

## Original Investigation

# Cognitive Decline in a Colombian Kindred With Autosomal Dominant Alzheimer Disease

## A Retrospective Cohort Study

Daniel C. Aguirre-Acevedo, PhD; Francisco Lopera, MD; Eliana Henao, MS; Victoria Tirado, MS; Claudia Muñoz, MS; Margarita Giraldo, MD; Shrikant I. Bangdiwala, PhD; Eric M. Reiman, MD; Pierre N. Tariot, MD; Jessica B. Langbaum, PhD; Yakeel T. Quiroz, PhD; Fabian Jaimes, PhD

**IMPORTANCE** Data from an autosomal dominant Alzheimer disease (ADAD) kindred were used to track the longitudinal trajectory of cognitive decline associated with preclinical ADAD and explore factors that may modify the rate of cognitive decline.

**OBJECTIVES** To evaluate the onset and rate of cognitive decline during preclinical ADAD and the effect of socioeconomic, vascular, and genetic factors on the cognitive decline.

**DESIGN, SETTING, AND PARTICIPANTS** We performed a retrospective cohort study from January 1, 1995, through June 31, 2012, of individuals from Antioquia, Colombia, who tested positive for the ADAD-associated *PSEN1* E280A mutation. Data analysis was performed from August 20, 2014, through November 30, 2015. A mixed-effects model was used to estimate annual rates of change in cognitive test scores and to mark the onset of cognitive decline.

**MAIN OUTCOMES AND MEASURES** Memory, language, praxis, and total scores from the Consortium to Establish a Registry for Alzheimer Disease test battery. Chronologic age was used as a time scale in the models. We explore the effects of sex; educational level; socioeconomic status; residence area; occupation type; marital status; history of hypertension, diabetes mellitus, and dyslipidemia; tobacco and alcohol use; and *APOE*  $\epsilon$ 4 on the rates of cognitive decline.

**RESULTS** A total of 493 carriers met the inclusion criteria and were analyzed. A total of 256 carriers had 2 or more assessments. At the time of the initial assessment, participants had a mean (SD) age of 33.4 (11.7) years and a mean (SD) educational level of 7.2 (4.2) years. They were predominantly female (270 [54.8%]), married (293 [59.4%]), and of low socioeconomic status (322 [65.3%]). Word list recall scores provided the earliest indicator of preclinical cognitive decline at 32 years of age, 12 and 17 years before the kindred's respective median ages at mild cognitive impairment and dementia onset. After the change point, carriers had a statistically significant cognitive decline with a loss of 0.24 (95% CI, -0.26 to -0.22) points per year for the word list recall test and 2.13 (95% CI, -2.29 to -1.96) points per year for total scores. Carriers with high educational levels had an increase of approximately 36% in the rate of cognitive decline after the change point when compared with those with low educational levels (-2.89 vs -2.13 points per year, respectively). Onset of cognitive decline was delayed by 3 years in individuals with higher educational levels compared with those with lower educational levels. Those with higher educational level, middle/high socioeconomic status, history of diabetes and hypertension, and tobacco and alcohol use had a steeper cognitive decline after onset.

**CONCLUSIONS AND RELEVANCE** Preclinical cognitive decline was evident in *PSEN1* E280A mutation carriers 12 years before the onset of clinical impairment. Educational level may be a protective factor against the onset of cognitive impairment.

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**Author Affiliations:** Neuroscience Group of Antioquia, University of Antioquia, Medellín, Colombia (Aguirre-Acevedo, Lopera, Henao, Tirado, Muñoz, Giraldo, Quiroz); Academic Group of Clinical Epidemiology, University of Antioquia, Medellín, Colombia (Aguirre-Acevedo, Jaimes); Department of Biostatistics, University of North Carolina at Chapel Hill (Bangdiwala); Banner Alzheimer's Institute, Phoenix, Arizona (Reiman, Tariot, Langbaum); Departments of Psychiatry and Neurology, Massachusetts General Hospital, Boston (Quiroz); Research Unit, Hospital Pablo Tobón Uribe, Medellín, Colombia (Jaimes).

**Corresponding Author:** Daniel C. Aguirre-Acevedo, PhD, Neuroscience Group of Antioquia, Calle 62 #52-59, Lab 412, Torre 1, Sede de Investigación Universitaria, University of Antioquia, Medellín, Antioquia, Colombia (daniel.aguirre@udea.edu.co).

**R**esearch diagnostic criteria have been published for preclinical Alzheimer disease (AD) based on biomarkers of AD-related neurodegeneration.<sup>1</sup> The study of carriers of AD-causing mutations provides a unique opportunity to characterize the preclinical changes associated with predisposition to AD.

For more than 25 years, the Neuroscience Group of Antioquia has studied a large kindred with autosomal dominant AD (ADAD) due to a single *PSEN1* E280A mutation (OMIM 104311.0009). Carriers from this kindred have an onset of mild cognitive impairment (MCI) at the age of 44 years and an onset of dementia at the age of 49 years.<sup>2</sup> Previous studies<sup>3-9</sup> have found that carriers have brain A $\beta$  plaque deposition and cerebrospinal fluid (CSF) and plasma biomarker evidence of A $\beta$  overproduction decades before clinical symptoms. Cognitive markers also have been reported during preclinical stages of ADAD.<sup>10</sup> However, given the heterogeneity of the cognitive profile of AD, it has been challenging to characterize cognitive changes that precede the onset of clinical impairment and to evaluate factors that may modify the rate and onset of cognitive decline during preclinical AD. Some of these factors, including genetic factors,<sup>11</sup> educational level,<sup>12</sup> socioeconomic status (SES),<sup>13</sup> history of vascular disease (eg, hypertension, diabetes mellitus),<sup>14</sup> and tobacco or alcohol use,<sup>14</sup> have been related to cognitive decline. Preclinical cognitive markers and early detection of AD are increasingly important as research on new treatments that may slow or halt cognitive decline in AD is under way.<sup>15</sup>

In this study, we tracked the longitudinal trajectory of cognitive changes for a period of 18 years in preclinical *PSEN1* E280A mutation carriers from Antioquia, Colombia. In addition, we estimated the onset and rate of cognitive decline during preclinical AD and the effect of socioeconomic, vascular, and genetic factors on the rate of cognitive decline.

## Methods

### Study Design and Participants

Participants who tested positive for the ADAD-associated *PSEN1* E280A mutation were enrolled from January 1, 1995, through June 31, 2012.<sup>2</sup> Data analysis was performed from August 20, 2014, through November 30, 2015. We included retrospective and longitudinal data from those carriers 18 years and older who had a complete neuropsychological assessment using the Consortium to Establish a Registry for Alzheimer Disease (CERAD) test battery. We excluded participants with a history of psychiatric disorders, illiteracy, stroke, epilepsy, traumatic brain injury, kidney failure, human immunodeficiency syndrome or AIDS, or substance abuse. All participants agreed to take part in this study and provided written informed consent before data collection. This study was approved by the ethics research committee of the University of Antioquia, Antioquia, Colombia. During clinical and neuropsychological assessments, physicians were masked to genetic status of the participants with no evident clinical symptoms to minimize the information bias. The genetic status was recorded in a database. Only the database's coordinator (a system engineer) pro-

### Key Points

**Question:** When is the onset of cognitive decline in the *PSEN1* E280A carriers with autosomal dominant Alzheimer disease (ADAD)?

**Findings:** In this retrospective cohort study, which included 493 *PSEN1* E280A carriers, a word list test provided the earliest indicator of preclinical cognitive decline at 32 years of age, which is 12 and 17 years before the kindred's respective median ages at mild cognitive impairment and dementia onset.

**Meaning:** The systematic assessment of ADAD carriers for more than 20 years is a unique opportunity to characterize the trajectory of some of the earliest preclinical changes, which might guide future preventive interventions.

vided the genetic status for statistical analysis, with the name of the participant presented as a numerical code and not a name.

### Procedures

All participants underwent comprehensive clinical and neuropsychological assessments. These assessments included an interview and medical and neuropsychological examinations. Medical examinations were performed by a neurologist or a physician trained in dementia assessment. Neuropsychological tests were conducted by psychologists. The neuropsychological protocol included the Mini-Mental State Examination (MMSE)<sup>16</sup> and the CERAD test battery, which have been validated in our population.<sup>2,17</sup> Clinical Dementia Rating (CDR)<sup>18</sup> was used to establish the presence or absence of dementia. A CDR score of 0 indicates cognitive normality; 0.5, very mild dementia; 1, mild dementia; 2, moderate dementia; and 3, severe dementia.

### Demographic Information

Socioeconomic status was defined according to the Colombian government classification system as low or middle/high. Our cohort comes from a population with a low educational level; accordingly, we classified educational level into 2 groups based on the median years of formal education: high ( $\geq 7$  years) and low ( $< 7$  years). Marital status was classified in 3 groups: married or cohabitant, single, and divorced or widowed. Occupation was classified into 2 groups based on the nature of the work: manual work (housewives, farmers, domestic service employees, or technician) or nonmanual work (all professionals and managers, higher administrators, or clerical employees). Place of residence was classified as urban or rural.

### Cardiovascular Factors

Hypertension was considered to be present if systolic blood pressure was 140 mm Hg or higher or diastolic blood pressure was 90 mm Hg or higher in the clinical assessment or if medications for hypertension were prescribed or self-reported. History of dyslipidemia was defined based on self-reports, the use of cholesterol-lowering agents, or a total cholesterol level greater than 200 mg/dL (to convert to millimoles per liter, multiply by 0.0259) registered in the clini-

cal record. History of diabetes or alcohol or tobacco use was defined based on patient self-report.

### Genetic Analyses

Genomic DNA was extracted from blood by standard protocols, and *PSEN1* E280A characterization was performed as previously described.<sup>19</sup> For exploratory analyses, *APOE* genotyping was performed in a subsample of 130 mutation carriers following methods previously described.<sup>20</sup> Given the low frequency of the  $\epsilon 2/3$ ,  $\epsilon 2/4$ , and  $\epsilon 4/4$  genotypes, data were classified into 2 categories (presence or absence of *APOE*  $\epsilon 4$ ) for statistical analyses.<sup>19</sup>

### Cognitive Outcomes

Memory, language, and praxis tests from the CERAD test battery were included, and a total score (CERADt) was calculated using the Chandler method<sup>21</sup> (range, 0-100) by adding the scores of the CERAD subtests (verbal fluency, 15-item Boston Naming Test, word list memory, word list recall, word list recognition [discrimination], and constructional praxis).

### Statistical Analysis

We estimated the statistical power of 90%<sup>22</sup> to detect a relative effect size of 0.30 (assuming a relative  $\beta$  coefficient related to time variable or other covariable in the model), with 162 participants and 3 or more assessments per individual assuming an intraclass correlation coefficient of 0.70 and a type I error of 0.05.

A mixed-effects model<sup>22</sup> was used to estimate the annual rate of cognitive decline. Previous reports<sup>23,24</sup> support the assumption that cognitive decline is not a constant linear process. Instead, the rate of cognitive decline increases after an unknown change point (CP) many years before clinical symptoms.<sup>25</sup> Indeed, previous studies have also found differences in cross-sectional analyses between asymptomatic carriers and noncarriers in several biomarkers<sup>5</sup> and cognitive markers<sup>2,10</sup> at different preclinical stages. Thus, a CP approach provides an indirect estimation of when that cognitive decline could start. The approach taken by Hall et al<sup>23</sup> was used to estimate the CP or onset of cognitive decline. The models used allow estimation of the rate of cognitive decline before and after the CP. To give an interpretation of the constant in the model, age was centered at 20 years. Fifty models were adjusted by varying the CP annually between the ages of 18 and 60 years. The likelihood approach was used to compare the models<sup>23</sup> based on the goodness-of-fit index as the Akaike information criterion and the Bayesian information criterion.<sup>26</sup> The lowest Bayesian information criterion was accepted as appropriate. The effect of sex, SES, educational level, vascular factors, tobacco or alcohol use, and *APOE*  $\epsilon 4$  on cognition was analyzed using the MMSE score, CERAD subtest scores, and CERADt. The interaction coefficient between age (as a time variable) and demographic and vascular factors was analyzed in the model to estimate the annual rate of change in the presence or absence of those factors.

**Table 1. Demographic and Clinical Characteristics of 493 *PSEN1* E280A Mutation Carriers**

Characteristic	Finding (N = 493) <sup>a</sup>
Women	270 (54.8)
Age at first assessment, mean (SD), y	33.4 (11.7)
Educational level, mean (SD), y	7.2 (4.2)
Socioeconomic status	
Low	322 (65.3)
Middle	166 (33.7)
High	5 (1.0)
Occupation	
Nonmanual	61 (12.4)
Manual	432 (87.6)
Residence area	
Urban	354 (71.8)
Rural	139 (28.2)
Marital status	
Married or cohabitant	293 (59.4)
Single	164 (33.3)
Divorced or widowed	36 (7.3)
Vascular factors	
Hypertension	43 (8.7)
Dyslipidemia	33 (6.7)
Diabetes mellitus	8 (1.6)
Tobacco use	123 (24.9)
Alcohol use	58 (11.8)
<i>APOE</i> (n = 130)	
$\epsilon 2/3$	11 (8.5)
$\epsilon 2/4$	4 (3.1)
$\epsilon 3/3$	83 (63.8)
$\epsilon 3/4$	32 (24.6)
MMSE score, mean (SD)	26.5 (5.5)
Clinical Dementia Rating	
0	386 (78.3)
0.5	51 (10.3)
1	43 (8.7)
2	13 (2.7)

Abbreviation: MMSE, Mini-Mental State Examination.

<sup>a</sup> Data are presented as number (percentage) of study participants unless otherwise indicated.

## Results

### Participants

From 703 *PSEN1* E280A mutation carriers, 210 were excluded. A total of 493 carriers met the inclusion criteria and were analyzed (eFigure 1 in the Supplement). There were 256 carriers with 2 or more assessments, the median time between assessments was 2 years (interquartile range, 1-3 years), and the median time of follow-up was 5 years (interquartile range, 3-10 years). At the time of the initial assessment, participants had a mean (SD) age of 33.4 (11.7) years and a mean (SD) educational level of 7.2 (4.2) years. They were predominantly female (270 [54.8%]), married (293 [59.4%]), and of low

Figure 1. Spaghetti Plot for Longitudinal Assessment of the Consortium to Establish a Registry for Alzheimer Disease Total Score (CERADts) in *PSEN1* E280A Mutation Carriers

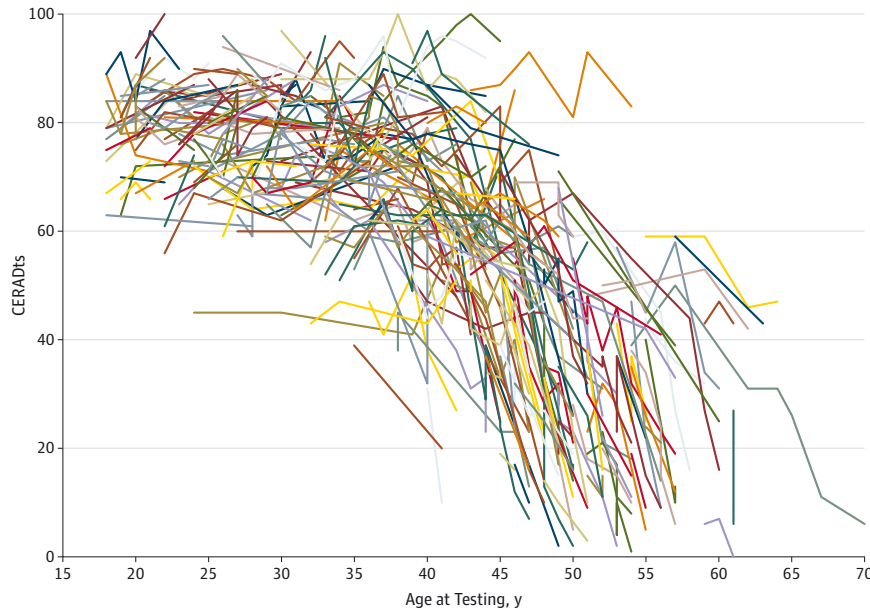


Table 2. Coefficients of the Estimated Cognitive Decline Before and After the CP for the CERADts, MMSE, and CERAD Subtests in 493 *PSEN1* E280A Mutation Carriers

Test	Age at CP, y	Raw Coefficient (95% CI)			Adjusted Coefficient (95% CI) <sup>a</sup>		
		Mean (95% CI)	Before CP (95% CI)	After CP (95% CI)	Mean (95% CI)	Before CP (95% CI)	After CP (95% CI)
CERADts	34	75.41 (73.65 to 77.17)	0.01 (-0.17 to 0.19)	-2.20 (-2.36 to -2.03)	82.10 (79.18 to 85.02)	0.10 (-0.08 to 0.28)	-2.13 (-2.29 to -1.96)
MMSE	36	29.45 (28.93 to 29.97)	0.02 (-0.03 to 0.07)	-0.71 (-0.77 to -0.65)	29.96 (29.01 to 30.91)	0.04 (-0.01 to 0.09)	-0.71 (-0.77 to -0.65)
WLR	32	6.38 (6.13 to 6.64)	-0.03 (-0.06 to 0.00)	-0.25 (-0.27 to -0.23)	7.09 (6.61 to 7.58)	-0.01 (-0.05 to 0.02)	-0.24 (-0.26 to -0.22)
WLM	34	17.65 (17.07 to 18.23)	0.00 (-0.06 to 0.06)	-0.60 (-0.65 to -0.55)	19.81 (18.73 to 20.89)	0.02 (-0.04 to 0.09)	-0.58 (-0.63 to -0.53)
WLRd	34	9.60 (9.33 to 9.88)	0.00 (-0.03 to 0.03)	-0.30 (-0.33 to -0.27)	9.76 (9.23 to 10.28)	0.01 (-0.02 to 0.04)	-0.29 (-0.32 to -0.27)
Verbal fluency	34	18.87 (18.18 to 19.56)	0.05 (-0.02 to 0.12)	-0.49 (-0.55 to -0.43)	21.52 (20.19 to 22.85)	0.10 (0.03 to 0.18)	-0.46 (-0.52 to -0.41)
BNT	34	12.75 (12.44 to 13.06)	0.01 (-0.03 to 0.04)	-0.20 (-0.23 to -0.18)	13.63 (13.10 to 14.16)	0.01 (-0.02 to 0.05)	-0.20 (-0.23 to -0.17)
Construction praxis	38	9.87 (9.59 to 10.14)	-0.02 (-0.04 to 0.01)	-0.34 (-0.37 to -0.31)	10.35 (9.85 to 10.85)	0.01 (-0.02 to 0.03)	-0.34 (-0.37 to -0.30)

Abbreviations: BNT, 15-item Boston Naming Test; CERADts, Consortium to Establish a Registry for Alzheimer Disease total score; CP, change point; MMSE, Mini-Mental State Examination; WLM, word list memory; WLR, word list recall; WLRd, word list recognition (discrimination).

<sup>a</sup> Adjusted by sex, educational level, socioeconomic status, residence area, occupation type, marital status, hypertension, dyslipidemia, diabetes mellitus, and tobacco and alcohol use.

SES (322 [65.3%]). A total of 432 participants (87.6%) had manual work occupations, 43 (8.7%) had a history of hypertension, 33 (6.7%) had dyslipidemia, and 8 (1.6%) had diabetes. A total of 123 participants (24.9%) had a history of tobacco use, and 58 (11.8%) had a history of alcohol use. The mean MMSE score was 26.5, and 386 (78.3%) were cognitively normal (CDR, 0). A subsample of 130 *PSEN1* mutation carriers underwent *APOE* genotyping; 36 (27.7%) tested positive for at least one  $\epsilon 4$  allele (*APOE*  $\epsilon 4$ ) (Table 1).

**Description and Estimate of Cognitive Decline**

Figure 1 shows the spaghetti plot for CERADts (eFigure 2 in the Supplement illustrates the MMSE and CERAD subtests). The goodness-of-fit indexes suggested a CP for CERADts at the age of 34 years. Word list recall scores provided the earliest indication of cognitive decline at the age of 32 years, followed by word list learning, word list recognition, verbal fluency, and naming at the age of 34 years and constructional praxis at the age of 38 years (eFigure 3 in the Supplement shows the Akaike

Table 3. Cognitive Decline in CERADts by Risk Factors in 493 *PSEN1*E280A Mutation Carriers

Characteristic	Raw Coefficient (95% CI)		Adjusted Coefficient (95% CI) <sup>a</sup>	
	Before 34 Years Old	After 34 Years Old	Before 34 Years Old	After 34 Years Old
<b>Sex</b>				
Female	-0.28 (-0.46 to -0.10)	-2.16 (-2.37 to -1.95)	0.11 (-0.11 to 0.33)	-2.10 (-2.31 to -1.90)
Male	0.46 (0.07 to 0.85)	-2.24 (-2.75 to -1.72)	0.09 (-0.43 to 0.61)	-2.15 (-2.66 to -1.65)
<b>Educational level<sup>b</sup></b>				
High (median years for formal education, ≥7)	0.11 (-0.08 to 0.29)	-2.89 (-3.25 to -2.52)	0.12 (-0.08 to 0.32)	-2.89 (-3.25 to -2.53)
Low (median years of formal education, <7)	-0.04 (-0.28 to 0.19)	-2.08 (-2.28 to -1.88)	-0.08 (-0.34 to 0.18)	-2.13 (-2.34 to -1.93)
<b>Socioeconomic status</b>				
Middle/high	0.14 (-0.12 to 0.40)	-2.65 (-3.02 to -2.29)	0.17 (-0.09 to 0.43)	-2.52 (-2.86 to -2.17)
Low	-0.07 (-0.74 to 0.59)	-1.92 (-2.63 to -1.22)	0.04 (-0.59 to 0.68)	-1.87 (-2.54 to -1.20)
<b>Residence area</b>				
Urban	0.00 (-0.19 to 0.19)	-2.32 (-2.70 to -1.94)	0.14 (-0.06 to 0.33)	-2.24 (-2.60 to -1.88)
Rural	-0.09 (-0.68 to 0.49)	-1.87 (-2.61 to -1.12)	0.00 (-0.57 to 0.56)	-1.84 (-2.56 to -1.12)
<b>Occupation type</b>				
Nonmanual	0.07 (-0.86 to 0.99)	-1.47 (-1.97 to -0.97)	0.02 (-0.88 to 0.93)	-1.48 (-1.95 to -1.02)
Manual	0.08 (-0.87 to 1.04)	-2.20 (-3.64 to -0.76)	0.11 (-0.79 to 1.01)	-2.15 (-3.53 to -0.77)
<b>Marital status</b>				
Single	0.08 (-0.55 to 0.72)	-2.49 (-3.12 to -1.86)	0.33 (-0.32 to 0.99)	-2.13 (-2.77 to -1.49)
Married	0.14 (-0.10 to 0.38)	-2.15 (-2.33 to -1.97)	0.39 (0.10 to 0.68)	-1.93 (-2.14 to -1.73)
<b>Hypertension</b>				
Present	0.30 (-1.28 to 1.87)	-2.24 (-2.86 to -1.63)	0.73 (-0.84 to 2.29)	-2.04 (-2.67 to -1.40)
Absent	0.00 (-1.39 to 1.39)	-2.20 (-2.63 to -1.77)	0.37 (-0.94 to 1.68)	-1.94 (-2.36 to -1.53)
<b>Dyslipidemia</b>				
Present	0.16 (-1.08 to 1.41)	-1.74 (-2.39 to -1.10)	0.30 (-0.91 to 1.51)	-1.61 (-2.27 to -0.94)
Absent	0.02 (-0.17 to 0.20)	-2.28 (-2.46 to -2.10)	0.38 (0.12 to 0.64)	-2.02 (-2.23 to -1.81)
<b>Diabetes mellitus</b>				
Present	1.72 (-2.51 to 5.96)	-3.10 (-4.45 to -1.75)	1.27 (-2.74 to 5.28)	-2.60 (-3.93 to -1.28)
Absent	0.00 (-0.18 to 0.18)	-2.19 (-2.35 to -2.02)	0.37 (0.12 to 0.63)	-1.95 (-2.14 to -1.75)
<b>Tobacco use</b>				
Present	0.00 (-0.54 to 0.54)	-2.41 (-2.62 to -2.20)	0.50 (-0.09 to 1.10)	-2.18 (-2.41 to -1.95)
Absent	0.01 (-0.19 to 0.21)	-2.05 (-2.26 to -1.85)	0.35 (0.09 to 0.61)	-1.83 (-2.06 to -1.60)
<b>Alcohol use</b>				
Present	-0.14 (-0.94 to 0.66)	-2.57 (-3.19 to -1.94)	0.53 (-0.29 to 1.35)	-2.44 (-3.08 to -1.81)
Absent	-0.01 (-0.62 to 0.61)	-2.09 (-2.53 to -1.65)	0.37 (-0.20 to 0.93)	-1.85 (-2.28 to -1.43)
<b>APOE ε4</b>				
Present	-0.66 (-2.19 to 0.87)	-2.16 (-3.00 to -1.33)	-0.26 (-2.01 to 1.49)	-2.31 (-3.33 to -1.29)
Absent	0.20 (-0.39 to 0.79)	-2.58 (-2.88 to -2.28)	0.37 (-0.37 to 1.11)	-2.45 (-2.82 to -2.08)

Abbreviations: CERADts, Consortium to Establish a Registry for Alzheimer's Disease total score; CP, change point.

<sup>a</sup> Adjusted coefficients by sex, educational level, socioeconomic status,

residence area, occupation type, marital status, hypertension, dyslipidemia, diabetes mellitus, and tobacco and alcohol use.

<sup>b</sup> The CP by educational level: high (CP, 37 years old) or low (CP, 35 years old).

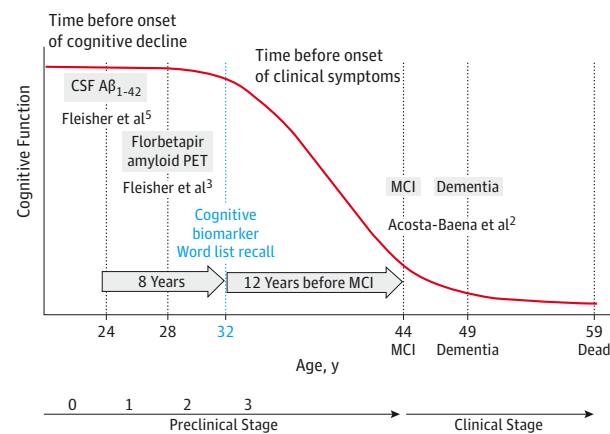
and Bayesian goodness-of-fit indexes for the models). **Table 2** gives the coefficients of the estimated cognitive decline before and after the CP for the CERADts, MMSE, and CERAD subtests. After the CP, the CERADts revealed a statistically significant cognitive decline with a loss of 2.13 (95% CI, -2.29 to -1.96) points per year.

Onset of cognitive decline on the word list recall test was delayed by 3 years in individuals with a high educational level (minimum Akaike information criterion, 2949) when compared with those with a low educational level (minimum Akaike information criterion, 2115). Mutation

carriers with high educational levels had a CP at the age of 37 years for CERADts; at the age of 38 years for the MMSE; at the age of 36 years for word list recall, word list learning, and word list recognition; at the age of 38 years for verbal fluency; and at the age of 39 years for naming and constructional praxis. Mutation carriers with low educational levels had a CP at the age of 35 years for CERADts; at the age of 36 years for the MMSE; at the age of 33 years for word list recall; at the age of 37 years for word list learning, word list recognition, and verbal fluency; and at the age of 38 years for naming and constructional praxis.



**Figure 2. Model for Preclinical and Clinical Stage in *PSEN1* E280A Mutation Carriers**



CSF indicates cerebrospinal fluid; MCI, mild cognitive impairment; and PET, positron emission tomography.

### Effects of Risk Factors on Cognitive Decline

Table 3 gives the coefficients of the estimated cognitive decline on CERADt in relation to the presence or absence of risk factors. Carriers with high educational levels had an increase of approximately 36% in the rate of cognitive decline after the CP when compared with those with low educational levels ( $-2.89$  vs  $-2.13$  points per year after adjustment). Similar results were found when cognitive decline was estimated in relation to SES, place of residence, diabetes, and tobacco or alcohol use (eTable 1, eTable 2, and eTable 3 in the Supplement estimate the cognitive decline in the MMSE and CERAD subtests). No statistical differences in the rate of cognitive decline were found after the CP in relation to sex, SES, occupation, residence area, marital status, and history of hypertension, diabetes, dyslipidemia, and tobacco and alcohol use.

### Exploratory Analysis With *APOE* Genotype and Cognitive Decline

The frequency of *APOE* genotypes was as follows: *APOE*  $\epsilon 2/3$ , 11 patients; *APOE*  $\epsilon 2/4$ , 4 patients; *APOE*  $\epsilon 3/3$ , 83 patients; and *APOE*  $\epsilon 3/4$ , 32 patients. No differences in cognitive decline on any measure were found between *APOE*  $\epsilon 4$  carriers and *APOE*  $\epsilon 4$  noncarriers. No statistically significant difference was found in frequency of *APOE*  $\epsilon 4$  status in demographic or vascular factors (sex:  $P = 0.48$ ; SES:  $P = 0.66$ ; educational level:  $P = 0.72$ ; occupation:  $P = 0.12$ ; residence area:  $P = 0.61$ ; marital status:  $P = 0.54$ ; history of hypertension:  $P = 0.34$ ; diabetes:  $P = 0.21$ ; dyslipidemia:  $P = 0.94$ ; tobacco use:  $P = 0.65$ ; and alcohol use:  $P = 0.56$ ).

### Sensitivity Analysis

Results of the analysis that included participants with 2 or more assessments ( $n = 256$ ) compared with the total sample ( $n = 493$ ) provided similar results in the estimation of CP and the rate of cognitive decline. For all cognitive tests before the CP, coefficients in those carriers with 2 or more assessments were similar to coefficients in the total sample. We found similar re-

sults in the estimation of the CP (eFigure 4 in the Supplement), and thereafter there was a median increase of 4.5% in the rate of cognitive decline in all subtests (range, 3.2%-5.7%) (eTable 4 in the Supplement). Moreover, additional analysis in carriers with a CDR of 0 provided similar results in CP estimation (eFigure 5 in the Supplement).

## Discussion

This study provides evidence of preclinical cognitive decline in *PSEN1* mutation carriers as early as 12 years before the estimated median age at MCI diagnosis and 17 years before dementia diagnosis. A memory test score provided the earliest indicator of cognitive decline. A higher educational level was associated with a delay in onset of cognitive decline and also with more rapid cognitive decline after onset.

Previous studies in sporadic AD have found that cognitive decline begins at approximately 3 years before MCI<sup>25</sup> and between 3 and 9 years before dementia.<sup>27</sup> On the basis of previous work at identifying early biomarkers<sup>3-5</sup> and the prevailing model of preclinical AD biomarker trajectory,<sup>28</sup> we propose a model (Figure 2) of this trajectory, including cognitive changes, from preclinical to clinical stages in ADAD due to the *PSEN1* E280A mutation.<sup>3</sup> According to this model, the first biomarker changes are evident as CSF  $A\beta_{1-42}$  abnormalities at the age of 24 years (stage 1) followed by increased fibrillar  $A\beta$  accumulation at the age of 28 years (stage 2) and onset of cognitive decline at the age of 32 years (stage 3).

In addition, high educational level delayed by 3 years the onset of cognitive decline. This finding is consistent with other studies<sup>12,29</sup> reported for sporadic AD. The theory of cognitive reserve could explain our findings.<sup>30</sup> Cognitive reserve has been conceptualized as a multifactor construct that may include educational level, SES, and occupation, as well as lifestyle factors, which may contribute to cognitive reserve as part of a more dynamic process that changes throughout life.<sup>30</sup> Studies<sup>12,30</sup> of cognitive reserve have found that older individuals whose life experiences include more daily, challenging cognitive activities may have more compensatory strategies in place before the onset of cognitive impairment. In contrast, an early study performed by Pastor et al<sup>19</sup> with *PSEN1* E280A mutation carriers found that those carriers with high educational levels had an earlier onset of dementia. Some explanations for these opposite results are the outcome and a potential information bias. Pastor et al<sup>19</sup> analyzed as the primary outcome the diagnosis of dementia using time to event models, and in some patients the diagnosis could be delayed because the onset of dementia was defined from information provided by a relative.

The main strength of the present study is the longitudinal follow-up of members from a large ADAD kindred with a single-gene mutation, with characterized ages at the onset of MCI and dementia<sup>2</sup> and previously characterized associations of brain imaging and CSF biomarkers in adulthood.<sup>3-5</sup> Another strength is the opportunity to evaluate the influence of risk factors on AD-related cognitive decline and clinical onset independent of potentially confounding effects of older age and age-related disorders.

This study also had several limitations. Exposures were measured retrospectively from clinical records, which does not account for the accumulative process of exposure, frequency, duration, and severity. Our analyses did not include other factors associated with the risk of dementia or cognitive decline (eg, obesity, physical activity, diet, cognitive stimulation, or cognitive or behavior-modifying drugs, such as memantine hydrochloride) because these were not systematically assessed and collected during the clinical assessments. In addition, the period of cognitive decline is larger than the time of observations for each participant. In our cohort, the data from carriers with 2 or more assessments had a median of 2 years between assessments in a mean longitudinal length of 5 years. Although mixed models can handle unbalanced design and missing data, the amount of information in our cohort limited the possibilities of more statistical analysis to determine how the CP varied among carriers. Further analysis is necessary, including a new cohort of carriers with a systematic assessment in the preclinical stage, to study how variation in the CP and the rate of cognitive decline between participants and how demographic, vascular, and other factors are related. Other methods using a Bayesian approach<sup>31</sup> are nec-

essary to find this variation. CERAD is sensitive to detect early changes associated with MCI.<sup>21</sup> However, the floor or ceiling effects of CERAD subtests may affect the sensitivity to evaluate cognitive decline in the preclinical stage. Our cohort comes from a population with a low educational level, which is an important limitation for comparison with other studies. Finally, given the conditions of our sample, it is uncertain to what extent our findings may be generalizable to other AD-causing mutations and late-onset AD.

## Conclusions

The systematic assessment of ADAD mutation carriers for more than 20 years is a unique opportunity to characterize the trajectory of some of the earliest preclinical changes and will guide future preventive interventions. Our findings suggest that cognitive decline could be detected by neuropsychological tests in preclinical AD more than a decade before the onset of clinical symptoms. Furthermore, our findings also support the idea that high educational level may be a protective effect against onset of cognitive decline.

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**Study concept and design:** Aguirre-Acevedo, Lopera, Bangdiwala, Langbaum, Jaimes.  
**Acquisition, analysis, or interpretation of data:** Aguirre-Acevedo, Lopera, Henao, Tirado, Muñoz, Giraldo, Bangdiwala, Reiman, Tariot, Quiroz, Jaimes.  
**Drafting of the manuscript:** Aguirre-Acevedo, Quiroz.

**Critical revision of the manuscript for important intellectual content:** Aguirre-Acevedo, Lopera, Henao, Tirado, Muñoz, Giraldo, Reiman, Tariot, Langbaum, Quiroz, Jaimes.

**Statistical analysis:** Aguirre-Acevedo, Bangdiwala, Jaimes.

**Obtaining funding:** Aguirre-Acevedo, Lopera, Reiman, Jaimes.

**Administrative, technical, or material support:** Aguirre-Acevedo, Lopera, Tariot, Langbaum, Jaimes.

**Study supervision:** Lopera, Bangdiwala, Jaimes.

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