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RESEARCH ARTICLE

The effect of years of schooling and age on CERAD-MX performance in Mexican preclinical carriers of the *APP*$_{V717I}$ mutation: Randomized data simulation

Angélica Zuno-Reyes[1] | **Karina Pérez-Rubio**[1] | **Martín Alonso Flores-González**[2] | **Ricardo Jauregui Torres**[2] | **Sofía Dumois-Petersen**[3] | **Luis E. Figuera**[4] | **John M. Ringman**[5] | **Esmeralda Matute**[1,6]

[1]Instituto de Neurociencias CUCBA, Universidad de Guadalajara, Jalisco, México

[2]Centro de Investigación en Matemáticas, CIMAT, Guanajuato, México

[3]Laboratorio de Ciencias Clínicas, CuValles, Universidad de Guadalajara, Jalisco, México

[4]División de Genética, CIBO-IMSS & Doctorado en Genética Humana, CUCS-Universidad de Guadalajara, Jalisco, México

[5]Alzheimer's Disease Research Center, Department of Neurology, Keck School of Medicine at USC, Los Angeles, California, USA

[6]Departamento de Estudios en Educación, CUCSH, Universidad de Guadalajara, Jalisco, México

Correspondence
Esmeralda Matute, Instituto de Neurociencias, CUCBA, Universidad de Guadalajara, Francisco de Quevedo 180, C.P. 44130 Guadalajara Jalisco, Mexico.
Email: maria.matute@academicos.udg.mx

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Abstract

INTRODUCTION: We aimed to determine the effect of years of schooling (YoS) and age on the Mexican adaptation of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-MX) scores in preclinical carriers group (PCG) and non-carriers group (NCG) of the *APP*$_{V717I}$ mutation.

METHODS: We included 39 first-degree Mexican relatives of *APP*$_{V717I}$ carriers (PCG = 15; NCG = 24). We report eight CERAD-MX tasks: Mini-Mental State Examination (MMSE), Word List Learning (WLL), Delayed Recall (WLD) and Recognition (WLR), Constructional Praxis Copy (CPC) and Recall (CPR), Semantic Verbal Fluency (SVF), and Verbal Boston Naming (VBN), comparing both groups' performance and simulating new samples' random vectors by inverse transform sampling.

RESULTS: PCG and NCG performed similarly on CERAD-MX. In both groups, YoS and age influence all *z* scores. A positive age effect resulted for PCG on CPC and SVF; for the NCG on MMSE, SVF, and VBN.

DISCUSSION: All tasks are influenced by YoS. Higher YoS/younger age or YoS/older age interactions affected different tasks, suggesting that YoS confounds outcomes.

KEYWORDS
age, autosomal dominant Alzheimer's disease, cognition, cross-cultural, dementia, early onset, genetics, Mexican adaptation of the Consortium to Establish a Registry for Alzheimer's Disease, neuropsychology, schooling

Highlights

- Years of schooling (YoS) and age affect the Mexican adaptation of the Consortium to Establish a Registry for Alzheimer's Disease scores of *APP*$_{V717I}$ preclinical carriers.
- Preclinical carriers underperformed non-carriers on Constructional Praxis Recall.

Angélica Zuno-Reyes and Karina Pérez-Rubio contributed equally to this study.

- Fewer YoS emerges as a confounding variable when detecting cognitive failures.
- Younger participants in both groups overperformed the older ones in the Memory tasks.
- Randomized data simulation increases statistical power when analyzing rare diseases.

1 | INTRODUCTION

Genetic conditions with Mendelian, autosomal dominant inheritance explain ≈ 1% of Alzheimer's disease (AD) cases.[1] The presence of mutations in the amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), or in presenilin 2 (*PSEN2*) genes are associated with autosomal dominant AD (ADAD) and are highly predictive of the early manifestation of dementia symptoms (usually between ≈ 30 and 50 years of age). ADAD patients have a continuous prodromal and preclinical stage that can be identified with biomarkers up to 30 years before dementia onset.[2]

In the state of Jalisco, Mexico, we identified numerous families with APP_{V717I} mutation.[3–5] Goate et al.[6] first recognized the link between this mutation in the *APP* gene and the subsequent development of ADAD. Since then, ≈ 73 mutations (32 pathogenic) have been described in *APP*; the most common of which is the Val717Ile "London" mutation.[7]

The neuropsychological assessment of preclinical ADAD mutation carriers enables the identification of subtle initial cognitive changes.[8] Prior reports of the cognitive profile of clinically symptomatic APP_{V717I} carriers suggest an amnestic-type presentation with memory loss for recently acquired information,[9] together with executive disfunction related to an impairment in shifting abilities, failures in anterograde memory, as well as constructional disabilities.[10] Mullan et al.[9] additionally identified gradual onset, slow disease progression, and dyscalculia as an early clinical trait. Zhang et al.[11] described APP_{V717I} mutation carriers with early dementia, reporting executive disfunction, disorientation, and subtle memory decline. They identified prominent cortical atrophy in the temporoparietal and frontotemporal regions in two symptomatic carriers but did not establish a correlation with their cognitive performance.

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological assessment is widely used in dementia contexts.[12,13] A recent study identified the effects of age and years of schooling (YoS) in a group of young Mexican neurotypical adults (18–59 years old) in their performance on the Mexican adaptation of CERAD (CERAD-MX) tasks[14] and showed that lower YoS was associated with greater variability of scores.

We first aimed to determine whether the preclinical carriers' group (PCG) showed lower scores than the non-carriers' group (NCG) of the APP_{V717I} mutation on the CERAD-MX, and second, to examine the effect of YoS and age on CERAD-MX scores in PCG and NCG scores.

2 | METHODS

This study was conducted in accordance with the Declaration of Helsinki, the ethical guidelines of the Mexican General Health Law, and approved by the institutional review board ethics committee of the Institute of Neurosciences (No. ET062017-251). Individually, each participant read and signed an informed consent form in which they declared their voluntary participation and that they would not receive information regarding their genetic status in the context of the research.

2.1 | Participants

Thirty-nine adults from the state of Jalisco, Mexico, known as first-degree relatives of a symptomatic ADAD carrier of the APP_{V717I} mutation fell into two groups, 15 PCG (*M*age = 37.27 years, standard deviation [SD] = 6.82; *M*YoS = 10.07 years, SD = 4.10), and 24 NCG (*M*age = 32.17 years, SD = 10.95; *M*YoS = 9.08, SD = 2.92). We found no significant differences between the two groups when analyzing the socio-demographic characteristics (Table 1). All participants live in the same rural location in the Cienega region. All are native Spanish speakers, and nonative language is spoken in this area. The genetic status of the PCG was confirmed by analysis of blood samples to obtain DNA and the characterization of the APP_{V717I} mutation was performed by the Sanger sequencing method.

TABLE 1 Socio-demographic characteristics.

Characteristic	PCG ($n = 15$) M (SD)	NCG ($n = 24$) M (SD)	Range	*p*-value
Sex (female/male)	(7/8)	(16/8)		0.367
Age	37.27 (6.82)	32.17 (10.95)	18–52	0.081
YoS	10.07 (4.1)	9.08 (2.92)	3–17	0.426

Notes: The socio-demographic characteristics were compared using the following tests: chi-square test for sex; *t* test for age; and Mann–Whitney *U* test for YoS.
Abbreviations: M, mean; NCG, non-carrier group; PCG, preclinical carrier group; SD, standard deviation; YoS, years of schooling.

2.2 | Materials

We used the Clinical Dementia Rating[15] (CDR) in its translated Spanish version adapted for the Mexican population to identify the clinical stage of participants, with a score of zero confirming that participants demonstrated no signs suggesting cognitive impairment.[16]

The protocol on which we based the cognitive assessment was the neuropsychological battery of the CERAD, originally developed in English,[17] adapted and standardized for the Mexican population[14] (CERAD-MX) from the Colombian version.[18]

The CERAD-MX consists of the eight original tasks[17] and eight complementary tasks that were added in Colombia[18] to assess more cognitive domains susceptible to ADAD. For this study, we used only the original tasks[17]: Mini-Mental State Examination (MMSE); Word List Learning (WLL), Delayed Recall (WLD), and Recognition (WLR); Constructional Praxis Copy (CPC) and Recall (CPR); Semantic Verbal Fluency (SVF; Animals); and Verbal Boston Naming (VBN). For the MMSE version included in CERAD-MX, the backwards spelling task was replaced by the serial subtraction subtest,[19] as spelling is less relevant for Spanish-speaking people due to Spanish writing shallowness.[20]

The cognitive domains assessed by each task, as well as the instructions, have been explained elsewhere.[14] Participants were free to ask questions and refuse to answer at will throughout the application of the research protocol.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature using PubMed. Prior studies, including APP_{V717I} mutation carriers with autosomal dominant Alzheimer's disease clinical symptoms, describe an amnestic phenotype with reduced information about cognitive changes in preclinical stages and limited data on how years of schooling (YoS) and age can modulate the outcomes of their neuropsychological assessment. The low frequency of APP_{V717I} mutation carriers limits the sample size and invites us to perform randomized data simulation to explore YoS and age effects on the Mexican adaptation of the Consortium to Establish a Registry for Alzheimer's Disease.
2. **Interpretation**: At the preclinical stage, YoS affected performance more than age or the condition of being an APP_{V717I} mutation carrier. We included mutation carriers and non-carriers as young as 18 years old, which is still many years away from the likely onset of symptoms for APP_{V717I} mutation carriers.
3. **Future directions**: YoS is known to have a pervasive effect on neuropsychological assessment. A longitudinal design will allow us to follow up on the trajectory of the cognitive decline of APP_{V717I} from Jalisco.

2.3 | Procedure

Data from this study were obtained from December 2017 to August 2019. From the overall sample (n = 41), we excluded two participants: one without genetic testing and another with CDR = 0.5 (Figure 1). Although informative to include participants with CDR = 0.5, we chose to focus on an entirely asymptomatic group due to the lack of such mildly affected persons.

Examiners and participants were blind to the participant's genetic status to avoid bias in the interpretation of the results. All participants completed the cognitive assessment in a single session. We assessed them in rooms provided by the local health center, adequately lit and isolated from noise, with no reported fatigue or lack of motivation.

2.4 | Statistical analysis

First, we analyzed whether the socio-demographic and CERAD-MX data had a normal distribution by applying the Shapiro–Wilk test (Appendix A in Table S1 in supporting information), where we found that only in age and the WLD task, the assumption of normality was met, thus opting to make the comparison between PCG and NCG with the non-parametric Mann–Whitney U test, in which we interpreted the effect size values according to the following thresholds[21]: 0.1 = small, 0.3 = medium, and 0.5 = large.

Second, we perform randomized data simulation (RDS) from standardized z scores obtained by each of the participants (Appendix B in supporting information). Third, we used RDS to identify the effect of age and YoS (Appendix C in supporting information). We considered RDS to give more statistical power to our data because of our relatively small study population and the fact that we have > 30 observations, which allows us to apply RDS according to the 68-95-99.7 rule.[22] We used R[23,24] for descriptive and comparison analysis, and Python[25] to perform RDS.

3 | RESULTS

3.1 | Contrast between groups

We found no significant differences between groups by Mann–Whitney U test. The effect size of the group was medium for the CPC and CPR tasks and small for the other tasks (Table 2).

3.2 | YoS and age effect

For the PCG, the A percentages are high except for the VBN task (with 13% not rejected). YoS affects all the PCG's scores, indicating that the more years completed, the higher the results. Age influences all

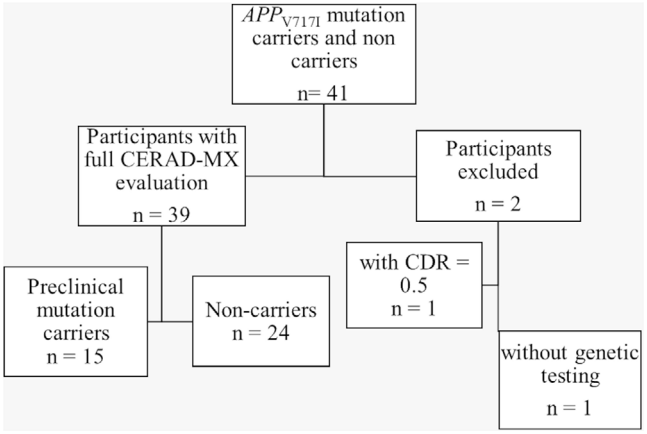


FIGURE 1 Diagram of included and non-included participants. CDR, Clinical Dementia Rating; CERAD-MX, Mexican adaptation of the Consortium to Establish a Registry for Alzheimer's Disease.

TABLE 2 Comparisons between PCG and NCG of the APP_{V717I} mutation in CERAD-MX task scores.

Task	PCG ($n = 15$) M (SD)	NCG ($n = 24$) M (SD)	*P* value	Effect size
Mini-Mental State Examination (MMSE)	29.13 (1.06)	29.00 (1.02)	0.623	0.08
Word List Learning (WLL)	16.40 (4.64)	15.71 (3.30)	0.908	0.02
Word List Delayed Recall (WLD)	6.60 (2.26)	6.13 (1.60)	0.568	0.09
Word List Recognition (WLR)	9.40 (1.12)	9.58 (0.83)	0.610	0.08
Constructional Praxis Copy (CPC)	8.87 (1.36)	9.50 (1.87)	0.066	0.30
Constructional Praxis Recall (CPR)	7.87 (1.77)	9.00 (1.96)	0.053	0.31
Semantic Verbal Fluency (SVF)	21.60 (6.58)	18.96 (4.15)	0.324	0.16
Verbal Boston Naming (VBN)	14.20 (.77)	13.63 (1.14)	0.127	0.25

Abbreviations: CERAD-MX, Mexican adaptation of the Consortium to Establish a Registry for Alzheimer's Disease; M, mean; NCG, non-carrier group; PCG, preclinical carrier group; SD, standard deviation.

tasks' performance; younger participants performed higher for PCG in MMSE, VBN, WLL, WLR, and CPR tasks, whereas older participants yielded higher scores in the SVF and CPC tasks (see $\bar{b}_2$). Meanwhile, all tasks are influenced by YoS. The coefficients associated with age are lower than those associated with YoS ($|\bar{b}_2| < |\bar{b}_3|$) on the MMSE, VBN, WLL, WLD, and WLR tasks, CPR, and SVF. Only the result of the CPC task is more influenced by age than YoS, as $|\bar{b}_2| > |\bar{b}_3|$ (Table 3).

For the NCG, the tasks with the lowest *A* percentages were WLR and CPR (with 8% and 3.4%, respectively). All tasks are influenced by age and by YoS, with $|\bar{b}_2| < |\bar{b}_3|$. The coefficients associated with age are lower than those associated with YoS ($|\bar{b}_2| < |\bar{b}_3|$) except for WLR. Younger participants obtained higher scores on WLD, WLR, CPC, and CPR. Meanwhile, older participants showed higher scores on MMSE, SVF, and VBN (Table 4).

In Figure 2, we plotted eq. (6) without $\in$ (Appendix B) using the parameters $\bar{b}_1, \bar{b}_2$ y $\bar{b}_3$, as shown in Tables 2 and 3. The performance of younger participants yielded higher scores for both groups in VBN, WLL, WLR, and CPR, whereas older participants scored higher on SVF. For PCG, higher score is associated to younger age in the MMSE and VBN, whereas older participants obtained higher scores on CPC. NCG younger participants obtained higher scores in WLD and CPC. Older participants showed higher scores in the MMSE and the VBN tasks.

Regarding the interaction between YoS and age, for both groups, individuals with higher YoS and younger ages showed higher scores on the WLL task (Figure 2C,D). In contrast, for SVF, higher scores are observed among those with more YoS and older age (Figure 2M,N).

For PCG, the combination of more YoS and younger age is associated with higher scores in WLD and WLR tasks (Figure 2E,G). For NCG, the younger individuals obtained higher scores on the WLD and WLR tasks (Figure 2F,H), whereas individuals with more YoS yielded higher scores regardless of their age on the CPC and CPR tasks (Figure 2J,L).

NCG obtained higher scores when they had more YoS and older age on MMSE and VBN (Figure 2B,P) whereas for PCG, even though the predominant color visualized in the figure for both the MMSE and the VBN tasks is blue, it is noticeable that the *z* score shows larger values as YoS increases (Figure 2A,O). Therefore, if an individual belongs to the PCG and has more YoS, it is expected that she/he will obtain higher scores on MMSE and VBN tasks (Figure 2A,O). Comparing PCG to NCG performance for WLD and WLR, YoS played a more relevant role in the PCG than in the NCG. Finally, on CPC and CPR tasks, NCG obtained higher scores than PCG (Figure 2I–L). However, in PCG, the *z* score scale illustrates those individuals with more YoS obtained higher scores in these tasks (Figure 2I,K). In particular, on the CPC task, individuals with more YoS and older ages are the ones who achieve higher scores (Figure 2I).

4 | DISCUSSION

This study provides information regarding cognitive status, as well as the effects of YoS and age on CERAD-MX scores obtained by PCG and NCG of the APP_{V717I} mutation, all coming from Jalisco, Mexico.

We found that the group effect was subtle when differentiating PCG from NCG in this young population when performing CERAD-MX tasks. Age and YoS contribute significantly to the results for both groups: for the PCG, YoS has a greater effect than age in all tasks except for the CPC, and for the NCG, except in the WLL, WLD, and WLR tasks. The interaction YoS/age is not significant in all tasks and differs slightly between groups.

To our knowledge, this is the first report on cognitive task performance in preclinical carriers of the APP_{V717I} mutation worldwide, with its value in diagnosis, prognosis, and intervention drawn from data that aid in the identification of sensitive tasks to initial cognitive difficulties[18] according to CERAD-MX scores. Also, we identified the confounding effect of socio-demographic variables like age and YoS that influence performance on these tasks in this population. The study

TABLE 3 Simulations results for PCG.

Parameter / Task	$\bar{b}_1$	$\bar{b}_2$	$\bar{b}_3$	A	$\bar{p}_1$	$\bar{p}_2$	$\bar{p}_3$
MMSE	−0.136	−0.036	0.114	99.9%	2.20×10^{-86}	8.703×10^{-7}	1.099×10^{-46}
WLL	−0.072	−0.285	0.382	100%	4.864×10^{-20}	6.15×10^{-231}	0*
WLD	−0.059	−0.365	0.510	100%	3.541×10^{-22}	0*	0*
WLR	−0.217	−0.120	0.166	100%	7.726×10^{-241}	2.597×10^{-67}	9.22×10^{-108}
CPC	0.171	0.175	0.125	100%	2.31×10^{-154}	2.603×10^{-134}	1.11×10^{-62}
CPR	−0.149	−0.066	0.267	100%	1.393×10^{-67}	1.16×10^{-12}	1.893×10^{-150}
SVF	0.181	0.258	0.738	100%	3.655×10^{-174}	4.451×10^{-285}	0*
VBN	−0.230	−0.018	0.285	13%	8.211×10^{-195}	0.021	4.078×10^{-223}

Notes: $\bar{b}_1$, $\bar{b}_2$, and $\bar{b}_3$: mean of the intercept estimates, coefficient estimates associated with age, and coefficient estimates associated with YoS, respectively; A: percentage of not rejected of simulations; $\bar{p}_1$, $\bar{p}_2$, $\bar{p}_3$: average of the P values of the intercept, the coefficient associated with age, and YoS respectively, P value $0^* < 1 \times 10^{-285}$.

Abbreviations: CPC, Constructional Praxis Copy; CPR, Constructional Praxis Recall; MMSE, Mini-Mental State Examination; PCG, preclinical carrier group;SVF, Semantic Verbal Fluency; VBN, Verbal Boston Naming; WLD, World List Delayed Recall; WLL, World List Learning; WLR, World List Recognition; YoS, years of schooling.

TABLE 4 Simulation results for NCG.

Parameter / Task	$\bar{b}_1$	$\bar{b}_2$	$\bar{b}_3$	A	$\bar{p}_1$	$\bar{p}_2$	$\bar{p}_3$
MMSE	−0.163	0.156	0.211	100%	9.532×10^{-79}	4.649×10^{-69}	5.077×10^{-12}
WLL	−0.041	−0.192	0.526	98.8%	5.519×10^{-6}	4.55×10^{-88}	2.262×10^{-56}
WLD	−0.333	−0.276	−0.314	100%	7.941×10^{-209}	4.823×10^{-140}	2.823×10^{-17}
WLR	−0.491	−0.085	−0.075	8%	0*	4.434×10^{-17}	0.031
CPC	−0.054	−0.042	1.295	95.6%	4.481×10^{-7}	1.526×10^{-4}	2.612×10^{-221}
CPR	−0.017	−0.040	1.345	3.4%	0.086	6.612×10^{-5}	6.296×10^{-284}
SVF	0.139	0.104	0.990	100%	5.234×10^{-44}	1.839×10^{-23}	8.988×10^{-154}
VBN	−0.194	0.142	0.850	100%	3.14×10^{-77}	2.766×10^{-40}	2.286×10^{-110}

Notes: $\bar{b}_1$, $\bar{b}_2$, and $\bar{b}_3$: mean of the intercept estimates, coefficient estimates associated with age, and coefficient estimates associated with YoS, respectively; A: percentage of not rejected of simulations; $\bar{p}_1$, $\bar{p}_2$, $\bar{p}_3$: average of the P values of the intercept, the coefficient associated with age, and YoS, respectively, P value $0^* < 1 \times 10^{-284}$.

Abbreviations: CPC, Constructional Praxis Copy; CPR, Constructional Praxis Recall; MMSE, Mini-Mental State Examination; NCG, non-carrier group; SVF, Semantic Verbal Fluency; VBN, Verbal Boston Naming; WLD, World List Delayed Recall; WLL, World List Learning; WLR, World List Recognition; YoS, years of schooling.

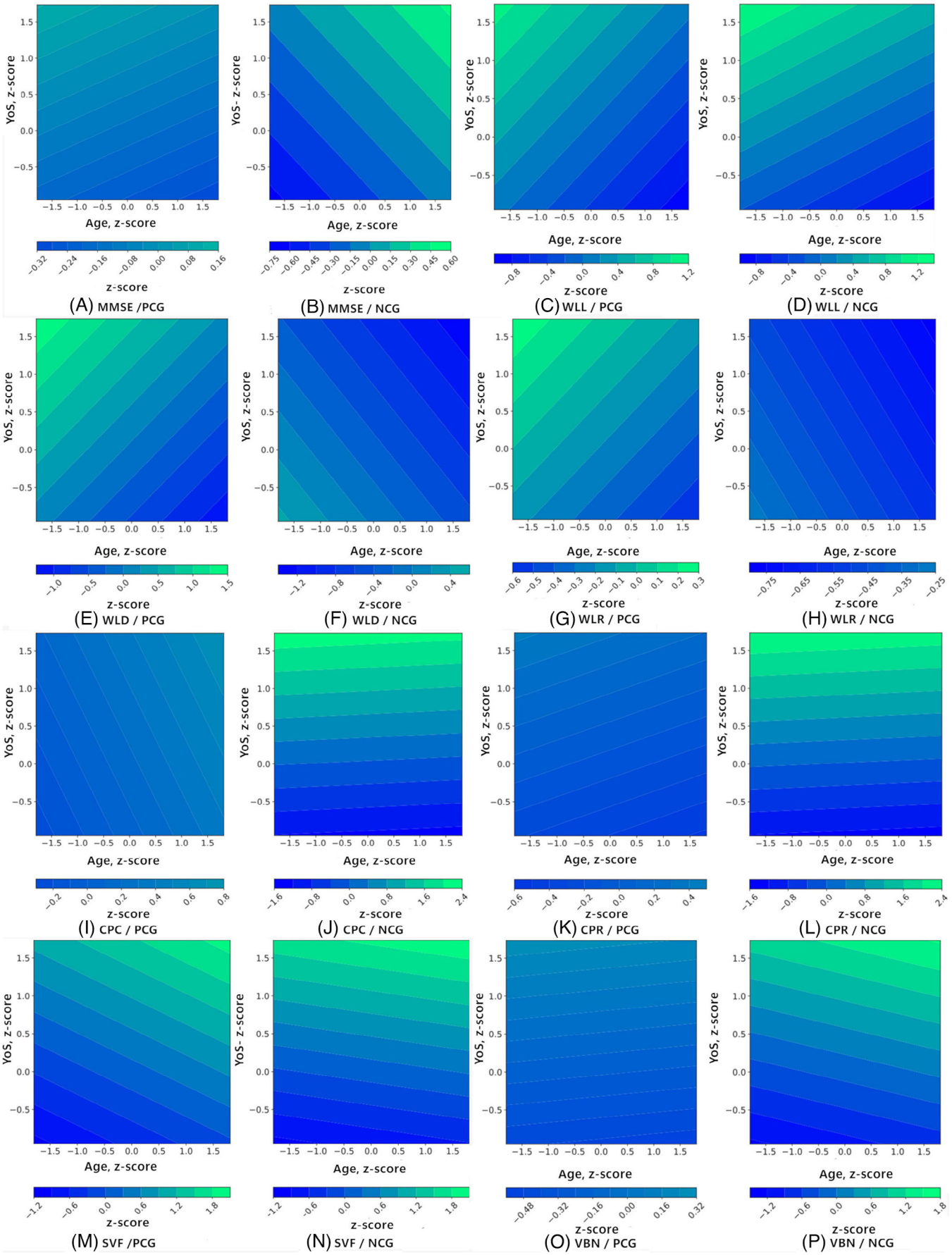
of ADAD provides insight into cognitive changes prior to the onset of dementia symptoms, which can be estimated with relatively high accuracy, aiding in the design of pharmacological and non-pharmacological interventions that prevent or mitigate the trajectory of cognitive decline.[26]

4.1 | Group effect

The group effect refers to how the condition of being a PCG or NCG of the APP_{V717I} mutation may be related to the scores obtained on the CERAD-MX. Comparing PCG and NCG, we found no significant differences in the performance on the CERAD-MX tasks, confirming that PCG participants maintain normal cognitive performance as measured by the scores obtained and in accordance with the cognitive profile that characterizes this stage.[27]

4.2 | YoS effect

The YoS effect can be analyzed from two perspectives. On one hand, social determinants of health, defined as the conditions in which people are born, work, and live daily (e.g., socioeconomic status and educational attainment), among other environmental factors,


YoS, z-score
Age, z-score
z-score
(A) MMSE /PCG
(B) MMSE / NCG
(C) WLL / PCG
(D) WLL / NCG
(E) WLD / PCG
(F) WLD / NCG
(G) WLR / PCG
(H) WLR / NCG
(I) CPC / PCG
(J) CPC / NCG
(K) CPR / PCG
(L) CPR / NCG
(M) SVF /PCG
(N) SVF / NCG
(O) VBN / PCG
(P) VBN / NCG

have been found to affect variability in the onset of cognitive failures due to sporadic AD[28] and ADAD.[29] On the other hand, studies have demonstrated the effect of socio-demographic variables on the performance of neuropsychological tasks,[30] which are the instruments typically used to discriminate between people with and without cognitive difficulties.[31] Formal education received in school plays a fundamental role in the learning and training of strategies for the solution of tasks included in the neuropsychological assessment, such as vocabulary, arithmetic operations, writing, and drawing, among others. Also, schooling brings people closer to the testing experience, familiarizing the procedure.[32] Finally, the effect of YoS differs depending on the type of task and the cognitive domain that the task assesses.[30]

In our study, we identified that YoS influences all tasks for both groups. This, in turn, confirms that YoS is a confounding variable in the attempt to discriminate cognitive failures in people with few YoS,[29] which is problematic given that the mean YoS of our participants is close to the estimated schooling of the Mexican population, which is 9.74 years.[33] According to Zuno-Reyes et al.,[14] in their normative study, < 10 YoS correspond to lower scores on the CERAD-MX than those observed in people with more YoS. Particular attention should be paid to the MMSE, a commonly used screening test to identify cognitive impairment. Therefore, it is necessary to adjust YoS thoroughly for its clinical use.

4.3 | Age effect

The onset of symptoms in carriers of mutations in the *APP* gene ranges from 45 to 60 years[34] and has a mean age of 52 with this APP_{V717I} variant[9] so the mean age of the PCG (37.27 years) in our study is far from the age at which ADAD symptoms onset.

Although in our study the age effect is smaller than the YoS effect in most of the tasks, age affects PCG and NCG performance on all tasks. In both groups, verbal productivity as measured through the SVF,[35] related to language but also to executive functions[35,36] (cognitive flexibility, shifting, and inhibition), increased with age.

At older ages, the PCG group obtained higher scores on the copy, but lower scores when recalling the Constructional Praxis drawings, suggesting that graphic skills are resistant, in the preclinical stage, to the effect of carrying the APP_{V717I} mutation. In contrast, the ability to remember these figures is affected.

Finally, performance on most memory-related tasks is better in younger participants than in older ones for both groups, even in our sample, which includes only young adults of < 60 years of age. Our results suggest that memory-related tasks do not allow us to differentiate between PCG and NCG of the APP_{V717I} mutation. We highlight these findings on the memory-related tasks because the mean age of the PCG is ≈ 13 years before the estimated onset of symptoms for *APP* mutation carriers[34] contrary to the report of Aguirre-Acevedo et al.,[18] in which WLD differentiated preclinical carriers from non-carriers of the $PSEN1_{E280A}$ mutation 17 years before dementia symptoms' onset, providing preliminary evidence for differential cognitive traits among mutation variants.

4.4 | Interactions between YoS and age

The interaction of YoS and age goes in two directions: higher YoS and older age are associated with higher scores on the SVF task (animals category) for both groups. For the solution of the SVF task, multiple cognitive functions are recruited, such as verbal productivity, verbal initiative, as well as cognitive flexibility, as first the most common words come to mind, but then more flexibility is required to come up with more unusual words,[36] shifting to move from one subcategory to another (e.g., in the animal category, from fish to feline). Also, inhibitory control is recruited to discard words that do not correspond to the target category.[37] It is evident that age and YoS effects go in the same direction suggesting that mastery of this task is improved by more years spent in school. Also, higher performance on CPC task performance is related to older age and a greater number of YoS in the PCG, suggesting that schooling protects APP_{V717I} carriers from presenting with an early decline in the performance of this task.

Age and YoS maintain an interaction on the memory-related tasks, for which less YoS and older age negatively affect the performance, mainly in the PCG, either because schooling has a protective effect on the trajectory of cognitive decline[29] or because the practice of school skills that are useful in testing facilitates task completion in participants with more YoS.[32] Thus, the effect of age and YoS found in this study replicates the results of our normative work,[14] in the way that the higher the age and less YoS, the more variable the scores, except for the tasks that assess language skills, for which the higher the age and YoS, the higher the scores.

Limitations in our study highlight that the age at which we recruited our participants allowed us to include people as young as 18 years old, which is still many years away from the likely onset of symptoms for APP_{V717I} mutation carriers. We found, as expected, a trend of decreasing PCG scores as participants age and approach the age of symptoms' onset, with no significant differences among groups, because participants included in the PCG are still in the preclinical stage. Therefore, we are performing a longitudinal follow-up of these participants to

FIGURE 2 Data simulation results of cognitive performance as a function of age and YoS, by task and group. The standardized values of age are in the abscissa and YoS in the ordinate, in the intervals [−1.5, 1.5] and [−1.0, 1.5], respectively. The blue color represents negative values, and the green color represents positive values. CPC, Constructional Praxis Copy; CPR, Constructional Praxis Recall; MMSE, Mini-Mental State Examination; NCG, non-carrier group; PCG, preclinical carrier group; SVF, Semantic Verbal Fluency; VBN, Verbal Boston Naming; WLD, World List Delayed Recall; WLL, World List Learning; WLR, World List Recognition; YoS, years of schooling.

better delineate the differences in the performance on cognitive tasks throughout the trajectory of the preclinical stage, with an age range as wide as possible. Considering that age has a different effect on each cognitive function, reflected in turn to the CERAD-MX task scores,[14] including such wide age ranges helps to provide more information about the PCG performance. Although the sample we recruited is small in terms of the number of participants, we have the advantage that they all come from the same small town of ≈ 2500 inhabitants. We can assume that sharing common family and genetic kinship, with similar cultural, socioeconomic, and educational aspects, homogenize to some extent at least, confounding variables that could affect the rare condition of being a carrier of a mutation that is a determinant for ADAD. Notwithstanding, we recommend caution in generalizing our results. Our outcomes can be more accurately reflected in research studies or clinical settings in which the participants have similar characteristics. Because migration to the United States is a common practice in the locality in which we work,[4,5] these results may be relevant to APP_{V717I} carriers and non-carriers residing there. Both socio-cultural and socio-demographic aspects should be considered when trying to apply them to populations with other characteristics, for example, in highly urbanized areas. Because schooling conditions in Mexico are variable, we identify the need for complementary information about our participants besides the YoS data, such as socioeconomic status of the parents,[38] and quality of education through reading testing.[39] Another limitation is that we lacked a standardized, systematic measurement of participants' effort and motivation throughout testing.

Finally, we did not obtain biological markers for determining the preclinical stage of ADAD. Establishing the correlation between the temporal cascade of changes of preclinical biomarkers and cognitive performance during the preclinical stage could help to delineate the interaction between these two factors, increasing the validity of the cognitive observations.[27] Such measures have great additional utility in helping understand the relationship between AD biology and cognitive performance, but their absence does not affect the validity of our findings.

Although the genotype and phenotype of APP_{V717I} mutation carriers have been described,[9–11,40–45] these studies focus on either the presence of biomarkers in ADAD or the cognitive performance in symptomatic carriers. Thus, this report adds novel information about preclinical APP_{V717I} cognitive features.

In summary, our study aimed to determine the effect in a preclinical stage of carrying the APP_{V717I} mutation on the CERAD scores. Considering that PCG and NCG scored at a similar level, we analyzed how YoS and age interact on these scores by performing a RDS procedure/analysis. Both age and YoS have an effect on all the CERAD-MX tasks, with a larger effect of YoS than the effect of age. At the preclinical stage, YoS affected performance more than age or the condition of being an APP_{V717I} mutation carrier. Younger participants obtained higher scores on memory-related tasks than older ones, whereas the opposite was true for the SVF task. Performance on lexical related tasks (SVF and VBN) is preserved in this APP_{V717I} PCG.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

An anonymized dataset used for this study will be made available by request of any qualified investigator.

CONSENT STATEMENT

All human subjects provided informed consent.

ORCID

Esmeralda Matute https://orcid.org/0000-0003-0118-9960

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