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Anticholinergic Drug Burden and Neurocognitive Performance in the Study of Latinos-Investigation of Neurocognitive Aging

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Abstract

Background: Studies of cumulative anticholinergic drug burden on cognitive function and impairment are emerging, yet few for Hispanics/Latinos.

Objective: To examine associations between anticholinergic use and neurocognitive performance outcomes among diverse Hispanics/Latinos.

Methods: This prospective cohort study included diverse Hispanic/Latino participants, enrolled in the Study of Latinos-Investigation of Neurocognitive, from New York, Chicago, Miami, and San Diego (n = 6,249). Survey linear regression examined associations between anticholinergic use (measured during baseline [Visit 1] and average 7-year follow up [Visit 2]) with global cognition, episodic learning, memory, phonemic fluency, processing speed, executive functioning, and average 7-year change.

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SUPPLEMENTARY MATERIAL

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Results: Anticholinergic use was associated with lower cognitive global cognition (β = −0.21; 95%CI [−0.36; −0.05]), learning (β = −0.27; 95%CI [−0.47; −0.07]), memory (β = −0.22; 95%CI [−0.41; −0.03]), and executive functioning (β = −0.22; 95%CI [−0.40; −0.03]) scores, particularly among those who took anticholinergics at both visits. Anticholinergic use was associated with faster decline in global cognition, learning, and verbal fluency (β: −0.28 [95% CI: −0.55, −0.01]; β: −0.28 [95% CI: −0.55, −0.01]; β: −0.25, [95% CI −0.47, −0.04], respectively). Sex modified associations between anticholinergic use with global cognition, learning, and executive functioning (F_3 = 3.59, F_3 = 2.84, F_3 = 3.88, respectively).

Conclusion: Anticholinergic use was associated with lower neurocognitive performance, especially among those who used anticholinergics at both visits, among a study population of diverse Hispanics/Latinos. Findings will support evidence-based decisions regarding anticholinergic prescriptions and efforts to minimize cognitive impact.

Keywords

Aging; cognition; cognitive function; cohort study; neurocognitive tests; hispanics; latinos

INTRODUCTION

In 1982, Bartus postulated in the *Cholinergic Hypothesis of Geriatric Memory Dysfunction* that cholinomimetic drugs (e.g., physostigmine) would help ameliorate memory loss among older adults [1]. Since then, anticholinergic drug use has been implicated in cognitive impairment and dementia risk [2-6]. There is limited scientific literature on the relationship between cumulative anticholinergic drug burden (ADB) and changes in cognitive function [7] and impairment [8], and even less for racial/ethnic minorities [9]. A better understanding of the effects of ADB on cognitive function among diverse community-dwelling older adults is needed.

Older adults have high anticholinergic use and are sensitive to effects of increased ADB [2, 10, 11]. Specifically, anticholinergic use is a risk factor for mild cognitive impairment (MCI) [8]. This is concerning because Hispanics/Latinos relative to non-Hispanics whites, have shown earlier onset of MCI and dementia [12]; furthermore, Hispanics/Latinos are projected to have the largest increase in Alzheimer's disease and related dementias (ADRD) by 2060 [13]. With projected growth of the United States (US) Hispanic/Latino population [14], there is a public health need to understand the impact of ADB on cognitive function and decline in Hispanics/Latinos and promote healthy cognitive aging.

Current literature has yet to examine relationships between ADB and cognition among diverse Hispanics/Latinos. Therefore, the objective of this prospective cohort study was to examine associations between anticholinergic use and neurocognitive performance outcomes among Hispanics/Latinos. We hypothesized that anticholinergic use is associated with lower neurocognitive performance and faster decline in measures of global cognition, episodic learning and memory, word fluency, and executive functioning compared to those that did not report anticholinergic use.

METHODS

Study design

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) is a multisite, population-based, prospective cohort study of cardiovascular and metabolic health among diverse Hispanics/Latinos (Visit 1 [V1] 2008–2011). The Study of Latinos–Investigation of Neurocognitive Aging (SOL-INCA; Visit 2 [V2] 2016–2018) is an ancillary study of HCHS/SOL. Study designs and sampling procedures are published and available online (https://sites.cscc.unc.edu/hchs/) [15]. HCHS/SOL and SOL-INCA used complex survey design and sampling procedures to obtain representative estimates of diverse Hispanics/Latinos in targeted areas (Bronx, NY; Chicago, IL; Miami. FL; and San Diego, CA). To address possible sample attrition biases, the HCHS/SOL Coordinating Center generated study-specific calibrated probability weights that adjust for non-response and allow generalization of estimates to metropolitan area target populations aged 50 years and older. Study protocol was approved at institutional review boards of all participating sites and participants provided informed consent.

Baseline cognitive testing

HCHS/SOL V1 cognitive testing was administered to middle-aged and older (ages 45–74 years) participants who were oversampled (n = 9,714) in the cohort. The Neurocognitive Reading Center trained, and field centers directly supervised, bicultural/bilingual technicians who administered the brief cognitive battery: 1) Brief-Spanish English Verbal Learning Test (B-SEVLT; verbal episodic learning [B-SEVLT Sum] and memory [B-SEVLT Recall]); 2) Word Fluency (WF; phonemic fluency); and 3) Digit Symbol Subtest (DSS; processing speed, executive functioning).

SOL-INCA V2 cognitive testing

Eligible HCHS/SOL participants were invited for SOL-INCA V2 which occurred, on average, 7 years after V1. Participants were administered all V1 tests and the Trails Making Test (TMT, Trail A [processing speed] and Trail B [executive functioning]). All measures from V1 and V2 were z-scored. Global cognition scores for each time point were generated by averaging across each domain specific measure.

Cognitive change

Cognitive change was operationalized using survey weighted linear models using regression-based techniques [16]. First, cognitive performance at V2 (T2) was modeled using regression analyses as a function of V1 performance (T1) and adjusting for days between V1 and V2. Based on this regression, a predicted T2 score was estimated, indicating expected performance at T2 given baseline cognitive function and adjusted for time lapse between V1 and V2. Given these values, standardized measures of cognitive change were calculated using the following formula: $(T2\text{-}T2_{pred})/RMSE$; T2 indicates the V2 cognitive outcome, T2pred is the predicted score by the model, and RMSE is the Root Mean Squared Error of the model. Further information on measures of change in studies where only two time points are available are detailed in Duff [16].

Anticholinergic drugs

There is little consensus on anticholinergic properties of several drugs [17, 18], thus we generated an anticholinergic drugs list based on results from Grey et al. [3] and Coupland et al. [5]. This list was refined by selecting drugs with strong anticholinergic properties defined by the Anticholinergic Burden Scale [19] and 2019 American Geriatrics Society Beers Criteria [20], yielding 108 anticholinergic drugs of interest (Supplementary Table 1).

Medication use

Medication use was ascertained at V1 and V2. At both visits, participants were asked to bring medications used in the past four weeks (see Supplementary Methods 1 for more details). We generated a four-category indicator of anticholinergic use based on medication lists from V1 and V2:1) neither V1 or V2 use: no evidence of anticholinergic medication use on V1 or V2; 2) V1 use only: anticholinergic medication use at V1 only; 3) V2 use only: anticholinergic medication use at V2 only; and 4) V1 and V2 use: anticholinergic medication use at both V1 and V2.

Covariates

All covariates of interest, except age, were measured at V1. In sensitivity analyses, we used categorical age at V1 to compare with our primary results that used categorical age at V2 and results were similar (data not shown). Covariates include sex, age (< 60 years, 60–69 years, ≥ 70 years), education (< 12 years, 12 years, > 12 years), Hispanic/Latino background (Dominican, Central American, Cuban, Mexican, Puerto Rican, South American), body mass index (BMI; kg/m^2), diabetes status (no diabetes, prediabetes, prevalent diabetes), and smoking (never, former, current). To account for potential indications, we adjusted for depressive symptoms (Center for Epidemiologic Studies-Depression-10 [21]; CESD-10), cardiovascular disease (no CVD, CVD: based on presence of coronary heart disease, angina, cerebrovascular events, heart failure, peripheral artery disease, or other heart problems) defined by the Framingham Cardiovascular Risk Score criterion [22], and number of medications taken to account for polypharmacy [10].

Analytic sample

Of the 6,377 participants (ages 50–86 years) enrolled in the SOL-INCA study, we excluded 14 individuals missing Hispanic/Latino background information and 114 individuals with missing covariates, yielding a final analytic sample of 6,249. Individuals included did not significantly differ by age, sex, or education compared to those excluded (Supplementary Table 2).

Statistical analysis

First, we generated descriptive measures by medication status (Table 1). Second, we used survey weighted linear regressions to test associations between medication status with cognitive scores at V2 and average 7-year cognitive change from V1 to V2. We computed two models for each outcome: 1) minimally adjusted models controlling for age, sex, education, Hispanic/Latino background, BMI, and diabetes; and 2) fully adjusted models that additionally controlled for CESD-10, smoking status, cardiovascular disease, and

number of non-anticholinergic medications taken at V1 and V2 (Table 2 and Supplementary Table 6). We plotted the marginal means and their 95% confidence intervals to facilitate interpretation of results (Figs. 1 and 2). In post-hoc analyses, we estimated and plotted average marginal estimates. To test for effect modification by sex and age, we refit survey weighted, fully adjusted models and tested product terms between 1) medication status and sex and 2) medication status and age (continuous and categorical) (Supplementary Table 4). Descriptive characteristics by sex are in Supplementary Table 3. If modification was evident, we present post-hoc marginal means estimates (Table 3 and Supplementary Table 7; Supplementary Figures 1-4) and compute ANOVA contrasts for marginal mean differences of cognitive function and change (Supplementary Tables 5 and 8, Supplementary Figures 5 and 6). Statistical analyses were conducted using the complex survey design suite in Stata version 16 (Stata Corp) and R version 4.0.3 [23]. All hypothesis tests were 2-tailed and used $p < 0.05$ to determine statistical significance.

RESULTS

Participant characteristics

More than 1 in 10 individuals (11.0%) used anticholinergics at V1 only, 7.5% reported use at V2 only, and 5.0% had evidence of use at both V1 and V2 (Table 1). The target population was 63.4 ± 8.2 years on average, 54.7% were females, 38.4% had less than a high school education, and mean BMI was 29.8 ± 5.4 kg/m^2. Individuals who reported using anticholinergics were more likely to be older on average, female, have elevated depressive symptoms, have higher prevalence of cardiovascular disease, and have higher mean BMI compared to individuals with neither V1 or V2 use. There were no differences in time lapse (between V1 and V2) by anticholinergic drug intake status.

Associations of anticholinergic use and neurocognitive scores

Minimally adjusted models were associated with lower SOL-INCA outcome scores for those in the V2 anticholinergic use only group across all trials (Table 2; Fig. 1). In fully adjusted models, results were attenuated after further adjustment for potential indications and health characteristics. V1 use only and both V1 and V2 anticholinergic use was associated with lower scores on SOL-INCA outcomes for global cognition (V1 use only: $\beta_{\text{Global Cognition}} = -0.09$, 95%CI [−0.16; −0.01]; V1 and V2 use: $\beta_{\text{Global Cognition}} = -0.21$, 95%CI [−0.36; −0.05]), learning (V1 use only: $\beta_{\text{B-SEVLT Sum}} = -0.11$, 95%CI [−0.21; −0.01]; V1 and V2 use: $\beta_{\text{B-SEVLT Sum}} = -0.27$, 95%CI [−0.47; −0.07]), and memory (V1 use only: $\beta_{\text{B-SEVLT Recall}} = -0.13$, 95%CI [−0.23; −0.04]; V1 and V2 use: $\beta_{\text{B-SEVLT Recall}} = -0.22$, 95%CI [−0.41; −0.03]) compared to individuals not taking medications at either timepoint (Table 2; Fig. 1). Additionally, anticholinergic use at both visits was associated with lower SOL-INCA outcomes scores for executive functioning ($\beta_{\text{Reversed Trails B}} = -0.22$, 95%CI [−0.40; −0.03]). Anticholinergic use at both visits was associated with more pronounced change in global cognition ($\beta_{\text{Golobal Cognition}} = -0.28$, 95% CI [−0.55; −0.01]), learning ($\beta_{\text{B-SEVLT Sum}} = -0.28$, 95%CI, [−0.55; −0.01]), and verbal fluency ($\beta_{\text{WF}} = -0.25$, 95% CI [−0.47; −0.04]) compared to neither V1 or V2 use (Table 2 and Supplementary Table 6; Fig. 2). V1 use, relative neither V1 or V2 use, was associated with change in memory ($\beta_{\text{B-SEVLT Recall}} = -0.12$, 95%CI [−0.22; −0.01]), but not for V2 use only and V1 and V2

use. Associations between anticholinergic use at V1 only and V2 only were not statistically significant for changes in learning, verbal fluency, and processing speed and executive functioning.

Age modification

There was no evidence of effect modification of associations between anticholinergic use and cognitive outcomes by age (Supplementary Table 4). This was consistent for continuous and categorical functional forms of age.

Sex modification

In fully adjusted models, there were statistically significant sex by anticholinergic use interactions for global cognition ($F = 3.59$; df = 3), learning ($F = 2.84$; df = 3), and executive functioning ($F = 3.88$, df = 3) (Supplementary Table 4). For fully adjusted cognitive change models, sex modified associations between anticholinergic use and verbal fluency ($F = 3.51$; df = 3) (Supplementary Table 4).

Estimates from fully adjusted models of *post-hoc* average marginal estimates showed that males taking anticholinergics at both V1 and V2 had lower SOL-INCA global cognition, learning, executive functioning, and verbal fluency scores ($ps < 0.01$) (Table 3 and Supplementary Table 7; Supplementary Figures 1 and 2). In fully adjusted change models, males taking anticholinergics at both visits had a statistically significant change in verbal fluency ($p < 0.01$) (Table 3 and Supplementary Table 7; Supplementary Figures 3 and 4). Contrasts of minimally and fully adjusted average marginal estimates showed that males taking anticholinergics had lower SOL-INCA global cognition, learning, memory, and executive functioning scores relative to females taking anticholinergics ($ps \leq 0.001$) (Supplementary Tables 5 and 8; Supplementary Figure 5). In minimally and fully adjusted cognitive change models, males taking anticholinergics at both visits had more pronounced declines in learning and verbal fluency compared to females ($ps < 0.05$) (Supplementary Tables 5 and 8; Supplementary Figure 6).

DISCUSSION

In this prospective cohort study of diverse middle-aged and older Hispanics/Latinos, anticholinergic use was associated with lower neurocognitive performance. Those with identified anticholinergic use had worse cognition globally, specifically for episodic learning, memory, and executive functioning. We observed 7-year declines in global cognition, learning, and verbal fluency performance among individuals who reported anticholinergic use at both visits. To our knowledge, this is one of the first studies in a representative Hispanic/Latino population to provide an estimate of anticholinergic use and assess its effect on neurocognitive function. Twenty-three and a half percent of our sample used medications with recognized anticholinergic activity at either timepoints, suggesting substantial opportunity for future ADRD prevention and intervention in the Hispanic/Latino community.

ADB effect sizes were strongest for those who reported anticholinergic use at both visits. Individuals with chronic conditions are typically exposed to multiple anticholinergic and

other central nervous system-active drugs as well [24]. Furthermore, most US Food and Drug Administration approved medications for symptomatic treatment of Alzheimer's disease (e.g., donepezil, galantamine, and rivastigmine) are cholinesterase inhibitors acting to *enhance* acetylcholine availability. Therefore, understanding and tailoring drug prescriptions may mitigate cumulative ADB's impact on cognitive decline and impairment, especially among older adults and those who may use anticholinergic drugs in the long-term.

Our findings suggest that long-term use of anticholinergic medications are associated with lower performance and 7-year cognitive decline, which aligns with previous literature [3-7, 9, 17, 25, 26]. The cholinergic system is involved in learning and memory [27]. There is a long-standing cholinergic hypothesis positing selective loss of cholinergic neurons and function in Alzheimer's disease [28]. A recent cross-sectional study mostly comprised of African American adults reported a negative correlation of ADB and learning/immediate memory but not delayed memory [9]. Others demonstrated declines in verbal learning [7] and memory with anticholinergic use [17]. Results of these studies together with our findings of associations of anticholinergic use with poorer performance and greater declines in learning and memory support a negative ADB effect on these cognitive domains.

Anticholinergic use at V1 and V2 was linked to poorer executive functioning at baseline. This suggests that cumulative use may affect executive functioning, but not over time. Consistent with our findings, a cross-sectional analysis of the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Indiana Memory and Ageing Study (IMAS) [25] found that those who used anticholinergic drugs had worse performance on Trail B and a composite measure of executive functioning, and poorer immediate recall memory. However, a recent longitudinal ADNI study by Weigand et al. [26] demonstrated 3-year declines in memory and language and observed a 47% higher risk of progression to MCI during a 10-year follow up with anticholinergic use but found no associations with executive functioning. In our sample, which has a high prevalence of CVD risk factors [29, 30], diabetes and other CVD risk factors may also contribute to associations between anticholinergic use and executive functioning [31, 32].

Notably, Weigand et al. [26] reported higher prevalence of taking at least one anticholinergic of 33%. Differences in prevalence compared to our study may be due to inclusion of beta-blockers and other medications with weaker anticholinergic properties. In contrast, we included medications deemed to have strong anticholinergic properties, resulting in conservative exposure classification. Additionally, ADNI, an older and largely White cohort, estimates may not be comparable to our own sample that is relatively younger in age. Moreover, disparities in pharmacy access in predominantly minority versus White communities may contribute to differences in prevalence [33]. Given that ADNI and other comparable studies were conducted on predominantly White populations [3-7, 17, 25, 26], future longitudinal studies across diverse study populations are warranted. Nonetheless, our findings support the hypothesis that anticholinergic use has negative effects on multiple cognitive functions.

Anticholinergic use was linked to declines in phonemic word fluency, a task requiring intact language and executive functions (e.g., strategizing) to efficiently search for appropriate

words. Few studies have examined relationships between anticholinergic use and word fluency. Existing evidence is cross-sectional, and, consistent with our findings, does not support relations between anticholinergic use and word fluency performance in older adulthood [34-37]. A large population-based, prospective study of French middle-aged and older adults detected poorer word fluency with anticholinergic use, but associations were null when accounting for health factors [37]. Anticholinergic use has been associated with poorer *semantic* word fluency, a task which relies less on executive functions than *phonemic* fluency [6]. However, more longitudinal studies are needed to confirm these associations.

We did not observe modification of associations between anticholinergic use and cognitive outcomes by age. Age-related changes in metabolism and pharmacokinetics can increase plasma drug levels in older adults [38, 39]. Therefore, our observed declines across neurocognitive scores among those that reported anticholinergic use may be attenuated in part to the younger age of our cohort who may also have lower cumulative ADB. Older adults (beyond the age range captured in our sample) are subject to polypharmacy, which may enhance vulnerability to ADB [10]. Older adults are more prone to cognitive impairment with increasing age [40, 41]; perhaps even more so for Hispanics/Latinos [12, 13]. Therefore, future research should consider longer time exposure periods of the effects of age and polypharmacy.

Anticholinergic drug use by males at both V1 and V2 was associated with poor performance and greater cognitive decline, particularly for verbal fluency, compared to anticholinergic drug use by females. This is consistent with findings from the Baltimore Longitudinal Study of Aging that found faster rates of verbal memory decline in males compared to females in sensitivity analyses [42]. Another study reported higher odds of 4-year declines in verbal fluency in females taking anticholinergics compared to females that were not [6]. Unadjusted effects on verbal fluency in males were marginal, contrary to our results and those of others [7, 25, 43]. Given sex differences in cognitive and ADRD trajectories [44-47], the role of anticholinergics should be explored using sex-specific models that incorporate sex-specific risk factors for ADRD (e.g., potentially protective effects of estrogen exposure in females [48]).

This study has several strengths. This is the first study, to our knowledge, on the effect of anticholinergic use on multiple aspects of cognition among Hispanics/Latinos. Second, our study used a large and highly representative cohort of Hispanics/Latinos with rich longitudinal data. The representativeness of this sample may support generalizability of these findings to a target population of Hispanics/Latinos across the US. Third, the study is timely due to the projected increase in the US Hispanic/Latino population and expected ADRD burden [13].

Limitations

One limitation of this study includes potential measurement error of anticholinergic medication ascertainment at both visits. Additionally, we did not have information regarding dosage and complete ABD exposure duration. This limits our ability to more precisely estimate cumulative ADB and directly compare results with Gray et al. [3], and others [4, 5, 26] who have employed more precise exposure measures. Dosing and exposure

underestimates may explain reduced magnitudes of our ADB estimates. Future studies would benefit from collecting dosing and historical use information and/or ascertaining medication use through medical and prescription records [49]. Secondly, our analysis controlled for many potentially confounding variables, but residual and unmeasured confounding may be present [50]. Nonetheless, our sample size enabled control of key confounding variables, and our primary findings proved robust to such adjustment. While we cannot completely rule out selection bias due to loss to follow-up, there were minimal differences between characteristics of retained and excluded participants. Our results may have been biased by confounding by indication. To minimize the effects of this bias, we adjusted for several indications and medications taken which may be associated with both anticholinergic use and cognition. Adding the potential indication of allergies did not change results in sensitivity analyses (data not shown). Moreover, we expected participants to be exposed to anticholinergic drugs for different durations, potentially contributing to exposure misclassification bias. We attempted to address this by using a four-category indicator of different durations of anticholinergic use. Future research must consider incorporating alternative methods for time-varying measures [51]. Finally, we did not account for multiple testing given that this is a hypothesis generating study to uncover associations that may inform future causal investigations.

Conclusions

Anticholinergic use was associated with lower neurocognitive performance in a cohort of middle-aged to older Hispanics/Latinos in the US. Individuals, particularly males, reporting anticholinergic drug use at both visits evinced significant 7-year declines in cognition. Anticholinergic drug use is an important health behavior to monitor given its cognitive side effects among aging adults. This is the first study to highlight such a relationship among diverse Hispanics/Latinos. With the expected rise in the US Hispanic/Latino population and ADRD burden, future studies are needed to confirm these findings and to understand underlying causal mechanisms, while considering differences of effects across different medications. This information will enhance evidence-based prescription guidelines thus minimizing ADB and favoring alternative interventions and treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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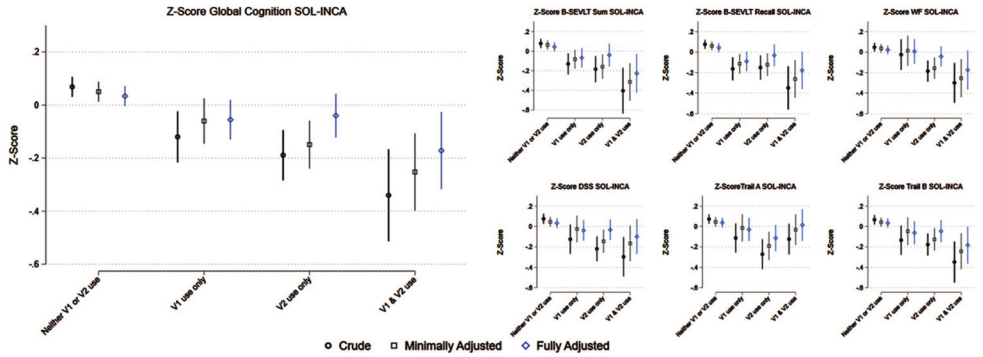

Fig. 1.

Average marginal estimates (and 95% confidence intervals) of mean cognitive outcomes at SOL-INCA by anticholinergic drug intake status. Minimally adjusted models include age (> 60 years, 60–69 years, ≥ 70 years), sex (male, female), education (< 12 years, 12 years, > 12 years), Hispanic/Latino background (Mexican, Puerto Rican, South American, Central American, Cuban, Dominican), continuous body mass index, and diabetes status at Visit 1 (no diabetes, prediabetes, prevalent diabetes). Fully adjusted models include the previously mentioned covariates in addition to continuous Center for Epidemiology Studies Depression Scale-10 score, a cigarette smoking status (never, former, current), presence of any cardiovascular disease (no CVD, CVD: based on presence of coronary heart disease, angina, cerebrovascular events, heart failure, peripheral artery disease, or other heart problems) defined by the Framingham Cardiovascular Risk Score criterion, and the number of medications taken to account for polypharmacy. B-SEVLT, Brief-Spanish English Verbal Learning Test; DSS, Digit Symbol Substitution; SOL-INCA, Study of Latinos-Investigation of Neurocognitive Aging, Visit 2 Cognitive Tests; V1, Visit 1; V2, Visit 2; WF, Word Fluency.

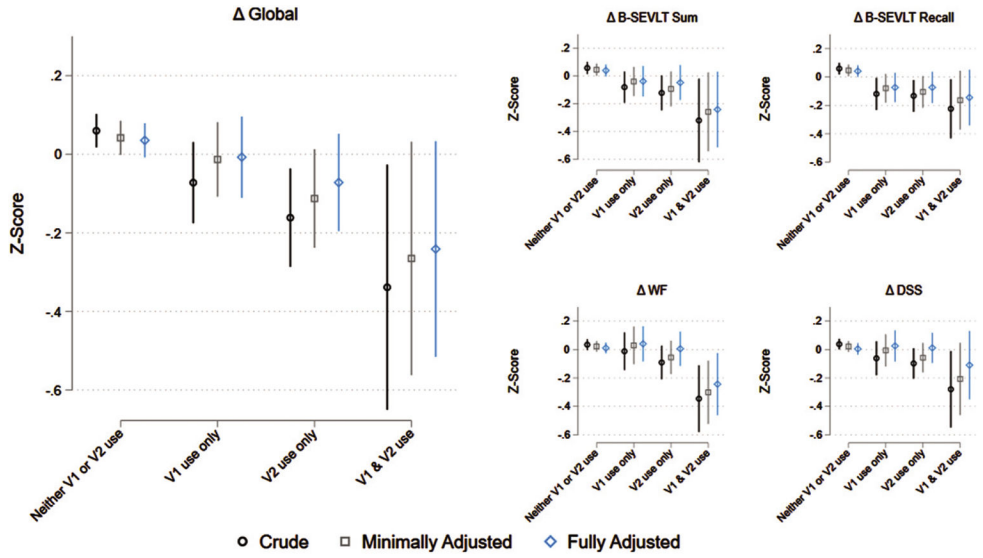

Fig. 2.

Average marginal estimates (and 95% confidence intervals) of average 7-year cognitive change of mean cognitive change by anticholinergic drug intake status. Minimally adjusted models include age (> 60 years, 60–69 years, ≥ 70 years), sex (male, female), education (< 12 years, 12 years, > 12 years), Hispanic/Latino background (Mexican, Puerto Rican, South American, Central American, Cuban, Dominican), continuous body mass index, and diabetes status at Visit 1 (no diabetes, prediabetes, prevalent diabetes). Fully adjusted models include the previously mentioned covariates in addition to continuous Center for Epidemiology Studies Depression Scale-10 score, a cigarette smoking status (never, former, current), presence of any cardiovascular disease (no CVD, CVD: based on presence of coronary heart disease, angina, cerebrovascular events, heart failure, peripheral artery disease, or other heart problems) defined by the Framingham Cardiovascular Risk Score criterion, and the number of medications taken to account for polypharmacy. Δ, change in cognition; B-SEVLT, Brief-Spanish English Verbal Learning Test; DSS, Digit Symbol Substitution; V1, Visit 1; V2, Visit 2; WF, Word Fluency.

Table 1

Descriptive characteristics of the SOL-INCA population by anticholinergic drug intake status

	Neither V1 or V2 use	V1 use only	V2 use only	V1 & V2 use	Total	*p*
Unweighted N (%)	4,821 (76.5)	647 (11.0)	490 (7.5)	291 (5.0)	6,249 (100)	
Education (y), %						
< 12	37.24	38.95	47.08	41.26	38.37	0.070
12	21.54	18.30	19.82	24.31	21.20	
> 12	41.21	42.75	33.09	34.43	40.43	
Sex, %						
Female	52.00	64.45	65.80	57.94	54.70	0.001
Male	48.00	35.55	34.20	42.06	45.30	
Age (y), %						
< 60	41.96	27.23	31.74	25.36	38.75	< 0.001
60–70	36.09	35.86	32.10	36.28	35.77	
70+	21.95	36.90	36.16	38.36	25.48	
Heritage, %						
Dominican	9.72	7.64	10.38	6.56	9.39	< 0.001
Central American	7.50	5.59	8.17	4.78	7.20	
Cuban	23.95	34.40	24.14	40.10	25.92	
Mexican	34.61	29.96	29.57	23.23	33.16	
Puerto-Rican	14.09	17.32	21.70	20.21	15.32	
South American	5.80	3.69	3.04	1.79	5.16	
More than one background	4.33	1.40	2.99	3.34	3.86	
Depression Score, %						
< 10 CESD-10	73.60	56.11	52.07	56.43	69.20	< 0.001
≥ 10 CESD-10	26.40	43.89	47.93	43.57	30.80	
CVD, %						
No CVD	61.77	52.76	42.36	40.33	58.25	< 0.001
CVD	38.23	47.24	57.64	59.67	41.75	
Smoking Status, %						
Never	55.82	55.64	52.79	49.53	55.26	0.480

	Neither V1 or V2 use	V1 use only	V2 use only	V1 & V2 use	Total	*p*
Former	26.15	26.71	23.85	30.16	26.24	
Current	18.03	17.64	23.36	20.31	18.50	
Age, mean (SD)	62.63 (7.98)	65.89 (8.04)	65.29 (8.66)	66.47 (7.79)	63.38 (8.15)	< 0.001
BMI, mean (SD)	29.61 (5.40)	29.88 (5.21)	30.84 (5.89)	30.55 (5.45)	29.78 (5.43)	0.003
Total Medication V1, mean (SD)	2.94 (3.09)	6.02 (3.69)	4.84 (4.11)	7.08 (4.17)	3.62 (3.56)	< 0.001
Total Medication V2, mean (SD)	3.20 (3.21)	5.16 (3.97)	6.62 (4.20)	7.59 (3.78)	3.89 (3.67)	< 0.001
Time between visits in years, mean (SD)	7.01 (1.17)	6.97 (1.14)	7.01 (1.12)	7.06 (1.10)	7.00 (1.16)	0.756

CVD is a binary indicator for presence of any cardiovascular disease (no CVD, CVD: based on presence of coronary heart disease, angina, cerebrovascular events, heart failure, peripheral artery disease, or other heart problems) defined by the Framingham Cardiovascular Risk Score criterion. BMI, body mass index (kg/m^2); CESD-10, Center for Epidemiology Studies Depression Scale-10; CVD, cardiovascular disease risk; SD, standard deviation; SOL-INCA, Study of Latinos-Investigation of Neurocognitive Aging; V1, Visit 1; V2, Visit 2. All covariables were measured at V1 except for age, which was measured at INCA.

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Table 2

Survey weighted linear regressions testing association between anticholinergic drug intake status and cognitive scores at SOL-INCA as well as average 7-year cognitive change

	SOL-INCA		Cognitive Change	
	Z-Score Global Cognition		Z-Score Global Cognition	
	β [95% CI] Minimally Adjusted	β [95% CI] Fully Adjusted	β [95% CI] Minimally Adjusted	β [95% CI] Fully Adjusted
Neither V1 or V2 use	Reference	Reference	Reference	Reference
V1 use only	−0.10 ** [−0.17; −0.03]	−0.09 * [−0.16; −0.01]	−0.06 [−0.17; 0.05]	−0.04 [−0.16; 0.07]
V2 use only	−0.11 ** [−0.19; −0.04]	−0.07 [−0.16; 0.01]	−0.12 [−0.25; 0.00]	−0.11 [−0.23; 0.02]
V1 & V2 use	−0.23 ** [−0.39; −0.08]	−0.21 ** [−0.36; −0.05]	−0.30 * [−0.59; −0.01]	−0.28 * [−0.55; −0.01]
	Z-Score B-SEVLT Sum		Z-Score B-SEVLT Sum	
	Minimally Adjusted	Fully Adjusted	Minimally Adjusted	Fully Adjusted
Neither V1 or V2 use	Reference	Reference	Reference	Reference
V1 use only	−0.14 ** [−0.24; −0.04]	−0.11 * [−0.21; −0.01]	−0.09 [−0.21; 0.02]	−0.08 [−0.19; 0.04]
V2 use only	−0.13 * [−0.25; −0.02]	−0.08 [−0.21; 0.04]	−0.09 [−0.22; 0.03]	−0.09 [−0.22; 0.04]
V1 & V2 use	−0.31 ** [−0.51; −0.11]	−0.27 ** [−0.47; −0.07]	−0.30 * [−0.58; −0.01]	−0.28 * [−0.55; −0.01]
	Z-Score B-SEVLT Recall		Z-Score B-SEVLT Recall	
	Minimally Adjusted	Fully Adjusted	Minimally Adjusted	Fully Adjusted
Neither V1 or V2 use	Reference	Reference	Reference	Reference
V1 use only	−0.16 ** [−0.26; −0.06]	−0.13 ** [−0.23; −0.04]	−0.12 * [−0.23; −0.01]	−0.12 * [−0.22; −0.01]
V2 use only	−0.12 * [−0.23; −0.01]	−0.07 [−0.19; 0.04]	−0.12 * [−0.24; −0.01]	−0.11 [−0.23; 0.00]
V1 & V2 use	−0.26 ** [−0.46; −0.07]	−0.22 * [−0.41; −0.03]	−0.19 [−0.40; 0.02]	−0.19 [−0.39; 0.01]
	Z-Score WF		Z-Score WF	
	Minimally Adjusted	Fully Adjusted	Minimally Adjusted	Fully Adjusted
Neither V1 or V2 use	Reference	Reference	Reference	Reference
V1 use only	−0.01 [−0.14; 0.12]	−0.01 [−0.14; 0.11]	0.01 [−0.12; 0.14]	0.03 [−0.10; 0.16]
V2 use only	−0.10 * [−0.20; −0.01]	−0.06 [−0.17; 0.04]	−0.06 [−0.17; 0.06]	−0.01 [−0.13; 0.12]
V1 & V2 use	−0.21 * [−0.40; −0.01]	−0.20 [−0.39; 0.00]	−0.30 ** [−0.53; −0.07]	−0.25 * [−0.47; −0.04]

	SOL-INCA		Cognitive Change	
	Z-Score DSS		Z-Score DSS	
	Minimally Adjusted	**Fully Adjusted**	**Minimally Adjusted**	**Fully Adjusted**
Neither V1 or V2 use	Reference	Reference	Reference	Reference
V1 use only	−0.08 [−0.18; 0.02]	−0.07 [−0.17; 0.02]	−0.02 [−0.13; 0.10]	0.02 [−0.09; 0.13]
V2 use only	−0.10 * [−0.20; −0.00]	−0.07 [−0.16; 0.03]	−0.04 [−0.15; 0.07]	0.01 [−0.11; 0.12]
V1 & V2 use	−0.15 [−0.33; 0.03]	−0.13 [−0.31; 0.04]	−0.19 [−0.44; 0.07]	−0.11 [−0.36; 0.13]
	Z-Score Reversed Trails-A		Z-Score Reversed Trails-A	
	Minimally Adjusted	**Fully Adjusted**	**Minimally Adjusted**	**Fully Adjusted**
Neither V1 or V2 use	Reference	Reference	n/a	n/a
V1 use only	−0.07 [−0.19; 0.05]	−0.07 [−0.18; 0.05]	n/a	n/a
V2 use only	−0.17 ** [−0.29; −0.05]	−0.15 * [−0.28; −0.02]	n/a	n/a
V1 & V2 use	−0.03 [−0.18; 0.13]	−0.02 [−0.19; 0.14]	n/a	n/a
	Z-Score Reversed Trails B		Z-Score Reversed Trails B	
	Minimally Adjusted	**Fully Adjusted**	**Minimally Adjusted**	**Fully Adjusted**
Neither V1 or V2 use	Reference	Reference	n/a	n/a
V1 use only	−0.10 [−0.22; 0.03]	−0.10 [−0.21; 0.02]	n/a	n/a
V2 use only	−0.10 * [−0.20; −0.00]	−0.08 [−0.19; 0.03]	n/a	n/a
V1 & V2 use	−0.22 * [−0.39; −0.04]	−0.22 * [−0.40; −0.03]	n/a	n/a

Notes: Minimally adjusted models include age (>60 years, 60–69 years, ≥70 years), sex (male, female), education (< 12 years, 12 years, > 12 years), Hispanic/Latino background (Mexican, Puerto Rican, South American, Central American, Cuban, Dominican), continuous body mass index, and diabetes status at Visit 1 (no diabetes, prediabetes, diabetes). Fully adjusted models include the previously mentioned covariates in addition to continuous Center for Epidemiology Studies Depression Scale-10 score, a cigarette smoking status (never, former, current), a binary indicator for presence of any cardiovascular disease (no CVD, CVD: based on presence of coronary heart disease, angina, cerebrovascular events, heart failure, peripheral artery disease, or other heart problems) defined by the Framingham Cardiovascular Risk Score criterion, and the number of medications taken to account for polypharmacy. Reversed Trails A and B: The two tests were reverse coded so that higher values indicate better function. Under the original metric of the Trails A and B higher values (in seconds) indicate lower function (Trails A and B tests were not available with the baseline battery).

* $p < 0.05$

** $p < 0.01$.

B-SEVLT, Brief-Spanish English Verbal Learning Test; CI, confidence interval; DSS, Digit Symbol Substitution; SOL-INCA, Study of Latinos-Investigation of Neurocognitive Aging, Visit 2 Cognitive Tests; V1, Visit 1; V2, Visit 2; WF, Word Fluency.

Table 3

Average marginal estimates (and 95% confidence intervals) of mean cognitive scores at SOL-INCA and average 7-year cognitive change of by anticholinergic drug intake status and sex modification

	SOL-INCA		Cognitive Change	
	Z-Score Global Cognition		Z-Score Global Cognition	
	β [95% CI]	β [95% CI]	β [95% CI]	β [95% CI]
	Minimally Adjusted	Fully Adjusted	Minimally Adjusted	Fully Adjusted
Female # Neither V1 or V2 use	0.13*** [0.09; 0.17]	0.14*** [0.10; 0.18]	0.06 * [0.01; 0.12]	0.07 * [0.01; 0.12]
Female # V1 use only	0.09 * [0.02; 0.16]	0.11 ** [0.04; 0.18]	0.07 [−0.04;0.18]	0.09 [−0.02;0.20]
Female # V2 use only	0.06 [−0.03; 0.16]	0.10 * [0.00; 0.20]	−0.07 [−0.20; 0.06]	−0.05 [−0.18; 0.08]
Female # V1 & V2 use	0.04 [−0.08; 0.16]	0.07 [−0.06; 0.19]	−0.03 [−0.20; 0.15]	−0.00 [−0.17; 0.17]
Male # Neither V1 or V2 use	−0.07 ** [−0.12; −0.02]	−0.09*** [−0.14; −0.04]	0.01 [−0.05; 0.07]	−0.01 [−0.07; 0.06]
Male # V1 use only	−0.28*** [−0.42; −0.14]	−0.28*** [−0.42; −0.15]	−0.16 [−0.35; 0.03]	−0.16 [−0.35; 0.03]
Male # V2 use only	−0.26*** [−0.39; −0.13]	−0.24 ** [−0.38; −0.10]	−0.08 [−0.33; 0.16]	−0.08 [−0.34; 0.17]
Male # V1 & V2 use	−0.50*** [−0.79; −0.20]	−0.50*** [−0.79; −0.22]	−0.58 [−1.24; 0.08]	−0.57 [−1.20; 0.06]
	Z-Score B-SEVLT Sum		Z-Score B-SEVLT Sum	
	Minimally Adjusted	Fully Adjusted	Minimally Adjusted	Fully Adjusted
Female # Neither V1 or V2 use	0.22*** [0.17; 0.28]	0.23*** [0.17; 0.28]	0.12*** [0.06; 0.18]	0.13*** [0.07; 0.18]
Female # V1 use only	0.15 ** [0.04; 0.26]	0.18 ** [0.06; 0.29]	0.09 [−0.05; 0.24]	0.11 [−0.03; 0.25]
Female # V2 use only	0.16 * [0.01; 0.30]	0.20 ** [0.05; 0.34]	0.06 [−0.08; 0.19]	0.06 [−0.08; 0.20]
Female # V1 & V2 use	0.09 [−0.07; 0.25]	0.13 [−0.04; 0.29]	0.02 [−0.15; 0.19]	0.03 [− 0.14;0.20]
Male # Neither V1 or V2 use	−0.16*** [−0.21; −0.10]	−0.18*** [−0.24; −0.12]	−0.06 * [−0.11; −0.00]	−0.06 * [−0.12; −0.01]
Male # V1 use only	−0.40*** [−0.57; −0.23]	−0.39*** [−0.56; −0.22]	−0.25 ** [−0.42; −0.09]	−0.25 ** [−0.42; −0.08]
Male # V2 use only	−0.40*** [−0.58; −0.22]	−0.37*** [−0.56; −0.18]	−0.18 [−0.41; 0.05]	−0.19 [−0.42; 0.05]
Male # V1 & V2 use	−0.72*** [−1.10; −0.33]	−0.70*** [−1.08; −0.32]	−0.61 [−1.24; 0.02]	−0.61 [−1.22; 0.00]
	Z-Score B-SEVLT Recall		Z-Score B-SEVLT Recall	
	Minimally Adjusted	Fully Adjusted	Minimally Adjusted	Fully Adjusted
Female # Neither V1 or V2 use	0.20*** [0.14; 0.25]	0.20*** [0.15; 0.26]	0.12*** [0.07; 0.18]	0.13*** [0.08; 0.18]
Female # V1 use only	0.09 [−0.03; 0.20]	0.11 [−0.00; 0.23]	0.02 [−0.10; 0.13]	0.03 [−0.08; 0.15]

	SOL-INCA		Cognitive Change	
Female # V2 use only	0.12 [−0.01; 0.25]	0.16 * [0.03; 0.29]	0.01 [−0.11; 0.14]	0.03 [−0.10; 0.15]
Female # V1 & V2 use	0.10 [−0.05; 0.25]	0.13 [−0.03; 0.28]	0.01 [−0.15; 0.18]	0.03 [−0.14; 0.20]
Male # Neither V1 or V2 use	−0.12*** [−0.19; −0.06]	−0.15*** [−0.21; −0.08]	−0.06 [−0.12; 0.01]	−0.07 * [−0.13; −0.00]
Male # V1 use only	−0.36*** [−0.52; −0.21]	−0.36*** [−0.52; −0.20]	−0.20 * [−0.39; −0.02]	−0.21 * [−0.40; −0.02]
Male # V2 use only	−0.31 ** [−0.49; −0.12]	−0.29 ** [−0.47; −0.10]	−0.20 [−0.41; 0.01]	−0.20 [−0.41; 0.01]
Male # V1 & V2 use	−0.61 ** [−0.98; −0.24]	−0.59*** [−0.95; −0.24]	−0.36 [−0.79; 0.06]	−0.37 [−0.78; 0.04]
	Z-Score WF		**Z-Score WF**	
	Minimally Adjusted	**Fully Adjusted**	**Minimally Adjusted**	**Fully Adjusted**
Female # Neither V1 or V2 use	0.02 [−0.03; 0.07]	0.03 [−0.02; 0.09]	−0.02 [−0.06; 0.03]	−0.01 [−0.05; 0.04]
Female # V1 use only	0.06 [−0.09; 0.22]	0.06 [−0.08; 0.21]	0.07 [−0.08; 0.22]	0.09 [−0.05; 0.23]
Female # V2 use only	−0.06 [−0.16; 0.05]	−0.02 [−0.13; 0.09]	−0.10 [−0.23; 0.03]	−0.05 [−0.18; 0.08]
Female # V1 & V2 use	−0.02 [−0.23; 0.19]	−0.01 [−0.22; 0.20]	−0.05 [−0.22; 0.12]	−0.02 [−0.19; 0.16]
Male # Neither V1 or V2 use	0.03 [−0.03; 0.09]	0.01 [−0.05; 0.07]	0.06 [−0.00; 0.12]	0.03 [−0.03; 0.10]
Male # V1 use only	−0.07 [−0.26; 0.12]	−0.08 [−0.27; 0.10]	−0.06 [−0.26; 0.15]	−0.06 [−0.26; 0.14]
Male # V2 use only	−0.11 [−0.29; 0.06]	−0.09 [−0.28; 0.10]	0.07 [−0.16; 0.29]	0.10 [−0.14; 0.33]
Male # V1 & V2 use	−0.40 * [−0.72; −0.09]	−0.43 ** [−0.75; −0.11]	−0.60 ** [−1.03; −0.16]	−0.58 ** [−1.01; −0.15]
	Z-Score DSS		**Z-Score DSS**	
	Minimally Adjusted	**Fully Adjusted**	**Minimally Adjusted**	**Fully Adjusted**
Female # Neither V1 or V2 use	0.09 ** [0.03; 0.15]	0.10*** [0.04; 0.16]	0.03 [−0.02; 0.08]	0.03 [−0.02; 0.08]
Female # V1 use only	0.07 [−0.05; 0.19]	0.09 [−0.03; 0.20]	0.06 [−0.07; 0.19]	0.09 [−0.03; 0.21]
Female # V2 use only	0.02 [−0.10; 0.15]	0.06 [−0.06; 0.19]	0.02 [−0.13; 0.16]	0.06 [−0.09; 0.20]
Female # V1 & V2 use	0.01 [−0.15; 0.16]	0.03 [−0.12; 0.18]	−0.02 [−0.23; 0.18]	0.04 [−0.17; 0.24]
Male # Neither V1 or V2 use	−0.03 [−0.09; 0.03]	−0.05 [−0.11; 0.01]	−0.01 [−0.06; 0.05]	−0.03 [−0.09; 0.04]
Male # V1 use only	−0.21 * [−0.39; −0.04]	−0.22 * [−0.39; −0.05]	−0.09 [−0.35; 0.16]	−0.07 [−0.32; 0.18]
Male # V2 use only	−0.18 * [−0.34; −0.02]	−0.17 [−0.33; 0.00]	−0.08 [−0.26; 0.09]	−0.05 [−0.23; 0.13]
Male # V1 & V2 use	−0.27 [−0.63; 0.10]	−0.28 [−0.64; 0.08]	−0.39 [−0.93; 0.15]	−0.31 [−0.83; 0.21]
	Z-Score Reversed Trails-A		**Z-Score Reversed Trails-A**	
	Minimally Adjusted	**Fully Adjusted**	**Minimally Adjusted**	**Fully Adjusted**
Female # Neither V1 or V2 use	−0.01 [−0.08; 0.05]	0.00 [−0.06; 0.07]	n/a	n/a

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	SOL-INCA		Cognitive Change	
Female # V1 use only	−0.03 [−0.17; 0.11]	−0.01 [−0.15; 0.13]	n/a	n/a
Female # V2 use only	−0.13 [−0.28; 0.02]	−0.09 [−0.25; 0.06]	n/a	n/a
Female # V1 & V2 use	−0.05 [−0.19; 0.09]	−0.03 [−0.18; 0.12]	n/a	n/a
Male # Neither V1 or V2 use	0.10*** [0.05; 0.15]	0.07** [0.02; 0.13]	n/a	n/a
Male # V1 use only	−0.06 [−0.24; 0.12]	−0.07 [−0.25; 0.10]	n/a	n/a
Male # V2 use only	−0.17 [−0.37; 0.04]	−0.17 [−0.38; 0.05]	n/a	n/a
Male # V1 & V2 use	0.09 [−0.22; 0.39]	0.06 [−0.24; 0.36]	n/a	n/a
	Z-Score Reversed Trails B		**Z-Score Reversed Trails B**	
	Minimally Adjusted	**Fully Adjusted**	**Minimally Adjusted**	**Fully Adjusted**
Female # Neither V1 or V2 use	0.03 [−0.02; 0.08]	0.05 [−0.00; 0.11]	n/a	n/a
Female # V1 use only	0.02 [−0.12; 0.17]	0.04 [−0.10; 0.18]	n/a	n/a
Female # V2 use only	−0.01 [−0.14; 0.12]	0.02 [−0.11; 0.16]	n/a	n/a
Female # V1 & V2 use	0.01 [−0.17; 0.20]	0.02 [−0.17; 0.21]	n/a	n/a
Male # Neither V1 or V2 use	0.04 [−0.03; 0.10]	0.01 [−0.05; 0.08]	n/a	n/a
Male # V1 use only	−0.21* [−0.39; −0.02]	−0.23* [−0.41; −0.05]	n/a	n/a
Male # V2 use only	−0.16* [−0.32; −0.00]	−0.17 [−0.34; 0.00]	n/a	n/a
Male # V1 & V2 use	−0.45*** [−0.70; −0.20]	−0.49*** [−0.77; −0.22]	n/a	n/a

Minimally adjusted models include age (>60 years, 60–69 years, ≥ 70 years), sex (male, female), education (< 12 years, 12 years, > 12 years), Hispanic/Latino background (Mexican, Puerto Rican, South American, Central American, Cuban, Dominican), continuous body mass index, and diabetes status at Visit 1 (no diabetes, prediabetes, prevalent diabetes). Fully adjusted models include the previously mentioned covariates in addition to continuous Center for Epidemiology Studies Depression Scale-10 score, a cigarette smoking status (never, former, current), a binary indicator for presence of any cardiovascular disease (no CVD, CVD: based on presence of coronary heart disease, angina, cerebrovascular events, heart failure, peripheral artery disease, or other heart problems) defined by the Framingham Cardiovascular Risk Score criterion, and the number of medications taken to account for polypharmacy. Reversed Trails A and B: The two tests were reverse coded so that higher values indicate better function. Under the original metric of the Trails A and B higher values (in seconds) indicate lower function (Trails A and B tests were not available with the baseline battery).

* p <0.05

** p <0.01.

B-SEVLT, Brief-Spanish English Verbal Learning Test; CI, confidence interval; DSS, Digit Symbol Substitution; SOL-INCA, Study of Latinos-Investigation of Neurocognitive Aging, Visit 2 Cognitive Tests; V1, Visit 1; V2, Visit 2; WF, Word Fluency.