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REVIEW ARTICLE

Driving research on successful aging and neuroprotection in Latin America: Insights from the inaugural symposium on brain resilience and healthy longevity

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Abstract

INTRODUCTION: Global life expectancy has steadily increased in recent decades, resulting in a significant rise in the number of individuals aged 80 years and older. This trend is also evident in Latin America, where life expectancy is improving, though at varying rates across countries and regions.

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METHODS: Partnering with the Neurosciences Group of Antioquia (GNA), we launched a Colombian study on resilience in families with autosomal dominant Alzheimer's disease and the oldest-old population. Over the past 2 years, the project has expanded to include participants from Peru, Chile, and Costa Rica.

RESULTS: This research led to the first symposium on Brain Resilience and Healthy Longevity, held in Medellín, Colombia, in August 2024.

DISCUSSION: The article summarizes key discussions from the symposium, highlighting the most promising opportunities for brain resilience and prevention research in the region and offering recommendations for future research to promote healthy aging and dementia-free communities.

KEYWORDS
Alzheimer's resistance, brain resilience, healthy aging, Latin America, oldest-old

Highlights

- Uncovering the genetic and physiological drivers of cognitive resilience, neurodegeneration resistance, and healthy longevity is essential for maintaining brain function as we age.
- "Superagers" and cognitively resilient individuals from Latin American families with Alzheimer's disease offer valuable insights into brain protection mechanisms.
- Studying the interplay of socio-environmental and genetic factors in the oldest-old is key to understanding healthy longevity and improving dementia prevention.
- The inaugural Brain Resilience and Healthy Longevity Symposium highlights the need for global collaboration to uncover factors that drive cognitive resilience and healthy aging in Latin America, advancing dementia prevention.

1 | INTRODUCTION

Life expectancy has steadily increased in recent decades, with the United Nations projecting a dramatic rise in the number of people aged 80 years and older—from 137 million in 2017 to 425 million by 2050. This global trend is mirrored in Latin America, where life expectancy is also improving, though at varying rates across different countries and regions.[1] Despite these overall gains, significant disparities persist throughout the region. Key factors driving this trend include advancements in healthcare, enhanced sanitation, broader access to education, and economic growth in many parts of Latin America.[2]

As people age, the risk of developing cognitive impairment and dementia increases.[3] However, many older adults maintain their cognitive abilities, demonstrating significant resilience against decline and experiencing minimal cognitive concerns.[4] This phenomenon, known as cognitive resilience, refers to the ability to preserve cognitive function despite the presence of pathological features commonly associated with Alzheimer's disease (AD), such as amyloid plaques and tau tangles[5] (See Table 1). Notably, about one-third of elderly individuals show plaque and tangle levels typical of AD but never develop dementia, suggesting that factors beyond these brain pathologies play a critical role in maintaining cognitive health.[6] Another key concept, resistance in AD, refers to the ability to avoid or limit the accumulation of amyloid and tau, even in those with genetic risk factors that usually predispose them to Alzheimer's.[5] While resilience remains less understood, it underscores the importance of protective mechanisms that can prevent or delay the onset of dementia, despite the presence of these key pathological markers. A significant challenge in understanding both resilience and resistance, particularly in Latin America, is the underrepresentation of ethnically and geographically diverse populations in aging research, which limits our ability to fully understand the factors that support healthy aging in these communities.

Dr. Francisco Lopera spent over three decades studying a Colombian family with the Presenilin-1 (*PSEN1*) E280A mutation (the Paisa mutation), which causes early-onset AD.[7,8] In 2019, his team and international collaborators identified a rare case of extreme resistance to Alzheimer's in a family member carrying the mutation. This individual carried the apolipoprotein E3 Christchurch (*APOE3ChC*) variant, which appears to protect against Alzheimer's by limiting tau pathology despite high amyloid levels.[9] In 2023, they identified a second resilient case in the same family, a man who, despite the Paisa mutation, remained cognitively healthy until age 67. Brain scans revealed significant amyloid plaques and tau tangles, but minimal tau damage in the entorhinal cortex. Genetic analysis identified a rare

TABLE 1 Cognitive resilience and AD resistance.

Concept	Definition	Mechanisms
Cognitive resilience "Coping with pathology"	The ability to maintain cognitive function despite significant brain pathology.	Cognitive reserve, neural compensation, or functional network efficiency.
AD resistance "Reducing pathology"	The ability to prevent or postpone the buildup of brain pathology and reduce neurodegeneration, thereby safeguarding against cognitive decline.	Genetic protection, reduced susceptibility to pathology.

variant in the *Reelin* gene, named "*Reelin-COLBOS*," which reduces tau pathology in this key brain region.[10] These findings suggest that cognitive resilience, even in individuals at high genetic risk for Alzheimer's, may depend on specific genetic variants and brain regions, opening new avenues for developing treatments to protect the brain from Alzheimer's pathology and delay cognitive decline.

Building on research into protected cases of dementia, and in collaboration with the Grupo de Neurociencias de Antioquia (GNA), a project was launched in Colombia to investigate resilience and resistance in individuals from families with autosomal dominant forms of dementia, as well as in the oldest-old population. Over the past 2 years, this initiative has expanded to include participants from Peru, Chile, and Costa Rica.

This research laid the foundation for the inaugural symposium on Brain Resilience and Healthy Longevity, held in Medellín, Colombia, in August 2024. The event brought together leading experts to discuss recent advances in cognitive resilience, healthy aging, and dementia prevention, with a special emphasis on Latin American research. It also marked the launch of the Latin American Network for Brain Resilience and Longevity, a new platform for fostering regional collaboration. Organized by the GNA and the Multicultural Alzheimer's Prevention Program, the symposium covered a wide range of topics, including current Alzheimer's treatments, modifiable risk factors, genetic protective variants, emerging neuroprotective mechanisms, the resilience of the oldest-old, and future directions for research on centenarians. This review highlights the key discussions and underscores the urgent need for targeted efforts to advance research on cognitive resilience and healthy longevity in the region.

2 | COGNITIVE RESILIENCE AND RESISTANCE AGAINST NEURODEGENERATION AND AD PATHOLOGY

2.1 | Unraveling resilience in Alzheimer's disease: insights from exceptional brains

At the Neurobanco of the GNA at the University of Antioquia, investigators have collected over 170 brains from individuals affected by familial Alzheimer's disease (FAD), specifically those with the E280A mutation in the *PSEN1* gene. This extensive collection has enabled the group to perform a wide range of analyses in some cases, exploring factors such as gender, age, and the presence of different *APOE* alleles, and their impact on disease progression and brain pathology.[11] Among their findings, they have identified cases that deviate from the typical progression, including individuals with extended disease duration, larger brain weights, and those who developed the disease later in life. Notably, they have studied the brain of *APOE3ChC* case, and the brain of the *Reelin*-COLBOS (*RELN* H3447R) case, previously reported by the GNA.[9,10] *Post mortem* examination of the *APOEChC* case showed extended amyloid-beta (Aβ) pathology, with almost no evidence of cerebral amyloid angiopathy (CAA). Meanwhile, hyperphosphorylated Tau deposits (pTau) were scarce in several cortical areas, with almost no evidence of pTau pathology in the frontal cortex, moderate pathology in the hippocampus, and severe pathology in the occipital cortex. Single nuclei RNA sequencing revealed that resistance against pTau pathology followed an *APOE* expression gradient in glial cells, with higher levels in more protected areas, showing a more homeostatic glial signature.[12] Contrastingly, the Reelin-COLBOS case presented with severe pathology for all neuropathological hallmarks of AD, except for the entorhinal cortex, presenting with mild Ab and pTau pathology, together with higher neuronal density in the supragranular neuronal layers.[10] These remarkable cases showed two different versions of protection against AD, resistance (*APOEChC*), and resilience (*Reelin-COLBOS*), suggesting that there could be several therapeutic strategies against this disorder.

In reviewing the brains of *PSEN1* E280A carriers, the group observed that brain weight and disease duration correlate negatively ($n = 125$, $r = -0.323$, $p \leq 0.0001$). However, resilient cases, particularly those carrying the *Reelin-COLBOS* mutation, exhibit lower brain weights compared to other E280A cases—measuring 745.4 and 645.0 g for the only two brains we have with these genotypes. Along with the lower brain weight, macroscopic examination reveals atrophy, suggesting that these individuals maintain resilience at the cost of the destruction of non-essential nervous system elements, while protecting neuronal populations in critical areas, that is, the entorhinal cortex.[10] This phenomenon is also observed in the super-elderly—individuals over 100 years old who remain cognitively intact despite varying degrees of atrophy, with brain weights ranging from 1192.0 to 771.7 g. These findings point also to the protection of critical brain structures from age-related damage.

In another study involving a family with seven different neurological diseases, the group identified both disease-specific genes and several shared genes (*PCLO*, *CTBP2*, *CNTN5*) across different conditions.[13] This "tautological" phenomenon may help explain the phenotypic variability seen in affected individuals and could provide insights into common genetic pathways in AD. They believe that similar shared genetic mechanisms could play a role in AD, highlighting the importance of con-

sidering genetic interaction, pleiotropy, and epistasis in understanding disease progression and protection against disease.

Additionally, in CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) cases with the R1031C mutation in the *Notch3* gene, they observed considerable variability in disease progression and brain lesions. These findings underscore the need for more detailed quantitative neuropathological studies to better understand the genetic co-segregation patterns in AD and other neurodegenerative diseases. These quantitative studies include the application of machine learning algorithms for the assessment of pathological features, together with macroscopic 3D modeling of *post mortem* brains.

2.2 | Vascular protection by *APOE3ChC*: insights into Notch signaling, extracellular vesicle pathology, and gliovascular disruption in CADASIL and Alzheimer's disease

Astrocytes play a complex role in AD, often underappreciated due to their variable responses. Posada and colleagues at the GNA have explored the mechanisms of vascular dysfunction and inflammation in both CADASIL and autosomal dominant Alzheimer's disease (ADAD), focusing on Notch signaling alterations, extracellular vesicles (EVs), and neurovascular pathology. Histological and 3D microscopy analyses of *post mortem* samples revealed a shared pathology of mural cell deterioration and vascular inflammation in both diseases, driven by reactive astrocytes and microglia, disrupting endothelial-mural-glial coupling. Notably, *APOE3ChC* carriers exhibited increased vascular density and preserved Notch3 signaling, suggesting a protective effect against these vascular changes.

Additionally, they found that AD increases both brain microvascular and systemic EVs, with different surface markers for sporadic AD (SAD) and ADAD. SAD-EVs are linked to leukocyte-endothelium interactions, while ADAD-EVs are associated with platelets. Proteomic analysis revealed distinct molecular signatures in these EVs, including activation of inflammation and coagulation pathways, with SAD-EVs having a greater impact on the vasculature. Both EV types contribute to endothelial disruption, astrocyte hyperactivation, and neuronal death.[14,15]

Astrodegeneration and vascular deterioration were more pronounced in SAD, while ADAD was marked by hyperreactive glial responses. *APOE3ChC* carriers exhibited the least astrocytic and vascular alterations, despite a higher Aβ burden. The study also highlighted the role of astrocytic phenotypes in astroglial, gliovascular, and vascular disturbances across conditions. These findings suggest that the gliovascular unit (GVU) plays a crucial role in both AD pathogenesis and potential protection, offering new insights into the importance of gliovascular integrity.[16,17]

These results underscore the significance of *Notch3* signaling in maintaining gliovascular coupling, which supports vascular protection and homeostasis. Dysregulation of Notch3 in CADASIL and ADAD contributes to similar vascular changes in these diseases, while *APOE3ChC* preserves gliovascular coupling and protects against inflammation. This research suggests that AD may be a form of small vessel disease (SVD), with microvascular and gliovascular dysfunctions shared between CADASIL and ADAD.

Future directions include exploring the ectopic *Notch3* redistribution in immune cells, identifying potential targets for therapeutic inhibition, and determine whether *APOE3ChC*'s protective effects extend to CADASIL. These insights into Notch3 signaling and EV-mediated pathology could lead to new strategies for treating neurodegenerative diseases by targeting gliovascular integrity and inflammation.

2.3 | Nature knows best: genetic insights into Alzheimer's resistance and therapeutic potential

Arboleda-Velasquez and colleagues explored how protective genetic variants, particularly *APOE3ChC* and *Reelin-COLBOS*, challenge the traditional amyloid-tau-centered approach to Alzheimer's therapy. They discussed studies of Colombian families with ADAD,[9,10] representing a paradigm shift, suggesting that natural protective mechanisms can inspire new therapeutic strategies.

Key genetic insights are as follows:

1. *APOE3 Christchurch* variant: Associated with delayed cognitive decline despite high amyloid pathology. This variant modulates Alzheimer's pathology by interacting with heparan sulfate proteoglycans (HSPG), reducing tau aggregation and neurodegeneration[9].
2. *Reelin-COLBOS* variant: A gain-of-function variant shown to protect neurons even in the presence of amyloid and tau pathology. Its neuroprotective effects were confirmed in mice, highlighting its role in Alzheimer's resistance.[10]

Therapeutic implications:

- Converging protective pathways: Both *APOE3* Christchurch and *Reelin-COLBOS* variants promote neuronal health over amyloid and tau removal.
- Targeted therapies: Genetic insights have led to the development of treatments like the 7C11 anti-APOE antibody[18] and potential Reelin-based therapies. The anti-APOE antibody shows promise in reducing *APOE4* toxicity and preserving cognitive function.

This work underscores a novel therapeutic approach: leveraging nature's inherent protective mechanisms to counteract Alzheimer's. This concept, first proposed by Dr. Francisco Lopera,[19] opens new therapeutic avenues focusing on genetic resilience, offering hope for future Alzheimer's treatments beyond current paradigms.

2.4 | Lipid signature in AD: an early message of protection or susceptibility by *APOE* isoforms and variants

Early detection of AD-related changes, particularly through biofluid markers, has proven essential in identifying preclinical

disease stages.[20,21] Advances in high-sensitivity platforms, such as SIMOA-Quanterix, have enabled accurate quantification of key biomarkers—Aβ, tau, and neurofilament light chain- providing valuable insights into disease progression.[22,23] Lipidomic research, leveraging high-resolution mass spectrometry, has also identified significant lipid alterations linked to AD risk, particularly in individuals carrying the *PSEN1E280A* mutation and specific *APOE* isoforms.[24,25] These findings underscore the complex interplay between lipid metabolism, genetic factors, and neurodegeneration.[26]

Despite these advances, the translation of these biomarkers into clinically applicable tools, particularly in diverse populations like those in Latin America, remains limited.[27,28] Cardona-Gomez and colleagues' pilot study addresses this gap by evaluating the sensitivity, specificity, and applicability of established and novel biomarkers for AD in clinically and demographically relevant contexts.[29] They examined protein markers using SIMOA-Quanterix and lipidomic profiles[30] through high-resolution mass spectrometry in serum samples from asymptomatic and symptomatic individuals across different age groups (6–12, 13–19, 20–30, 31–40, and 41+ years).

Preliminary data show lipidomic signatures with area under the curve (AUC) values of 92%–100% in an age-dependent manner. Additionally, they performed latent profile analysis (LPA) of participants, blinded to genetic status, which revealed clear clinical clustering associated with the *PSEN1-E280A* mutation (97%) and non-carriers (85%). This analysis also identified age-related and comorbidity associations, segregating protective effects of *APOE2/2* and *APOE3/3* isoforms and susceptibility linked to APOE4/4, even in individuals as young as 6 years old. Expanding this research will help validate novel biofluid markers and contribute to the development of diagnostic tools that could be implemented across Latin America, facilitating identification of candidates for pharmacological and non-pharmacological clinical trials in AD. This study also offers new insights into the impact of *PSEN1–E280A* mutation on lipid metabolism and neurodegeneration, improving our understanding of the brain-periphery relationship in AD and informing primary prevention strategies.

2.5 | The astounding improbability of familial Alzheimer's protection from the *APOE3 Christchurch* variant

Rare events happen all the time. In fact, of all possible things that can happen, those that are unlikely are far more numerous than those that are likely. So, when rare events happen it should not be a surprise. Mutations follow this rule: Some gene variants are very common, generally considered greater than 0.5% of the population, whereas those below this frequency are far more numerous. Compared to a reference human genome, the approximately six billion-nucleotide genome sequence will have approximately 5,000,000 single nucleotide variants, approximately 600,000 insertion/deletion variants involving approximately 2,000,000 nucleotides and approximately 25,000 structural variants involving more than 20,000,000 nucleotides. By the law of large numbers, the human genome provides ample opportunity for rare events. The very rarest variants have been referred to as private mutations because they may appear in a single family, and when present over several generations are often due to a founder effect. The family that harbors the *PSEN1–E280A* mutation in Colombia, the largest family of autosomal dominant AD in the world, falls in this category. By the law of inevitability, mutations will happen somewhere to somebody, so the existence of such a mutation is no surprise.

What is a surprise is the occurrence of a second rare mutation in the same family that can exert a protective effect on the primary mutation in presenilin. The allele frequency of the *APOE*3 Christchurch variant is reported to be around 0.004%.[31] Only a very small percentage of people carry this variant; however, population-wide frequencies of rare alleles obscure the possibility of higher allele frequencies in specific populations. It is known that the frequency of the APOE Christchurch variant is higher in the very large *PSEN1E280A* family than in the overall population. At some historical point, this protective variant entered the family tree via an unknown individual.

The improbability of the rare *APOE*3ChC variant co-occurring with the autosomal dominant Alzheimer gene mutation so rare that it is probably present in only one case in the entire world, is truly against all odds. Dr. Lopera liked to say that nature found the cure for this familial form of AD. We might add that the person who brought the APOE3- Christchurch variant to the large Colombian family is reminiscent of the gypsy in Garcia Marquez's, *One Hundred Years of Solitude*, who brought the cure for memory loss to the town of Macondo.

2.6 | Decoding resilience and resistance in AD through neuroimaging and genetics

Genome-wide association studies (GWAS) have identified 98 genetic loci associated with an increased risk of late-onset AD,[32] which can be used to create a polygenic risk score (PRS) predicting AD risk with 84% accuracy.[33,34] This score strongly correlates with neuroimaging and plasma biomarkers of AD.[35] By combining PRS with amyloid and tau positron emission tomography (PET) data, we can identify individuals who exhibit resistance to pathology (lower-than-expected amyloid or tau despite genetic risk) and resilience to cognitive decline (maintaining cognitive function despite high pathological burden).

Neuroimaging studies show that resilient individuals preserve gray matter, glucose metabolism, and have reduced tau PET burden, even in the presence of high amyloid burden.[36,37] This suggests that resilience may involve resistance to tau accumulation. However, other studies highlight that cognitive preservation can occur even with high tau burden, particularly in medial temporal and precuneus, where enhanced frontoparietal functional connectivity compensates for default mode network disruption. These findings suggest multiple mechanisms of resilience.[38–40] While neuroimaging has been used to explore resilience,[41,42] the role of PRS in identifying genetic factors underlying resistance and resilience remains underexplored. To date, 18 protective variants have been identified, delaying cognitive decline in late-onset AD.[43,44] Preliminary data indicate that some variants, like APOE2, affect global amyloid accumulation, while others only protect

specific brain regions, such as precuneus. This region-specific protection highlights the complexity of AD progression, as various subtypes, such as typical AD, hippocampal-sparing, and limbic-predominant forms, show different patterns of genetic influence.[45–47]

Diez and colleagues' preliminary findings suggest that these diverse progression patterns may result from the combination of polygenic risk factors, influencing how protective variants exert their effects. However, the small sample sizes of existing GWAS datasets with both genetic and PET data limit their power. Expanding these datasets and incorporating environmental factors will be crucial to discovering novel protective variants. To improve the generalizability of these findings, efforts to include more diverse populations in neuroimaging-genetic studies are essential.

2.7 | Secondary prevention strategies for Alzheimer's disease using monoclonal antibodies targeting Aβ protein

Therapeutic strategies inspired by genes associated with resistance and resilience may eventually lead to effective treatments. In the meantime, the current pharmacological approach for treating late-stage AD relies on high doses of anticholinesterase drugs (such as rivastigmine, galantamine, and donepezil), combined with the NMDA receptor antagonist Memantine. This treatment is most effective when started in the mild stages (Clinical Dementia Rating Scale-Sum of Boxes [CDR-SB] 3-9) and continued until the terminal stage (CDR-SB $\geq$16), slightly modifying cognitive and functional decline, with effects lasting up to 36 months.[48–50] When combined with non-pharmacological interventions—such as regular physical exercise, a healthy diet, and cognitive stimulation—the efficacy of medications can improve by 15%–25%,[51–53] potentially delaying AD progression by 2–4 years and reducing dementia prevalence by 15%–20% in the next 5 years.[54]

Tertiary prevention efforts have recently shifted toward more effectively targeting the specific neuropathology of AD. A key pathological hallmark of AD is the accumulation of abnormal Aβ protein oligomers (42 amino acids) in the extracellular space, a process that begins up to three decades before the onset of symptoms.[20,55] This strategy involves the use of monoclonal antibodies designed to neutralize and clear toxic Aβ oligomers while sparing soluble Aβ monomers of 40 amino acids. These antibodies aim to mitigate progressive synaptic alterations caused by oligomer/plaque deposition.

Monoclonal antibodies such as lecanemab and donanemab, which target Aβ, have shown promise in treating early-stage AD.[56] Lecanemab has demonstrated significant efficacy in reducing amyloid plaques and slowing cognitive decline in patients with early AD (CDR-SB 1-6).[57,58] Similarly, donanemab's effectiveness appears to be influenced by tau protein levels, showing greater efficacy in patients with low tau PET,[59,60] suggesting that early intervention prior to significant tau accumulation may have a more pronounced impact on slowing disease progression.[59,60]

However, several factors may affect the timing and outcomes of such treatments.[61] While amyloid reduction is achieved, cognitive improvements might be delayed due to the time required for synaptic repair and neuronal stabilization. Moreover, cognitive decline in AD is influenced by multiple factors beyond amyloid, including tau pathology, neuroinflammation, vascular changes, and comorbidities, which vary among individuals. Additionally, the efficacy of amyloid-reducing therapies may be limited if target engagement is sub optimal or treatment is initiated too late in the disease course or if factors other than amyloid are more directly linked to cognitive decline.[62]

These findings underscore the potential value of clinical trials in asymptomatic individuals over 60, with biomarkers indicating early-stage neuropathology. Such early interventions could help delay AD onset by up to 5 years. Combined with existing tertiary prevention strategies, this could result in a 10-year delay in disease progression,[63] potentially reducing AD prevalence by 80% over the next decade. Predictive models suggest this shift could delay the onset of AD from the 60–79 age range to 70–79 and reduce the prevalence in those over 95 from 78% to 20%.[54]

2.8 | Protective lifestyle and genetic factors against cognitive decline

While one goal is to identify mechanisms of resistance and resilience against neurodegeneration, other genetic modifiers, environmental factors, and lifestyle conditions can also have a cumulative effect on protection or risk in neurodegeneration. Identifying factors that counteract cognitive decline and promote resilience in aging is a critical area of research. In one study, Pluim et al. explored the role of a strong sense of purpose in life (PiL) among older Latino adults, as it has been linked to better psychological well-being, health, and longevity,[64] and may mitigate the impact of AD-related pathology on cognition. In a cohort of 64 Spanish-speaking Latinos from the Boston Latino Aging Study (BLAST), PiL was assessed using a 10-item questionnaire, and cognitive function was measured with the Mini-Mental State Examination (MMSE),[65] and the Free and Cued Selective Reminding Test (FCSRT).[66] The results indicated that higher PiL was associated with better cognitive performance, including higher MMSE scores ($\beta = 2$, $p < 0.006$) and higher FCSRT scores ($\beta = 5.6$, $p < 0.011$). These findings suggest that PiL may play a protective role in cognitive aging, particularly in the Latino population.

In a separate study examining genetic and environmental factors influencing cognitive decline in ADAD, Langella et al. analyzed data from 675 *PSEN1E280A* mutation carriers and 594 non-carriers from the largest known ADAD kindred.[67] They found that the ε4 allele of the *APOE4* gene and education level both impacted the clinical onset of dementia, with *APOE4* carriers showing earlier cognitive decline. Specifically, MMSE scores began to diverge by age 45, with *APOE4* carriers demonstrating faster cognitive impairment compared to non-carriers. Furthermore, the interaction between *APOE4* and education level showed that higher education provided a protective effect against accelerated cognitive decline.

Together, these studies highlight the complex interplay between genetic, environmental, and psychosocial factors in cognitive resilience. While genetic factors like *APOE4* and educational attainment significantly influence the course of cognitive decline in ADAD,

psychosocial factors, such as a strong sense of PiL, may offer additional protective benefits against cognitive impairment, particularly in aging populations. Further research using advanced neuroimaging techniques and larger, more diverse samples is needed to deepen our understanding of how PiL interacts with genetic and lifestyle factors in protecting against dementia.

2.9 | Resilience from the brain to the muscle: understanding frailty in aging

Observations in medicine have long been vital for understanding disease processes. Examining the iconic image of Auguste Deter, one can infer that the impairment extends beyond cognitive symptoms, with notable involvement of facial and hand muscles, suggesting an early link between brain disease and muscle tissue.

Recent research underscores the temporal relationship between muscle and brain degeneration. As both organs undergo pathological changes, muscle tissue is replaced by fat, while brain matter is replaced by cerebrospinal fluid. Emerging evidence highlights muscle's endocrine role, with myokines like brain-derived neurotrophic factor (BDNF), FNDC5/Irisin, and insuin-like growth factor-1 (IGF-1) influencing brain function, including neuronal growth, neuroplasticity, memory, learning, and inflammation.[68]

Could loss of muscle function predict cognitive decline? Studies show that slowed performance in muscle tests, like the Timed Up and Go (TUG) test,[69] correlates with accelerated cognitive decline, as assessed by CERAD[70] and MMSE.[71,72] Our group has observed similar trends in Colombia, linking gait speed and cognitive decline in studies like SABE Bogotá and SABE Colombia, with established cutoff points for grip strength and gait speed to identify at-risk individuals.[73–75]

Low muscle mass is also associated with cognitive impairment. The Canadian Longitudinal Study on Aging found that reduced muscle mass is linked to poorer executive function and psychomotor speed,[76] while tongue muscle mass, measured by MRI, was associated with reduced hippocampal volume in Lewy body dementia.[77]

Frailty syndrome, a reversible condition marked by diminished stress responses, is closely tied to both muscle and brain dysfunction. It is associated with cognitive decline and dementia,[78] especially vascular dementia,[79] and is predictive of dementia risk in Parkinson's disease.[80] Because frailty is modifiable, its identification and treatment are crucial in protecting brain function and improving outcomes in those with dementia and frailty.[81–83]

3 | ASSESSING RESILIENCE AND PROTECTION FOR HEALTHY LONGEVITY IN THE OLDEST OLD

Building on the discussion of resilience across systems and the role of protective lifestyle and genetic factors in mitigating cognitive decline, it is essential to consider how these elements contribute to healthy longevity, particularly in the oldest old. This demographic, often defined as individuals over the age of 80, provides a unique opportunity to study the interplay of resilience and protection at the intersection of advanced age and functional health. Understanding how cognitive, physical, and systemic resilience aligns with protective factors in this population can reveal strategies for promoting longevity while maintaining quality of life. The following section focuses on assessing resilience and protective mechanisms in the oldest old in Latin America, shedding light on some biological, environmental, and lifestyle factors that underpin healthy aging in this exceptional group.

3.1 | Functional ability and healthy aging in Chilean adults

The World Health Organization (WHO) defines healthy aging as the ongoing process of maintaining the functional ability that supports well-being in older age.[84] Functional ability refers to the health-related traits that enable people to do what they value in life.[85] This is particularly important in neurocognitive disorders, where functional impairment is a key factor in differentiating mild cognitive impairment (MCI) from dementia.[86]

However, the relationship between healthy aging, MCI, and dementia based on functional ability is still unclear. Older adults without cognitive impairment often experience limitations in activities of daily living (ADL), influenced by sociocultural factors.[87] Additionally, age-related conditions like motor, sensory, or cognitive decline can cause functional impairments.

Defining functional ability is a challenge, especially as diagnostic criteria for MCI and dementia evolve. Early MCI criteria excluded functional impairment, while newer definitions include ADL difficulties.[88] Similarly, while the DSM-IV defined dementia by "significant functional impairment," DSM-5 requires impairment that prevents independence.[86]

Challenges in evaluating functional ability: Assessing functional ability in older adults is complex, as cultural, educational, and gender factors significantly influence how functional impairments are perceived. In some societies, elders may rely on others for administrative tasks due to limited education or illiteracy, making standard assessments of ADLs potentially biased.[89,90] Gender, age, and culture further shape how functional decline is evaluated, highlighting the need for context-specific assessments.[91]

To address this, two key questions are proposed[1]: What ADLs are essential for independence, considering environmental and individual factors like age, gender, and cognitive abilities?[2] How can functional ability differentiate healthy aging from pathology, accounting for individual differences and environmental demands?[87]

Current ADL assessments often miss critical aspects of functionality, such as the use of compensatory strategies (e.g., alarms, lists, help-seeking) and social, cognitive, and movement abilities, which are key in both healthy aging and neurocognitive disorders.[92,93] Slachevsky and colleagues advocate for a multidimensional approach to better capture the full scope of functional ability and its deviations.

In conclusion, functionality is a multidimensional concept, encompassing physical, cognitive, social, and cultural factors.[87] To accurately

distinguish healthy aging from neurocognitive decline, assessments must consider these variables, posing a challenge in developing culturally sensitive tools for effective measurement.

3.2 | Cognitive resilience in the oldest-old: two studies with people aged 90 and older

The "oldest-old" (ages 80 and older) are the fastest-growing demographic worldwide, with projections showing sharp increases, especially in countries like China and Colombia. By 2060, the number of oldest-old individuals in Colombia could rise by over 600%, from 150,000 to 1.1 million.[94]

Dementia risk escalates exponentially with age, with the risk reaching about 40% per year in centenarians.[95] As the oldest-old population grows, dementia is becoming a major public health issue. At this advanced age, dementia often results from multiple neuropathologies.[96,97] While Alzheimer's is commonly associated with dementia, conditions like LATE-NC, hippocampal sclerosis, Lewy body disease (LBD), and vascular changes are also prevalent, and many can only be diagnosed *post mortem*.

Cognitive resilience refers to the ability to maintain cognitive function despite brain changes or pathology.[98] The oldest-old are ideal for studying this resilience, as they often exhibit resistance to cognitive decline despite common neuropathologies. Studies like the 90+ Study and Life After 90 have shown that fewer than 20% of participants are considered SuperAgers—those who remain cognitively normal despite age-related brain changes.[99] SuperAgers tend to show greater cortical thickness and resilience to Alzheimer's pathology, though they also show resistance to other conditions like LBD or hippocampal sclerosis.[100,101]

Despite these findings, no clear lifestyle factors have been identified to explain resilience, highlighting the need for further research. Additionally, most aging studies have focused on predominantly white, European populations, limiting their applicability to diverse ethnic groups. Increasing diversity in research is critical, as exemplified by multiethnic studies like Life After 90.[102]

In conclusion, studying the oldest-old is crucial for understanding dementia and cognitive resilience. With a rising population at risk, research must address various neuropathologies, not just Alzheimer's, to develop effective strategies for maintaining cognitive function at advanced ages.

3.3 | Brain resilience and resistance in older Andean adults from Peru

Dementia is shaped by a combination of biological, socioeconomic, and social factors that impact both its prevalence and presentation.[103] Research in Peru indicates an increase in dementia cases, particularly among individuals with lower levels of education or those residing in disadvantaged urban areas, while rural regions show a lower prevalence.

Peru's diverse population—80% Native American—[104], mostly located in the Andean region, has shown important variations in the epidemiology of dementia. For example, a study in Arequipa (southern Andes) found dementia prevalence lower than in Lima, with key risk factors linked to education and socioeconomic status, while cardiovascular factors seemed less impactful. Although cardiometabolic diseases are increasing along the Peruvian coast and in some urban areas of the Andes, residents of rural Andean Mountain regions generally have lower body mass indexes and reduced rates of hypertension and diabetes.[103,105] These cardiovascular risk factors are even less prevalent at higher altitudes, potentially contributing to brain resilience against dementia.[104,105] Similar findings have been reported in other Native American populations. For instance, among Bolivian forager-farmers, only one case of atrial fibrillation, a condition typically linked to aging, hypertension, obesity, chronic inflammation, and diabetes, was recorded out of 1314 participants. This lower risk of cardiometabolic diseases in Native American groups is thought to result from high levels of physical activity and diets that are fiber-rich and low in ultra-processed carbohydrates.[106]

On the other hand, bilingualism appears to be a protective factor, especially for illiterate Andean individuals.[107] A recent study suggests that bilingualism mitigates the effects of the APOE e4 gene, reducing dementia risk.[108] Additionally, a pilot study of older high-performing adults (superagers) in Peru found superior cognitive performance, compared to adults 15–20 years younger, along with an EEG profile indicative of brain resistance.[109] These factors—low cardiovascular risk, bilingualism, and ethnicity—suggest a convergence of elements promoting both brain resistance and cognitive resilience in Peru.

This research highlights the need to further explore these protective factors by incorporating biomarkers, neuroimaging, and cognitive testing. Ongoing projects in Peru are addressing these issues using p-tau 217 plasma biomarkers,[110] volumetric MRI, and language markers in native languages.[111] It is also important considering social determinants of health to understand the broader mechanisms influencing brain and cognitive resilience in Peru's older population.

3.4 | Thriving into old age: the Costa Rican model of successful aging

Costa Rica, with a population of nearly 5 million, has 10.1% of its people aged 65 years and older, reflecting a growing trend of population aging. The country's fertility rate is ultra-low at 1.3, and the aging population is increasingly impacting social security and the economy.[112]

Costa Rica has a universal health system organized into three regions with primary care units that cover about 4000 people each. This system, along with a reliable national registry, enabled the development of the Costa Rica Longevity and Healthy Aging Study, which began in 2005.[113] This longitudinal study tracks a representative sample of people born in 1946, including biological markers, longevity, life expectancy, and lifestyle factors. The study revealed a region in the Pacific coast—specifically the Chorotega region—with mortality rates 29% lower than the rest of the country and some of the highest

life expectancies globally.[114] This region also shows longer telomeres, a sign of longevity.[115] Research highlights that the health system, combined with possible genetic factors, may explain these findings.

Costa Rica's life expectancy is 13% higher than that of 13 high-income countries, with men living an additional 14% longer. The average age of men over 90 in Chorotega is 4.4 years older than those in other countries with similar data.[116] However, recent studies show a potential decline in this longevity advantage. In response, Costa Rica is developing regional policies to preserve the longevity zone, making further research into this phenomenon a priority.

3.5 | Clinical and neuropsychological study of people over 80 years old in Colombia

Colombia is home to over 6 million elderly individuals, including 22,945 centenarians.[117] Some of these individuals maintain exceptional physical and cognitive function, suggesting that physical decline could serve as an early indicator of cognitive impairment in older adults. Studying this population could help identify protective factors. Our study aims to describe the clinical and neuropsychological characteristics of individuals over 80 years old in Colombia. Adults aged 80 years and above were included, without apparent cognitive impairment, via snowball sampling. Participants underwent medical evaluations [gait speed, grip strength, Clinical Frailty Scale (CFS), cognitive-motor risk syndrome], neuropsychological (MMSE, CERAD), emotional (GAD-7, GDS [Geriatric Depression Scale]), and functional (FAST, Lawton & Brody Index, Barthel Index) assessments[65,118–123] either at home or in an office setting. Data were analyzed using Kruskal-Wallis, Mann-Whitney-Wilcoxon tests, and Spearman correlation.

A total of 89 participants (80% women, 53% aged 90–99 years, 50% with ≤5 years of schooling) were assessed. The median MMSE score was 22 for women and 24.5 for men. Seventy-four percent had no depression (GDS < 5), 55% had no anxiety (GAD-7 < 5), and 62% showed no impairment in instrumental ADLs (FAST 1-3). Of the 72 participants with CFS data, 57% were not frail, and 64% had no cognitive-motor syndrome. MMSE scores correlated with frailty ((K-W $p < 0.001$) and grip strength ($\rho = 0.4$, $p = 0.06$), but not gait speed ($p = 0.18$). FAST scores correlated with frailty (K-W $p < 0.001$), gait speed ($\rho = -0.36$, $p = 0.042$), and grip strength ($\rho = -0.34$, $p = 0.026$). This study underscores the importance of understanding the physical and cognitive factors contributing to healthy aging. The findings suggest that some elderly individuals may experience a dissociation between physical frailty and cognitive impairment, warranting further investigation into potential protective factors.

3.6 | Exceptional cases of cognitive resilience in the oldest-old from Colombia

In Colombia, most neuropsychological studies on older adults focus on individuals up to 85 years old. However, with an increasing number of centenarians, there is a growing need to understand the cognitive and functional characteristics of this population. The ongoing "Resist Alzheimer's Project" aims to explore neuropsychological profiles, genetics, and biomarkers in people over 80, with 112 participants recruited so far, including 26 centenarians. The cognitive and functional profiles of five centenarians (ages 100–105 years) without dementia, considered examples of cognitive resilience are discussed. Participants underwent a variety of cognitive and functional assessments, with preliminary data compared to normative values for individuals over 85. All five centenarians performed on the average range on the MMSE (median = 26) and demonstrated orientation. They correctly performed auditory attention tasks[124] (median Digit Span forward Wechsler Adult Intelligence Scale [WAIS] = 5.5) but required longer time during visual attention tasks[125] (median Trail Making Test A = 160 s). Their praxis abilities were on the average range[126,127] (Median CERAD praxis = 10, median semi-complex figure = 9.5). Although free verbal recall was limited, they properly performed recognition tasks[126] (median CERAD delay recall = 3; recognition = 8). Performance in lexical access tasks[126] was variable among participants (median semantic fluency = 12; BTN-15 = 9.5). Most were independent in basic daily activities but showed slight dependence in instrumental activities, mainly due to motor and sensory changes. These findings emphasize the need for tailored diagnostic criteria, normative data, and interdisciplinary assessments for centenarians, as well as the importance of adjusting evaluation tools to their specific health conditions.

4 | CONCLUSION

Cognitive resilience, resistance to neurodegeneration and pathology, and healthy longevity are interconnected facets of a single phenomenon—reflecting the brain's extraordinary capacity to develop and maintain protective mechanisms that preserve its function and stability over time. These mechanisms can compensate for neurodegenerative processes or cellular aging, helping the brain maintain its vitality for longer. Whether rooted in genetics, shaped by lifestyle choices, or influenced by the environment, this brain resilience creates a phenotype robust enough to support individuals who remain cognitively unimpaired well beyond the typical age of onset for neurodegenerative diseases (such as in hereditary dementia cohorts), or the usual age-related cognitive decline observed in the general population. Identifying these individuals and understanding the unique protective mechanisms at play is key to advancing translational research in neurodegeneration and aging.

In recent years, Latin America has emerged as a treasure trove of such exceptional cases. Breakthroughs in understanding FAD extreme resistance, the identification of "superagers" clusters, and even the discovery of regions with unusually high concentrations of cognitively resilient individuals are shining examples of the rich cultural and biological diversity that the region offers. These findings have the potential to provide transformative insights into the mechanisms that protect the brain.

As such, supporting research in this region is essential—not only to ensure the inclusion of genetic diversity in large-scale studies but also

TABLE 2 Recommendations of the inaugural symposium on Brain Resilience and Healthy Longevity.

• Investigate genetic variants linked to resilience, such as the apolipoprotein E3 Christchurch, particularly in the oldest-old and those at increased risk for dementia, as these may uncover nature's intrinsic mechanisms for combating Alzheimer's disease and related dementias.
• Examine the contribution of the neuroimmune system to safeguarding against Alzheimer's disease and small vessel disease.
• Identify and address modifiable risk factors for dementia, such as frailty, to help preserve brain function.
• Foster research that integrates multiple methods, such as quantitative neuropathological analysis, advanced neuroimaging, and cognitive testing, in diverse oldest-old cohorts to explore protective mechanisms.
• Consider social determinants of health and psychosocial factors in studies of brain resilience to gain a more comprehensive understanding of the elements that impact cognitive health in the oldest-old and centenarians.
• Develop culturally appropriate assessments for the physical, cognitive, and social aspects of functioning in the oldest-old to more accurately define healthy aging in this population
• Bolster international partnerships to uncover the factors that drive cognitive resilience, healthy aging, and resistance to neuropathology in the Latin American countries and regions.

to tap into Latin America's unique genetic and socio-environmental resources. By investigating these populations, the field can directly uncover natural, potent mechanisms that promote brain health and resilience—gifts from nature that could shape the future of aging and neurodegenerative research.

In conclusion, the inaugural symposium on Brain Resilience and Healthy Longevity put forth recommendations that urge the global scientific community to take decisive and proactive measures to enhance research in this critical yet underexplored area (see Table 2). By advancing this field, we can foster meaningful progress toward improving dementia prevention in Latin America and making a lasting impact on public health.

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CONFLICT OF INTEREST STATEMENT

Yakeel T. Quiroz serves as consultant for Biogen. Joseph Arboleda-Velasquez is a cofounder of Epoch Biotech, a company developing resilient case-inspired therapeutics. Kenneth Kosik consults with Expansion Therapeutics, ADRx Pharma, and Herophilus, and serves on the board of directors of the Tau Consortium. All other co-authors report no competing interests. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

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

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