Received: 26 December 2025 | Revised: 23 February 2026 | Accepted: 11 March 2026

DOI: 10.1002/alz.71373

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

A harmonized framework for studying exceptional cognitive aging in Latin America

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Abstract

INTRODUCTION: Biological, genetic, and sociocultural factors underlying cognitive resilience and resistance to pathology remain unexplored in Latin America. The Life-Course Epidemiology of Aging, Resilience, and Neurodegeneration in Alzheimer's Disease (LEARN-AD) study and Latin American SuperAgers Study (LASAS) establish

Funding information
Alzheimer's Association, Grant/Award Numbers: ALZSI-25-1464205, AARG-25-1485687, 24HPE-1287320

the first harmonized frameworks to characterize resilience and exceptional cognitive aging phenotypes in the region.

METHODS: The shared protocol integrates cognitive, neurological, psychosocial, and genetic data. SuperAgers are deeply phenotyped, while successful cognitive agers are identified through harmonized criteria applied to existing cohorts, ensuring regional adaptation and international comparability. Centralized training and shared procedures ensure cross-site consistency.

RESULTS: We define eligibility criteria and standardized assessments to classify successful cognitive agers and SuperAgers in Latin America and examine biological and psychosocial profiles supporting better-than-expected cognition.

DISCUSSION: LEARN-AD and LASAS represent the first Latin American infrastructure for studying cognitive resilience, resistance, and exceptional cognitive aging, which will generate unprecedented regional databases and grow into larger networks, providing foundations for research, prevention strategies, and precision approaches to promote brain health in Latin America.

KEYWORDS
exceptional memory aging phenotype, healthy cognitive aging, Latin America, resilience, resistance, successful cognitive aging, SuperAgers

Highlights

- This is the first harmonized study of resilience and exceptional memory aging phenotypes in Latin America.
- The study integrates diverse cognitive, psychosocial, genetic, and proteomic data.
- Exceptional memory phenotype criteria are regionally adapted and internationally comparable.
- The protocol aids regional harmonization and the identification of pathways to resilience.
- The study builds regional capacity and fosters future multimodal research on aging.

1 | BACKGROUND

Over the past decades, remarkable progress has been made in identifying genetic, vascular, and lifestyle risk factors that contribute to the development and progression of Alzheimer's disease and related dementias (ADRD). This has shaped the foundation for contemporary models of neurodegenerative risk.[1,2] However, despite these advances, an equally important question remains: Why do some individuals maintain intact cognition even at advanced ages or despite significant neuropathological burden?[3] Addressing this question has prompted a shift from deficit-based frameworks toward models that emphasize cognitive reserve, resilience, and resistance in aging.

Cognitive reserve is defined as the brain's capacity to optimize or maximize performance by flexible recruitment of neural networks or cognitive strategies, thereby maintaining function amid age- or disease-related changes.[4] Within this broader framework, two related yet distinct mechanisms have been described: resistance, defined as the absence or delay of pathological processes during aging, and resilience, defined as the capacity to preserve cognitive function despite the presence of pathology.[5] Neuropathological and neuroimaging studies suggest that both resistance and resilience contribute to successful cognitive aging.

Within this literature, a subset of older adults who demonstrate memory performance that is substantially better than expected for their age, often comparable to individuals decades younger, has been identified. These individuals are frequently referred to as "SuperAgers."[6] More broadly, such individuals may be conceptualized as exhibiting an exceptional memory aging phenotype, defined by preserved or superior episodic memory performance relative to age-matched peers.

Although interest in reserve and exceptional cognitive aging has expanded rapidly, most of the existing evidence originates from high-income countries (HICs).[6–12]

This geographical restriction limits our understanding of how sociocultural, genetic, and life-course exposures influence cognitive reserve and brain health in highly diverse settings. In low- and middle-income countries (LMICs), particularly in Latin American and Caribbean (LAC) countries, factors such as access and quality of education, socioeconomic inequality, cardiovascular burden, health behavior, healthcare accessibility, and social engagement differ substantially from those observed in HIC cohorts. Furthermore, recent estimates of life expectancy indicate broad variability within the region, ranging from ≈ 65 years in countries such as Haiti and Bolivia to > 81 years in Chile and Puerto Rico.[13]

As a result, HIC-derived definitions may not be applicable to successful cognitive agers in LMICs, either underestimating exceptional performance or incorrectly labeling normative performance. Overall, much of what is currently known about "SuperAgers" or exceptional memory aging phenotypes may not directly translate to non-HIC regions.[14]

In LAC, studies exploring exceptional or preserved cognitive aging are limited to Brazil and Argentina. These studies suggest that individuals with exceptional memory aging phenotypes may preserve high cognitive performance despite amyloid burden, consistent with mechanisms of cognitive resilience rather than neuropathology or resistance.[15–17] Studying healthy cognitive aging in LAC populations is essential for refining global models of successful aging and providing insights into how adaptation and compensation unfold under structural and economic inequities.

To address gaps in the study of cognitive resilience and exceptional aging in LAC populations, we established two coordinated initiatives in the region. The Life-Course Epidemiology of Aging, Resilience, and Neurodegeneration in Alzheimer's Disease (LEARN-AD) study is a multisite, multimodal observational cohort designed to investigate mechanisms of cognitive reserve, resistance, and resilience in older adults across diverse cultural and socioeconomic settings, with an emphasis on Latin America. Nested within LEARN-AD, the Latin American SuperAgers Study (LASAS) is a subprotocol designed to characterize individuals aged ≥ 75 who demonstrate better-than-expected memory and cognitive performance relative to normative expectations, referred to as SuperAgers.[6,7,18,19]

In this article, we describe the methodological framework and harmonized protocols of LEARN-AD and LASAS. We detail the study design, participant selection, cognitive and biological assessments, and analytic strategy underlying these initiatives, highlighting complementary roles in characterizing resilience, resistance, and exceptional cognitive aging in LAC.

RESEARCH IN CONTEXT

1. **Systematic review**: Most studies on cognitive resilience, healthy cognitive aging, and SuperAging originate from high-income countries (HICs). These demonstrate that certain older adults maintain brain morphology and better-than-expected cognition despite age or neuropathology. However, Latin American populations remain underrepresented. No multicountry framework in the region has integrated cognitive, psychosocial, genetic, and proteomic data to examine multidimensional mechanisms of resilience and exceptional aging across heterogeneous contexts.
2. **Interpretation**: The initiatives proposed (Life-Course Epidemiology of Aging, Resilience, and Neurodegeneration in Alzheimer's Disease [LEARN-AD] and Latin American SuperAgers Study [LASAS]) establish the first multisite platform in Latin America to characterize resilience, healthy cognitive aging, and SuperAging-like phenotypes by integrating biological, cognitive, psychosocial, and clinical data under a unified framework, and enabling the development of a genetic, biological, and socio-cognitive map of resilience and exceptional aging. They expand the understanding of cognitive maintenance beyond HICs.
3. **Future directions**: Longitudinal follow-up, neuroimaging, network expansion, and international comparisons are planned. This infrastructure supports culturally grounded preventive strategies and scientific capacity to promote brain health across Latin America.

2 | METHODS

2.1 | Study design

LEARN-AD is a multisite, multimodal observational cohort study designed to investigate mechanisms of cognitive resilience and resistance in older adults across diverse sociocultural and economic contexts, with a particular emphasis on LMICs. At the time of manuscript submission, LEARN-AD and LASAS include a core of active sites (Argentina, Dominican Republic, and Mexico) with secured funding and regulatory approval, with additional Latin American sites planned for phased inclusion as funding becomes available. Although the initial implementation of LEARN-AD includes predominantly Spanish-speaking Latin American countries, the study was designed as a harmonizable and extensible framework rather than a linguistically or nationally restricted cohort. The LEARN-AD protocol is intentionally structured to allow incorporation of additional Latin American populations, including Portuguese-speaking countries such as Brazil, as compatible cohorts, infrastructure, and funding become available. The study team has identified potential aging cohorts in Argentina, Brazil, Chile, Colombia, Cuba, Dominican Republic, Mexico, Peru, and Uruguay.

LEARN-AD implements a harmonized assessment framework and a shared governance structure to ensure the use of a standardized protocol across participating countries. Individuals may be classified across the spectrum of cognitive aging using harmonized criteria applied to existing cohort data, including identification of exceptional memory

aging phenotypes (SuperAgers). This harmonized approach allows for retrospective identification of individuals with better-than-expected cognitive performance across diverse cohorts, supporting large-scale and cross-regional analyses of resilience and resistance mechanisms.

Within LEARN-AD, LASAS constitutes a nested sub-protocol focusing on the upper extreme of the cognitive aging continuum. While LEARN-AD aims to characterize the full spectrum of successful cognitive aging and identify cognitively resilient individuals, LASAS targets SuperAgers, adults aged ≥ 75 years who exhibit exceptional cognitive performance. Both initiatives share a harmonized conceptual model and common core assessments, while LASAS incorporates additional phenotyping for a selected subgroup (SuperAgers).

All study sites will adhere to a common protocol, standardized training, cultural adaptation procedures, and centralized data management to ensure comparability and reproducibility of findings. Participants are recruited primarily through existing and deeply characterized longitudinal cohorts. Leveraging these cohorts enables efficient identification of individuals across the cognitive aging spectrum, reduces screen failure rates, and enhances the feasibility of identifying resilient and SuperAgers.

This two-tier design offers several scientific advantages. LEARN-AD integrates cognitive, psychosocial, clinical, and biological data to capture the full continuum of cognitive aging and the multiple layers at which resistance and resilience operate. LASAS, in turn, concentrates on defining and characterizing the SuperAger phenotype within the Latin American context, adapting classical criteria to regional differences in life expectancy, education attainment, and socioeconomic inequalities. Together, LEARN-AD and LASAS advance cognitive reserve research to a more inclusive and representative understanding, broadening global knowledge of the mechanisms that support successful cognitive aging in populations historically and currently underrepresented in dementia research. In addition, the design enables cross-country comparisons and provides the foundation for modeling life-course pathways to cognitive resilience, as well as identifying biological and psychosocial markers associated with successful and exceptional aging.

2.2 | Key definitions

To ensure conceptual clarity, we provide the operational definitions that guide the LEARN-AD and LASAS protocols. In this study, resilience refers to cognitive performance that is superior to what would be expected based on an individual's demographic, psychosocial, and biological risk profile, even in the presence of age-related or disease-related neuropathology. Resistance refers to normal cognitive aging, with a relative absence, delay, or attenuation of neuropathological processes despite exposure to established risk factors.[20] All subsequent analyses and interpretations in LEARN-AD and LASAS are anchored in these definitions, ensuring consistent use of terminology across cognitive, clinical, and biological domains.

2.2.1 | SuperAgers

SuperAgers are adults aged ≥ 75 years who demonstrate exceptional episodic memory performance, defined as delayed recall scores at or above the average range for individuals in their 50s to 60s, along with preserved performance (within 1 standard deviation [SD] of local normative data) for non-memory domains such as language, processing speed, and executive function, adjusted for age, education, and sex.[6–9]

2.2.2 | Successful cognitive agers

Individuals aged ≥ 75 years who perform within the normal range (within 1 SD from age-, education-, and sex-adjusted local norms) across core cognitive domains including memory, language, and executive function and who maintain functional independence are referred to as successful cognitive agers.[4]

2.2.3 | Resilient cognitive agers

Resilient cognitive agers are those individuals aged ≥ 75 years who exhibit preserved or superior cognitive performance across memory, language, and executive function despite evidence of biological risk of Alzheimer's disease (AD) or neurodegeneration. Biological risk indicators may include the presence of genetic susceptibility (e.g., carriage of the apolipoprotein E ε4 allele), abnormal plasma-based biomarkers consistent with AD pathophysiology (e.g., amyloid-related markers, tau-related markers, or neurodegeneration-associated proteins aligned with the amyloid/tau/neurodegeneration [ATN] framework), and/or proteomic signatures reflecting inflammatory, synaptic, vascular, or neurodegenerative processes.[5] These individuals perform better than expected based on their risk profile.

2.2.4 | Resistant cognitive agers

Individuals aged ≥ 75 years who exhibit preserved or superior cognitive performance, particularly in episodic memory, but also within normal limits across other cognitive domains, in the absence of significant AD-related pathology or neurodegeneration are referred to as resistant cognitive agers.

2.3 | Participants and recruitment

Participants will be recruited primarily from existing, well-characterized longitudinal cohorts to maximize feasibility and reduce screening failure rates. Recruitment sources will include community-based and clinic-based cohorts affiliated with recent cognitive and functional assessments, for example, the 10/66 Dementia Research

BOX 1 Overview of Study Aims and Eligibility Criteria for LEARN-AD and LASAS

Life-Course Epidemiology of Aging, Resilience, and Neurodegeneration in Alzheimer's Disease (LEARN-AD)	Latin American SuperAgers Study (LASAS)
Aims	
Aim 1. Identify older adults who demonstrate cognitive resilience, defined as cognitive performance that exceeds expectations based on demographic, social, clinical, and biological risk profiles. **Aim 2**. Characterize the cognitive, psychosocial, clinical, and biological features associated with resilience using harmonized assessments across sites. **Aim 3**. Compare resilient and non-resilient individuals to identify key factors tha differentiate these groups across diverse sociocultural contexts. **Aim 4**. Generate hypotheses on modifiable protective mechanisms by integratin cognitive data with genomic and proteomic markers.	**Aim 1**. Identify demographic, psychosocial, cognitive, and clinical factors associated with exceptional cognitive performance (SuperAging) in Latin American adults aged ≥ 75. **Aim 2**. Characterize genetic contributors to SuperAging and to resilience or resistance to Alzheimer's disease pathology. **Aim 3**. Identify proteomic signatures associated with exceptional cognitive aging and preserved cognitive function
Inclusion criteria:	
Age ≥ 75 years at the time of assessment and functional independence in basic and instrumental activities of daily living. Availability of recent cognitive and functional data confirming performance within or above age- and education-adjusted norms. Cognitive performance within one standard deviation of normative averages for their age and education. Willingness to complete cognitive, clinical, psychosocial, and biological evaluations.	Participants must meet all LEARN-AD inclusion criteria plus: Age ≥ 75 years with episodic memory performance at or above the normative average for individuals in their 50s–60s. Preserved non-memory cognitive performance (naming, fluency, processing speed) within one standard deviation of age- and education-adjusted norms.
Exclusion criteria:	
No exclusions will be applied based on education, literacy, socioeconomic status, or rural/urban residence, ensuring representativeness of diverse Latin American populations.Participants will be excluded for: - Prior diagnosis of dementia or evidence of significant cognitive decline at their last assessment. - Major neurological disorders, including stroke with sequelae, Parkinson's disease with significant impairment, severe traumatic brain injury, epilepsy with poor control. - Major psychiatric disorders, such as schizophrenia or active major depression, which affect cognitive validity. - Severe uncorrected sensory impairments (vision or hearing) that prevent reliable cognitive testing. - Medical conditions likely to prevent completion of study procedures (terminal or severely incapacitating conditions). - Inability to complete study procedures due to insufficient proficiency in the primary language of testing at the research site.*	

Note: *At the time of manuscript submission, all approved study sites administer assessments in Spanish. The protocol is designed to be linguistically adaptable, and additional languages may be incorporated in future study phases following appropriate cultural adaptation and validation.

Group in Mexico and Dominican Republic, and the Fleni Aging Cohort in Argentina, which currently comprises >10,000 individuals and enrolls ≈ 1700 cognitively healthy older adults per year. Additional community and clinical cohorts may be incorporated as recruitment progresses. Participant eligibility criteria for both studies are provided in Box 1.

Individuals meeting broad age and cognitive performance criteria will be contacted by phone or in person and invited to participate. Recruitment materials and procedures will be adapted to local languages and cultural norms at each site. Written informed consent will be obtained from all participants and, when applicable, from informants. A purposive sampling strategy will be used to ensure adequate representation of both successful cognitive agers and SuperAgers, allowing direct comparison across cognitive aging trajectories within and across sites.

2.4 | Harmonization framework, core protocol, and outcome measures

Both LEARN-AD and LASAS use a harmonized, multisite protocol and a multidimensional assessment battery that covers sociodemographic, cognitive, neurological, psychiatric, functional, psychosocial, lifestyle, and biological domains. Key outcome measures and the conceptual framework are presented in Table 1. Selection of cognitive, functional, and psychosocial instruments was guided by their prior use in large population-based studies and major Latin American research initiatives, including the 10/66 Dementia Research Group and LatAm-FINGER studies (Table S1 in supporting information), ensuring feasibility, cultural appropriateness, and availability of regional experience. For a detailed list of tests used and prior used in the Latin American context, see Table S1.

TABLE 1 Conceptual framework illustrating life-course determinants, reserve mechanisms, and resilience pathways in the LEARN-AD and LASAS studies.

Conceptual layer	Key components	Instruments used for assessment
Life-course & contextual determinants	• Early-life conditions: nutrition, adversity, education access • Education quality and literacy • Socioeconomic context and inequality • Life-course adversity and psychosocial stressors • Environmental exposures: rural/urban context, pollution • Vascular and metabolic risk profiles • Social networks, engagement, and community participation	• Personal history and social determinants of health questionnaire • Other clinical history and medications (SNOMED)
Cognitive reserve & psychosocial/lifestyle pathways	• Cognitive reserve mechanisms: enrichment, stimulation • Lifestyle behaviors: physical activity, sleep, diet • Psychosocial resources: optimism, coping, emotional regulation • Mental health and well-being	• Personal history and social determinants of health questionnaire • Pittsburgh Sleep Quality Index • Geriatric Depression Scale • Neuropsychiatric Inventory questionnaire
Biological mechanisms & pathways	• Resistance pathways: Reduced or delayed amyloid, tau, vascular pathology • Resilience pathways: Preserved cognition despite pathology	• Biofluid collection: whole blood samples, buffy coat, plasma
Cognitive aging outcomes	• Successful cognitive aging (LEARN-AD) • Exceptional cognitive aging/SuperAgeing (LASAS; deep phenotyping)	• Harmonized cognitive assessment battery, cognitive screening, verbal and visual memory, attention, executive processing, language, and visuospatial abilities • Functional and autonomy assessment

Note: Table illustrates the integrated conceptual model guiding the LEARN-AD and LASAS studies. Life-course and contextual factors—including early-life conditions, education quality, socioeconomic context, adversity, vascular risk, and environmental exposures—influence the development of cognitive reserve and behavioral pathways related to lifestyle, psychosocial resources, and coping. These behavioral and contextual processes interact with biological mechanisms, including genetic contributors, proteomic signatures, inflammatory and metabolic pathways, and brain maintenance processes. Together, these multi-level influences shape individual trajectories of aging, ranging from successful cognitive aging (LEARN-AD) to exceptional cognitive aging/SuperAging (LASAS). For a detailed list of tests used in the neuropsychological assessment battery, see supporting information.
Abbreviations: LASAS, Latin American SuperAgers Study; LEARN-AD, Life-Course Epidemiology of Aging, Resilience, and Neurodegeneration in Alzheimer's Disease; SNOMED, Systematized Nomenclature of Medicine.

1. Sociodemographic, health, and clinical-neurological measures: Standardized questionnaires and clinical interviews capture age; sex/gender; race/ethnicity; education; occupation; socioeconomic indicators; medical history; cardiovascular, neurological, psychiatric, and metabolic risk factors; lifestyle characteristics; environmental exposures; and early-life conditions (nutrition, adversity, and psychosocial stressors, social networks, engagement, and community participation).[21] These measures enable characterization of life-course determinants of cognitive resilience and resistance.
2. Cognitive assessment: A harmonized neuropsychological battery is administered to evaluate global cognition and performance across key domains including episodic memory, executive function, language, visuospatial abilities, processing speed, and attention. The battery is aligned with international aging and SuperAger initiatives and adapted for cultural and educational diversity across Latin American sites.[22,23]
3. Functional assessment: Functional independence is assessed using validated measures of basic and instrumental activities of daily living. These tools enable differentiation between successful cognitive aging and exceptional cognitive performance.
4. Informant-based measures: Informants provide collateral information regarding participants' daily functioning, behavioral and neuropsychiatric symptoms, sleep-related behaviors, and perceived cognitive changes. Informant data enhances the accuracy of cognitive classification and functional profiling.
5. Psychological and well-being measures: Validated questionnaires assess mood, anxiety, psychological well-being, personality traits relevant to resilience, perceived cognitive decline, and quality of life. These measures support a biopsychosocial characterization of aging trajectories.
6. Mobility and sleep: Mobility, life-space, sleep quality, and sleep-related disturbances are measured using standardized self-report and informant instruments. These variables capture daily activity patterns and health behaviors associated with cognitive resilience.
7. Biofluid collection: Blood samples will be collected from all participants to identify biological molecules that allow the identification and characterization of cognitive

resilience and resistance. Whole blood samples will be processed and stored for future use. Buffy coat will be stored for future DNA extraction and genomic analyses; plasma will be extracted and stored for multi-omic characterization. Overall, we aim to identify multi-omic profiles associated with neuroprotection and reduced susceptibility to AD pathology.[24–27] Blood-based biomarkers will be used to characterize AD-related pathophysiology and related neurodegenerative processes. Core biomarker domains will include amyloid pathology (A), tau pathology (T), and neurodegeneration or neuronal injury (N). Additional domains related to vascular dysfunction, neuroinflammation, synaptic integrity, and cellular stress will be explored using proteomic and other omics-based approaches. Biospecimen collection, processing, storage, and shipment will follow harmonized standard operating procedures consistent with internationally established guidelines for blood-based biomarker research and biobanking in aging and dementia studies.

Neuroimaging and other in vivo biomarkers (e.g., cerebrospinal fluid) will not be collected in the present LEARN-AD and LASAS protocols. Future study phases will attempt to incorporate structural and functional brain imaging as site infrastructure and funding permit, at which time standardized acquisition, harmonization, and quality control procedures will be defined.

2.5 | Study schedule

The LEARN-AD and LASAS procedures are designed to balance scientific rigor while maximizing participant comfort and feasibility. All participants complete a baseline evaluation within one session, though they may be divided into shorter appointments to accommodate older adults or local field conditions; when split into two appointments, the second session should occur within 21 days of the first. Remote options, including telephone-based informant interviews and adapted cognitive or psychosocial questionnaires, may be used when necessary. Missed or incomplete assessments will be rescheduled whenever possible, and partial data will be retained for analysis in accordance with established missing-data procedures (see Figure 1).

2.6 | Research ethics and participant protection

The LEARN-AD and LASAS studies were reviewed and approved by the local institutional ethics committees in each participating country. All procedures comply with the ethical principles outlined in the Declaration of Helsinki and follow local regulatory requirements for the protection of human subjects. Written informed consent is obtained from all participants prior to enrollment. When applicable, informants provide additional consent for collateral interviews. Participants are informed of the voluntary nature of the study, their right to withdraw at any time, and the measures taken to ensure privacy and confidentiality. All biological samples and study data are de-identified using unique study codes prior to transfer and centralized storage. No procedures involving deception, coercion, or undue inducement are included in the protocol.

2.7 | Data management and sharing plan

Data collected for LEARN-AD and LASAS will managed through a centralized, secure data repository housed at Washington University in St. Louis to facilitate harmonization, quality control, and reproducible multisite analyses. Each participating site uploads de-identified data through encrypted channels, while identifiable information remains stored locally and is never shared outside the originating institution. Biological samples (including but not limited to plasma, serum, and buffy coat) follow standardized operating procedures for collection, processing, aliquoting, and storage, and are tracked through a Part 11-compliant unified biobanking management system. All shipments follow validated cold-chain protocols. Centralized biospecimen management will enable uniform application of data validation procedures, version control, and inter-site harmonization reviews, which are essential for cross-national observational studies.

Of note, data ownership remains with the originating Latin American institutions. Access to the LEARN-AD/LASAS dataset is governed by a data access committee composed of representatives from participating sites, ensuring shared governance, equitable access, and alignment with local regulations and scientific priorities. All data access and secondary use requests require committee approval and are conducted under formal data use agreements.

2.8 | Statistical analysis plan and sample size and power considerations

Analyses for LEARN-AD and LASAS will be primarily descriptive and exploratory. For LEARN-AD, participants will be classified into data-driven cognitive groups based on the harmonized baseline assessment, which may include individuals with performance within expected norms (successful cognitive agers) and individuals demonstrating better-than-expected cognitive performance (SuperAgers). Descriptive statistics and general regression approaches will be used to examine demographic, psychosocial, clinical, and biological characteristics across these groups, accounting for age, sex, education, and site differences. For LASAS, SuperAgers will be compared to age- and education-matched older adults to characterize cognitive, psychosocial, neurological, psychiatric, and biological features associated with exceptional cognitive performance. In addition, participants will be classified according to plasma-based ATN biomarker profiles. Within both SuperAger and age- and education-matched comparison groups, ATN profiles will be used to distinguish individuals who maintain preserved cognition despite evidence of AD pathophysiology (resilience) from those who show preserved cognition in the absence of such biological abnormalities (resistance; see Figure 2). Additional markers of neurodegeneration and brain injury, including synaptic integrity, neuroinflammation, vascular dysfunction, and cellular stress will be

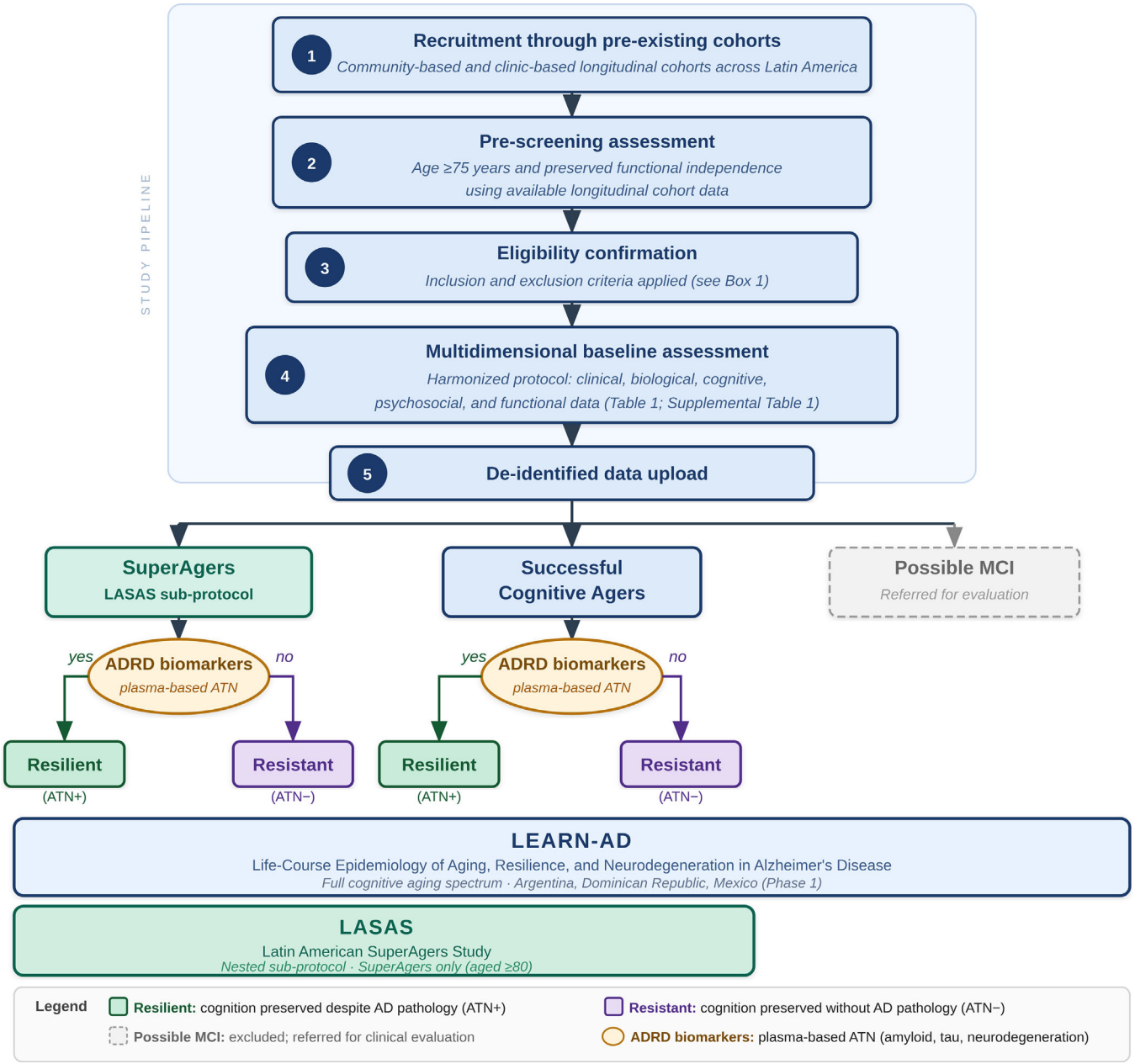

FIGURE 1 Flowchart for the LEARN-AD and LASAS initiatives. The flowchart illustrates the harmonized recruitment, assessment, and participant classification implemented across the two complementary studies. Participants are classified according to cognitive performance into successful cognitive agers or SuperAgers and further stratified according to the presence or absence of AD biomarkers. This integrated framework enables the study of cognitive resilience and resistance across the spectrum of healthy and exceptional cognitive aging. AD, Alzheimer's disease; ADRD, Alzheimer's disease and related dementias; ATN, amyloid/tau/neurodegeneration framework; LASAS, Latin American SuperAgers Study; LEARN-AD, Life-Course Epidemiology of Aging, Resilience, and Neurodegeneration in Alzheimer's Disease; MCI, mild cognitive impairment.

considered to enable a more comprehensive characterization of biological pathways associated with resilience and resistance beyond the core ATN framework.

Analyses will emphasize descriptive summaries, group comparisons, and exploratory evaluations of genetic and proteomic markers when available.

For the primary analyses in LEARN-AD, comparing cognitively defined groups, we selected a conservative minimum sample size to ensure stable multivariable modeling of risk, protective, psychosocial, and biological factors. A total sample of 240 participants (≈ 120 per group) provides the minimum needed to support regression models with up to 8 predictors, yielding ≈ 12 to 15 observations per parameter (consistent with events per variable recommendations to minimize overfitting and unstable coefficient estimates). This sample size ensures adequate precision for detecting meaningful between-group differences in risk-factor, psychosocial, and ATN profiles while maintaining model stability across participating countries. For LASAS, the primary comparison is between individuals who meet SuperAger

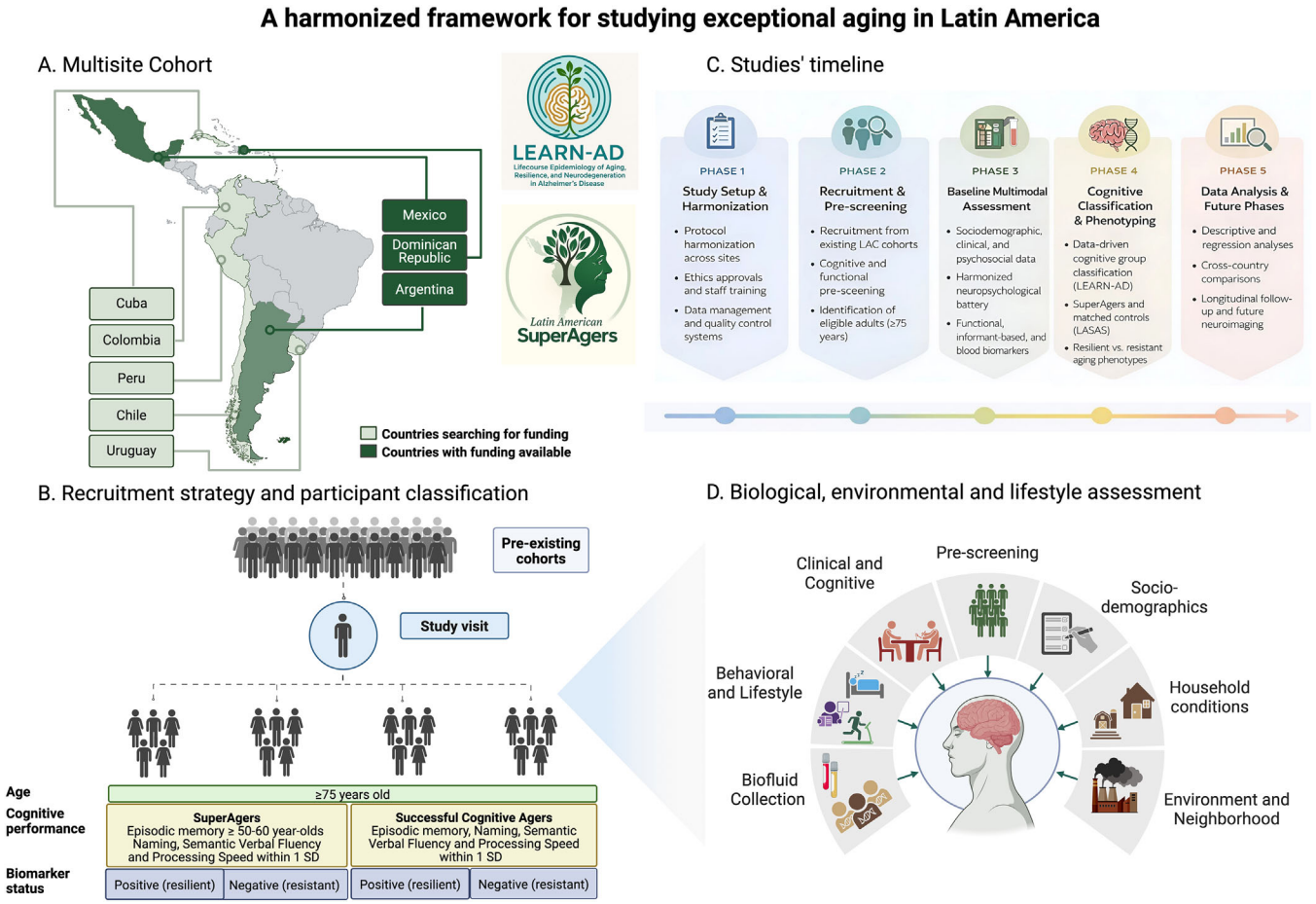

FIGURE 2 Integrated conceptual and operational framework for the LEARN-AD and LASAS studies across Latin America and the Caribbean. A, Participating sites across Latin America and the Caribbean; dark green represents countries funded to be included in phase 1, light green represents countries with existing aging cohorts to be included upon securing additional funds. B, Recruitment pipeline and participant classification strategy, combining existing population-based and clinic-based cohorts to identify successful cognitive agers and high cognitive performing agers (SuperAgers). C, Study timeline and phased workflow, illustrating the progression from study set-up to data analysis and future steps. D, Multidimensional assessment domains integrated across LEARN-AD and LASAS—cognitive and clinical evaluation, psychosocial and behavioral measures, biological and genetic profiling, and environmental and lifestyle characterization—providing a harmonized framework for studying cognitive resilience and exceptional aging. LAC, Latin America and Caribbean; LASAS, Latin American SuperAgers Study; LEARN-AD, Life-Course Epidemiology of Aging, Resilience, and Neurodegeneration in Alzheimer's Disease; SD, standard deviation.

criteria and age- and education-matched older adults. We selected a conservative, robust sample size to ensure model stability and adequate statistical power across participating countries. We propose a balanced design of 240 participants total (120 SuperAgers and 120 successful cognitive agers), with balanced recruitment across the three participating sites (≈ 80 participants per country: 40 SuperAgers and 40 successful cognitive agers per site). This choice yields ≈ 15 events per variable (EPV) when fitting models with up to eight predictors total (age, sex, education, and at least four lifestyle factors), which is consistent with conservative recommendations to minimize overfitting and bias in regression coefficient estimates. The balanced sample (120 SuperAgers total) allows reliable estimation of moderate-to-small effects, with ≥ 80% statistical power ($\alpha = 0.05$) to detect odds ratios of ≈ ≥ 1.5 for key protective factors. This design produces narrower confidence intervals and greater stability compared to smaller or minimally powered designs (e.g., 160 participants total with 80 SuperAgers), increasing power, reducing estimator variance, and improving robustness to predict collinearity and missing data. Country will be included as a covariate or stratification variable in the multivariable models to account for regional differences.

2.8.1 | Screening considerations

The minimal target sample sizes are feasible because LEARN-AD and LASAS recruit directly from large, well-established cohorts in Latin America that provide up-to-date cognitive and functional data for efficient pre-screening.

The Fleni Aging Cohort (Argentina) is a longitudinal cohort of older adults with detailed cognitive, functional, and clinical assessments conducted under standardized protocols. The cohort includes a substantial number of individuals aged ≥ 75 with

preserved independence, providing a strong base for identifying successful cognitive agers, resilient individuals, and potential SuperAgers.

The 10/66 Dementia Research Group Study (initial phase will include Mexico and Dominican Republic) is a large, community-based cohort with harmonized cognitive and functional assessments collected across multiple waves. The cohort includes thousands of older adults and offers extensive representation of sociocultural and educational diversity. These existing cohorts collectively include > 2300 older adults aged ≥ 75 years, with ≈ 600 meeting initial pre-screening criteria for inclusion, supporting efficient pre-screening for LEARN-AD cognitive groups and subselection into LASAS. Because SuperAgers represent a selected subgroup within the larger LEARN-AD group, the number of participants to screen depends on the prevalence of the SuperAgers phenotype in source cohorts and on conversion rates. Assuming a conservative 10% prevalence of SuperAgers among screened candidates and a 25% buffer for ineligibility and non-participation, ≈ 1500 candidates must be screened to reach 120 SuperAgers across all sites (≈ 375 screened per country). If local prevalence is higher (e.g., 20%), the screening burden decreases substantially (≈ 750 screened total, or ≈ 190 per country). We will implement an initial pilot screening exercise to estimate site-specific SuperAgers prevalence and to refine recruitment targets. Enrichment strategies, such as preselecting candidates with high prior cognitive scores from existing cohorts, will substantially reduce the screening workload and improve recruitment efficiency. As additional funding becomes available, LEARN-AD and LASAS can incorporate existing cohorts from other LAC countries, further enhancing recruitment feasibility and regional representation.

3 | DISCUSSION

The LEARN-AD and LASAS initiatives represent a coordinated, large-scale effort to investigate cognitive resilience, resistance, and exceptional aging across LAC countries. By integrating harmonized multimodal assessments across diverse sociocultural contexts, LEARN-AD and LASAS build a foundational framework for examining the biological, psychological, and environmental mechanisms that sustain cognitive health in late life.

LEARN-AD and LASAS will advance the field by adopting a multidimensional, life-course perspective that incorporates cognitive, psychosocial, biological, and environmental factors in one of the fastest-aging yet least represented regions in global dementia research. This approach moves beyond deficit-based models and emphasizes adaptation, compensation, and maintenance as key processes in successful cognitive aging.[4] In addition, LASAS will establish the first deeply phenotyped SuperAger cohort in Latin America, enabling the characterization of diverse individuals with exceptional cognitive performance despite advanced age. LASAS will also adapt SuperAging criteria to regional realities, such as shorter life expectancy,[13] variable literacy, and socioeconomic heterogeneity, ensuring that the construct remains valid and inclusive.[14] Use of the classical criterion[6] allows cross-cohort comparability and generation of evidence relevant to populations with lower average education levels.

Together, these initiatives create an unprecedented opportunity to explore resilience and resistance among cognitively normal older adults in a region marked by rapid demographic aging, cultural diversity, socioeconomic disparities, and historic underrepresentation in large-scale studies. By integrating harmonized cognitive, clinical, psychosocial, genetic, and proteomic data, LEARN-AD and LASAS enable a rich, multidimensional characterization of aging under conditions of heightened ADRD risk and demographic variability. Importantly, the limited representation of Latin American populations in prior research constrains not only external validity but also the internal validity of prevailing models of cognitive reserve, resilience, and resistance, which have largely been derived from relatively homogeneous cohorts in HICs. In LMICs, particularly across LAC, life-course exposures relevant to cognitive aging differ not only in magnitude but also in structure. Education attainment spans an unusually wide distribution, ranging from illiteracy and incomplete primary education to highly educated subgroups, often within the same communities. Socioeconomic inequality is substantially greater than in most HICs, generating pronounced within-country variation in income, occupational complexity, nutrition, health-care access, and vascular risk across the lifespan. These exposure contrasts with distinct genetic ancestries, variable treatment of cardiometabolic conditions, and sociocultural contexts, shaped by both strong family networks and chronic structural stressors—are increasingly compressed or absent in HIC cohorts. As a result, research conducted in Latin America offers a unique opportunity to disentangle the independent and interactive effects of social, biological, and environmental factors on cognitive aging. Insights derived from these populations therefore contribute not only to equity and inclusion, but also to a more accurate and mechanistically informative understanding of cognitive reserve, resilience, and neurodegenerative disease across populations.

LEARN-AD and LASAS have several methodological strengths that enhance the impact of these studies. Leveraging existing, well-characterized cohorts improves feasibility and reduces screen failure rates while ensuring access to a broad spectrum of cognitive aging trajectories. Harmonized assessments, standardized procedures, and alignment with established initiatives including the SuperAger Research Initiative at the University of Chicago Healthy Aging & Alzheimer's Research Care (HAARC) Center and other international efforts; will support cross-site comparability and expand global diversity in SuperAging research. Alignment with multinational prevention programs such as LatAm-FINGERS[23] also provides the basis for culturally sensitive interventions aimed at strengthening cognitive reserve and resilience.

LEARN-AD and LASAS also face challenges. Differences in education quality, literacy, and cultural practices require careful interpretation of cognitive scores, even with harmonized protocols. Variation in infrastructure, testing environments, and participant characteristics may introduce heterogeneity that limits certain comparisons. In addition, although LEARN-AD and LASAS include culturally diverse

populations, the current protocol has been implemented in Spanish-speaking countries, with the capacity for adaptation to Portuguese where appropriate. As the study expands and additional countries and cohorts are incorporated, the inclusion of individuals who primarily speak indigenous or other non-Spanish languages will need to be explicitly addressed through further cultural and linguistic adaptation of study instruments.

Looking ahead, LEARN-AD and LASAS will enable longitudinal analyses to delineate cognitive trajectories and dynamic molecular and psychosocial changes. Future phases will incorporate neuroimaging to characterize structural and functional correlates of resilience and expand the network to recruit in other LAC countries. Comparative analyses with international cohorts from HICs will help identify both universal and context-specific determinants of cognitive resilience. Ultimately, insights from these studies may inform regionally grounded prevention strategies, interventions to strengthen cognitive reserve, and a more equitable understanding of aging and brain health globally. A key contribution is capacity building and collaboration among Fleni, Washington University in St. Louis, and Latin American academic institutions which will strengthen regional research infrastructure through shared standards, harmonized methodologies, and training opportunities, laying the foundation for a sustainable scientific network dedicated to dementia prevention and healthy aging across the region.

ACKNOWLEDGMENTS

We acknowledge the contributions of the investigators and research teams across all participating Latin American and Caribbean sites, as well as the SuperAging Research Initiative, whose collaboration enabled the development and harmonization of the LEARN-AD and LASAS protocols. We also thank the institutional partners for supporting cohort integration, methodological standardization, and coordination activities across the network. This work is supported by the Alzheimer's Association (ALZSI-25-1464205, AARG-25-1485687, 24HPE-1287320), which provides funding for the development, coordination, and implementation of the LEARN-AD and LASAS protocols. The funding agency had no involvement in the design of the study, the analysis plan, or the writing of this manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Alzheimer's Association.

CONFLICT OF INTEREST STATEMENT

L. Crivelli reports support from the Alzheimer's Association (AARG-25-1485687) and additional grants or contracts (Alzheimer's Association, Alzheimer's Disease Data Initiative, NIH 3R01AG081394-02S1). She has also received support for attending meetings and/or travel from the Alzheimer's Association, as well as leadership or fiduciary roles in the WHO Guideline Post-COVID Workgroup and World Young Leaders in Dementia (WYLD). A. L. Sosa reports grants from the Alzheimer's Association. E. Surace reports support for attending the Alzheimer's Association Satellite Symposium in Lima, Perú, in 2025. D. Aguillón reports receiving grants from the National Institutes of Health (NIH), as well as honoraria for participation on an Advisory Board for Eli Lilly Colombia. L. Duque Peñailillo reports receiving grants from the Alzheimer's Association (LatAm-FINGERS Study). N. Custodio reports support from NIH (AG057234, 24AARG-D-1246942, R56AG069118-01, SG-21-715176-LatAm-FINGERS). He has also received payment for expert testimony on cognitive health and Alzheimer's disease diagnosis and management support by WebMD. A. Damian reports support for attending the Neuroscience Next Buenos Aires Hub in 2025, organized by the Alzheimer's Association. M. Prina reports support from the Alzheimer's Association (24HPE-1287320 and additional grants or contracts (NIHR Policy Research Unit in Dementia and Neurodegeneration: NIHR206120). He has also received consulting fees from Phoenix's Group, honoraria for participation in Wellcome Trust Grant Panels, and support for attending meetings and/or travel (UK-China Health Research Alliance). E. Rogalski reports support from the NIH and grants from the Simons Foundation, as well as support for attending as an invited speaker. She has also received honoraria for lectures and leadership or fiduciary roles (ADRC Imaging Core Steering Committee; Medical Advisory Committee Member for AFTD; Faculty Advisory Committee; External Advisory Committee, Center for Health Equity in Cognitive Aging - Joining Population Science and Health Promotion; and Aging and Neurodegeneration Review Branch at CSR, Cognitive Disorder and Brain Aging, NIH). J. J. Llibre-Guerra reports support from the Alzheimer's Association (ALZSI-25-1464205 and 24HPE-1287320) and additional grants or contracts (K01AG073526, MJFF-020770, AARFD-21-851415, SG-20-690363, 24HPE-1287320). The remaining authors declare that they have no conflicts of interest to disclose. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All participants enrolled in the LEARN-AD and LASAS studies will provide written informed consent prior to participation, in accordance with the respective study protocols and local institutional ethics approvals.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Crivelli L, Fernandez R, Corvalán N, et al. A harmonized framework for studying exceptional cognitive aging in Latin America. *Alzheimer's Dement*. 2026;22:e71373. https://doi.org/10.1002/alz.71373