer's dementia. *J Alzheimers Dis*. 2015;43:949–55.
9. Liu-Seifert H, Siemers E, Price K, Han B, Selzler KJ, Henley D, et al. Cognitive Impairment Precedes and Predicts Functional Impairment in Mild Alzheimer's Disease. *J Alzheimers Dis*. 2015;47:205–14.
10. Zahodne LB, Manly JJ, MacKay-Brandt A, Stern Y. Cognitive declines precede and predict functional declines in aging and Alzheimer's disease. *PLoS ONE*. 2013;8:e73645.
11. Reppermund S, Brodaty H, Crawford JD, Kochan NA, Draper B, Slavin MJ, et al. Impairment in instrumental activities of daily living with high cognitive demand is an early marker of mild cognitive impairment: the Sydney memory and ageing study. *Psychological Medicine*. 2013;43:2437–45.
12. Selig JP, Preacher KJ. *Mediation Models for Longitudinal Data in Developmental Research*. *Research in Human Development* [Internet]. Routledge; 2009 [cited 2020 Sep 17];6:144–64. Available from: <https://doi.org/10.1080/15427600902911247>
13. Voelkle MC, Gische C, Driver CC, Lindenberger U. The Role of Time in the Quest for Understanding Psychological Mechanisms. *Multivariate Behav Res*. 2018;53:782–805.

14. Aalen OO, Røysland K, Gran JM, Kouyos R, Lange T. Can we believe the DAGs? A comment on the relationship between causal DAGs and mechanisms. *Stat Methods Med Res.* 2016;25:2294–314.
15. Proust-Lima C, Amieva H, Dartigues J-F, Jacqmin-Gadda H. Sensitivity of four psychometric tests to measure cognitive changes in brain aging-population-based studies. *Am J Epidemiol.* 2007;165:344–50.
16. Proust-Lima C, Dartigues JF, Jacqmin-Gadda H. Misuse of the linear mixed model when evaluating risk factors of cognitive decline. *Am J Epidemiol.* 2011;174:1077–88.
17. Taddé BO, Jacqmin-Gadda H, Dartigues J-F, Commenges D, Proust-Lima C. Dynamic modeling of multivariate dimensions and their temporal relationships using latent processes: Application to Alzheimer’s disease. *Biometrics.* 2020;76:886–99.
18. 3C Study Group. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. *Neuroepidemiology.* 2003;22:316–25.
19. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Press; 1994.
20. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer’s disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer’s Disease. *Neurology.* 1984;34:939–44.
21. Sarazin M, Berr C, De Rotrou J, Fabrigoule C, Pasquier F, Legrain S, et al. Amnestic syndrome of the medial temporal type identifies prodromal AD: a longitudinal study. *Neurology.* 2007;69:1859–67.
22. Grober E, Sanders AE, Hall C, Lipton RB. Free and cued selective reminding identifies very mild dementia in primary care. *Alzheimer Dis Assoc Disord.* 2010;24:284–90.
23. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist.* 1969;9:179–86.
24. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189–98.
25. Isaacs B, Kennie AT. The Set test as an aid to the detection of dementia in old people. *Br J Psychiatry.* 1973;123:467–70.
26. Benton AL. *Test de rétention visuelle (2e éd.).* les Editions du Centre de Psychologie Appliquée. Paris; 1965.
27. Reitan RM. Validity of the Trail Making Test as an Indicator of Organic Brain Damage. *Percept Mot Skills* [Internet]. SAGE Publications Inc; 1958 [cited 2021 Mar 19];8:271–6. Available from: <https://doi.org/10.2466/pms.1958.8.3.271>
28. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of Illness in the Aged: The Index of ADL: A Standardized Measure of Biological and Psychosocial Function. *JAMA* [Internet].

American Medical Association; 1963 [cited 2020 Oct 15];185:914–9. Available from: <https://jamanetwork.com/journals/jama/fullarticle/666768>

29. Barberger-Gateau P, Rainville C, Letenneur L, Dartigues JF. A hierarchical model of domains of disablement in the elderly: a longitudinal approach. *Disabil Rehabil.* 2000;22:308–17.

30. Edjolo A, Proust-Lima C, Delva F, Dartigues J-F, Pérès K. Natural History of Dependency in The Elderly. A 24-Year Population-Based Study using a Longitudinal Item Response Theory Model. *American Journal of Epidemiology.* 2015;accepted.

31. Proust-Lima C, Amieva H, Jacqmin-Gadda H. Analysis of multivariate mixed longitudinal data: a flexible latent process approach. *Br J Math Stat Psychol.* 2013;66:470–87.

32. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics.* 1982;38:963–74.

33. Njegovan V, Hing MM, Mitchell SL, Molnar FJ. The hierarchy of functional loss associated with cognitive decline in older persons. *J Gerontol A Biol Sci Med Sci.* 2001;56:M638-643.

34. Ishizaki T, Yoshida H, Suzuki T, Watanabe S, Niino N, Ihara K, et al. Effects of cognitive function on functional decline among community-dwelling non-disabled older Japanese. *Arch Gerontol Geriatr.* 2006;42:47–58.

35. Verlinden VJA, van der Geest JN, de Bruijn RFAG, Hofman A, Koudstaal PJ, Ikram MA. Trajectories of decline in cognition and daily functioning in preclinical dementia. *Alzheimer's & Dementia.* 2016;12:144–53.

36. Little RJ, Rubin DB. *Statistical analysis with missing data.* John Wiley & Sons; 2019.

37. Proust-Lima C, Amieva H, Letenneur L, Orgogozo JM, Jacqmin-Gadda H, Dartigues JF. Gender and education impact on brain aging: a general cognitive factor approach. *Psychol Aging.* 2008;23:608–20.

38. Szlyk JP, Myers L, Zhang Y, Wetzel L, Shapiro R. Development and assessment of a neuropsychological battery to aid in predicting driving performance. *J Rehabil Res Dev.* 2002;39:483–96.

39. Newkirk LA, Kim JM, Thompson JM, Tinklenberg JR, Yesavage JA, Taylor JL. Validation of a 26-point telephone version of the Mini-Mental State Examination. *Journal of Geriatric Psychiatry and Neurology.* 2004;17:81–7.

40. Amieva H, Jacqmin-Gadda H, Orgogozo J-M, Le Carret N, Helmer C, Letenneur L, et al. The 9 year cognitive decline before dementia of the Alzheimer type: a prospective population-based study. *Brain.* 2005;128:1093–101.

41. Center for Drug Evaluation and Research. *Alzheimer's Disease: Developing Drugs for Treatment Guidance for Industry* [Internet]. Food and Drug Administration; 2018. Report No.: FDA-2013-D-0077. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/alzheimers-disease-developing-drugs-treatment-guidance-industry>

## TABLES AND FIGURES

**Table 1.** Characteristics of Participants at Baseline (n=297), COGICARE study

	CN (N=102)	MCI (N=123)	AD (N=72)	All (N=297)
Age in years: Median (min-max)	83.4 (75.6-92.8)	82.0 (74.2-95.2)	84.4 (76.0-93.5)	82.9 (74.2-95.2)
Male sex (%)	32.35	41.46	34.72	36.70
Education level higher than primary school (%)	77.45	65.85	62.50	69.02
ApoE4 carriers (%)	14.71	13.82	36.11	19.53
Limitation in Activities of Daily Living (%):				
Bathing				
No Limitation	96.08	95.93	66.67	88.89
Partial Limitation	1.96	2.44	16.67	5.72
Total Limitation	1.96	1.63	16.67	5.39
Dressing				
No Limitation	96.08	97.56	73.61	91.25
Partial Limitation	0.98	1.63	13.89	4.38
Total Limitation	2.94	0.81	12.50	4.38
Toileting				
No Limitation	100.00	99.19	95.83	98.65
Partial Limitation	0.00	0.00	4.17	1.01
Total Limitation	0.00	0.81	0.00	0.34
Transferring				
No Limitation	99.02	99.19	94.44	97.98
Partial Limitation	0.98	0.81	5.56	2.02
Total Limitation	0.00	0.00	0.00	0.00
Eating				
No Limitation	99.02	100.00	95.83	98.65
Partial Limitation	0.98	0.00	4.17	1.35
Total Limitation	0.00	0.00	0.00	0.00
Limitation in Instrumental Activities of Daily Living (%):				
Telephone use				
No Limitation	100.00	95.12	56.94	87.54
Partial Limitation	0.00	4.88	36.11	10.77
Total Limitation	0.00	0.00	6.94	1.68
Shopping				
No Limitation	78.43	77.24	36.11	67.68
Partial Limitation	13.73	19.51	26.39	19.19
Total Limitation	7.84	3.25	37.50	13.13
Transportation				

	No Limitation	79.41	83.74	44.44	72.73
	Partial Limitation	19.61	15.45	48.61	24.92
	Total Limitation	0.98	0.81	6.94	2.36
Medication					
	No Limitation	99.02	95.12	48.61	85.19
	Partial Limitation	0.00	4.07	25.00	7.74
	Total Limitation	0.98	0.81	26.39	7.07
Finances					
	No Limitation	89.22	86.99	41.67	76.77
	Partial Limitation	10.78	11.38	26.39	14.81
	Total Limitation	0.00	1.63	31.94	8.42
Cognitive Scores: Median (min-max)					
	MMSE	28 (17-30)	27 (20-30)	23 (11-28)	27 (11-30)
	IST	45 (22-82)	39 (20-61)	29 (12-62)	39 (12-82)
	BVRT	12 (6-15)	11 (5-15)	9 (5-14)	11 (5-15)
	TMT-B	26.5 (3.0-60.0)	21.3 (0.5-62.6)	7.3 (0.7-40.0)	20.0 (0.5-62.6)
	Limitation score: Median (min-max)	0 (0-7)	0 (0-14)	3 (0-13)	0 (0-14)
Number of measures by subject over follow-up: Median (min-max)					
	MMSE	5 (2-6)	5 (2-7)	4 (1-7)	5 (1-7)
	IST	4 (1-6)	5 (1-7)	4 (1-7)	4 (1-7)
	BVRT	2 (1-4)	5 (2-6)	3 (1-7)	3 (1-7)
	TMT-B	2 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)
	Limitations	5 (2-6)	5 (2-7)	5 (2-7)	5 (2-7)

**Table 2.** Estimated associations with the underlying cognitive ability and functional dependency level at baseline (n=297), COGICARE study.

	Cognitive ability at baseline		Functional dependency at baseline	
	Coefficient*	95% Confidence Interval	Coefficient*	95% Confidence Interval
Clinical stage by education level				
higher than primary school				
CN	0	-	0	-
MCI	-0.882	-1.284, -0.480	0.171	-0.275, 0.617
AD	-2.878	-3.419, -2.337	1.974	1.415, 2.532
lower or equal to primary school				
CN	-0.868	-1.308, -0.429	0.188	-0.417, 0.793
MCI	-1.531	-2.044, -1.018	0.089	-0.412, 0.591
AD	-3.572	-4.219, -2.926	2.811	2.105, 3.518
Age at baseline				
<=79.1	0	-	0	-
]79.1-82.0]	-0.284	-0.680, 0.113	0.069	-0.396, 0.534
]82.0-84.5]	-0.461	-0.870, -0.053	0.304	-0.167, 0.775
]84.5-87.7]	-0.288	-0.691, 0.116	0.284	-0.200, 0.767
>87.7	-0.754	-1.146, -0.362	1.028	0.508, 1.549
APOE ε4 carrier				
No				
Yes	-0.010	-0.351, 0.331	-0.355	-0.741, 0.031
Sex				
Male				
Female	-0.016	-0.270, 0.238	0.316	-0.017, 0.650

\*one-unit difference corresponds to the standard deviation of the dimension at baseline in the category reference (CN men with a higher educational level and less than 79.6 years old at baseline)

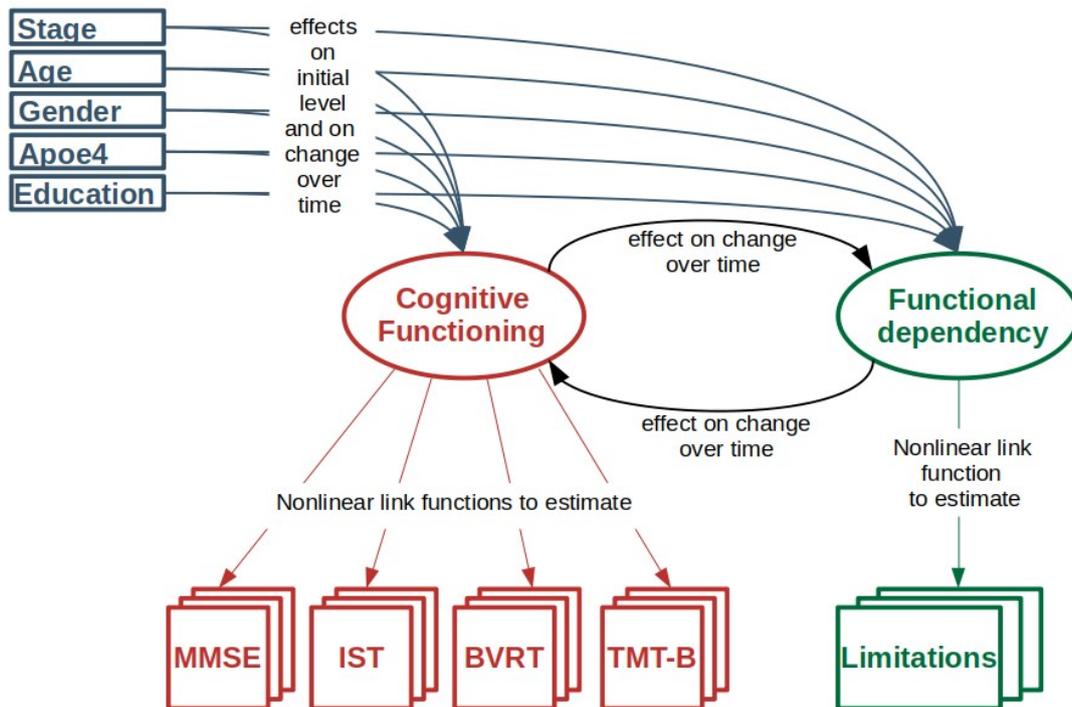
**Table 3.** Estimated associations with the rate of change of underlying cognitive ability and functional dependency (n=297), COGICARE study.

	change over time of Cognitive ability		change over time of Functional dependency	
	Coefficient*	95 % CI	Coefficient*	95 % CI
Intercept	-0.247	-0.371, -0.122	0.201	-0.370, 0.772
Clinical stage				
CN	0	-	0	-
MCI	0.176	0.021, 0.332	0.194	-0.223, 0.611
AD	0.377	-0.031, 0.785	2.166	0.784, 3.549
Age at baseline				
<=79.6	0	-	0	-
]79.60-82.60]	-0.021	-0.165, 0.124	-0.144	-0.552, 0.264
]82.60-85.12]	-0.040	-0.191, 0.110	-0.091	-0.508, 0.325
]85.12-88.34]	0.003	-0.141, 0.148	0.175	-0.248, 0.599
>88.34	0.043	-0.119, 0.204	0.732	0.114, 1.349
APOE ε4 carrier				
No	0	-	0	-
Yes	-0.017	-0.139, 0.104	-0.211	-0.582, 0.159
Sex				
Male	0	-	0	-
Female	0.061	-0.036, 0.157	0.117	-0.201, 0.436
Education level				
> primary school	0	-	0	-
≤ primary school	0.239	0.124, 0.355	-0.471	-0.828, -0.114
Current functional level**				
CN	-0.086	-0.254, 0.082	-1.105	-1.943, -0.267
MCI	-0.010	-0.141, 0.122	-0.643	-1.247, -0.038
AD	-0.032	-0.160, 0.096	-0.877	-1.484, -0.269
CN x time	0.032	-0.035, 0.100		
MCI x time	-0.008	-0.057, 0.042		
AD x time	0.033	-0.003, 0.069		
Current cognitive level**				
CN	0.154	0.052, 0.255	-0.403	-0.783, -0.023
MCI	0.185	0.081, 0.290	-0.307	-0.609, -0.006
AD	0.235	0.130, 0.340	-0.342	-0.601, -0.083
CN x time			-0.281	-0.468, -0.095
MCI x time			-0.215	-0.413, -0.018
AD x time			-0.043	-0.099, 0.014

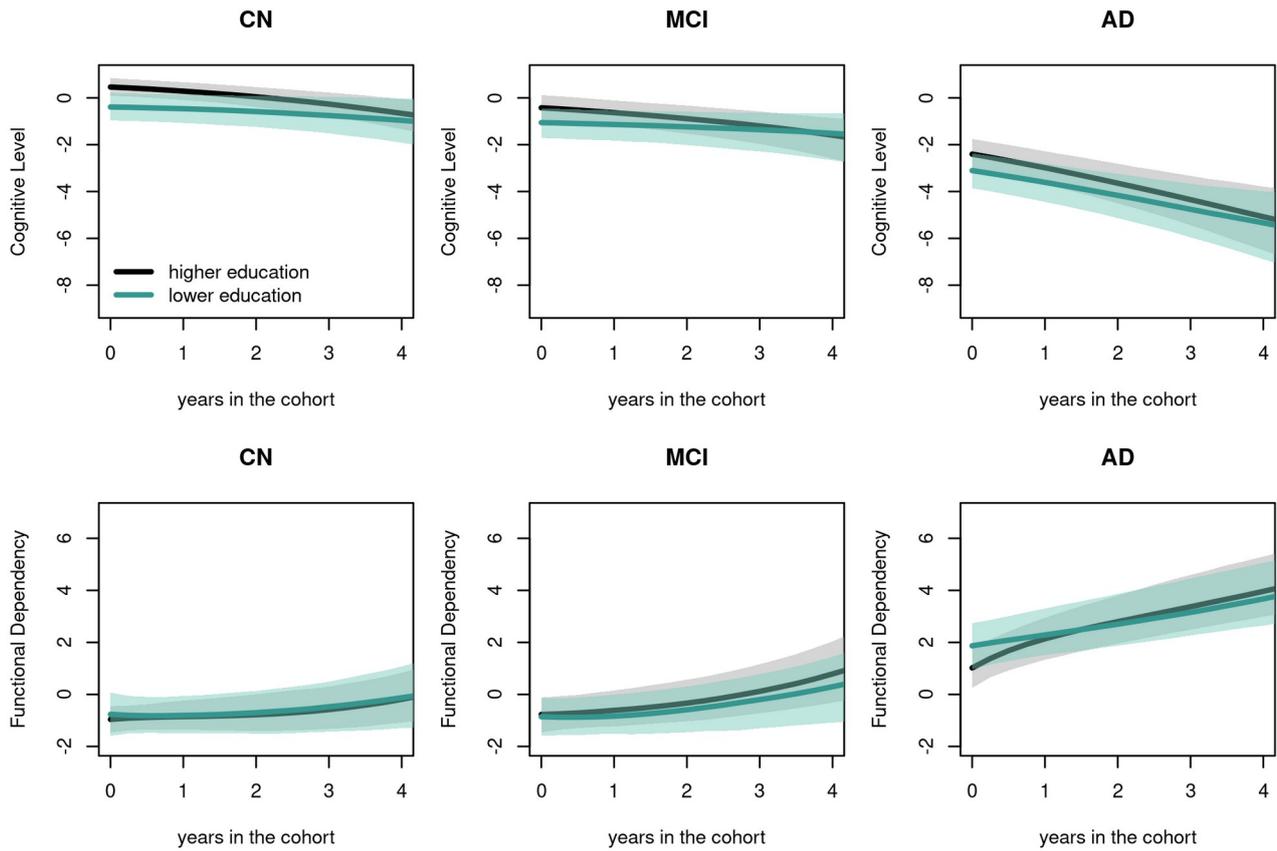
\* one unit corresponds to an annual change of the same size as one standard deviation of the dimension at baseline in the reference category (CN men with a higher educational level and less than 79.6 years old at baseline)

\*\* one unit corresponds to the standard deviation of the dimension at baseline in the reference category (CN men with a higher educational level and less than 79.6 years old at baseline)

**Figure 1:** Theoretical graph of the dynamic causal model



**Figure 2.** Predicted mean trajectories over time (plain line) and associated 95% confidence intervals (shades) of the underlying cognitive ability and functional dependency according to clinical stage (CN, MCI and AD) and education; trajectories are displayed for non APOE  $\epsilon 4$  carriers; male sex and aged between [82.60-85.12]. 95% confidence intervals were obtained using a Monte Carlo method with 2000 draws.



**Figure 3.** Estimated trajectory of temporal influence (and associated 95%CI) of the cognitive level on the subsequent functional dependency change according to the time in the cohort by clinical status (CN, MCI and AD). The reported temporal influence corresponds to the difference in the annual change of functional dependency for a one-unit increase of current cognitive level.

