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
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 to 167,483 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 (PercivityAD™; Kirmess et al. 2021), but the opportunity exists to develop a broader biomarker signature that extends beyond amyloid-β, 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, Guévrémont 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 (Rodrique 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 et 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 assess-
ments; 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 calcu-
lation 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
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

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**Table 1.** Demographic characteristics of current sample.

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

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 Alzheimer’s 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.

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**Table 2.** Clinical and Lifestyle Measures.

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

### Table 3. Neuropsychological test battery.

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

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 Cen-tiloid 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 genotyping 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 diplo-type 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 whakawhanaungatanga (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
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 \( (p < 2.2 \times 10^{-16}, \ p = 1.6 \times 10^{-4}, \text{respectively}) \) 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 \( (p = 4.5 \times 10^{-4}) \).

**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.

<table>
<thead>
<tr>
<th>Reference General Population^a Freq. (%)</th>
<th>Control n = 35 Freq. (%)</th>
<th>SCD n = 60 Freq. (%)</th>
<th>MCI 124 Freq. (%)</th>
<th>AD 27 Freq. (%)</th>
<th>Reference AD cohort^b Freq. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \varepsilon 2/\varepsilon 2 )</td>
<td>0.8</td>
<td>1 (2.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.2</td>
</tr>
<tr>
<td>( \varepsilon 2/\varepsilon 3 )</td>
<td>12.7</td>
<td>4 (11.4)</td>
<td>9 (15)</td>
<td>4 (3.2)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>( \varepsilon 2/\varepsilon 4 )</td>
<td>2.6</td>
<td>1 (2.9)</td>
<td>5 (8.3)</td>
<td>4 (3.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>( \varepsilon 3/\varepsilon 3 )</td>
<td>60.9</td>
<td>21 (60)</td>
<td>24 (40)</td>
<td>40 (32.3)</td>
<td>9 (33.3)</td>
</tr>
<tr>
<td>( \varepsilon 3/\varepsilon 4 )</td>
<td>21.3</td>
<td>8 (22.9)</td>
<td>20 (33.3)</td>
<td>58 (46.8)</td>
<td>13 (48.2)</td>
</tr>
<tr>
<td>( \varepsilon 4/\varepsilon 4 )</td>
<td>1.8</td>
<td>0 (0)</td>
<td>2 (3.33)</td>
<td>18 (14.5)</td>
<td>4 (14.8)</td>
</tr>
</tbody>
</table>

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.

**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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