



Associations between Metformin Therapy and Cognitive Outcomes in Middle and Older Aged Latinos: Insights from the Study of Latinos-Investigation of Neurocognitive Aging (SOL-INCA)



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Introduction

- Metformin may confer cognitive aging benefits in people with diabetes; few studies have focused on Latinos, who experience increased risk of both diabetes and dementia¹⁻³
- This study examined associations between metformin use and cognitive outcomes over 7-years in middle- and older-aged Latinos with prediabetes and diabetes**

Methods

- Participants:**
 - Individuals in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL; 2008–2011; **Visit 1**) and its cognitive ancillary study, SOL-Investigation of Neurocognitive Aging (SOL-INCA; 2015-2018; **Visit 2** conducted 7-years later)
 - The current study included individuals with prediabetes or diabetes (American Diabetes Association criteria, n=1,629)
- Exposures:**
 - Metformin use via medical inventory at Visit 1 (yes/no)
 - Participants were categorized into four groups:
 - (1) Not taking diabetes medication (**No Meds**),
 - (2) Metformin only (**Metf**; reference group),
 - (3) Metformin and other diabetes medication(s) (**Metf+Other**)
 - (4) Other diabetes medications only (**Other**)
- Cognitive Outcomes:**
 - Verbal Learning & Recall:** Brief-Spanish English Verbal Learning Test Sum of Trials and Delayed Recall (B-SEVLT-Sum and -Recall)
 - Phonemic verbal fluency:** Word Fluency (WF)
 - Processing speed & attention:** Digit Symbol Substitution (DSS)
 - Processing speed:** Trail Making Test A (TMT-A) *Visit 2 only*
 - Executive functioning:** TMT-B *Visit 2 only*
 - Global cognition:** Composite scores were generated for each visit by averaging the z-scores of tests that were administered at both visits (B-SEVLT-Sum and Recall, WF, and DSS)
 - Cognitive change:** Modeled by Visit 2 cognitive score as a function of Visit 1 cognitive score to account for baseline performance and adjust for time between assessments
 - Calculated as (T2 - T2pred)/RMSE, where T2 is the score at Visit 2, T2pred is the predicted score, and RMSE is Root Mean Squared Error of the fitted model
 - Mild cognitive impairment (MCI):** *Visit 2 only*
 - National Institute on Aging- Alzheimer's Association criteria
 - Statistical analysis:**
 - To test the associations between diabetes medication use and cognitive outcomes from Visit 1, Visit 2, and cognitive change scores, we used a series of survey weighted linear regressions
 - For MCI, we used survey weighted logistic regression to estimate the Odds Ratios (OR)

Results

Table 1. Demographic and clinical characteristics for SOL-INCA.

	No Meds (n=682)	Metf (n=306)	Metf + Other (n=439)	Other (n=202)	Total (n=1629)
	Mean ± SD or % (SE)				
Age*	64.7 ± 8.1	66.3 ± 8.3	67.1 ± 7.7	69.1 ± 7.5	66.2 ± 8.1
Sex (%Female)	53.9 (2.8)	54.7 (4.9)	56.2 (3.7)	52.8 (5.1)	54.5 (1.8)
Education					
Less than HS	44.8 (2.9)	52.0 (4.8)	51.6 (3.9)	38.2 (4.9)	46.8 (1.9)
HS or equivalent	22.2 (2.3)	14.9 (2.5)	18.6 (2.3)	23.5 (4.3)	20.2 (1.4)
More than HS	33.0 (2.8)	33.1 (5.1)	29.8 (3.2)	38.3 (5.6)	33.0 (1.7)
CKD (% yes)*	22.3 (2.4)	24.6 (3.7)	32.5 (3.1)	43.4 (5.7)	28.5 (1.6)
APOE ε4 Carrier	25.2 (2.4)	15.8 (2.7)	18.8 (2.6)	22.0 (3.6)	21.5 (1.5)
BMI	31.1 ± 5.4	31.5 ± 5.8	32.2 ± 6.1	31.5 ± 5.2	31.5 ± 5.6
CES-D-10	7.6 ± 6.0	8.1 ± 6.9	8.5 ± 6.5	8.7 ± 5.5	8.1 ± 6.3
HbA1c %*	7.1 ± 1.9	7.2 ± 1.6	8.0 ± 1.7	7.8 ± 1.7	7.4 ± 1.8
FRS*	0.2 ± 0.2	0.3 ± 0.2	0.3 ± 0.2	0.3 ± 0.2	0.3 ± 0.2

Abbreviations:
Meds=medication;
Metf = Metformin;
SE = Standard Error;
SD = Standard Deviation;
HS = high school;
CKD = chronic kidney disease;
APOE= Apolipoprotein;
BMI = Body Mass Index;
CES-D-10 = Center for Epidemiologic Studies Depression Scale, 10 item version;
HbA1c = Hemoglobin A1c; FRS = Framingham Risk Score
Note: *p <0.001 comparing across all four medication groups.

- Age, CKD, HbA1c and FRS were significantly different between the diabetes medication groups (p<0.001; see **Table 1**)

Table 2. Associations of diabetes medication use with cognitive performance 7-years later and cognitive change over 7-years.

	No Meds b[95% CI]	Metf b[95% CI]	Metf + Other b[95% CI]	Other b[95% CI]
Visit 2 WF Scores				
M4	-0.07 [-0.29,0.15]	Ref	-0.27* [-0.50,-0.05]	-0.16 [-0.43,0.11]
M5	-0.07 [-0.29,0.14]	Ref	-0.26* [-0.49,-0.03]	-0.15 [-0.42,0.13]
M6	-0.14 [-0.35,0.08]	Ref	-0.29** [-0.51,-0.07]	-0.17 [-0.45,0.10]
Visit 2 DSS Scores				
M4	-0.04 [-0.20,0.11]	Ref	-0.21* [-0.38,-0.04]	-0.28* [-0.52,-0.03]
M5	-0.05 [-0.20,0.10]	Ref	-0.18* [-0.35,-0.01]	-0.26* [-0.50,-0.01]
M6	-0.04 [-0.20,0.11]	Ref	-0.18* [-0.35,-0.01]	-0.25* [-0.50,-0.01]
ΔWF				
M4	-0.17 [-0.39,0.05]	Ref	-0.30* [-0.53,-0.06]	-0.41** [-0.70,-0.12]
M5	-0.17 [-0.39,0.04]	Ref	-0.28* [-0.52,-0.04]	-0.40** [-0.70,-0.10]
M6	-0.23* [-0.45,-0.02]	Ref	-0.31** [-0.54,-0.08]	-0.42** [-0.71,-0.12]
ΔDSS				
M4	-0.05 [-0.28,0.18]	Ref	-0.29* [-0.54,-0.04]	-0.38* [-0.73,-0.03]
M5	-0.06 [-0.29,0.17]	Ref	-0.23 [-0.49,0.02]	-0.34 [-0.70,0.03]
M6	-0.07 [-0.31,0.17]	Ref	-0.24 [-0.51,0.03]	-0.34 [-0.71,0.02]

Notes. M1-M3 are not shown. M1: unadjusted; M2: adjusted for age, sex, heritage, education; M3: adjusted for M2 + APOE ε4 Status and BMI; M4: adjusted for M3 + CKD and CES-D-10; M5: adjusted for M4 + HbA1c; M6: adjusted for M5 + FRS.

Discussion

- Compared to metformin users with prediabetes and diabetes, use of non-metformin diabetes medications was associated with worse executive function and more decline over 7-years (trends observed for no medications)
- Metformin use may confer cognitive benefits in people with diabetes through both glycemic and nonglycemic pathways, including improved insulin sensitivity, reduced systemic inflammation, modulation of mitochondrial function, and potential effects on neurovascular health⁴
- A prior meta-analysis reported that elevated circulating inflammatory markers, including interleukin-6, C-reactive protein, advanced glycation end products, and soluble vascular cell adhesion molecule-1 were associated with cognitive impairment in individuals with type 2 diabetes⁵
- Metformin has been shown to reduce several of these inflammatory markers in cellular and diabetic rodent models³, and in humans^{6,7}
- Future studies should consider metformin use duration and additional markers of diabetes severity

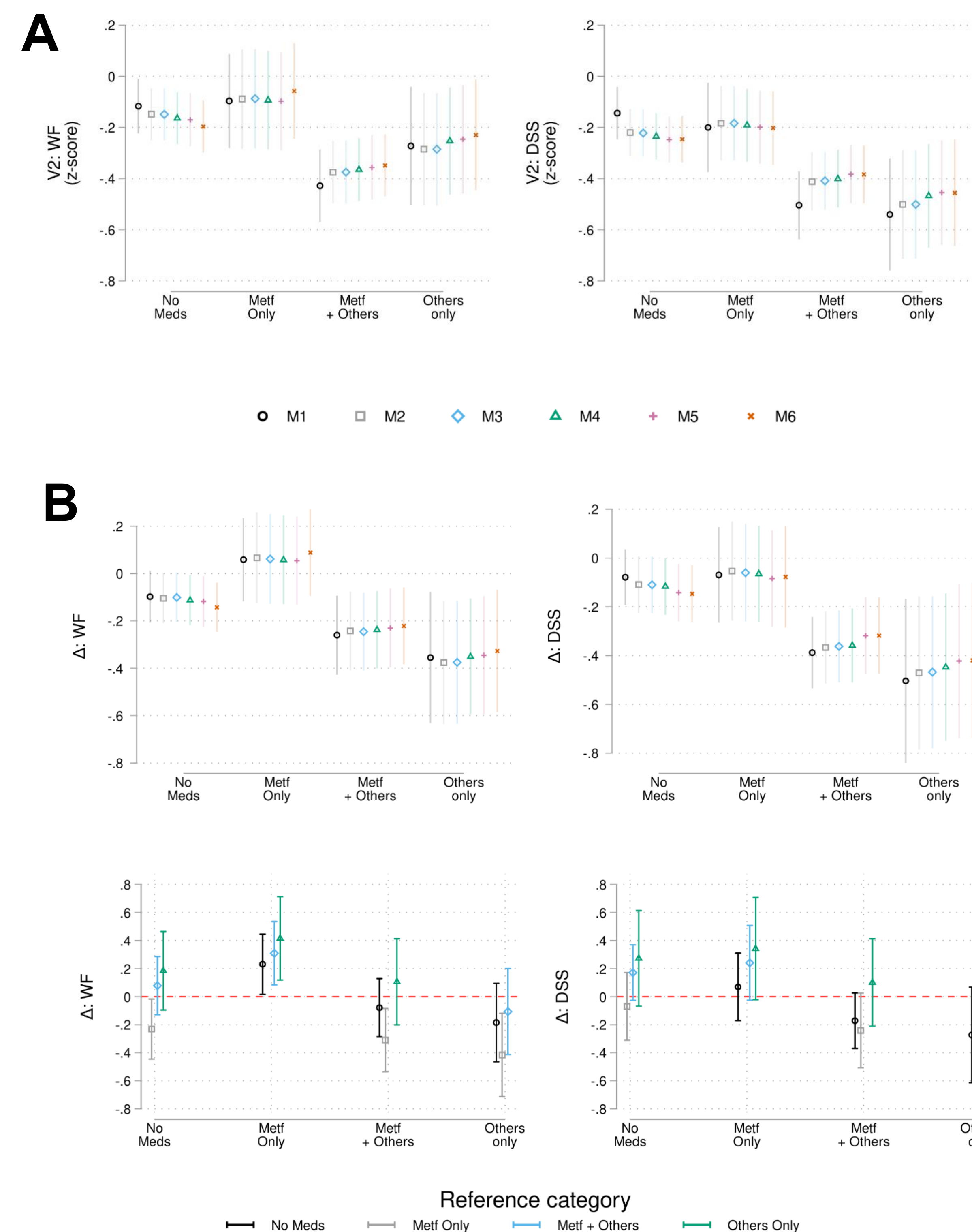


Figure 1. A) Associations of diabetes medication use with cognitive performance 7-years later and B) cognitive change over 7-years, with the bottom plots showing pairwise group differences.

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