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RESEARCH ARTICLE

Dementia Prevention Research Clinic: a longitudinal study investigating factors influencing the development of Alzheimer's disease in Aotearoa, New Zealand

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ABSTRACT

Aotearoa New Zealand's population is ageing. Increasing life expectancy is accompanied by increases in prevalence of Alzheimer's Disease (AD) and ageing-related disorders. The multicentre Dementia Prevention Research Clinic longitudinal study aims to improve understanding of AD and dementia in Aotearoa, in order to develop interventions that delay or prevent progression to dementia. Comprising research clinics in Auckland, Christchurch and Dunedin, this multi-disciplinary study involves community participants who undergo biennial investigations informed by international protocols and best practice: clinical, neuropsychological, neuroimaging, lifestyle evaluations, *APOE* genotyping, blood collection and processing. A key research objective is to identify a 'biomarker signature' that predicts progression from mild cognitive impairment to AD. Candidate biomarkers include: blood proteins and microRNAs, genetic, neuroimaging and neuropsychological markers, health, cultural, lifestyle, sensory and psychosocial factors. We are examining a range of mechanisms underlying the progression of AD pathology (e.g. faulty blood–brain barrier, excess parenchymal iron, vascular dysregulation). This paper will outline key aspects of the Dementia Prevention Research Clinic's research, provide an

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overview of data collection, and a summary of 266 participants recruited to date. The national outreach of the clinics is a strength; the heart of the Dementia Prevention Research Clinics are its people.

Introduction

Aotearoa New Zealand's (NZ) population is ageing, with increasing life expectancy of all ethnicities. This is associated with rapidly increasing numbers of people with ageing-related brain disorders that severely impact psychological, social, and economic functioning of individuals, their whanau (family) and communities. The number of New Zealanders with dementias such as Alzheimer's Disease (AD) is projected to increase from an estimated 69,713 in 2020 to167,483 people in 2050, increasing from 1.4% to 2.7% of the population (Ma'u, Cullum, Yates et al. 2021). In 2020 the economic costs of dementia in Aotearoa NZ were estimated at $2.46 billion ($3.62 billion if unpaid care is valued as a replacement cost). The costs associated with loss of healthy life and disability were estimated at a further $5 billion. The numbers affected by dementia in Māori and Pacific populations are not known. Critically, however, the number of Māori kaumātua (Māori elders) 65 years or older increased by 41% between 2013 and 2018 (Statistics New Zealand 2018), so a disproportionate increase in the prevalence of dementia for Māori is expected. Determining effective methods to alter the current trajectory of burden and disability associated with dementia will increase well-being in the later years of life for all New Zealanders. The potential impact of delaying dementia onset is profound: delaying dementia onset by five years would reduce its prevalence by 50% (Brookmeyer 1998).

AD is the most common form of dementia, making up 50-75% of cases (Prince et al. 2014). The dominant conceptualization of AD is the amyloid cascade hypothesis. Increasing levels of amyloid-β (Aβ) peptide may trigger a cascade of events including excessive hyperphosphorylation of tau, which ultimately leads to cellular death and brain atrophy, leading to cognitive impairment and dementia (Ballard et al. 2011). Millions of dollars invested in the development of disease-modifying drugs largely focused on modulating amyloid pathophysiology have thus far either failed or resulted in controversial outcomes. The FDA in the USA approved in 2021 the use of the anti-amyloid, aducanumab, for individuals with mild cognitive impairment (MCI) and early AD (Cavazzoni 2021), with the caveat that ongoing clinical trials are needed to fully determine the drug's efficacy (Knopman et al. 2020). One possible reason for the lack of success of anti-amyloid therapies is that to date they have been tested either on individuals with dementia or those with MCI, in whom extensive neuronal damage has already occurred. This treatment approach may be better suited earlier in the disease process. Nevertheless, the significant failure rate of drug development also highlights our incomplete understanding of the mechanisms underlying AD. Clearly, a range of other factors and molecular processes need also to be explored (Brothers et al. 2018; Ray and Buggia-Prevot, 2021; Rayaprolu et al. 2021). In addition, a number of modifiable factors, even in later life, may significantly alter dementia risk (Livingston et al 2017, 2020).

Testing both pharmacological and non-pharmacological interventions to slow or reverse the development of AD needs reliable biomarkers that are detectable in the pre-clinical stages of AD. Biomarkers must also detect disease progression and be easily measured, repeatable, accessible, and cost-effective. Ideally, such biomarkers will offer opportunities for interventions that prevent development of a significant level of irreversible neural injury.

Several international longitudinal studies aim to identify a range of biomarker signatures for AD, including neuroimaging, genetic, blood-based and lifestyle characteristics (Lawrence et al. 2017). Living in Aotearoa NZ provides a unique developmental experience (educational, occupational, nutritional, social, lifestyle, historical) that will likely influence the contributory role of identified risk factors, may add novel risk factors, and/or be associated with unique protective factors. Aotearoa NZ additionally has a unique ethnic composition, with varying susceptibility within ethnic groups to modifiable risk factors identified internationally (Ma'u, Cullum, Cheung et al. 2021). Thus, there may be both biological and non-biological factors that provide a local context to the risk of dementia. Together, these points highlight the critical need for a longitudinal study based in Aotearoa NZ.

The Dementia Prevention Research Clinic (DPRC) study is a multi-centre, multi-disciplinary, longitudinal research study, with an anticipated duration of at least 10 years. It currently comprises three research clinics in Auckland, Christchurch, and Dunedin. Established by Brain Research New Zealand - Rangahau Roro Aotearoa Centre of Research Excellence, the clinic network represents a national collaboration currently involving four tertiary institutions, clinicians, scientists, and members of the community. The main goal is to improve understanding of AD and dementia using a multidisciplinary approach, in order to develop interventions that delay or prevent progression to dementia. Beyond identifying a 'biomarker signature' for progression in clinically at-risk individuals, we aim to identify other factors that influence cognitive decline in a sample that represents all New Zealanders aged 55 years and older. This will reveal an interacting collection of biological, genetic, lifestyle and psychological elements. As different ethnic groups in Aotearoa NZ differ in their risk factor profiles, biomarker signatures may vary by ethnicity, lifestyle, and possibly genetic factors (Ma'u, Cullum, Cheung et al. 2021). Identification of ethnic-specific biomarker signatures, however, will only be possible if over-sampling of Māori (and other ethnic minority groups) is achieved. A further objective is to investigate the mechanisms leading to MCI and AD dementia utilizing novel Magnetic Resonance Imaging (MRI) and blood-based methods. Finally, we will explore the experience of individuals and their whanau/family (e.g. factors influencing well-being).

In this paper we outline key issues in the AD literature that are a focus of current DPRC research. We also provide a summary of the study population to date, an overview of data collected routinely within the study and highlight important qualities about the functioning of the DPRCs.

Mechanisms of AD: a single pathway or multiple routes?

Increased levels of Aβ, hyperphosphorylation of tau and neurodegeneration are key events in the aetiology of AD (Jack et al. 2018), but alone they may not fully

explain the majority of cases with sporadic AD. A recent genome-wide association study (GWAS) meta-analysis connects immunity, lipid metabolism, tau binding proteins, and amyloid precursor protein metabolism with sporadic AD (Kunkle et al. 2019). Strong molecular evidence also connects inflammation, astrocyte, vascular and blood brain barrier (BBB) dysfunction with AD. Analysis of known risk factors, such as ageing, cardiovascular and vascular disease, viral and bacterial infection and metabolic disease, reinforce the relevance of these alternate molecular indicators and suggest a model where accumulative 'stress' contributes to AD. This is congruent with an emerging viewpoint that there are multiple pathways by which a cascade of events leading to AD is set in motion (Hampel, Vergallo et al. 2018; Yu et al. 2018).

The DPRC study is investigating a wide range of potential processes that might contribute to the onset of AD pathogenesis and the conversion from MCI to dementia, using combined neuroimaging, blood and clinical data embedded within a longitudinal design. There is growing interest, for example, in the possibility that vascular dysregulation and changes may be influential factors in AD (Koncz and Sachdev 2018). One of the key controversies is whether vascular factors not only co-occur with AD but promote AD pathogenesis. While there is widespread acceptance that individuals with the clinical syndrome of AD dementia frequently have additional neuropathology beyond the hallmark plaques and tangles which contribute to the clinical syndrome, there is considerable disagreement as to whether vascular mechanisms are causally associated with AD pathology (Brickman et al, 2015; Iturria-Medina et al., 2016; Jagust et al, 2019; Sweeney et al., 2019).

Biomarker signatures

To provide hope that it may be possible to delay or prevent the development of AD and other dementias, it is vital to identify early, accurate indicators of incipient disease and understand how these alter throughout the course of the disease. This will allow early detection and early intervention with current and emerging therapies.

Genetic factors

In a small percentage of cases (1-5%), AD is present in family pedigrees with known mutations in one of three different genes (*APP, PSEN1* and *PSEN2*). These mutations result in the overproduction of Aβ — specifically, the 42 amino acid Aβ isoform (Aβ1-42) and are associated with early onset of the disease (Masters et al., 2015). In sporadic late onset AD the *APOE* gene, specifically the *APOE* ε4 allele, on chromosome 19 is the strongest genetic risk factor, but by itself is not strongly predictive of progression to AD (Stocker et al. 2018).

Genome wide association studies (GWAS) have identified many other common variants that modify the genetic risk of developing late onset AD (LOAD) or the age of onset. These variants and their identified effects on risk have been used to calculate Polygenic Risk Scores (PRS), which estimate the cumulative risk of LOAD and hold promise as one important step in identifying factors that influence the onset and progression of LOAD from MCI (Escott-Price et al. 2015). PRS will be used in DPRC efforts to identify biomarker signatures.

Fluid biomarkers

The field of fluid biomarkers for AD until recently has focused primarily on cerebrospinal fluid (CSF). CSF has direct contact with the extracellular space of the brain, providing an ideal source of fluid likely to reflect biochemical changes occurring in the brain. Jack et al. (2018) proposed core CSF biomarkers for detection of the 'ATN' AD-related pathologies: CSF Aβ1-42 for Aβ plaque pathology (A), CSF total tau (t-tau), CSF phosphorylated tau species (p-tau) for tau pathology (T) and neurofilament light (NfL), the neuronal injury marker for neurodegeneration (N). CSF Aβ1-42 is the most specific biofluid marker for Aβ plaque pathology, having 100% concordance with amyloid PET (Janelidze et al. 2017). Given this high concordance, amyloid PET and CSF Aβ1-42 can be used interchangeably to aid research and clinical practice and are considered the gold-standard for *in vivo* detection of AD pathology. CSF can also be utilized to investigate other processes that may contribute to AD pathology such as neuroinflammation, BBB dysfunction or synaptic dysfunction.

More recently the search for a blood-based signature of markers capable of predicting onset of AD has gathered momentum, as the collection of blood is minimally invasive and more cost effective than CSF testing (Hampel, O'Bryant et al. 2018). New methods enable measurement of minute amounts of brain-derived proteins in blood samples, thus making it possible to develop a blood biomarker test that can predict development of AD. A test focused on Aβ levels and APOE has recently been released (PrecivityAD™; Kirmess et al. 2021), but the opportunity exists to develop a broader biomarker signature that extends beyond amyloid-ß, which is more representative of the various stages of disease progression.

One such advance using ultra-sensitive immunoassay methods is the Single Molecule Array (SiMoA), which now allows the assessment of key markers of AD pathology and potential identification of novel markers in blood (Li et al. 2019). The DPRCs are currently undertaking analysis of a range of analytes in 617 blood samples including longitudinal participant visits, in collaboration with a Swedish research group expert in measuring blood proteins with this technology (Zetterberg 2019; Karikari et al. 2021). These include Aβ1-42, t-tau, p-tau species, NfL and glial fibrillary acidic protein and novel markers. Furthermore, recent studies have shown that the expression of small non-coding RNA, microRNAs, are altered throughout the course of neurodegenerative diseases such as AD (Gerbert et al. 2019). Interestingly, while microRNA can be detected in cerebrospinal fluid, microRNA cross the blood-brain barrier and are protected from degradation by association with protein complexes and sequestration into membrane bound vesicles, such as exosomes (Kou et al. 2020). Thus, circulating levels of microRNA may represent a robust, stable, and easily measurable biomarker that accurately reflects not only build-up of Aβ, but the progression of AD. Indeed, Guévremont et al (2022) recently identified disease stage-specific microRNA biomarkers that successfully predicted membership of amyloid-positive, aMCI and AD participants, relative to their respective controls. As microRNA are easily measured in plasma using routine PCR-based methods, microRNA signatures may be useful in identifying individuals at risk of developing AD.

Neuroimaging biomarkers

International research generated by longitudinal studies such as ADNI (Weiner et al. 2012), utilizes MRI and PET imaging modalities, in the search for predictive and reliable

biomarkers. Combined modalities can measure components of the 'ATN' framework, yet predicting incipient AD remains elusive. Neuroimaging studies contribute significantly to investigating vascular changes in AD. While there are many findings demonstrating the impact of vascular abnormalities (e.g. white matter hyperintensities, arterial stiffening) on cognition and AD dementia (Puzo et al. 2019; Werhane et al. 2021), it has been more difficult to demonstrate a causal association with AD pathology.

We recently reported a neuroimaging study in which we evaluated the spatial coefficient of variation (sCoV) of cerebral blood flow maps, measured in DPRC participants who met criteria for healthy/cognitively normal older adults, subjective cognitive decline (SCD), amnestic MCI and AD dementia (Morgan et al. 2021). The sCoV, an imaging metric derived from arterial spin labelling (ASL) MRI, is related to vascular health. sCoV in whole brain grey matter and in the temporal lobe progressively increased in line with increased cognitive deficits. This measure, related to vascular transit time in the brain, is thus sensitive to increasing levels of cognitive change, suggesting that vascular health contributes to cognitive decline along the AD continuum.

Some PET findings suggest that cerebrovascular risk factors such as hypertension and hyperlipidaemia may play a role in increasing brain Aβ (Rodrigue et al. 2013; Gottesman et al. 2017). Others, however, have used amyloid imaging and failed to find associations between vascular factors and AD amyloid pathology (Vemuri et al. 2015). The fundamental question of whether there is a causal link remains a focus, which may be best solved by appropriately designed longitudinal studies (Koncz and Sachdev 2018).

The DPRC study is utilizing biennial multimodal MRI brain imaging comprising seven different types of clinical and research scans (described below) in the DPRC participant groups. Employing both cross-sectional and longitudinal analyses, we will leverage the unique information provided by each modality to shed light on the brain changes associated with disease development. In addition, these neuroimaging measures can be combined with a range of other measures (e.g. neuropsychological, genetic and blood biomarker profiles, lifestyle factors) in machine-learning models that predict the probability of disease progression in individuals. We are also developing and testing novel MRI protocols to measure a targeted range of potential processes that might contribute to the onset of AD pathogenesis, for example, parenchymal iron (Moon et al. 2016), cerebral blood flow (4D-flow imaging; Rivera-Rivera et al. 2017) and a contrast-agent free MRI method to measure the integrity of the BBB (Dickie at al. 2020).

Modifiable risk factors

The Lancet Commission into dementia prevention, intervention and care has identified 12 potentially modifiable risk factors comprising 40% of the risk for dementia: less education, hypertension, hearing impairment, traumatic brain injury, smoking, obesity, excessive alcohol consumption, depression, physical inactivity, diabetes, traumatic brain injury, air pollution and low social contact (Livingston et al. 2017, 2020). Ma'u et al. recently estimated the weighted population attributable factors of the 12 factors for the four largest New Zealand ethnic groups (Māori, European, Asian, and Pacific peoples) (Ma'u, Cullum, Cheung, et al. 2021). They determined that 47.7% of dementia in New Zealand was attributable to the 12 risk factors, but there were differences across the four ethnic groups (Asian 40.8%; European 47.6%; Pacific peoples 50.8%; Māori 51.4%), as well as differences in the relative contribution of individual risk factors

within the different ethnicities. Overall, this suggests a high potential for dementia prevention in Aotearoa NZ, and that strategies should be tailored for different ethnic communities. While there is evidence suggesting that targeting the identified risk factors may be successful in lowering incidence of dementia (Wu et al. 2017; Gao et al. 2019), whether interventions for each risk factor in clinically at-risk individuals will result in a significant change in trajectory for that individual is as yet unclear and needs further research.

Equally importantly within different ethnic communities may lie unique protective factors. A recent study conducted in Aotearoa NZ suggests Māori are more likely to have Alzheimer's or other dementias than non-Māori and that they present at an earlier age (Cullum et al. 2018). Yet in a study of the very old, Māori did not have an increased incidence compared with age matched non-Māori (Teh et al. 2014), despite a higher prevalence of known risk factors for dementia (e.g. low education, deprivation, cardiovascular disease, diabetes). This suggests that potential protective factors related to cultural practices and identity may influence development of dementia in Māori and that this may be related to age and stage of life. Additionally, non-modifiable genetic differences between Māori and other ethnic groups may also influence dementia risk.

Overview of the DPRC study

The target population for the DPRCs is individuals clinically at risk for short-term progression to AD dementia, who have memory difficulties noticed by themselves or others, with or without objective memory impairment. This includes individuals with amnestic MCI (single or multi-domain) with subjective and objective indicators of memory impairment who maintain normal functional ability in everyday life (Peterson et al. 2014), and individuals with subjective memory difficulties (SCD) only (Jessen et al. 2014). These groups are prioritized because they fall on the continuum to AD (Sperling et al. 2011), yet both classifications not only include individuals who will progress to dementia, but others whose cognition will remain stable or even improve back into the normal range (Peterson et al. 2018). Identifying reliable predictive factors or biomarkers of these outcomes in aMCI and SCD is a critical step. We also include individuals with non-amnestic MCI, also at elevated risk of progression to dementia but not specifically AD, cognitively normal older adults who do not report memory or other cognitive difficulties, and individuals in the early stages of dementia due to AD. These groups enable both cross-sectional and longitudinal comparisons with the high-risk groups. Below we present a general overview of the current study population (recruitment is ongoing) and general methods.

Methods and materials

Participants

Potential clinical participants are referred to the DPRCs by GPs or medical specialists. Inclusion criteria require participants to be ≥ 55 years or older, have memory or other cognitive difficulties noticed by themselves or others, and not living in a long-term care facility. Exclusion criteria include a significant history of psychiatric disorders, significant past or current alcohol problems, moderate-severe traumatic brain injury,

pacemaker or neurological conditions other than mild probable AD including moderate dementia. Individuals with a history of symptomatic stroke are excluded. Common findings in this age group of small vessel disease on MRI and/or a small number of asymptomatic lacunes are not exclusionary. Cognitively normal older adults who do not report memory difficulties have to date been recruited from a number of sources: information pamphlets left at GPs, public talks, media information or articles, hearing about the study from others. All participants nominate a study partner who knows them well and has regular contact (most commonly a family member).

To receive a classification of amnestic MCI the participant must report subjective memory difficulties, have objective indicators of memory impairment and maintain normal functional ability in everyday life (Albert et al. 2011). Objective evidence of memory difficulty is defined as performing more than 1 standard deviation lower than expected for age and education/ability levels on at least two measures of verbal memory (delayed recall) or two measures of visual memory (delayed recall) (Peterson et al. 2014). When cognitive difficulties are limited to memory, the classification is amnestic MCI (single domain), but impairment on memory plus one other cognitive domain is classified as amnestic MCI (multi-domain). If objectively measured cognitive impairments do not involve memory (despite subjective reports of memory problems), the classification is non-amnestic MCI (single or multi-domain). A classification of SCD is made if an individual reports memory difficulties over and above reported in normal ageing in a structured interview but has no objective evidence of impairment (Jessen et al. 2014). The mild Alzheimer's dementia group have significant impairments in at least two cognitive domains, including memory, with a gradual onset and evidence of progression (McKhann et al. 2011). All had evidence of significant decline in their ability to function in their usual activities. Only individuals with an ACE-III score of 76 or higher were invited to continue, in order to ensure they had only mild dementia.

The Auckland DPRC began participant recruitment mid-2016, the Dunedin DPRC in 2017, and the Christchurch DPRC in mid-2019. Recruitment and re-assessment progress has been significantly impacted by COVID-19 during 2020 and 2021 in all clinics, but particularly for the Auckland DPRC, which is also the largest of the clinics. Nevertheless, by August 2021, 266 participants had been enrolled and completed all baseline assessments; general characteristics of participants are summarized in Table 1.

Clinical assessment

All participants undergo in-depth multidisciplinary assessments, conducted biennially ± 6 months, with specialist medical clinicians, research nurses and neuropsychologists. Assessments cover clinical, neurological and health evaluations, a global cognitive screen with the Addenbrooke's Cognitive Examination-III (ACE-III), sleep quality, perceived hearing functioning, lifestyle assessment, and nutrition (see Table 2). Part of the medical evaluation includes measurement of height and weight (enabling calculation of body mass index) and current medications. Additionally, blood pressure is measured (for possible untreated hypertension), blood analyses of dyslipidaemia and, diabetes conducted, and history of smoking gathered by interview. This will enable evaluation of the role of a range of vascular factors, and of a combined vascular risk metric, in cognitive decline and progression to AD dementia. Mood is

Table 1. Demographic characteristics of current sample.

	Control n = 36	SCD n = 66	aMCI (single) n = 57	aMCI (multi) n = 53	Non-amn. MCI n = 25	Early AD n = 29
Females (%)	27 (75)	42 (63.5)	27 (47.4)	28 (52.8)	10 (40.0)	9 (36)
Age (years) Mean (SD)	67.14 (8.86)	68.30 (8.41)	69.88 (8.04)	71.43 (7.05)	67.28 (8.57)	72.95 (7.50)
Yrs Education Mean (SD)	15.47 (3.23)	15.09 (3.04)	14.25 (2.88)	15.87 (3.26)	14.36 (3.08)	14.14 (3.38)
ACE-III Mean (SD)	95.11 (4.25)	91.68 (5.42)	87.58 (6.97)	84.00 (5.88)	89.36 (7.11)	81.22 (5.67)

Notes: SCD = subjective cognitive decline; aMCI (single) = amnestic mild cognitive impairment, single domain; aMCI (multi) = amnestic mild cognitive impairment, multi domain; Non-amn. MCI = non-amnestic mild cognitive impairment; Early AD = early Alzheimers dementia; ACE-III = Addenbrooks Cognitive Examination-III. ACE-III was significantly different between groups. Games-Howell pairwise comparisons showed the control group differed from all other groups. The SCD group differed from all groups except for non-amnestic MCI, as did the aMCI (single) group. The aMCI (multi) and AD groups did not differ, but differed from all other groups.

assessed by clinical interview and mood scales, and also via a questionnaire filled out by the study partner. The study partner also completes questionnaires related to the participants' everyday cognition and functioning in everyday life (see Table 2).

Neuropsychological assessment is conducted on a separate day by expert clinical neuropsychologists and includes a minimum of two tests in each of six cognitive domains: verbal and visual memory, executive functioning, attention, processing speed, visuospatial and language/semantic skills (see Table 3 for list of neuropsychological measures). All measures are administered to all participants.

Neuroimaging

MRI scanning is conducted on a 3T Siemens Skyra in all three DPRC clinics (Centre for Advanced MRI at the University of Auckland; Pacific Radiology Group in Christchurch

Table 2. Clinical and Lifestyle Measures.

Domain	Measures	Reference
Sleep	Epworth Sleepiness Scale	Johns (1992)
Mood	Geriatric Depression Scale	Sheikh and Yesavage (1986)
	Generalised Anxiety Inventory	Pachana et al. (2007)
	P4 Suicidality Screener	Dube et al. (2010)
Hearing	The Hearing Handicap Inventory for the Elderly Screening (HHIE-S)	Jupiter and DiStasio (1998)
Nutrition	Food Frequency Questionnaire – Short Version	Sam et al. (2020)
Lifetime Experiences	Lifetime Experience Questionnaire	Valenzuela and Sachdev (2007)
Study Partner Questionnaires	Neuropsychiatric Inventory – Questionnaire (NPI-Q)	Kaufer et al. (2000)
	Measurement of Everyday Cognition	Farias et al. (2008)
	Functional Activities Questionnaire	Pfeffer et al. (1982)
	Zarit Burden Inventory	Hébert et al. (2000)
Clinician-rated functioning	Clinical Dementia Rating Scale-Sum of Boxes and Global CDR	Hughes et al. (1982) O'Bryant et al (2008)

Table 3. Neuropsychological test battery.

Cognitive domain	Measures	Reference
Global cognition	ACE-III	Hsieh et al. (2013)
Attention	WAIS-IV Digits Forwards	Wechsler et al (2008)
	WAIS-IV Digits Back	
	CVLT-II Trial 1	Woods et al. (2006)
Processing speed	WAIS-IV Digit Symbol Coding	Wechsler et al. (2008)
	DKEFS Stroop colour naming & word reading	Delis et al. (2001)
	TMT Trails A	Reitan (1958)
Memory – Verbal		Woods et al. (2006)
Learning	CVLT-II Total Trials 1–5	Wechsler (1997)
Immediate	WMS-III Logical Memory I	
	CVLT—II Short Term Delay	
	WMS-III Logical Memory II	
	CVLT-II Long Term Delay	
Memory – Visual		
Learning	BVMT-R Total	Benedict et al. (1996)
Immediate Recall	Rey Complex Figure Immediate	Meyers and Meyers (1995)
Delayed Recall	BVMT-R Delay	
	Rey Complex Figure delayed	
Visuospatial	Rey Complex Figure copy	Meyers and Meyers (1995)
	Line Orientation Test	Benton et al. (1978)
	WAIS-IV Block Design	
Language/semantic		
Naming	Boston Naming Test	Kaplan et al. (1983)
	SydBat Naming	Savage et al. (2013)
Comprehension	SydBat Comprehension	
Semantic	SydBat Semantic Associates	
Executive function	DKEFS Verbal Fluency letter	Delis et al. (2001)
	DKEFS Category Fluency	
	DKEFS Switching Accuracy	
	DKEFS Stroop Inhibition	
	Hayling Sentence Completion	Burgess and Shallice (1997)
	TMT Trails B	Reitan (1958)
Additional Measures	WAIS-IV Matrix Reasoning	Wechsler et al (2008)
	WAIS-IV Similarities	

NOTES: ACE-III: Addenbrooke's Cognitive Examination–III; BVMT-R: Brief Visuospatial Memory Test Revised; CVLT-II: California Verbal Learning Test – second edition; DKEFS: Delis-Kaplan Executive Function System; RCFT: Rey Complex Figure Test; SYDBAT: Sydney Language Battery; TMT: Trail Making Test; WAIS-IV: Wechsler Adult Intelligence Scale Fourth Edition; WMS-III: Wechsler Memory Scale Third Edition.

and Dunedin). Biennial MRI scans are 45 min in length, and incorporate four clinical sequences: T1-weighted, T2-weighted, FLAIR, and susceptibility-weighted imaging. These are viewed and interpreted by a neuroradiologist blind to group status. Additional 'research' sequences measuring structural and functional connectivity (diffusion MRI and resting state functional MRI; consistent with the UK Biobanking Imaging study [Thompson et al. 2015]) and perfusion (arterial spin labelling, ASL) are collected. Figure 1 shows examples of a number of the sequences.

To compare imaging metrics collected at the three clinic sites, five additional non-study participants have been scanned at all three sites (referred to as 'travelling heads'; N = 5, 2 female), regularly over the period of the study (Morgan et al. 2022).

Amyloid PET scans with the radioactive tracer, 18F-Florbetaben (FBB), are a recent addition to the DPRC protocol. The tracer, previously manufactured in Australia and

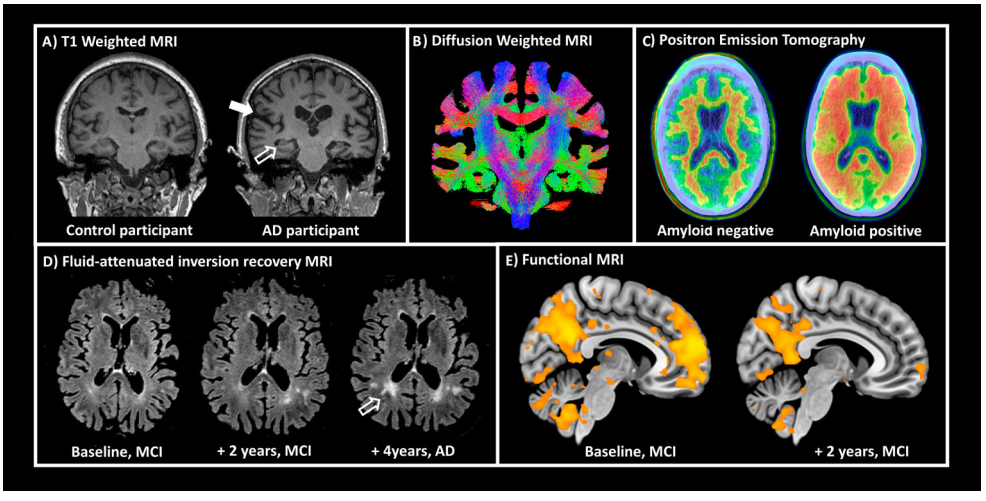

Figure 1. Dementia Prevention Research Clinic imaging protocol, which includes: **A**, T1 weighted imaging, here of a control participant (71 years) left, and an age matched AD participant (72 years), right. Brain atrophy in AD is clearly seen (filled arrow) including around the hippocampus (open arrow), important for memory control; **B**, Diffusion weighted MRI, depicting white matter tracks connecting left and right regions of the brain (red), superior and inferior regions of the brain (blue) and anterior and posterior regions of the brain (green). Data shown is a group template from participants in the Auckland, Christchurch and Dunedin DPRCs; **C**, 18F-Florbetaben Positron Emission Tomography (FBB-PET) in DPRC participants classified as amyloid negative (left) and amyloid positive (right); **D**, Fluid-attenuated inversion recovery (FLAIR) images, show progression of white matter hyperintensity lesions (open arrow), at baseline and in the same participant in follow up scans at 2 and 4 years and **E**, Functional MRI, in the same participant as D, showing loss of default mode network connectivity 2 years after baseline scan.

flown to NZ, meant significant limitations on the number of examinations possible before the tracer decayed. COVID-19 flight restrictions subsequently caused major disruptions in the availability of the tracer. Now manufactured in Wellington and distributed to two sites (Ascot Radiology in Auckland and Pacific Radiology Group in Christchurch), amyloid PET scans are underway in the cohort. Presence of amyloid is reported separately for each hemisphere in the frontal lobe, temporal lobe, parietal lateral, mesial parietal region and striatum, by neuroradiologists trained specifically in reading PET amyloid images. In addition, the PET data will be analysed using the Centiloid scale (Klunk et al. 2015) a standardized scale for reporting PET tracer uptake, which we have implemented for FBB-PET (Melzer et al. 2019).

Bloods

Fasting blood samples are collected biennially from study participants who fast overnight for a minimum of 8 h. Approximately 51.5 mL of blood is drawn and processed within 4 h of collection. Blood samples are processed into derived fractions of serum, plasma (EDTA and heparin), platelets, red and white blood cells according to strict standard operating procedures which align with the Australian Imaging, Biomarkers and Lifestyle study procedures (Ellis et al. 2009) and international guidelines for standardization of preanalytical

variables (O'Bryant et al. 2016). Derived fractions are stored in Nunc high density biobanking systems with long term sample storage in −80°C and liquid nitrogen.

Clinical classifications by expert multidisciplinary teams

Following evaluations, clinical classification is by consensus of multidisciplinary expert clinicians, according to the clinical criteria of the NIA-AA workgroup (Albert et al 2011; McKhann et al 2011). MRI results contribute to the classification, but amyloid status and *APOE* status does not. Participants are given in-person feedback about their assessments and classifications, and a summary is sent to their GPs to inform clinical care.

Genetic analysis

*APOE g*enotyping further characterizes our sample. *APOE* genotype classifications are currently available for 246 DPRC participants. A white blood cell rich fraction was set aside for each study participant for genotyping. The QIAsymphony nucleic acid isolation instrument was utilized for genomic deoxyribonucleic acid (DNA) purification and these samples were genotyped for the presence of the three *APOE* variants (ε2, ε3 and ε4) using Agena MassARRAY® MALDI-TOF MS platform, and using custom oligonucleotides designed using Agena software (performed by Grafton Clinical Genomics Ltd). Five percent of DNA samples were genotyped in duplicate for quality control purposes. *APOE* genotypes were determined from nucleotide calls at variants rs429358 (either a T or C nucleotide) and rs7412 (C or T) in the *APOE* gene. The *APOE* alleles are a diplotype of these two loci. These cause changes in the amino acid residues of the apolipoprotein E molecule, which drives the observed biological effects.

Efforts are currently underway to develop a PRS for DPRC participants. PRS variants have been selected to encompass published variant sets in comparable studies (Porter et al. 2018), while extending the variant set to include additional variants identified through GWAS (deRojas et al., 2021, Tan et al., 2021; Zettergren et al., 2021). The Agena MassARRAY® platform will be used to perform future PRS genotyping work on genomic DNA samples and risk scores for variants will be derived from published risk (OR) values. Sixty variants associated with 45 genes have been selected, although this list will be further refined.

General procedure

The study procedure was approved by the national Health and Disability Ethics Committee. All participants provide informed written consent before taking part in the clinical assessment. A separate consent is provided on a separate day for storage of the blood for use in future studies. New Māori participants are offered the opportunity to have a respected Kuia (Māori woman elder), Dr Waiora Port, who also has longstanding community knowledge of Māori health issues, walk alongside them on the first day. She helps facilitate tikanga Māori practices including karakia (prayers), mihimihi (greetings) and whakawhānaungatanga (establishing relationships). The sessions are conducted over multiple days and may take 3–4 weeks to complete.

Statistical analyses

One-way analysis of variance was used to compare the groups on age, years of education, and performance on the ACE-III. If Levene's test of homogeneity of variances was violated the Welch F-statistic was reported. If significant, multiple pairwise comparisons were conducted using the Games-Howell test, as recommended by Sauder and DeMars (2019) in the case of unequal sample sizes. Significance level was set at $p < .05$. Categorical variables are analysed using Chi-square tests.

Count data for *APOE* genotypes, grouped by classification were compared to published genotype frequencies for the general population and AD cases, using a G-test for goodness of fit (as data did not meet criteria for the Chi-square test). A comparison was made to each comparator population; a Bonferroni correction was applied for multiple hypothesis testing.

Results

A total of 405 individuals have been referred to the study by late 2021. Of these, 30 declined when contacted and 53 were excluded based on information in the referral that indicated they did not meet inclusion criteria. A further 56 were excluded following the initial assessment for failing to meet the inclusion criteria (moderate dementia, incidental findings on MCI scan, significant mood disturbance, other neurological diagnosis). Table 1 shows the demographic characteristics of the 266 participants who had completed baseline assessments by August 2021, subdivided by diagnostic group. There are marginally more females in the overall sample (143; 53.8%). Currently there is a significant difference in the distribution between groups, $X^2(5) = 18.0$, $p = .003$, accounted for by the difference between the control group (75% female) and the AD group (64% male). There is a significant difference between the groups in terms of age, $F(5,260) = 3.00$, $p = .01$. Games-Howell pairwise comparisons, however, found that only one comparison between the control group and the mild AD group approached significance, $p = .06$. There was a marginal significant difference between the groups on years of education, $F(5,259) = 2.30$, $p = .05$. However, no pairwise comparison was significant. As expected, there was a significant difference between groups on performance on the ACE-III, Welch $F(5, 97.07) = 45.65$, $p < .001$ (see Table 1 for pairwise comparisons). To date, 168 two-year follow-ups have been completed (86% of those eligible). Reasons for not completing the follow-up were 7 deaths or terminal illness diagnoses: 3 had dementia symptoms advanced, 4 cited distances of travel, 13 withdrew (4 of whom had AD dementia). A further thirty-two 4-year follow-ups have been completed (81% of those eligible). Twenty participants have progressed from MCI to Alzheimer's dementia. Their distribution of ethnicity across groups does not at this point of recruitment match population distributions, with only 7% of the sample Māori or Pacifica (NZ population estimates 16.5% and 8.1%, respectively).

APOE genotypes within the clinically-classified groups in our cohort are shown in Table 4 and Figure 2. Published genotype and allele frequencies for a general Caucasian population (Liu et al. 2013) and an AD sample (Farrer et al. 1997) are included for contrast. The distributions of *APOE* genotypes within DPRC classification groups were compared to expected genotype frequencies in the general population and AD patients using

Table 4. APOE genotype frequencies in 246 DPRC participants stratified by baseline group classification and expected frequencies in the general population and an AD cohort.

	Reference General Population[a] Freq. (%)	Control n = 35 Num. (Freq. %)	SCD n = 60 Num. (Freq. %)	MCI 124 Num. (Freq. %)	AD 27 Num. (Freq. %)	Reference AD cohort[b] Freq. (%)
ε2/ε2	0.8	1 (2.9)	0 (0)	0 (0)	0 (0)	0.2
ε2/ε3	12.7	4 (11.4)	9 (15)	4 (3.2)	1 (3.7)	4.8
ε2/ε4	2.6	1 (2.9)	5 (8.3)	4 (3.2)	0 (0)	2.6
ε3/ε3	60.9	21 (60)	24 (40)	40 (32.3)	9 (33.3)	36.4
ε3/ε4	21.3	8 (22.9)	20 (33.3)	58 (46.8)	13 (48.2)	41.1
ε4/ε4	1.8	0 (0)	2 (3.33)	18 (14.5)	4 (14.8)	14.8

Notes: [a]General population expected frequencies based on Liu et al. (2013); [b]AD population expected frequencies based on cohort Farrer et al. (1997). SCD = subjective cognitive decline; MCI = mild cognitive impairment; AD = Alzheimer's disease/dementia.

a G-test for goodness of fit. The distribution of genotypes within cognitively normal controls was not found to be different from the general population, but was significantly different from the distribution in the AD published sample $p = 2.1 \times 10^{-4}$. Conversely, the distribution of genotypes within the MCI and AD groups in our cohort were found to be different from the general population ($p < 2.2 \times 10^{-16}$, $p = 1.6 \times 10^{-4}$, respectively) but not from published AD distributions. The distribution in our SCD cohort was found to differ from those in the general population ($p = 0.01$) and AD ($p = 4.5 \times 10^{-4}$).

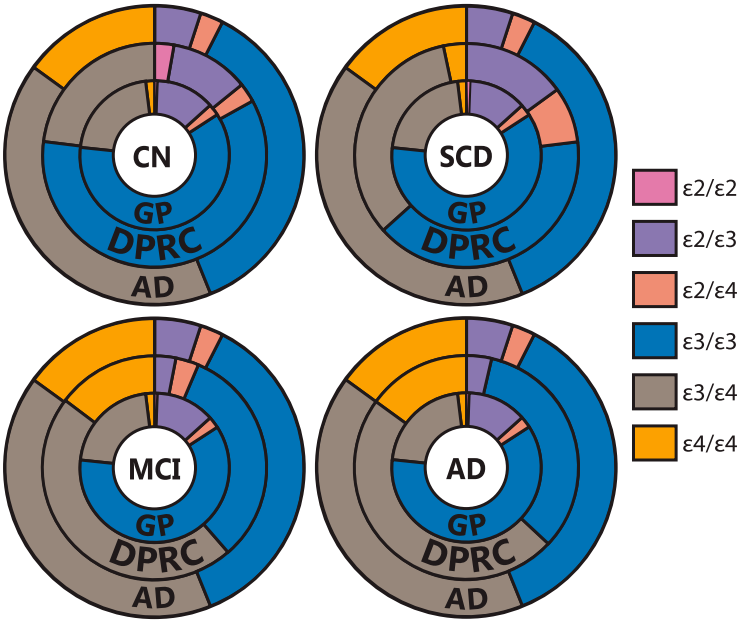

Figure 2. Distribution of *APOE* genotypes available in 246 participants in the DPRC cohort by classification (middle ring) compared to published *APOE* genotypes for the general Caucasian population (inner ring; GP); and Alzheimer's disease sample population (outer ring; AD). General Caucasian population ranges from Liu et al (2013); Alzheimer's Disease sample population ranges from Farrer et al. (1997). Graphs correspond to participant classification at baseline assessment: CN (cognitively normal), SCD (subjective cognitive decline), MCI (mild cognitive impairment), and AD (Alzheimer's disease).

Discussion

In this paper we describe the development of a longitudinal cohort of older adults encompassing the entire AD risk spectrum, from healthy older adults with no memory concerns through to individuals with mild Alzheimer's dementia in Aotearoa, New Zealand. The strengths of this developing cohort are the national participation of the community, the opportunity to explore potential risk or protective factors within the ethnic diversity of the New Zealand population (although, as discussed below, more effective outreach and inclusion of ethnic communities is required), and the extensive multi-disciplinary data gathered, with a focus on precision and cross-site consistency. Together this will enable multimodal phenotyping of participants with different trajectories, and potentially identification of a multimodal biomarker signature of AD in individuals before clinical symptoms become apparent. The data from this cohort will also promote mechanistic studies of the contribution of a range of other molecular processes and factors to AD in addition to amyloid. The ultimate goal is that this improved understanding of AD and dementia will enable the development of targeted interventions to delay or prevent progression to dementia.

The *APOE* genotypical distributions of the sample analysed to date shows that the DPRC MCI and AD groups are remarkably congruent with the reference AD distribution, as is the distribution of the DPRC control sample relative to the reference general population. The SCD group falls midway. This suggests that these participant cohorts represent a good sample of their populations, from the perspective of genetic variability. It also provides converging evidence supporting the accuracy of the clinical classifications, which is particularly important for the target MCI group. Currently, an insufficient number of participants have advanced in their classification to provide any meaningful analysis of conversion rates.

The DPRC study has been established incorporating procedures that meet the highest standards for scientific excellence in the field of AD research, which will enable international collaborations. One limitation of the study design is the absence of measurement of CSF markers, including CSF Aβ1-42 for detection of Aβ plaque pathology, but also markers of pathophysiological pathways involved in AD. This decision was in part because in New Zealand there would be a recruitment bias due to the reluctance of many to have a lumbar puncture. Instead, we are utilizing amyloid PET and focusing on blood-based biomarkers.

Equally important in the methodology is the influence of the cultural context of Aotearoa NZ and the incorporation of general principles from Kaupapa Māori research in the day-to-day operations of the DPRCs: valuing of research participants, the role of enduring relationships, respectfulness, caring and reciprocity in the research process. Participation is demanding, and because of the challenges they face, many participants are vulnerable. The DPRCs, and the clinical research staff, place the participants and their whanau (family) in the centre of the endeavour, and work to acknowledge their contribution and effort at a time in their lives where many are vulnerable. Connections are maintained between assessment times in a variety of ways including phone contact, annual events for participants and whanau in order to provide information on DPRC progress, latest research, and question-and-answer panels with participant-driven content. The integrity of data collection is a requirement, but so too is the responsibility

for DPRC clinical staff to give quality time to participants and whanau and their issues, to communicate clearly, and to be able to link them with appropriate resources and supports as needed.

Despite this, however, the DPRC cohort to date is largely European and well-educated. Recruitment bias is a challenge for many longitudinal studies and clinical trials in AD and other dementias (e.g. Ashford et al. 2021; Franzen et al. 2022). Edwards and Dykema (2021) found that a number of factors influence participation of under-represented communities in US studies, including ethnicity of people recruiting, concern about disruption of work and family responsibilities, availability of transportation and whether the results are used to help others. A number of similar factors contribute to difficulties in recruitment and retention in the DPRCs: the amount of time involved, the distance for many people to travel and associated costs, traffic (particularly in Auckland), the physical space of the clinics, and, for some, research assessments inducing discomfort. One factor related to discomfort is that in the conduct of scientific research little attention is paid to the concept of spirituality. Yet Dudley et al (2019) found that when exploring Māori understandings of dementia with Māori elders and their whānau (family), disruption of wairua (spiritual dimension of Māori) was a central and unifying theme to emerge. Similarly, Crouch and Rosich (2021) identified spirituality as one of eight themes that emerged in a study assessing culturally derived meanings of memory loss and disease with Alaskan Native (AN) Elders. Possibly successful engagement of currently under-represented ethnic groups requires sufficient incorporation of such cultural beliefs and practices as appropriate into all research processes in a way that complements scientific excellence.

In summary, our current efforts to make the DPRC environment welcoming to Māori have not been enough to encourage participation, nor to enable Māori (and Pacific peoples) to feel the research process is about them. Consultation with a number of Māori researchers indicates that in order to engage more Māori, we need to not only involve more Māori staff, but take the research to local Māori communities, to discuss the research design and co-develop changes that will encourage inclusive engagement. This development is underway and co-led by Dr Makarena Dudley. The primary aim during the next two years is to increase significantly participation of Māori and other ethnic groups in the sample.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, et al. 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia. 7(3):270–279.

Ashford MT, Miller G, Raman R, Donohue MC, Okonkwo OC, Mindt MR, Nosheny RL, Petersen RC, Aisen PS, Weiner MW. 2021. The screening and enrollment of underrepresented ethnoracial and educational populations in the Alzheimer's Disease Neuroimaging initiative. Alzheimers Dement. Dec. 17:e057424.

Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. 2011. Alzheimer's disease. The Lancet. 377(9770):1019–1031.

Benedict RHB, Schretlen D, Groninger L, Dobraski M, Shpritz B. 1996. Revision of the Brief Visuospatial Memory Test: studies of normal performance, reliability, and validity. Psychological Assessment. 8(2):145–153.

Benton AL, Varney NR, Hamsher KD. 1978. Visuospatial judgment - clinical test. Archives of Neurology. 35(6):364–367.

Blennow K, Mattsson N, Schöll M, Hansson O, Zetterberg H. 2015. Amyloid biomarkers in Alzheimer's disease. Trends in Pharmacological Sciences. 36(5):297–309.

Brookmeyer R, Gray S, Kawas C. 1998. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. American Journal of Public Health. 88 (9):1337–1342.

Brothers HM, Gosztyla M, Robinson SR. 2018. The physiological roles of amyloid-β peptide hint at new ways to treat Alzheimer's disease. Frontiers in Aging Neuroscience. 10:118.

Burgess PW, Shallice T. 1997. The Hayling and brixton tests. Thurston, Suffolk: Thames Valley Test Company.

Cavazzoni P. 2021. FDA's decision to approve new treatment for Alzheimer's Disease. US Food and Drug Administration. FDA's Decision to Approve New Treatment for Alzheimer's Disease | FDA.

Crouch MC, Rosich RM. 2021. Alaska Native elders' cultural beliefs, practices, and values: The case for culturally informed holistic dementia care. Alzheimers Dement. Dec. 17:e051895.

Cullum S, Mullin K, Zeng I, Yates S, Payman V, Fisher M, Cheung G. 2018. Do community-dwelling Māori and Pacific peoples present with dementia at a younger age and at a later stage compared with NZ europeans? International Journal of Geriatric Psychiatry. 33:1098–1104.

Delis DC, Kaplan E, Kramer JH. 2001. The Delis-Kaplan Executive Function System: examiner's manual. San antonio. Texas: The Psychological Corporation.

de Rojas I, Moreno-Grau S, Tesi N, Grenier-Boley B, Andrade V, Jansen IE, Pedersen NL, Stringa N, Zettergren A, Hernandez I, et al. 2021. Common variants in Alzheimer's disease and risk stratification by polygenic risk scores. Nature Communications. 12:1–6.

Dickie BR, Parker GJM, Parkes LM. 2020. Measuring water exchange across the blood-brain barrier using MRI. Progress in Nuclear Magnetic Resonance Spectroscopy. 116:19–39.

Dube P, Kurt K, Bair MJ, Theobald D, Williams LS. 2010. The p4 screener: evaluation of a brief measure for assessing potential suicide risk in 2 randomized effectiveness trials of primary care and oncology patients. The Primary Care Companion for CNS Disorders. 12(6): 27151.

Dudley M, Menzies O, Elder H, Nathan L, Garrett N, Wilson D. 2019. Mate wareware: understanding 'dementia' from a Māori perspective. New Zealand Medical Journal. 132(1503):66–74.

Edwards DF, Dykema J. 2021. Tailoring recruitment message content to reach diverse communities for AD research participation. Alzheimers Dement. Dec. 17:e054989.

Ellis KA, Bush AI, Darby D, De Fazio D, Foster J, Hudson P, Lautenschlager NT, Lenzo N, Martins RN, Maruff P, et al. 2009. The Australian imaging, biomarkers and lifestyle (AIBL) study of aging: methodology and baseline characteristics of 1112 individuals recruited for a longitudinal study of Alzheimer's disease. International Psychogeriatrics. 21(4):672–687.

Escott-Price V, Sims R, Bannister C, Harold D, Vronskaya M, Majounie E, Badarinarayan N, Gerad/Perades Ic, Morgan K, Passmore P. 2015. Common polygenic variation enhances risk prediction for Alzheimer's disease. Brain. 138(12):3673–3684.

Farias ST, Mungas D, Reed BR, Cahn-Weiner D, Jagust W, Baynes K, Decarli C. 2008. The measurement of everyday cognition (ECog): scale development and psychometric properties. Neuropsychology. 22(4):531–544.

Farrer LA. 1997. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. JAMA. 278(16):1349.

Franzen S, Smith JE, van den Berg E, Rivera Mindt M, van Bruchem-Visser RL, Abner EL, Schneider LS, Prins ND, Babulal GM, Papma JM. 2022. Diversity in Alzheimer's disease drug trials: the importance of eligibility criteria. Alzheimer's & Dementia. Apr. 18(4):810–823.

Gao S, Burney HN, Callahan CM, Purnell CE, Hendrie HC. 2019. Incidence of dementia and Alzheimer disease over time: a metaanalysis. Journal of the American Geriatrics Society. 67 (7):1361–1369.

Gebert LFR, MacRae IJ. 2019. Regulation of microRNA function in animals. Nature Reviews Molecular Cell Biology. 20(1):21–37.

Gottesman RF, Schneider AL, Zhou Y, Coresh J, Green E, Gupta N, Knopman DS, Mintz A, Rahmim A, Sharrett AR, et al. 2017. Association between midlife vascular risk factors and estimated brain amyloid deposition. JAMA. 317:1443–1450.

Guévremont D, Tsui H, Knight R, Fowler CJ, Masters CL, Martins RN, Abraham WC, Warren P, Tate WP, Cutfield NJ, Williams JM. 2022. Plasma microRNA vary in association with the progression of Alzheimer's disease. Alzheimer's Dement. 14(1):e1225.1.

Hampel H, O'Bryant SE, Molinuevo JL, Zetterberg H, Masters CL, Lista S, Kiddle SJ, Batrla R, Blennow K. 2018. Blood-based biomarkers for Alzheimer disease: mapping the road to the clinic. Nature Reviews Neurology. 14(11):639–652.

Hampel H, Vergallo A, Aguilar LF, Benda N, Broich K, Cuello AC, Cummings J, Dubois B, Federoff HJ, Fiandaca M, et al. 2018. Alzheimer Precision Medicine Initiative (APMI). Precision pharmacology for Alzheimer's disease. Pharmacological Research. 130:331–365.

Hébert R, Bravo G, Préville M. 2000. Reliability, validity and reference values of the Zarit Burden interview for assessing informal caregivers of community-dwelling older persons with dementia. Canadian Journal on Aging / La Revue canadienne du vieillissement. 19(4):494–507.

Hsieh S, Schubert S, Hoon C, Mioshi E, Hodges JR. 2013. Validation of the Addenbrooke's Cognitive Examination III in frontotemporal dementia and Alzheimer's disease. Dementia and Geriatric Cognitive Disorders. 36(3-4):242–250.

Hughes CP, Berg L, Danziger W, Coben LA, Martin RL. 1982. A new clinical scale for the staging of dementia. British Journal of Psychiatry. 140(6):566–572.

Iturria-Medina Y, Sotero RC, Toussaint PJ, Mateos-Pérez JM, Evans AC. 2016. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. Nature Communications. 7:11934.

Jack Jr. CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman DM, Jagust W, Jessen F, Karlawish J, Liu E. 2018. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimer's & Dementia. 14:535–562.

Jagust W, Jack Jr CR, Bennett DA, Blennow K, Haeberlein SB, Holtzman DM, Jessen F, Karlawish J, Liu E, Molinuevo JL, Montine T, et al. 2019. "Alzheimer's disease" is neither "Alzheimer's clinical syndrome" nor "dementia". Alzheimer's & Dementia. 15:153–157.

Janelidze S, Pannee J, Mikulskis A, Chiao P, Zetterberg H, Blennow K, Hansson O. 2017. Concordance between different amyloid immunoassays and visual amyloid positron emission tomographic assessment. JAMA Neurology. 74:1492–1501.

Jessen F, Amariglio RE, Van Boxtel M, Breteler M, Ceccaldi M, Chételat G, Dubois B, Dufouil C, Ellis KA, Van Der Flier WM, Glodzik L. 2014. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimer's & Dementia. 10(6):844–852.

Johns MW. 1992. Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep. 15 (4):376–381.

Jupiter T, DiStasio D. 1998. An evaluation of the HHIE-S as a screening tool for the elderly homebound population. Journal of the Academy of Rehabilitative Audiology. 31:11–21.

Kaplan E, Goodglass H, Weintraub S. 1983. The Boston naming test. Philadelphia, PA: Lea & Fibiger.

Karikari TK, Benedet AL, Ashton NJ, Lantero Rodriguez J, Snellman A, Suárez-Calvet M, Saha-Chaudhuri P, Lussier F, Kvartsberg H, Rial AM, et al. 2021. Diagnostic performance and prediction of clinical progression of plasma phospho-tau181 in the Alzheimer's Disease Neuroimaging initiative. Molecular Psychiatry. 26(2):429–442.

Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillian A, Sheeley T, Lopez OL, DeKosky ST. 2000. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric inventory. The Journal of Neuropsychiatry and Clinical Neurosciences. 12(2):233–239.

Kirmess KM, Meyer MR, Holubasch MS, Knapik SS, Hu Y, Jackson EN, Harpstrite SE, Verghese PB, West T, Fogelman I, et al. 2021. The PrecivityAD™ test: accurate and reliable LC-MS/MS assays for quantifying plasma amyloid beta 40 and 42 and apolipoprotein E proteotype for the assessment of brain amyloidosis. Clinica Chimica Acta. 519:267–275.

Klunk WE, Koeppe RA, Price JC, Benzinger TL, Devous MD, Jagust WJ, Johnson KA, Mathis CA, Minhas D, Pontecorvo MJ, et al. 2015. The Centiloid project: standardizing quantitative amyloid plaque estimation by PET. Alzheimer's & Dementia. 11:1–15. e4.

Knopman DS, Jones DT, Greicius MD. 2020. Failure to demonstrate efficacy of aducanumab: an analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019. Alzheimer's & Dementia. 17(4):696–701.

Koncz R, Sachdev PS. 2018. Are the brain's vascular and Alzheimer pathologies additive or interactive? Current Opinion in Psychiatry. 31(2):147–152.

Kou X, Chen D, Chen N. 2020. The regulation of microRNAs in Alzheimer's disease. Frontiers in Neurology. 11:288.

Kunkle BW, Grenier-Boley B, Sims R, Bis JC, Damotte V, Naj AC, Boland A, Vronskaya M, Van Der Lee SJ, Amlie-Wolf A, Bellenguez C. 2019. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates abeta, tau, immunity and lipid processing. Nature Genetics. 51(3):414–430.

Lawrence E, Vegvari C, Ower A, Hadjichrysanthou C, De Wolf F, Anderson RM. 2017. A systematic review of longitudinal studies which measure Alzheimer's disease biomarkers. Journal of Alzheimer's Disease. 59(4):1359–1379.

Li Y, Mielke MM. 2019. An update on blood-based markers of Alzheimer's disease using the SiMoA platform. Neurology and Therapy. 8(Suppl 2):73–82.
Liu CC, Kanekiyo T, Xu H, Bu G. 2013. Apolipoprotein e and Alzheimer disease: risk, mechanisms and therapy. Nature Reviews Neurology. 9:106–118.
Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, et al. 2020. Dementia prevention, intervention, and care: 2020 report of the Lancet commission. The Lancet. 396(10248):413–446.
Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, Ballard C, Banerjee S, Burns A, Cohen-Mansfield J, Cooper C. 2017. Dementia prevention, intervention, and care. The Lancet. 390(10113):2673–2734.
Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL. 2015. Alzheimer's disease. Nature Reviews Disease Primers. 1:15056.
Ma'u E, Cullum S, Cheung G, Livingston G, Mukadam N. 2021. Differences in the potential for dementia prevention between major ethnic groups within one country: a cross sectional analysis of population attributable fraction of potentially modifiable risk factors in New Zealand. The Lancet Regional Health - Western Pacific. 13:100191.
Ma'u E, Cullum S, Yates S, Te Ao B, Cheung G, Burholt V, Dudley M, Krishnamurthi R, Kerse N. 2021. Dementia economic impact report 2020. Auckland, New Zealand: University of Auckland.
McKhann GM, Knopman DS, Chertkow H, Hyman BT, JackJrCR, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, et al. 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia. 7:2639.
Melzer TR, Stark MR, Keenan RJ, Myall DJ, MacAskill MR, Pitcher TL, Livingston L, Grenfell S, Horne KL, Young BN, et al. 2019. Beta amyloid deposition is not associated with cognitive impairment in Parkinson's disease. Frontiers in Neurology. 10:391.
Meyers JE, Meyers KR. 1995. Rey complex figure test under four different administration procedures. The Clinicial Neuropsychologist. 9(1):63–67.
Moon Y, Han S-H, Moon W-J. 2016. Patterns of brain iron accumulation in vascular dementia and Alzheimer's dementia using quantitative susceptibility mapping imaging. Journal of Alzheimer's Disease. 51:737–745.
Morgan CA, Melzer TR, Roberts RP, Wiebels K, Mutsaerts HJ, Spriggs MJ, Dalrymple-Alford JC, Anderson TJ, Cutfield NJ, Deib G, Pfeuffer J. 2021. Spatial variation of perfusion MRI reflects cognitive decline in mild cognitive impairment and early dementia. Scientific Reports. 11 (1):1–9.
Morgan CA, Roberts RP, Chaffey T, Tahara-Eckl L, van der Meer M, Günther M, Anderson TJ, Cutfield NJ, Dalrymple-Alford JC, Kirk IJ, et al. 2022. Reproducibility and repeatability of magnetic resonance imaging in dementia. Physica Medica. 101:8–17.
O'Bryant SE, Lista S, Rissman RA, Edwards M, Zhang F, Hall J, Zetterberg H, Lovestone S, Gupta V, Graff-Radford N, Martins R. 2016. Comparing biological markers of Alzheimer's disease across blood fraction and platforms: comparing apples to oranges. Alzheimers Dement. 3:27–34.
O'Bryant SE, Waring SC, Cullum CM, Hall J, Lacritz L, Massman PJ, Lupo PJ, Reisch JS, Doody R. Texas Alzheimer's Research Consortium. 2008. Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's research consortium study. Archives of Neurology. 65(8):1091–1095.
Pachana NA, Byrne GJ, Siddle H, Koloski N, Harley E, Arnold E. 2007. Development and validation of the Geriatric Anxiety inventory. International Psychogeriatrics. 19 (1):103–114.
Petersen R, Caracciolo C, Brayne B, Gauthier C, Jelic VS, Fratiglioni L. 2014. Mild cognitive impairment: a concept in evolution. Journal of Internal Medicine. 275:214–228.
Petersen RC, Lopez O, Armstrong MJ, Getchius TS, Ganguli M, Gloss D, Gronseth GS, Marson D, Pringsheim T, Day GS, Sager M. 2018. Practice guideline update summary: mild cognitive impairment. Neurology. 90(3):126–135.

Pfeffer RI, Kurosaki TT, Harrah CH, Chance JM, Filos S. 1982. Measurement of functional activities of older adults in the community. Journal of Gerontology. 37:323–329.
Porter T, Burnham SC, Savage G, Lim YY, Maruff P, Milicic L, Peretti M, Ames D, Masters CL, Martins RN, Rainey-Smith S. 2018. A polygenic risk score derived from episodic memory weighted genetic variants is associated with cognitive decline in preclinical Alzheimer's disease. Frontiers in Aging Neuroscience. 10:423.
Prince M, Albanese E, Guerchet M, Prina M. 2014. World Alzheimer Report 2014: dementia and risk reduction: an analysis of protective and modifiable risk factors.
Puzo C, Labriola C, Sugarman MA, Tripodis Y, Martin B, Palmisano JN, Steinberg EG, Stein TD, Kowall NW, McKee AC, Mez J. 2019. Independent effects of white matter hyperintensities on cognitive, neuropsychiatric, and functional decline: a longitudinal investigation using the national Alzheimer's coordinating center uniform data set. Alzheimer's Research & Therapy. 11(1):1–13.
Ray WJ, Buggia-Prevot V. 2021. Novel targets for Alzheimer's disease: a view beyond amyloid. Annual Review of Medicine. 72:15–28.
Rayaprolu S, Higginbotham L, Bagchi P, Watson CM, Zhang T, Levey AI, Rangaraju S, Seyfried NT. 2021. Systems-based proteomics to resolve the biology of Alzheimer's disease beyond amyloid and tau. Neuropsychopharmacology. 46(1):98–115.
Reitan RM. 1958. Validity of the Trail Making Test and an indicator. Perceptual and Motor Skills. 8:271–276.
Rivera-Rivera LA, Schubert T, Turski P, et al. 2017. Changes in intracranial venous blood flow and pulsatility in Alzheimer's disease: a 4D flow MRI study. Journal of Cerebral Blood Flow & Metabolism. 37:2149–2158.
Rodrigue KM, Rieck JR, Kennedy KM, Devous MD, Diaz-Arrastia R, Park DC. 2013. Risk factors for beta-amyloid deposition in healthy aging: vascular and genetic effects. JAMA Neurology. 70:600–606.
Sam CH, Skidmore P, Skeaff S, Parackal S, Wall C, Bradbury KE. 2020. Relative validity and reproducibility of a short food frequency questionnaire to assess nutrient intakes of New Zealand adults. Nutrients. 12(3):619.
Sauder DC, DeMars CE. 2019. An updated recommendation for multiple comparisons. Advances in Methods and Practices in Psychological Science. 2(1):26–44.
Savage S, Hsieh S, Leslie F, Foxe D, Piguet O, Hodges JR. 2013. Distinguishing subtypes in primary progressive aphasia: application of the Sydney language battery. Dementia and Geriatric Cognitive Disorders. 35:208–218.
Sheikh JI, Yesavage J. 1986. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. Clinical Gerontologist. 5(1-2):165–173.
Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack Jr CR, Kaye J, Montine TJ, Park DC. 2011. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia. 7 (3):280–292.
Statistics New Zealand. 2018. Census. Statistics New Zealand; 2018. https://www.stats.govt.nz/2018-census/.
Stocker H, Möllers T, Perna L, Brenner H. 2018. The genetic risk of Alzheimer's disease beyond APOE ε4: systematic review of Alzheimer's genetic risk scores. Translational Psychiatry. 8 (1):166.
Sweeney MD, Montagne A, Sagare AP, Nation DA, Schneider LS, Chui HC, Harrington MG, Pa J, Law M, Wang DJ, Jacobs RE. 2019. Vascular dysfunction-the disregarded partner of Alzheimer's disease. Alzheimer's & Dementia. 15:158–167.
Tan MS, Yang YX, Wang HF, Tan L, Zuo CT, Dong Q, Tan L, Suckling J, Yu JT. 2021. Associations of Alzheimer's disease risk variants with amyloidosis, tauopathy and neurodegeneration. Alzheimer's Research & Therapy. 13:1–11.
Teh R, Kerse N, Kepa M, Doughty RN, Moyes S, Wiles J, Wham C, Hayman K, Wilkinson T, Connolly M, Mace C. 2014. Self-rated health, health related behaviours and medical

conditions of Māori and non-Māori in advanced age: LiLACS NZ. New Zealand Medical Journal. 127:13–29.
Thompson SG, Willeit P. 2015. UK Biobank comes of age. The Lancet. 386(9993):509–510.
Valenzuela MJ, Sachdev P. 2007. Assessment of complex mental activity across the lifespan: development of the Lifetime of Experiences Questionnaire (LEQ). Psychological Medicine. 37 (7):1015–1025.
Vemuri P, Lesnick TG, Przybelski SA, Knopman DS, Preboske GM, Kantarci K, Raman MR, Machulda MM, Mielke MM, Lowe VJ, Senjem ML. 2015. Vascular and amyloid pathologies are independent predictors of cognitive decline in normal elderly. Brain. 138:761–771.
Wechsler D. 1997. WMS-III administration and scoring manual. San Antonio, TX: The Psychological Corporation.
Wechsler D, Coalson DL, Raiford SE. 2008. WAIS-IV: Wechsler adult intelligence scale. San Antonio, Texas: Pearson.
Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, Green RC, Harvey D, Jack CR, Jagust W, Liu E, Morris JC. 2012. The Alzheimer's disease neuroimaging initiative: a review of papers published since its inception. Alzheimer's & Dementia. 8:S1–68.
Werhane ML, Thomas KR, Bangen KJ, Weigand AJ, Edmonds EC, Nation DA, Sundermann EE, Bondi MW, Delano-Wood L. 2021. Arterial stiffening moderates the relationship between type-2 diabetes mellitus and white matter hyperintensity burden in older adults with mild cognitive impairment. Frontiers in Aging Neuroscience. 13:716638.
Woods SP, Delis DC, Scott JC, Kramer JH, Holdnack JA. 2006. The California Verbal Learning test–second edition: test-retest reliability, practice effects, and reliable change indices for the standard and alternate forms. Archives of Clinical Neuropsychology. 21(5):413–420.
Wu YT, Beiser AS, Breteler M, Fratiglioni L, Helmer C, Hendrie HC, Honda H, Ikram MA, Langa KM, Lobo A, Matthews FE. 2017. The changing prevalence and incidence of dementia over time - current evidence. Nature Reviews Neurology. 13(6):327–339.
Yu L, Petyuk VA, Gaiteri C, Mostafavi S, Young-Pearse T, Shah RC, Buchman AS, Schneider JA, Piehowski PD, Sontag RL, Fillmore TL. 2018. Targeted brain proteomics uncover multiple pathways to Alzheimer's dementia. Annals of Neurology. 84(1):78–88.
Zetterberg H. 2019. Blood-based biomarkers for Alzheimer's disease-an update. Journal of Neuroscience Methods. 319:2–6.
Zettergren A, Lord J, Ashton NJ, Benedet AL, Karikari TK, Lantero Rodriguez J, Snellman A, Suárez-Calvet M, Proitsi P, Zetterberg H, et al. 2021. Association between polygenic risk score of Alzheimer's disease and plasma phosphorylated tau in individuals from the Alzheimer's disease neuroimaging initiative. Alzheimer's Research & Therapy. 13:1–10.