Advancements in Dementia Research, Diagnostics and Care in Latin America: Highlights from the 2023 Alzheimer's Association International Conference Satellite Symposium in Mexico City

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Abstract

While Latin America (LatAm) is facing an increasing burden of dementia due to the rapid aging of the population, it remains underrepresented in dementia research, diagnostics and care. In 2023, the Alzheimer's Association hosted its eighth Satellite Symposium in Mexico, highlighting emerging dementia research, priorities, and challenges within LatAm. A wide range of topics were covered, including epidemiology, social determinants, dementia national plans, risk reduction, genetics, biomarkers, biobanks, and advancements in treatments. Large initiatives in the region including intra-country support showcased their efforts in fostering national and international collaborations; genetic studies unveiled the unique genetic admixture in LatAm; emerging clinical trials discussed ongoing culturally specific interventions; and the urgent need to harmonize practices and studies, improve diagnosis and care and implement affordable biomarkers in the region was highlighted.

1. Introduction

The prevalence of Alzheimer's Disease and Related Dementia (ADRD) is growing rapidly across the globe, posing significant health and economic challenges. A coordinated global response coupled with prioritizing research efforts is imperative to effectively address the global burden of ADRD [1,2]. Since 2015, the Alzheimer's Association International Conference (AAIC) has hosted AAIC Satellite Symposiums in various world regions to highlight regional research advancements in ADRD and foster international collaborations aimed at identifying research gaps and priorities for diagnosis, prevention, and treatment. In 2023, the eighth AAIC Satellite Symposium was hosted in partnership with the Global Brain Health Institute (GBHI) in Mexico City, Mexico, to explore emerging approaches, priorities, and challenges in ADRD research within Latin America.

Latin American countries are encumbered by increased ADRD prevalence and incidence due to a fast demographic shift with accelerated growth of the aging population [2,3]. Such trends place profound healthcare, social, and economic burdens on patients, caregivers, public health and social systems [4,5]. A growing body of evidence also highlights the underrepresentation of vulnerable populations in Latin America in dementia research and healthcare settings [6,7]. In recognition of the challenges and scientific opportunities in the region, the research landscape in Latin America has achieved a four-fold increase in funding from the Alzheimer's Association since the first AAIC Satellite Symposium in Mexico City in 2015. Indeed, in 2023, Alzheimer's Association funding supported 41 active research grants totaling over four million dollars. This funding includes the Multi-Partner Consortium to Expand Dementia Research in Latin America (ReDLat consortium, supported by the National Institute of Health-National Institute of Aging [NIH-NIA], the Alzheimer's Association, the Rainwater Charitable Foundation, The Bluefield project, Takeda, Alector, and GBHI), the Latin America Initiative for Lifestyle Intervention to Prevent Cognitive Decline (LatAm-FINGERS), which is taking place simultaneously in 12 LatAm countries, and the Dominantly Inherited Alzheimer's Disease Network in Latin America (DIAN-LatAm) operating in four countries, amongst others.

In this review, we provide a summary of the topics discussed at the 2023 AAIC Satellite Symposium in Mexico City. The topics included epidemiological research on dementia, the development and implementation of dementia National plans, and molecular, genetic, and biomarker advancements within the region Latin America. Further topics included the study of social determinants, Latin American initiatives, harmonizing and sharing data to develop collaborative research, strategies to reach diverse populations, progress in pharmacological and non-pharmacological interventions, and clinical trial experience in Latin America. The contribution of Biobanks to dementia science and their organization into networks in Latin America and the Caribbean were also discussed.

2. Epidemiology

The global population is aging due to an accelerated increase in life expectancy and a decline in fertility rates. This demographic transition is occurring faster in Latin America than in high-income countries (HICs). Comparing the population pyramids in Latin America between 1950 and 2022 reveals a continuous population growth in all age groups over a period spanning 70 years [8].

Over this period, the life expectancy in the region has increased from 48.6 years in 1950 to 75.2 years in 2019, and it is projected to be more similar to the life expectancy in North America by 2100. Consequently, Latin America is experiencing a rapid aging phase, with projections suggesting that by 2047, individuals aged 60 and over will outnumber those under 15 years of age. These demographic transitions have profound implications and present challenges, such as a heightened prevalence of multimorbidity in the region [8].

Epidemiologic studies on the prevalence of dementia in Latin America have reported varying prevalence estimates in different regions, primarily due to methodological differences. However, the 10/66 Dementia Research group (DRG) has shown more consistent results by using the same protocols, clinical assessments and validated instruments for low- and middle-income countries (LMICs). Their findings demonstrate that the prevalence of dementia across Latin America is more similar than previously reported, ranging from 6.7% to 12.6% in 2008 [2,9,10]. According to the Global Burden of Disease (GBD), the prevalence of dementia in Latin America in 2019 was the highest in Argentina, Chile, and Uruguay [2]. A recent systematic review and meta-analyses reported that the prevalence of all-cause dementia in Latin America is 8-10%, with a higher prevalence for women, lower-educated individuals, and rural residents [11]. The GBD estimates also suggested a 205% increase in the number of people aged 60 and above in the region between 2010 and 2015, compared to a 102% increase in North America [2]. Looking into the incidence of dementia in Latin America, the incidence rates range from 18.2 in Peru to 30.4 in Mexico per 1000 person-years for people aged 65 years and older [3]. In Brazil the incidence varies from 11.2 to 26.1 per 1000 person-years [12–14].

The impact of dementia can be assessed from a number of indicators, such as mortality rates, disability-adjusted life years (DALYs), and annual costs. There has been an increase in ADRD mortality rates in Latin America between 1990 and 2019 [2]. Dementia ranked as the eighth and fourth leading cause of DALYs among men and women aged 70+ years, respectively, between 2000 and 2019 [2]. According to GBD, the annual cost of dementia per person in Central, Southern, and Tropical regions of Latin America increased by up to 87% between 2010 and 2015, while the Andean region experienced a decline in dementia annual costs [2]. Furthermore, dependency (need for care) was found to be inversely associated with educational level and be a leading contributor to disability among older people with dementia in the 10/66 DRG population-based surveys conducted in both urban and rural catchment areas in Latin America. These findings have significant implications for the economy and burden of the caregivers [15].

Taken together, such statistics show that dementia will continue to pose an increasingly significant challenge in Latin America, given the rapid aging of the population and its growing socioeconomic impact. More research is urgently needed to improve the accuracy of the disease estimates in the region. The harmonization of the methodologies used in prevalence, incidence, and mortality studies in Latin America is crucial. Population-based longitudinal studies with longer follow-ups are essential to gather evidence of dementia trends in the region.

3. Global and national dementia plan: experiences and challenges

3.1 Dementia global plan

The World Health Organization (WHO) recognizes dementia as a public health priority and has developed *The global action plan on the public health response to dementia 2017-2025* [16]. This comprehensive plan includes seven action areas, providing a guide for policymakers and international and national partners to address dementia globally and regionally [16]. Despite national and international efforts to meet the targets outlined in the dementia action plan, the WHO's *global status report on the public health response to dementia in 2021* revealed insufficient progress toward reaching the 2025 target [17]. Only 50 WHO Member States currently have stand-alone or integrated dementia plans, 43 of which are part of the Global Dementia Observatory (GDO). These figures are significantly less than the 2025 global target, which aims for 75% of the 194 WHO Member States to have a dementia plan in place. Furthermore, while two-thirds of countries conduct awareness-raising campaigns or dementia-friendly initiatives, the majority are concentrated in HICs [17]. To support the implementation of the dementia global action plan, the WHO has developed valuable resources for each of the action plans (www.globaldementia.org). However, urgent actions are required at the national levels to address this pressing issue. This includes implementing policy responses, awareness, and risk reduction campaigns, equitable access to diagnosis, treatment, and care services, improving health information systems for dementia, investment in research and innovation strategies, and ensuring equitable inclusion of people with dementia in research and healthcare settings.

3.2 Dementia national plans in Latin America

At the 2023 AAIC Satellite Symposium, Alzheimer's Disease International (ADI, https://www.alzint.org/) noted the importance of integrating civil society organizations in developing and implementing dementia national plans (NDPs). ADI's #WhatsYourPlan campaign has gained momentum this year, with 52 country associations and stakeholders participating, 154 official letters, 29 meetings with ministries of health, and 20 commitments to develop NDPs. The ADI experience in past years has demonstrated that among the seven action areas in the WHO's dementia global plan, support for dementia carers is particularly important. Supporting dementia carers goes beyond the care they provide for dementia patients but also contributes to capacity building by fostering strong advocates of the dementia national plans within their community.

In Latin America, seven countries, including Chile, Costa Rica, Cuba, Mexico, Puerto Rico, the Dominican Republic, and Uruguay, have already established dementia national plans, and a plan is under development in Peru, Honduras, and Panama [18]. In Brazil, the national plan is under Congressional observation, to be approved. However, most countries do not have adequate funding to implement their dementia plans. Mexico was among the first Latin American countries to establish a dementia national plan, but is facing multiple challenges in the implementation of this plan. Barriers to implementing dementia national plans in Latin America range from lack of financial resources to societal stigma and misconception, physician burnout, political challenges, lack of educational resources and lack of continuity of public policy over time. The National Institute of Geriatrics (NIG) in Mexico has made significant efforts to revise the dementia national

plan in Mexico and strengthen the response of the Mexican health system. The 2021 Workshop on Revising the National Plan in Mexico has been particularly important. In this workshop, policymakers and leaders gathered to discuss obstacles and challenges in implementing the dementia national plan in Mexico and identify potential solutions. Accordingly, an updated dementia national plan has been developed to be presented to the policymakers in the health sector in Mexico.

Other topics relating to the dementia national plan in Mexico discussed in the 2023 AAIC Satellite Symposium included the efforts of the Mexican Federation of Alzheimer's (FEDMA) to combat stigma around dementia (https://www.fedma.mx/). FEDMA, founded in 1988, brings together the different Alzheimer's Associations in the Mexican Republic and is a member of ADI and Alzheimer Iberoamerica. An example of FEDMA efforts in Mexico is the Dementia Friends Mexico initiative that aims at changing society's perception of people with dementia, as those living with dementia experience social exclusion, loneliness, abuse, and neglect. Through Dementia Friends Mexico, it was reported that since 2019, 8,500 people have committed to changing their perception of people living with dementia. Finally, the dementia caregiver experience was highlighted by the FEDMA chair who personally cared for her mother diagnosed with dementia in the 1990s. Challenges in caring for her mother were emphasized, including a prolonged diagnostic process and insufficient support from the society.

4. Genetics

Characterizing the genetic landscape of ADRD provides a unique opportunity to gain a deeper understanding of the underlying pathophysiology of diseases and develop treatment strategies. While significant progress has been made in unraveling the genetic profiles associated with ADRD [19], there remains an inadequate representation of ethnically diverse populations, as most studies have been based on European populations [20]. Analysis of genome-wide association (GWAS) studies across human diseases conducted up until 2019 showed that 79% of the GWAS studies had been conducted in samples of non-hispanic European descent, while less than 3% were among admixed Latin American individuals [20,21]. This disparity hampers the translation of genetic research findings into clinical practice and drives many current efforts to increase diversity in AD genetic studies [20]. In the 2023 AAIC Satellite Symposium, a session was dedicated to the genetics of ADRD in Latin America, where researchers discussed topics related to autosomal dominant dementia, founder effects and the impact of ancestry on AD genetics, summarized below.

4.1 Autosomal dominant Alzheimer's Disease: founder effects in Jalisco state and Colombia

Less than 1% of AD cases worldwide have an autosomal dominant inheritance pattern and are caused by pathogenic variants in presenilin 1 (*PSEN1)*, presenilin 2 (*PSEN2*), or amyloid precursor protein (*APP*) genes. Of these, *PSEN1* is the most common gene associated with genetic AD, with disease-causing variants found in approximately 65% of early-onset familial AD cases, and more than 200 distinct variants have been described in this gene [22,23]. There are unique characteristics of dominantly inherited Alzheimer's Disease (DIAD) families in LatAm, including the presence of common ancestors and suggestive evidence of a high grade of admixture including African, Western European, Asia, and Native American ancestry [24]. In Latin America,

four major “founder effects” - increased prevalence of a specific genetic variant when a new population is established by a small number of individuals - in *PSEN1* have been described, including E280A in Colombia [25], G206A in Puerto Rico [26], A431E in Jalisco, Mexico [19] and the M146L in the northeastern region of Argentina [24]. Each of these variants represents large extended families within Latin America. Below we describe the general characteristics of the most common variants in the region.

The *PSEN1* A431E (rs63750083) was first described by Yescas et al., reporting nine affected families with early-onset AD in Jalisco State, Mexico [27]. Subsequent work identified 15 additional families in Guadalajara (n=2), in Chicago (n=1), and Southern California (n=12), nine of which could trace the illness to ancestors from Jalisco [28]. Haplotype analyses showed that all examined carriers had the same dinucleotide repeat alleles flanking the *PSEN1* gene, suggesting that this variant arose from a common founder [28]. Currently, more than 100 families with this variant have been identified, and as many as 1,260 persons were estimated to be at risk. Systemic phenotyping of the carriers showed that the mean age of onset is around 42 years (± 3.9 years), with a high frequency of spastic paraparesis occurring during the first two years of the disease [28,29]. Diffusion tensor imaging (DTI) analyses of *PSEN1* A431E variant carriers with spastic paraparesis showed widespread white matter abnormalities that were not confined to the corticospinal tract, suggesting an effect of *PSEN1* A431E variant on the white matter integrity in the brain [30]. In the 2023 Symposium, it was further highlighted that future work is underway in Mexico, the U.S., and in Belgium to characterize the pathologic hallmarks of *PSEN1* A431E variant and develop potential treatments in clinical, imaging, neuropathologic, and animal studies.

The *PSEN1* E280A (rs63750231) variant was first described in 1987 in a Colombian family with early-onset AD. Over the past decades, subsequent work has identified additional families affected with this variant who primarily live in Antioquia, Colombia. Haplotype analyses of the carriers suggested a founder effect that could be traced back to a founder in the 18th century [31]. This cohort forms the largest family in the world with autosomal dominant AD, consisting of 25 multigenerational families with approximately 6,000 family members [32]. The disease is characterized by several progressive clinical stages, including asymptomatic pre-mild cognitive impairment (MCI), symptomatic pre-MCI, MCI, and dementia, with a median age of onset of 35, 38, 44, and 49 years, respectively [25,33]. However, analyses of more than 300 *PSEN1* E280A variants carriers have shown that the age of onset is variable [34]. While age at onset for most carriers appears to be a polygenic factor, for some distinct outliers, there are variants that are protective. For example, the Apolipoprotein E (*APOE*) ε3ch/ε3ch R154S Christchurch (R136S in the mature protein) variant was observed in an *PSEN1* E280A carrier who did not develop MCI until her seventies [35]. More recently, the second case of resilience to autosomal dominant AD was described in a male carrying rare RELN variant [36]. Three more candidate protective variants are currently being studied in this population.

4.2 Autosomal dominant dementia in DIAN-LatAm and ReDLat projects

In Latin America, the DIAN-LatAm study is leading an effort to identify families affected by dominantly inherited AD [24]. DIAN-LatAm is part of the global DIAN observational study

(https://dian.wustl.edu/) [37,38] and is aimed at establishing a Latin American multicenter registry of dominantly inherited AD families by collecting comprehensive clinical, psychometric, neuroimaging, and biomarker data. Furthermore, the DIAN-LatAm network aims to create a cohort-ready population to implement the DIAN-Trail Unit (DIAN-TU) platform in the region [24,39]. The DIAN-TU platform was launched in 2012 to implement therapeutic trials for dominantly inherited AD individuals and help in the identification of disease-modifying agents that can also be translated to sporadic AD [40]. To date, the DIAN-LatAm centers include those in Puerto Rico, Mexico, Colombia, Brazil, and Argentina, and new centers are being launched, such as Chile. The clinical trial-ready centers in Latin America within the DIAN-TU platform include Brazil, while Mexico and Colombia are pending national regulatory approval to initiate trial enrollment in the DIAN-TU NextGen trial and Primary prevention trial. More information about the DIAN-TU platform within Latin America is available in *Section 9*.

DIAN-LatAm has made significant progress in identifying the distribution of at-risk families, providing resources for genetic testing, and raising awareness about the disease. Notably, twenty-four dominantly inherited AD pathogenic variants within Latin America have been reported, with the highest frequencies in Colombia, Puerto Rico, Argentina and Mexico that are mostly attributed to founder effects [24]. Furthermore, five novel variants in the *PSEN1* gene from Brazilian and Mexican families have been identified, four of which were described as likely pathogenic variants [39]. Collectively, these genetic studies suggest that the frequency of dominantly inherited AD in Latin America is high, with unique characteristics including common ancestors, large extended families usually related to founder effects, and evidence of a high grade of admixture and ancestry background [24].

At the 2023 AAIC Satellite Symposium, the experience of the ReDLat project in genetic screening of autosomal dominant-like frontotemporal dementia (FTD) was also highlighted. Utilizing mobile memory clinics in Colombia has led to the identification of large families affected with autosomal dominant-like FTD who are living in isolated, difficult-to-reach areas. The efforts of this mobile memory clinic have created the opportunity to construct large family histories through direct contact with patients and their families. The consortium has identified multiple families with known variants including PGN, TREM2, TARBP, MAPT, *PSEN1* and *PSEN2*, among others. More details about the ReDLat project is available in *Section 8*.

4.3 Role of ancestry

The genetic diversity of Latin American individuals often results from the process of *admixture*, which is the exchange of genes between populations that had been previously isolated. The makeup of today's populations, particularly in the Americas, represents admixed individuals of European, African, Amerindian, and Asian ancestry among others. In countries like Colombia, the demographic history of admixture, followed by bottlenecks and founder effects played a significant role in the genetic risk of ADRD. Analyses of genomes from a large sample of Colombian individuals from "The Admixture and Neurodegeneration Genomic Landscape" (TANGL) study revealed several rare variants associated with ADRD that resulted from founder effects [41]. These founder effects were present not only for the *PSEN1* variants, but also in other genes, such as microtubule associated protein tau (MAPT). Despite the genetic and

environmental similarity among members of families that carry a specific variant, the phenotypic variability in the disease presentation is significant, generating opportunities to better understand risk and resilience factors. For example, the researchers reported how genes traditionally associated with specific phenotypes (e.g. SOD1 and amyotrophic lateral sclerosis) were presenting differently when the variant occurred in other ancestral haplotypes (SOD1 variant manifesting as frontotemporal dementia when present in Amerindian haplotypes). Therefore, ancestry may significantly impact ADRD phenotypic expression, reinforcing the importance of inclusiveness in genetic studies [41].

Global and local ancestry can also affect AD risk associated with a particular gene. For example, while ApoE4 has been shown to substantially increase the risk for AD in Caucasians [42], studies across populations with diverse ancestral backgrounds have shown various effect sizes [43–45]. In 2018, Rajabli and colleagues demonstrated that the reason for this difference was due to the surrounding inherited local genomic ancestry [46]. Specifically, it was shown that among Puerto Rican and African American individuals, only the local ancestral background of the APOE alleles influenced AD risk such that APOE ε4 allele on an African ancestral background conferred a lower risk of AD compared to those with a European ancestral background [46]. Similarly, recent evidence suggests that the effect of APOE-e4 allele on AD is attenuated among Caribbean populations with higher African ancestry proportions [47–49]. A recent study performed in the Peruvian population, known to concentrate up to 80% of Amerindian ancestry, suggest that the AD risk conferred by the APOE ε4 allele is higher than observed in non-Hispanic white populations suggesting a role of the local APOE Amerindian ancestry [50]. A large, one of a kind, clinicopathological study with a Brazilian population, showed that people of African ancestry have a lower likelihood of accumulating amyloid plaques than Caucasians and that APOE ε4 allele of African origin does not add an increased risk for AD compared to APOE ε3 allele, as occurs with APOE of European origin [51]. Attenuation of APOE4 risk in African ancestry was also demonstrated in a clinical cohort from the Caribbean [51,52]. Postmortem analyses of the frontal cortex of AD patients also showed differences in APOE gene expression based on diverse ancestral backgrounds [53]. Ongoing work is studying the role of ancestry on AD risk from different genes in Peru and Puerto Rico.

Taken together, genetic risk factors for AD can be different depending on ancestral background, and ancestral background can impact phenotypic disease expression. Investigating the relationship between genetic ancestry, social determinants of health, and disease may inform precision medicine initiatives, risk assessment, and the development of ancestry-specific therapeutics and prevention strategies for ADRD.

5. Biomarkers

Over the past decade, several biomarkers for AD have been developed that provide valuable insight into the underlying disease pathology. Some of them have been incorporated into revised or updated diagnostic criteria for AD [54–56]. Since these groundbreaking developments in the field, collaborative efforts in Latin America starting in 2011 with the Alzheimer's Disease Neuroimaging Initiative (ADNI), have been instrumental in addressing the challenges of implementing AD biomarkers in the region. A recent survey in Latin America showed a lack of

funding as the most important barrier to implementing biomarkers, followed by insufficient infrastructure and training. Despite these challenges, biomarker research in Latin America has witnessed significant advancements, including through the Caribbean Consortium on Dementia (LAC-CD) and the ReDLat initiatives [57]. At the 2023 AAIC Satellite symposium, a session was dedicated to biomarkers, discussing advancements and challenges in biomarkers research within Latin America, including neuroimaging, blood-based, and speech and language biomarkers.

5.1 Neuroimaging biomarkers

Neuroimaging is increasingly being utilized as a biomarker to assess dementia in Latin America. A recent online survey in Latin America that was answered by 48 participants from 10 countries showed that neuroimaging is the most widely used biomarker, with magnetic resonance imaging (MRI) being the most commonly used modality, followed by fluorodeoxyglucose (FDG)-positron emission tomography (PET), DTI, amyloid PET, functional MRI (fMRI), and tau PET. However, widespread implementation of neuroimaging in the region is met with challenges, notably a need for more funding resources. Moreover, degree of experience in using neuroimaging is another challenge that varies greatly between countries [57].

New regional initiatives in Latin America are allowing the standardization and harmonization of neuroimaging protocols across different countries while generating high-quality information. A notable example is the LatAm-FINGERS study, where significant effort has been made to develop standardized protocols for use in different countries. Novel MRI quantification techniques, such as Quantitative Susceptibility Mapping (QSM), are also being developed that may allow early detection of neurodegenerative diseases [58]. Other approaches have developed specific methodologies to perform regional comparisons (i.e., North vs South) that are robust to multiple levels of heterogeneity [59].

The Argentina-Alzheimer's Disease Neuroimaging Initiative (arg-ADNI), established in 2011, was the first ADNI center in Latin America [60]. Since then, this collaboration has resulted in better characterization of ADRD pathology in Latin America, particularly by implementing neuroimaging techniques such as PET, and MRI and CSF biomarkers. Currently, various brain PET imaging techniques are being utilized in Argentina, such as amyloid PET (^{11}-C-PIB, and Florbetapir), metabolic PET (^{18}FDG), and Tau PET (AV1451 and MK6240). Several publications have emerged from this group, highlighting the importance of defining dementias on a biological basis using biomarkers [61–64]. For example, in a study of 60 participants from the arg-ADNI cohort, it was found that 14% of controls, 30% of early MCIs, 53% of late MCIs, and 83% of those with dementia of AD type were amyloid positive using PET imaging (^{11}-C-PIB). Applying the ATN framework showed that the conversion rate from MCI to dementia after five years of follow-up was 85% and 50% for A+T+N+ and A-T-N+ patients, respectively [62]. Furthermore, in the first report from Brazil in a sample from Sao Paulo, 21% of controls, 36% of amnestic MCI, and 74% of AD patients had positive PIB-PET scans [65]. Despite these advances, AD diagnosis in Latin America remains primarily based on clinical information, while neuroimaging tools such as PET are limited to a few centers [64]. This reinforces the importance of cross-regional collaboration in the region to reshape the dementia diagnostic landscape in Latin America.

5.2 Blood-based biomarkers

Blood-based biomarkers (BBMs) have shown significant promise in revolutionizing the clinical work-up of dementia patients and improving the design of clinical trials. Compared to well-established CSF and PET methods, BBMs offer a less invasive, more feasible, and cost-effective option for application in clinical practice. Additionally, BBMs significantly reduce screening costs and time in clinical trials and may be used as surrogate endpoints to evaluate the effectiveness of therapies [66]. Over the past years, several BBMs have been identified, with the most promising ones being plasma phosphorylated tau (p-tau), Aβ42/Aβ40, neurofilament light (NfL), and plasma glial fibrillary acidic protein (GFAP) [67–72]. For example, plasma p-tau, especially p-tau181, is a reliable biomarker for supporting AD diagnosis as it correlates well with amyloid and tau pathology and can differentiate AD from other neurodegenerative disorders [68].

In Latin America, a recent survey showed that peripheral fluid biomarkers are among the least common dementia biomarkers used in the region [57]. A systematic review of biomarkers of FTD in Latin America found only a few studies focused on peripheral fluids with a lack of focus on NfL, TDP-43, p-tau, or inflammatory markers [73]. Therefore, utilization of BBMs remains limited in Latin America despite the high potential of BBMs to improve diagnostic and clinical work-up. Efforts from different regional initiatives are underway to pave BBMs use in clinical and research settings, including LAC-CD, ReDLat, and The Latin American Institute of Brain Health (BrainLat). There is an urgent need to promote and facilitate the use of BBMs in Latin America.

5.3 Speech and language biomarkers

While discussions of linguistic deficits in dementia are often restricted to primary progressive aphasia (PPA), verbal dysfunction is common across neurodegenerative disorders. For example, the prevalence of speech and language deficits is 36-90% in early-stage AD and 60-90% in early-stage Parkinson's disease (PD). In early-stage behavioral type FTD, this figure ranges from 5 to 55% depending on the language domain affected [74]. Therefore, speech and language profiles are promising markers of neurodegenerative disorders that can provide novel complementary information to the standard biomarkers.

Researchers from Latin America have developed novel automated approaches using artificial intelligence and natural language processing to automatically capture speech and language alterations in neurodegenerative disorders from patients' audio recordings. In a study of Chilean participants, machine learning analyses of natural speech data showed that semantic granularity and semantic variability discriminated between AD individuals and controls with an AUC of 80% while yielding near-chance classifications between PD patients and controls [75]. Moreover, automated analysis of word properties in verbal fluency tasks can identify Latino AD patients with an AUC of 89%, predict their neuroanatomical and neurofunctional abnormalities, and differentiate them from bvFTD patients [76]. Other studies with automated tools have revealed novel speech and language markers of cognitive decline in Latin American PD cohorts [77,78]. Therefore, such automatic speech and language markers may contribute to the identification, differentiation, and characterization of diverse neurodegenerative disorders [79]. In the 2023 AAIC Satellite Symposium, various initiatives from Latin America have been highlighted that aim to foster international collaborations to study speech and language alterations in neurological

disorders, such as the International Network for Cross-Linguistic Research on Brain Health (Include network) and NIH-funded projects in the region. Moreover, a novel web-based app, called TELL, has been developed specifically to capture such markers in Latino populations [80]. Promisingly, these efforts address the urgent call to increase linguistic diversity and equity in the field [81].

6. Biobanks

Biobanks are invaluable resources in the study of neurodegenerative disorders by providing insights into population-specific risk and protective factors and helping determine the prevalence of dementia subtypes. Such information is critical to guide and shape public health policy efforts. Furthermore, biobanks provide great opportunities to advance our understanding of the pathologic underpinning of dementia. However, most biobanks are in HICs despite most people living with dementia residing in LMICs [82]. Data from emerging biobanks in Latin America have shown the importance of biobanking in LMICs, as they can provide valuable insights into disease mechanistic pathways in the context of diverse ethnoracial backgrounds.

A notable example of brain biobanks in Latin America is the Biobank of Aging Studies (BAS) in Sao Paulo, Brazil. Since its inception in 2003, the BAS aimed at maximizing available resources in the region and providing high-quality material for multidisciplinary researchers to advance knowledge of age-related disorders of the brain. The BAS follows international standards and principles, especially standardized protocols from the Netherlands Brain Bank [83]. Leveraging BAS resources, important discoveries into the prevalence and pathology of ADRD in the region have been made. For example, while over 60 percent of cases in the BAS have a Clinical Dementia Rating Score of 0, neuropathological examination showed that the prevalence of vascular dementia is substantially high, with small-vessel disease present in 39% of all dementias and 17% of those without cognitive impairment [84,85]. Other studies from the BAS showed that genetically determined African ancestry individuals tended to accumulate significantly less neuritic plaques, even among individuals who self-declared as White [86]. Another larger follow-up study showed that a higher African ancestry proportion in AD patients was associated with less plaque accumulation in the brain. Interestingly, however, after normalizing the number of plaques across individuals, African ancestry was associated with worse cognitive function. Further analyses of genotypes revealed that the relationship between higher African ancestry proportion and worse cognition disappeared in those with the ApoE4 genotype [51]. These findings underscore the interaction between ancestral background and ApoE genotype in AD risk in diverse populations.

The Argentina brain bank is another example that was highlighted in the 2023 AAIC Satellite Symposium. The surveillance of the prion disease cases was the foundation of establishing this biobank, with a report of the first ten neuropathologically confirmed Creutzfeldt-Jakob disease cases published in the 1980s [87]. Other notable findings from the Argentina biobank include the first reports of an Argentine kindred affected by the Gerstmann-Sträussler-Scheinker syndrome [88], insomnia associated with thalamic involvement in E200K Creutzfeldt-Jakob disease [89], and a case of MM1+2C sporadic Creutzfeldt-Jakob disease presenting as rapidly progressive nonfluent aphasia [90]. Resources from this biobank were further instrumental in developing the

final diagnosis of neuropathologically complex disorders [91]. Currently, the biobank hosts tissue from 149 cases of prion disease and 48 cases of other types of dementia.

Other notable biobanks in Latin America that were highlighted at the Symposium were the Colombian brain bank known as the Neurobanco, the National Dementia Biobank (BND) in Mexico, and the DNA Bank Neurogenetics in Peru. Established in 1995, the Neurobanco in Colombia has the largest repository of familial AD E280A mutations. Dr. Raúl Mena López founded the BND 30 years ago, making it the oldest biobank in Latin America. The BND is a diagnostic and research unit, in the Polytechnic University of Pachuca with the aim of supporting the confirmatory diagnosis of neurodegenerative diseases. The BND has focused on the research for biomarkers and non-invasive methods for early diagnosis of AD [92]. The BND highlighted collaboration with several entities, such as the Latin American and Caribbean Brain Bank Network, the Brain Bank of the Dominican Republic, the Brain Bank of Peru, the DIAN Network, and several academic institutions. The DNA Bank Neurogenetics, founded in 2020, became the first DNA biobank of the public healthcare system in Peru. It supports various collaborative research projects, such as the Latin American Research Consortium on the Genetics of Parkinson's Disease (LARGE PD) and the Peruvian Alzheimer's Disease Initiative (PeADI). However, developing local capacities, long-term sustainability, and recruitment of participants were the most relevant challenges faced by this Peruvian DNA Bank [93].

7. Modifiable risk factors for dementia and vulnerable populations

While 12 potentially modifiable risk factors across the life course have been shown to account for 40% of dementia cases worldwide [94], the population attributable fraction (PAF) differs between LMICs and HICs [95]. The 10/66 DRG data found that in Latin America, 56% of dementias are attributed to modifiable risk factors, whereas the PAF in the United States is around 30% [2,95]. In Brazil, 48% of all-cause dementias are attributed to the 12 modifiable risk factors, with low education, and midlife hearing loss, hypertension, and obesity being among the most important ones [96]. These figures suggest that targeting modifiable risk factors for dementia may give more room for dementia prevention in LMICs, including in Latin America, than in HICs [2]. Furthermore, health communication campaigns should consider including dementia as a possible consequence of chronic diseases. Recent studies, utilizing methodological innovations and larger datasets, have shown that social and health disparities are the primary drivers of many significant risk factors in the entire region, underscoring the need for more sensitive and tailored models [97,98].

To address the role of dementia risk factors in Latin America, the 2023 AAIC Satellite Symposium devoted a session to dementia risk factors in vulnerable populations. Researchers from ReDLat highlighted their ongoing work on assessing the association between social determinants of health and brain health, researchers from Peru highlighted their study on assessing the impact of socioeconomic status, lifestyle factors, and health care providers on cognitive function in indigenous people in Peru, and researchers from Argentina highlighted their work on gender-specific modifiable risk factors for dementia. In addition, the role of education and cardiovascular risk factors were highlighted and are summarized below.

7.1 Education and literacy

Mounting evidence from HICs suggests that dementia is more common amongst illiterate populations, and higher education is associated with lower dementia risk. In Latin America, the prevalence of dementia is two times higher in illiterate individuals than in literate individuals [11,99]. Even more striking is the incidence of dementia, which has been shown to be five times higher in illiterate people compared to literate populations in Brazil [14]. In the BAS, education, but not occupation, was associated with better cognitive function as measured by the Clinical Dementia Rating sum of boxes [96]. A cross-sectional door-to-door study in Puente Piedra, one the most socially and economically vulnerable districts of Lima, the capital of Peru, reports that among 247 participants with a median age of 46 years, one-fourth had not completed secondary school and more than 50% completed only secondary school. In this cohort, there was a high frequency of possible neurocognitive disorders (NCDs) with younger adults showing levels of NCD higher than expected [100]. The mechanism underlying the relationship between illiteracy and dementia risk has been explored by researchers from Latin America using neuroimaging tools. One study with 31 participants showed that literate older adults had better white matter integrity, meaning, stronger brain connections than their illiterate counterparts [101]. Later, this finding was replicated in a large cohort of more than 600 US middle-aged individuals in which literacy levels were also associated with better white matter integrity, especially in temporal and parietal regions [102]. Furthermore, because the hippocampus is one of the most plastic regions of the brain and plays an important role in episodic memory, it has become the target of investigation on the mechanisms of cognitive reserve in low literacy populations. It has been shown that the relationship between hippocampal volume and episodic memory seems to be moderated by educational level [103,104].

7.2 Cardiovascular risk factors

Vascular dementia (VaD) is the second most common cause of dementia after AD, accounting for 15% of dementia cases in HICs. However, emerging data suggests that the burden of VaD in LMICs is higher than reports from HICs [105]. In Latin America, results from the BAS revealed that the prevalence of VaD is 35% and this figure could reach 49% if the diagnostic criteria included neuropathologic features of small vessel disease [84]. In line with this, the prevalence of cardiovascular risk factors in Latin America remains high. The Brazilian Longitudinal Study of Adult Health showed that 53% of the participants had poor cardiovascular health as measured by the American Heart Association's 'Life Simple 7' criteria [106]. Importantly, this study showed that poor cardiovascular health was associated with worse performance on several domains of cognitive function such as executive function, language and memory [107]. In Chile, it has been reported that the proportion of dementia associated with modifiable risk factors is 45.8%, with high blood pressure, obesity, and hearing loss being the most important modifiable risk factors [108].These findings underscore the importance of effective management of cardiovascular risk factors in Latin America, as these factors play important roles in mitigating the rising burden of dementia in the region.

8. Harmonizing large data and developing collaborative research

Establishing effective guidelines for data harmonization, data collection, and data sharing is essential to adopting methodologies and interventions according to the best clinical practice.

These guidelines are instrumental in creating robust clinical cohorts and research studies that advance our knowledge of diseases, especially neglected or rare diseases [109]. Furthermore, data harmonization and sharing guidelines can help guide public health policies and foster scientific collaboration. However, harmonizing large data and developing collaborative research in Latin America is faced with challenges. A recent study in the region showed that factors such as cultural, linguistic, socioeconomic, and educational diversities, as well as limited access and coverage of biomarkers and dementia awareness and stigma, remain significant barriers to collaborative dementia research in Latin America [5]. Despite these difficulties, regional ongoing initiatives such as the Brazilian REDONE (Registro Brasileiro de Doenças Neurológicas) databank of neurological diseases [110], since 2003 the 10/66 DRG protocols, the ReDLat project (https://red-lat.com/), DIAN-LatAm and the LatAm-FINGERS study [111] show the potential of collaborative research and large data harmonization procedures in Latin America. For example, ReDLat has developed post-recording harmonization procedures using different computational methods for clinical and cognitive data [112], neuroimaging [59,113], epidemiological data [97,114], and assessment of various measures of socioeconomic disparities [115]. Furthermore, collaboration and harmonization efforts in Latin America need to pursue the development of accessible and scalable cognitive and functional screening tools to aid advance both clinical and research efforts. Recent regional developments in the region are making strides in addressing this gap [116–118].

8.1 Data harmonization and collaborative research in Latin America: 10/66 DRG, RedDLat, LatAm-FINGERS and DIAN LatAm initiatives

In 2000, the 10/66 DRG was established with the aim of readdressing the worldwide imbalance in epidemiological research on dementia in LMICs. The name “10/66” symbolizes the situation at that time, where more than two-thirds (66%) of the population with dementia were living in LMICs, while only 10% of the epidemiologic research originated from these regions. The 10/66 DRG program utilizes population studies, with standardized protocols and training across all centers. It is primarily focused on the evaluation of the elderly's mental health, with an emphasis on dementia. The 10/66 DRG protocols have conducted three waves: baseline evaluation or prevalence phase (2003-2009), 1st follow-up approximately three to five years after, and a 2nd follow-up approximately ten years later, and ongoing to present. This initiative has produced more than 200 papers, with more than half involving data from Latin America.

ReDLat [117] is a 5-year project aimed at expanding dementia research in Latin America and the Caribbean by utilizing socioeconomic, genomic, neuroimaging, and behavioral measures in diverse populations. This project creates an unprecedented opportunity to foster multidisciplinary research to promote harmonizing global strategies to treat and prevent dementia in underserved populations. Since its establishment, harmonized and cross-regional approaches across 13 sites from 7 countries in the American continent have led to several achievements. Notably, ReDLat has produced over 150 publications in the top scientific journals and provided 12 seed grants fostering 22 projects through the BrainLat Institute. Examples of ongoing ReDLat research projects are the genomic data showing the level of genetic admixture in Latin America [119], machine learning approaches that were able to minimize sources of

heterogeneity in cognitive assessment tools [112], development of fully automated approaches for analyzing whole-brain neuroimaging data [59], assessing the impact of social determinants of health on dementia [120], developing novel theoretical models to understand the biological underpinning of dementia [121,122], and development of educational resources for brain health and dementia in the region.

LatAm-FINGERS is an ongoing multidomain lifestyle intervention trial for dementia prevention in Latin American countries that are often underrepresented in dementia clinical trials [111,123]. Extensive harmonization processes and protocols have been implemented both externally with the original FINGERS (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) [124] and U.S. POINTER (U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk, https://alz.org/us-pointer/home.asp) trials and internally across Latin American countries. The harmonization processes extended to interventions by adopting the FINGER trial concept while considering cultural differences and affordability factors. For example, a new LatAm MIND diet was established that includes core components that must be respected (nutrient components and portions) while allowing ingredient flexibility. The outcome measures were harmonized by selecting variables from FINGERS and U.S. POINTER trials while allowing alignment with linguistics differences and ensuring validity for comparisons within Latin America and externally. Various outcome measures are being collected, such as blood and DNA samples, neuroimaging, and cognitive and clinical assessments. The LatAm-FINGERS data is embargoed for two years, after which data will be available to the scientific community through The Global Alzheimer's Association Interactive Network (GAAIN) platform (https://www.gaain.org/). More information on LatAm-FINGERS is provided in section *9.1*.

9. Pharmacological and non-pharmacological interventions

Individuals living in LMICs are often underrepresented in dementia clinical trials, limiting the relevance of clinical trials conducted in HICs to LMICs, due to factors such as ethnic, socioeconomic, and educational differences, as well as variations in disease profiles and healthcare access. A study of AD clinical trials in 2013 showed that among 715 worldwide AD clinical trials, only 34 were performed in South America [125]. Similarly, a 2020 study showed that only 6% of dementia clinical trials occurred in Latin America, primarily in Brazil, Argentina, Chile, Mexico and Colombia [5]. A recent systematic review of the distribution of ADRD clinical trials showed that less than three percent of trials are conducted in Latin America and Africa [126]. These figures highlight the inequity in ADRD clinical trials in LMICs despite these regions bearing the greatest burden of dementia. Between 2013 and 2022, the API Colombia study was carried out in Colombia, one of the most important clinical trials of secondary prevention for AD demonstrating the ability to carry out this type of studies in the region. LatAm-FINGERS is an example of non-pharmacological interventions in the region, underscoring the need for more study on non-pharmacological interventions in the region.

Recent developments in AD disease-modifying interventions have opened up a new landscape in AD diagnosis, care, and treatment [127]. However, the application of such therapies to Latin America is challenged by factors such as delay in MCI and dementia diagnosis, a higher burden of neurovascular pathologies in Latinos[84], costs, and a shortage of dementia specialists. For

example, a study in Brazil found that it took 1.5 years for patients to receive a dementia diagnosis, mainly due to physicians' inability to reach a conclusion and families attributing symptoms to normal aging [128]. Furthermore, a systematic review of AD biomarkers found significant discrepancies between developed and developing countries [129]. These findings highlight the need for targeted and concentrated efforts in Latin America to improve early dementia diagnosis, raise dementia awareness, and establish infrastructure toward developing and implementing dementia disease-modifying interventions.

In the 2023 AAIC Satellite Symposium, ongoing pharmacological and non-pharmacological interventions for dementia in Latin America were highlighted, including LatAm-FINGERS, DIAN-TU, and API Colombia, which are summarized below.

9.1 LatAm-FINGERS

The LatAm-FINGERS study is part of the World Wide FINGERS Network funded by the Alzheimer's Association (https://www.alz.org/wwfingers/overview.asp). LatAm-FINGERS is a non-pharmacological multicenter randomized clinical trial (RCT) in 12 Latin American countries (Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, Mexico, Peru, Puerto Rico, and Uruguay) assessing the feasibility and efficacy of a multidomain lifestyle intervention on cognitive function. The aim is to enroll 1200 individuals (100 from each country) aged 60 to 77 years who are at a high risk of cognitive deterioration due to a sedentary lifestyle and suboptimal metabolic-cardiovascular profile. The two lifestyle interventions include the Systemic Lifestyle Intervention (SLI) and Flexible Lifestyle Intervention (FLI). The multidomain lifestyle intervention, or SLI, consists of adherence to the LatAm-MIND diet, physical exercise, cognitive training, and control of cardiovascular risk factors, while the FLI includes regular general health advice. Participants will be evaluated every six months to collect data on clinical and neuropsychological assessments, blood samples, and brain MRI [111]. The major challenges experienced by LatAm-FINGERS were training team members across 12 countries, finding adequate facilities to perform interventions, and harmonization efforts (as described in *section 8.1.*). Adapting the dietary intervention and cognitive training to Latin America was particularly challenging. For example, new foods, such as avocado replacing olive oil, were incorporated into the LatAm-MIND diet only after confirming their nutritional profile equivalence to the MIND diet. Furthermore, customized solutions have been established to ensure participants' adherence to interventions, especially the computerized cognitive training component [111]. Collectively, the LatAm-FINGERS study provides a groundbreaking opportunity for collaborative studies in Latin America, generating valuable data from a region often underrepresented in dementia RCTs. This data is poised to significantly impact the development of health policies for dementia prevention in Latin America.

9.2 DIAN-TU

The aims of the DIAN-TU are to execute effective preventive and treatment strategies for DIAD, determine the timing of AD treatment for improved clinical outcomes, identify changes in biomarkers to track therapeutic effectiveness and test AD hypotheses through treatment trials. The DIAN-TU platform has been split into two main trial design approaches: the primary prevention trial for treating participants up to 11 years before the estimated age of AD onset and

the secondary prevention trial for those within -10 to +10 estimated age of AD onset. [37,38,130]. In 2012, the first DIAN-TU trial was launched, where two monoclonal antibodies of gantenerumab and solanezumab were tested in asymptomatic and symptomatic patients. Gantenerumab showed a clear reduction in brain amyloid accumulation and improvement in other downstream biomarkers of AD. However, gantenerumab and solanezumab did not meet their primary endpoint of improving cognitive function [131]. Therefore, alternative treatments are being explored for the primary prevention trial. In the secondary prevention trial (Tau NextGen trial) [40], two drugs will be tested: Lecanemab [132] and a new anti-tau antibody, E2814 [133]. Eligible participants with a known mutation on *PSEN1*, *PSEN2*, and *APP* will be grouped based on CDR scores into symptomatic (cohort 1) or asymptomatic (cohort 2) cohorts. The order of intervention randomization will depend on these cohorts, with two main combinations of Lecanemab+E2814 or Lecanemab+placebo at the end of the first year. The trial endpoints are stage-specific, with tau PET being the primary outcome for cohort 1 (symptomatic) and CSF tau biomarkers being the primary outcome for cohort 2 (asymptomatic). In Latin America, Argentina has started trial enrollment, Brazil has recently received approval to start the DIAN-TU trial, while Mexico, Colombia, and other countries are underway. A remarkable aspect of the DIAN-TU in Latin America is the collaborative and supportive work across countries, such as Colombian participants undergoing PET in Argentina. The DIAN-LatAm initiative has supported technology and tracer development at imaging centers (Argentina and Mexico) across the trial network.

9.3 API ADAD Colombia

The Alzheimer's Prevention Initiative Autosomal Dominant Alzheimer's Disease Colombia Trial (API ADAD Colombia) was launched in 2013 to evaluate the efficacy, safety, and tolerability of crenezumab (an anti-Aβ drug) in cognitively unimpaired E280A mutation carriers [134]. The study was conducted at the University of Antioquia in Medellin, Colombia, with satellite sites in Yarumal, Bogota, and Armenia for dosing and safety assessments. A total of 252 individuals were enrolled, including 169 E280A mutation carriers and 83 non-carriers, and the enrollment ended in 2017. The E280A mutation carriers were randomized to active treatment or placebo, and non-carriers received placebo [134]. The modifications in the API trial led to the dose of crenezumab increasing more than 7-fold throughout the study. The primary outcome was the annualized rate of change in API ADAD composite score. Key secondary outcomes were changes in amyloid PET, time to progression to MCI or dementia due to AD, and changes in dementia severity and neurocognitive functioning. The study showed excellent adherence and retention rates over eight years, with 90% of participants completing the treatment. Results numerically favored crenezumab across primary and secondary outcomes, but they did not reach statistical significance [135,136]. While the API ADAD Colombia trial results were negative, it led to the discovery of protective genetic variants [35,36,137] and additional pathogenic *PSEN1* mutations in Colombia [41], as described in more detail in the *Section 4* of this manuscript.

10. Conclusion

The myriad of topics discussed at the 2023 AAIC Satellite Symposium highlighted the growing research efforts in Latin America, providing valuable insights into dementia biology, genetics, epidemiology, treatment, and care. Large research initiatives such as 10/66 DRG studies, LAC-CD, RedLat, DIAN-LatAm, and LatAm-FINGERS studies have played critical roles in promoting regional

scientific exchange and fostering national and international collaborations. Such initiatives have provided unique insights into the etiology of AD in Latin America and paved the way toward tailored interventions suited to the needs of Latin America's diverse and culturally rich population. Furthermore, genetic studies conducted in the region have significantly enriched our understanding of the variation and complexity of dementia risk and resilience factors and the importance of genetic ancestry. These findings hold the promise of global translatability, offering hope for developing effective preventive or treatment strategies for dementia.

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