

Mindy Katz¹ Gabriel de Erausquin² Gabriela Gonzalez Alemán³ Laura Rabin¹ Caroline Carlton¹ Daria Brigitte Neidre² Richard B. Lipton¹ Peter Fox² Ali Ezzati⁴ Sudha Seshadri² Meredith Zozus² John Blangero⁵ Thom Petterson² Heather Synder⁶

1: Saul R. Krey Department of Neurology, Albert Einstein College of Medicine, 2: The Glenn Biggs Institute for Alzheimer’s & Neurodegenerative Diseases, UT Health San Antonio, 3: Universidad Católica Argentina, 4: University of California Irvine, 5: University of Texas Rio Grande Valley, 6: Alzheimer’s Association

BACKGROUND

Coronavirus Disease 2019 (COVID-19) has caused > 6 million deaths and affected >500 million people. Beyond respiratory manifestations, COVID-19 involves central nervous system (CNS) manifestations during the acute phase resulting from inflammatory, cerebrovascular, anoxic, or viral mechanisms. In some, CNS involvement results in chronic neurocognitive or neuropsychiatric sequelae. This study explores environmental, genetic, clinical, and neuroimaging predictors of risk and resilience, and examines the relationship between well-validated blood-based biomarkers (BBB), infection history, and measures of brain structure and function.

GOALS

ISAVRAD is designed to determine the mechanisms that link exposure to COVID-19 to cognitive decline, and Alzheimer Disease and Related Dementias (ADRD). Mechanisms of interest include genetic interactions with infection, cerebrovascular disease, accelerated accumulation of ATN biomarkers, and inflammation, leading to changes in brain structure and function as revealed by neuroimaging , neurocognitive, and clinical assessment.

METHODS

- Participants:**
- ISAVRAD is a longitudinal, multi-country cohort study targeting 4,300 adults aged ≥ 60 years from 4 sites across 2 countries—USA, Argentina (**Table 1**).
 - Recruitment strategies are adapted to local registry characteristics.
- Data collection:**
- Baseline, 18 and 36 months.
 - Protocol includes (**Table 2**):
 - Demographics
 - Clinical history
 - Cognitive assessments
 - Olfactory testing
 - Neuroimaging
 - BBB testing
 - Whole genome sequencing
 - Clinical dementia assessments

BBB are obtained to assess inflammatory, vascular and neurodegenerative disease pathways. Cognitive evaluations employ the *Language Independent Neurocognitive Battery* (LINB), which was designed following Uniform Data Set (UDS) protocols to minimize educational and linguistic bias across diverse populations (**Table 3**).

RESULTS

Enrollment is ongoing at all sites, with longitudinal measures being collected in Argentina (**Table 1**). Centralized coordination ensures harmonized data acquisition. The LINB enables culturally adaptable cognitive assessments in local languages, facilitating cross-site comparison of cognitive trajectories (**Table 3**). The battery provides data that can be standardized using local norms across multiple cognitive domains. Diagnostic consensus conferences are conducted within and across sites for outcome validation.

Table 1. Characteristics of ISAVRAD Study Sites					
	San Antonio, TX	Laredo, TX	Seattle, WA	Bronx, NY	Jujuy, Argentina
Site demographics	Mexican American	Mexican American	Native American, Asian, Hawaiian Native, Pacific Islander	Hispanic, non-Hispanic Black, non-Hispanic White	Amerindian Ancestry
Source population	2,003,554	276,652	2,252,782	1,418,207	770,881
% aged ≥ 60 years	12.4%	4.7%	13.5%	13.3%	12.0%
# affected by COVID-19 as of 12/31/2021	340,000	58,076	200,873	244,271	50,035
Recruitment goal/ Recruitment as of 6/23/2026	250/69	250/60	250/10	250/37	3000/2421

Table 2. Summary of Measures and Key Outcomes	
Category	Measures
Language Independent Neurocognitive Battery (LINB)	see Table 3
Comprehensive Neuropsychiatry and Behavior Assessment	World Health Organization for Clinical Assessment in Neuropsychiatry (WHO SCAN)
Clinical Cognitive Diagnosis/ Neurological Exam	Mild Cognitive Impairment (Petersen Criteria), Clinical Dementia Rating (CDR), and dementia subtypes (AD, VaD, DLB, FTD)
Psychosocial Questionnaires	Quality of Life, Stressful Life Events, Poverty and Financial Hardship
Clinical Symptoms	Anosmia/hyposmia, headache, fatigue
MRI/PET	Structural and functional MRI, diffusion tensor imaging, FDG PET
Genetics	GWAS, Ancestry Genetics
Blood Based Biomarkers	AD biomarkers, inflammatory markers

Table 3. ISAVRAD Neuropsychological Battery		
Cognitive Domain	Subdomain	Neuropsychological Test/Subtest
Global Cognition		MoCA ^a
Memory	Associative semantic memory	Modified Camel and Cactus Test
	Verbal learning, Episodic memory	Rey Auditory Verbal Learning Test ^b Hopkins Verbal Learning Test – Spanish WMS-V Verbal Paired Associates – Spanish
Working Memory	Visuospatial working memory	Corsi Block-Tapping Task
	Processing Speed	Five Digit Test OTMT Digit Symbol Substitution Test
Executive Functioning	Inhibition, task-switching	Five Digit Test
	Decision-making	Tower of Hanoi
	Risk Aversion	Iowa Gambling Task
Language	Category Fluency	Animals list generation ^a
	Naming	MiNT ^a Boston Naming Test – Spanish
	Verbal Fluency	Phonemic test, F-words ^a
Visuospatial Processing		Bells Test OTMT
Social Cognition	Theory of Mind	Frith-Happé animations
<i>Note.</i> MoCA, Montreal Cognitive Assessment; WMS-V, Weschler Memory Scale-V; OTMT, Oral Trail Making Test; MiNT, Multilingual Naming Test ^a NAAC UDS Version 3 Neuropsychological Battery ^b Test added to the most recent version of the NAAC UDS		

CONCLUSION

ISAVRAD’s diverse, multi-ancestry design enhances generalizability and allows for harmonization of data across varied cultures and settings. Despite inherent challenges of cross-national implementation, the study will provide critical insights into how SARS-CoV-2 infection and ancestral genomic variation interact to influence ADRD risk and other CNS outcomes.