Misidentification subtype of Alzheimer's disease psychosis predicts a faster cognitive decline

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CONFLICT OF INTEREST

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ABSTRACT

The presence of psychosis is associated with more rapid decline in Alzheimer's disease (AD), but the impact of paranoid (persecutory delusions) and misidentification (misperceptions and/or hallucinations) subtypes of psychosis on the speed of decline in AD is still unclear. Here we analysed data on Alzheimer's Disease Neuroimaging Initiative (ADNI)2 participants with late mild cognitive impairment or AD and we described individual trajectories of Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) scores using a semi-mechanistic, logistic model, with a mixed effects based approach, which accounted for drop-out, and adjusted for baseline Mini Mental State Examination scores. The covariate model included psychosis subtypes, age, gender, education, medications and Apo-e ε4 genotype. We found that ADAS-cog rate of increase was doubled in misidentification ($\beta_{r,misid\_subtype}$=0.63, p=0.031) and mixed (both subtypes) (($\beta_{r,mixed\_subtype}$=0.70, p=0.003) compared to non-psychotic (or paranoid) subjects suggesting that the misidentification subtype may represent a distinct AD sub-phenotype associated with an accelerated pathological process.

INTRODUCTION

Psychosis symptoms (delusions, hallucinations) are common in Alzheimer's disease (AD)[1] and manifest early in the illness course. They are associated with an accelerated speed of cognitive and functional decline and precipitate earlier institutionalisation[2]. Research which aims to elucidate the pathophysiology of AD psychosis and its relationship with disease progression could help to direct future treatment strategies. Factor analysis of AD psychosis symptoms has identified two broad categories: a "paranoid" subtype, characterised by delusions of theft, harm and abandonment, and a "misidentification" subtype, comprised of misperceptions, misidentification delusions, and visual or

auditory hallucinations[3,4]. Studies which have investigated the phenotypic aspects of AD psychosis subtypes have reported greater performance deficits on tests of visual sustained attention and visuoperceptual function[5], reduced volume in functional networks involved in perception and context based recognition of visual stimuli[6,7] and greater hippocampal/limbic pathology at post-mortem[8,9,10], but only in association with the misidentification subtype. It is unclear whether AD psychosis subtypes are part of the same biological continuum [3,4] with misperceptions emerging later in the AD process [4,11] or whether the two subtypes have distinct disease course trajectories.

This study aimed to investigate longitudinal data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) with the following objectives:

1) To describe the trajectory of cognitive decline, indexed by the rate of increase in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog)[12] scores, in early AD, using a mixed effects based approach[13].

2) To test the hypothesis that the misidentification subtype would be associated with a faster rate of cognitive decline.

METHODS

Participants

Data were obtained from ADNI, a multicentre longitudinal study which collected clinical, neuroimaging, neuropsychological and blood/cerebrospinal, data from healthy controls (HC), and those with both mild cognitive impairment (MCI) and early AD, with the aim of identifying markers of AD progression (adni-info.org). MCI was classified as early (EMCI) and late MCI (LMCI) based on a cut off for objective memory impairment determined using the Wechsler Memory Scale Logical Memory II (adni.loni.usc.edu). Data of interest (downloaded 18th January, 2016) included all participants diagnosed with AD and LMCI at baseline and those who developed MCI and AD over the observation period, but excluded those who subsequently reverted to HC or ECMI as they did not

show a cognitive decline over the time accordingly to AD NIA-AA criteria.[14] The analysis was restricted to ADNI2 participants, as full Neuropsychiatric Inventory (NPI)[15] data (which was not included in earlier phases of ADNI) was required to assign subtype[3,4,5]. Participants were coded as "psychotic" if symptoms were coded as present (scores of 1 or more on delusions or hallucinations domains) either at baseline or any follow-up visit. The paranoid subtype included items 1,2,3,7 from the delusions domain ("In danger/others are planning to hurt him or her", "Others are stealing from him or her", "Spouse is having an affair", "Family members plan to abandon him or her"); the misidentification subtype included items 4,5,6,8 from the delusions domain ("Unwelcome guests are staying in his or her house", "His or her spouse or others are not who they claim to be", "His or her house is not his or her own", "Television/magazine figures are present in his or her home") and items 1,2,3 from the hallucinations domain ("He or she can hear voices", "Talks to people who are not there", "Seeing things not seen by others"); those who were coded positive on items from both paranoid and misidentification symptoms were described as "mixed"; and non-psychotic phenotype was assigned if no items were coded positive at any of the visits. Cognitive and functional status were measured using ADAS-cog, Mini Mental State Examination (MMSE)[16], Clinical Dementia Rating scale (CDR)[17] and Functional Activities Questionnaire (FAQ)[18] scores. Assessments were carried out at baseline, 6 months, 12 months and annually thereafter. The longest observation period was 4 years, corresponding to a baseline and 4 or 5 follow-up visits. Between-AD and psychosis subtypes differences for age, gender, education, Apo-e ε4 genotype, MMSE, CDR, FAQ, ADAS-cog and NPI total score at baseline were analysed using chi-squared tests and Analysis of Variance (ANOVA). Data collection and sharing in ADNI were approved by the Institutional Review Board of each participating institution, and written informed consent was obtained from all participants.

ADAS-cog score trajectory model

The non-linear trajectory of cognitive decline was described using the general logistic function model (an equation based on Richard's function)[19,20,21] below:

$$ADAS - cog(t) = \frac{ADAS - cog0 * 70}{[ADAS - cog0^{\alpha} + (70^{a} - ADAS - cog0^{\alpha}) * e^{-\alpha * r * t}]^{1/\alpha}}$$

The model comprised three parameters: Baseline ADAS-cog scores (ADAS-cog0); rate (slope) of increase in ADAS-cog scores (*r*); and a shape parameter (α) which controls an inflection point in the trajectory, beyond which rate of decline slows. Higher values of *r* and α indicate faster cognitive decline and steeper trajectory respectively.

Non-linear mixed effects (NLME) modelling was used to explore sources of variability in the trajectory of decline separating inter-individual variability (IIV) and residual unexplained variability (RUV)[13]. Inter-individual random effects and residual unexplained errors were assumed to be independent. A log transformation of the observations ADAS-cog$_{ij}$ of subject *i* at time t$_{ij}$ and model predictions $ADAS - cog(t_{ij}, ADAS - cog0_i, r_i, \alpha_i)$ was used to ensure positivity and we used an additive error model as follows:

$$\log(ADAS - cog_{ij}) = \log\left(ADAS - cog(t_{ij}, ADAS - cog0_i, r_i, \alpha_i)\right) + \sigma\varepsilon_{ij}$$

This allows the standard deviation σ of the residual errors ε_{ij}, which follow a Gaussian, to be expressed as a coefficient of variation on predicted ADAS-cog scores.

Inter-individual random effects were estimated on ADAS-cog0, r and α. A probit-normal transformation was used for ADAS-cog0 to ensure predicted individual values were between 0 and 70, as follows:

$$ADAS - cog0_i = \Phi^{-1}\left(\mu_{ADAS-cog0} + \eta_{ADAS-cog0_i}\right)$$

With μ_{Adas0} the population value for ADAS-cog0, Φ^{-1} the inverse cumulative distribution function (quantile function) associated with the standard normal distribution N(0,1) and $\eta_{ADAS-cog0_i}$ following

a normal distribution of mean 0 and standard deviation $\omega_{ADAS-cog0}$.

For r and α, a log-normal transformation was used to ensure positivity, as follows:

$$r_i = \mu_r e^{\eta_{r_i}}$$

$$\alpha_i = \mu_\alpha e^{\eta_{\alpha_i}}$$

With μ_r and μ_r the population value for r and α, respectively and η_{r_i} qnd η_{α_i} following normal distributions of mean 0 and standard deviations ω_r and ω_α, respectively. All covariate-parameter associations were modelled using a linear regression on the random effect scale e.g.:

$$r_i = \mu_r e^{\eta_{r_i}} e^{\beta_{r,cov} cov_i}$$

With cov_i, the value for the covariate of interest for subject i and $\beta_{r,cov}$ the effect coefficient of cov on parameter r. Paranoid, misidentification and mixed subtypes were each compared to non-psychotic phenotype and other covariates previously shown to have an effect on disease progression parameters (baseline age, baseline MMSE score, gender, education, presence of Apo-e ε4 alleles, age, baseline use of cognitive enhancers)[20,21] were tested on parameters ADAS-cog0 and r with a Wald test at level 0.05. Continuous covariates were centred on the mean, and gender, Apo-e ε4 genotype and use of cognitive enhancers were encoded as categorical covariates; with "male gender", "not being a carrier of Apo-e ε4" and "no medication" used as reference values.

Drop out model

A Survival (time to event) model was used to fit attrition rate, using a Weibull baseline hazard function[22] $h_0(t)$ as risk was expected to change over time. This model includes a shape parameter, k which, when greater than 1, indicates an increase in attrition rate over time, when equal to 1 that attrition is constant over time (such as in the exponential model), and when less than 1 that the attrition rate decreases with time; and a scale factor λ, with $1/\lambda$ corresponding to the mean time before drop out if k is equal to 1:

$$h_0(t) = \frac{k}{\lambda} * (\frac{t}{\lambda})^{(k-1)}$$

An effect of the current predicted ADAS-cog score was tested on the hazard function of drop-out, h(t) as follows:

$$h(t) = h_0 * e^{(-\beta_{h_0,\text{ADAS-cog}} * ADAS-cog(t_{ij}, ADAS-cog0_i, r_i, \alpha_i))}$$

With $\beta_{h_0,\text{ADAS-cog}}$ the effect coefficient of the unobserved ADAS-cog score value on the risk of drop-out, corresponding to a missing not at random mechanism.

Drop out and ADAS-cog models were jointly estimated.

Model evaluation and predictions

Model parameters were estimated using the Stochastic Approximation to the Expectation Maximization algorithm [23]. Appropriateness of base and covariate models were evaluated using goodness-of-fit plots (e.g. visual predictive check (VPC)) and metrics, (standard errors and Bayesian information criteria (BIC)).

Parameter fixed effect estimates were used to plot typical ADAS-cog trajectories for each subtype, accounting for other significant covariate effects.

Softwares

Demographic and clinical data were analysed using SPSS 23(www.spss.com). The data set was prepared using R (version 3.2.1) and the Monolix software was used for model fit and evaluation (version 2016 R1; www.lixoft.eu).

RESULTS

Demographic and clinical characteristics

ADAS-cog trajectories from 528 participants are shown in spaghetti plots in figure 1 on the natural (A) and on the log scale (B). In median, patients attended 3 visits ranging from 1 to 6 visits over 4 years (total 1783 observations). Demographic information about the subjects is summarized in Table 1. The sample consisted of 212 AD, 239 LMCI and 29 EMCI subjects at baseline. Forty-eight HC converted to LMCI or AD over the observation period. Attrition rate was high (92%), with only 42 participants remaining at the final follow-up visit (year 4). Possible explanations for the high attrition are the i) worsening of cognitive and functional impairment of the patients (tested via the effect of predicted current ADAS-cog scores on the hazard of drop-out), ii) the occurrence of an age-related disease and iii) death. Of note, vital status was not informed in the ADNI2 data set. There were 96 patients with psychosis symptoms (38 paranoid, 29 misidentification, and 29 mixed), who did not differ significantly from non-psychotic patients in terms of age, and education (Table 1). At baseline there were 38 patients with psychosis, 33 patients developed psychosis at 1st follow-up visit, 17 patients at 2nd follow-up visit, 7 at 3rd follow-up visit and 1 at 4th follow-up visit. A gender difference was found across psychotic status (62% male non psychotic vs. 61% paranoid vs. 38% Misid. vs 48% mixed). Participants with psychosis symptoms were more cognitively and functionally impaired than non-psychotic patients at baseline (see cognitive and functional scores mean ($\pm$ SD) in Table 1 and Figure 2). In post-hoc analyses on the basis of subtype, only the mixed subtype had significantly higher baseline ADAS-cog scores (p=0.001) and lower baseline MMSE scores (p=0.001) compared to the non-psychotic group; whereas the mixed and misidentification subtypes had significantly higher baseline CDR (p=0.042 and p<0.001, respectively) compared to the non-psychotic group (Figure 2).

ADAS-cog trajectory model

Baseline Model

Parameter estimates for the base model (without covariates) and for the final model (including covariates) are shown in Table 2. The final model estimated an inflection point when ADAS-cog scores reached 38.2 with 95% confidence interval=[32.9-41.8], beyond which rate of decline slows.

Covariate model

The paranoid subtype was found to have an estimate of the rate of progression not significantly different from the non-psychotic subtype, therefore paranoid and non-psychotic subtypes were combined in a reference subtype in the following analyses. Compared to this reference subtype, misidentification, and mixed subtypes had significantly higher estimates of the rate of progression (multiplied by a factor 1.87 and 2 with p<0.031 and <0.003, respectively).

The presence of at least one allele of Apo-e ε4 gene was found to double the rate of progression (p<0.001), leading to a rate of progression fourfold higher in patients having at least one Apo-e ε4 allele and being categorised into the misidentification or mixed subtypes. A significant effect of baseline MMSE score was found on the parameter ADAS-cog0 (p<0.001) with an ADAS-cog0 of 7.02 associated to a MMSE score of 30 and an ADAS-cog0 of 57.50 for a MMSE score of 6, accounting for the association between ADAS-cog0 and MMSE score at baseline lowered the IIV estimates on ADAS-cog0 by 40%.

Drop out model

The k parameter was estimated greater than 1 (2.03) confirming that drop-out hazard rate increases with time. The current predicted ADAS-cog score was found to significantly increase the drop-out hazard, with a drop-out hazard rate at 12 months 5 times higher for those with an ADAS-cog score of 50 compared to those with a score of 13 ($\beta_{h0,ADAS\text{-}cog}$ =0.04, p <0.001).

Model evaluation

Visual predictive checks (VPC) on log-transformed ADAS-cog scores are shown in Figure 1 C. Observed percentiles are adequately included in the predicted bands from model simulations, but on one occasion for the median and upper band and on two occasions for the lower band. Further goodness of fit plots are provided in the supplementary material along with the mlxtran code and the data set.

Model predictions

Model fixed effect estimates were used to plot the ADAS-cog trajectory for a typical patient from each of the following categories: baseline MMSE score of 10, 25 or 29; non-psychotic (or paranoid), misidentification and mixed subtypes; non-carrier (Figure 3A) or carrier (Figure 3B) of at least one Apo-e ε4 allele.

DISCUSSION

This study investigated the impact of psychosis subtype on the rate of disease progression/cognitive decline in AD, using a semi-mechanistic model to describe the trajectory of change in ADAS-cog scores. In line with our hypothesis, the misidentification subtype (alone or as part of a mixed subtype) was associated with an increased rate of decline compared to non-psychotic or paranoid subtype.

These findings were not explained by differences in baseline cognitive status in those who presented solely with misidentifications, as ADAS-cog (and MMSE) were similar across paranoid, misidentification and non-psychotic group, with only the mixed subtype being more impaired at baseline.

Faster rate of decline in misidentification subtype might be associated with earlier and greater pathological change in functional networks involved in perception, recognition of visual stimuli. Indeed previous studies evidenced in patients with misidentification subtype poorer performance on neuropsychological tests, which localise to the ventral visual stream[5], and greater volume loss in functionally connected regions[6] including the parahippocampal gyrus, which is involved in the processing and retrieval of contextual memories[24,25]. There is also evidence of greater neurofibrillary tangle burden in frontal[26] and limbic/paralimbic regions including the parahippocampal gyrus[8,9,26] in AD patients with a history of misidentifications and/or hallucinations. Our findings, supported from those of previous studies, suggest that the misidentification subtype may be a distinct sub-phenotype of AD, and one which is associated with an accelerated cognitive decline.

The greater proportion of women in the misidentification subtype warrants further discussion, as psychosis occurs more frequently in women and histopathologic studies have shown higher levels of phosphorylated tau in the frontal cortex of females with AD psychosis compared to their male couterparts[27]. However, when gender was incorporated into the model during covariate testing, we could not estimate a significant impact on the 'rate of progression' parameter. The presence of at least one Apo-e ε4 allele increased the rate of cognitive decline in all groups. The effect of the presence of Apo-e ε4 on the rate of disease progression has been already demonstrated in previous AD progression models[20,21,28] but, here, in contrast to Conrado et al. we did not distinguish between the presence of one or two alleles. The effect of Apo-e ε4 genotype on rate of decline further supports the suggestion that misidentification subtype have a greater neuropathological burden, as Apo-e ε4 is involved in the deposition of both neurofibrillary tangles and amyloid[29] and regulates Aβ clearance[30,31]. We found an effect of MMSE scores at baseline on ADAS-cog0, as showed by Ito et

al.; MMSE values are highly correlated to ADAS-cog values and this could explain the improved model fit[28].

There were several study limitations. ADNI represents a highly selective dataset, which includes very mildly impaired subjects, with high educational attainment, and low vascular burden. As a result of mild baseline severity, cognition declined slowly over the 4-year observation period, which meant that it was not possible to fully capture the nonlinear trajectory of decline, as managed in previous studies[19,20] and our decision to use a nonlinear model was essentially based on its superiority over a linear model in a previous comparative study[20,21].

It is possible that the absence of differences in rate of decline between paranoid and non-psychotic groups reflects poor sensitivity of the ADAS-cog to detect deficits in fronto-executive functioning (subscales largely focus on memory, language, visuospatial and praxis functions)[32] which are perhaps most relevant to the paranoid subtype[4]. This could be investigated in future analyses, using a similar (mixed effects) based approach to describe changes in digit span; a measure of fronto-executive function previously shown to decline more rapidly in those with psychosis in previous analyses of ADNI data[33]. Neither can we completely rule out an effect of gender, given the relatively small sample size of psychotic subtypes, and this needs to be explored in a larger sample.

The majority of researchers who have investigated subtype dependency have reported lower MMSE scores in those with the misidentification subtype[4,11,34], although this has not been consistently shown[5,6]. In ADNI2 participants, only the mixed group were more impaired, using ADAS-cog and MMSE as markers of cognitive status and disease stage. However, all subtypes were impaired in functional activities compared to the non-psychotic group, and it will be important to investigate this further in future studies, as it is possible that specific functional domains may be more sensitive markers of psychosis symptoms.

All patients diagnosed AD or LMCI during the follow up period were included in the study. However, many of the participants were in the early stages of dementia, or still diagnosed with MCI, and they would not have progressed far enough through their illness by the end of the 4 years' follow-up period

to develop psychotic symptoms. It is thus possible that they were assigned a false-negative psychosis phenotype.

The decision to not use a threshold cut-off for NPI scores to define the presence of delusions or hallucinations was based on our previous approach[5,6] and our aim to examine psychosis 'trait' as opposed to 'state'. However this approach increases the risk of false positives.

The fact that ADNI2 excluded people who had psychotic symptoms within the previous three months, or those prescribed antipsychotic or sedative medication, limited the sample size of the psychotic group and reduced the power of the study to compare subtypes, or to establish any correlation between symptom severity (or antipsychotic use) and cognitive trajectory. Neither was it possible to determine the individual contributions of misidentification phenomena and hallucinations to subtype specific differences in rate of decline, as the majority of participants had visual and/or auditory hallucinations (n=20), with a smaller number having misidentification delusions (n=6) or both (n=3).

We cannot rule out the possibility that a proportion of ADNI2 participants assigned to the misidentification subtype represent undiagnosed cases of Lewy body disease (DLB), given the occurrence of visual hallucinations and misidentifications at a relatively mild stage of disease[26]. However post-mortem studies have shown that the early occurrence of these symptoms may also represent a greater expression of AD-related pathology[26].

Given the relatively small sample size of each subtype, our findings should be viewed as preliminary and investigated prospectively in future studies. The development of positron emission tomography ligands which bind to tau and α-synuclein[35,36] means that it is now possible to simultaneously collect clinical (psychosis subtype, neuropsychological test performance), molecular (pathological, neurochemical), morphological and functional information in vivo. This approach could be used to further elucidate the pathophysiology of the psychosis subtypes in early AD and other neurodegenerative disorders (DLB, Parkinson's disease psychosis) in which the misidentification subtype is highly prevalent.

Study highlights:

What is the current knowledge on the topic?

The psychosis phenotype in Alzheimer disease (AD) predicts an accelerated speed of cognitive and functional decline, but it is unclear if phenomenological differences in psychosis subtypes have distinct disease trajectories.

What question did this study address?

Does the presence of paranoid (persecutory delusions) or misidentification (misperceptions and/or hallucinations) subtypes of psychosis have an impact on the speed of cognitive decline in early AD.

What does this study add to our knowledge?

The misidentification subtype (alone or in conjunction with paranoid delusions) is associated with a faster speed of AD progression. These findings may reflect additional AD (or other) pathology in functional networks that are involved in the perception and contextual association of visual stimuli.

How might this change drug discovery, development, and/or therapeutics?

These findings suggest that treatment approaches addressed to AD patients with misidentification psychotic subtype, should aim to target functional networks involved in the processing of sensory stimuli, to improve psychotic symptoms and to slow down the rate of disease progression.

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Figure Legends

Figure 1 Individual ADAS-cog scores trajectories over time of patients included in the ADNI2 data set on the natural (A) and log (B) scale and visual predictive check of the final covariate model of ADAS-cog scores trajectories over time on the log scale (C). The shaded areas correspond to the 95% confidence intervals around the 5th and 50th and 95th model predicted percentiles and the solid lines correspond to 5th, 50th and 95th percentiles of observed data.

Figure 2 Box Plots of Mini Mental State Examination (MMSE) (A), Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) (B), Clinical Dementia Rating scale (CDR) (C), Functional Activities Questionnaire FAQ (D), Neuropsychiatric Inventory (NPI) (E) scores at baseline in non-psychotic AD and in each psychotic AD subtype (Paranoid, Misidentification and mixed). Overall comparison was performed using Analysis of Variance

(ANOVA). Black lines indicate post-hoc pairwise comparisons of interest and * indicates significant difference (p <0.05).

Figure 3 Typical ADAS-cog trajectories over 20 years (using model parameter fixed effect estimates) for the non-psychotic or paranoid subtype (left), misidentification subtype (centre) and mixed (right) subtype for a non-carrier (A) and a carrier (B) of at least one Apo-e ε 4 allele. The black, green and red lines correspond to a MMSE score at baseline of 25, 29 and 10, respectively. Vertical lines represent the end of the follow-up in the current study i.e. 4 years after inclusion.

Supplementary Materials

(PSP-2018-0170R1_Figure_S1.tif)

Figure S1

(PSP-2018-0170R1_Figure_S2.tif)

Figure S2

(PSP-2018-0170R1_Figure_S3.tif)

Figure S3

(PSP-2018-0170R1_Mlxtran_code.txt)

Mlxtran code

(PSP-2018-0170R1_Dataset_description.docx)

Dataset description

(PSP-2018-0170R1_Supplementary_Figure_Legends.docx)

Supplementary Figure Legends

(PSP-2018-0170R1_Dataset_1.csv)

Dataset 1

Table 1. Demographic and clinical characteristics at baseline (n=528)

	Non Psychotic (n=432)	Paranoid (n=39)	Misid. (n=29)	Mixed (n=29)	Test	df	p value
Mean (± SD)							
Age in years	75.9 (±7.9)	76 (±7.2)	74.3 (±8.3)	74.3 (±8.3)	F=0.4	3	0.734
Education in years	16 (±2.7)	15.9(±2.8)	15.1(±2.4)	16.1(±2.9)	F=0.9	3	0.421
ADAS-cog	14.4 (±8.7)	16.9 (±7.8)	17.6 (±9.9)	20.8 (±9.9)	F=6.2	3	<0.001
MMSE	25.7 (±3.9)	24.6 (±3.2)	24.1 (±5.6)	22.7 (±4.3)	F=6.5	3	<0.001
NPI	5.4 (±7.1)	12 (±10.8)	10.1 (±9.6)	14.6(±12.6)	F=21	3	<0.001
CDR	0.6 (±0.3)	0.7 (±0.3)	0.8 (±0.5)	1 (±0.5)	F=11.8	3	<0.001
FAQ	7.1 (±7.7)	11.4 (±7.6)	13.2(±8.6)	17.1 (±8.2)	F=21.2	3	<0.001
Number (%)							
Gender "Male"	267(62)	24 (61)	11 (38)	14 (48)	X^2=8.3	3	0.04
Apo-e ε4 non-carrier	208 (48)	10 (25)	11 (38)	8 (27)	X^2=11.7	3	<0.001
Cognitive enhancer not prescribed	379 (88)	32 (82)	21 (72)	24 (83)	X^2=6.4	3	0.092

Misid. misidentification; df degrees of freedom; n.s. non significant; ADAS-cog :Alzheimer's Disease

Assessment Scale-Cognitive Subscale ; MMSE: Mini Mental State Examination;NPI: Neuropsychiatric Inventory; n.s.; non significant; CDR: Clinical Dementia Rating scale ; FAQ :Functional Activities Questionnaire

Table 2 Parameter estimates, relative standard errors (RSE in %) and 95% confidence intervals (95CI) for models of cognitive decline trajectory in ADNI2 participants without and with covariates

	Without covariate			With covariate			
	Estimate	RSE	95%CI	Estimate	RSE	95%CI	p value
ADAS-cog trajectory model							
Typical value (fixed effects)							
ADAS-cog0	13.60	3	12.80/14.40	13.80	2	13.26/14.34	
$\beta_{ADAS-cog0,MMSE}$	ne	ne	ne	-0.09	4	-0.10/-0.08	<0.001
r	0.14	19	0.09/0.19	0.07	15	0.05/0.09	
$\beta_{r,\ misid\ subtype}$	ne	ne	ne	0.63	46	0.06/1.19	<0.031
$\beta_{r,\ mixed\ subtype}$	ne	ne	ne	0.70	34	0.23/1.16	<0.003
$\beta_{r,1\ allel\ Apo-e\ \varepsilon4}$	ne	ne	ne	0.76	21	0.45/1.07	<0.001
α	1.09	46	0.11/2.07	1.54	27	0.73/2.35	
IIV							
$\omega_{ADAS-cog0}$	0.42	4	0.39/0.45	0.25	4	0.23/0.27	
ω_r (%)	67	15	47/87	0.66	12	0.50/0.82	
ω_α (%)	176	19	110/242	145	14	105/185	
RUV							

σ (%)	26.1	2	25.08/27.12	26	2	25/27
Drop-out model						
Typical values (fixed effects)						
λ	4.14	7	3.58/4.70	3.99	5	3.60/4.38
k	2.02	6	1.79/2.25	2.03	5	1.83/2.23
$\beta_{h0,\text{ADAS-cog}}$	0.05	14	0.04/0.06	0.04	10	0.03/0.05
						<0.001
Bayesian Information Criterion (BIC)	3562			3066		

ADAS-cog0 : ADAS-cog score at baseline, r: rate of decline/disease progression, α: shape parameter controlling the inflection point of the decline slope, $\beta_{\text{ADAS-cog0, MMSE}}$: effect size of baseline MMSE score on ADAS-cog0, MMSE score at baseline was centred around the mean, $\beta_{r, \text{misid subtype}}$: effect size of misidentification subtype on r, $\beta_{r, \text{mixed subtype}}$: effect size of mixed subtype on r, misidentification and mixed subtype were compared to the reference "non-psychotic (and paranoid)", $\beta_{r, \text{Allele Apo-e } \varepsilon4}$ effect size of Apo-e ε4 allele carrier on r, Apo-e ε 4 allele carrier status was compared to the reference "not carrier", IIV: inter-individual variability expressed in standard deviation or coefficient of variation (%), RUV : residual unexplained variability expressed in coefficient of variation (%), λ: scale parameter in the Weibull hazard model, k: shape parameter in the Weibull hazard model, $\beta_{h0,\text{ADAS-cog}}$: effect of current predicted ADAS-cog score on the baseline hazard, ne : not estimated