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## Alzheimer's disease research progress in Australia: The Alzheimer's Association International Conference Satellite Symposium in Sydney

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### CONFLICTS OF INTEREST

K. Anstey is an advisor for StaySharp. C.J. Barnum is a full-time employee and stockholder at INmune Bio Inc. K. Blennow has served as a consultant, on advisory boards, or on data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. H. Brodaty is a member of the Advisory Board, Nutricia Australia. S. Burnham, Patent: Method for detection of a neurological disease 2014. M.C. Carrillo and C.E. Sexton are full-time employees of the Alzheimer's Association. M. Koronyo-Hamaoui is a co-founding member and a consultant of NeuroVision Imaging Inc. S. Landau has consulted for NeuroVision and Cortexyme. S. Laws is a member of an advisory panel, Cytos Ltd. C. Rowe is on advisory boards for Biogen Australia, Cerveau Technologies Research Grants from Eisai, Biogen, Enigma, Abbvie. P. Sachdev is on the advisory committee for Biogen Australia. E.M. Sigurdsson has served as a consultant for H. Lundbeck A/S, Biogen, and GlaxoSmithKline, and received seminar fees from Merck, Bristol Myers Squibb, and Voyager Therapeutics. He is an inventor on several patents that are assigned to New York University. Some of the patents on tau immunotherapy and related diagnostics are licensed to and are being co-developed by H. Lundbeck A/S. C. Szoeki has provided clinical consultancy and been on scientific advisory committees for the Australian Commonwealth Scientific and Industrial Research Organisation and other relationships that are subject to confidentiality clauses. D. Wilcock is a paid consultant for AC Immune, Alector, and Eisai Inc. None of the work presented is related to these agreements. M. Tansey serves on the Michael J. Fox Foundation for Parkinson's Research Emerging Targets Advisory Committee, on the W. Weston Garfield Brain Institute Advisory Board, the Quebec Parkinson's Network, World Parkinson Coalition Board, Alzheimer's Association Medical and Scientific Advisory Group, and is a consultant to INmune Bio., Longevity Bio, Cerebral Therapeutics, RegeneX, and Prevail Therapeutics.

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## Abstract

The Alzheimer's Association International Conference held its sixth Satellite Symposium in Sydney, Australia in 2019, highlighting the leadership of Australian researchers in advancing the understanding of and treatment developments for Alzheimer's disease (AD) and other dementias.

This leadership includes the Australian Imaging, Biomarker, and Lifestyle Flagship Study of Ageing (AIBL), which has fueled the identification and development of many biomarkers and novel therapeutics. Two multimodal lifestyle intervention studies have been launched in Australia; and Australian researchers have played leadership roles in other global studies in diverse populations.

Australian researchers have also played an instrumental role in efforts to understand mechanisms underlying vascular contributions to cognitive impairment and dementia; and through the Women's Healthy Aging Project have elucidated hormonal and other factors that contribute to the increased risk of AD in women. Alleviating the behavioral and psychological symptoms of dementia has also been a strong research and clinical focus in Australia.

## Keywords

Alzheimer's; dementia; behavioral symptoms; biomarkers; prevention

## 1 INTRODUCTION

The worldwide effort to identify and develop effective therapies for Alzheimer's disease (AD) and other dementias has accelerated in recent years with increased funding and a proliferation of global collaborations.<sup>1</sup> Since 2015, the Alzheimer's Association

International Conference (AAIC) has helped fuel the globalization of AD research through its Satellite Symposia, a series of international meetings designed to highlight regional research and place it in the context of the global effort to identify new cures and treatments for AD and other dementias. Launched in 2015 in Mexico City, AAIC Satellite Symposia have also been held in Varna, Bulgaria; Buenos Aires, Argentina; Bengaluru, India; and Sao Paulo, Brazil. In 2019, the Association selected Sydney, Australia for a Satellite Symposia to ensure the strategic alignment of dementia research in Australia with that of the international research community.

Research in Australia has been instrumental in advancing global efforts to better understand the disease and develop strategies and technologies that will lead to improved treatments and cures. According to Dementia Australia, an estimated 459,000 Australians currently live with dementia, with this number predicted to grow to more than 1.1 million by 2058. Dementia is the second leading cause of death among all Australians and the most common cause of death among women. The cost of caring for Australians with dementia was estimated at \$14.25 billion in 2016.<sup>2</sup>

The National Health and Medical Research Council (NHMRC), Australia's chief funding agency for medical research, announced its Boosting Dementia Research Initiative in 2014, which committed \$200 million over 5 years and established the National Institute for Dementia Research (NNIDR) in July 2015 to coordinate an expansion of dementia research. In 2018, \$20 million was committed to establish the Australian Dementia Network to bring together researchers to create a national dementia clinical quality registry, to network and standardize memory clinics, and to boost participation in clinical trials.

At the Sydney Symposium, Australian scientists joined with other leaders in the field to focus on translation of research into new interventions, including novel biomarkers and novel therapeutics. Investigators shared the latest discoveries regarding genetic and vascular risk factors as well as multidomain lifestyle interventions designed to address these risk factors and treat the behavioral and psychological symptoms of dementia (BPSD).

## 2 BIOMARKERS

The development of AD biomarkers has fueled much of the progress in understanding the neuropathological and clinical progression of the disease and in developing a range of intervention strategies. The Australian Imaging, Biomarker, and Lifestyle Flagship Study of Ageing (AIBL), launched in 2006 as a longitudinal prospective study of cognition in people over the age of 60, capitalized on the pioneering work of Colin Masters, Christopher Rowe, and others at the University of Melbourne. At the time of the Sydney Satellite Symposium, AIBL had enrolled and collected longitudinal data from 2500 participants. These data are freely available to researchers worldwide.

AIBL, in collaboration with the Alzheimer's Disease Neuroimaging Initiative (ADNI), is credited with identifying and developing many the important AD biomarkers currently used in both research and clinical settings and continues to lead the field in the discovery and

development of novel biomarkers, particularly in the areas of molecular imaging and blood biomarkers.

## 2.1 | Molecular imaging

Imaging of processes and pathologies at the molecular level through positron emission tomography (PET), magnetic resonance spectroscopy (MRS), and optical retinal imaging techniques improves diagnostic and prognostic accuracy. Until relatively recently, these technologies were used primarily in research settings; however, as technologies have improved over the years and better reagents have become available, they have begun to be incorporated into clinical care. For example, Austin Health in Melbourne currently performs  $\approx 1000$  brain fluorodeoxyglucose (FDG)-PET scans each year. These scans assess brain glucose metabolism and provide much greater sensitivity and specificity in diagnosing AD compared to clinical diagnosis when verified against pathological findings,<sup>3</sup> leading to more appropriate management of patients with dementia.<sup>4</sup>

The advent of amyloid PET imaging has taken the specificity of diagnosis to an even higher level.<sup>5</sup> As demonstrated in the AIBL study, advances in amyloid PET imaging have also proven useful in predicting the development of mild cognitive impairment (MCI) and AD in cognitively normal adults.<sup>6</sup> Now, with a standardized method for quantitating amyloid plaque deposition across multiple scanners and using different PET ligands by using a scale of 0 to 100 “Centiloid units,” amyloid imaging has become even more useful as a diagnostic tool.<sup>7</sup> Amyloid imaging as a tool for identifying early pathological changes in the AD brain has also been incorporated into revised diagnostic criteria developed by the International Working Group (IWG),<sup>8</sup> the National Institute on Aging and Alzheimer’s Association (NIA-AA) working group,<sup>9</sup> and the recent NIA-AA Research Framework.<sup>10</sup>

Molecular imaging also may play multiple important roles in clinical trials: (1) for proof of target engagement; (2) to estimate target floor and ceiling values for trial inclusion; (3) to predict cognitive decline and disease progression, which can be used to stratify participants; and (4) as an outcome measure to monitor effectiveness. Amyloid PET imaging has been incorporated in many recent clinical trials for these purposes. For example, in a phase 2 trial of the monoclonal antibody bapineuzumab, amyloid PET imaging demonstrated that bapineuzumab blunts amyloid accumulation in the brain<sup>11</sup> whereas another monoclonal antibody, aducanumab, has been shown to reduce plaque burden.<sup>12</sup> These differences in kinetics may result from the antibodies targeting different forms of amyloid beta ( $A\beta$ ), which could explain differences in therapeutic efficacy at different stages of disease.<sup>13</sup> These findings also need to be considered when using PET as an outcome measure in clinical trials.

AIBL has collected  $>1600$  PET amyloid scans, making it the largest longitudinal study of amyloid imaging. A 2013 paper showed for the first time that amyloid load as measured by PET begins to rise about 20 years before cognitive impairment is apparent, and more recent data has refined understanding of the relationship between the amount of amyloid present in the brain and subtle changes in cognition as well as the effect of apolipoprotein E (*APOE*)  $\epsilon 4$  carriage.<sup>14,15</sup> Recent research has also revealed that in the AD brain, amyloid exists in multiple biochemical “pools” comprising both soluble and insoluble forms, but that PET only quantifies insoluble forms deposited as plaque. University of Melbourne researchers

are exploring the relationship of different  $A\beta$  pools with PET amyloid values across the continuum of the disease.

More recently, tau PET imaging has emerged as a tool for identifying early signs of neurodegeneration and monitoring disease progression in presymptomatic stages; and there have also been substantial molecular imaging advances to assess neuroinflammation, another hallmark of AD pathogenesis.

## 2.2 Blood biomarkers

Blood-based biomarkers have the potential to provide easily accessible and cost-effective solutions for the detection of pathological signs of AD, but until recently had been thought to lack the required analytical sensitivity to measure proteins derived from the brain in peripheral blood samples. However, recent technological advances, specifically ultrasensitive immunoassays and mass spectrometry techniques, have enabled dramatic improvements in the ability to quantify AD biomarkers in blood. Recent blood biomarker studies incorporate not only various species of  $A\beta$  and the neurodegeneration biomarker neurofilament light (NfL), but also novel methods for assessing levels of phosphorylated tau (p-tau). Consequently, these assays show great promise for use as screening tests, as well as tools to study AD pathophysiology in clinical, epidemiological, and genetic research. The development of blood biomarkers reflecting the complex and heterogeneous pathophysiology of AD is the cornerstone for early diagnosis, reliable prognosis, and drug response prediction. In addition, as AD is multifaceted, it's likely that a multiple biomarker approach will be needed for a correct stratification of the disease and its tailored treatment.<sup>17</sup>

A recent collaboration between scientists from Australia and Japan demonstrates the utility of plasma  $A\beta$  biomarkers to predict brain amyloid burden. Using a technique combining immunoprecipitation with mass spectrometry (IP-MS), and applying the technique to two independent datasets, the investigators showed that a composite of plasma biomarkers showed a diagnostic accuracy of 90% when amyloid PET was used as the standard of truth.<sup>18</sup> Several other plasma biomarker assays in development have shown similar levels of accuracy (e.g., Schindler et al.<sup>19</sup>). More recent longitudinal data further shows that plasma  $A\beta$  levels track with cognitive decline.

A novel and very promising blood biomarker for AD-type tau pathology is p-tau181. In 2018, a study using an electrochemiluminescence (ECL) immunoassay developed at Lilly Research Laboratories in the United States reported increased plasma p-tau181 in AD and correlations with both amyloid and tau PET.<sup>20</sup> These findings were replicated in a large cohort using the same ECL immunoassay, also demonstrating that plasma and cerebrospinal fluid (CSF) levels of p-tau181 correlate strongly, and that p-tau181 levels are normal in other neurodegenerative disorders.<sup>21</sup> Importantly, the increase in plasma p-tau181 was significant before amyloid PET, but after CSF and plasma  $A\beta_{42}$ , at sub-PET threshold amyloid pathology.<sup>21</sup> Very similar results were found using a novel assay based on the Simoa platform, validated in four independent cohorts, also in patients with cognitive complaints in the primary care setting.<sup>22</sup> Importantly, plasma p-tau181 measured by Simoa in samples taken 8 years prior to autopsy could differentiate AD from non-AD neurodegenerative diseases in neuropathologically confirmed cases with high (area under the curve [AUC]

0.97) accuracy.<sup>23</sup> These data support plasma p-tau181 as a robust blood biomarker that shows promise for implementation in clinical diagnostic routine.

### 2.3 | Novel biomarkers

Other novel biomarkers discussed at the Sydney Satellite Symposium included markers of mitochondrial abnormalities and inflammation, such as molecular imaging of the mitochondrial translocator protein (TSPO)<sup>24</sup> and mitochondrial complex I;<sup>24,25</sup> endothelial-derived plasma exosome proteins that may serve as markers of vascular contributions to cognitive impairment and dementia (VCID);<sup>27,28</sup> other CSF, plasma, and clinical biomarkers of VCID; advanced magnetic resonance imaging (MRI) markers of VCID;<sup>29</sup> and retinal imaging biomarkers of amyloid, vascular changes, and neurodegeneration.<sup>30–36</sup>

Alpha-synuclein is a biomarker associated with synucleinopathies such as Parkinson's disease (PD) and dementia with Lewy bodies (DLB) but also represented in limbic cerebral areas in both MCI and AD.<sup>37</sup> Recent studies demonstrated that measurement in CSF with innovative techniques (real-time quaking-induced conversion test assay [RT-QuIC]<sup>17</sup> and protein misfolding cyclic amplification [PMCA]<sup>38</sup>) or in peripheral red blood cells<sup>39,40</sup> could enrich the biomarker array for a precise stratification of typical and atypical phenotypes of AD.

## 3 | NOVEL THERAPEUTICS

Disappointing clinical trials of amyloid-targeting AD therapies have propelled the development of alternative therapeutic approaches. Among those discussed at the Sydney Satellite meeting were immunotherapies and other compounds that target tau by inhibiting kinases or aggregation or stabilizing microtubules. Because tau pathology correlates more strongly with the severity of dementia than  $A\beta$  pathology, targeting tau may be more efficacious than targeting  $A\beta$  once cognitive impairment begins. Sigurdsson provided an overview of the work of his laboratory in which initial studies demonstrated the efficacy of active and passive tau immunotherapies.<sup>41,42</sup> These studies have since been confirmed and extended by numerous groups, resulting in several ongoing clinical trials.<sup>43</sup> Currently, his group is clarifying the mechanisms of tau antibody therapies, and developing tau antibody fragments, including single domain antibodies derived from llama, both for in vivo detection of tau and as therapeutic agents.<sup>44–46</sup>

Another target that has received increasing attention in the AD field and at the Sydney meeting is inflammation. Inflammation appears to contribute substantially to disease progression in AD and other neurodegenerative diseases, with the brain-resident innate immune cells called microglia as key effector cells.<sup>47</sup> Genetic studies have also identified immune-related genes as important risk factors. Thus, although trials of anti-inflammatory drugs have failed thus far to show efficacy in AD, targeting inflammatory pathways and other interacting pathways such as metabolic and insulin resistance pathways continue to be viewed as potentially promising therapeutic strategies.<sup>48</sup> For example, INmuneBio, with support from the Alzheimer's Association, is currently conducting a Phase 1 study of XPro1595®, a drug that inhibits inflammation by selectively targeting and neutralizing soluble tumor necrosis factor (TNF). TNF has been shown to affect multiple metabolic and

immune pathways and contribute to insulin resistance and AD<sup>49</sup> and XPro1595 has been shown in multiple AD mouse models to be neuroprotective and anti-inflammatory but not immunosuppressive.<sup>49–53</sup> The trial, funded by the Alzheimer's Association Part the Cloud Translational Research program, is underway at five sites across Australia.

One of the challenges in developing treatments for AD is the blood-brain barrier, a continuous endothelial membrane that seals off the circulating blood from the interstitial space in the brain.<sup>54</sup> Numerous physiological transport systems have been exploited to deliver drugs across the blood-brain barrier and direct infusions into the brain have been developed but have met with limited success.

One novel non-invasive approach being developed at the University of Queensland in Brisbane, Australia, uses low-intensity ultrasound in combination with intravenously injected microbubbles to transiently and safely disrupt the blood-brain barrier.<sup>55</sup> Testing this approach in a mouse model of AD, Götz et al. have demonstrated the ability of repeated treatments with scanning ultrasound (SUS) to reduce amyloid plaque burden and restore memory even in the absence of anti-amyloid drugs.<sup>56</sup> They went on to show that the technique does not increase cerebral amyloid angiopathy (CAA) or microbleeds, which are thought to be associated with an increased risk of vascular dementia and that SUS also stimulates microglia activation and increased phagocytosis of amyloid.<sup>57</sup> Moreover, they have shown that SUS facilitates the uptake of therapeutic antibodies by the brain and into neurons more than tenfold, suggesting SUS as a drug delivery tool.<sup>58</sup>

In a mouse model of tauopathy, Götz et al. showed that repeated SUS treatments also cleared neuronal tau and improved motor and memory functions through the induction of autophagy.<sup>59</sup> They have since upscaled their research to test the approach in sheep, an animal model with a more human-like skull,<sup>60</sup> and are moving toward human safety trials and optimization of the technique in humans.

#### 4 | TARGETING VASCULAR, GENETIC, AND LIFESTYLE RISK FACTORS

Vascular risk factors including diabetes, hypertension, smoking, and stroke have long been known to increase the risk of cognitive decline and dementia.<sup>61</sup> While the impact of stroke on the development of dementia is seen primarily in late life, exposure to cardiovascular risk factors in early and mid-life has also been linked to cognitive worsening.<sup>62</sup> Moreover, multiple mechanisms have been shown to contribute to VCID, including ischemia, inflammation, oxidative stress, and impaired amyloid clearance; and other factors that may contribute throughout a person's life course including low socioeconomic status, low literacy, and environmental factors have been linked to poorer cardiovascular fitness and thus, cognitive decline.

Australian researchers are among the leaders in efforts to better understand both the mechanisms underlying VCID and the potential to identify modifiable risk factors to prevent cognitive decline. For example, they lead the Stroke and Cognition consortium (STROKOG), an international consortium that has developed harmonized methods for collecting longitudinal data from individuals who had a stroke or are at elevated risk of



stroke or transient ischemic attack (TIA).<sup>63</sup> STROKOG has merged data from >18,000 participants in 28 studies conducted in 17 countries. A recent analysis of data from 13 studies in 8 countries confirmed a high prevalence of post-stroke cognitive impairment (PSCI) and identified a history of past stroke, diabetes, hypertension, smoking, atrial fibrillation, and congestive heart failure as factors that increase the risk of PSCI.<sup>64</sup> The study further highlighted differences among different ethno-racial groups in terms of the influence of various risk factors. Other studies that have contributed to the understanding of the interplay among vascular disease, cognition, diabetes, and functional cognitive indicators such as gait include the Tasmanian Study of Cognition and Gait (TASCOG) and the Cognition and Diabetes in Older Tasmanians (CDOT) study.

Worldwide, women have a higher prevalence of dementia than men,<sup>65</sup> and female sex is the second strongest risk factor for late-onset AD after advanced age.<sup>66</sup> Factors that may contribute to the elevated risk of dementia in women include longer lifespan, genetics, hormonal differences, and an increased prevalence of metabolic and vascular risk factors.<sup>67,68</sup> Research has shown that heart disease in women differs from that in men in terms not only of risk factors but in symptoms and approaches to management and prevention; and similar sex differences are now being revealed in dementia research studies.

The influence of sex hormones on dementia risk remains poorly studied and understood although there is substantial evidence pointing to dramatic brain effects associated with hormonal changes during the menopausal transition.<sup>69</sup> For 30 years, the Women's Healthy Aging Project (WHAP), a longitudinal study of Australian-born women, has been collecting multi-domain data—including hormone levels; cognitive measurements; brain imaging; and vascular, genetic, and lifestyle risk factors—on women through the menopausal transition and into aging.<sup>70,71</sup> Recent research by Szoek et al. at the University of Melbourne showed that the combination of *APOE ε4* and midlife dyslipidemia compounded the risk of brain amyloid deposition in late life.<sup>72</sup> These findings may help explain why carriage of *APOE ε4* increases the risk of developing AD to a greater extent in women than in men.<sup>73</sup>

*APOE ε4* is the strongest known genetic risk factor for AD, yet multiple international genome-wide association studies (GWAS) have also identified 40 susceptibility loci and are using functional genomics studies to map these loci to genes, variants, and genetic pathways.<sup>74</sup> Across multiple sites in Australia, AIBL researchers have investigated whether it is possible to develop polygenic risk scores (PRS) to predict preclinical cognitive decline. While their research indicates that AD risk-weighted PRS are no better than *APOE ε4* alone in predicting cognitive decline, combining AD risk genes with genes associated with cognition and using phenotypic weighting appears to have some utility for predicting cognitive performance.<sup>75–77</sup>

While genetic factors clearly increase the risk of dementia, there is also strong evidence that lifestyle and environment also play important roles in increasing dementia, leading research groups worldwide to study whether lifestyle interventions may mitigate that risk. A recent study showed that a favorable lifestyle is associated with decreased dementia incidence even in older adults at high genetic risk.<sup>78</sup> Thus, given the overwhelming evidence that mid-life

exposure to vascular risk factors contribute to AD,<sup>79</sup> recent primary prevention studies have focused on lifestyle modifications to reduce these risk factors.

Evidence for the benefits of physical activity on cognition are particularly intriguing in part because of the face validity of putative mechanisms: improved cardiovascular health and cerebral blood flow, increased neuroplasticity and neurogenesis, and increases in blood levels of mediators of these physiological functions, including brain-derived neurotrophic factor (BDNF), insulin growth factor 1 (IGF-1), vascular growth factors, homocysteine, and nitric oxide.<sup>80</sup> In Australia, investigators enrolled older adult participants from the AIBL study in a 24-month physical activity intervention trial (the AIBL Active Study), which demonstrated excellent adherence and positive cardiovascular health benefits, suggesting that physical intervention may reduce risk factors for dementia.<sup>81</sup> The study also demonstrated that among older adults, long-term adherence to physical activity interventions is feasible. Another trial in Australia—the Individual Goal Setting (INDIGO) study—uses peer mentors and goal setting as motivators to increase physical activity among sedentary community-dwelling older adults with subjective memory complaints (SMC) or MCI.<sup>82</sup> Sleep disturbances and unhealthy diet have also been associated with increased brain amyloid burden.<sup>83,84</sup> In the case of the former, AIBL researchers have shown this to be significantly moderated by genetic factors.<sup>85</sup> This emphasizes the importance of understanding gene–environment interactions to improve potential efficacy of lifestyle interventions. Given the AIBL research group’s focus on lifestyle, it is no surprise that they have led the way in clinical and physiological studies investigating the links between AD and exercise, sleep, diet, and other modifiable lifestyle factors, including their interaction with genetic factors.

#### 4.1 | **FINGERS and other global efforts to combat dementia**

The World-Wide FINGERS (WW-FINGERS) network, co-led by the FINGERS team and the Alzheimer’s Association, aims to replicate the landmark Finnish Geriatric Intervention Study to Prevent Cognitive Impairment (FINGER) in different populations.<sup>86</sup> FINGER was the first large study to demonstrate that a multidomain intervention combining exercise, diet, cognitive training, and vascular risk monitoring could prevent cognitive decline in elderly participants at risk of cognitive decline based on their cardiovascular risk score.<sup>87</sup> WW-FINGERS studies in the United States (U.S. POINTER), Singapore (SINGER), Australia (AU-ARROW), China (MIND-CHINA), four European countries (MIND-ADmini), and the Basque population (GOIZ ZAINDU) use harmonized clinical trial methods and outcome measures adapted to the specific geographical, ethnic, cultural characteristics, and lifestyle practices of their populations.

Since the AAIC-SS in Sydney, the Alzheimer’s Association and the Medical Research Future Fund have funded the launch and implementation of the Australian Multidomain Approach to Reduce Dementia Risk by Protecting Brain Health with Lifestyle Intervention (AU-ARROW). The AU-ARROW intervention and assessment model builds on AIBL research findings and a lifestyle intervention study that demonstrated improved cognition and increased cerebral glucose metabolism resulting from a combination of physical activity with computerized brain training.<sup>88</sup> The 2-year trial will be conducted in Sydney and

Perth, comparing a multidomain intervention (aerobic exercise, nutritional counseling, computerized cognitive training, social engagement, and vascular risk monitoring) with a control group receiving health education and support. AU-ARROW has been harmonized to the U.S. POINTER study, which is wholly funded and led in collaboration with the Alzheimer's Association. This coordination is a key aspect for both studies, and supported through WW FINGERS.

Also in Australia, investigators have launched a 3-year online multimodal lifestyle intervention study called Maintain Your Brain (MYB), aimed at reducing cognitive decline in older adults.<sup>89</sup> If effective, this intervention could be easily and broadly implemented in diverse populations.

Other global studies have been examining other aspects of cognitive impairment in diverse populations around the world. For example, starting in 2012, the Cohort Studies of Memory in an International Consortium (COSMIC) began collecting and harmonizing data from population-based longitudinal studies of aging and dementia, now including 41 cohorts in 31 countries across six continents.<sup>90</sup> By exploring risk factors that contribute to cognitive decline across 20 cohorts, including different ethno-racial groups, Lipnicki et al. showed that certain risk factors such as high cholesterol, diabetes, smoking, and female sex are more strongly associated with cognitive decline among Asians than Whites, suggesting that prevention strategies may need to be adapted according to geography and ethnicity.<sup>91</sup> Brain structural and neuropathological changes have also been shown to differ among individuals with dementia from diverse ethnic and racial groups.<sup>92</sup> In Australia, increased dementia prevalence and incidence was demonstrated among Aboriginal and Torres Strait Islander peoples compared to non-Aboriginal older people<sup>93</sup> and has led to the development and validation of cognitive and well-being assessments and resources for Aboriginal people<sup>94,95</sup> community models of dementia care,<sup>96</sup> and interventional partnerships such as the Dementia Prevention and Risk Management Program for Aboriginal Australians (DAMPAA) program aimed at reducing dementia risk through exercise, cardiovascular risk management, cognitive and social engagement, and education in partnership with Aboriginal community-controlled health services and communities.

Globally, efforts are also underway to increase participant engagement and recruitment efficiency in clinical studies worldwide. In Australia, for example, StepUp for Dementia Research is a platform that connects individuals with research studies. Similar platforms have also been developed in the United States (the Alzheimer's Association's TrialMatch®, Banner Health's Alzheimer's Prevention Registry, and UCSF's Brain Health Registry); the United Kingdom (Join Dementia Research); and Netherlands (Amsterdam UMC VU University's Hersenonderzoek).

The *Journal of Alzheimer's Disease* recently published a special issue from the International Research Network on Dementia Prevention (IRNDP). The IRNDP is a network of researchers and stakeholders with a common interest in dementia risk reduction, especially incorporating low- and middle-income countries. The special issue included articles on risk factors, trials, and population-level modeling related to dementia risk factors.<sup>97</sup> While it highlights the growing evidence suggesting that lifestyle and environmental factors<sup>98</sup> may

be targeted to reduce the risk of dementia, it also recognizes the substantial knowledge gaps that remain and that there are limitations in the quality and quantity of evidence.<sup>99</sup>

The World Health Organization (WHO) has published the first global guidelines for risk reduction of cognitive decline and dementia. The guidelines, developed using the GRADE methodology involving a range of international experts, draw mostly from the literature on interventions to reduce risk of dementia and cognitive impairment. Observational research was used to inform the guidelines where there was a lack of randomized controlled trials. There are also guidelines emerging that focus on specific risk factors and populations. For example, the Australian Dementia Collaborative Research Centres at the University of Melbourne have published physical activity guidelines for older Australians with MCI or SCD.<sup>100</sup> A global call for action on dementia risk reduction must involve consumers and clinicians and be informed by new evidence as it emerges. To that end, recommendations for clinicians have been published to guide patients regarding the potential benefits of physical activity on brain health while taking into account individual patients' health problems or other limitations.<sup>101</sup>

## 5 | THE ROLE OF PSYCHOGERIATRICS IN DEMENTIA CARE

For patients and caregivers, behavioral and psychological symptoms associated with dementia are among the most burdensome.<sup>102</sup> Agitation, delusions, hallucinations, sleep disturbances, and apathy occur commonly in patients with dementia as well as in patients with depression, and many patients with a psychiatric disorder mimicking dementia actually have other conditions that are treatable, such as depression or apathy.<sup>103–105</sup>

International consensus groups including the International Psychogeriatrics Association (IPA), International Society to Advance Alzheimer's Research and Treatment (ISTAART) Neuropsychiatric Symptoms (NPS) Professional Interest Area (PIA), and other expert panels have begun to develop diagnostic criteria for agitation, psychosis, and apathy in major and minor neurocognitive disorders (the terminology advocated as a replacement for "dementia" in the Diagnostic and Statistical Manual for Mental Disorders, 5th edition [DSM-5]).<sup>82–84</sup> These criteria are essential for developing appropriate pharmacological and non-pharmacological interventions.

Several studies in different parts of the world have documented that many people in residential long-term care facilities have treatable psychiatric disorders but receive inappropriate drug treatments.<sup>106–109</sup> In Australia, two studies—the Halting Antipsychotic Use in Long-Term Care (HALT) trial and the Reducing Use of Sedatives (RedUSE) trial have achieved reductions in the use of psychotropic medications.<sup>110,111,17</sup> These investigators and others advocate an increased focus on non-pharmacological interventions through a person-centered care paradigm<sup>112</sup> and using novel strategies such as humor therapy.<sup>113</sup> Another novel approach to reducing BPSD in people with dementia is being developed by researchers at Griffith University in South East Queensland, Australia. They have been researching the use of "social robots" with artificial intelligence systems to interact with people and tap into their need for social connections.<sup>114</sup> A recent systematic review showed that social robots were able to improve or increase pleasure affect, decrease

depressive symptoms and loneliness scores, increase quality of life, and reduce agitation.<sup>115</sup> Indeed, evidence indicates that the use of appropriate technologies can enable older adults to continue living in their homes longer, maximize individual autonomy, and promote social participation.<sup>116</sup>

## 6 | GUT–BRAIN AXIS REGULATION OF ALZHEIMER’S DISEASE PATHOLOGY

The gut—brain—microbiota axis plays a critical role in determining the long-term health of the brain. This axis describes a bidirectional communication between the gut microbiota residing in the gastrointestinal tract and the brain, which influences many of the biochemical and vascular processes in the brain at every stage from development to neurodegeneration. The main mechanisms of gut–brain axis communication include direct vagal signaling, endocrine factors, metabolic processes, and immune signaling.<sup>117</sup> Variations in the gut microbiota due to stress, antibiotic usage, or aging alters the homeostatic processes in the periphery and the brain, ultimately predisposing the aging population to the accumulation of amyloid plaques and tau tangles. This novel idea is in line with recent findings, including a report released by the WHO, which has identified lifestyle-related risk factors as a critical part of AD etiology and may even precipitate the canonical pathological changes in  $A\beta$  and tau.<sup>118</sup> In this sense, the physiological adaptations elicited by gut–brain axis signaling can prevent the onset and/or progression of AD creating a novel therapeutic strategy involving the use of gut microbiota altering probiotics and prebiotics.

Several preclinical and clinical studies have supported the role of probiotic and prebiotic supplements for promoting resilience to the clinical and biochemical signatures of AD. In a randomized, double-blind, placebo-controlled trial, 12 weeks of *Bifidobacterium breve* A1 supplementation to patients with cognitive impairment complaints improved their immediate memory scores.<sup>119</sup> A similar study using *Lactobacillus plantarum* C29 fermented soybean showed an increase in cognitive function related to memory and attention in patients with MCI.<sup>120</sup> This study also showed that the improvement in cognitive impairment increased serum BDNF levels validating the biochemical changes in the brain elicited by probiotic treatment.

One of the main mechanisms of gut—brain—microbiota axis communication that can promote resilience to AD is the prevention of neuroinflammation, a major risk of AD progression.<sup>121</sup> For example, low-grade Ab accumulation has been associated with microglia activation leading to a higher retention of the amyloid plaques<sup>122</sup> and stimulation of proinflammatory nuclear factor kappa-light-chain-enhancer of activated B cell (NF- $\kappa$ B) signaling and associated gliosis.<sup>123</sup> Along these lines, there have been several preclinical studies demonstrating how the gut microbiota and gut–brain axis signaling can positively impact neuroinflammation by attenuating microglia activation.<sup>124</sup> In a PD model, fecal transplants from healthy human donors into a mouse model of PD attenuated the associated physical and cognitive impairments.<sup>125</sup> One study showed a direct relationship between the probiotic *Clostridium butyricum*’s butyrate production and the attenuation of microglia activation and proinflammatory cytokine release.<sup>126</sup> This and other gut

microbiota–metabolite relationships have been identified as potential therapeutic strategies that could be capitalized on for the delay of the onset and/or progression of AD.<sup>127</sup>

## 7 | CONCLUSION

Recent increased funding for AD and other dementia research has enabled Australia to play a leading role across multiple disciplines in international research efforts to fight these diseases. Australia has also supported the efforts of low- and middle-income countries in the Asia-Pacific region, for example, by providing research capacity for the development of a national dementia action plan in Vietnam.

In addition to presentations by leaders in the field, the Symposium highlighted innovative work underway by junior investigators and others who were selected to share their data through two “lighting poster rounds.” These sessions confirmed that Australian AD research will continue to thrive in the coming years.

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## RESEARCH IN CONTEXT

### **Systematic Review:**

The authors report the updates and advances in Alzheimer's disease and dementia research presented at the Alzheimer's Association International Conference (AAIC) Satellite Symposium in Sydney.

### **Interpretation:**

The findings highlight both established and emerging research from Oceania spanning biomarkers, novel therapeutics, risk factors, and dementia care.

### **Future Directions:**

Previous AAIC Satellite Symposia have been hosted by Mexico City, Mexico; Varna, Bulgaria; Buenos Aires, Argentina; Bengaluru, India; and São Paulo, Brazil. The 2021 AAIC Satellite Symposia, hosted in collaboration with the Global Brain Health Institute, will be a virtual conference that will explore dementia research in the Mediterranean region.