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Predicting Cognitive Decline across Four Decades in Mutation Carriers and Non-carriers in Autosomal-Dominant Alzheimer's Disease

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Abstract

Objectives: The aim of this study was to investigate cognitive performance including preclinical and clinical disease course in carriers and non-carriers of autosomal-dominant Alzheimer's disease (adAD) in relation to multiple predictors, that is, linear and non-linear estimates of years to expected clinical onset of disease, years of education and age. **Methods:** Participants from five families with early-onset autosomal-dominant mutations (Swedish and Arctic APP, PSEN1 M146V, H163Y, and I143T) included 35 carriers (28 without dementia and 7 with) and 44 non-carriers. All participants underwent a comprehensive clinical evaluation, including neuropsychological assessment at the Memory Clinic, Karolinska University Hospital at Huddinge, Stockholm, Sweden. The time span of disease course covered four decades of the preclinical and clinical stages of dementia. Neuropsychological tests were used to assess premorbid and current global cognition, verbal and visuospatial functions, short-term and episodic memory, attention, and executive function. **Results:** In carriers, the time-related curvilinear trajectory of cognitive function across disease stages was best fitted to a formulae with three predictors: years to expected clinical onset (linear and curvilinear components), and years of education. In non-carriers, the change was minimal and best predicted by two predictors: education and age. The trajectories for carriers and non-carriers began to diverge approximately 10 years before the expected clinical onset in episodic memory, executive function, and visuospatial function. **Conclusions:** The curvilinear trajectory of cognitive functions across disease stages was mimicked by three predictors in carriers. In episodic memory, executive and visuospatial functions, the point of diverging trajectories occurred approximately 10 years ahead of the clinical onset compared to non-carriers. (*JINS*, 2017, *23*, 195–203)

Keywords: Autosomal-dominant, Alzheimer's disease, Mutation carrier, Cognition, Predictors, Age of onset

INTRODUCTION

Alzheimer's disease (AD) is typically thought of as a disease with a unitary origin (Lippa et al., 1996), although the cause can vary in that it is related to multiple factors such as age, genetics, metabolic factors, lifestyle, as well as other factors (Winblad et al., 2016). The disease mechanism is thought to be related to abnormal beta-amyloid processing (changes associated with overproduction, turnover, deposition, and clearance), which results in extracellular neuronal changes such as senile plaques and intracellular neuron changes of neurofibrillary tangles. These neuropathological

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changes have been observed many years before the clinical onset of dementia.

Cognitive changes seem to occur later and result in functional difficulties in daily life and a clinical diagnosis of AD. The timing of these changes in relation to the clinical diagnosis and their sequence in terms of onset and progression across the cognitive domains are not well understood. The study of families known to harbor autosomal-dominant mutations leading to AD (adAD) might offer an optimal model to investigate the behavioral manifestations in the course of AD pathology. It is considered that various adAD mutations develop into the same disease as shown by the same neuropathological hallmarks (senile plaques and neurofibrillary tangles), which makes it possible to aggregate cases with various mutations (Selkoe & Hardy, 2016). In particular, it is possible to study incident disease in mutation carriers before symptoms appear and in relation to a time-scale of disease advancement.

Previous research regarding cognitive function in the preclinical stages of familial AD has involved case studies (Godbolt et al., 2005; Newman, Warrington, Kennedy, & Rossor, 1994), studies of mutation carriers in specific families (Almkvist, Axelman, Basun, Wahlund, & Lannfelt, 2002; Ardila et al., 2000; Ringman, 2005), and studies of individuals at risk, that is, individuals in families known to be associated with familial AD but in whom the individual mutation status was not known (Díaz-Olavarrieta, Ostrosky-Solis, Garcia de la Cadena, Rodriguez, & Alonso, 1997; Fox, Warrington, Seiffer, Agnew, & Rossor, 1998). Previous research has shown that, already in the preclinical period in adAD, mutation carriers develop deficits in episodic memory and executive function (Almkvist et al., 2002; Ardila et al., 2000; Ringman, 2005).

To date, few studies of familial AD have included investigation of multiple cognitive domains in more than one family (Bateman et al., 2012; Storandt, Balota, Aschenbrenner, & Morris, 2014; Yau et al., 2015). It is a typical finding in familial AD studies that asymptomatic mutation carriers show some cognitive impairment compared to non-carriers, and that the degree of impairment increases when the carriers approach the expected time of clinical onset (Bateman et al., 2012; Ringman, 2005; Storandt et al., 2014), irrespectively of chronological age at clinical onset that may vary from the 30 s to the 60 s. The estimated onset of cognitive impairment has been reported to occur approximately 10 years before symptom onset in a recent study (Bateman et al., 2012) or much later in another recent study (Yau et al., 2015). The earliest cognitive change is frequently reported as impairment of episodic memory (Almkvist et al., 2002; Ardila et al., 2000; Bateman et al., 2012; Ringman, 2005; Yau et al., 2015).

It is still an open question how the change in cognition should be described. Time to the expected clinical onset (negative values for the preclinical stage and positive values for the clinical stage) is commonly used as a predictor because this measure is directly disease-related while age is not as the clinical onset may vary from the 30 s to the 60 s (see, e.g., Aguirre-Acevedo et al., 2016; Bateman et al., 2012). Both linear and curvilinear time predictors have been suggested in addition to years of education and age. A significant curvilinear time predictor indicates that the cognitive performance declines more rapidly as individuals approach their age of expected onset and that this decline is accelerated across time. However, it is not known if this type of decline continues for the whole clinical stage or not. A significant linear time predictor indicates that the cognitive performance declines by a certain constant rate over time. There is no consensus in previous research on the time-related cognitive decline in adAD since empirical support for both linear (Aguirre-Acevedo et al., 2016) and non-linear models (Bateman et al., 2012; Yau et al., 2015) have been presented.

The purpose of this study was to address two questions: Is a simple time-related model of the effects on cognitive function adequate, or do multiple factors (e.g., non-linear time estimate, education, and age) add predictive power when both the preclinical and clinical stage of disease is investigated? When does the cognitive course for carriers and non-carriers separate?

METHODS

Participants

Adult members of five families known to have a mutation leading to AD were invited to a clinical examination at the Memory Clinic, Karolinska University Hospital Huddinge, Stockholm, Sweden. No invited individual declined participation. This study includes clinical examination data for mutation carriers and non-carriers.

Two families had a mutation in the APP gene on chromosome 21: the Swedish mutation (APP_{SWE}; Axelman, Basun, Winblad, & Lannfelt, 1994; Mullan et al., 1992) and the Arctic mutation (APP_{ARC}; Basun et al., 2008; Nilsberth et al., 2001); three families had mutations in the presenilin 1 gene on chromosome 14: PSEN1 M146V (Haltia et al., 1994), PSEN1 H163Y (Axelman, Basun, & Lannfelt, 1998), and PSEN1 I143T (Keller et al., 2010). There were 24 individuals from the APP_{SWE} family, 22 from the APP_{ARC} family, 17 from the PSEN1 M146V family, 12 from the PSEN1 H163T family, and four from the PSEN1 I143T family.

The analysis of mutation status followed standard procedure as described previously (Thordardottir et al., 2015). The mutation status of the participants was unknown to both the clinicians involved in the study and the participants, except for three patients who opted for presymptomatic genetic testing after completion of the clinical examination. The pathology and clinical characteristics of these families were typical for AD (Axelman et al., 1994, 1998; Basun et al., 2008; Haltia et al., 1994; Keller et al., 2010; Mullan et al., 1992; Nilsberth et al., 2001; Thordardottir et al., 2015), making it possible to aggregate carriers as well as non-carriers from different families. The aggregation of various adAD mutations is also supported by the present state of the art knowledge, which considers adAD mutations to result

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into the same disease with equivalent clinical presentation. The comparability of mutation carriers and non-carriers was secured by assessment of premorbid cognitive function (Almkvist, Adveen, Henning, & Tallberg, 2007).

Diagnosis

Based on the clinical examination, seven individuals were diagnosed as having dementia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994) and AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ARDRA) criteria (McKhann et al., 1984); all of them were mutation carriers. The estimated and observed age of AD were in close correspondence as demonstrated by the Pearson correlation coefficient ($r = 0.92$; $p < .001$). None of the mutation carriers were diagnosed as having mild cognitive impairment (MCI; Winblad et al., 2004). None of the non-carriers were diagnosed as having dementia or MCI. No health problems or remarkable symptoms were identified for the non-carriers except for two healthy non-carriers who had had lifelong selective cognitive difficulties due to specific syndromes (e.g., dyslexia). The data for these two participants were retained in the study but excluded for selectively impaired tests.

Procedure

All individuals went through a standard comprehensive clinical examination, which included an interview with the participant and often with a close informant. The examination included somatic, neurological, and psychiatric status, cognitive screening using MMSE, sampling of blood and cerebrospinal fluid, brain imaging using magnetic resonance imaging, an electroencephalography examination, and a comprehensive assessment of specific cognitive functions. Although clinical examinations started as far back as 1993, roughly the same protocol has been followed throughout the study (Wahlund et al., 1999).

Theory and Calculation

For each individual, the time-table of disease advancement was defined by the number of years to the expected clinical onset (YECO), that is, the age of the individual minus the expected family-specific age at AD diagnosis. The clinical onset was defined as the age at which the first relevant symptoms appeared (Thordardottir et al., 2015). For each mutation, there is a relatively fixed mean age at which clinical onset can be expected; this can be calculated from the previous history of each family (see Thordardottir et al., 2015). The values vary with the mutation: 36 ± 3 years for PSEN1 M146V (Haltia et al., 1994), 54 ± 5 years for APP_{SWE} (Axelman et al., 1994; Thordardottir et al., 2015), 52 ± 7 years for PSEN1 H163Y (Axelman et al., 1998; Thordardottir et al., 2015), 56 ± 3 years for APP_{ARC} (Nilsberth et al., 2001; Thordardottir et al., 2015), and 36 ± 2 years for PSEN1 I143T (Keller et al., 2010).

The mean expected clinical onset is a disease-related measure in adAD, which is family-specific and valid across generations within a family with a specific mutation. It is also a reliable measure as shown in previous research (Bateman et al., 2012; Ryman et al., 2014; Thordardottir et al., 2015). Thus, the YECO is time-related in relation to expected clinical onset and not collinear with the participant's age. The preclinical stage is here defined as $YECO < 0$ and the clinical stages as $YECO \geq 0$. In addition to YECO, $YECO^2$ was investigated as a possible predictor of cognitive decline, because recent research has indicated that curvilinear components may be involved in the disease course (Bateman et al., 2012). A third possible predictor of cognitive decline may be cognitive reserve often measured by years of formal education (Stern, 2009). This factor appears to dampen disease-related cognitive decline. Finally, age was added as a possible predictor as it is documented in epidemiological research as a strong negative factor for AD (Winblad et al., 2016).

Assessment of Cognitive Function

Current global cognitive function was assessed using five subtests (Information, Digit Span, Similarities, Block Design, and Digit Symbol) from the Swedish version of the Wechsler Adult Intelligence Scale Revised (Bartfai, Nyman, & Stegman, 1994; Wechsler, 1981). These subtests can be summarized as a measure of current global cognitive function, that is, intelligence quotient (current IQ; see Almkvist et al., 2007; Almkvist & Tallberg, 2009). In addition, visuospatial ability was assessed by the Rey-Osterrieth (RO) copy test (Lezak, Howieson, & Loring, 2004).

Short-term memory was assessed using the Digit Span Forward test and the Corsi Block Tapping test (Lezak et al., 2004). Episodic memory was assessed using the total learning and 30 min retention scores from the Rey Auditory Verbal Learning (RAVL) test (Lezak et al., 2004) and the 30 min retention score from the RO retention test (Lezak et al., 2004). Attention was assessed using the time to complete the Trail Making Test A (TMTA) and executive function was measured using Trail Making Test B (TMTB) tests (Lezak et al., 2004). Premorbid global cognitive function, that is, intelligence quotient (premorbid IQ) was assessed from demographic information (Almkvist et al., 2007). Raw scores were converted to *z*-scores using a reference group of healthy adults from Karolinska University Hospital at Huddinge (Bergman, Blomberg, & Almkvist, 2007).

Ethics

All participants were aware of their risk of inheriting AD. This information was given before the clinical examination. They also received genetic counselling in connection with the study and no-one asked for information on their genetic status

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before the first visit. All subjects provided written informed consent to participate in the study. The study was approved by the Ethics Committee of Karolinska University Hospital at Huddinge and was conducted according to the declaration of Helsinki and subsequent revisions.

RESULTS

The background characteristics of mutation carriers (seven demented diagnosed as AD, six in the clinical stage and one in the preclinical stage) and non-carriers (none of them with Alzheimer's dementia, any other disease affecting the brain or MCI). All participants were divided into preclinical (YECO < 0) and clinical (YECO ≥ 0) stages of disease are presented in Table 1. Mutation carriers and non-carriers did not differ significantly in age, gender distribution, years of education, and estimated premorbid IQ (Almkvist et al., 2007).

Cognition in the Preclinical and Clinical Stages in Mutation Carriers versus Non-carriers

The neuropsychological test results in the preclinical (YECO < 0) and clinical (YECO ≥ 0) stages for mutation carriers and non-carriers are presented in Table 2. The interaction between disease stage and mutation status was significant in the majority of neuropsychological tests according to two-way (stage × mutation status) analyses of variance (ANOVAs) on each test (Current IQ: $F(1,69) = 4.40$; $p < .05$; $\eta^2 = 0.06$; Similarities: $F(1,73) = 4.34$; $p < .05$; $\eta^2 = 0.06$; Block Design: $F(1,73) = 5.51$; $p < .05$; $\eta^2 = 0.07$; RO copy: $F(1,69) = 14.50$; $p < .001$; $\eta^2 = 0.17$; Corsi Span: $F(1,66) = 4.34$; $p < .01$; $\eta^2 = 0.09$; RAVL learning: $F(1,71) = 12.81$; $p < .001$; $\eta^2 = 0.15$; RO retention: $F(1,69) = 6.75$; $p < .01$; $\eta^2 = 0.08$; Digit Symbol: $F(1,72) = 4.34$; $p < .05$; $\eta^2 = 0.06$). This was due to a significantly poorer performance in the preclinical stage on three tests (RAVL learning: $t(58) = 1.77$; $p < .05$; $d = 0.47$; Digit Symbol: $t(59) = 2.07$; $p < .05$; $d = 0.54$; TMTA: $t(60) = 2.34$; $p < .05$; $d = 0.54$).

In contrast, the carriers performed poorer than the non-carriers on all tests and on current IQ in the clinical stage and significantly poorer in eight tests as expected and in agreement with disease diagnosis. There was a clearly significant difference between the preclinical and clinical stages in all domains of cognition in mutation carriers, whereas the changes were only minor and relatively selective in non-carriers.

Regression of Cognitive Performance by YECO

To explore time-related changes in cognitive function in mutation carriers and non-carriers, YECO and YECO^2 were used to predict performance in tests of cognitive function to account for linear and possible curvilinear effects. YECO was assumed to be normally distributed, since the Shapiro-Wilk's test of normality was not significant neither for carriers nor for non-carriers; this assumption was supported by data from a recent study (Thordardottir et al., 2015). In addition, education and age were introduced as possible predictors because it is well known in normal cognitive aging that

Table 1. Demographic characteristics, YECO, estimated premorbid intelligence quotient (premorbid IQ) and global cognitive screening (MMSE) results for mutation carriers and non-carriers from five early-onset autosomal-dominant Alzheimer's disease families divided into two age groups according to the number of years to the expected clinical onset (YECO) of AD

	Mutation carriers		Non-carriers	
	YECO < 0	YECO ≥ 0	YECO < 0	YECO ≥ 0
N (female/male)	28 (10/18)	7 (2/5)	34 (14/20)	10 (7/3)
Age, years	40.8 ± 10.1	53.8 ± 11.2	36.6 ± 10.1	51.9 ± 9.6
Education, years	11.1 ± 2.2	9.3 ± 3.9	10.8 ± 1.9	9.9 ± 3.5
YECO, years	−11.4 ± 8.0	5.4 ± 3.9	−12.3 ± 6.5	6.7 ± 5.3
Premorbid IQ	101.6 ± 8.1	96.9 ± 11.7	100.3 ± 5.5	96.1 ± 11.5
MMSE	27.6 ± 3.1	18.5 ± 6.6	29.2 ± 1.3	29.0 ± 1.0

Note. Data are presented as mean ± *SD*. Among the mutation carriers, seven individuals were diagnosed with AD dementia: six from the clinical stage group (YECO ≥ 0) and one from the preclinical stage group (YECO < 0); none of the mutation non-carriers were diagnosed with Alzheimer's dementia or any other disease affecting the brain or MCI. YECO < 0 denotes the preclinical stage, and YECO ≥ 0 denotes the clinical stage.
YECO = subject's present age minus the family-specific age for expected clinical onset of AD; IQ = intelligence quotient.

Table 2. Neuropsychological test results in z-score for mutation carriers and non-carriers from five early-onset autosomal-dominant Alzheimer's disease families divided into two clinical groups according to the number of years to the expected clinical onset (YECO) of AD

	Mutation carriers		Non-carriers	
	YECO < 0	YECO ≥ 0	YECO < 0	YECO ≥ 0
Current IQ*	−0.9 ± 1.2	−2.5 ± 1.6	−0.5 ± 1.1	−0.7 ± 0.9
Information	−1.1 ± 1.2	−3.0 ± 1.8	−1.3 ± 1.1	−1.7 ± 1.3
Similarities*	−0.7 ± 1.5	−2.3 ± 2.0	−0.8 ± 1.2	−0.8 ± 1.3
Block Design*	0.3 ± 1.6	−2.8 ± 1.8	0.6 ± 1.3	−0.6 ± 1.2
RO copy***	0.0 ± 1.2	−3.5 ± 4.8	0.0 ± 0.6	0.0 ± 0.7
Digit Span	−0.3 ± 0.8	−0.8 ± 1.0	−0.1 ± 1.1	−0.2 ± 0.9
Corsi Span**	0.4 ± 1.5	−2.6 ± 3.2	0.8 ± 1.3	0.3 ± 0.7
RAVL learning***	−0.4 ± 1.2	−2.8 ± 0.8	0.1 ± 1.0	−0.1 ± 0.8
RAVL retention	−0.1 ± 1.1	−1.6 ± 0.2	0.1 ± 1.0	0.1 ± 0.9
RO retention**	−0.2 ± 1.3	−2.0 ± 1.2	0.0 ± 1.0	0.1 ± 0.4
Digit Symbol*	0.0 ± 1.4	−2.1 ± 1.8	0.6 ± 0.9	0.0 ± 1.2
TMTA	0.2 ± 1.2	0.0 ± 0.8	0.8 ± 0.7	0.2 ± 0.5
TMTB	−0.1 ± 1.7	−0.7 ± 1.8	0.5 ± 0.9	0.1 ± 1.0

Note. Data are presented as mean ± *SD*. Significant interactions between disease stage (YECO < 0, YECO ≥ 0) and mutation status are marked by asterisks. YECO <0 denotes the preclinical stage, and YECO ≥ 0 denotes the clinical stage.
YECO = subject's present age minus the family-specific age for expected clinical onset of AD,
*$p < .05$.
**$p < .01$.
***$p < .001$.

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age is negatively associated with function in some cognitive domains and that education may be positively associated with cognition (Stern, 2009). The Spearman correlation coefficients between test outcomes and the four hypothetical predictors showed that YECO, YECO^2, and education are relevant for mutation carriers and that age and education are relevant for non-carriers, according to the pattern of significant correlation coefficients (see Supplementary Table 1). In addition, a comparison of 4- (YECO, YECO^2, education, and age) and 3-predictor models (excluding YECO^2) demonstrated that the four-predictor model had a higher goodness-of-fit than the three-predictor model (Supplementary Table 2).

Linear regression analyses were performed for each test and current IQ, with YECO, YECO^2, education, and age as possible predictors, for carriers and non-carriers. The multiple correlation coefficient and the standardized beta weights of significant predictors are displayed in Table 3. The regression model was strongly significant for mutation carriers and for non-carriers. The pattern of significant predictors differed between mutation carriers and non-carriers. For mutation carriers, YECO contributed most frequently to cognitive function, followed by education, and YECO^2. For non-carriers, education contributed most frequently to cognitive function, followed by age. The negatively accelerated trajectory was significant in several tests for mutation carriers; there was no similar trend for non-carriers.

This model using four predictors of cognitive function was supported by the proportion of variance accounted for and it was more powerful than a linear model using YECO as a single predictor and it was also more powerful than the curvilinear model with YECO and YECO^2 as predictors. The multiple correlation coefficients were higher with the curvilinear model than with the linear model in all 12 tests and current IQ for both carriers and non-carriers. This outcome supported the use of the more complex model with four predictors over simpler models. In addition, the predictive power for the curvilinear (including all four predictors) *versus* the linear model (without YECO^2) was

Table 3. Multiple regression analyses with cognitive function tests as dependent variable and four predictors (YECO, YECO^2, years of education, and age) for mutation carriers and non-carriers showing significant standardized beta weights

		Predictors, standardized beta weights			
Test	$r_{multiple}$	YECO	YECO^2	Educ	Age
Non-carriers					
Current IQ	**0.602*****	—	—	**+0.569*****	—
Information	**0.588****	—	—	+0.364*	**+0.600****
Similarities	**0.609****	—	—	**+0.438****	**+0.582****
Block Design	**0.554****	—	—	+0.375*	—
RO copy	—	—	—	—	—
Digit Span	**0.591****	—	—	**+0.495*****	—
Corsi Span	—	—	—	—	—
RAVL learn	—	—	—	—	—
RAVL ret	**0.711****	**+0.830****	—	—	**–1.02*****
RO ret	—	—	—	—	—
Digit Symbol	**0.673*****	—	–0.398*	+0.336*	**–0.640*****
TMTA	—	—	—	—	—
TMTB	**0.550****	—	–.477*	—	—
Mutation carriers					
Current IQ	**0.799*****	**–0.825****	—	**+0.523*****	—
Information	**0.814*****	**–1.01*****	—	**+0.585*****	+0.544*
Similarities	**0.702*****	**–0.851****	—	+0.308*	—
Block Design	**0.832*****	**–0.887*****	—	**+0.416*****	—
RO copy	**0.807*****	**–1.43*****	**–1.09****	—	—
Digit Span	0.539*	—	—	+0.409*	—
Corsi Span	**0.807*****	**–1.03****	**–0.854*****	—	—
RAVL learn	**0.831*****	**–0.809****	–0.548*	+0.285*	—
RAVL ret	—	—	—	—	—
RO ret	**0.747*****	–0.772*	—	—	—
Digit Symbol	**0.825*****	**–0.719****	—	**+0.356****	—
TMTA	0.606*	—	—	+0.411*	—
TMTB	—	—	—	—	—

Note. Bolded values indicate correlations that survived Bonferroni correction. "-" denotes non-significant data.
Educ = education; learn = learning; RAVL = Rey Auditory Verbal Learning; ret = retention; RO = Rey-Osterrieth; TMT = Trail Making Test.
*p < .05.
**p < .01.
***p < .001.

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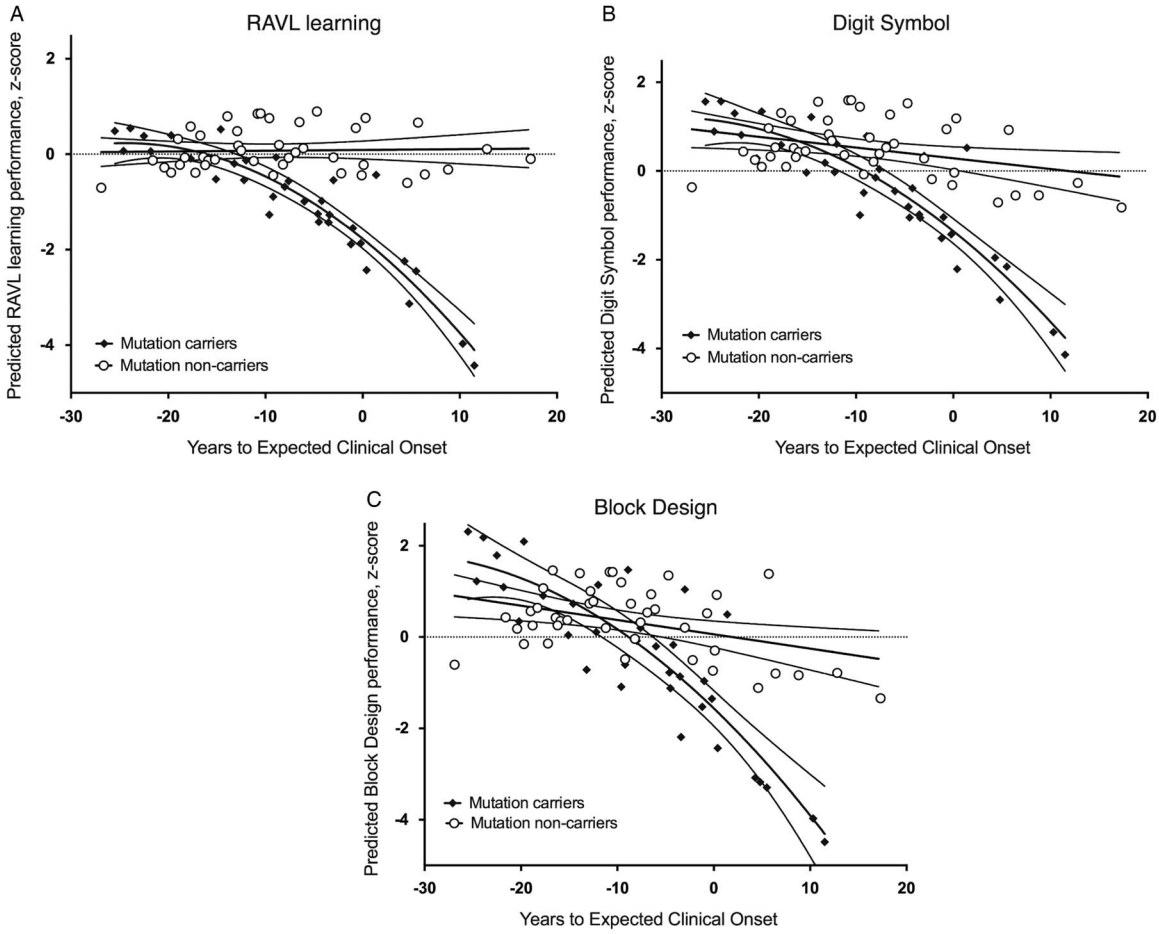

Fig. 1. Scatter plots of non-standardized predicted RAVL learning (**A**), Digit Symbol (**B**), and Block Design (**C**) cognitive test values *versus* the number of years to expected clinical onset (YECO) of AD with curvilinear regression lines and 95% confidence intervals for mutation carriers and non-carriers.

tested using Akaike Information Criterion (AIC) and results showed that the model including a curvilinear predictor was preferable (see Supplementary Table 2).

The hypothesis that mutation type (APP *vs.* PSEN1) is associated with different cognitive trajectories was investigated using a model in which mutation type and interaction (YECO by mutation type) were included in addition to the four previous predictors. The results showed that the main effect of mutation type and the YECO by mutation type interaction were not significant on any test neither in carriers nor in non-carriers.

Separation of the Course of Cognitive Performance in Mutation Carriers and Non-carriers

The onset of cognitive change in mutation carriers was estimated by calculating the intersection between the regression lines as well as the confidence intervals for mutation carriers and non-carriers. The formulae for the regression lines were based on the non-standardized predicted values obtained from previous analyses (see Table 3), which were used as the dependent variable, and YECO, which was used as the independent variable. This procedure was repeated for each test. The results for the point of intersection showed that this point differed considerably in time to expected clinical onset across the cognitive tests. The earliest change was observed in the RAVL learning test, followed by the Digit Symbol test and the Block Design test, see Figure 1. A conservative estimate of the change is the point of non-overlapping confidence intervals in these tests. This occurred approximately 10 years ahead of the expected clinical onset for the RAVL learning test, closely followed by the Digit Symbol and the Block Design tests indicating a long preclinical stage of continuous and progressive cognitive deterioration for carriers. The test showing the latest changes was the Information test, where changes occurred approximately at clinical onset.

DISCUSSION

This study investigated multiple aspects of cognitive function in the preclinical and clinical stages of early-onset autosomal-dominant AD. In the preclinical stage (YECO < 0), all carriers except one (criteria for AD were fulfilled) were

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asymptomatic, which may be related to the relatively young age of most of them, their life conditions were characterized by good health and propitious lifestyles (except for ongoing development of AD) and good social networks, and most of them had full-time jobs. Three mutation carriers in the preclinical stage with clear cognitive dysfunction verified by neuropsychological assessment were not diagnosed with AD because they or their close informants did not report or admit any symptoms or difficulties in daily life; their daily life was associated with low cognitive demands.

However, within 1 year they were diagnosed with AD. In the clinical stage, six of the seven mutation carriers were diagnosed as having AD and dementia according to the DSM-IV and one carrier was not diagnosed with AD, but 4 years later probably as a result of a high cognitive reserve. All non-carriers in the preclinical and clinical stages were asymptomatic.

A main finding was that cross-sectional cognitive changes across time in mutation carriers was best fitted to a formulae including both linear and curvilinear time-related predictors (YECO and $YECO^2$) as well as demographic predictors (education and age). A direct comparison of models based on four (including YECO, $YECO^2$, education, and age) *versus* three predictors (without $YECO^2$) demonstrated that inclusion of $YECO^2$ improved the goodness-of-fit. This has not been demonstrated previously to our knowledge.

A consequence of the curvilinear relationship between cognition and time is illustrated by the finding that the annual rate of change for mutation carriers was faster in the clinical stage than in the preclinical stage and this negatively accelerated trajectory for mutation carriers in several test was not observed in non-carriers. The finding that the trajectory was curvilinear, may be driven by the inclusion of clinical cases in the present study in addition to the preclinical cases. By analyzing both preclinical and clinical cases, it was possible to describe a large part of the disease course. Furthermore, since neuropathological hallmarks (senile plaques and neurofibrillary tangles) are considered to be the same for various adAD mutations, the curvilinear trajectory may generalize across adAD mutations.

Our results are in agreement with previous research reporting that cognitive reserve could be used to improve the predictive power, for example clinical onset might be postponed or occur earlier, depending on the individual's cognitive reserve (Aguirre-Acevedo et al., 2016). The relatively poor performance in verbal tests for some individuals, both carriers and non-carriers, may have been the result of cultural conditions, poor schooling, too few years in school, dyslexia, or a mixture of languages in childhood, indicating that non-optimal environmental influences could also influence cognitive development as a kind of negative cognitive reserve (Stern, 2009).

The study also indicated that the estimated onset of cognitive decline occurred around 10 years before the expected clinical onset of AD or some years earlier according to non-overlapping confidence intervals for carriers and non-carriers. Of interest, the onset varied considerably across the cognitive tests and domains. The earliest estimated onset was seen in an episodic memory learning test (RAVL). The next early-onset signs of cognitive decline were observed in tests demanding executive function (Digit Symbol) and visuospatial knowledge (Block Design). In tests tapping verbal knowledge, semantic memory and attention (Information, Similarities and Digit Span), the onset of deterioration appeared close to the expected clinical onset.

In addition, a summary measure of global cognition, that is, current IQ, demonstrated poorer performance in mutation carriers compared to non-carriers in the preclinical stage of disease and pronounced difference in the clinical stage. Thus, the different cognitive domains appear to vary in terms of sensitivity to the disease process. Similar data concerning estimated onset of cognitive decline in familial AD (Aguirre-Acevedo et al., 2016) and in sporadic AD have been reported previously (Almkvist & Bäckman, 1993; Nestor, Scheltens, & Hodges, 2004). Hypothetically, the sequence of decline in cognition could be related to the sequence of brain regions affected by the neuropathology of AD (Braak & Braak, 1991).

In non-carriers, the time-related cognitive change was linear and minimal, with a slightly progressive decline in the clinical stage, when the non-carrier had passed the age of expected clinical onset for carriers. The finding that verbal cognitive function is preserved is typical for crystallized cognition (Salthouse, 2010). The finding that certain cognitive functions such as episodic memory and executive function decline with normal aging is typical for fluid cognition (Salthouse, 2010). It is worth noting that there were minimal changes in cognition in all the neuropsychological tests, which is not a typical finding in current research on normal cognitive aging (Salthouse, 2010). This discrepancy may be related to the fact that all the non-carriers were given a health examination, and were found to be healthy. A comprehensive health examination is seldom performed in aging research, which may lead to inclusion of subjects with health problems in the normally aging groups (Sliwinski, Lipton, Buschke, & Stuart, 1996).

The design of this cross-sectional and exploratory study was unique in that several cognitive domains were investigated and the time span of AD covered was approximately 40 years. Participants emanated from five adAD families with mutations in the APP and PSEN1 genes. Although there are different mutations responsible for AD, the present state of the art knowledge is that it is the same disease with the same clinical presentation. The cognitive phenotypes of these genotypes might have differed subsequently causing a type II error. However, there was no support in the present data that the mutations differed in cognitive profile as shown by a linear mixed-effect model analysis on each cognitive test with the specific mutation as a random intercept together with the four previous predictors.

The inclusion of the specific mutation as a random intercept did not change the results compared to those obtained from linear regression models. Furthermore, it is a common assertion that familial AD and sporadic AD is driven by the same pathophysiological mechanism and that they have similar clinical characteristics (Bateman et al., 2012;

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Duara et al., 1993; Lippa et al., 1996; Storandt et al., 2014). Given these prerequisites, the findings of the present study may be generalized to knowledge of sporadic AD. Another implication of this study is that it may be possible to detect AD earlier than currently expected (Bateman et al., 2012; Storandt et al., 2014). The results of our study lend support to the new criteria suggested for the diagnosis of AD (Dubois et al., 2007; Sperling et al., 2011).

Finally, it has to be noted that our data were well fitted to a curvilinear model of the cognitive decline in mutation carriers and including four predictors. Other models of fitting data have been used in previous research such as linear (Storandt et al., 2014), biphasic linear using change-point analysis (Aguirre-Acevedo et al., 2016), or sigmoidal (see Fleisher et al., 2015, Jack & Holtzman, 2013). Future studies using large material will clarify this issue.

CONCLUSIONS

Based on cross-sectional data covering preclinical as well as clinical stages of disease course, the time-related changes in specific cognitive functions were inversely related to the expected time to clinical onset, following a curvilinear formulae (including time, squared time, and education), in mutation carriers of early onset autosomal-dominant AD. In non-carriers from the same AD families, the time-related changes in cognition were minimal and predicted by age and education. The trajectories of carriers and non-carriers diverged approximately 10 years before the time of family-specific clinical onset. The time of onset varied among the cognitive domains, appearing earliest in episodic memory followed by executive and visuospatial functions. For both carriers and non-carriers, cognitive reserve had an advantageous influence on cognition.

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SUPPLEMENTARY MATERIAL

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