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Australian Dementia Research Forum 2023

ABSTRACTS

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Detecting Alzheimer's disease pathology in blood: exploring the meaning of change, applications for therapeutic trials and clinical implementation

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Abstract
Blood biomarkers that accurately indicate Alzheimer's disease (AD) pathophysiology now offer a realistic, cost-effective, and non-invasive assessment that will aid the diagnostic process in clinical care. In some instances, the performance of plasma p-tau biomarkers is comparable or only marginally inferior to established cerebrospinal fluid (CSF) or positron emission tomography (PET) examinations of amyloid-β (Aβ) and tau pathologies, but with the advantage of greater availability and tolerability for both clinicians and patients. Several p-tau isoforms (p-tau181, p-tau217, p-tau231) have shown application in therapeutic trial recruitment and but have different longitudinal profiles (Ashton et al., Nature Medicine, 2022).

In this talk, we will evaluate the latest data in blood biomarkers for several applications: strategies for implementation in clinical routine, optimal biomarker for therapeutic recruitment or disease monitoring. We will also consider how analytical and biological variation may impact on these results. Importantly, and with a focus on p-tau, we will discuss the meaning of these biomarkers change in blood. Is increased p-tau in blood a reflection of amyloid, tau, or neurodegeneration? Is GFAP a marker of astrogliosis? And what can we learn from measuring these biomarkers in other disorders not in the dementia spectrum *e.g.,* cardiac arrest, traumatic brain injury and stroke.

Lastly, we will look forward. Are there methods where we can omit strict pre-analytical processing for blood biomarkers for wider application or would a capillary collection be viable option for remote testing? How do we tackle the challenge of discovering blood biomarker for dementia's outside of AD?

Increasing neuronal resistance by targeting autophagy to counter neurodegeneration

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Abstract
Alzheimer's Disease is a multifactorial (multigenetic) and highly complex disorder. Despite intensive research efforts—especially in the last four decades—and a vast amount of molecular knowledge on selected proteins and processes associated with it, the exact causes of the disease remain elusive. In addition, to date, no striking therapy breakthrough could be reported. The research field appears to be divided into different yet distinct research camps: (1) amyloid research, conducted by supporters of the view that amyloid beta peptide is the initial trigger of the disease and who are convinced that the 'amyloid-cascade-hypothesis', which was introduced 30 years ago, will be the basis of a future disease-modifying therapy, and (2) research focusing on alternative views on how Alzheimer's could develop, involving multiple pathogenic processes and with age as one key factor. Moreover, due to the high number of identified genetic risk and disposition factors, the disease appears to be highly individual in its pathogenesis; consequently, Alzheimer's Disease could be a prime candidate for a more personalized medicine therapy approach.

A deeper understanding of such (individual) neuronal factors and mechanisms, which could provide a strong basis for disease prevention, would be a promising way to encounter targetable pathways and tackle Alzheimer's. Enhancing processes that mediate increased nerve cell resilience and resistance could help the human brain to withstand the onset of neurodegeneration by various triggers. During aging, intracellular protein homeostasis becomes disturbed, which is especially relevant for post-mitotic cells such as neurons; the stabilization and maintenance of proteostasis could thus be one approach. One of the key mechanisms controlling proteostasis is autophagy, an intracellular degradation and recycling process that clears damaged proteins and organelles. Autophagy depends on active intracellular vesicle trafficking and intact lysosomes as the ultimate degradation compartments. Distinct macroautophagy pathways target distinct cargos, such as aggregated proteins ('aggrephagy'), damaged mitochondria ('mitophagy'), or disintegrated ER parts ('ER-phagy'). These three selective macroautophagy processes are of particular importance for neurons during aging when they encounter increasing protein, oxidative as well as ER-stress and the demand for autophagic activity becomes higher. Consistent with this view are recent data proving that a disturbance of the endosomal-lysosomal degradation pathway is one of the earliest observable pathological alterations in Alzheimer's Disease. Stabilizing autophagy by targeting selective macroautophagy pathways could therefore prove to be a key disease-targeting approach.

Maintain Your Brain: an online RCT to prevent cognitive decline in 55-77 year olds

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Background:
Limited progress in developing disease modifying treatments for dementia has underscored the importance of prevention. While cohort studies have identified 12 potentially modifiable risk factors accounting for 40% of population attributable risk of dementia, prospective intervention trials have had little success in delaying age-associated cognitive decline. We present results from the first online randomised controlled trial to demonstrate cognitive benefits.

Methods:
We targeted 55–77-year-olds from the 45 and Up study, a population-based cohort study of one-in-ten people aged 45 years and older in New South Wales (n=267,000), who had at least two of four risk factors - physical inactivity, poor diet, low cognitive activity or depression/anxiety. Participants were randomised equally to active personalised coaching modules addressing 2-4 risk factors (intervention) or static information-based modules (control). Interventions were delivered over two, three or four 10-week intensive modules in Year 1 followed by monthly boosters for eligible modules through to end of Year 3. The primary outcome was change in an online combined multi-domain cognitive score. Secondary outcomes included specific cognitive domains and ANU-ADRI risk scores.

Results:
Of 96,418 invitees, 14,064 (14%) consented, 11,026 (11%) were eligible and 6,104 (6%) completed all baseline assessments. Over three years, on ITT analysis the intervention group improved significantly more in the global composite cognition z-score ($p<0.001$). Significant benefits were also found in complex attention, executive function and learning and memory (all $p<0.001$), as well as on a validated dementia risk instrument ($p=0.007$). Results were similar when adjusted for baseline age, gender, dementia risk and number of modules eligible and when re-analysed for those completing follow-up.

Discussion/Conclusion:
Participants in the intervention group experienced better cognition over three years than those in an active control group. Online interventions are eminently scalable nationally with potential for significant delay in onset and reduction in prevalence of dementia.

What can we learn from national routine dementia care?

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Dean Karolinska Institutet
Registry holder of SveDem

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Background:
To improve quality of care, national quality registers for different disorders have been developed in Sweden since early 2000. SveDem, the national quality registry on cognitive/dementia disorders was established in 2007 with the aim to obtain a dementia care of high and equal quality in the whole country. In addition to improvements of care another aim is to increase knowledge about the whole dementia population.

Methods:
SveDem, www.svedem.se is to date the largest database in the world on different dementia disorders and from 2021 also on mild cognitive impairment (MCI). The registry includes individuals at the time of the MCI or dementia diagnosis with annual follow-ups, at present with >110 000 persons, who are followed through the chain of care. The main purpose is to improve quality of dementia care by following national guidelines using quality indicators.
By linking SveDem to other registers, important new knowledge on diagnostics, comorbidities, treatment, care, mortality and prognosis can be obtained.

Results from SveDem have shown that mortality in dementia disorders over a 10-year time period is decreasing, partly associated with changes in drug prescribing practices. Data on the cognitive benefit and reduction in mortality as well as reduction of cardiovascular events by the cholinesterase inhibitors in persons with Alzheimer´s disease, novel findings on dementia and kidney failure as well as the usefulness of artificial intelligence methods will be presented.

Conclusion. Big data on persons with different dementia disorders in clinical routine long-term provide important knowledge on prognosis, progression, mortality of different dementia disorders in relation to medications and comorbidities.

Genetic epidemiology in Alzheimer's disease and the use of genetic risk prediction

Michelle K Lupton
QIMR Berghofer Medical Research Institute, Brisbane

Biography
Michelle Lupton is an NHMRC Boosting Dementia Leadership Fellow, specialising in Alzheimer's disease (AD) genome-wide genetic association (GWAS) studies, neuroimaging genetics, genetic risk prediction, and Mendelian Randomisation. Michelle has contributed to world class consortia including the leading worldwide GWAS Meta-analysis and sequencing consortia. Michelle is the Global Regional Lead for Oceania for the DEMON network; an international network for applying data science and AI to dementia.

Background
The heritability of common late onset AD is estimated to be 60- 80%. The strongest genetic risk factor for AD is the *APOE* ε4 allele, accounting for approximately one quarter of the heritability. Through GWAS we have identified an additional 75 common genetic risk loci. I will present the most recent findings in the identification of genetic risk factors for Alzheimer's disease.

I will present my work in the use of large scale genetic data in Mendelian Randomisation (MR) analysis. AD is predicted to affect 132 million people by 2050, and targeting modifiable lifestyle risk factors could prevent a large proportion of dementia cases. However, evidence obtained from observational studies does not take into account how risk factors are correlated with one another, and whether they causally contribute to increased AD risk. We test for a causal relationship between previously speculated AD risk factors and AD susceptibility.

Finally, using examples from my own work I will show how genetic risk variants can be used in risk prediction, and in the identification of biomarkers for AD. This will include investigations in our PISA study (Prospective Imaging Study of Aging; Genes, Brain and Behaviour), which aims to 1) Identify healthy middle-aged Australians at high risk of dementia; 2) Discover biological markers of early neuropathology; 3) Identify modifiable risk factors, and 4) Establish the very early phenotypic and neuronal signs of disease conversion.

Unlocking the secrets of sleep for optimising brain health: mechanisms, treatments and translation

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Abstract
Sleep is critical to alertness, mood and cognition including the overnight consolidation of memories. Basic science data also shows that sleep facilitates synaptic plasticity, neurogenesis and the promotion of neurotrophins and new discoveries have revealed that during sleep, the brain 'clears away' neurotoxins and metabolic waste via the 'glymphatic' system.

Disturbances of sleep and sleep disorders are common in older people and appear to be especially pronounced in people with Mild Cognitive Impairment and dementia. While we don't yet know if sleep problems play a direct causal role in dementia pathogenesis, evidence to date supports the notion that the link between sleep and dementia may be bidirectional. This offers the opportunity for detection of sleep problems in people at risk for dementia, and importantly for providing interventions that target sleep in key critical periods for secondary prevention.

This keynote will overview the existing evidence linking sleep-wake disturbances with dementia. Drawing particularly on the work of the NHMRC Centre of Research Excellence to Optimise Sleep in Brain Ageing and Neurodegeneration (CogSleep CRE), the talk will present research linking various forms of sleep-wake dysfunction with cognitive and imaging markers of neurodegeneration in cognitively intact cohorts, as well as those with Mild Cognitive Impairment. Possible mechanisms linking sleep and dementia will be discussed. Finally, treatment options for sleep-wake problems and their current evidence base will be presented, as well as future considerations for the field.

Frontotemporal Dementia

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Background
Frontotemporal dementia encompasses a range of clinical presentations and different pathologies, the defining feature being a predilection for degeneration of frontal and/or temporal lobes. The majority have one of two histopathologies, namely either tau or TDP-43 containing inclusions. Compared to other forms of degenerative dementia, it has the highest risk of being dominantly genetically inherited although it is important to stress that for the majority of people diagnosed with a form of frontotemporal dementia, it will not have a genetic basis. Clinically, the disease typically presents with either language dysfunction—in turn subdivided into semantic or non-fluent types—or a syndrome of altered personality and behaviour denoted as “behavioural variant” (bvFTD). Furthermore the clinical syndromes of frontotemporal dementia can, in some people, overlap with motor disorders. For instance, the progressive non-fluent aphasic presentation is often underpinned by tau pathology and, with time, features of progressive supranuclear palsy or corticobasal syndrome may emerge. Likewise, frontotemporal dementia can co-exist with motor neuron disease. There are presently no evidence-based therapies for frontotemporal dementia; management is supportive.

Aside from the paucity of therapeutic options, a major ongoing research challenge is to tackle the misdiagnosis rate, particularly in the case of bvFTD—delay in diagnosis of actual bvFTD as well as misdiagnosis of non-degenerative diseases as bvFTD remain unfortunately high.

Perspective from Alzheimer's Association: Need for Real World Evidence in New Era of Treatment, Research & Care

Heather M. Snyder, Division of Medical & Scientific Relations, Alzheimer's Association, Chicago, IL, USA
Maria C. Carrillo[1], Gil D. Rabinovici[2], Michael S. Rafii[3], Rebecca Edelmayer[1], Andrew M. March[4] on Behalf of the ALZ-NET Study Team[5]

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[5]ALZ-NET Study Team, alz-net.org

Background
The Alzheimer's disease (AD) field is entering new phase of research, treatment and care. In 2021, U.S. FDA approved first novel treatment aimed at the underlying biology of AD and more recently approved the second novel treatment in 2023. The Alzheimer's Network for Treatment & Diagnostics (ALZNET) is a regulatory-grade, longitudinal study assessing safety, cognition and function in patients treated with novel AD therapies.

Methods
Led by the Alzheimer's Association, in partnership with academic experts, American College of Radiology, American Society of Neuroradiology, Critical Path Institute and Brown University School of Public Health, ALZ-NET is a voluntary provider-enrolled patient network to collect real world evidence about Alzheimer's patient care and long-term clinical and safety data for enrolled patients evaluated for and treated with novel FDA-approved Alzheimer's disease therapies. ALZ-NET will also track long-term health outcomes (effectiveness and safety) associated with the use of these FDA-approved therapies in real-world settings. Patients are to followed until withdrawal of consent, death or loss to follow-up. Patients being evaluated, starting or already treated with novel AD therapies will be enrolled at approved ALZNET sites. Notably, the prescribing information for one of the new therapeutics encourages clinicians and patients to participate in ALZ-NET. ALZNET will partner with affiliated studies acquiring additional data relevant to specific treatments.

Results
ALZNET is actively initiating new sites, enrolling patients being treated with novel FDA approved treatments. Further details will be shared.

Discussion/Conclusion
As novel therapies enter clinical practice, there is a need to track long-term safety and effectiveness in diverse populations representative of real-world practice. ALZ-NET is voluntary provider-enrolled patient network to do this and is actively working to collaborate with other international efforts, including in Australia, to align and harmonize data collection globally.

Medications and dementia: current challenges and future directions

Edwin Tan
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Abstract
Achieving quality use of medicines in people living with dementia is a global challenge. People living with dementia are high users of medications, used to treat not only symptoms of dementia but also multiple comorbidities. However, there is limited guidance for prescribing in people with dementia and this population are particularly vulnerable to adverse drug events. Inappropriate medication use can lead to an increased risk of negative outcomes including morbidity and mortality.

In this keynote presentation, Dr Tan will present an overview of current work investigating the safety and effectiveness of medication use in the treatment and care of people living with dementia. He will discuss nationwide data linkage studies he has led using data from Australia and Sweden. Future research priorities and directions will be discussed.

Development of MRNA-encoded antibodies for enhanced therapeutic targeting of Tau.

Rebecca Nisbet[1]
Patricia Wongsodirdjo, Alayna Caruso, Laura Vella, Ya Hui Hung, Jürgen Götz and Colin Pouton

[1] University of Queensland

Background
In Alzheimer's disease (AD), the protein tau forms intraneuronal aggregates known as neurofibrillary tangles. Therapeutics targeting tau have gained significant interest in recent years and monoclonal antibodies (mAbs) targeting tau are becoming the predominant treatment modality due to their high specificity and ease of production. However, mAbs are unable to cross the plasma membrane of neurons to target and neutralise intracellular antigens, such as tau. To enhance intracellular engagement of tau, we have generated an intracellular antibody (intrabody) of our lead candidate tau mAb. The aim of this study was to investigate whether functional tau intrabodies can be generated following delivery of the intrabody mRNA, encapsulated within lipid nanoparticles (LNPs).

Methods
The cDNA encoding the intrabody was cloned into a mammalian expression plasmid with a T7 promotor. Plasmid DNA was linearized and underwent *in vitro* transcription. The resulting mRNA contained a Poly(A) tail and was ARCA capped. mRNA was loaded into a classical '50:1:5' OnPattro LNP formulation and loading determined using dynamic light scattering and a RiboGreen RNA assay. Wild-type human neuroblastoma SH-SY5Y cells were treated with the mRNA-LNP and intrabody expression was determined following western blotting of the cell lysates. Intrabody engagement of tau was determined using a GFP pull-down assay in cells co-transfected with the intrabody and Tau-GFP.

Results
Capped mRNA with a Poly(A) tail encoding the tau intrabody was successfully packaged within LNPs. Incubation of wild-type SH-SY5Y cells with the intrabody mRNA-packaged LNPs resulted in successful expression of the tau intrabody within the cell cytoplasm. In cells expressing tau, the intrabody co-localised with tau in the cytoplasm and demonstrated positive binding to tau.

Discussion/Conclusion
This study demonstrates for the first time successful therapeutic engagement of intracellular tau and highlights the potential of mRNA-encoded tau antibody therapeutics for the treatment of AD.

Low-intensity ultrasound as a treatment modality for Alzheimer's disease

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Gerhard Leinenga, Daniel Blackmore, Jae Song, Peter Nestor and Rachel de las Heras

[1] University of Queensland

Background
Ultrasound is routinely used for diagnostic imaging but despite being long recognized for its therapeutic potential, it has only recently attracted widespread attention from advocates of classical pharmacological interventions in both academia and industry. A decade ago, we initiated a program of applying this technology to Alzheimer's disease, performing studies in mice and sheep, building a clinical trial ready device and initiating a safety study in Alzheimer patients. Here, we aimed to understand the bio-effects of ultrasound used together with microbubbles to achieve blood-brain barrier opening and without microbubbles to achieve neuromodulation in mouse models of senescence and Alzheimer's disease.

Methods
Here, we explored two ultrasound strategies, scanning ultrasound with microbubbles (SUS^{+MB}) which achieves blood-brain barrier opening, and scanning ultrasound without microbubbles (SUS^{only}), over a range of ultrasound parameters in amyloid-depositing APP23 mice and senescent wild-type mice, with several weekly treatment sessions. Analysis tools included an extensive behavioural, electrophysiological, biochemical, histological, proteomics and imaging (MRI) analysis.

Results
We will discuss data that reveal that SUS^{+MB} reduces amyloid pathology and restores cognition (Leinenga & Götz, ScienceTranslMed 2015, Leinenga et al., Bioeng & TranslMed 2022), that BBB opening is required for amyloid clearance (Leinenga et al., BrainResBull 2019) and whether SUS^{only} is sufficient to restore cognition (Leinenga et al., in progress). We will further discuss work that reveals that both SUS^{+MB} and SUS^{only} restore LTP deficits and improve cognition in senescent mice via pleiotropic mechanisms including NMDAR-dependent signalling (Blackmore et al., MolPsych 2021). Finally, we have built a clinical-trial ready ultrasound device and initiated a clinical trial in Alzheimer disease patients.

Discussion/Conclusion
We conclude that therapeutic ultrasound is a non-invasive modality for the treatment for Alzheimer's disease and other brain diseases. We also conclude that this modality has the potential of cognition enhancement in physiological ageing.

Monoclonal antibody therapy for Alzheimer's disease.

Chris Rowe[1]
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Background
Acetylcholine esterase inhibitors were FDA approved for dementia treatment in the 1990's but then nothing more for 20 years. The Amyloid Cascade Hypothesis *(Harding & Higgins 1992)* states that accumulation of beta-amyloid initiates or drives a series of events that lead to AD. Much research time and money has been spent on development of anti-amyloid monoclonals. Aducanumab effectively cleared amyloid plaques in Phase III trials and received FDA accelerated approval on this basis in June 2021. However, controversial cognitive results and cost led to a backlash from many in the AD medical field and there has been little clinical uptake. Based on effective plaque clearance, Lecanemab received accelerated FDA approval early this year. Following positive Phase III cognitive results in late 2022, an application for full FDA approval is being submitted. Conversely in late 2022, negative results from the gantenerumab Phase III trial were announced. The donanemab Phase III results are expected in the first half of 2023. Is lecanemab a vital breakthrough first step on the road to effective AD therapeutics?

Methods
Review of published data and data presented at international scientific meetings.

Results
The Clarity Phase III study of lecanemab infused fortnightly for 18 months in persons with MCI or mild dementia due to AD showed clearance of amyloid plaques with a 27% slowing in cognitive decline and 33% slowing in functional decline, with 10% having mild early infusion reactions and 3.4% having symptomatic ARIA (focal cerebral oedema or microhaemorrhages).

Discussion
These very encouraging findings raise many questions. Does the rate of slowing in decline persist? Is earlier treatment more beneficial? At $23,000 USD for the drug alone per year, what is the cost vs benefit to society? Optimal duration of dosing is unclear. What clinical and genetic factors influence risk vs benefit in an individual? Subcutaneous formulations are under development and competition from other antibodies may drive down the burden and cost of treatment.

SARS-CoV-2 infection and the presence of viral fusogens cause neuronal and glial fusion

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Background
Viruses from diverse families, such as rabies virus, herpes simplex virus, dengue virus, and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can infect the brain and cause multiple neurological manifestations, including headache, fever, loss of taste or smell, confusion and, in more severe cases, encephalitis, meningitis, and death. Growing evidence is pointing towards a direct correlation between episodes of viral exposure and the later development of common neurodegenerative diseases, such as Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease and multiple sclerosis. Unfortunately, the underlying causes of neuropathology upon viral infection are still poorly understood.

Methods
We used SARS-CoV-2 virus, as well as the fusogen spike (S) from SARS-CoV-2 and p15 protein from the baboon orthoreovirus, to investigate the effect on neurons and glia. The studies were performed in different systems, including mice cultured neurons, human embryonic stem cell (hESC)-derived 3D brain organoids, as well as the nematode *C. elegans* and mice *in vivo*.

Results
Our results revealed that SARS-CoV-2 infection induces fusion between neurons and between neurons and glia. We have discovered that this is caused by the presence of specialised viral surface molecules, fusogens, as this effect is fully mimicked by the expression of the SARS-CoV-2 spike (S) protein or the unrelated fusogen p15 from the baboon orthoreovirus. We demonstrate that fusion events are progressive, leading to the formation of multicellular syncytia, causing the spread of large molecules and organelles, and severely compromising neuronal activity.

Discussion/Conclusion
Our results provide mechanistic insights into how SARS-CoV-2 and other viruses affect the nervous system causing neuropathological symptoms, with direct implications to finally understand the long-term neurological sequelae reported in survivors of viral infections.

Ferroptosis as a mechanism of neuronal death in Alzheimer's disease

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Background
Allelic variation to the *APOE* gene confers the greatest genetic risk for sporadic Alzheimer's disease (AD). Independent of genotype, low abundance of apolipoprotein E (apoE), is characteristic of AD cerebrospinal fluid (CSF), and predicts cognitive decline. The mechanisms underlying the genotype and apoE level risks are uncertain. Recent fluid and imaging biomarker studies have revealed an unexpected link between apoE and brain iron, which also forecasts disease progression, possibly through ferroptosis, an iron-dependent regulated cell death pathway.

Methods
Ferroptosis was induced in the N27 neuronal cell model of ferroptosis using multiple agents (erastin, RSL3, iron, cysteine depletion). The severity of ferroptosis was measured by several toxicity assays (MTT, LDH) and lipid peroxide probe (C11BODIPY).

Results
We report that apoE is a potent inhibitor of ferroptosis (EC_{50}≈10 nM). We demonstrate that apoE inhibits ferroptosis via activation of the PI3K/AKT signalling pathway and subsequent inhibition of the autophagic degradation of ferritin (ferritinophagy), thus preventing iron release and ferroptosis. Although protection against ferroptosis did not differ between apoE isoforms in vitro, other factors associated with the apoE risk allele in vivo, such as low abundance of apoE protein and higher levels of polyunsaturated fatty acids (which fuel ferroptosis) could mediate the increased risk associated with allelic variation of apoE in AD.

Discussion/Conclusion
Our finding that apoE has such a potent effect on the ferroptosis pathway suggests that inhibition of ferroptotic signalling is a previously unrecognised and physiological function of this protein. Indeed, we proposed that the reduced capacity to protect against ferroptotic signalling could underlie a major mechanism of neurodegeneration in ageing. These findings support ferroptosis as a mechanism of neurodegeneration in AD and provide a rational for the use of anti-ferroptosis drugs for the treatment of AD.

Interneuron subpopulations in Alzheimer's disease

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Background
In Alzheimer's disease (AD), where amyloid-β (Aβ) and tau deposits in the brain, hyperexcitation of neuronal networks is an underlying disease mechanism, but its causes remain largely unknown.

Methods
Here, we used the Collaborative Cross forward genetics platform to identify modifier genes of neuronal hyperexcitation in mice. We found LAMP5 as a novel regulator of hyperexcitation in mice. Functionally, neuronal *LAMP5* was largely uncharacterised but more recently has been identified as a maker of a distinct subpopulation of inhibitory interneurons. We next examined the LAMP5 expression in different regions of brain sections from human AD, tau-only form of Frontotemporal lobar degeneration (FTLD-tau) patients, as well as neurologically healthy controls (CTR).

Results
We found a marked reduction of LAMP5+ neurons and their neuronal projections/synaptic boutons in the frontal cortex and other brain regions compared to CTR. Similarly, LAMP5+ neurons were reduced in numbers in a range of AD mouse models with either Aβ or tau expression and pathology, including the APP23, APP/PS1 and TAU58 lines. We furthermore showed that genetic reduction of LAMP5 levels led to the degeneration of LAMP5 interneurons in cortex and dentate gyrus in 3 months old Lamp5-deficient ($Lamp5^{\Delta/\Delta}$) mice and augmented functional deficits and neuronal network hypersynchronisity in Aβ- or tau-driven AD mouse models.

Discussion/Conclusion
To this end, our work defines the first specific function of LAMP5 interneurons in neuronal network hyperexcitation in AD and related forms of dementia with tau pathology.

Mechanisms underpinning altered calcium signaling and early phenotypes of Alzheimer's disease

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Background
Identifying the mechanisms underpinning early changes in Alzheimer's disease phenotypes may provide new therapeutic targets that could limit disease progression. Previous studies using measurements in living patients, as well as in cell models, and mouse models have suggested that alterations in neuronal function occur early in the disease course. The aim of this research was to identify the mechanisms that give rise to changes in ion channel function and neuronal survival, with a focus on understanding cellular mechanisms in late-onset (sporadic) Alzheimer's disease (LOAD) patients.

Methods
The research used a combination of induced pluripotent stem cell (iPSC) derived neurons from LOAD patients and controls and human post mortem tissue, analysed using a range of molecular and cellular techniques, including immunostaining, western blotting, calcium imaging, cell viability assays and lipidomics by mass spectrometry.

Results
Immunostaining and western blotting identified increased neuronal nitric oxide synthase (nNOS) in both LOAD patient tissue and iPSC derived LOAD neurons. In neurons the increased nNOS led to aberrant glutamatergic calcium signalling that could be reversed by blocking nNOS function or scavenging nitric oxide (NO). The data highlighted a divergent functional impact of NO that included strengthening the calcium response in control neurons, while dysregulating calcium signalling and altering the amplitude and kinetics of the calcium responses to glutamate in the LOAD neurons. Furthermore, LOAD neurons exhibited an increased susceptibility to ferroptosis and alterations in lipid membrane composition that impacted on glutamatergic calcium signalling. Blocking ferroptosis by targeting the membrane led to neuroprotection and the reversal of some LOAD phenotypes.

Discussion/Conclusion
These data suggest that NO modulation of glutamatergic calcium signalling may be neuroprotective under non-pathogenic conditions, with increased nNOS and NO contributing to pathogenic signalling changes during LOAD. Together this research highlights the crucial interplay between lipid membrane composition, ion channel function and neuronal survival.

Type I interferon response triggers cell-autonomous neurodegeneration and propagates TDP-43 pathogenesis

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Background
Cytoplasmic build-up of TDP-43 protein is a disease hallmark for amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Both pathological conditions are associated with an inflammatory profile related to upregulated of NF-κB and type I Interferon (IFN-I) signalling. Recently, we uncovered the cGAS/STING pathway as a key mediator of these neuroinflammatory signals in the context of TDP-43 proteinopathy, and demonstrated that this inflammation appears before the neuronal death. In this project, we sought to identify the role of IFN-I plays in TDP-43 pathogenesis and further explore the therapeutic potential of targeting the IFNAR-JAK-STAT signalling axis.

Methods
We employed a neuronal cell model (SH-SY5Y) of TDP-43 proteinopathy and iPSC-derived motor neurons from patients with ALS-FTD. These were subjected to pharmacological inhibition of signalling molecules within the IFN-I pathway. For in vivo studies a transgenic mouse model with human A315T mutant TDP-43 was used and crossed to mice that were genetically deficient for *Ifnar1*.

Results
Here we show that loss of *Ifnar1* mitigates motor deterioration, spatial learning and neurodegeneration in TDP-43^{A315T} mice. Immunohistochemical analyses demonstrate that TDP-43-mediated gliosis and $CD45^{+}$/$Ly6C^{+}$ peripheral monocyte infiltration can be prevented when *Ifnar1* is depleted. Surprisingly, RNAscope and FACS indicate that neuronal cells are primary cell type producing IFNβ compared to other brain cells, including microglia, astrocytes and infiltrating monocytes. This is supported by in vitro observations, in which TDP-43-induced phosphorylation of TBK1 and STAT1 correlates with exacerbated LDH release, axonal degeneration and formation of the Complement Membrane Attack Complex (MAC). Of note, these neuronal cell-autonomous degenerative cascades can be protected using IFNAR1 neutralisation antibody or JAK inhibitors.

Discussion/Conclusion
We demonstrate a rationale to target IFN-I signalling to intervene in immune-mediated neurodegenerative cascades by TDP-43 proteinopathy. This will be foundational for development of brain penetrant therapeutics to new clinical trials for ALS-FTD.

Heart racing, blood pressure climbing, feeling muddled?… something in the air?

Ruth Peters[1]
[1] University of New South Wales

Background
99% of the world's population live in places where air pollution levels exceed the WHO guideline limits for health. This means we are all exposed to potentially dangerous air pollution. Air pollution comes from multiple sources including household combustion devices, motor vehicles, industrial facilities, and wider environmental factors such as volcanoes, windblown dust, and wildfires. Air pollution can have multiple constituent particles and the WHO lists the pollutants of major public health concern as particulate matter, carbon monoxide, ozone, nitrogen dioxide and sulphur dioxide. In particular 'PM2.5' or fine particulate matter, with a diameter ≤2.5μm has been shown to be a risk factor for various noncommunicable diseases and cardiovascular (CV) risk factors and is an emerging risk factor for dementia. We review the evidence for air pollution acting to amplify or exacerbate the CV risk factors for dementia and the evidence linking air pollution to dementia itself.

Methods
The key evidence on air pollution and dementia and on air pollution, CV disease and dementia was collated using a mixture of umbrella review and traditional systematic review methodology

Results
We present a brief overview of the potential mechanisms and an assessment of the size and strength of the evidence linking air pollution to CV dementia risk factors and to dementia. We highlight the sources of bias in the current evidence and the remaining gaps in the evidence base.

Discussion/Conclusion
Whilst there is a strong evidence base that points persuasively to air pollution and increased dementia risk and to air pollution exacerbating CV risk there are important knowledge gaps. Given the global impact and pervasive reach of air pollution and the need for policy and government involvement to change exposure levels such gaps need urgent attention. We make recommendations for the next research in this area.

Implementation of cognitive interventions for mild cognitive impairment in Australian memory clinics

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Loren Mowszowski[2], Alex Bahar-Fuchs[3], Alessandra Lee[2], Amit Lampit[3], Adam Bentzelven[4], Inga Mehrani[4] and Sharon Naismith
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Background
Despite the evident benefits of cognitive interventions for older adults, including those with mild cognitive impairment and dementia, there remains a large evidence-practice gap with these interventions unavailable in clinical practice. Our work in addressing this gap, through the Australia Dementia Network (ADNeT) Cognitive Interventions Working Party, will be described.

Methods
Using an implementation science approach, we conducted a scoping review regarding international practices in implementing cognitive interventions for older adults. This has informed the development of an online clinician-training toolkit for choosing and delivering interventions and the design for our pilot implementation feasibility study using the RE-AIM Implementation Framework in six memory clinics across Australia.

Results
Of 29 studies included in our scoping review, only 4 used formal implementation frameworks (3 used RE-AIM). Studies commonly measured acceptability, feasibility, and effectiveness, whereas cost-effectiveness and maintenance were rarely reported. Barriers and facilitators to implementation were noted in terms of stakeholders (clients; intervention facilitators; and the stakeholder relationships), as well as the context regarding the intervention as well as the service, and in terms of reach of the intervention. Progress of clinician training and implementation in practice will be described.

Discussion/Conclusion
This is the first Australian study to address the evidence-practice gap in cognitive intervention research. Using implementation science frameworks enables a more structured approach to addressing the evidence-practice gap, including the role of clinicians, manager, and consumers in advocating for service-level changes. Improving post-diagnostic support for people with MCI in the memory clinic setting is likely to not only improve cognition and wellbeing in the short-term, but ultimately follows a secondary prevention approach, ideally contributing to attenuated cognitive, functional, and psychosocial decline, or delayed onset of dementia.

Sex and gender differences in dementia incidence, prevalence, and cognitive reserve: Implications for dementia prevention

Kaarin Anstey[1]
Md Hamidul Huque[1]
[1] University of New South Wales, Neuroscience Research Australia

Background
With far greater prevalence of dementia in women, there is an urgent need to identify sex and gender related determinants of dementia subtypes. We investigated how cognitive reserve is associated with global estimates of incidence and prevalence of dementia, and how it influences risk of cognitive decline in women and men at the individual level.

Methods
A systematic review of the global literature on AD, Vascular Dementia (VaD) and all cause dementia prevalence and incidence for males and females was undertaken. Meta-regression of country level data evaluated how education (a measure of cognitive reserve) and life expectancy, influenced prevalence and incidence. Multilevel analyses of a cohort spanning ages 40 to 78, followed for 12 years, was conducted to evaluate gender differences in cognitive reserve longitudinally. Cognitive reserve was operationalized as a composite of education, occupational complexity and cognitive and social engagement. Cognitive outcomes included processing speed and verbal ability.

Results
Results from 205 eligible studies, representing 998,187 participants across 43 countries showed that when men and women were compared at equivalent ages, incidence was higher in women, but this was not statistically significant. Higher prevalence of AD and dementia among women was influenced by differences in education and women's longer life expectancy. Additionally, longitudinal analysis of midlife (n = 2513) and late-life (n = 2403) cohorts showed that for participants with lower baseline cognitive reserve, processing speed declined rapidly over time compared to high cognitive reserve. However, this decline was slower for women compared to men and independent of *APOE* genotype.

Discussion/Conclusion
Both sex and gender associated factors influence risk of dementia. Increasing cognitive reserve has greater benefit for women than men. Global dementia prevention strategies need to emphasise the importance of reducing gender inequality in education and promote equal opportunities for women to engage in cognitively complex occupations.

Payment strategies for interventions and treatments in dementia

Brenda Gannon[1]

[1] University of Queensland

Background
Technological advances and innovation have meant that new interventions and treatments for dementia and related conditions are moving into markets at an accelerated pace. While effectiveness has been proven, parallel discussions on, and modelling of, payment strategies are an imperative. Who will pay for the new, often expensive technologies, and what is the public preference towards such payment mechanisms? This talk will focus on two different methods, utilised to establish cost-effectiveness firstly, and then willingness to pay towards budgeting and planning secondly, both focusing on dementia specific interventions.

Methods
The first part of this talk discusses the use of a decision analytical model (DAM) to establish if a treatment is cost-effective. Utilising the iTAP Australia, an intervention designed to provide occupational therapy for people with dementia at home, to improve their functioning and quality of life, the model structure is presented. Parameters necessary for such modelling include, intervention effectiveness, generally predicted through analysis of randomised control trial data, or previous literature. Effectiveness could include quality adjusted life years, disease specific effectiveness, or simply reduced admissions to hospital, to help towards health system savings. Costs of health care resources used are generally calculated as averages, based on literature, or if available individual level consumer data. Statistical modelling is introduced into the overall DAM, to provide precision, followed by bootstrapping of results, to determine overall cost-effectiveness. The second part of the talk then moves to payment strategies. Budget planning will require population numbers affected, and the larger question of, who will pay – public, private funders or the individual tax-payer, or the consumer via out-pocket-expenditure. Using a discrete choice experiment (DCE), is one way to determine the public preferences and amount deemed viable for them to contribute. Again, using the iTAP examples, a DCE model is built, data collected from 1000 people and willingness to pay figures analysed. The key points of the model will be presented.

Results
Results will be presented at the conference.

Discussion/Conclusion
In conclusion, discussions on the most sustainable funding models, can be informed by DAM and DCE.

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Results
Results will be presented at the conference.

Discussion/Conclusion
In conclusion, discussions on the most sustainable funding models, can be informed by DAM and DCE.

Post diagnostic support in general practice

Dimity Pond[1]
[1] University of Tasmania

Background
There is little in the literature about how GPs provide post diagnostic support for people living with dementia. GP Dementia Guidelines focus on identification, with some focussed guidelines around specific features of dementia. The principles of ongoing primary care of the whole person are not clearly agreed.

Methods
This brief presentation will discuss some principles for post diagnostic support in primary care. It should be noted that most people with dementia have one or more chronic diseases. People in the age ranges most commonly associated with dementia see GPs 12-15 times per year in Australia.

Results
1. Dementia may affect every part of a person's life and medical care. GPs need to keep this in mind when treating patients for their multiple comorbidities when they are living with dementia.
2. The model of self care developed for most chronic diseases will need modifying when the person develops dementia. Exercise regimes, diet, self referral to allied health etc will alter in the presence of cognitive changes. The GP therefore needs to adjust the plan of care.
3. The GP should have regular meetings with the carer(s) if possible, in order to support carer stress. In addition the carer can update the GP on dementia symptoms, which may indicate further modification of the usual care regime outside of dementia (e.g. introducing Webster packing of medications).
4. GPs should learn about local dementia services, and refer the person and their carer to these services, including those provided by Dementia Australia.

Discussion/Conclusion
Dementia is a complex chronic disease which affects every part of a person's functioning, including their ability to care for their other chronic diseases**.** GPs should take dementia into account in their approaches to chronic disease management beyond dementia itself.

The importance of creating smart goals and using the reablement approach to move forward with your life.

William (Bill) Yeates[1]
[1] Vice-Chair of Dementia Alliance International Dementia Australia Advocate

The incurable and progressive nature of Alzheimer's Disease brings with it a myriad of challenges. One of which, is how best to manage this disease so that you can remain independent for as long as possible, while enjoying the best possible quality of life and living a life that you value.
Based on the reablement approach, I developed a template that consists of six different components – Current situation (barriers), SMART Goal, Core actions (strategies), Responsibility and Time frame. For me, it is the setting of SMART goals which is the most important step, as they allow me to focus on those aspects of my life that I value.

I use this template to create a Reablement Plan for each of the SMART Goals that I want to achieve. When combined, these reablement plans represent the Post Diagnostic Care Plan that I designed for myself.

The importance of post diagnostic support that is tailored to individual needs

Heather Fitzpatrick[1]
[1] Dementia Australia Dementia Advocates Program

Background
Heather's husband, Noel, was diagnosed at 61 with younger onset dementia. Noel has always been very physically fit and a keen cyclist. Leading up to his diagnosis, Noel was losing his confidence, started behaving differently and was getting flustered by small things. Heather cared for Noel at home before he recently moved into residential care.

After his diagnosis, Noel was referred to a memory clinic for support where he has seen a psychologist, speech pathologist and psychiatrist, as well as many other staff. Heather will share the importance of post diagnostic support for dementia that is tailored to individual needs and highlight the support that worked for her family.

"Dementia is such an individual journey, and no two cases are the same. There are no straightforward or common pathways for families who are impacted by dementia."

Basal forebrain cholinergic neurodegeneration impairs glymphatic influx in Alzheimer's disease

Kai-Hsiang Chuang[1]
Xiaoqing Alice Zhou[1], Lei Qian[1], Zengmin Li[1], Grace Ngiam[1] and Elizabeth J. Coulson[2]
[1] University of Queensland
[2] Queensland Brain Institute, The University of Queensland

Background
Recent studies suggested that waste from the brain is cleared from the interstitial space via a fluid exchange pathway termed the glymphatic system. Glymphatic dysfunction is associated with the accumulation of pathogenic molecules, such as the amyloid-beta aggregates in Alzheimer's disease (AD). How glymphatic flow is regulated and why it is impaired in AD are still unclear. As glymphatic influx is mediated by vascular pulsation and cholinergic neurons regulate cerebral vasodilation, we hypothesized that degeneration of basal forebrain cholinergic neurons in AD underlie the glymphatic dysfunction.

Methods
All animal experiments were approved by the Animal Ethics Committee of the University of Queensland. Cholinergic neurons in young C57BL/6 mice were lesioned by p75NTR-saporin and compared to sham controls. A triple transgenic mouse model of AD, expressing APP Swedish, MAPT P301L, and PSEN1 M146V mutations, was used to test the hypothesis in AD. Glymphatic imaging was conducted by intracisternal injection of Gd contrast agent using a 9.4T preclinical MRI.

Results
We found that degeneration of basal forebrain cholinergic neurons in mice leads to glymphatic deficits. Lesioning cholinergic neurons in the medial part of the basal forebrain, which project to the hippocampus, reduced the pulsation of the hippocampal artery and the corresponding periarterial fluid transport and tissue glymphatic flow. These changes are also recapitulated in a mouse model of AD that exhibits cholinergic neurodegeneration.

Discussion/Conclusion
Our results demonstrate a neural mechanism by which glymphatic flow is modulated by cholinergic neurons via arterial regulation. This finding would have strong implication for the diagnosis and treatment of glymphatic dysfunction in AD.

Effects of genetic variants in the clusterin gene in relation to cognitive function in healthy adults

Martina Gyimesi[1]
Duy Nguyen[1], Heidi Sutherland[1], Hannah Stewart[1], Rod Lea[1], Rachel Okolicsanyi[1], David Shum[2], Lyn Griffiths[1] and Larisa Haupt[3]
[1] Queensland University of Technology (QUT), Centre for Genomics and Personalised Health, Genomics Research Centre, School of Biomedical Sciences, 60 Musk Ave., Kelvin Grove, Queensland 4059, Australia
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Background
Alzheimer's disease (AD) accounts for approximately 70% of all dementia cases and is currently the second leading cause of death in Australia. Despite some breakthrough discoveries in the past decade, the genetic mechanisms underlying the pre-clinical phases of AD are still unknown. In this study common variants in the Clusterin (*CLU*) gene were examined for their contribution to healthy cognitive function.

Methods
Four single nucleotide polymorphisms (SNPs) in *CLU*, were tested for association with various cognitive function measures in a healthy adult cohort (n=597). The cohort was phenotyped for cognitive traits in episodic, semantic, verbal, visual, prospective and retrospective memory as well as learning processes. Genotyping was performed using the MassARRAY system and statistical associations were tested using general linear regression ($p<0.05$) analysis followed by additive genotypic and dominant/recessive heritability tests ($p<0.0167$). P-values were corrected for multiple testing.

Results
SNP_CLU1 demonstrated a significant positive effect on visual memory when analysed using a recessive model ($p=0.013$), while SNP_CLU2 showed an association with verbal learning scores using a dominant model ($p=0.015$). Finally, SNP_CLU2 and SNP_CLU3 were found to be associated with general intelligence scores ($p=0.025$ and $p=0.04$, respectively). SNP_CLU4 showed no effects on the cognitive traits explored.

Discussion/Conclusion
These findings suggest the involvement of *CLU* gene variants in healthy cognitive processes perhaps through its involvement in neurogenesis and neuroprotection. Although further biological validations are necessary, this study suggests that the exploration of *CLU* in neuronal processes may provide new insights into its role in the regulation of the memory decline symptomatic of AD.

Predictive selection of non-toxic and non-allergenic b-cell epitopes in the amyloid precursor protein for Alzheimer's disease treatment

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Sachin Kumar[1], John Hardy[2] and Mourad Tayebi[3]
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[2] University College London, London, United Kingdom
[3] Western Sydney University

Background
Alzheimer's disease (AD) is recognized as a significant health burden, affecting the quality of life of many people around the world, but no effective treatment or preventive vaccine is available. To date, research in this area focused mainly on attempting to eliminate/neutralize the neurotoxic beta amyloid peptides derived from the amyloid precursor protein (APP).

Methods
Our study aimed at uncovering novel 'non-toxic-non-allergenic' (NTNA) B-cell epitopes located on the entire APP using immunoinformatic approaches in order to develop an effective passive immunotherapy for the prevention and treatment of AD. To that end, we used 18 APP forms, including wild-type (WT) and 17 APP with known reported mutations associated with Alzheimer. We conducted extensive physicochemical analysis, protein 3D modelling, conformational and linear NTNA B-cell epitope predictions.

Results
Initially, we found a total of 192 linear B-cell epitopes derived from the 3D WT and mutated APP structures; out of which only seven NTNA B-cell epitopes (19-48 amino acid residues) were identified and found to be common to A2V, English, Flemish, Italian, Florida, Lowa, Osaka, Swedish, and Tottori Alzheimer mutations. Of importance, these seven epitopes are localized to the conserved E2 domain of APP. Similarly, we found 225 conformational B-cell epitopes derived from the 3D WT and mutated APP structures, whereas 36 out of 225 were located in the E2 domain region. Epitopes with long peptide sequences can be toxic and or allergenic to cells following processing by antigen presenting cells into shorter peptide sequences. Since our predicted linear epitopes ranged between 19-48 amino acids, we analysed 10-mer peptides from the seven NTNA peptides and identified eighteen short peptides (10 amino acid long) that were NTNA. The physicochemical properties analysis revealed that the predicted epitopes are hydrophilic, highly thermostable, has optimum half-life, suggesting that these epitopes can be used as potential therapeutic targets outside the Aβ peptide region in order to stablise APP and potentially inhibit synthesis of amyloidogenic Aβ peptides.

Conclusion
Consequently, these findings indicate that the E2 domain of APP might be an effective new target for the screening and development novel drug/biologic therapeutics or peptide-based active immunization strategy for the prevention of AD.

Prognostic utility of plasma p217+tau vs amyloid and tau PET in the Alzheimer's continuum

Azadeh Feizpour
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[3] Florey Institute of Neuroscience and Mental Health

Background
We evaluated the association of plasma p217+tau with longitudinal cognition and its comparative performance to amyloid-β (Aβ) and tau PET in predicting prospective cognitive decline.

Methods
153 cognitively unimpaired (CU) and 50 cognitively impaired (CI) participants underwent baseline p217+tau SIMOA assay, ^{18}F-MK6240 tau-PET and ^{18}F-NAV4694 Aβ-PET with neuropsychological follow-up (MMSE, CDR-SB, AIBL-PACC) over 2.4 ± 0.8 years. The association of baseline biomarkers with cognitive decline was evaluated. Sample size to detect a 30% slowing in cognitive decline in a 2-year trial and selection cost using p217+tau (pT+) were compared to Aβ-PET (A+) and tau-PET (T+) with and without p217+tau pre-screening.

Results
In the CI, plasma p217+tau predicted change in MMSE (β = -0.55, $p < 0.001$) and CDR-SB (β =0.61, $p < .001$) with effect size larger than Aβ Centiloid (MMSE β = -0.48, $p = 0.002$; CDR-SB β = 0.43, $p = .004$) but smaller than tau_{MetaT} SUVR (MMSE: β = -0.62, $p < .001$; CDR-SB: β = 0.65, $p < .001$). In the CU, only tau_{MetaT} SUVR predicted change in AIBL-PACC (β = -0.22, $p = 0.008$). Screening CI for pT+ led to 24% reduction in sample size compared to screening with PET for A+ and 6-13% compared to T+ (different regions). This translated to an 80% test cost-saving assuming p217+tau costed one-fifth of PET. In a trial requiring PET T+ or A+, pT+ pre-screening followed by PET would cost more in the CI group with AD prevalence of 70%, compared to 35% cost-saving in the CU group with preclinical AD prevalence of 25%.

Conclusion
Substantial cost reduction can be achieved using p217+tau alone to select participants with CI for a trial, compared to selection by PET. Pre-screening with p217+tau followed by PET provides cost-saving in preclinical trials but is questionable in MCI/AD trials.

The use of human mesenchymal stem cells to investigate methylation and gene expression correlations during neural lineage specification

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Background
Due to their high *ex vivo* and *in vitro* capacity, their ability to transdifferentiate and their relative ease of isolation, human mesenchymal stem cells (hMSCs) are promising candidates for therapeutic applications for neurodegenerative disorders, including Alzheimer's disease (AD). hMSCs can be induced to form neurospheres (hMSC-INs), a neural precursor-like cell type. Heparan sulfate proteoglycans (HSPGs) are a family of proteins ubiquitous to the cell surface and the extracellular matrix. Through their complex and tuneable side chains, two major families of HSPGs, the syndecans (SDC) and (GPCs) participate in the highly regulated control of critical cellular processes including cellular proliferation and neural lineage specification/differentiation.

Methylation is a reversible change made to the DNA that encodes an additional regulatory mechanism to influence gene expression and thereby, cellular functions. Syndecan-3 (SDC3) is an HSPG core protein of specific interest in neural lineage specification of hMSCs. DNA methyltransferase I (DNMT1) is responsible for the addition of methyl groups to specific CpG structures, the process of DNA methylation.

Methods
hMSCs were grown under basal, proliferative (heparin) and neurosphere inductive conditions and examined at early, mid and late phase of growth for gene expression and methylation changes. In addition, siRNA knockdown experiments were undertaken at late growth phase to examine the effect of reduced SDC3 and DNMT1 gene expression on methylation profiles.

Results
We determined that basal SDC3 gene expression increases over extended time in culture (early to late growth phase). Following heparin treatment, gene expression non-significantly increased at early and mid-growth phases. At late growth phase, gene expression was non-significantly decreased.

Discussion/Conclusion
We expect that SDC3 knock-down will reduce hMSC ability to form hMSC-INs. In addition, we anticipate that the siRNA induced reduction in gene expression will correlate with the methylation changes observed between monolayer and hMSC-IN cultures.

Uncovering the impact of Alzheimer's disease aggregates on brain cell physiology through bioorthogonal labelling

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Background
Alzheimer's disease (AD) impacts millions of people worldwide. At the cellular level, AD is characterised by extracellular aggregates composed of amyloid-β (Abeta) plaques and intraneuronal accumulation of hyperphosphorylated microtubule-associated Tau (pTau) protein. Despite ongoing efforts, a deeper understanding of the impact of these aggregates on brain cell physiology is still needed.

Methods
To uncover novel molecular aspects by which brain cell physiology is altered in AD, we employed bioorthogonal labelling with non-canonical amino acids and click chemistry. These methods allowed us to tag, visualise and identify the newly synthesised proteins in neurons and microglia, the resident immune cells of the brain parenchyma that accumulate around plaques, in the presence of Abeta and pTau.

Results
We revealed that in neurons, Abeta induces the synthesis of Tau and that pTau leads to a marked decrease in the synthesis of proteins associated with microtubule physiology, endocytosis, mitochondria, and ribosomal biogenesis and functions. In microglia, we observed an Abeta-dependent alteration of the overall protein synthesis, as well as an activation of the integrated stress response, an adaptational signalling pathway that is triggered when cellular homeostasis is severely imbalanced.

Discussion/Conclusion
We have revealed novel mechanistic insights in which AD-specific aggregates alter the physiology in neurons and microglia, which could eventually lead to novel treatment avenues against the disease.

What can blood biomarkers tell us about dementia pathology?

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[2] ACROSS, University of Tasmania
[3] Deakin University

Background
Blood biomarkers are increasingly being used in a diagnostic capacity, however, few studies have directly examined their relationship with brain pathology. We measured serum biomarkers in the inducible Tg4510 tauopathy mouse model to determine alterations during induction of pathology and how biomarkers were altered when pathology induction was halted following removal of transgene expression.

Methods
Pathology was induced from 8 weeks until 18 months (n=20 equal male/female; tau transgenic and non-transgenic) by removal of doxycycline (dox) diet. Dox diet was returned to half the animals from 18-23 months to inhibit pathology. Levels of Nfl and p-tau181 were measured using SIMOA. Immunohistochemical assays were performed to quantitate numbers of neurons (NeuN) and tau load (PHF-1) in hippocampus.

Results
Nfl was significantly higher in tau transgenics relative to non-transgenics at 18 months ($p<0.05$). Between 18-23 months, male but not female mice, on dox, significantly reduced the rate of increase of serum Nfl so that by 23 months levels of Nfl in transgenics was not different to non-transgenics. Similarly, the numbers of neurons in the hippocampus of male mice on dox at 23 months was significantly higher than their female counterparts ($p<0.05$). Nfl was significantly negatively correlated with NeuN (Nfl: $R = -0.6$, $p < 0.001$). The proportion of NeuN cells PHF-1 positive in the hippocampus was also significantly positively correlated with p-tau181 ($R = 0.78$, $p < 0.001$). When looking at levels of p-tau181 at 23 months, there were significantly ($p<0.05$) higher levels in male mice on dox than female mice, despite the inhibition of neurodegeneration in male mice.

Conclusion
These data suggest that blood biomarkers correlated with brain pathology and can predict brain related changes. The longitudinal use of biomarkers to indicate cellular changes in the brain may offer potential to obtain mechanistic insight into disease progression.

Younger onset dementia: New insights using linked data

Ingrid Evans[1]
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[1] Dementia Unit, Australian Institute of Health and Welfare (AIHW)

Background
It is estimated that 27,800 Australians had younger onset dementia (YOD) in 2021, projected to increase to 39,000 by 2050. The experiences and care requirements of people with YOD are often different from those of older people. There is a need for better evidence to inform policy and service responses to support people with YOD.

Methods
People with YOD were identified in 2 multi-source enduring linked data sets using pharmaceutical claims for dementia-specific medication (anticholinesterases) in 2011–2012. The linked data were used to describe the social and financial circumstances of people with YOD, their health and aged care service use (general practitioner and specialist attendances, medicines dispensed, emergency department visits and hospital stays, respite and permanent residential aged care (RAC)) and mortality outcomes between 2011 and 2016.

Results
The study cohort comprised about 5,400 Australians aged 30–69 who were dispensed anticholinesterases in 2011–2012. Nearly one third (28%) lived in regional or remote areas and 21% were born in a non-English speaking country. A high proportion of people with YOD received income support through Centrelink, most commonly the Disability Support Pension. Only 25% of the cohort used respite RAC, but more than half (58%) lived in permanent RAC at some time during the study period. Of these, 25% were aged under 65 when they first entered permanent RAC. Dispensing of antipsychotic medicines increased after entry to permanent RAC. About 2 in 5 people (42%) had died by the end of the 6-year study period.

Discussion/Conclusion
The use of linked data enabled dementia-specific reporting from data sets that on their own contain no information about dementia, and allowed analysis of service use over time. These insights can be used to better plan and deliver services to improve outcomes for people living with YOD, their families and carers.

Apathy and fatigue, but not depression associated with lifestyle risk index in older adults

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[4] Centre for Healthy Brain Ageing (CHeBA), University of New South Wales, Sydney, NSW, Australia

Background
There is increasing evidence for dementia risk reduction through changed lifestyle and health behaviours. However, changes are difficult to achieve and sustain long-term, which is a key challenge for multidomain interventions for dementia prevention. Emerging theoretical frameworks suggest apathy, depression and fatigue may be barriers to engaging in healthy lifestyles, but this has been little researched. This study investigates whether symptoms of apathy, depression and fatigue are associated with a lifestyle risk index.

Methods
In a community-dwelling cohort of older adults without dementia (n=1,037), a lifestyle risk index was computed, by summing presence or not of four risk factors: physical inactivity, inadequate dietary intake, excessive alcohol consumption and smoking. Self-report apathy, fatigue and depressive symptoms were assessed using questionnaires (Geriatric Depression Scale and Assessment of Quality of Life-2). Multinomial regression analysis investigated associations of apathy, fatigue and depression scores with the risk index (measured as one, two or three/four risks, with zero as reference category). Covariates were socio-demographics, cognition, health conditions and APOE4 status.

Results
Apathy symptoms were significantly associated with the risk index (p=.003), controlling for covariates. Specifically, relative risk of one, two or three/four risk factors (compared to zero) was 97%, 60% and 62% higher, respectively, with greater apathy. Fatigue was also associated with elevated risk of 77% and 122%, for two or three/four risks. Unexpectedly, depressive symptoms were linked only with 22% reduction in risk for one risk factor (compared to zero).

Discussion/Conclusion
Older adults experiencing apathy or fatigue were more likely to have multiple lifestyle risk factors, over and above covariates such as health conditions, cognition and socio-demographics. Findings suggest apathy and fatigue - but not depression – are barriers to engaging in key components of multidomain interventions, such as physical activity. Addressing apathy and fatigue symptoms may help support long-term efficacy of dementia risk reduction and health promotion activities in older adults.

Association of acquired hearing loss with social isolation and depression in adults aged 50 years or over in Tasmania

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Background
Acquired hearing loss (HL) in adult life is one of the most prevalent health conditions and, if untreated, a significant risk factor for dementia. This study aimed to explore the association between acquired HL and social isolation, anxiety, and depression.

Methods
A cross-sectional study was conducted on a sample of Australian residents aged 50 years or over (n = 7,442) between October 2020 and March 2022. Regression analysis was used to assess the association between acquired HL and social isolation, anxiety, depression, and the size of supportive social networks.

Results
A total of 1,274 participants (17.1%) had acquired HL. Males were more likely to have HL, with 46.0% in the HL group and 46.2% in the HLcorrected group being male, compared to 25% in the No-HL group. HL was significantly associated with both size of supportive social network ($F(2,7362) = 4.9$, $p = .007$) and support ($F(2,7362) = 11.5$, $p = .001$). There was a significant difference between No-HL and HL groups (corrected or uncorrected) on the supportiveness sub-scale of the Lubben Social Networks Scale (LSNS-18), $p = .03$, with little numerical difference between uncorrected and corrected HL groups, 8.4 (SD 2.8) and 8.8 (SD 2.6), respectively. Uncorrected HL was also significantly associated with both anxiety ($F(2,7362) = 15.4$, $p < .001$) and depression ($F(2,7362) = 11.0$, $p < .001$).

Discussion/Conclusion
Untreated HL is a significant contributor to mental health symptoms and poor social isolation, compounding the risk for dementia. Hearing aid use mitigates some of these effects, but much remains to be done to address this issue and decrease dementia risk.

Blood pressure, antihypertensive use and dementia risk: An IPD meta-analysis of 17 cohort studies in an international consortium

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Background
Mid-life hypertension is a known risk factor for dementia but in late-life, blood pressure (BP) has variously been shown to have nil, positive and negative associations. A recent IPD meta-analysis found that in late-life, lowest risk for dementia occurred at around systolic BP (SBP) of 185 mmHg and some studies have suggested that continuing antihypertensive use in late-life may increase dementia risk.

Methods
An IPD meta-analysis was carried out on 17 longitudinal studies of ageing (n = 43,258). The key outcome was dementia and the key predictor variables were a previous diagnosis of hypertension status/baseline antihypertensive use as 3-group variable ("controls", "treated hypertensives" and "untreated hypertensives") and baseline SBP and diastolic blood pressure (DBP), including linear and quadratic terms (SBP, SBP^2, DBP and DBP^2). The main analysis was a partially adjusted Cox proportional hazards model adjusting for age, age^2, sex, education and ethnicity.

Results
In the main analysis, compared to "healthy controls", untreated hypertensives had 32% increased dementia risk ($p<0.001$) whereas treated hypertensives overall had no elevated dementia risk. Comparing untreated to treated hypertensives, there was a 28% increased dementia risk ($p<0.001$). There was a significant curvilinear relationship between baseline SBP ($p_{linear}<0.001$, $p_{quadratic}<0.001$), DBP ($p_{linear}=0.008$, $p_{quadratic}<0.001$) and dementia risk with lowest risk points at SBP 153 mmHg and DBP 84 mmHg. For both SBP and DBP, low BPs posed a greater risk than high BPs and restricting analysis to >5-years follow-up, only DBP remained significantly associated with dementia risk.

Discussion/Conclusion
Hypertension remains a risk factor for dementia in late life. Antihypertensive use is associated with decreased dementia risk in those with hypertension through all ages. Measured SBP and DBP in late life have a curvilinear relationship with dementia risk, with DBP, particularly low DBP, being more robustly associated than SBP. Effects of and treatments for low DBP in late life are an important area for future research.

Cardiovascular disease risk scores and risk of cognitive decline and dementia in older men and women

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Background
Risk factors for cardiovascular disease (CVD) also increase the risk of dementia. However, whether commonly used CVD risk scores are associated with dementia in older adults who do not have a history of CVD remains unclear. The aim of this study was to determine whether CVD risk scores are associated with subsequent cognitive decline and dementia in initially healthy older men and women.

Methods
Participants were from a prospective cohort of 19,114 individuals aged 65+ years without prior CVD event or major cognitive impairment. The Atherosclerotic Cardiovascular Disease risk score (ASCVDRS), SCORE2-Older Persons (SCORE2-OP) and the Framingham risk score (FRS) were calculated at baseline. Dementia was adjudicated by clinical experts according to DSM-IV. Cognitive decline was defined as a >1.5 SD decline in cognitive score from their own baseline value on any of the four cognitive domains [global cognition, episodic memory, psychomotor speed or verbal fluency].

Results
Over a median follow-up of 6.4 years, 850 individuals developed dementia and 4,325 individuals had cognitive decline. Both ASCVDRS and SCORE2-OP, were associated with dementia and cognitive decline. For example, men and women in the highest ASCVDRS tertile had a 41% and 45% increased risk of dementia compared to the lowest tertile respectively (HR [95%CI] men: 1.41 [1.08,1.85], women: 1.45 [1.11,1.89]). Similarly, men and women in the highest SCORE2-OP tertile had a 64% and 60% increase in dementia risk compared to the lowest tertile respectively (men: 1.64 [1.24,2.16], women: 1.60 [1.22,2.11]). Higher FRS was not associated with incident dementia and only associated with an increased risk of cognitive decline among women (FRS continuous: 1.08 [1.02,1.15]; highest vs. lowest tertiles: 1.12 [1.01-1.25]).

Conclusion
These results provide evidence for both ASCVDRS and SCORE2-OP as a measure of shared CVD risk factors for identifying dementia and cognitive decline risk in older adults.

Factors associated with participation in a multidomain web-based dementia prevention trial: evidence from Maintain Your Brain (MYB)

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Background
The Maintain Your Brain (MYB) trial aimed to prevent cognitive decline and dementia through multidomain, web-based risk-reduction. To facilitate translation, it is important to understand drivers of participation. This study aimed to describe characteristics associated with participation in MYB.

Methods
This was an observational ancillary study of MYB, a randomized controlled trial nested within the 45 and Up Study in New South Wales, Australia. We linked 45 and Up Study survey and MYB participation data. The study cohort comprised 45 and Up Study participants, aged 55-77 years at 1 Jan 2018, who were invited to participate in MYB. 45 and Up Study participant characteristics and subsequent MYB consent and participation were examined.

Results
Of 98,836 invited, 13,882 (14%) consented to participate and 6,190 participated (6%). Adjusting for age and sex, a wide range of factors were related to participation. Higher educational attainment had the strongest relationship with increased MYB participation (university vs. school non-completion; AdjOR=5.15; 95%CI:4.70-5.64) and lower self-rated quality of life with reduced participation (Poor vs. Excellent: AdjOR=0.19; 95%CI:0.11-0.32). A family history of Alzheimer's disease was related to increased participation but most other dementia risk factors such as diabetes, obesity, stroke, high blood pressure and current smoking were associated with reduced participation.

Discussion/Conclusion
Higher socio-economic status, particularly educational attainment, is strongly associated with engagement in online dementia prevention research. Increasing population awareness of dementia risk factors, and better understanding the participation barriers in at-risk groups, is necessary to ensure online interventions are optimally designed to promote maximum participation.

Multi-domain modifiable dementia risk factors are associated with rate of change in cognition and brain volume in older adults

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Background
Multi-domain modifiable dementia risk factors (MDRF) are associated with poorer cognitive performance in cognitively normal (CN) adults. However, how multi-domain MDRFs relate to changes in cognition and Alzheimer's disease (AD) biomarkers over time remain unclear. This study aimed to determine associations between multi-domain MDRFs and rates of change in cognition, brain volume and beta-amyloid (Aβ) for up to 162 months in CN older adults.

Methods
Participants aged 60+ enrolled in the AIBL study who had ≥75% complete baseline data on 10 MDRFs and had ≥2 neuropsychological assessments (n=673), MRI assessments (n=302) and Aβ PET scans (n=211) were included. MDRFs were measured using self-report surveys or objective measures (e.g., blood pressure). Participants were classified according to number of domains in which they reported ≥1 MDRF. Domains included mood symptomatology, risky lifestyle behaviors, cardiovascular conditions, and cognitive engagement. Linear mixed models assessed interactions between MDRF domain (0-4) groups (0 domains=reference group) and time on outcomes for cognition (PACC, episodic memory, executive function, language, attention), brain volume (ventricular, white matter, hippocampal), and Aβ (centiloid). Age, sex, education and *APOE* ε4 were included as covariates.

Results
Significant MDRF group x time interactions were observed for the PACC, episodic memory and language, and ventricular, and white matter volumes. Compared to the 0 MDRF group, groups with MDRFs in ≥2 domains had poorer cognitive performance over time. Compared to the 0 MDRF group, participants with MDRFs in 1-4 domains showed increased ventricular volume, and participants with ≥2 domains showed a significant reduction in white matter volume over time. Magnitude of difference ranged from small to moderate (d=0.25-0.49).

Conclusion
In CN older adults, multi-domain MDRFs were associated with worse cognition and greater brain volume loss, but not Aβ accumulation, over time. These results suggest that MDRFs increase risk for dementia through neurodegenerative processes unrelated to AD.

Participation in the ISLAND study linking ageing and neurodegenerative disease (ISLAND) results in positive changes in dementia risk behaviours

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Background
The Island Study Linking Ageing and Neurodegenerative Disease (ISLAND) is a public health initiative that seeks to impact dementia risk in people > 50 years old.

Methods
Participants complete surveys annually and are provided tailored feedback on their risk level (low, medium, high) across 9 domains via a traffic-light style Dementia Risk Profile (DRP). Participants are provided information about managing risks and encouraged to do the Preventing Dementia Massive Open Online Course (PDMOOC). Linear mixed effects regression models were used to assess changes in the number of high-risk domains indicated in DRP data over time and relative to PDMOOC exposure. Changes in individual risk domains were then examined at cohort level using ordinal logistic regression.

Results
Data from baseline (n=7270), 12 months (n=3459), 24 months (n=2993) and 36 months (n=3428) were included in analyses. The sample had a mean age (in 2022) of 64 years and 73.2% were female. Overall, baseline DRP data showed a mean total 2.08 (95%CI 2.00, 2.16) at-risk domains, which reduced by 0.036 domains (95%CI -0.070, -0.001) for each exposure to the DRP. Doing the PDMOOC led to a stronger reduction (p=0.019) in the number of at-risk domains relative to non-PDMOOC participants. Improvements were observed in the proportion of the sample engaging in sufficient cognitive and physical activity and meeting recommendations for alcohol consumption and body-mass-index, however, regression results showed effects were significant only for stopping smoking, improved management of diabetes and adherence to a Mediterranean style diet.

Discussion/Conclusion
Participating in ISLAND was associated with sustained improvement in health behaviours related to dementia risk over 3 years. This was augmented by engagement with the PDMOOC. Providing education and tailored feedback on dementia risk may provide benefit, and some health risk factors may be more amenable to change than others.

Preliminary results of the let's chat (community health approaches to) dementia implementation program for detection of cognitive impairment and dementia in Aboriginal and Torres Strait Islander communities

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Background
High prevalence of cognitive impairment (CI) and dementia (D) coupled with low detection rates in Aboriginal and Torres Strait Islander communities has prompted research to improve detection and management of these conditions. One such project is Let's CHAT Dementia in Aboriginal and Torres Strait Islander Communities, working in collaboration with 12 Aboriginal Community Controlled Health Services (ACCHSs) to implement a best-practice model of care through staff education and co-designed practice change initiatives.

Methods
Medical file audits of a sample of patients aged ≥50 years conducted six-monthly from late 2018 to January 2023 recorded: basic demographic information, presence of dementia risk factors (reported previously), detection rates and current care practices in relation to dementia and co-morbid conditions.

Results
Audits were conducted in 12 ACCHSs (1655 patient records) across four states. This presentation reports on results available at time of writing (11 services; 1530 records). Patients' mean age was 60.3 (range 50-95). At baseline, identified CI/D and documentation of concerns relating to cognition were 3.8% (n=58) and 8.9% (n=136) respectively. At study conclusion, rates of CI/D had doubled to 7.6% (n=116) and concerns documented had more than doubled to 20.3% (n=311).
Concerns relating to cognition were most likely to be raised by a GP, followed by patients, and patients' family members/carers.
Care practices relating to brain health also increased: evidence of staff asking clients about their memory and thinking (from 27.6% to 49.2%), use of cognitive assessment tools (13.4% to 24.9%), laboratory investigations (4.4% to 7.8%), CT- or MRI-brain (4.8% to 13.4%).

Discussion/Conclusion
While detection rates remain below the known prevalence in these populations (~20%), our findings indicate increased awareness and detection of CI/D across the sample. The upsurge in concerns raised is a promising indicator that ACCHS staff are implementing best-practice care guidelines imparted during the Let's CHAT program.

Accelerated brain volume loss caused by anti-amyloid beta drugs: A systematic review and meta-analysis

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Background
The potential benefit of anti-Aβ drugs to cognition in Alzheimer's disease (AD) remains under active debate. Anti-Aβ drugs also frequently cause accelerated changes to brain volume. This is concerning because loss of brain tissue is the proximate cause of cognitive dysfunction in AD and volume changes are supportive and objective evidence of disease progression.

Methods
PubMed, Embase and Clinicaltrial.gov databases were searched to evaluate brain volume changes caused by different sub-classes of anti-amyloid beta (Aβ) drugs trialed in patients with Alzheimer's disease. The inclusion criteria for this systematic review and meta-analysis were: (1) randomized controlled trials of patients treated with anti-Aβ drugs that have demonstrated to favorably change at least one biomarker of pathological Aβ; and (2) detailed MRI data sufficient to assess the volumetric changes in at least one brain region. Amyloid-Related Imaging Abnormalities (ARIA) were investigated when reported in clinical trials. Of the 145 trials reviewed, 31 were included in the final analyses (n=8062 to 10279).

Results
A meta-analysis on the highest dose of each trial on hippocampus, ventricle, and whole brain revealed drug-induced acceleration of volume changes that varied by anti-Aβ drug class. Secretase inhibitors accelerated atrophy to the hippocampus (mean difference: -37.1 µL [-19.6% relative to change in placebo]; 95% confidence interval: -47.0 to -27.1) and whole brain (-3.3mL [-21.8% relative to change in placebo]; 95% confidence interval: -4.1 to 2.5). Conversely, ARIA-inducing monoclonal antibodies accelerated ventricular enlargement (mean difference: +2.1mL [+38.7% relative to change in placebo]; 95% confidence interval: 1.5 to 2.8) where a striking correlation between ventricular volume and ARIA frequency was observed ($r=0.86$, $p=6.22\times10^{-7}$).

Discussion/Conclusion
These findings reveal the potential for anti-Aβ therapies to compromise long-term brain health by accelerating brain atrophy and provide new insight into the adverse impact of ARIA. Six recommendations emerge from these findings.

Dementia and suicide in Australia

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Background
Older adults are at high risk for suicide, but the relationship between dementia and suicide in older people is not well understood. Our objective was to better understand how dementia influences death by suicide in Australia.

Methods
We conducted two population-based epidemiological studies: (1) a retrospective study of all individuals who died while accessing or waiting for residential aged care or home care packages in Australia in 2008-2017 (*n*=532,507) using linked data available in the Registry of Senior Australians, and; (2) a mixed-methods analysis of coronial data of all individuals who died by suicide in South Australia and New South Wales between 2011 and 2020 where dementia was relevant to their death (*n*=152).

Results
From study 1, 354 suicide deaths were recorded among those using or waiting for aged care services. Of these, 52 (14.7%) were diagnosed with dementia with mostly moderate to severe impairment. A diagnosis of dementia was associated with a 58-70% lower odds of death by suicide, and dementia attenuated the risk for suicide associated with a mental health condition. From study 2, coronial records of suicide deaths included 73 people with dementia with varying levels of impairment, 19 suspected cases of dementia, 56 family members/friends of people with dementia, and 4 people who cited fear of dementia as a contributing factor. Evidence that death by suicide may have reflected a decision to pre-empt cognitive decline was identified in 16 cases. Qualitative themes included that dementia, fear of dementia, and the secondary effects of dementia (e.g. loss of autonomy, housing availability) were contributors to death by suicide.

Discussion/Conclusion
The relationship between dementia and death by suicide is complex and may vary with functional impairment. Mitigation of secondary effects of dementia, as well as fear and stigma, may prevent some death by suicide.

Describing and evaluating specialist dementia care program units in Australia

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Background
A small proportion of people living with dementia experience very severe and intractable behaviors that cannot be supported by mainstream care. This led the Australian Government to announce in 2016 the funding for 35 Specialist Dementia Care Program Units (SDCPUs) across Australia. SDCPUs are purpose built, cottage-like units staffed by specialist multidisciplinary teams who provide person-centred care for people living with very severe and intractable behaviour. To date (Dec, '22), 10 SDPCUs were operational across Australia.

SDCPUs aim to improve quality of life, and reduce BPSD and inappropriate prescribing, with the goal of successfully transitioning residents to mainstream care within 12 months.

Methods
We describe the eligibility criteria, assessment process, model of care, and characteristics of people supported by two of the currently operating SDCPUs (i.e., those operated by HammondCare). We describe resident demographic characteristics, length of stay, and longitudinal performance across a range of measures, including measures of behaviour (Neuropsychiatric Inventory), quality of life (Quality of Life in Late Stage Dementia), activities of daily living (Physical Self maintenance Scale), and prescribed medications.

Results
From January 2020 to November 2022, the SDCPUs have supported 41 residents (average age 77.6 years; 83.0% male). Of these 20 (48.8%) were successfully transitioned into mainstream aged care, 10 (24.4%) died or entered palliative care, and 10 (24.4%) currently remain in the SDCPU. For those who were successfully transitioned, their average length of time in the SDCPU was 8.8 months. For residents who were fully supported by the SDCPUs, performance across measures demonstrated a 10.6% reduction to behaviour, and small improvements to quality of life and activities of daily living (4.9% and 9.1%, respectively).

Discussion/Conclusion
Evidence from this review demonstrates the benefits and validation of SDCPUs in the support of people living with dementia experiencing BPSD.

Mapping and patterns of dementia post diagnostic care provision in Australian capital territory

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Background:
Classifying dementia care services using a standard classification system is not only useful for local policy makers, but it is also necessary for national and international comparisons. This study aimed to evaluate and describe the pattern of service provision for people living with dementia in the Australian Capital Territory (ACT).

Methods:
We used the internationally standardized service classification instrument, the Description and Evaluation of Services and Directories (DESDE), to typify and describe all services for dementia care in the ACT. Publicly available information and interviews with representatives of the service providers were utilised for the classification dementia care services.

Results:
The 48 identified service providers offered 106 services: 28 (26%) specialised services, and 78 (74%) generic services. Of 106 services, 45 (42%) were residential services, 41 (39%) outpatient services, 6 (5%) day care services, 3 (3%) information services, 6 (6%) evaluation services, and 5 (5%) accessibility services respectively. The target population for most service providers was people aged 65 or older for non-aboriginal, and 50 years or older for aboriginal Australians. There were government supports for most types of care through Medicare, residential subsidy, the Home Care Package, the Commonwealth Home Support Program, the National Disability Insurance Scheme, and some other limited programs. Service providers commented that there were significant issues with the integration of dementia care in the local dementia care system, its access, availability, capacity, and workforce.

Discussion/Conclusion:
In terms of availability, residential care was the dominant type of care for people living with dementia, with a lack of diversity in types of care. Most providers reported that the capacity of dementia care in the ACT could not meet the needs of people with dementia, because majority of care providers offered generic services. The findings should be complemented with information about aged care and service use in the ACT.

New technology assisted interventions to combat anxiety and depression in dementia

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Background
Anxiety and depression reduce quality of life in people living with dementia; however, they are under-recognized and poorly treated. Our research program focuses on the development and implementation of technology assisted interventions to reduce anxiety and depression in people living with dementia in community hospital and aged care settings.

Methods
The program includes the following components. (1) A large cross-sectional study examined the identification and treatment of anxiety and depression in dementia in residential aged care (RAC) using existing data systems. 2) Co-design of an industry specific benchmarking tool (MHICare) has been initiated to improve mental health practices in RAC. 3) Interventions using fully immersive virtual environments were developed and delivered individually and in groups, with feasibility testing conducted in RAC. 4) A remotely delivered Cognitive Behavioural Therapy intervention tailored for people living with dementia was developed to reduce anxiety (Tele-CBT). 5) Tele-CBT was further modified through co-design to include a new digital platform (My Anxiety Care) to assist with delivery of therapy and a voice app (Quiet Mind) to assist with home-based practice. A hybrid II randomized controlled trial will evaluate feasibility and implementation into health systems (Tech-CBT). All projects involved people living with dementia and their care partners via our established Consumer and Community Involvement Group.

Results
1) Depression often leads to inappropriate prescription of psychotropics in RAC. 2) Fully immersive virtual experiences demonstrated feasibility, and reduced depression and apathy. 3) The Tele-CBT intervention demonstrated feasibility of delivering psychotherapy interventions via video-conferencing, with significant reductions in anxiety in people living with cognitive impairment.

Discussion/Conclusion
Novel tools and technology assisted interventions are promising to improve the diagnosis and treatment of anxiety and depression in dementia.

Prevalence of frailty among long-term care residents living with dementia and its association with medication use: A retrospective cross-sectional study

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Background
Frailty is an important geriatric syndrome that affects many older adults, however, the prevalence of frailty among people with dementia living in long-term care facilities (LTCFs) and association with medication use is unknown. This study aims to estimate the prevalence of frailty among people living with dementia in LTCFs and explore differences in medication use according to frailty status.

Methods
A cross-sectional retrospective analysis was performed using data retrieved from residential medication management reviews performed by accredited pharmacists in 343 LTCFs in Australia from January to December 2019. Pharmacists captured comorbidity data for each resident using the ICD-10 codes. Individuals with dementia were identified using ICD-10 codes indicative of dementia. Frailty was assessed using a modified 36-item frailty index applied to the ICD-10 comorbidity codes for residents. Polypharmacy was defined as the concurrent use of ≥ 9 medications. Potentially inappropriate medications (PIMs) were identified according to the updated Beers criteria 2019. Logistical regression was used to determine the likelihood of exposure to polypharmacy and PIMs according to frailty status.

Results
Among 5076 residents, 80% (n=4062) were frail, 20% (n=1014) were non-frail with a median age of 86 years (interquartile range 81.0-91.0), and 43.5% of the cohort were males. Polypharmacy was present in 70.2% of frail and 44.1% of non-frail individuals, while 83.8% of the frail group were exposed to PIMs compared to 79.5% of the non-frail. Frail individuals displayed higher likelihood of exposure to polypharmacy (adjusted odds ratio [AOR]: 2.67; 95% Confidence interval [CI]:2.29-3.11), and PIMs (AOR: 1.18, 95% CI: 0.98-1.42).

Discussion/Conclusion
Frailty, polypharmacy, and PIMs exposure are highly prevalent among people with dementia in LTCFs. Future studies should systematically document frailty and design and test interventions to improve medication use in this setting and population.

Reduction of anxiety symptoms in people living with cognitive impairment after CBT-based telehealth psychotherapy: Results from a pilot trial.

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Background
Despite the recent increase in telehealth use, there is a paucity of studies focusing on telehealth cognitive-behavior therapy (CBT) for people living with cognitive impairment. The objective of this pilot randomized control trial (RCT) was to explore the feasibility of a telehealth CBT program (Tele-CBT) on reducing anxiety symptoms in people living with cognitive impairment.

Methods
This was a single-blind sequential pilot RCT with participants randomized (1:1) into intervention (Tele-CBT) and control (usual care). Outcomes were measured at baseline and post-intervention, with primary outcome measure Rating Anxiety in Dementia (RAID). Secondary outcomes included stress, depression, and quality of life. Paired-samples and independent *t*-tests were used to compare clinical outcomes at post-intervention and the mean difference in change between the groups.

Results
In total, ten participants completed the study ($n_{intervention}$ = 5 and $n_{control}$ = 5). Significant clinical outcomes were observed in participants who received Tele-CBT (n=5) with mean change in RAID score at post- of -14.20 (SD 10.64; $t(4) = -2.984$, $p = .041$; 95% CI [-27.411, -0.989]). Secondary clinical outcomes of reduced perceived stress were also noted ($t(4) = 3.668$, $p = .021$; 95% CI [-17.219, -2.381]). There was no statistically significant difference in anxiety outcomes (RAID) between the Tele-CBT compared to usual care ($t(8) = -1.439$, $p = .188$).The intervention significantly reduced depression symptoms (GDS-15) compared to usual care ($t(8) = -2.329$, $p = .048$).

Conclusion
The results indicate a potential of the Tele-CBT intervention improving the anxiety symptoms post-intervention. Considering the small sample of this pilot, a sufficiently powered RCT should follow to deliver generalizable results.

The experiences of informal caregivers of people with dementia in online psychoeducation programs: a systematic review and meta-synthesis

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Background
Informal caregivers of people living with dementia experience a higher level of physical and mental stress compared to other types of caregivers. Psychoeducation programs are viewed as beneficial for building caregivers' knowledge and skills and decreasing caregiver stress. This review aimed to experiences and perceptions of informal caregivers of people with dementia when participating in online psychoeducation programs; and 2) to factors that enable and impede informal caregivers' engagement in online psychoeducation programs.

Methods
The review followed the Joanna Briggs Institute protocol of systematic review and meta-aggregation of qualitative studies. We searched four English databases, four Chinese databases and one Arabic database in July 2021.

Results
A total of nine studies written in the English language were included in this review. From these studies, 87 findings were extracted and grouped into 20 categories. These categories were further synthesised into five findings: 1) online learning as an empowering experience; 2) peer support; 3) satisfactory and unsatisfactory program content; 4) satisfactory and unsatisfactory technical design; and 5) challenges encountered in online learning.

Discussion/Conclusion
High quality and carefully designed online psychoeducation programs offered positive experiences for informal caregivers of people living with dementia. To meet broader caregiver education and support needs, program developers should consider information quality and relevancy, support offered, individual needs, flexibility in delivery and connectedness between peers and program facilitators.

Evidence for neurophysiological patterns predisposing to delirium subtypes: An EEG and ERP study

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Background
Delirium is a common neurocognitive disorder in older adults following cardiac procedures and a major risk factor for dementia (9-fold) It is preventable in 30-40% of cases, therefore a method of identifying those at risk prior to elective surgery is crucial. The interaction between brain vulnerabilities and acute stressors is key to delirium pathophysiology, however neural markers of delirium vulnerability are not well defined. We aimed to identify preoperative electroencephalogram (EEG) and event-related potential (ERP) markers of incident delirium in older adults undergoing cardiac procedures.

Methods
58 participants (mean age=75.6 years, SD=7.1; 46 male/12 female) were recruited. In the weeks prior to surgery cognitive and depression assessment were conducted, as well as a four-minute resting state recording and a five-minute frequency alteration auditory oddball paradigm. Resting EEG peak power, peak frequency, bandwidth, offsets, and exponents were extracted, and ERP components were indexed by mean amplitude (P1, N1, P3, and mismatch negativity) relative to standard and deviant auditory stimuli.

Results
Incident delirium occurred in 20 participants: 45% hypoactive, 30% mixed, and 25% hyperactive. Incident hyperactive delirium was associated with significantly higher preoperative eyes closed offsets (p=.031, d=1.1) and lower eyes open offsets (p=.049, d=1.0). Incident mixed delirium was associated with significantly larger preoperative P1 deviant (p=.032, d=1.0), P3 deviant (p=.038, d=1.0) and P3 standard (p=.023, d=1.0) amplitudes. Other non-significant but moderate to large effects were shown in relation to all subtypes.

Discussion/Conclusion
We were able to capture neurophysiological markers of delirium risk weeks prior to elective cardiac surgeries in older adults. Findings indicate patterns of dysfunction in brain excitation/inhibition balance and arousal relative to subtypes of delirium. Preventing delirium is a novel dementia prevention strategy. Findings will help identify those at risk of developing delirium prior to surgery, which will enable better management and targeted preventative interventions.

Frailty and other modifiable risk factors for dementia in the national Alzheimer's coordinating center database

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Background
Frailty is a risk factor for dementia as well as a cause and consequence of other modifiable dementia risk factors. However, the roles of modifiable risk factors are frequently reported without considering the role of frailty. Our objective was to investigate the degree to which frailty mediates the association between modifiable risk factors and dementia risk.

Methods
This study used data from a prospective cohort of 7,510 participants attending National Alzheimer's Coordinating Center memory clinics across the United States between June 2005 and May 2022. Participants were included if at baseline they were cognitively unimpaired and aged 60 or over. Frailty was measured using a frailty index. Other modifiable dementia risk factors included hearing loss, low education, smoking, depression, traumatic brain injury, hypertension, and diabetes. Multivariable statistical models (linear regression/Cox proportional hazards) adjusted for age, sex and APOE ε4 status were used while varying the composition of the frailty index to exclude confounding deficits.

Results
During a total of 50,216 years of follow-up, 786 (10.5%) participants received a diagnosis of all-cause dementia. Longitudinally, each 10% increase in frailty was associated with higher dementia risk both before (hazard ratio [HR]=1.57 [95% CI=1.39–1.78]) and after (HR=1.48 [95% CI=1.31–1.68]) adjustment for the other risk factors (relative change in HR=5.9%). Similarly, adjustment for frailty reduced the HRs for the other risk factors by between 0.9%–6.3%. The measure of explained variation for incident dementia increased by 1.5% when other risk factors were added to a model including covariates and frailty, and by 2.0% when frailty was added to a model including covariates and other risk factors.

Conclusion
Frailty plays a significant and unique role in explaining differences in dementia incidence. Even so, a comprehensive approach including all risk factors simultaneously provides the most accurate estimate of dementia risk.

Online hand movement analysis to detect preclinical Alzheimer's disease: Validation against plasma pTau181 and episodic memory

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Background
Dementia prevention and drug development would benefit from scalable tests to identify preclinical Alzheimer's disease (preAD). Evidence suggests motor impairments are indicative of preAD. We developed TAS Test, an online automated hand-movement test, and evaluated it in predicting preAD biomarkers (plasma ptau181 and episodic memory performance) in a cognitively asymptomatic cohort.

Methods
Participants undertook TAS Test online from their own homes; it comprised several 10-30 second finger-tapping exercises using index finger and thumb, recorded using a keyboard and webcam. The movement features (frequency, rhythm, pauses, accuracy) were analyzed. Participants also completed CANTAB Paired Associate Learning test. Some provided blood samples for ptau181 analysis. The accuracy of regression models that predicted CANTAB scores and plasma ptau181 were compared to null models (which only considered age, gender, education, anxiety, and depression) using R^2_{adj} and ranked by AIC. ΔAIC >2 was considered significant.

Results
1,228 adults (mean [SD] age 65.8 [7.4] years; 73% female) completed TAS Test and CANTAB; 459 provided blood for ptau181 analysis. All keyboard tests improved prediction of asymptomatic episodic memory performance; the 3-step (ΔAIC = 11.2; R^2_{adj} = 8.1%) and alternate-key (ΔAIC = 3.3; R^2_{adj} = 7.5%) tests ranked highest and were the only keyboard tests to improve prediction of ptau181 (3 step ΔAIC = 7.0; R^2_{adj} = 17.8%; alternate key ΔAIC = 3.4; R^2_{adj} = 17.4%). All webcam measures improved predictions of CANTAB and ptau181; the highest ranked tests were dominant hand tapping (CANTAB ΔAIC = 2.9; R^2_{adj} = 8.2%; ptau181 ΔAIC = 2.4; R^2_{adj} = 12.9 %) and both hands dual task tapping (CANTAB ΔAIC = 3.0; R^2_{adj} = 6.8 %; ptau181 ΔAIC = 8.7; R^2_{adj} = 11.9 %).

Conclusion
TAS Test provides an internet-based test for identifying preAD. This novel approach holds potential as a screening tool for identifying at risk cohorts.

Prediction of longitudinal progression of cognitive and mood dysfunction in Parkinson's disease using a combination of baseline biological and behavioural markers

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Background
Although characterised as a motor disorder, one quarter of individuals with Parkinson's disease (PD) have some degree of cognitive impairment at diagnosis, with up to 80% eventually developing dementia. Similarly, ~50% experience depression and ~40% have anxiety. Despite implications for quality of life, factors that predict risk/rate of progression of these symptoms are still largely unknown. This study assessed whether a combination of baseline biological and behavioural markers predicts cognitive and mood dysfunction at 5-year follow-up in PD.

Methods
Data (n=132) were extracted from the Parkinson's Progression Markers Initiative. Combined cognitive and mood scores were derived from principal components analysis of five cognitive tests and two mood questionnaires, respectively. Subgroups were identified via Fuzzy C-Means clustering on Year-5 cognitive and mood scores. Probability of belonging to the more impaired cluster was assessed via multiple linear regression, with predictors including demographic information (age/sex/education), neuroimaging markers (proxy substantia nigra volume, striatal DaT binding), prodromal assessments (sleep, olfactory and autonomic function) and baseline cognitive, mood and motor measures. Cluster membership was retroactively used to assess baseline differences.

Results
Two clusters were identified, with cluster two (n=38) related to older age and worsened cognitive, mood and motor function at follow-up compared to cluster one (n=94). Membership in the more impaired cluster was predicted by several baseline variables, including more impaired cognition, greater mood dysfunction and reduced olfaction, explaining 40.1% of variance. At baseline, members of this cluster displayed significantly ($p<0.05$) greater impairment on prodromal measures.

Discussion/Conclusion
Greater impairment in prodromal symptoms at baseline suggests that the pathology may already be advanced at the time of diagnosis, leading to more pronounced impairment in cognitive and mood function at 5-year follow-up. This highlights that incorporating cognitive and mood assessments, in addition to motor measures, may have utility for predicting long-term prognosis in PD.

The cerebrospinal fluid biomarkers identify Alzheimer's disease as a differential diagnosis of Creutzfeldt-Jakob disease

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Background
Diagnosis of Creutzfeldt-Jakob disease (CJD) can be challenging due to its non-specific symptoms, which can overlap with other neurological disorders such as Alzheimer's disease (AD). CJD biomarkers in cerebrospinal fluid (CSF), 14-3-3 and total-Tau (T-tau) proteins and real-time quaking-induced conversion (RT-QuIC, used to amplify PrP^{Sc}), assist accurate diagnosis of CJD in life. This study investigates the utility of AD CSF biomarker proteins (Aβ1-42, phospho-Tau181 (P-tau) and T-tau) and neurofilament light (NfL) in the diagnostic work-up of patients presenting with rapid dementias, such as suspected CJD.

Methods
CSF biomarkers were measured in patients with suspected CJD, which were referred to the Australian National CJD Registry (ANCJDR) for diagnostic testing. Samples with sufficient volume for the AD test were used (n=419). AD CSF biomarker were measured using the Elecsys® immunoassay. RT-QuIC and 14-3-3 results were obtained from the ANCJDR. CSF NfL was measured via commercial ELISA kits in a subset of specimens (n=107).

Results
Using the cut-off values provided by the testing manual supporting an AD profile as Ab1-42 < 1030pg/ml and P-Tau181 > 27pg/ml, 14.8% (n=62) of the cohort had the AD biomarker profile; 58.7% (n=246) had a profile with only abnormal pathological Aβ1-42 concentrations in CSF; 20.3% (n=85) had profiles inconsistent with AD with normal Aβ1-42 concentration; 1.9% (n=8) had profiles consistent with comorbid AD/CJD (with AD profile and RT-QuIC positive). Differential diagnoses were obtained from clinicians for a subset of patients (n=143). Of the patients diagnosed with AD (n=32), only 12 had the AD biomarker profile. CSF NfL concentrations were significantly increased in patients diagnosed with AD compared to patients with normal AD biomarker concentrations ($p<0.05$).

Discussion/Conclusion
This study supports the routine use of AD and CJD CSF biomarkers in the clinical setting for the differential diagnosis of suspected CJD by highlighting the potential improvement in patient care they provide.

The effect of basal forebrain atrophy on the rate of cognitive decline in older adults without dementia

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Background
In early Alzheimer's disease (AD), degeneration of the cholinergic basal forebrain (BF) system correlates with amyloid-β (Aβ) burden and contributes to cognitive decline, particularly in memory and attention processing. However, the nature of these interrelationships remains unclear. This study investigated the effects of Aβ and BF atrophy on cognitive decline of memory and attention in older individuals without dementia.

Methods
The BF volumes were quantified from MRIs of 577 participants (73.3±6.3 years old, 55.1% female) from the Australian Imaging, Biomarker and Lifestyle (AIBL) study, including 495 cognitive unimpaired (CU) individuals and 82 with mild cognitive impairment. Aβ-PET assessment was completed at baseline, and Aβ+ was determined using Centiloid > 20. The cognitive decline in memory and attention was assessed using the relevant AIBL composite scores, over 6.0 ± 3.1 years (up to 13 years). BF z-scores were calculated using the mean and standard deviation of BF volumes in the CU Aβ- group, and z-scores < -1 was classified as BF atrophy (BF+). Participants were grouped according to the Aβ status and presence of BF atrophy. Linear mixed-effects models assessed differences in rates of cognitive decline in memory and attention across different classification groups.

Results
In Aβ- individuals, BF atrophy was associated with faster rates of cognitive decline in both memory and attention, with medium effect sizes. In re-analyses restricted to Aβ+ subjects, BF atrophy remained related to memory decline but not to decline in attention. Compared to Aβ- subjects without BF atrophy, both Aβ+ groups had faster decline in both domains, with large effect sizes.

Discussion/Conclusion
These findings indicate that the effects of Aβ and BF atrophy are additive in terms of their influence on the rate of decline in memory. However, BF atrophy influences the rate of decline in attention only in the absence of abnormal Aβ burden.

Exploring protective factors against affiliate stigma experienced by family members of people living with dementia: A cross-sectional study

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Background
Research on caregivers of people with a mental illness has shown that affiliate stigma has been associated with poor mental health outcomes and burden of care. The implications of affiliate stigma on family members caring for someone with dementia, and the potential for protective factors, has not been established due to limited research on this association. We therefore explore the relationship of potential protective factors on affiliate stigma in family members of people with dementia.

Methods
A cross-sectional survey is being conducted from August 2022 to April 2023. Family members (aged 18 and above) caring for a person with dementia are invited to complete an online survey including the affiliate stigma scale (with cognitive, behavioural, affective subscales), and measures assessing psychosocial factors, mental health, and dementia knowledge. Bivariate and hierarchical multiple regression analyses will be performed to identify factors associated with affiliate stigma.

Results
A subset of 51 family caregivers was analysed, the majority of which were female (86.3%) with a mean age of 63 (± 12.1 years). Respondents were spouses or children of the person with dementia, 53% and 41% respectively. Statistically significant relationship-differences were found for affiliate stigma between spouses and children. Spouses report experiencing higher levels of stigma ($t_{43}=2.102, p<0.041$). In particular, spouses scored highest on the affective subscale of the affiliate stigma scale (2.37/4). Factors associated with low scores on the affective subscale in spouses were high self-compassion (*r=-0.541, p=0.004*), positive attitudes towards ageing (psychosocial loss) *(r=0.456, p=0.019)*, high resilience scores (*r=-0.407, p=0.039),* and dementia knowledge *(r=0.418, p=0.038)*.

Discussion/Conclusion
It is important to account for the relationship between family member and the person for whom they are caring, when targeting the prevention of affiliate stigma. These results suggest that to promote wellbeing, caregiving spouses might benefit from future interventions that target self-compassion, such as mindfulness-based interventions.

Results from the Australian pitch study: A national stepped-wedge cluster RCT evaluating a dementia training program for home care workers

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Background
The NHMRC-funded Promoting Independence Through quality Care at Home (PITCH) project aimed to improve outcomes for people living with dementia and their paid and family carers via an evidence-based dementia specialist training program for home care workers (HCWs).

Methods
Stepped-wedge cluster RCT including 18 home care services in rural and urban VIC, NSW, and SA cluster-randomised into one of two arms.

Results
N=213 HCWs completed baseline measures, N=144 completed 6-month follow-ups, and N=120 completed 12-month follow-ups. 172 HCWs completed the training program. N=148 (86%) completed all training sessions; N=81 face-to-face (F2F) and 67 online.

Primary outcome measure: HCWs' Sense of Competency in Dementia Care Staff (SCIDS) was higher after training (p=0.04), driven by F2F training: SCIDS for HCWs completing F2F training was higher vs no training (p=0.003) and online training (p=0.015). There was no difference between online training and no training (control condition).

Secondary outcome measures: Overall, HCW scores on the Dementia Attitudes Scale (DAS) showed no difference between training and no training. However, F2F training was associated with higher DAS compared to no training (p=0.05) and online training (p=0.05).

Training improved scores on the Dementia Knowledge Assessment Scale (DKAS, p=0.03), driven by F2F training (F2F vs no training p=0.024; F2F vs online p=0.026).

There was no difference between online training and no training for DAS and DKAS. Training had no effect on Strain in Dementia Care Scale (SDCS) scores.

Discussion/Conclusion
Receiving F2F PITCH training improved dementia attitudes, dementia knowledge, and sense of competence in delivering dementia care for HCWs *versus* no training and online training.

The HCW workforce has unique challenges to accessing and completing training and education to deliver evidence-based dementia care. Minimising these challenges is critical to the delivery of quality home care. PITCH training now has evidence for its efficacy but only when delivered face-to-face.

The carer assessment of medication management guidance for people living with dementia at hospital discharge (CATCH) tool: Results from a national cross-sectional survey

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Background
Transitions of care is a major contributing factor to medication-related events among people living with dementia. This study aimed to evaluate carers' experiences of medication management guidance for people with dementia at discharge using recently developed Carer Assessment of medicaTion management guidanCe for people living with dementia at Hospital discharge (CATCH) tool and to explore the underlying factors of the CATCH tool to provide preliminary validation of the tool.

Methods
A cross-sectional survey of the CATCH tool was distributed across Australia between March and November 2022. The CATCH tool contains 30 Likert-type items and three dichotomous (yes/no) items. The results of the survey were analysed descriptively, and exploratory factor and regression analyses were performed.

Results
A total of 185 survey responses were completed. Most participants were informal carers (62.7%,116), and were predominantly provided medication management guidance on the day of discharge (42.7%,79). One-third (33.0%,61) responded that guidance could be improved. Regarding the safe use of medications, participants felt information was not well provided on: medications that may interact with each other (17.6%,30), possible side-effects of medications (16.1%,28), and medications that might act on the brain (15.8%,27). Almost 18% of participants stated that they were not included in medication decisions by hospital staff. Exploratory factor analysis revealed two factors in the CATCH tool: 1) person-centred guidance in the safe use of medications at discharge; and 2) support of carers in medication management. Carer reported measure of how medication management guidance is provided is positively related to their confidence in management of medications post-discharge ($p < 0.05$).

Discussion
The CATCH tool is the first scale developed that evaluates aspects of person-centred medication management guidance provided to carers of people with dementia at discharge. We found that carers information needs on medications for people with dementia and engagement in discussions could be improved.

3D in vitro models of human neurogenesis for understanding Alzheimer's disease

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Background
The extracellular matrix (ECM), a major constituent of the stem cell niche, is a complex 3D macromolecular structure providing support and directing spatiotemporal cues mediating stem cell behaviour in adult neurogenesis and pathological conditions. Proteoglycans (PGs) are ubiquitous proteins within the cell microenvironment localising within the ECM (Perlecan, chondroitin sulfate PGs) or found on the cell surface as membrane-bound molecules (heparan sulfate (HSPGs; syndecans/glypicans)).

Methods
We have investigated terminal neurogenesis, in human brain derived iPSCs ReNcell VM (ventral mesencephalon)/CX (frontal cortex) using short-term differentiation protocols through the addition of known HS interactive neuroregulatory factors brain-derived neurotrophic factor (BDNF), and platelet-derived growth factor (PDGF). Cells were cultured in 3D using LunaGel™ (Gelomics) hydrogels consisting of photocrosslinkable ECM based on chemically modified gelatin. Characterisation of key stages of neurogenesis has focused on HSPG, Wnt pathway and bHLH.

Results
Preliminary work has highlighted HSPG, Wnt pathway and bHLH gene expression differences in the cell lines. Expression of the three bHLH regulatory genes in ReNcell VM cultures, suggest their classification as Type 2a neural progenitors, a key stage of neural lineage specification before neuronal or glial commitment. In contrast, ReNcell CX only expresses HES1, suggesting they are astrocyte precursors with limited neuronal potential.

Discussion/Conclusion
Gel stiffness mediates the biochemical and mechanical cues of the cells, with gels of ~1 kPa more representative of neural ECM, ~8 kPa gels representative of astrocytic ECM. Our data has identified PG core proteins and PG biosynthetic machinery enzymes as key markers at all stages of *in vitro* human neurogenesis. Neurones differentiated *in vitro* in the presence of HS–binding neuroregulatory factors, BDNF and PDGF, produced phenotypically different neurons. Understanding the regulatory mechanisms at these key timepoints and interactions may enable the development of targeted stem cell therapies for a wide range of neurological disorders including Alzheimer's disease.

A centaur scale based on 18f-MK6240

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Background:
A standardized scale for the quantification of tau PET imaging would allow comparison and combination of data across tracers and sites resulting in large meta-analysis and the application of universal cut-offs. The proposed approach called CenTauR (CTR) was evaluated on ^{18}F-MK6240 using both global and regional anchoring.

Methods:
375 ^{18}F-MK6240 PET & T1w MRI scan pairs (HC A□- =179; MCI A□+ =98; AD A□+ =98) from AIBL & ADNeT were spatially normalised using SPM8 and SUVR normalised using the cerebellar cortex. PET scans were then quantified in 4 ROIs [Mesial-Temporal (Me), Meta-Temporal (MT), Temporo-Parietal (TP) and Frontal (FT)] derived from a previously defined "Universal" cortical ROI mask. To anchor the 0 and 100 CTR, we only included HC Ab- (<10CL) and AD Ab+ (>25CL) individuals younger than 75y, with MMSE ≥20. We also excluded HC with quantification higher than the 75%tile in the Me ROI and AD patients with quantification lower than the 25%tile in the MT ROI, resulting in 69 HC A□- and 29 AD A□+. We investigated two CTR scaling approaches using either a single transform based on the TP ROI anchors to transform SUVR into CTR for all composites or using region-based equations scaled with regional anchors.

Results:
The mean and standard deviation (std) for the HC and AD groups are reported in Table 1.

Using a single transformation resulted in the following equation:

CTR = 100x(SUVR-0.97)/2.26

Region-based equations can be extrapolated from Table 1. Figures 1 and 2 show that regional CTR overstretches quantification in FT compared to single equation-derived CTR. Thresholds set at 2 std above the HC were 2.38, 9.43, 7.66, 1.82, and 6.16 CTR for Me, MT, TP, FT and Universal ROI respectively, and were 7.05, 7.48, 7.66, 10.20, 7.68 CTR when using regional equation-derived CTR.

Conclusion:
The region-based approach provided slightly more consistent CTR distributions in the HC across the ROIs however, this approach tends to over-stretch the CTR values in the frontal region.

Bring out the music: Social and emotional well-being framework for people with dementia

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Background
The use of music as a non-pharmaceutical treatment approach for Aboriginal and Torres Strait Islander People with dementia has positive implications in future practice. Providing timely, culturally safe and appropriate programs in rural and remote aged care homes is becoming a critical area to close the cultural divide in treatment approaches. The Social and Emotional Wellbeing framework alongside music within dementia care will be explored.

Methods
A literature search on current music treatment approaches in dementia care and the relevance of application into Aboriginal and Torres Strait Islander population was conducted. The Social and Emotional Wellbeing tool is discussed and how this can be implemented alongside family and care staff. The author includes case study examples from her own professional practice whilst working as a Registered Music Therapist, where tailored music programs were implemented in small group or individual sessions.

Results
First line treatment guidelines support the use of music approaches for people with dementia. Music has been shown to work well within Aboriginal and Torres Strait Islander populations in the Northern Territory. This is particularly evident when people are distressed and socially and culturally isolated. The Social and Emotional Wellbeing frameworks can be adapted as a critical thinking tool for care staff to enhance connection with the person with dementia and their family.

Discussion/Conclusion
The use of music as an extension from culture has a long history of healing for the population and has the potential to be expanded into relieving distress when applied within a cross cultural context. Providing opportunities for music to be used more widely may add value to the care giving role as people connect in a non-invasive manner. Considering the current limited uptake of music therapy in dementia care, further explorations will study how music can be implemented with larger family and care staff involvement.

Changes in the prevalence of dementia in Australia and its association with geographic remoteness

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Background
The exact prevalence of dementia in Australia is ambiguous. Australia is a vast continent with a small population, and 80% live in five cities. This study explores recent changes in the prevalence of dementia. It also investigates geographic remoteness as a potential risk factor for developing dementia.

Methods
This cross-sectional study uses the 2015 and 2018 Survey of Disability, Ageing and Carers (SDAC), nationally representative databases, comprising 74,862 and 65,487 individuals of all ages, respectively, in Australia. A multivariable logistic regression model was used to evaluate the association between dementia and geographic remoteness.

Results
The results reveal that the prevalence of dementia was higher in 2018 (0.89%) than in 2015 (0.84%) across all age groups. From 2015 to 2018, the incidence rate of dementia among adults 60 and over grew by 0.12 percentage points (from 3.87% to 3.99%). Significant regional differences in the prevalence of dementia are observed among Australian adults, and it appears to be increasing. Furthermore, the adjusted model revealed that, in 2015, adults living in major cities were 1.13 (AOR: 1.13, 95% CI: 1.02-1.25) and in inner regional cities, 1.17 (AOR: 1.17, 95% CI: 1.04-1.31) times more likely to develop dementia compared with their counterparts from outer regional and remote areas. In 2018, the likelihood of having dementia was 1.12 (AOR: 1.12, 95% CI: 1.01-1.25) times higher among adults living in major cities compared with their peers living in outer regional and remote areas.

Discussion/Conclusion
There is a rising prevalence of dementia in Australia. Further investigation is required to identify the causes of this increase. Increased public health initiatives should concentrate on behavioural characteristics and contextual environmental factors to ameliorate this trend.

Chlamydia pneumoniae can infect human glial cells and modulate metabolism-related gene expression

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Background
Neurodegenerative diseases are the leading cause of disability-adjusted-life-years (DALYs) globally. The infectious hypothesis has been proposed as one of the underlying causes of certain neurodegenerative diseases such as Alzheimer's disease (AD). Respiratory pathogens including intracellular bacteria *Chlamydia pneumoniae* may infiltrate the central nervous system (CNS) via the nasal cavity and initiate a cascade of host inflammatory responses over the lifetime of a patient. This hypothesis is supported by several studies which have found the presence of pathogens more commonly in the CNS of AD patients.
Beside the well described characteristics of profuse neurofibrillary tangles and Aβ deposits, metabolic dysfunction is a core feature of different types of neurogenerative diseases, including Alzheimer's disease (AD). Thus, early detection of the metabolic changes in glial cells, may reflect the role of infection determinants in contribution to the neurodegenerative diseases such as AD.

Methods
Advanced NanoString nCounter analysis system was used to study 770 metabolism-related genes from infected human glial cells (Astrocytes and microglia, n=3 for each) after 24h, 48h and 72h. Data analysis was performed using the nCounter advanced analysis and Rosalind software packages.

Results
C.pneumoniae can infect human glial cells which is comparable to our previously established results on mouse models. We have also showed that bacterial infection was able to regulate the genes related to host cell metabolism such as lipid, amino acids, and carbohydrates at transcription level in different stages of acute infection.

Discussion
We have demonstrated that *C.pneumoniae* can infect and replicate to form inclusion bodies within human glial cells of the CNS. Interestingly, *C.pneumoniae* infection led to the changes in expression of the genes related to metabolism following 72 h of infection (life cycle of the bacteria) in Astrocytes but not in microglia. These results provide a new understanding of bacterial contribution in dementia.

Creating regulatory-endorsed drug development tools for optimization Alzheimer's disease clinical trial design

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Background
There is a growing need for a quantitative basis for designing efficient clinical trials, particularly in the early stages of Alzheimer's disease (AD). The Critical Path for Alzheimer's Disease (CPAD) Consortium, a global, neutral convener, brings together diverse stakeholders across industry, regulatory agencies, patient advocacy organizations and academia within a pre-competitive forum to generate actionable, regulatory-endorsed drug development tools (DDTs) for optimization of clinical trial design.

Methods
Patient-level data and neuroimages from contemporary clinical trials and observational studies are acquired through formal data contribution agreements with CPAD. As of March 2023, CPAD's database (www.codr.c-path.org) contains 69 studies with 97,527 individual anonymized patient records, rich in multimodal Amyloid-Tau-Neurodegeneration (ATN) biomarkers. We develop disease progression models (DPMs) which address unmet needs at multiple points in the drug development and clinical trial design process. Tau Positron Emission Tomography (PET) measures will also be incorporated, leveraging ongoing collaborative efforts to validate a standardized quantification scale across different tau tracers. A web-based platform that allows for bi-directional sharing of modeling code is under development to fit users' models on CPAD data or fit CPAD models users' data in their own secure workspace, with modeling results shared with the AD research community.

Results
A prototype version of the modelling platform includes the harmonized CPAD dataset and statistical models fit on the CPAD data, including mixed effects models with various cognitive endpoints as longitudinal outcome, a variety of different ATN biomarker predictors, combined with demographic variables and genetic information (ApoE). Preliminary findings from the tau-PET harmonization work support a standardized scale for tau-PET using both a Centiloid-like or joint propagation model approach.

Discussion/Conclusion
Pre-competitive sharing of contemporary clinical trial data will allow us to develop a comprehensive understanding of the disease continuum in AD, enable fully informed trial design and advance effective drug development in AD.

Effects of nutrigenomic activators against neurotoxicity induced by amyloid beta in human glioma cells

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Background
Alzheimer's disease (AD) is the leading cause of dementia. Extracellular amyloid beta (Aβ) plaques are one of the main pathological hallmarks of AD. Strategies aimed at reducing amyloid burden have failed, indicating the need for new treatment strategies. Oleoylethanolamide (OEA) and Sulforaphane (SFN) have demonstrated promising neuroprotective effects for AD. However, the molecular targets associated with OEA and SFN remain unclear. In this study, we investigated the effects of OEA and SFN against Aβ toxicity in U251 astroglioma cells.

Methods
U251 cells were exposed to pathophysiological concentrations of Aβ42 oligomers for 24 hrs and then, post-treated with 10 uM of OEA and SFN respectively. The potential protective effects of OEA and SFN on Aβ-treated cells was analyzed using LDH, ROS/Superoxide detection, and DNA damage assays. Furthermore, we performed a proteomic screening by LC-MS/MS analysis to identify differentially expressed proteins. Bioinformatic analysis was performed to annotate protein functions and pathways associated using Gene Ontology and Canonical pathways.

Results
We found that OEA had no cytotoxicity, while SFN exhibited a hormetic effect (cytotoxicity above 50 uM). Treatment with 10 uM concentrations of OEA and SFN reduced Aβ-induced ROS and DNA damage. Quantitative proteomic analysis identified hundreds of differentially expressed proteins (DEPs) with 1.2-fold change and classified gene ontology and canonical pathways following treatment with Aβ, OEA and SFN. Both OEA and SFN showed association with NRF2-mediatiaed Oxidative stress response, Glutathione biosynthesis, and NAD+ biosynthesis as the likely mechanisms of protection against Aβ42 oligomers in human astrocytes.

Discussion/Conclusion
Our findings provide valuable insights into how OEA and SFN may play a role in treating Alzheimer's disease and the mechanisms involved.

Identification of gut microbiome markers associated with more severe cognitive impairment in elderly Australians

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Background
Despite affecting more than half of those in long-term residential aged care, ageing-associated cognitive decline is difficult to predict. Emerging research suggests that, by interacting with systemic regulators of host physiology, the gut microbiome represents an important link between modifiable dementia risk factors and severity of cognitive impairment (CI). However, whether altered gut microbiome markers are evident in those with ageing-associated CI has not been determined.

Methods
A cross-sectional study of 159 participants recruited from five aged care facilities in South Australia (median age 88.7 years, 68.6% female) was conducted. Using the Psychogeriatric Assessment Scale-Cognitive Impairment Scale, individuals were classified as having mild (n=46, 28.9%), moderate (n=58, 36.5%), and severe (n=55, 34.6%) CI. Faecal microbiome composition and functional characteristics were then related to cognitive function. Metabolomic profiling was used to characterize potential mediators of microbiome-host interaction. Multivariate regression model analyses adjusted for age, sex, medication, and diet, and corrected for multiple comparisons.

Results
Microbiome composition differed significantly with CI severity ($p<0.01$), independent of age, sex, medication, and diet. Proinflammatory bacterial species, including *Methanobrevibacter smithii* and *Alistipes finegoldii*, were positively associated with severe CI ($q<0.001$), while bacterial species considered broadly beneficial, including *Bacteroides uniformis* and *Blautia producta*, were associated with mild and moderate CI ($q<0.001$). Microbiome functional capacity and metabolic output varied significantly with CI. Severe CI was associated with lower capacity for microbial biosynthesis of short-chain fatty acids (butyrate, acetate, propionate), neurotransmitters (glutamate, gamma-aminobutyric acid), and arginine, an amino acid required for autophagy ($q<0.001$). Severe CI was also associated with a higher microbial capacity for methanogenesis.

Discussion/Conclusion
The reported relationships between faecal metagenome traits and CI severity are consistent with the contribution of multiple microbiome-gut-brain pathways, including systemic inflammation, neurotransmission, and autophagy, with ageing-associated neurological decline. Our findings highlight the potential to predict, and perhaps prevent, cognitive decline through gut microbiome-targeted strategies.

Inflammation and cognitive function in mild cognitive impairment and Alzheimer's disease: A systematic review, meta-analysis, and meta-regression of case-control studies

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Background
Chronic inflammation is recognised as an important component of Alzheimer's disease (AD), yet its relationship with cognitive decline is not well understood. This study investigated the relationship between inflammatory markers and cognition in individuals with mild cognitive impairment (MCI) and AD.

Methods
A systematic review was performed to identify case-control studies which measured global cognitive function and inflammatory markers in serum, plasma, cerebrospinal fluid, or urine in individuals with MCI or AD who were compared with healthy control (HC) participants. Means and standard deviations were extracted for each inflammatory marker, and meta-analysis was performed with Hedges' *g* (HG) calculated in a random effects model. Meta-regression was conducted using age, sex, and mini-mental status exam (MMSE) values. Subgroup analysis was performed to compare groups (AD/MCI vs. HCs) and plasma versus serum levels of inflammatory markers.

Results
Fifty-two studies were included in the meta-analysis. IL1β in serum and plasma (HG 0.825, $p = 0.014$) and IL6 in serum (HG 0.656, $p = 0.044$) were significantly higher in individuals with AD c.f. HC. CSF YKL-40 was higher in both AD (HG 1.096, $p < 0.001$) and MCI (HG 1.156, $p < 0.001$) c.f. HC. Regression analysis found that MMSE was negatively correlated with IL6, IL10, and TNFα in individuals with MCI.

Discussion/Conclusion
Elevated levels of IL6 and YKL40 may reflect neuroinflammatory activity in both MCI and AD. Systemic inflammation may interact with the central nervous system (and vice versa), as poor cognitive function in individuals with MCI was associated with higher levels of proinflammatory cytokines IL6 and TNFα and the anti-inflammatory cytokine IL10; a novel finding. While proinflammatory cytokines appear to mediate systemic inflammation in MCI, anti-inflammatory cytokines may be upregulated to attenuate these inflammatory processes. Longitudinal evidence can elucidate the relationship between inflammation and cognition in individuals with MCI and AD.

Introducing the Spatial Performance Assessment for Cognitive Evaluation

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Background
Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) are known to adversely affect the hippocampus and entorhinal cortex. These two neural structures are also critical for supporting spatial navigation. Indeed, patients suffering from MCI and AD experience deficits in navigation ability in addition to a decline in other cognitive functions. Targeted assessments designed to evaluate individual differences in navigation ability may help uncover novel digital markers of cognitive impairment and help overcome some of the limitations of current cognitive screening tests (e.g., Montreal Cognitive Assessment: MoCA) as well as fluid and imaging biomarkers. In this presentation, we will showcase the Spatial Performance Assessment for Cognitive Evaluation (SPACE) that will be used to investigate the link between spatial deficits and cognitive status.

Methods
SPACE is a novel gamified tool played on tablet that measures different aspects of spatial ability. In SPACE, participants assume the role of an astronaut tasked with exploring a new planet and collecting objects at various landmarks. Following a training phase, participants are asked to complete five spatial tasks designed to engage different aspects of their spatial ability. The performance in each task is quantified using a combination of different measures such as angular and distance error from starting point.

Results
Preliminary findings (n=23) have shown that lower scores in the MoCA were associated with a path integration task that required participants to keep track of changes in their position and orientation as they navigated through the environment (angular error, rho=-0.51, p=0.02; distance error, rho=-0.44, p=0.04).

Discussion/Conclusion
The results from the path integration task suggest that SPACE may be a promising digital marker to assist in the early detection of cognitive impairment. Additional data on the validity of other tasks in SPACE and usability of the tool for testing elderly participants will also be presented.

Investigation of genetic variants in major prion protein and low-density lipoprotein receptor-related protein 1 in relation to cognitive function

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Background
Understanding normal cognitive function such as intelligence, memory, and learning, has become increasingly important to understand the complexity of the human brain. Our current knowledge of the genes and pathways involved in the regulation of cognitive performances and their influence on the development of diseases, such as Alzheimer's disease (AD), is limited. Investigating the genetic basis of these traits in healthy individuals will enhance our pre-clinical understanding of pathologies associated with AD.

Methods
Single nucleotide polymorphisms (SNPs) in the major prion protein (PRNP) and the low-density lipoprotein receptor-related protein 1 (LRP1) were examined by MassARRAY in a healthy cohort of 597 Caucasian, European, and mixed ethnicity individuals previously assessed through a series of memory tests. These tests included the Wechsler Abbreviated Scale of Intelligence (WASI) and one information subtest of the Wechsler Adult Intelligence Scale (WAIS) to gain an understanding of the subject's intelligence quotient, visual learning, and semantic and working memory. Saliva samples were collected from participants for genotyping and statistical associations were tested using general linear regression. Further analysis was conducted under the assumption of dominant or recessive models, and the significance of these tests was adjusted for multiple testing through Bonferroni correction.

Results
Our results suggest that SNPs in the *PRNP* and *LRP1* genes may influence performance on these psychological tests. Results showed a general association between the *PRNP*-X and WASI-IQ scores (p=0.0041). Similarly, an association was found between *LRP1*-Y and WAIS-INFO (p=0.013) and in WASI-IQ (p=0.016) scores, indicating an impact of this variant on test performance. Dominance deviation and additive models revealed significant associations with PRNP-X and WASI-IQ test scores (p=0.015). Further analysis of the dominance model also showed associations between PRNP-X (p=0.010) and LRP1-Y (p=0.008) and WASI-IQ scores.

Discussion/Conclusion
The study found an association between the presence of two common SNP variants, *PRNP*-X and *LRP1*-Y, and decreased scores in intelligence and memory traits in a healthy cohort. The association was statistically significant in overall WASI and one WAIS subtests, indicating a potential involvement of other cognitive genes/pathways. Further research is needed including replication of these findings to understand the potential implications for the early detection and treatment of AD.

Leveraging highly-comparative time-series analysis to study properties of neural activity related to amyloid plaque burden

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Background
Alzheimer's disease is characterized by neuropathological changes including neurodegeneration and aggregation of amyloid-beta (Aβ) plaques throughout the brain. Prior neuroimaging studies suggest a link between Aβ plaque deposition and altered neural activity[1,2], particularly in the default mode network (DMN). However, such work has focused on a few statistical properties of neural activity data, which could overlook nuanced changes in activity dynamics in individual parts of the brain.

Methods
Resting-state functional magnetic resonance imaging (rs-fMRI) and Aβ positron emission tomography (PET) data were collected for participants with mild cognitive impairment (N=40) or healthy cognition (N=150); (Age = 60.5 ± 6.2 years, Sex = 116 Female). Global Aβ levels were summarised using the centiloid method[3], and following rs-fMRI pre-processing, group spatial independent component analysis was performed to derive functional cortical networks. Four networks were visually selected as representing areas comprising the DMN. We leveraged highly comparative time-series analysis[4] to comprehensively compare 5846 properties of the rs-fMRI data for each DMN component with brain-wide Aβ centiloids using Spearman's rank correlation analysis.

Results
The activity dynamics of one component covering the precuneus and posterior cingulate regions of the DMN yielded a time-series feature with a significantly negative correlation to Aβ centiloids (ρ = -0.35, Benjamini-Hochberg false discovery rate[5] adjusted $p = 7.7\times10^{-3}$). The significant feature represents a pattern in a symbolized transformation of the time-series, with rs-fMRI signal values varying in the repeated sequence: high, low, low, moderate.

Discussion
The activity dynamics in the precuneus and posterior cingulate DMN component, which is particularly susceptible to Aβ deposition[6], exhibited decreased temporal pattern structure with increased global Aβ burden. These preliminary findings highlight the utility of comprehensively characterizing local activity dynamics in the context of neuropathological burden.

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Longitudinal follow up of data-driven cognitive subtypes in Parkinson's disease

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Background
The dual syndrome hypothesis proposes that frontal and posterior-cortical subtypes exist in Parkinson's disease (PD). The frontal subtype presents with executive/attention dysfunction, whereas the posterior-cortical subtype presents with memory/visuospatial deficits and rapid cognitive decline. The present study aimed to test the predictions of the dual syndrome hypothesis by assessing the longitudinal rate of cognitive decline for each subtype over 5 years.

Methods
k-means cluster analysis was used to identify frontal, posterior-cortical, globally impaired, and cognitively intact subtypes at baseline among 85 people living with PD. Baseline and follow up cognitive assessments were performed. Progression of subtypes on global cognition, psychological symptoms, parkinsonism, and each measure of the level 2 PD-MCI cognitive test battery were compared using linear mixed effects models.

Results
A total of 29 participants (34%) completed the follow up visit. Mean follow up was 4.87 years after baseline. The frontal subtype was entirely lost to attrition. While rate of change in parkinsonism, anxiety, and apathy differed between subtypes, no differences in rate of global cognitive decline were revealed. Performance on measures within the PD-MCI test battery revealed that the posterior-cortical subtype exhibited rapid decline in verbal memory, card sorting, trail-making, and judgement of line orientation. The globally impaired subtype deteriorated in attention, executive, and visuospatial function, with the greatest decline in judgement of line orientation. The cognitively intact group showed the most rapid decline in verbal memory and semantic fluency.

Discussion/Conclusion
The present study provides preliminary evidence for the differential progression of the posterior-cortical subtype compared to cognitively intact and globally impaired people with PD. These results encourage further longitudinal investigations of cognitive subtypes in PD and show value in the use of comprehensive cognitive testing over brief cognitive measures.

Mindful: A protocol for a randomized, placebo-controlled, double-blind study of XPRO1595 in patients with mild Alzheimer's disease with biomarkers of inflammation

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Background
Alzheimer's disease (AD) and related dementia afflict 44 million people worldwide, with a devastating effect on patients and caregivers, and with no effective therapy available. While therapeutic development continues to focus on anti-amyloid therapies, an effective management of AD may also require an anti-inflammatory strategy. As a pro-inflammatory cytokine, soluble TNF (solTNF) is secreted by inflammatory cells and is implicated in inflammation-associated neurodegeneration. INmune Bio, Inc. is developing XPro1595, which specifically blocks solTNF, as a therapy for patients with AD who have elevated inflammatory cytokines in their blood.

Methods
MINDFuL is a multicenter, double-blind, randomized, placebo-controlled Phase 2 clinical trial of XPro1595 to treat patients with mild Alzheimer's Disease with biomarkers of inflammation (ADi; NCT05318976). The primary endpoint in this trial is the Early and Mild Alzheimer's Cognitive Composite (EMACC and secondary endpoints are measured by a host of cognitive and biological measurements, which will be assessed over 24 weeks with a weekly subcutaneous injection of XPro1595.

Results
Here, we describe the design and the rationale leading to our Phase 2 clinical trial, which objectives are to determine the safety, tolerability, and efficacy of XPro1595 in patients with mild Alzheimer's Disease with biomarkers of inflammation (ADi), and to inform a Phase 3 clinical trial design.

Conclusion
The MINDFuL clinical trial for the treatment of dementia with XPro1595 is designed to be as informative as possible, while acknowledging the burden to the participants. This trial is currently enrolling in multiple sites across Australia including Sydney, Melbourne, and Perth.

The soluble TNF inhibitor, XPRO1595, has a favorable safety profile, decreases inflammation, and improves imaging metrics of brain health in a biomarker-focused phase 1b open-arm trial in Alzheimer's disease

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[2] Imeka

Background
Alzheimer's disease (AD) and related dementia afflict 44 million people worldwide, with a devastating effect on patients and caregivers, and with no effective therapy available. While therapeutic development continues to focus on anti-amyloid therapies, an effective management of AD may also require an anti-inflammatory strategy. As a pro-inflammatory cytokine, soluble TNF (solTNF) is secreted by inflammatory cells and is implicated in inflammation-associated neurodegeneration. INmune Bio, Inc. is developing XPro1595, which specifically blocks solTNF, as a therapy for patients with AD who have elevated inflammatory biomarkers.

Methods
We conducted a Phase 1b open-label clinical trial of XPro1595 in patients with AD with the main goal to evaluate safety and tolerability to XPro1595 in this population. XPro1595 was provided as a subcutaneous (SC) injection once a week for 12 weeks. Uniquely, to increase the probability of responsiveness to the therapeutic we selected patients with elevated biomarkers of inflammation.

Results
Treatment with XPro1595 was well-tolerated and safe within the tested population (n=20) and led to decreased measures of inflammation compared to baseline. In addition, we assessed the effect of treatment on MRI metrics and saw improvements on FreeWater (neuroinflammation), Apparent Fiber Density (axonal integrity), and Radial Diffusivity (myelination) compared to baseline.

Conclusion
We hereby conclude that in this limited study XPro1595 has a favorable safety profile and was well tolerated by the participants of this study, which is stark contrast to other TNF inhibitors. In addition, the chronic treatment with XPro1595 improved many imaging measures of brain health. Larger clinical trials are needed to confirm our results provided here and to assess the role of XPro1595 on cognitive measurements in AD and MCI

Pathological link between APOE and lipid dyshomeostasis in tauopathies

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Background
Emerging evidence demonstrated that lipid droplets (LD) and associated proteins are involved in neurodegenerative diseases. Genetic polymorphisms in a lipid transport protein, apolipoprotein E, (i.e. ApoE-ε4), haven been associated with late-onset Alzheimer's disease (AD). ApoE-ε4 has been shown to modulates tau aggregation, neurotoxicity, glial neuroinflammation, and accumulation of peroxidised lipids in neurons. However, the relationship between ApoE polymorphisms and LD remains poorly understood. This study aims to investigate the roles of LD and LD-associated proteins in the tauopathies.

Methods
Human neuroblastoma SH-SY5Y cells stably expressing WT or FTD-associated P301L tau-GFP were challenged with bacterial cell wall components, including LPS and Pam_3CSK_4 to trigger phosphorylation of tau (p-tau) under the context of infection. Co-transfection of tau-GFP (WT or P301L) and different ApoE isoforms (ApoE-ε2 or -ε4) were also performed in SH-SY5Y cells to assess the impacts of immune stimulation on tau and cytosolic ApoE proteins in neurons. Assessment of p-tau and ApoE was conducted via western blot analysis.

Results
Pam_3CSK_4 stimulation robustly induced p-tau-S262 and total-tau expression, which was accompanied with increased ApoE expression. As SH-SY5Y cells express low level of ApoE, co-transfection using tau-WT-GFP or tau-P301L-GFP with different ApoE isoforms was performed. Likewise, in these cells, Pam_3CSK_4 stimulation promotesd cytosolic ApoE protein expression, and changes in LC3 expressions were observed implying that the elevated ApoE could be due to changes in autophagic flux. We also observed differential modification between ApoE variants in these cells. Critically, this alteration in ApoE correlated with changes in LipidTox red suggesting LD may be dysregulated.

Discussion/Conclusion
Tau aggregation may dysregulate lipid trafficking which could potentially lead to aberrant accumulation of cytosolic LD, particularly in ApoE-ε4 expressing cells. Further investigation is warranted whether this may (1) augment propagation of tau pathology, (2) chronic inflammatory responses and (3) lipid peroxidation which altogether predispose the neuron to ferroptosis susceptibility.

Role of cerebral arterial mechanisms on variability in brain and cognitive systems changes in healthy older adults

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Background
Executive functions and the prefrontal brain areas that support them are highly sensitive to ageing, especially in the presence of cardiovascular risk factors (CVRF) whose prevalence increases with age. CVRFs are associated with subtle changes in arterial properties (eg. elasticity, reactivity) that impact global and regional brain perfusion. These cerebrovascular changes may contribute to variability in brain and cognition amongst otherwise healthy older adults. Pulse-diffuse optical tomography (pulse-DOT) measures properties of the cerebral arterial pulse wave. The pulse relaxation function (PReFx) is a measure of regional cerebral arterial elasticity that is associated with age, cardiorespiratory fitness (CRF), cortical white and grey matter volumes and executive function. PReFx may provide a sensitive measure of regional cerebral vascular changes, before the emergence of cardio- and cerebro- vascular disease. In this study, we characterise the relationship between PReFx over the prefrontal cortex (PFC) and measures of dementia risk and cognitive functioning.

Methods
Cross-sectional data from the Newcastle cohort of the ACTIVate Study are used (200 adults 55-85yrs). PReFx measures were derived from left, midline and right PFC. The ANU-ADRI and CANTAB composite scores assessed dementia risk and three cognitive domains. CRF and CVRF were estimated using demographic and biological indices.

Results
Preliminary analyses in a subsample showed the anticipated pattern of relationship between CVRF presence and type, CRF, PReFx and cognitive outcomes. As >65% of the sample reported 1 or more CVRF, analyses will consider accommodate the moderating effect of CVRF on these effects across the whole sample. We will also examine the mediating effect of PReFx on the relationship between CVRF, CRF and cognitive outcomes.

Discussion/Conclusion
These findings are discussed in terms of the potential for pulse-DOT measures to provide an early sensitive biomarker of subclinical brain and cognitive changes and guide early intervention approaches to reduce dementia risk.

Sex specific impact of chronic psychological stress on Alzheimer's disease related brain changes

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Background
Chronic stress is increasingly recognized as an external factor in development of Alzheimer's disease (AD). Numerous labs/studies have shown that chronic stress worsens AD phenotype in animal models, however the underlying mechanisms remain poorly understood. Furthermore, a long-standing lack of female inclusion in pre-clinical research has restricted our understanding of sexual dimorphic patterns in neurodegenerative and neuropsychiatric diseases. The aim of this study was to identify potentially dysregulated pathways in frontal cortex and hippocampus of chronic stress animals that may contribute to neurodegeneration and increase risk of AD.

Methods
We subjected 8 week old female and male C57Bl/6 mice to a novel chronic social stress model, which involved 56 days of social isolation, with intermittent social confrontation encounters twice daily over the final 20 days. Behavioral testing (open field and sucrose preference tests) was completed at baseline and experimental endpoint. Frontal cortex and hippocampus samples were collected and prepared for comparative proteomic profiling using label-free liquid chromatography-tandem mass spectrometry (LC-MS/MS). Identification of enriched and depleted pathways was performed using the QIAGEN Ingenuity Pathway Analysis software.

Results
Chronic social stress (CSS) in females produced anxiety-like behavior without anhedonia, whilst CSS in males produced anhedonia without changes to anxiety-like behavior. Pathway analysis revealed distinct sex-specific impacts of chronic social stress in both the frontal cortex and hippocampus. In the frontal cortex, females had multiple enriched neurogenesis pathways, whilst the most perturbed pathway in the males was protein translation and initiation. Within the hippocampus, CSS depleted protein translation and initiation, and enriched mitochondrial dysfunction and NRF2- mediated oxidative stress response pathways in females. On the contrary, males had enriched senescence, oxidative stress, inflammatory and autophagy pathways.

Discussion/Conclusion
This study demonstrates the distinct sex-specific outcomes of chronic psychological stress on the neurodegenerative pathways observed in Alzheimer's disease.

Strategies for translating proteomics discoveries into drug discovery for dementia

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Background
Although there have been recent developments in dementia biomarkers and disease-modifying treatments, limitations remain in their effectiveness, accessibility and cost-benefit in frail, comorbid and cognitively impaired populations. Ongoing progress is urgently required to ensure tauopathy treatments are available for the rapidly ageing population. “Big data” studies, such as proteomics, can generate information on thousands of possible new targets for dementia diagnostics and therapeutics, but remain underutilised due to the lack of clear process by which targets are selected for future drug development. The aim of our study is to develop criteria by which proteins from large data sets could be objectively stratified in terms of favourable therapeutic potential.

Methods
Quantitative scoring criteria for drug development potential were developed using information from open access databases OpenTargets, Agora and TSomics. Points were allocated across five domains; 1) evidence base for mechanistic role in disease, 2) brain specificity, 3) predicted safety, 4) accessibility of protein by cellular location and 5) ligandability. These criteria were applied to our group’s recent tau interactome dataset (Kavanagh et al, 2022) to identify new attractive drug targets for dementia.

Results
Out of 261 proteins confirmed to interact with tau in human tissue or cell models, 15 proteins (5.7% of total proteins in the dataset) scored above 11 points in our criteria, suggesting they are attractive drug targets. Protein targets identified as most favourable for drug development included known targets such as amyloid and tau, as well as less explored targets in dementia such as *GFAP, LANCL2, CAMK2B, NAPB, HSP90AA1* and *PARP1.*

Discussion/Conclusion
Overall, our criteria successfully stratified potential dementia drug candidates from proteomics data, including targets such as *PARP1*, which already has an FDA-approved inhibitor. Further mechanistic studies of identified targets and exploration of drug development potential may be warranted.

The effect of genetic predisposition to Alzheimer's disease and related traits on recruitment bias

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Background
The recruitment of participants for research studies may have bias due to over representation of those more willing to participate voluntarily. No study has analysed the effect of genetic predisposition to Alzheimer's disease (AD) on study participation. The Prospective Imaging Study of Ageing (PISA), aims to characterise the phenotype and natural history of healthy adult Australians at high future risk of AD. PISA participants were recruited from existing cohort studies with genome-wide genetic data available for both successfully and unsuccessfully recruited participants, allowing us to investigate the genetic contribution to voluntary recruitment.

Methods
Contact was made with the recruitment pool (N=15,351, age 40-80) and 63% of participant records were successfully updated. We computed polygenic risk scores (PRS) in order to test to what extent the genetic risk for AD, and related risk factors (including educational attainment, and IQ) predicted participation in PISA (completion of the core survey module). We examined the associations between PRS and *APOE* ε4 with recruitment bias using logistic regression while accounting for sex, age and genetic ancestry.

Results
We found significant associations of age and gender with study participation, where older and female participants were more likely to complete the core module. We did not observe a significant association between *APOE* ε4 positivity or PRS for AD with study participation. We did observe significant associations with PRS for IQ, and years of education.

Discussion/Conclusion
We did not identify a significant association of genetic risk for AD with study participation, but we do identify significant associations with genetic scores for key causal risk factors for AD, IQ and years of education. This shows the importance of considering bias in the recruitment of individuals for AD cohort studies.

The use of human mesenchymal stem cells to investigate methylation and gene expression correlations during neural lineage specification

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Background
Due to their high *ex vivo* and *in vitro* capacity, their ability to transdifferentiate and their relative ease of isolation, human mesenchymal stem cells (hMSCs) are promising candidates for therapeutic applications for neurodegenerative disorders, including Alzheimer's disease (AD). hMSCs can be induced to form neurospheres (hMSC-INs), a neural precursor-like cell type. Heparan sulfate proteoglycans (HSPGs) are a family of proteins ubiquitous to the cell surface and the extracellular matrix. Through their complex and tuneable side chains, two major families of HSPGs, the syndecans (SDC) and (GPCs) participate in the highly regulated control of critical cellular processes including cellular proliferation and neural lineage specification/differentiation.

Methylation is a reversible change made to the DNA that encodes an additional regulatory mechanism to influence gene expression and thereby, cellular functions. Syndecan-3 (SDC3) is an HSPG core protein of specific interest in neural lineage specification of hMSCs. DNA methyltransferase I (DNMT1) is responsible for the addition of methyl groups to specific CpG structures, the process of DNA methylation.

Methods
hMSCs were grown under basal, proliferative (heparin) and neurosphere inductive conditions and examined at early, mid and late phase of growth for gene expression and methylation changes. In addition, siRNA knockdown experiments were undertaken at late growth phase to examine the effect of reduced SDC3 and DNMT1 gene expression on methylation profiles.

Results
We determined that basal SDC3 gene expression increases over extended time in culture (early to late growth phase). Following heparin treatment, gene expression non-significantly increased at early and mid-growth phases. At late growth phase, gene expression was non-significantly decreased.

Discussion/Conclusion
We expect that SDC3 knock-down will reduce hMSC ability to form hMSC-INs. In addition, we anticipate that the siRNA induced reduction in gene expression will correlate with the methylation changes observed between monolayer and hMSC-IN cultures.

Transforming ageing research with dementias platform Australia

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Background
Dementias Platform Australia (DPAU) is a data-driven platform enabling scientists from around the world to discover and access data, which can be utilised to identify new ways to prevent, diagnose and treat dementia and age-related diseases. DPAU makes data from Contributing Research Studies (CRS) Findable, Accessible, Interoperable and Reusable (FAIR).

Methods
The DPAU Data Portal provides a Directory and Matrix providing an overview of available studies; a Data Explorer providing in-depth information on the CRS data; an online data application form enabling researchers to apply for access to data from different CRS in a single application. CRS data are organised by a standardised ontology, making it easier to conduct analyses of data across multiple studies. Data from archival and extant studies will be hosted on the Secure eResearch Platform (SeRP) and accessed by virtual desktops with multi-factor authentication login, thereby removing the risks associated with physical data transfer.

Results
DPAU has identified >80 studies of health and ageing, representing data from >200,000 research participants, which are prime candidates for onboarding to the DPAU. We have established the necessary Data Portal tools and a tenancy on the SeRP at Monash University. We are following the C-Surv data ontology developed by Dementias Platform UK (DPUK) and also utilized by the Alzheimer Disease Data Initiative (ADDI).

Discussion/Conclusion
The Data Portal is an end-to-end data management solution designed to support sharing of data from multiple and diverse research studies. DPAU complements DPUK and ADDI and other satellite dementias platforms around the globe. Work is ongoing to develop interoperability across platform architectures to allow federated analyses to be performed across datasets located in multiple regions. With its diverse network of researchers, FAIR data sharing, and collaboration with similar platforms globally, DPAU will transform the study of ageing and dementia.

Uncovering the impact of Alzheimer's disease aggregates on brain cell physiology through bioorthogonal labelling

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Background
Alzheimer's disease (AD) impacts millions of people worldwide. At the cellular level, AD is characterised by extracellular aggregates composed of amyloid-β (Abeta) plaques and intraneuronal accumulation of hyperphosphorylated microtubule-associated Tau (pTau) protein. Despite ongoing efforts, a deeper understanding of the impact of these aggregates on brain cell physiology is still needed.

Methods
To uncover novel molecular aspects by which brain cell physiology is altered in AD, we employed bioorthogonal labelling with non-canonical amino acids and click chemistry. These methods allowed us to tag, visualise and identify the newly synthesised proteins in neurons and microglia, the resident immune cells of the brain parenchyma that accumulate around plaques, in the presence of Abeta and pTau.

Results
We revealed that in neurons, Abeta induces the synthesis of Tau and that pTau leads to a marked decrease in the synthesis of proteins associated with microtubule physiology, endocytosis, mitochondria, and ribosomal biogenesis and functions. In microglia, we observed an Abeta-dependent alteration of the overall protein synthesis, as well as an activation of the integrated stress response, an adaptational signalling pathway that is triggered when cellular homeostasis is severely imbalanced.

Discussion/Conclusion
We have revealed novel mechanistic insights in which AD-specific aggregates alter the physiology in neurons and microglia, which could eventually lead to novel treatment avenues against the disease.

What are the earliest protein changes in Alzheimer's disease brain tissue?

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Background
Proteomic studies analysing human Alzheimer's disease (AD) brain tissue provide a potential data gold-mine about the pathogenesis of AD. However, studies are often limited by small sample size or analysis of a single brain region or clinical disease stage. Our aim was to combine all AD proteomic studies to generate a comprehensive map of protein changes in human brain tissue throughout the progression of AD.

Methods
38 proteomic studies were included in our analysis. Inclusion criteria included: human brain tissue, use of LC-MS, raw data available, comparison of AD (any clinical stage) to controls or analysis of neuropathological lesions. Data were manually standardized to enable direct comparison.

Results
5,311 proteins were identified as significantly altered in human AD brain tissue. Protein changes were characterized in 12 different brain regions and at three disease stages (preclinical AD, mild cognitive impairment [MCI], advanced AD). Using stringent filtering criteria, we identified 600 high-confidence protein changes that occur in AD. Of these, 258 protein changes were present in early AD (preclinical AD or MCI); 93% of which were altered in the same direction in early and advanced AD. Intriguingly, 64 of these protein changes were also observed in brain regions typically resistant in AD, suggesting that these protein changes may occur prior to neuropathology development. This group of very early protein changes included increases in well-known AD proteins (e.g. APOE, AQP4, MAOB, BAG3) and decreases in many key synapse proteins (e.g. HOMER1, SYT12, SYNPO). Notably, these changes were present in the absence of APP and Tau accumulation.

Discussion/Conclusion
We hypothesize that these 64 protein changes occur prior to the development of neuropathology in human AD brain tissue. As such, these proteins may be excellent drug targets in early AD. The role of many of these proteins in AD is unknown, warranting further study.

3-month melatonin supplementation to reduce brain oxidative stress and improve sleep in mild cognitive impairment: A randomised controlled feasibility trial

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Background
Melatonin has multiple proposed therapeutic benefits including antioxidant properties, circadian rhythm synchronisation and sleep promotion. Since these areas are also recognised risk factors for dementia, melatonin has been hypothesised to slow cognitive decline in older adults.

Methods
Participants with Mild Cognitive Impairment (MCI) were recruited from the community for a 12-week randomised placebo-controlled parallel, feasibility trial of 25mg oral melatonin daily. Primary outcomes were feasibility, acceptability, and tolerability. Secondary outcomes were brain oxidative stress, cognition, mood, and sleep at 12 weeks.

Results
Forty participants were randomised to receive melatonin or placebo. Feasibility, determined by the percentage of people who met inclusion and exclusion criteria and could potentially join the study, was 42/389, 11%. The most common exclusion criteria was age. Acceptability, the number of people who agreed to be randomised as a fraction of all potential participants, was 40/42, 95%. Adherence to the intervention and completion of the main secondary outcome (oxidative stress) was over the pre-defined 80% threshold for all participants and reported safety outcomes were balanced between groups.
The current protocol was feasible and acceptable as we reached our target of 40 participants between 60-80 years of age with MCI. All participants were able to complete all aspects of the trial, including online visits and assessments.

Discussion/Conclusion
This is promising for future trials which should conduct the study with a higher sample size and longer duration to yield necessary efficacy data.

The effect of light exposure on cognitive outcomes at long term follow up in an at-risk dementia population

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Background
Circadian disturbances are a common occurrence in older adult population but are more prevalent people with dementia. For some individuals, these occurrences begin many years prior to the onset of clinical symptoms and have been suggested as a potential risk factor. As light is the primary synchroniser of the circadian system, the current study aimed to examine if 14-day light exposure could predict cognitive outcomes of older adults with varying risks of dementia at 2-year follow-up.

Methods
The study was a retrospective analysis of 195 participants (age=67, 60.7% female) who attended the Healthy Brain Ageing Clinic in Sydney. At baseline, participants were neurocognitively assessed and wore an actigraph for 14 days and then completed another neurocognitive test battery at their follow-up. Binary logistic regression was used to determine if participants converted to either Mild Cognitive Impairment or dementia was predicted from light exposure (average and maximum) and average time spent in >1000 lux (OR=1.00), adjusting for age, sex and years of education. Linear regression was used to investigate the relationship between light variables and differences in memory, processing speed and executive function composite scores from baseline to 2 years.

Results
Light exposure at 2 years prior did not appear to predict cognitive performance. There was a trend towards moderate to bright light increasing risk of cognitive decline.

Discussion/Conclusion
Further research is needed to understand light exposure and the relationship to circadian rhythms and cognition. As previous light therapy research has been inconclusive, future research will inform treatment approaches.

A model for help-seeking for dementia diagnosis

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Background
Dementia diagnosis is often delayed. Without a diagnosis people with dementia and carers are unable to access treatments and services, understand and manage the symptoms and plan ahead. In Australia there is a gap of 1.9 years between first noticing symptoms and first doctor's appointment. Families often play a key role. This paper presents a model for help-seeking for dementia diagnosis.

Methods
The model was based on behaviour change theories (transtheoretical and health belief models) and the socioecological framework. Help-seeking related actions, barriers and facilitators were identified through a literature review, and interviews with people with dementia, carers, older people with memory and thinking concerns and families of older people with concerns (n = 23 total). The model was refined iteratively through team discussion and abductive reasoning.

Results
Individual help-seeking actions were a) deciding that experienced difficulties or observed behaviours were symptoms of concern; b) obtaining confirmation from significant others that symptoms were of concern; c) deciding to seek medical help for symptoms; and d) persisting with help-seeking if concerns were not adequately addressed by first health professional. When deciding if difficulties were symptoms of concern, many people normalized, minimized or denied those difficulties. Most people discussed symptoms with significant others, who sometimes normalized and assured. The decision to seek medical help weighed up perceived threats such as fear of loss of independence and social stigma against the low perceived benefits of the diagnosis. Help-seeking occurs in a context of intrapersonal and community stigma and reluctance to discuss dementia, and challenges in accessing primary care.

Discussion/Conclusion
This model highlights the multiple barriers and stoppage points to help-seeking for people noticing cognitive and behavioral changes. The model will inform the design of a public campaign to reduce stigma and increase help-seeking.

A randomised controlled trial of a multidomain dementia risk reduction intervention for adults with subjective cognitive decline and mild cognitive impairment - MyCoach

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Background:
There is a lack of evidence-based interventions to reduce risk of dementia in adults with subjective cognitive decline (SCD) and mild cognitive impairment (MCI) that are effective, accessible, and affordable. We developed an online tailored dementia risk reduction program (MyCoach) and evaluate this in a 64-week randomized controlled trial.

Methods:
We aim to recruit 286 adults aged 65+ with SCD or MCI from social media, newspapers, community groups other health related venues. Eligible participants are randomly allocated to one of two intervention arms for 12 weeks: (1) the MyCoach program, or (2) emailed bulletins with general healthy ageing information. The MyCoach course provides information on memory impairments and dementia, memory strategies, and the association of different lifestyle factors with brain ageing. The course is complemented with practical support including goal setting, motivational interviewing, brain training, dietary and exercise consultations, and a 3-month post-intervention booster session. Follow-up assessments are conducted for all participants 12 and 64 weeks from baseline, with exposure to dementia risk factors measured using the ANU-Alzheimer's Disease Risk Index (ANU-ADRI). Secondary measures include cognitive function, quality of life, motivation to change behaviour, self-efficacy, functional impairment, morale, and dementia literacy.

Results:
Recruitment commenced on 08/11/2021. As at 09/02/2023, 218 (76% of the planned sample size) participants have completed baseline and been randomised (MyCoach arm: n = 112; Control arm: n = 106). Thirteen participants withdrew from the study (2 before randomisation; 8 from MyCoach arm; 3 from Control arm), with most citing other demands, finding the platform too technical or stressful. Post-intervention follow-up has been completed for 146 participants, with 49 completing 6-month follow-up interviews.

Discussion:
There has been a high level of interest in an online intervention among adults meeting criteria for SCD and MCI with a relatively low attrition rate 5% after 12-weeks.

A universal neocortical mask for centiloid quantification

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Background
The Centiloid (CL) project was developed to harmonise the quantification of Ab-PET scans to a unified scale. The CL neocortical mask was defined using ^{11}C-PiB, overlooking potential differences in regional distribution among Ab tracers. We created a universal mask using an independent dataset of 5 Ab tracers, and investigated its impact on inter-tracer agreement, tracer variability and group separation.

Methods
Using data from the ADOPIC study (AIBL+ADNI+OASIS), age-matched pairs of mild Alzheimer's disease (AD) (MMSE=20-24;CL>25) and healthy controls (MMSE>=28;CDR=0;CL<15) were selected: ^{18}F-Florbetapir (N=147 pairs), ^{18}F-Florbetaben (N=22), ^{18}F-Flutemetamol (N=10), ^{18}F-NAV (N=42), ^{11}C-PiB (N=63). The images were spatially normalised using the SPM CL pipeline and transformed into SUVR (whole cerebellum). For each tracer, the mean AD-HC difference image was computed and mirrored. The threshold for the difference image was optimised to maximise the overlap with the standard CL mask. The universal mask was defined as the intersection of all 5 masks. It was evaluated on the GAAIN head-to-head calibration datasets in terms of inter-tracer agreement and variance in the young controls (YC) and on the ADOPIC dataset with the effect-size between HC/AD and HC/MCI at baseline.

Results
The overlap between each tracer specific mask was high (mean Dice=0.82). The universal mask was 26% smaller than the standard one, but the overlap was high (Dice=0.74). The universal mask led to a small reduction in the variance of the YC in most tracers (-3.4%) and a small increase in the R^2 between each of the ^{11}C-PiB/^{18}F-tracer pairs (+0.24%). In ADOPIC, it led to higher effect-size between HC/AD (1.43 vs 1.42) and HC/MCI (0.71 vs 0.70).

Discussion/Conclusion
The universal CL mask led to an increase in inter-tracer agreement and group separation. Those increases were however small indicating that the existing standard CL mask is suitable for the quantification of all Ab tracers.

Ante-mortem cognitive trajectories of older adults with cerebrovascular disease across Aβ and tau biomarker profiles determined at autopsy in the national Alzheimer's coordinating center database

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Background
Effects of biological Alzheimer's disease (AD) on cognition in the context of concurrent cerebrovascular disease (CVD) remain unclear. In older adults with CVD pathology, this study sought to determine *ante-mortem* cognitive trajectories associated with Aβ/tau positivity/negativity (+/−) at autopsy.

Method
Participants aged 65-95 classified as cognitively unimpaired at baseline from the National Alzheimer's Coordinating Center, with ≥1 follow-up, and available autopsy/*APOE* data were included (N=924). Autopsy indicated that all participants had at least one of six CVD pathology markers. Participants were classified into four groups (A−T−, A+T−, A−T+, A+T+) based on semiquantitative Consortium to Establish a Registry for Alzheimer's Disease neuritic plaque staging and Braak staging. Linear mixed models including group × time interactions assessed rate of change in Preclinical Alzheimer's Cognitive Composite scores, episodic memory, and executive function. Interactions between age, sex, *APOE* ε4 × time and the interval between death/final visit were included as covariates.

Results
A+T+ adults demonstrated significantly faster decline on all outcomes in the ~10 years preceding death compared to A−T−, A+T−, and A−T+ adults (d=0.15 – 0.39). At final visit prior to death, a greater proportion of A+T+ adults (36%) received a dementia diagnosis compared to A−T+ (14%) or A+T− (15%) (p<.001). When analyses excluded dementia diagnoses, significantly faster decline on all outcomes (d=0.06 – 0.36) was similarly observed in A+T+ adults compared to A−T−, A+T− and A−T+. Cognitive trajectories were equivalent between A−T− and A+T− for all outcomes.

Conclusion
In older adults with CVD pathology, A+T+ at autopsy was associated with greater cognitive decline over 10 years preceding death compared to A+T−, A−T+, and A−T− older adults. Faster cognitive decline in this group in the context of low final visit dementia diagnoses may suggest that *post-mortem* A+T+ is associated with a steep trajectory of cognitive decline *ante-mortem*, but that dementia progression is not inevitable.

Synergistic contributions of vascular risk factors and APOE ε4 carriage to cognitive performance in middle-aged adults enrolled in the healthy brain project

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Background
Midlife vascular risk factors (VRFs) and *APOE* ε4 carriage are individually associated with poor cognitive performance. However, the extent to which VRFs interact with *APOE* ε4 carriage to influence cognition in midlife remains unclear. This study aimed to investigate interactions between VRFs and *APOE* status on cognitive performance in cognitively normal (CN) middle-aged adults.

Method
CN adults aged 40-70 enrolled in the Healthy Brain Project with ≥75% complete baseline data on five VRFs and *APOE* status were included (N=1610; 546 ε4 carriers). Cardiovascular risk was operationalized by assessing history of hypertension, hypercholesterolemia, diabetes mellitus, body mass index (BMI) ≥25, and current cigarette smoking. Participants were categorized into low (0) or high vascular risk groups (≥1 VRF) determined via median split. Analyses of covariance (ANCOVAs) investigated interactions between VRF group × *APOE* status on attention/memory composites (derived from Cogstate Brief Battery), controlling for age, sex, education, ethnicity, and depressive/anxiety symptoms. Linear regression analyses explored contributions of individual VRFs on memory in ε4 carriers and non-carriers.

Results
A significant VRF group × *APOE* status interaction was observed for memory (p=.04), but attention was lower in those at high vascular risk, regardless of ε4 status. For memory, ε4 carriers with high vascular risk demonstrated worse performance compared to ε4 carriers and non-carriers with low vascular risk. Linear regression analyses revealed that BMI and hypercholesterolemia were significantly associated with poorer memory in ε4 carriers only (both p's<.05).

Conclusion
In CN middle-aged adults, *APOE* status significantly modified associations between vascular risk and memory, such that ε4 carriers with high vascular risk demonstrated the lowest memory performance. Higher BMI and hypercholesterolemia were significantly associated with lower observed memory performance within this group. Results suggest that middle-aged ε4 carriers with vascular risk factors may be an important sub-group to target within prevention trials to reduce future risk of cognitive impairment/decline.

The Betterbrains trial: Baseline characteristics and trial progress of an online multi-domain lifestyle intervention trial to delay cognitive decline in middle-aged adults at risk of dementia

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Background
BetterBrains is a prospective, blinded endpoint, 24-month randomised controlled trial to test the effectiveness of an online, person-centred, modifiable risk factor (RF) management program in delaying cognitive decline in middle-aged adults (aged 40-70) with dementia family history. This study describes blinded baseline characteristics of the randomised sample and provides trial engagement statistics.

Methods
Participants enrolled in BetterBrains complete all assessments online. RF assessment related to vascular health, sleep, mood, and social/cognitive engagement was conducted and participants with ≥1 RF were eligible. Participants complete assessments of cognition, general health, medical history, and lifestyle at baseline, 12, and 24-months post-randomisation. Primary outcome is absence of decline on at-least one out of four cognitive tests at 24-months. Intervention participants receive at-least 6 telehealth consultations over 12-months with an allied health clinician trained in motivational interviewing. All participants receive monthly educational blogposts.

Results
Since August 2021, 1518 participants have enrolled and 856 (56%) were randomised. Blinded baseline analyses reveal that randomised participants are mostly female (84%), white (93%), live in metropolitan areas (73%), and all report a first-degree dementia family history. Mean age is 60 years (±6.7) and participants have 15.4 years of education (±3.9) on average. Mean number of reported RFs is 5 out of a possible 19. Readiness to change lifestyle behaviors to reduce dementia risk was high, with 71% of participants indicating implementation of some lifestyle changes prior to trial entry. Only 3% of randomised participants have withdrawn. Of participants who have reached 12-months (N=349), 74% have completed follow-up cognitive testing.

Conclusion
Low attrition/high follow-up rates suggest high acceptability/feasibility of the online methodology. The sample is at increased dementia risk, due to high prevalence of first-degree dementia family history, female gender, and co-occurrence of multi-domain modifiable RFs. Presentation of findings will include detailed breakdown of trial methodology, baseline characteristics, and trial progress.

Combining anti-tau and anti-amyloid therapy: Next generation prevention trial for familial Alzheimer's disease

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Background
Dominantly Inherited Alzheimer's Disease (DIAD) is caused by mutations in the *APP, PSEN1* or *PSEN2* genes with >99% penetrance and consistent age of symptom onset. DIAD is a relatively pure form of AD with autopsy studies showing amyloid plaques, tau tangles, and Lewy bodies, similar to sporadic AD. Prior trials in DIAD targeting amyloid pathology have not yet provided clinically positive results. With or without amyloid removal, tau pathology may be a more promising target due to a strong association between soluble p-tau and amyloid plaque formation, and stronger associations between clinical onset and tau pathology, compared to amyloid pathology. The Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) are recruiting DIAD families at 38 sites across 15 countries, including Australia, for an adaptive clinical trial platform. The DIAN-TU Tau Next Generation Prevention Trial (Tau NexGen) is the first trial of combination therapy targeting both amyloid and tau pathology concurrently, and aims to slow cognitive/clinical decline or improve disease-related biomarkers.

Methods
Individuals with a known DIAD-causing mutation, who are between 10 years younger and 10 years older than their expected age of symptom onset, and are asymptomatic or have mild dementia symptoms (Clinical Dementia Rating ≤1) are eligible. All participants will receive active anti-amyloid therapy and will also be randomised to either active anti-tau therapy or placebo. Biomarkers, including tau PET, amyloid PET, CSF and blood samples, as well as clinical and cognitive status will be monitored throughout the study.

Discussion
The DIAN-TU Tau NexGen study has successfully launched overseas, and the Australian sites are set to launch in 2023. A cohort of approximately 15 trial-ready participants across our Australian sites who participated in the DIAN-TU cognitive run-in study are currently awaiting enrolment, and participant outreach and recruitment is ongoing, with many potential participants yet to be identified.

Could assessment of upper limb motor function help identify cognitive impairment and dementia?

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Background
Motor biomarkers such as gait help identify people at higher risk of developing dementia and cognitive impairment. Upper limb motor function (ULMF) is emerging as a new and more accessible motor biomarker, but it remains unclear which assessment methods to use. This knowledge gap hinders developing and including ULMF protocols in cognitive clinics. The aim of this study was to determine what ULMF assessment methods (including tests, recruitment settings and conditions causing cognitive impairment) have been used and to describe the associations found between ULMF and cognitive impairment.

Methods
A scoping review of all published study types was conducted using PubMed, CINAHL, and Web of Science. A systematic search using JBI guidelines was undertaken, including synonyms for key concepts 'upper limb', 'motor function' and 'cognitive impairment'. Selection criteria included dynamic and volitional tests of ULMF in adults. Analysis was by narrative synthesis.

Results
Sixty papers published between 1995 and 2022, comprising 41,800 participants, were included. The most common ULMF assessment tasks were finger tapping, Purdue Pegboard Test and functional tasks such as drawing and grasping an object. Methods of measurement were diverse, ranging from visually counting repetitions during a defined period to more detailed quantification of speed and rhythm using advanced motion capture systems. Participants were mostly recruited from clinical settings. Alzheimer's Disease was the most studied cause of cognitive impairment. Generally, slower speed, lower frequency, more errors, and greater variability in ULMF movement measures was associated with cognitive impairment, but results were mixed.

Discussion/Conclusion
This review maps the methods used in assessing ULMF and summarises the available evidence on how ULMF associates with cognitive impairment. It identifies research gaps and may help guide ULMF protocols for future cognitive clinics and research. There is potential for ULMF to be used in clinical assessments of dementia and cognitive impairment.

CSF Aβ42 and tau biomarkers in cognitively unimpaired Aβ- middle-aged and older APOE ε4 carriers

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Background
This study aimed to determine the relationship between the apolipoprotein E (*APOE*) ε4 allele and abnormalities in cerebrospinal fluid (CSF) and neuroimaging biomarkers of AD, and cognition in cognitively unimpaired (CU) middle-aged adults with a family history of dementia. The extent to which these relationships occurred in Aβ- CU older adults was also examined.

Methods
CU middle-aged adults (n=82; M_{age}=58.2) enrolled in the Healthy Brain Project (HBP) and Aβ- CU older adults (n=71; M_{age}=71.8) enrolled in the Australian Imaging Biomarker and Lifestyle (AIBL) study were included. CSF $Aβ_{42}$, total tau (t-tau), phosphorylated tau (p-tau_{181}), and neurofilament light (NfL), and neuroimaging markers of total brain and hippocampal volume were obtained. Cognition was characterised using an unsupervised cognitive composite and an in-clinic Preclinical Alzheimer's Cognitive Composite (PACC).

Results
Aβ+ was classified in thirteen (17%) middle-aged (HBP) participants. Aβ- CU middle-aged ε4 carriers showed lower CSF $Aβ_{42}$ levels, higher levels of CSF t-tau and NfL, and poorer performance on the PACC, compared to non-carriers (Cohen's d: 0.30-0.56). In Aβ- CU older adults (AIBL), ε4 carriers also had lower CSF $Aβ_{42}$ levels and higher levels of CSF t-tau and p-tau181, compared to non-carriers (Cohen's d: 0.65-0.74).

Discussion/Conclusion
In Aβ- CU middle-aged adults, *APOE* ε4 is associated with altered levels of Aβ, tau, NfL, and worse cognition. Similar relationships were observed in Aβ- CU older adults. These results have implications for understanding clinicopathological relationships between *APOE* ε4 and the emergence of cognitive and biomarker abnormality in Aβ- adults.

Dementia education and motivations for risk reduction among English, Arabic, Chinese, and Vietnamese speaking people in Australia

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Background
By 2050, there will be a 600% increase in dementia prevalence in Australia's older Asian migrant population. Reducing dementia risk is a national priority, but current services and education programs do not meet the unique needs of culturally and linguistically diverse people who typically have low health literacy levels. Our study aimed to pilot a dementia education initiative and explore motivations for risk reduction among English, Arabic, Chinese, and Vietnamese-speaking people.

Methods
We co-created a culturally sensitive dementia education initiative with the Canterbury-Bankstown Dementia Alliance. Community members were invited to attend a 2-hour in-language presentation with bilingual facilitators. Following the session, participants completed the Dementia Knowledge Assessment Scale (DKAS) and the motivations to change behaviour to reduce dementia risk (MOCHAD-10) scale. These scales respectively captured knowledge about dementia and motivation for lifestyle change for risk-reduction. Descriptive statistics were calculated to ascertain knowledge about, and positive/negative motivational cues toward, dementia risk-reduction.

Results
Of the 75 attendees, 54 (72%) participated in the surveys (English=13; Arabic=2; Chinese=33; Vietnamese=6). According to the DKAS, 61% of respondents recognised that a healthy lifestyle could mitigate dementia risk. Concerning the MOCHAD-10, the mean score for positive motivational cues to reduce dementia risk was higher than the mean score for negative cues to action, across and between the cultural groups. The positive cues with the highest scores included: learning more about dementia from the media; having risk factors; and feeling able to make changes to reduce risk.

Discussion/Conclusion
Participants' motivations to reduce dementia risk were predominantly driven by positive cues to action involving the media, personal risk, and empowerment. Language-specific health advice/resources, tools, and media campaigns should thus focus on these motivational factors to promote better brain health in these communities. Ongoing culturally sensitive dementia education initiatives are needed to support knowledge about risk-reduction.

Dementia risk factors among middle-aged adults in australian primary care participating in a practice nurse-led multi-domain dementia prevention trial

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Background
Interventions targeting modifiable risk factors for dementia may be more effective when delivered to patients in mid-life with elevated risk. The Holistic Approach in Primary care for PreventIng Memory Impairment aNd Dementia (HAPPI MIND) Study is a 3-year cluster randomised controlled trial to test the effects of a multi-domain intervention on dementia risk in individuals in the primary care setting.

Methods
People aged 45 to 65 years with ≥2 recognised risk factors for dementia were recruited from 40 Australian general practices. The Australian National University Alzheimer's Disease Risk Index (ANU-ADRI) assesses 15 domains (age, sex, education, BMI, depression, diabetes, cholesterol, smoking, traumatic brain injury, physical activity, cognitive activity, social engagement, alcohol intake, dietary fish intake, pesticide exposure), producing a composite score weighted to each risk factor's effect size. Scores for adults <65 years can range from -18 to +38, with a lower score indicating less risk. Participants' baseline characteristics were analysed.

Results
As of January 2023, 384 participants had completed their baseline ANU-ADRI. Most participants were female (62%). The average age of participants was 56 years (SD 5.7) and average education was 14 years (SD 4.0). One-third of participants reported a family history of dementia. The median composite ANU-ADRI score was 2 (IQR -3 to 7). The risk factors most commonly reported were low cognitive activity, being overweight or obese, and low fish intake. Low education and low social activity were infrequently reported.

Discussion/Conclusion
Participants in the HAPPI MIND study formed a cohort of middle-aged patients attending Australian general practice with elevated dementia risk. They had the potential to benefit from a multi-domain intervention for reducing dementia risk factors.

Supporting general practitioners and nurses to promote dementia risk reduction in australian general practices: Development of an intervention to change practitioner behaviour and a targeted approach to implementation

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Background
People in Australia have limited awareness of the potential for dementia risk reduction (DRR). General practice is an appropriate setting for promoting DRR, yet it is not routinely discussed. The objectives of this PhD research were to: (1) develop an intervention for promoting DRR in Australian general practice, (2) assess barriers to implementing the intervention, and (3) select and tailor strategies to support implementation of the intervention.

Methods
Guided by the Knowledge-to-Action Framework, the research comprised six separate studies. These were: (1) a scoping review of clinical guidelines to identify which behaviours are important for promoting DRR; (2) assessment of barriers to performing those behaviours, through a scoping review of the existing literature; (3) primary qualitative interviews with Australian primary care practitioners; (4) retrospective analysis of discussion board posts from participants in the Preventing Dementia Massive Open Online Course; (5) development, by a team of researchers and stakeholders, of an intervention to change practitioner behaviour based on the Behaviour Change Wheel approach; and (6) development of a tailored approach to implementation based on existing research matching barriers to implementation strategies.

Results
The Umbrella intervention comprises a waiting room survey and information cards for use in consultations, designed to prompt specific practitioner behaviours. Implementation is supported by educational materials, local consensus discussions, champions to drive implementation within general practices, and capturing and sharing knowledge across general practices.

Discussion/Conclusion
Six studies led to the development of a behaviour change intervention and tailored implementation approach designed to support the promotion of DRR in Australian general practices. Together, the intervention and implementation approach are hypothesised to improve practitioners' capability and motivation to perform specific behaviours important for promoting DRR. The intervention and implementation approach have been pilot-tested in five general practices in South East Melbourne, with evaluation currently underway.

Dementia risk tools for use in the community settings: A comparative analysis using data from three well-known cohorts

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Background
While the ANU-ADRI, the CAIDE and the LIBRA dementia risk tools have been widely used in clinics, research and community settings for the assessment of dementia and Alzheimer's (AD) risk, a large body of new evidence has emerged since their publication. Recently, CogDrisk and CogDrisk-AD have been developed using contemporary evidence that also include more risk factors than previous risk tools. Comparison of the relative performance of these risk tools is limited. We aimed to evaluate the performance of CogDrisk, ANU-ADRI, CAIDE, LIBRA and modified-LIBRA (LIBRA with age and sex estimates from ANU-ADRI) in predicting dementia, along with CogDrisk-AD and ANU-ADRI in predicting AD using three well-known dementia cohorts.

Methods
Baseline risk factors and dementia/AD diagnosed through follow-up were obtained from the Rush Memory and Aging Project (MAP), the Cardiovascular Health Study (CHS) and the HRS - Aging, Demographics and Memory Study (HRS-ADAMS). Risk scores were calculated based on available risk factors in each of these cohorts. Area Under the Curve (AUC) were calculated to measure the predictability of each risk score. Multiple imputation was used to assess the impact of missing data.

Results
We obtained similar AUC (95% CI) for dementia using the CogDrisk, the ANU-ADRI and the modified-LIBRA in all three cohorts (for HRS-ADAMS: 0.75 (0.71-0.79); 0.74 (0.70-0.78) and 0.75 (0.71-0.79); for CHS: 0.70 (0.67-0.72), 0.69 (0.66-0.72), and 0.70 (0.68-0.73); and for MAP: 0.65 (0.61-0.68), 0.65 (0.61-0.69) and 0.65 (0.61-0.69); respectively). The CAIDE and LIBRA also provided similar but lower AUCs than the above three tools. The performance of CogDrisk-AD and the ANU-ADRI in predicting AD were also similar in each of three cohorts.

Discussion/Conclusion
CogDrisk/CogDrisk-AD and ANU-ADRI were found to have similar accuracy for predicting dementia and AD. Inclusion of a greater range of modifiable risk factors in cogDrisk/CogDrisk-AD make them more informative for risk reduction.

Differential associations between empirically derived dimensions of modifiable dementia risk factors and cognition in early and late middle-aged adults

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Background
Modifiable dementia risk factors (MDRF) co-occur in middle-aged adults indicating complex and shared contributions of MDRFs to cognitive deficits and, ultimately, dementia risk. These relationships may also vary with age. Using a data-driven method to synthesize MDRFs, we aimed to determine whether differential associations exist between MDRFs and cognition in early and late middle-aged adults.

Methods
Early (40-55 years; n=570) and late (56-70 years; n=1023) middle-aged adults enrolled in the Healthy Brain Project (healthybrainproject.org.au) completed questionnaires on health/lifestyle, and subjective cognition, and the Cogstate Brief Battery. Factor Analyses of Mixed Data were conducted for MDRF dimension reduction. Dimensions with eigenvalues>1 were selected and labelled according to MDRFs surpassing cut-offs for expected average contribution. Dimension scores were extracted for individual participants. Linear regressions were conducted in early and late middle-aged groups to determine associations between simultaneous MDRF dimensions and subjective and objective cognition; covariates were age, sex, education and ethnicity.

Results
Six dimensions yielded eigenvalues>1. Dimension 1, representing mood symptomatology, explained the most variance (19.05%). In early middle-age, only mood symptomatology was significantly associated with worse attention/psychomotor function. No dimensions were associated with learning/working memory. Both mood symptomatology and health characteristics/lifestyle behaviors were associated with subjective cognitive concerns in early middle-age. In late middle-age, mood symptomatology and lifestyle behaviors/characteristics were independently associated with worse attention/psychomotor function. Mood symptomatology, cognitive/social engagement and health characteristics/lifestyle behaviors were independently associated with worse learning/working memory in late middle-age. For late middle-age, every MDRF dimension except for cognitive/social engagement was associated with subjective cognitive concerns.

Conclusion
Results demonstrate contributions of empirically derived MDRF dimensions to cognition in early and late middle-age. Many MDRF dimensions overlapped conceptually indicating the complexity of quantifying/synthesizing multiple related MDRFs. Elucidating the dynamic nature of associations between MDRFs and cognition across midlife will support the development of targeted dementia prevention strategies.

Estimating pre-symptomatic episodic memory impairment using simple hand movement tests: A cross sectional study of a large sample of older adults

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Background
Finding low-cost, accessible methods to detect people with early-stage Alzheimer's disease is a research priority for neuroprotective drug development. Subtle motor impairment of gait occurs years before episodic memory decline but there has been little investigation of whether self-administered hand motor tests can detect this pre-symptomatic period. This study evaluated how home-based keyboard tapping tests from the TAS Test protocol predict episodic memory performance in a sample of cognitively asymptomatic older adults, a proxy measure of preclinical Alzheimer's disease.

Methods
1,177 community participants (65.8 ± 7.4 years old; 73% female) without any cognitive symptoms completed a 40-second single key tapping test and a 60-second alternate key tapping test from TAS Test and validated cognitive tests of episodic memory, working memory and executive function. Frequency, variability, key press duration and accuracy scores were calculated for each tapping test. Generalized linear models examined associations between keyboard tapping and cognitive performance, adjusted for confounders including age, gender, depression, anxiety and education.

Results
All motor features of the single key (R^2_{adj} = 8.8%, ΔAIC = 4.9) and alternate key tapping tests (R^2_{adj} = 9.1%, ΔAIC = 7.8) improved estimation of episodic memory performance relative to models with demographic and mood confounders only (R^2_{adj} = 8.1%). No tapping features improved estimation of working memory. Only single key tapping features improved the estimation of executive function performance (R^2_{adj} = 16.0%, ΔAIC = 7.2).

Discussion/Conclusion
Brief self-administered online keyboard tapping tests predict asymptomatic episodic memory decline. This provides a potential low-cost and brief home-based method for risk stratification of enriched cohorts for further assessment.

Use of keyboard tapping test (TAS test) to discriminate between clinical cases presenting to a cognitive clinic

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Background
Assessing cognitive symptoms in clinic is time consuming, expensive and usually requires multiple clinicians. keyboard tapping tests may be an accessible, quick, low-cost method to aid stratification of people on the dementia continuum. This study evaluated the accuracy of TAS Test tapping tests to discriminate dementia, mild cognitive impairment (MCI), subjective cognitive decline (SCD) and cognitively healthy controls (HC).

Methods
238 participants (68.8 ± 8.9 years old) were recruited in Tasmania, Australia: 133 HC and 105 from the ISLAND Cognitive clinic with 40 diagnosed with dementia, 44 with MCI and 21 with SCD. Participants completed a 60-second alternate key tapping test on the TAS Test website; Frequency, variability, duration and accuracy of key presses were calculated. Area under the curve (AUC) and bootstrap test were used to compare the model with combination of tapping features, adjusted for age and sex, against a model with age and sex only.

Results
Tapping feature data improved the discrimination of MCI (AUC=0.7, 95%CI [0.61,0.79], $p < 0.01$) and SCD (AUC=0.79, 95%CI [0.68,0.89], $p = 0.04$) from cognitively normal participants compared to the respective null models. The motor features also helped distinguish MCI from SCD (AUC=0.82, 95%CI [0.71,0.93], $p < 0.01$). Keyboard tapping features did not improve the discrimination of MCI and HC from people with dementia compared to age and sex (AUC = 0.72 and 0.75, respectively, for null models).

Discussion/Conclusion
A 60 second simple keyboard tapping test could help distinguish people at the earliest stages of the dementia continuum (i.e., at MCI stage) from cognitively normal participants, and also between participants with SCD and MCI. It could potentially be used as a population screening test for identifying people at high risk of dementia for further medical assessments.

Feasibility, acceptability, and initial efficacy of a pilot habit-based physical activity behaviour change intervention for people with age-related cognitive concerns: The HabitHealth study

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Background
For older people experiencing mild cognitive impairment (MCI) or subjective cognitive decline (SCD), keeping physically active is important to reduce risk of dementia. Recent research suggests that automatic, context-dependent habits play an important role in supporting physical activity engagement. The current project aimed to a) develop and pilot the feasibility, acceptability and efficacy (participant increase in habit completion/automaticity) of a 12-week habit-based physical activity behaviour change intervention for people with MCI/SCD, and b) compare outcomes when either administered online or in-person.

Methods
We adapted a smartphone app which included cognitive assessment, questionnaires and daily habit monitoring, integrated with Apple watch activity data. 19 insufficiently active (<150 mins moderate activity p/week) participants with SCD (>24 on MAC-Q; 17 women; Mage: 73.3 years +/-5.6) undertook either an online (n=10) or in-person (n=9) group education workshop on habits, and an individual exercise physiology session, to plan a daily aerobic habit. Participants wore an Apple watch, and self-reported their habit engagement on the app over 12 weeks.

Results
On average, participants wore the watch 14 .1 hours per day, and logged their habit 67% of days. Participants reported completing their habit 71.5% of days. Habit completion rate, and the automaticity of the habit, both significantly increased from Month 1 to Month 3 (ps<.007). Further, there was a significant, positive relationship between habit engagement and both step count (r=.46) and minutes of stand time (r=.64) per day. There were no apparent differences between online or in-person groups for self-reported habit completion.

Discussion/Conclusion
HABIThealth was feasible, acceptable, and showed preliminary efficacy in building a daily habit which supports increased physical activity. This pilot has created valuable data that will be used to design a larger-scale RCT of the intervention. Supporting habits are a promising approach to increasing physical activity in people with cognitive concerns.

Investigating sex differences in risk and protective factors in the progression of mild cognitive impairment (MCI) to dementia: A systematic review

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Background
Effective dementia risk-reduction strategies rely on a detailed understanding of risk and protective factors in the progression of mild cognitive impairment (MCI) to dementia. We aimed to systematically review the evidence for sex differences in these factors.

Methods
Five online databases (PubMed/CINAHL/EMBASE/PsycINFO/Cochrane) were searched from inception until 17th of October 2022 for cohort studies with sex stratified data on risk and protective factors in the progression of MCI to dementia.

Results
A total of 2304 studies were identified, of which 12 studies from five countries were included in the systematic review. There was significant variability in study design, populations and outcome measures. Sex differences were evident in the impacts of genetic, sociodemographic, health and psychological factors as well as magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) markers on the progression of MCI to dementia. APOE4 status and depression appeared to increase the risk of progression for females, whereas history of stroke, MRI markers and CSF biomarkers appeared to increase the risk of progression for males. APOE2 status and marital status (unmarried) were noted to reduce risk of progression in males and females, respectively.

Conclusion
Simply controlling for the effects of sex and gender can limit ability to identify relationships between risk factors and outcome variables as relationships that differ for males and females may be missed or inappropriately applied to both sexes. There is a significant need for research to examine prospective risk factors for dementia in males and females with MCI individually, which can then be applied to targeted sex-specific interventions and education programs.

Machine learning based-composite cognitive test scores for tracking cognitive decline in early stages of dementia: Adopic study

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Background:
Clinical trials of early dementia use cognitive measures that assess multiple cognitive domains to reflect disease progression. Current cognitive endpoints are computed by averaging standardized change from baseline scores (i.e., Preclinical Alzheimer Cognitive Composite (PACC)). We compare the PACC to data driven Machine Learning (ML)-based composite scores with optimal combinations of performance scores for tracking cognitive decline on a large, harmonised data set of 3 cohorts, namely ADOPIC.

Methods:
A dataset harmonised across various cognitive scores derived from ADNI (n=1470), AIBL (n=1105) and OASIS (n=412) was used to construct composite scores using ML-based algorithms: a Uniform Manifold Learning dimension reduction technique (UMAP), principal component analysis (PCA) and Latent variable analysis (LVA). Data with ≥3 assessments ≤5 years before clinical progression/last visit were included. Participants were classified clinically as stable cognitively unimpaired (CU), CU progressing to mild cognitive impairment (MCI) or dementia, stable MCI, MCI progressing to dementia, or AD dementia. The sensitivity of ML-based composites compared to PACC to separate progressives relative to stable participants was evaluated using linear mixed model (LMM) analysis. Signal-to-noise ratios (SNRs) were calculated (mean change/SD change) for each composite. The mean change was measured in progressives relative to stable participants of each group.

Results:
The PACC and the three ML-based cognitive composites demonstrated high sensitivity to cognitive decline in the progressor groups. PCA and UMAP composites showed significantly higher SNRs in the MCI progressors than PACC ($P<0.01$), while LVA's performance was not significantly better. For the CU progressors, PCA and LVA showed similar results to PACC, but UMAP performed worse than PACC ($P<0.01$).

Conclusion:
ML-based cognitive composite score computed using PCA provides a practical solution to detect cognitive decline with improved performance in tracking cognitive decline in MCI progressors compared to PACC, while being comparable in CUs.

Mediterranean-dietary approaches to stop hypertension (MIND) diet intervention of the Australian multidomain approach to reduce dementia risk by protecting brain health with lifestyle intervention study (AU-ARROW)

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Background
Multidomain lifestyle approaches to prevent cognitive decline such as the FINGER study, that combine healthy diets, physical activity, brain training and medical counselling, have been found to improve or maintain cognitive functioning in at-risk elderly people in Finland. The AUstralian multidomain Approach to Reduce dementia Risk by prOtecting brain health With lifestyle intervention study (AU-ARROW) also adopts an approach targeting diet, physical activity and cognitive training. The study is currently ongoing; specifically, the dietary intervention of this study aims to reduce dementia risk through adherence to the Mediterranean-Dietary Approaches to Stop Hypertension (MIND) diet.

Methods
A total of 600 participants (300 each from Sydney and Perth) aged 60-79 years will be recruited and randomized into either the intervention group: structured, multidomain lifestyle (ML) or the control group: health education and coaching (HC) groups. The ML group will receive education sessions delivered by dietitians on the MIND diet and Australian Dietary Guidelines principles. Monthly individualized dietary counselling via telehealth will be provided to the ML group to encourage adherence to the MIND diet. Participants will self-monitor their dietary intake via the Easy Diet Diary app for the week before each telehealth check-in. The HC group will be provided with information about healthy eating at group meetings. Changes in diet quality will be assessed using the validated online version of the Cancer Council of Victoria Food Frequency Questionnaire at baseline and then every 6 months and the online MIND diet survey every 3 months.

Discussion/Conclusion
The dietary outcomes of AU-ARROW will be combined with findings from US-POINTER which is also involved in the world-wide initiative for dementia risk reduction (world-wide-FINGERS) to develop translational focus programs, policies and dietary guidelines for at-risk elderly population and to support advocacy of the role of dietitians in dementia risk reduction.

Memory clinics in Australia – Learnings after 1 year of national guidelines implementation

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Background
Considerable variability in resources, staffing and service protocols across Australian memory and cognition clinics (MCs), has negatively impacted their ability to provide timely and equitable access to a dementia diagnosis and support. One crucial step to achieving greater harmonisation, was the publication of Australia's first *Memory and Cognition Clinic Guidelines*. In this presentation we will report on the learnings after one year of Guidelines implementation in Australia.

Methods
The *Monitoring and Quality Improvement Pilot Progra*m (MQIPP) was developed to quantify the extent to which Australian MCs can apply the Guidelines in their clinical practice and to test the evaluation framework. Seven clinics from five jurisdictions participated. They performed a self-assessment including the submission of documentary evidence of Guideline compliance, and a non-identifiable case note audit. Site specific reports outlining the MC's level of compliance and areas of achievement and improvement were produced. Each clinic attended a feedback meeting to discuss results, and the clinic's feedback on the MQIPP and the Guidelines.

Results
Overall, the Guidelines were viewed favourably and deemed particularly useful for newly establishing MCs and single-discipline clinics seeking to extend their service delivery model. Adherence to the Guidelines in the MQIPP ranged from 18 to 83%. All clinics perceived the evaluation process as valuable, albeit too lengthy, and identified opportunities for immediate service improvements. Lower adherence ratings were often explained by underdefined referral processes and a lack of case-conferences and sufficient post-diagnostic support provision. Some clinics commented that while the largest number of Standards pertained to these sections, they did not align with the core remit of a MC.

Discussion/Conclusion
The Guidelines are a useful benchmarking tool for Australian MCs. Based on stakeholders' feedback, adjustments to Guidelines document and monitoring process are currently being made and funding for a national MC accreditation program will be sought.

Neuropsychological and clinical risk factors for incident delirium: Two systematic reviews and meta-analyses

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Background
Delirium is a distressing condition associated with a 9-fold increased dementia risk in older adults. It affects 20-40% of hospitalised older adults and costs over $8b/year.

Methods
We dovetail two recently published systematic reviews and meta-analyses, both following PRISMA guidelines. In the first, we aimed to understand the neuropsychological profile of delirium vulnerability relative to cognitive impairment status (Neurosci Biobehav Rev. 2022). In the second, we aimed to assess how clinical predisposing factors differed between delirium motor subtypes (Age and Ageing. 2022).

Results
First: Across 44 studies, poor performance in all cognitive domains except perception was significantly associated with incident delirium. The largest effects were seen for orientation and construction/motor performance. However, these effects were no longer significant in the subgroup without pre-existing cognitive impairment, where executive functions and verbal functions and language skills were associated with incident delirium. Second: Across 61 studies, factors such as sex and cerebrovascular disease discriminated between subtypes. Hypoactive cases were older, had poorer cognition and higher physical risk scores than hyperactive cases and were more likely to be women, living in care homes, taking more medications, with worse functional performance and history of cerebrovascular disease than all remaining subtypes. Hyperactive cases were younger than hypoactive and mixed subtypes and were more likely to be men, with better cognition and lower physical risk scores than all other subtypes.

Conclusion
Specific neuropsychological and clinical factors signal risk for incident delirium, and these factors are sometimes dependent on pre-existing cognitive impairment and delirium subtype. Findings can improve the stratification of delirium risk, enabling the targeting of known delirium prevention strategies. Delirium prevention stands as an untested dementia risk reduction approach.

Pareidolias are related to visuoperceptual ability

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Background
Pareidolias, or the misperception of meaningful objects, are complex visual illusions thought to be phenomenologically similar to Visual Hallucinations (VH). VH are a major predictor of dementia in Parkinson's Disease (PD) and are included as a core clinical feature in Dementia with Lewy Bodies (DLB). A newly developed Noise Pareidolia Test (NPT) was proposed as a surrogate marker for VH in DLB patients as their high number of pareidolic responses correlated with informant-corroborated accounts of VH. We hypothesised that pareidolic responses in this patient group more likely reflect the underlying visuoperceptual impairment, rather than being a marker for VH.

Methods
We contrasted patient groups with visuoperceptual impairments that experienced VH (DLB and PD with Dementia (PDD): *n* = 13) to those without VH (PD, *n* = 12; typical Alzheimer's Disease (tAD): *n* = 11; Posterior Cortical Atrophy (PCA): *n* = 5).

Results
We found that all patient groups reported pareidolias. Within the Lewy Body Disorders (PD, DLB, PDD), there was no difference in pareidolic responses between hallucinating and non-hallucinating patients. Visuoperceptual deficits and pareidolic responses were more frequent in non-hallucinating PCA compared to hallucinating DLB-PDD. Regression analysis showed that performance on visuoperception cognitive tasks significantly predicted pareidolias whereas a history of VH did not.

Conclusion
These findings suggest that pareidolias reflect the underlying visuoperceptual impairment of Lewy Body disease, rather than a marker for VH.

Amyloid-targeted iron oxide nanoparticles as MRI contrast agents for Alzheimer's disease diagnosis

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Background
The currently available means of detecting Aβ and tau and providing a definitive diagnosis of Alzheimer's disease (AD) are Positron Emission Tomography (PET) imaging or cerebrospinal fluid analysis, which are hindered by their cost, invasive nature, and in the case of PET, exposure to radiation. Magnetic resonance imaging (MRI) is a widely used and accessible imaging modality which may be rendered sensitive enough to detect amyloid pathology with Aβ-targeted superparamagnetic iron oxide nanoparticle IONPs contrast agents. Here, we show the potential for an Aβ-targeted IONP formulation (IONP-Ab) for use as an MRI tracer for the diagnosis of AD.

Methods
Following initial assessment of *in vitro* compatibility and imaging efficacy, IONP and IONP-Ab were subsequently evaluated for their *in vivo* efficacy in a transgenic mouse model of AD. APPSwe/PSEN1 and wild type mice were treated with either saline, Aβ-targeted or non-targeted nanoparticles (10 µg Fe/g). 30 minutes following administration, mice were euthanised and their tissues were collected for *ex vivo* imaging in MRI and histological evaluation. Acute toxicity was evaluated in a preliminary cohort of mice observed for 24 h following injection to evaluate any acute toxicological effects. Inductively coupled plasma mass spectrometry (ICP-MS) was used to evaluate biodistribution of the nanoparticles.

Results
IONP and IONP-Ab were stable in solution, non-toxic to cells, and showed good T2-weighted MRI signal. No adverse effects were observed in mice in the 24 h following injection. Extracted brains of mice treated with targeted nanoparticles demonstrated MRI signal changes. ICP-MS results confirmed that the MRI signal in the brain was from the tracer. In addition, the IONP and IONP-Ab were detected in the liver, spleen, and kidneys.

Discussion/Conclusion
The present work shows promising preliminary results in the development of a targeted non-invasive method of early AD diagnosis using contrast enhanced MRI.

Predicting risk of dementia in high and low- and middle-income countries: Risk model development and application

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Abstract

For the feasible future, reducing risk of dementia is likely to be the only effective and economical method to decrease the social and health impacts of this disease. Therefore, new strategies for early identification of high-risk cases are needed for targeted risk reduction and prevention. This is particularly important in Low- and Middle-Income Countries (LMICs) where most dementia cases live. Therefore, this presentation will explore the current state of knowledge in dementia risk prediction modelling including new advances in algorithm development across different countries and in minority groups. The results will highlight that we cannot simply extrapolate findings from high-income and majority Caucasian populations to ethnically diverse settings. This raising important methodological issues for developing models and predicting risk in different societal groups; particularly in multicultural countries such as Australia. There is an urgent need to identify the key risk factors for dementia unique to each country (and the different groups within a specific country), to inform the development of context-relevant risk reduction and prevention strategies.

Profiling of various neurodegenerative conditions using simultaneous - FMRI–PET-A novel clinical translational study

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Background
We are exploring role of simultaneous rs-fMRI/PET as a clinical tool in dementia.

Methods
Participants (n = 19) with different types of dementia including frontotemporal dementia (5 FTD),dementia with Lewy bodies (3 DLB), Alzheimer's disease (2 AD), Parkinson's disease - dementia (3 PDD), multiple system atrophy- Parkinson's (1 MSA-P), progressive supranuclear palsy (2 PSP), Corticobasal degeneration (1 CBD), normal pressure hydrocephalus (2 NPH) were compared with healthy controls(10 HC). Patient underwent PET scan and rs – fMRI and T1MPRAGE in T1MPRAGE scan in 3T MR/PET mMR system. data were processed using FSL.

Results
HC had a mean of 8 biological networks with 5 non–cognitive (NC) and 3 cognitive (C) networks. In dementia group, mean of 7 biological networks with 5 NC and 2C. DLBD, PSP and CBD showed NC > C network involvement. Further, when hypo-connectivity of posterior and anterior DMN were analysed. PSP and CBD had more of an anterior pattern(AP) while DLBD had posterior pattern (PP) of DMN involvement. To further differentiate PSP from CBD, CBD had additional involvement of executive and fronto parietal networks whereas PSP had additional involvement of auditory network. FTD, AD, PDD, MSA-P, and NPH, showed C>NC network involvement. Further subtyping, AP was more affected in FTD, PDD, and MSA-P, whereas PP in AD and NPH. FTD had additional involvement of V1 and auditory network, PDD had V3 and cerebellar network, while, MSA- P had cerebellum, sensory, auditory and executive networks.While, AD had additional involvement of V1 and V3, and NPH had sensory network. rs-fMRI and PET correlations were analysed based on anatomical regions implicated in each modality for correlation/anti-correlation.

Discussion/Conclusion
In this simultaneous rs-fMRI - PET, correlated HC and patients, subtypes of dementia, and dementia patterns with PET, conclude that rs-fMRI may have a potential clinical role in differentiating subtypes of dementia.

“The whole is more than the sum of its parts”- whole brain spectroscopy metabolite patterns in different type of dementia – An MR/PET correlational study

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Background
Metabolite map pattern of N-acetyl aspartate(NAA), Lactate (Lac), Choline(Cho), Glutamate(Glx), Myoinositol(MI) and Creatine(Cr) in subtypes of dementia were studied.

Methods
9 healthy(HC) and 11 cases of dementia were included in study including progressive supranuclear palsy(PSP), Alzheimer's disease(AD), fronto-temporal dementia(FTD), Parkinson's disease(PD), normal pressure hydrocephalus(NPH). Diagnosis of dementia was confirmed by PET/MRI. Patient underwent EPSI and T1-MPRAGE scan in 3T MR/PET mMR system. MIDAS pipeline was used for in-vivo quantification .Metabolite pattern of HC, PET/MRS correlation of metabolite maps in dementia and with increasing severity of AD is also studied.

Results
Normative distribution was NAA, Glx, Cr Gray Matter>White Matter and for Cho, water WM>GM PET pattern correlated ,in FTD with decreased NAA and Glx in frontal lobe. In PD, decreased NAA and Cho at mid brain noted. In PSP, decreased NAA, Cho, Glx, and Cr in putamen and decreased NAA at midbrain. In AD decreased NAA correlated with atrophy and decreased Cho correlated with PET in parietal lobe. In case of NPH, routine metabolite maps were not interpretable due to artifacts. Normative distribution on water map was PVWM>DWM>GM, Ventricles. In NPH it was in GM>DWM>PVWM>Ventricles. Increased water in GM can help differentiate NPH from AD, PD and FTD. With increasing MTA score in AD, NAA correlated with atrophy and Cho correlated with FDG PET. In Grade 4 AD artifactual increased metabolites was noted. In grade 4 AD, pattern of water distribution was PVWM>>DWM, GM>ventricles. Grade 2 and 3 AD was showing spectrum between that ofHC and AD.

Discussion/Conclusion
NAA and Cho map correlates with PET pattern and severity in early dementia and water map in severe dementia in this simultaneous MRPET study.

Real-world implementation of an electronic diagnostic support tool (AID-DST) designed to identify the cause(s) of delirium. A study protocol and work in progress

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Background
The Aetiology in Delirium - Diagnostic Support Tool (AiD-DST) is an electronic aid to help identify the multifactorial causes of delirium. AiD-DST has been validated in the clinical setting and found to be user friendly. AiD-DST was implemented into the medical unit of a metropolitan hospital.

Methods
A real-world implementation study that uses a RE-AIM framework to describe AiD-DST use by medical doctors over a 10-week period will be conducted. Engagement will comprise the proportion of doctors using AiD-DST. Retention will be defined by the proportion of regular users of AiD-DST over the 10-week period. Survival analysis will be performed for each doctor group. Usability and usefulness will be measured using a standard survey.

Results
Description of use among doctors within the medical unit will be described and break down against doctor characteristics reported. The percentage retention will be presented. Characteristics of the different patterns of users will be compared to identify factors related to discontinuation of AiD-DST. Descriptive statistics to report on usability.

Discussion/Conclusion
A real-world implementation study protocol is proposed prior to roll-out of a new diagnostic support tool in delirium.

Retinal detection of amyloid beta oligomers in rodent models using single domain nanobodies

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Background
Early and accurate diagnosis of Alzheimer's disease (AD) is a major goal in order to reduce the impact of dementia and also represents an unmet medical need globally. The underlying molecular mechanisms of Alzheimer's disease begins years before clinical onset. Previously, a non-invasive optical coherence tomography angiography was developed to identify retinal abnormalities associated with AD. However, a link between these abnormalities and retinal Aβ deposition was not established

Methods
Here, we used formalin-fixed paraffin-embedded (FFPE) retinal and cerebral tissue sections derived from different age groups of 5xFAD and APP/PS1 mice and their littermates. The sections were immunoassayed with antibodies specifically targeting both Aβ oligomers (Aβo) or plaques in the retina and brain. Further, levels of blood-borne Aβo were correlated with retinal Aβo.

Results
In both mouse models of AD, high levels of Aβo were detected at early stages of the disease following immunohistochemistry and immunofluorescence assessment. We also show that Aβo was present in all retinal cell layers but was more prominent in the ganglion layer. Aβo co-localised to late endosome within the cytosol of retinal cells, indicating alteration of the endocytic pathway. Of importance, retinal Aβo accumulation while coincident with their accumulation in blood, preceded their presence in the brain and occurred months before cognitive decline in these mice.

Discussion/Conclusion
Our data supports the hypothesis that soluble Aβo can be detected in the retina of AD animal models in early disease stage before brain onset and cognitive deficits. The development of a diagnostic test screen for preclinical and/or early AD stage using camelid anti-Aβo nanobody for the detection of retinal oligomers is a major milestone towards the development of a human AD diagnosis.

Significant diffusion mri changes in the callosal genu in progressive supranuclear palsy compared to Lewy body diseases

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Background:
The overlapping motor and non-motor features of progressive supranuclear palsy (PSP) with Lewy body disorders (LBD comprising Parkinson's disease ± dementia, and, dementia with Lewy bodies) may lead to misdiagnosis. Previous studies have suggested white-matter changes measured by diffusion-weighted MRI are prominent in PSP. We aimed to assess the usefulness of diffusion metrics to discriminate PSP from LBD. We focused on the corpus callosum as a proof-of-concept because the confounds of partial volume effects and crossing fibres can be eliminated in this region.

Method:
Thirty-nine healthy controls, 21 LBD (including 10 with dementia) and 12 PSP patients underwent 3.0T MRI. Multi-shell diffusion-weighted images (DWI) were acquired using 9 non-diffusion weighted images (b = 0 s/mm2) as well as 27 (b = 1000 s/mm2) and 62 (b = 2500 s/mm2) unique directions. The DWI metrics fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were estimated using MRTrix toolbox after performing standard data cleaning. Two regions of interest (ROI) were manually placed on the centre of the genu (GCC), and splenium (SCC), of corpus callosum. Differences between groups were assessed using two-tailed unpaired Wilcoxon-rank sum tests (after correcting for age and sex).

Results:
FA, MD and RD were significantly different in PSP compared controls in GCC (p=0.001, p=0.03 and p=0.0003, respectively). FA and RD were also significantly different between PSP and PD patients in GCC (p=0.008 and p=0.006, respectively). None of the diffusion metrics showed a statistically significant change in SCC.

Discussion/Conclusions:
White-matter changes in the rostral corpus callosum (decreased FA and increased RD) were found to separate PSP from LBD patients. As part of a multimodal diagnostic imaging algorithm, diffusion MRI metrics in the GCC may have the potential to help differentiate individuals with PSP from LBD.

Social determinants of modifiable dementia risk in Māori and non-Māori: Results of the New Zealand health, work and retirement study

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Background
Dementia risk varies along the social gradient. Revealing links of social determinants of health (SDOH) and modifiable health and lifestyle factors for dementia holds clues towards maximizing dementia risk reduction opportunities, especially for vulnerable populations. Therefore, we investigated associations of SDOH and a dementia risk score in Indigenous Māori and Non-Māori (mainly European descent) in midlife and early late-life.

Methods
A subsample of the New Zealand Health, Work and Retirement study completed standardized face-to-face cognitive assessments (adapted 'Kiwi' Addenbrooke's Cognitive Examination/ACE-R) in 2010. We computed the Lifestyle for Brain Health (LIBRA) dementia risk score, comprising 8 modifiable risk factors. Higher scores indicate higher dementia risk (range= -1;+9.2). First, we assessed associations of LIBRA and cognition. Second, we performed adjusted regression analysis for area-based (socioeconomic deprivation, health care access, neighbourhood safety) and individual SDOH (education, employment status, net income, social loneliness) with LIBRA stratified for Māori and Non-Māori.

Results
In 918 participants (age: *M*=62.9 years, *SD*=6.7, range= 48-75; females= 52.8%; Māori= 26.2%), a higher LIBRA score (*M*=1.8, *SD*=1.6, observed range= -1;+7.4) was associated with lower cognitive functioning (b=-0.30, 95%CI=[-0.48;-0.11], *p*=.002) and cognitive impairment (OR=1.41, 95%CI=[1.10;1.81], *p*=.007), adjusted for age, sex, education, ethnicity and area-based socio-economic deprivation. Higher area-based socio-economic deprivation was associated with higher LIBRA in Māori (b=.10, 95%CI=[0.02;0.18], *p*=.020), but not in Non-Māori (b=0.01, 95%CI=[-.03;0.05], *p*=.677). Employment status and lower neighbourhood safety were associated with higher LIBRA in Non-Māori only. Health care access difficulties and social loneliness were associated with higher LIBRA in both populations, while education and net income were not.

Conclusion
SODH are differentially associated with dementia risk in midlife and early late-life New Zealanders. Area-based socioeconomic deprivation was linked to dementia risk in Māori, but not in Non-Māori. This points to systematic inequities in dementia risk, which require equity-focused policy-based public health approaches to risk reduction.

Staying a step ahead of the prodrome: How estimating distance in virtual reality could be the future of preclinical Alzheimer's disease detection

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Background
The current gold standard diagnostic cognitive tests for Alzheimer's disease (AD) involve recollection of previously encountered information. These tests are predicated on neurobiological evidence that neurodegeneration impacts the hippocampus early in the disease progression, leading to clinical symptoms. However, new evidence points to a neighbouring brain area, the entorhinal cortex (EC), as the initial site of AD pathology preceding clinical symptoms. Neurons in EC support navigation, particularly in estimating distances. The future of cognitive screening tools for preclinical AD is, therefore, dependent on developing tests that assess EC-supported navigation.

Methods
Experiment 1: As part of a validation study, thirty-five university students performed a distance estimation task in different virtual reality (VR) environments across two digital platforms (non-immersive, computer screen v. fully-immersive, head mounted display (HMD)).
Experiment 2: Fifty Tasmanian >50 years registered with the Island Study Linking Ageing and Neurodegenerative Disease (ISLAND) Project were recruited to complete the abovementioned VR task. Participants also completed PAL and SWM cognitive screens from the CANTAB and donated blood tested for an AD blood biomarker, plasma p-tau 181.

Results
Experiment 1: The pattern of distance estimation in both digital platforms matched EC-supported, real-world distance estimation. Interestingly, distance estimates were closer to the target specifically in the HMD platform.
Experiment 2: Distance estimation data collection is on-going (60% completed) and will be finished by the middle of February 2023. CANTAB scores and plasma p-tau 181 samples have already been analysed independently and will be compared against distance estimation performance.

Conclusion
We have validated VR as a means of assessing EC-supported distance estimation, with HMDs offering a naturalistic navigation environment akin to exploring the real world. Findings from experiment 2 will examine distance estimation as a potential preclinical AD cognitive biomarker. This project has been featured on ABC TV Tasmania and ABC Radio Sydney (2022).

Targeting chronic conditions that increase dementia risk: Nonpharmacological approaches for pain and symptoms of depression in people with osteoarthritis

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Background
Osteoarthritis is associated with a 1.5-fold increase in dementia risk and rises to 5.7-fold when associated with another chronic condition. Further, osteoarthritis and pain-related conditions have been reported to occur in 40-50 percent of people living with dementia. Targeting chronic conditions and symptoms (e.g., pain and depression) that increase dementia risk may reduce dementia prevalence as well as improve health outcomes in people living with osteoarthritis. These meta-analyses examine nonpharmacological approaches for pain and symptoms of depression in people living with osteoarthritis.

Methods
Electronic databases EMBASE, PUBMED & MEDLINE, Web of Science, CINAHL and PEDro were searched for relevant studies published from inception up until April 2022. Pooled effect sizes (ES) and 95% confidence intervals (CI) for pain and depression were calculated using random-effects meta-analyses. Heterogeneity was examined using the I^2 index and prediction intervals. Intervention subtypes were examined using subgroup analyses of aerobic/resistance exercise, therapeutic approaches, movement meditation (yoga/tai-chi/qigong), and multimodal approaches (i.e., combined physical activity and therapeutic/mindfulness/education-based approaches).

Results
For pain, 29 interventions (n=4382; 65±6.9 years; 70% female) showed nonpharmacological approaches significantly reduced pain (ES=0.43, 95%CI [0.25,0.61], p<.001). Sub-group analysis revealed significant effect sizes for movement meditation (ES=0.52; p<.001), multimodal approaches (ES=0.37; p<.001), and therapeutic approaches (ES=0.21; p<.001). Resistance or aerobic exercise alone did not significantly improve pain. For depression, 28 interventions (n=3377; 63±7.0 years; 69% female) showed nonpharmacological approaches significantly reduced symptoms of depression (ES=0.29, 95%CI [0.08,0.49], p<.001). Sub-group analysis revealed significant effect sizes for movement meditation (ES=0.30; p=.008), and multimodal interventions (ES=0.12; p<.001). Resistance/aerobic exercise or therapeutic approaches alone did not improve symptoms of depression.

Discussion/Conclusion
Multimodal or mind-body approaches were more effective than aerobic/resistance exercise or therapy alone for reducing pain and symptoms of depression in people with osteoarthritis.

The association between a healthy lifestyle and incident dementia in various sociodemographic and geographical groups: An individual participant data meta-analysis from the cosmic collaboration

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Background
Despite the growing body of evidence on lifestyle-related risk factors for dementia, risk stratification beyond age has rarely been explored. This study addressed the potential moderating effect of sociodemographic characteristics (i.e. age, gender, years of formal education, socioeconomic position) and geographical location (i.e. continent) on the association between a comprehensive modifiable dementia risk score ("LIfestyle for BRAin health" (LIBRA) index) and dementia incidence. This index integrates the presence or absence of twelve modifiable risk and protective factors for dementia (i.e. cognitive activity, physical activity, healthy diet, smoking, low-to-moderate alcohol consumption, obesity, hypertension, dyslipidemia, diabetes, depression, ischemic heart disease and chronic kidney disease).

Methods
Individual participant data from 21 prospective cohort studies from the COSMIC collaboration, including 31,680 individuals (57.8% women) from 18 countries was harmonized. Potential interactions between sociodemographic characteristics and geographical location, and the LIBRA score were examined by pooling estimates from cohort-specific Cox proportional hazard regression analysis in a two-step individual participant data meta-analysis.

Results
During 172,425 person-years of follow-up, 2,330 cases of incident dementia were observed. One standard deviation increase in LIBRA score was associated with a 22% higher risk of dementia when controlling for age, gender and years of formal education (hazard ratio (HR) = 1.22, 95% confidence interval (CI) = 1.14–1.31). This association was moderated by age at baseline, with the association being stronger for people up to 75 years old (HR = 1.34, 95%CI = 1.22-1.46) compared to older individuals (HR = 1.17, 95%CI = 1.08-1.26). No interaction with gender, years of formal education, socioeconomic position or geographical location was observed.

Discussion/Conclusion
These findings suggest that the association between a healthy lifestyle, as measured with the LIBRA index, and dementia risk does not differ across diverse sociodemographic groups or broad geographical locations, though it appears to be stronger at younger ages.

The effect of BDNF val66met on memory, CSF total-tau, CSF pTau181 and CSF Aβ42 in early sporadic Alzheimer's disease

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Background
Allelic variation in the brain-derived neurotrophic factor (*BDNF*) Val66Met polymorphism has been shown to moderate rates of cognitive decline in preclinical sporadic Alzheimer's disease (i.e., Aβ+ older adults), and pre-symptomatic dominantly inherited Alzheimer's disease (DIAD). In DIAD, Met66 was also associated with greater increases in CSF levels of total tau and phosphorylated tau (p-tau$_{181}$). This study sought to determine the extent to which *BDNF* Val66Met is also associated with changes in episodic memory and CSF total-tau and p-tau$_{181}$ in Aβ+ older adults in early-stage sporadic AD.

Methods
Aβ+ Met66 carriers (*n*=94) and Val66 homozygotes (*n*=192) enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI) who did not meet criteria for AD dementia were included. Only participants with at least one follow-up neuropsychological and CSF assessment were included. Episodic memory was measured by the ADNI Memory Composite and CSF samples were collected via lumbar puncture to determine levels of total-tau, p-tau$_{181}$ and Aβ$_{42}$. A series of linear mixed models were conducted to investigate changes in each outcome variable over 10 years, covarying for CSF Aβ$_{42}$ (except when examining changes in CSF Aβ$_{42}$), *APOE* ε4 status, sex, age, baseline diagnosis and years of education.

Results
When followed over 10 years, Aβ+ Met66 carriers demonstrated significantly faster memory decline (*d*=0.33) and significantly greater increases in CSF total-tau (*d*=0.30) and p-tau$_{181}$ (*d*=0.29) compared to Val66 homozygotes, despite showing equivalent rates of change in CSF Aβ$_{42}$.

Discussion/Conclusion
In non-demented Aβ+ older adults, Met66 carriers showed greater memory decline and greater increases in both CSF total-tau and CSF p-tau$_{181}$ over 10 years compared to Val66 homozygotes, despite showing equivalent changes in CSF Aβ$_{42}$. This suggests that Met66 carriage, which is associated with lower BDNF availability and lower neurotrophic support, may confer greater vulnerability to Aβ-related increases in tau compared to Val66 homozygosity in the early stages of sporadic AD.

The effect of dementia-friendly training on the risk assessment of bank staff towards elder financial abuse

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Background
Financial abuse is a common form of abuse for people with dementia (PWDs). Our team has developed a training course targeted at bank staff to assist customers suspected with dementia. This study aimed to evaluate whether bank staff changed their risk assessment of financial abuse after receiving dementia-friendly training.

Methods
We used a pre- and post-test study design to survey dementia-friendly training participants from six banks across Taiwan. They were asked six vignette questions representing different scenarios of financial abuse to a PWD by family members or strangers to assess their risk scores, and whether the bank staff would decline to service under each scenario. Having dementia-related experience was defined by whether the staff attended dementia training before, had family members or friends with dementia, or cared for a family or friend with dementia. The generalized estimating equations (GEE) models were used to compare the changes in the risk scores and decisions of bank staff before and after training.

Results
Among 282 bank tellers in our sample, more than half were female (54.96%), 50~59 years (31.91%), and 65.96% had no dementia-related experience. The overall mean risk scores of financial abuse changed from 49 to 50 after training, with significant improvement among those with no dementia-related experience (49.3 to 49.7). McNemar analysis showed that in five out of six financial abuse scenarios, the proportion of bank staff who declined to service was significantly higher after training. According to GEE analysis results, the risk scores in vignettes 4 and 5 (financial abuse by relatives) significantly increased from 7.7 to 8.3 and 8.2 to 8.6 after training.

Discussion/Conclusion
Findings from this pre- and post-test study showed that our training helped bank staff to become more sensitive to the risk of financial abuse and protecting the assets of customers suspected with dementia.

The impact of social isolation on cognition and predictors of loneliness in older people at risk of dementia

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Background
The Covid-19 pandemic and resulting lockdowns increased social isolation, especially in older people who are more likely to live alone and have fewer social interactions. The impact on cognition is uncertain.

Methods
We investigated whether cognition was affected in older people during Melbourne's lockdown in 2021. Furthermore, we examined whether social isolation and loneliness reduced after lockdowns ended, and whether mood in older people was impacted by the pandemic. Participants were 147 older people (70% females) with subjective memory complaints aged 63 to 87 years (M=70.2 years) and had taken part in a 6-month exercise and diet intervention in 2017/18. The Montreal Cognitive Assessment (MoCA), Depression Anxiety Stress Scale (DASS) and CHAMPS were repeated 4 to 6 times over an average of 4.5 years. The Social Connectedness Scale, UCLA Loneliness Scale, were completed at 3.8 years (during lockdown) and 6 months after the final lockdown. A restricted maximum likelihood linear mixed model accounting for age, sex and treatment allocation assessed changes in outcomes over time.

Results
Overall, 118 participants completed the additional lockdown follow-ups. MoCA score significantly improved by 0.9 (95% CI 0.19, 1.03) over average 4.5 years (p=.005). MoCA score was significantly reduced during lockdown (p=.002) with a trend to improve 6 months after lockdowns ended (p =.056). Total DASS scores significantly increased by mean of 5 points (95% CI 3.10, 6.79) over average 4.5 years (p=.005). Hours spent in social activities reduced by 61% during lockdown (p<.001). There was a trend for participants to feel more socially connected after lockdown (p=.064), yet experiences of loneliness were unchanged.

Discussion/Conclusion
A small reduction in cognition of older Melbournians was observed during lockdown. Small increases in cognition over the entire study duration may reflect attrition of poorer performers. Symptoms of psychological distress increased from prior to the pandemic to post-lockdown.

The influence of baseline sleep on exercise-induced cognitive change in older adults: A randomised clinical trial

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Background:
Observational studies consistently demonstrate that physical activity is associated with enhanced cognitive function and reduced risk for dementia. However, there remains significant heterogeneity in study findings regarding the effect of exercise interventions on cognitive function. Individual variation in sleep behaviours are hypothesized to be a source of this variability in the effectiveness of exercise to influence cognition, however this has not yet been investigated. Thus, the current study aimed to 1) investigate the influence of a 6-month exercise intervention on sleep pre- and post-intervention and 2) investigate whether baseline sleep measures moderate exercise-induced cognitive changes.

Method:
We utilised data from the Intense Physical Activity and Cognition (IPAC) study (n=89), a 6-month moderate intensity and high intensity exercise intervention, in cognitively normal community-dwelling older adults aged 60-80 years (68.76 ± 5.32). Exercise was supervised and completed on a stationary exercise bicycle, and cognitive function was measured using a comprehensive neuropsychological battery administered pre- and post-intervention. Sleep was measured using the Pittsburgh sleep quality index (PSQI) to yield measures of sleep duration, efficiency, and sleep latency.

Results:
There was no effect of the exercise intervention on any sleep outcomes from pre- to post-intervention. There was a significant moderating effect of baseline sleep efficiency on both episodic memory and global cognition within the moderate intensity exercise group (β = -0.024, SE = 0.008, p = .004; β = -0.011, SE = 0.005, p = .036), such that those with poorer sleep efficiency at baseline showed greater exercise-induced cognitive improvements.

Discussion/Conclusion:
These results indicate that those with poorer sleep may have the greatest exercise-induced cognitive benefits and that baseline sleep behaviours may be an important source of heterogeneity in previous exercise interventions targeting cognitive outcomes.

The influence of traffic lights presentation of dementia risk screening information on older adults' motivations for risk reduction in primary care

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Background
Assessing and treating lifestyle factors could reduce the onset of new dementias by 40%. Primary care is a practical setting to operationalise risk identification and treatment. However, little is known about how to communicate risk information to maximise motivation for sustained behaviour change.

Methods
A convenience sample of community-dwelling older adults (≥60 years, N=89, M_{age}=72.93, SD=6.36, 68 females, 21 males) received dementia risk factor information in two formats: "traffic lights" (green = risk absent, amber = risk emerging, and red = risk present) or more concise presentation formats (red-only = risk present). Participants reported their motivation to make changes to improve their health on personally relevant risk factors, motivation to maintain good health behaviours, and liking of the formats on 4-point Likert scales. Additionally, categorical preference for traffic lights vs. red-only formats was measured, followed by an open-ended question on reasons for preferences. Motivation to Change Lifestyle and Health Behaviour for Dementia Risk Reduction (MCLHB-DRR-27 Scale) was also measured.

Results
Traffic lights presentation was more motivating (Z=4.16, p=<.001) and more liked (Z=4.80, p=<.001) than red-only. There was a strong preference for traffic lights on the categorical measure, $N_{Traffic}$=71, N_{Red}=14, $\chi^2(1)$=38.22, p<.001. Green-light feedback motivates maintenance (67% highly motivated). Major themes from qualitative data included (1) Traffic lights are easy to understand and comprehensive/informative, and (2) green-light information is positively reinforcing and increases self-efficacy. Traffic lights presentation was positively correlated with MCLHB-DRR-27 cues to action and self-efficacy.

Discussion/Conclusion
Traffic lights presentation increases patient motivation to reduce dementia risk. There are more cues to action with the amber-light presentation of emerging risks. Green-light information increases self-efficacy. Maximising motivation through information presentation can improve the successful implementation of dementia risk screening and risk reduction in primary care and this can have large impacts on dementia prevalence, healthcare costs, and on caregiver burden.

The relationship between sleep duration and cortical sulcal width in midlife and older adults

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Background
Emerging evidence suggests that poor sleep is associated with worse cognitive and structural brain health, and an increased risk of developing dementia. The present study investigated the influence of sleep duration on the cognition-brain relationship in older adults using sulcal width (SW). The influence of napping, depression likelihood, and genetic risk for dementia was also explored.

Methods
Participants were 137 cognitively normal adults, aged 46-72 from the Prospective Imaging Study of Ageing (PISA). Demographic information, sleep duration, and depressive symptoms were collected via online questionnaires. Cognition was assessed using the Cambridge Brain Systems battery. *APOE* genotype was determined from blood-extracted DNA. Imaging data was acquired using a 3T Siemens PRISMA scanner. SW was extracted using the Morphologist pipeline.

Canonical Partial Least Squares (PLS) were used to obtain latent variables of cognition and SW. ANCOVAs measured the effect of sleep duration categories (7-7.5 hours versus {<7 or ≥8 hours}) on the cognitive and SW components, with sex and age as covariates. Status of depression likelihood was added as a covariate of interest. The effect of napping, and APOE ε4 allele on these same components were measured by ANCOVAs, with sex and age as covariates.

Results
We observed a significant effect of sleep duration on SW ($F(1, 133)=4.17$, $p=0.043$). This effect remained significant ($F(1,132)=4.89$, $p=0.029$) after including depression likelihood as a covariate, which was also significant in the model ($F(1,132)=4.62$, $p=0.034$). A significant interaction between *APOE* ε4status and age ($p=0.050$) on SW was also observed.

Discussion/Conclusion
Results add weight to studies suggesting that not too much or too little sleep is needed to maintain brain health in later life. Depression, another risk factor for dementia, was also associated with poorer brain health. At approximately 60 years of age, the influence of a positive *APOE* ε4 status was associated with increasing age-related brain atrophy.

The test of emotion recognition in social context (TERIC): A novel social cognition test for clinical practice

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Background
Social cognition broadly encompasses the perception, understanding and implementation of social cues. It includes facets such as emotion recognition, mentalizing (theory of mind) and empathy. In certain dementias, such as the behavioural variant of frontotemporal dementia (bvFTD), social cognition is characteristically impaired. Unfortunately, social cognition is not routinely assessed in clinical practice as the established neuropsychological tests for social cognition are cumbersome and unreliable. We developed a novel social cognition test for use in clinical settings that combines both emotion recognition with social context cues (the Test of Emotion Recognition In social Context, TERIC).

Methods
The TERIC was designed to assess the recognition of basic emotions in realistic social situations. The participants were shown an image and asked to identify one of six basic emotions: happiness, sadness, fear, anger, surprise, and disgust. Alternatively, they could answer 'neutral' for no emotion. The TERIC was also designed to be a user friendly, electronic, and quick test of social cognition that can be used in clinical practice. Performance in bvFTD and controls were compared to the Ekman's faces test.

Results
Controls showed similar performance on both the TERIC and Ekman's faces task. Participants with bvFTD however, scored much worse on the TERIC compared to the Ekman's faces task. The TERIC was quicker to administer than the Ekman's faces task for both controls and participants with bvFTD.

Discussion/Conclusion
Though social cognition is thought to be characteristically impaired in bvFTD, valid tests for use in routine clinical practice are lacking. The TERIC is a quick electronic test with early experience suggesting it is more sensitive to impairments in social cognition than traditional tests, such as the Ekman's faces task.

Update on the current state of speech and language testing in Alzheimer's disease (AD)

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Screening and disease monitoring are two core challenges of disease management in AD. Digital speech and language features have shown promise as clinical outcomes in related disorders. We reviewed how speech digital markers are currently used in AD, focusing on how behaviours are connected to underlying disease pathology.

The rate of cognitive decline can be predicted by poor performance on language tests. The capacity of current language tests to distinguish between those with mild cognitive impairment (MCI) and healthy controls is limited. In some cases, disease progression can only be detected when significant changes in severity occur. Poor standardisation and limited clinical data are currently restricting communication outcomes uptake in clinical trials. The potential advantages of speech analytics and mobile health technology lie in their cost-effectiveness, accessibility (non-invasive), and automated analytical protocols. They have the capacity to improve assessment procedures, enhance screening and provide meaningful outcomes in clinical settings.

High-dimensional data can be collected by automatically and objectively analysing speech. Developments in machine learning, signal processing and natural language processing techniques will further optimise outcomes.

Validating ASHS-T1 automated entorhinal and transentorhinal cortical segmentation in Alzheimer's disease

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Background
Entorhinal and transentorhinal cortical volumes are reduced early in the Alzheimer's disease (AD) process and may therefore be potential biomarkers to aid early detection. To measure entorhinal and transentorhinal cortical volumes, manual segmentation is generally regarded to be the "gold standard", but it is laborious and time-consuming. Automated methods to segment the entorhinal and transentorhinal cortices are available, but these regions are challenging to segment due to anatomical complexities. Recently, an automated segmentation method, Automatic Segmentation of Hippocampal Subfields (ASHS-T1), was developed that has been suggested to overcome the issues associated with previous automated segmentation methods. The current study aimed to validate entorhinal and transentorhinal cortical volumes measured by ASHS-T1.

Methods
Thirty-four healthy controls (HC), 37 individuals with amnestic mild cognitive impairment (aMCI), and 29 individuals with dementia due to AD were drawn from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Entorhinal and transentorhinal cortical volumes were measured using ASHS-T1, manual segmentation, and a widely used automated segmentation tool, FreeSurfer. Mean differences, intraclass correlations, and Bland–Altman plots were used to compare the volumes between the three methods.

Results
Entorhinal and transentorhinal cortical volumes measured by ASHS-T1 tended to be significantly smaller than those measured by manual segmentation and FreeSurfer. Moderate correspondence was observed between the ASHS-T1 and manual segmentation volumes, and low to no correspondence was observed between the ASHS-T1 and FreeSurfer volumes. ASHS-T1 was sensitive to group differences in both entorhinal and transentorhinal cortical volumes, whereas FreeSurfer was only able to reliably detect group differences in entorhinal cortex volume.

Discussion/Conclusion
Despite suboptimal concordance between ASHS-T1 and manual segmentation volumes, ASHS-T1 was nonetheless sensitive to AD-related volume loss in the entorhinal and transentorhinal cortices. The findings of the current study suggest that ASHS-T1 has potential utility for measuring entorhinal and transentorhinal cortical volume in individuals with AD.

Validation of a digit symbol substitution test for use in supervised and unsupervised assessment in mild Alzheimer's disease

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Introduction:
The Digit-Symbol-Substitution Test (DSST) is used widely in neuropsychological investigations of Alzheimer's Disease (AD). A computerised version of this paradigm, the DSST-Meds, utilises medicine-date pairings and has been developed for administration in both supervised and unsupervised environments. This study determined the utility and validity of the DSST-Meds for measuring cognitive dysfunction in early AD.

Method:
Performance on the DSST-Meds was compared to performance on the WAIS Coding test, and a computerized digit symbol coding test (DSST-Symbols). The first study compared supervised performance on the three DSSTs versions in cognitively unimpaired (CU) adults (n = 104). The second compared supervised DSST performance between CU (n = 60) and mild-symptomatic AD (mild-AD, n = 79) groups. The third study compared performance on the DSST-Meds between unsupervised (n = 621) and supervised settings.

Results:
In Study 1, DSST-Meds accuracy showed high correlations with the DSST-Symbols accuracy (r = 0.81) and WAIS-Coding accuracy (r = 0.68). In Study 2, when compared to CU adults, the mild-AD group showed lower accuracy on all three DSSTs (Cohen's d ranging between 1.39 and 2.56) and DSST-Meds accuracy correlated moderately with Mini-Mental State Examination scores (r = 0.44, p < .001). Study 3 observed no difference in DSST-meds accuracy between supervised and unsupervised administrations.

Conclusion:
The DSST-Meds showed good construct and criterion validity when used in both supervised and unsupervised contexts and provides a strong foundation to investigate the utility of the DSST in groups with low familiarity to neuropsychological assessment.

Validation of the CogDrisk instrument as predictive of dementia in four general community-dwelling populations

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Background
Lack of external validation of dementia risk tools is a major limitation for generalizability and translatability of prediction scores in clinical practice and research. Using four independent cohort studies, we aimed to validate a new dementia prediction risk tool called CogDrisk and a version for predicting Alzheimer's disease (AD) - CogDrisk-AD.

Methods
Four cohort studies were identified that included clinical diagnosis of dementia and the majority of risk factors required for computing CogDrisk scores. These studies included Swedish National Study on Aging and Care in Kungsholmen (SNACK), the Cardiovascular Health and Cognition Study (CHS-CS), the Health and Retirement Study – Aging Demographics and Memory Study (HRS-ADAMS) and the Rush Memory and Aging Project (MAP). Participants who were free of dementia at baseline were included in the analysis. The component variables in the CogDrisk tool were entered into analyses as predictors of dementia diagnosis, including self-reported demographics, medical risk factors and lifestyle habits. Risk scores for Any Dementia and AD were computed and the area under the curve (AUC) was assessed. To examine only modifiable risk factors for dementia, the CogDrisk tool was also tested by excluding age and sex estimates from the model.

Results
The performance of the tool varied between studies. The overall AUC and 95% CI for predicting dementia was 0.77 (0.57, 0.897) for the SNACK study, 0.76 (0.70, 0.83) for the HRS-ADAMS study, 0.70 (0.67,0.72) for the CHS-CS study, and 0.66 (0.62,0.70) for MAP. Removing the age and sex estimates reduced accuracy with the new AUCs ranging from 0·61 (0.56, 0.65) to 0·54 (0.49, 0.58).

Discussion/Conclusion
CogDrisk and CogDrisk-AD are valid tools for assessing individualized risk factors for dementia and AD in various population settings. The new tools include a wider range of modifiable risk factors based on the most recent evidence base compared to existing tools.

A dementia behaviour support care program for aged care homes in England during COVID-19: Model of care, feasibility and acceptability

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Background
Behaviours and psychological symptoms of dementia (BPSD) are prevalent, complex, and typically distressing for aged care home (ACH) residents and staff and are frequently associated with poor health and care outcomes. The COVID-19 pandemic has placed additional and significant stress on residents living with dementia and their caregivers in ACHs. The HammondCare Dementia Support (HCDS) is a new telecare program that provides psychoeducational support to ACH staff caring for people living with BPSD in England during COVID-19. This study aims to describe the HCDS's model of care and evaluate its feasibility and acceptability in the context of the pandemic.

Methods
A six-month pilot study of the program was conducted between 1 June – 15 December 2020. Feasibility was assessed using the program activity data, whereas acceptability was captured via feedback surveys completed by ACH staff (i.e., HCDS users).

Results
A total of 82 referrals were received during the pilot. Of whom, 63 residents (Mean age: 85 years, 70% female) from 39 ACHs were completely supported. Alzheimer's disease was the most common diagnosis (30%) among referrals. Delirium (32%) and pain (29%) were the primary causes of BPSD. During the pilot, HCDS consultants recommended a total of 676 interventions and provided approximately 263 resources. User survey (n = 17) indicated positive outcomes including BPSD reduction (71%) and reduction in stress levels linked to BPSD (65%). Most respondents (82%) felt confident to use HCDS advice and resources for other residents with 71% reporting that the HCDS recommended actions were fully implemented. All respondents (100%) reported that they will likely use the HCDS service again.

Discussion/Conclusion
The study demonstrated the feasibility and acceptability of the HCDS program during the pandemic. The findings will inform further refinement and future roll-out of the HCDS program in other contexts and settings.

A national survey on current cognitive intervention practice, training and service needs in Australian memory clinics

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Background
There is good evidence that cognitive interventions (CIs) benefit older adults, including those with mild cognitive impairment (MCI) or dementia. Despite this, there remains a research-to-practice gap where these interventions are not readily available in clinical practice. Appropriate training of clinicians in the delivery of CIs is critical to their translation into routine practice. However, we do not have a clear understanding of the preferences and unmet needs for CIs in the memory clinic setting. This work will describe the results of a multi-stakeholder survey which informed the methodology of a pilot/feasibility implementation study rolling out CIs for older adults with MCI in the Australian Dementia Network (ADNeT) of Memory Clinics.

Methods
The ADNeT Cognitive Intervention Working Party is tasked with bridging the evidence-to practice gap in Australian memory clinics. We conducted a national, online survey to canvas the current practice, training, and service needs of memory clinic neuropsychologists and neuropsychology trainees as they relate to CIs.

Results
Clinicians and trainees believe it is very/extremely important to offer CIs as part of routine practice. 32% of clinicians did not receive training in CIs during their degree and 54% had not received training specific to older adults. 69% of trainees believe their degree should include more training in CIs. 63% of clinicians would like to be doing more CI in their clinical work, with lack of time, resources, funding, and training identified as the key barriers.

Discussion/Conclusion
This is the first study to canvas the specific needs and priorities of memory clinic neuropsychologists and neuropsychology trainees as they relate to CIs for older people. These findings informed the methodology of our larger feasibility implementation trial of clinician training and CI rollout within memory clinics around Australia.

Active twelve-week multicomponent intervention for people with dementia and their carers: Findings from the pilot study

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Background
Considering the challenges in accessing appropriate and timely post-diagnostic dementia care, more evidence is needed to determine if intensive, multicomponent interventions for people with dementia and their carers are effective.

Methods
The Sustainable Personalised Interventions for Cognition, Care, and Engagement (SPICE) Program is an active twelve-week dyadic intervention currently being evaluated at the University of Canberra Hospital. SPICE involves in-person cognitive stimulation therapy, carer support and capacity building, and physical activity twice weekly in small groups. Dyads also receive the Care of People with dementia in their Environments (COPE) program and dietary assessment and advice. The present study examines the program's feasibility, acceptability, and effectiveness. Four groups are planned using a waiting-list design. Here we report preliminary findings from the first intervention and waiting list groups and perspectives of clinicians on implementing a new service. Validated pre- and post-intervention outcome measures for participants included quality of life, neuropsychiatric symptoms, and cognitive and physical function. Qualitative interviews with participants and clinicians were thematically analysed.

Results
The first people with dementia and carers to complete the SPICE program reported high acceptance and satisfaction with all program components. Attendance to the in-person activities was 94% for people with dementia and 92% for carers, 100% for the COPE program, and 94% for the dietary appointments. Quantitative outcome measures suggest benefits to the first group, while the waiting-list group outcomes remained similar over twelve weeks. People with dementia, carers, and clinicians reported a range of benefits, including social engagement, satisfaction from physical activity, and a range of strategies for carers to implement immediately and in the future.

Conclusion
The new combination of evidence-based interventions was feasible and considered valuable. However, final results, due in January 2024, are required to confirm these findings and support a longer-term trial.

Advances in human mesenchymal stem cell therapy research against Alzheimer's disease

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Background
In 2021, over 400,000 Australians were affected by Alzheimer's disease (AD). The genetic factors and expression changes contributing to neurodegeneration and disease-modifying therapies remain elusive. Their relative ease of isolation and extensive *in vitro* expansive potential make human mesenchymal stem cells (hMSCs) ideal therapeutic candidates for AD research. Heparan sulfate proteoglycans (HSPGs) are a family of macromolecules, decorated with glycosaminoglycan (GAG) chains that facilitate interactions with protein families and ligands. The transmembrane syndecans (SDCs) and glycosylphosphatidylinositol anchored glypicans (GPCs) are of interest due to their role in mediating neurogenesis.

Methods
The formation of hMSC-induced neurospheres (hMSC-INs) is an essential preliminary step in neurogenesis from hMSCs. Comparisons between established induction media and normal growth media have been conducted to determine the optimal environment for hMSC-IN formation and proliferation. Doses of heparin, a highly sulfated analogue of heparan sulfate that increases cellular proliferation, was compared in hMSC-IN formation, in treated (5µg/mL and 10µg/mL) and untreated cultures. Cell proliferation and viability was assessed using FDA/PI (live/dead) staining to determine whether the inclusion of heparin stimulated proliferation in hMSC-INs. The impact of media composition on hMSCs when differentiated into neurons, astrocytes and oligodendrocytes continue to be examined via gene expression analysis, immunocytochemistry, transcriptome and methylation analysis.

Results
Our findings demonstrate that hMSC-INs can be formed in growth media both with and without exogenous heparin treatment. Preliminary data also suggests that hMSC-INs may continue to proliferate *in vitro*. Work is under way to more fully elucidate the factors mediating hMSC-IN proliferation and the role of HSPGs in this process to determine their potential application in AD treatments.

Discussion/Conclusion
The proliferative capacity of hMSC-INs would reduce required cell numbers for neurogenesis from hMSCs, improving efficiency of stem cell therapies against neurodegenerative diseases. Elucidating the functions of HSPGs in neurogenesis will refine their potential in treatments of AD.

Barriers and facilitators to the delivery of CBT interventions to people with mild cognitive impairment and dementia: Technology assisted and non-technology assisted approaches

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Background
It is common for people living with mild cognitive impairment (MCI) and dementia to develop anxiety, which can worsen cognitive symptoms such as poor focus and attention. People living with MCI and dementia experiencing repeated anxiety may benefit from psychotherapeutic support such as cognitive behavioural therapy (CBT). However, there is limited guidance on the barriers and facilitators to delivering CBT to people living with MCI and dementia, including the use of telehealth and technology assisted modes of delivery.

Methods
A systematic literature review is currently being conducted following PRISMA guidelines to identify, appraise, and synthesize existing published evidence regarding the barriers and facilitators to the delivery and implementation of CBT interventions for people living with MCI and dementia. The review will assess both technology assisted approaches (telehealth, video sessions, computerised programs) as well as non-technology assisted approaches. Data will be analyzed and reported using formal approaches to narrative synthesis. Findings may be grouped in relation to subgroups such as delivery type, care setting, participant characteristics, specialisation of the care professional or volunteer.

Results
We will report the synthesized findings from the systematic review.

Discussion/Conclusion
The findings will identify barriers and facilitators to the delivery and implementation of CBT interventions for people living with MCI and dementia, which may be of benefit to mental health practitioners. The findings will also inform the development of an implementation plan for an ongoing technology assisted CBT for anxiety program (Tech-CBT) for people living with MCI and dementia consisting of a several created components; a therapist training package, the delivery of tech-assisted therapy sessions, and the My Anxiety web portal providing coordination and management of therapy with a client interface supporting self-managed practice. Early identification of potential barriers and facilitators may assist in the delivery and implementation success of the Tech-CBT program.

Improving implementation: Protocol for a mixed-methods process evaluation of a technology-assisted CBT program for anxiety in people living with mild cognitive impairment and dementia

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Background
This protocol describes the planned investigation of the feasibility, usability and acceptability of a technology-assisted and remotely delivered CBT intervention (Tech-CBT) to enhance delivery of anxiety treatment for people living with dementia and mild cognitive impairment (MCI). The Tech-CBT program consists of a several created components; a therapist training package, the delivery of tech-assisted therapy sessions, and the My Anxiety web portal providing coordination and management of therapy with a client interface supporting self-managed practice. A mixed-methods, theory-driven process evaluation will be undertaken in parallel to the Tech-CBT randomized controlled trial (RCT). Process evaluations are crucial to interpreting trial outcomes and understanding contextual factors and causal chains necessary for successful implementation.

Methods
Evaluation is guided by the Medical Research Council and RE-AIM frameworks. We will collect both qualitative and quantitative data including system usage details, a modified Unified Theory of Acceptance and Use of Technology questionnaire, and interviews with trial participants, therapists, supervisors and stakeholders. Interviews will draw from the 'Theoretical Framework of Acceptability', the 'Theoretical Domains Framework', and the 'NASSS' (non-adoption, abandonment, scale-up, spread, sustainability) framework to explore factors influencing the delivery of Tech-CBT, and to understand barriers and facilitators to further scale-up and implementation. Data will be explored using framework analysis and a data-driven inductive thematic analysis approach.

Discussion/Conclusion
The use of a theory-based process evaluation aims to enhance interpretation and generalizability of the RCT findings and reduce the implementation gap of the Tech-CBT program into healthcare services. We will utilize the findings of the process evaluation to develop an implementation plan for future translation within both community and hospital settings. This study will also contribute to the implementation research field by furthering understanding of the conditions necessary for implementation success.

Bridging the implementation gap for reablement and rehabilitation for Australians with dementia: Steps to strategy development and piloting

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Background
Reablement (and/or 'rehabilitation') for people living with dementia are promoted in research and clinical practice guidelines for addressing a variety of functional, physical, cognitive, and behaviour needs. While freely available reablement resources to guide practice exist, these evidence-informed interventions are still not being offered as standard care for Australians with dementia. Effective implementation of this approach within the community aged care sector requires an evidence-informed implementation strategy intentionally informed by the sector.

Methods
Using implementation science, this project involves a series of iterative project activities to design and test an implementation strategy to drive uptake of reablement for people with dementia. A mix of retrospective and prospective approaches will be used over four research phases: (1) current reablement practice will be evaluated via a clinical audit. Focus groups with allied health teams will review audit results to identify targets and goals for changing practice. (2) Clinical audit outcomes will inform a Delphi survey involving a range of stakeholders. Through national consultation, Delphi outcomes will inform a draft implementation strategy. (3) The draft implementation strategy will then be trialed in a hybrid effectiveness-implementation pilot. This trial design will allow for parallel evaluation of the implementation strategy and of the reablement interventions within the real-world context of community aged care. (4) The final stage of the project will be around capacity building for broader implementation within the sector.

Discussion/Conclusion
Outcomes from the project will include a freely available reablement implementation protocol that is nationally relevant to the community aged care sector. By evaluating the reablement program outcomes in parallel with the implementation protocol, outcomes will also include data on real-world effectiveness of reablement programs on a national scale for community-dwelling people with dementia. Ultimate outcomes have potential to change the landscape of Australian dementia care.

Caring for people with dementia from culturally and linguistically diverse backgrounds in residential aged care: A scoping review

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Background
People with dementia from culturally and linguistically diverse (CALD) backgrounds are less likely to access residential aged care (RAC) due to concerns about the facility's inability to provide culturally appropriate care. While previous literature reviews have explored care needs and engagement, little is known about salient aspects of care provision to this population in the RAC context. This review aims to map and synthesise available literature on care provision among people with dementia from CALD backgrounds in RAC and identify literature gaps that could inform future research.

Methods
Literature search was performed in six academic databases. Inclusion criteria were: (1) primary research articles; (2) focused on the care of people with dementia from CALD backgrounds who are living in RACF (or equivalent); (3) related to the experiences of the person with dementia, their family and nursing staff in the provision of care to people from CALD backgrounds. Study quality was assessed using JBI critical appraisal tool. Data was analysed using thematic analysis.

Results
Of the 1159 articles identified, 23 were included. Majority of the articles were qualitative (n=16) and conducted in western countries such as Europe (n=10), Australia (n=5) and the US (n=3). Data analysis led to the development of three themes: (1) maintaining a sense of home; (2) fostering communication and interaction; (3) barriers and facilitators to care provision.

Discussion/Conclusion
Providing culturally appropriate care to people with dementia from CALD backgrounds in RAC entails an environment which enables them to live up to the standards of what "home" means to them, including engagement in meaningful activities and availability of traditional food. A shared language and efficient use of nonverbal communication are essential in addressing the person's needs and preferences. Predominant barriers to care provision relate to language and the facility's resources and capacity to deliver culture specific care.

Co-designing better conversations with smart assistants to support self-managed therapy practice

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Background
Smart Assistants such as Amazon Alexa, Google Home and Apple Siri are now part of everyday life for many people. These devices have been recognised as having potential to improve the daily lives of many people including people living with dementia. However, current conversational interfaces do not always meet the unique needs and preferences of people living with dementia resulting in reduced acceptance. In this study, we formed a team of people to codesign better conversations with smart assistants for individuals living with dementia by involving them in the codesign process. Our objective was to create a conversational interface that supported people's practice of cognitive behavioural therapy techniques as part of a technology supported therapy program for anxiety (TechCBT).

Methods
Our codesign team consisted of people (*N*=15) with expertise in: the experience of living with dementia (including care partners), technology design, allied health fields, and conversation design. Most codesigners had expertise in multiple areas. The codesign team adopted an iterative design process that included methods such as design walkthroughs and wizard-of-oz prototyping. From this process the codesign team then identified key design considerations that were followed in the development of an Alexa Voice App for TechCBT.

Results
Key design considerations included (a) improving usability through additional scaffolding in multiple forms to support the conversation rather than requiring the person to memorise these commands, (b) providing additional information to support error recovery, and (c) using device screens effectively to support the conversation.

Discussion/Conclusion
Our results will contribute to the development of more inclusive technology for individuals living with dementia, improving their quality of life and providing them with more opportunities to live independently. We speculate that these results also have broader application to the design of conversations between people and smart assistants.

Co-designing novel resources to provide medication management guidance for people living with dementia and their carers during hospitalisation

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Background
During a hospital admission and at discharge, people with dementia are more likely to experience medication-related harm than people without dementia. However, they often receive inadequate medication management guidance during healthcare transitions. To address this gap, we co-designed medication management resources for people with dementia admitted to hospital and their carers.

Methods
This mixed-methods study applying the principles of co-design involved five stages: i) generating resource topics by content analysing a scoping review and a previous qualitative study; ii) developing the first version of the resources; iii) obtaining input from dementia expert advisory panels; iv) undertaking focus groups with people with dementia, carers, and healthcare professionals Australia-wide; v) quantitative analysis using validated tools for readability, understandability, actionability, and suitability. Focus groups were recorded and the transcripts were content analysed to explore participants' perceptions of the resources' topics, content, layout, and meeting their needs. The resources were edited during each stage, the graphic design modified, and final copies produced.

Results
Stage one generated six topics including: participating in shared decision-making; identifying common medications that may affect cognition; and describing hospital processes and the role of the carer or person with dementia. The advisory panels recommended for the resources to introduce the topic of informed consent, and define the discharge summary and medications list. In focus groups with carers (n=4) and healthcare professionals (n=3), participants felt the topics generated would be useful and beneficial. They suggested: removing the term "carer" from the title; limiting medical terminology; and providing the resources at hospital admission. The resources were of an adequate reading level, understandable, actionable, and suitable.

Discussion/Conclusion
Using co-design approaches, we identified key content topics that support people with dementia and carers' involvement in medication management decisions during hospitalisation. Further studies will conduct user-testing and formative evaluation of the resources.

Dementia care resource use in the community: baseline data from the homeside study

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Background
Fifty-five million people live with dementia worldwide, accounting for US$1.3 trillion in costs annually, with 40-75% related to informal care. This study aims to investigate the differences in resource use in the care of people living with dementia (PwD) in five countries trialling HOMESIDE, a home-based training for family carers (CG), to implement music interventions that target behavioural and psychological symptoms of dementia.

Methods
A three-arm randomised controlled trial recruitment took place from July 2019 to July 2022 in Australia, Germany, Norway, Poland and the UK. We used the Resource Use in Dementia questionnaire to capture resources used in the last month before the baseline assessment.

Results
We recruited 432 dyads, formed of PwD (age 76.8 ±8.9 years, 54.9% male) and CG (age 64±12 years, 81.3% female), which were mainly spouses or partners (63.4%). There was a substantial difference in resource use between countries: 48% of CGs were the only carers for the PwD, except in Poland (25%, p=0.018), which resulted in 59.6% of CGs keeping paid work, compared to 36.1% in total. The time spent supporting daily activities or supervising the PwD accounted for 5.1±6.4 hours/day (p=0.009), although it can be smaller in countries with reportedly accessible social support (3.3±5 hours/day in Norway). The burden of care may affect CG's health: 52% had at least one medical appointment (p<0.001), and PwD 69.4% (p<0.001). Hospital admission and emergency care were more prevalent in Australia and Norway.

Discussion/Conclusion
A first glimpse at the resource use in dementia features the impact of informal care and health resource use for both PwD and CGs, even in the early stages of the dementia journey. Differences between countries may be related to health and social systems or caregivers' characteristics, which should be investigated to optimise dementia care and reduce the social burden.

Dementia friends unite! An education program for communities and workforces to better support people with dementia

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Background
Dementia is highly stigmatised in culturally and linguistically diverse (CALD) communities, like South Western Sydney (SWS) where 54 % of households speak a language other than English. SWS is also expected to have the highest increase in NSW dementia cases by 2050. Our ongoing work with English, Arabic, Vietnamese, and Chinese communities in SWS identified evidence-to-practice gaps regarding dementia care practices. This project will address these by co-creating and pilot-testing a dementia education initiative to increase knowledge about dementia-enabling social and environmental practices.

Methods
The education program will be facilitated through the SWS Dementia Network, comprising councils, multicultural service providers, and people with dementia and their caregivers. Co-creation workshops with Network members will determine the program's delivery, structure, and content related to dementia care practices. Once 70% consensus on content is reached, program materials in English will be translated into Arabic, Vietnamese, Mandarin, Cantonese, and Greek. Trained bilingual facilitators will deliver the program to families and community care workers. Using the RE-AIM framework, mixed methods will evaluate the program's impact by its: Reach on participants; Effectiveness on dementia knowledge and implementation practices, Adoption by stakeholders; Implementation fidelity; and Maintenance costs.

Results
Co-creation of program materials is expected from April to June with delivery anticipated from September to November in 2023. A total of 126 participants across the six languages are expected. We hypothesise that this program will increase knowledge about dementia and lead to the adoption of practices that encourage social inclusion and the enablement for people living with dementia.

Discussion/Conclusion
The stakeholder-driven education program was designed to address the unmet needs of a multicultural community experiencing stigma and inequitable access to dementia information. Our model of multisectoral collaboration and co-creation will ensure meaningful implementation and, if successful, the initiative's long-term sustainability in the community, service delivery and policies.

Development of a digital training package to upskill psychologists in the delivery of a technology-assisted CBT program (TECH-CBT) to target anxiety in people with mild cognitive impairment and dementia

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Background
Mental health disorders (e.g., anxiety) are highly prevalent in individuals with dementia, which makes the work of mental health clinicians critical for managing disease progression. Cognitive behavioral therapy (CBT) is the first-line treatment for anxiety in older adults and there is growing evidence that CBT can be successfully employed in people with cognitive impairment with appropriate adaptions. Although many mental health clinicians are trained in anxiety and CBT, there is a lack of adequate knowledge and training about dementia and how to tailor CBT to suit the needs of this population. Therefore, the current study aimed to develop a digital package to train mental health clinicians in the delivery of a technology-assisted CBT program (Tech-CBT) to target anxiety in people with mild cognitive impairment (MCI) and dementia.

Methods
The Tech-CBT training package includes (1) online pre-recorded lectures and accompanying written guides developed by the authors who have extensive experience delivering CBT and working with people with cognitive impairment; (2) links to online dementia training modules about biological, behavioural and psychological symptoms, communication strategies and the lived experience of dementia, developed by external service providers (3); and a question-and-answer session after completing the training to reinforce new learning. Postgraduate psychology trainees will undergo the training and a pre-post mixed methods design will be used to examine the acceptability of the Tech-CBT training package, utilizing the Theoretical Framework of Acceptability (TFA), Confidence in Dementia Scale (CODE) and Dementia Knowledge Assessment Scale (DKAS).

Results
We will report the initial findings from the Tech-CBT training package evaluation.

Discussion/Conclusion
A therapist training package was developed to upskill mental health clinicians in dementia care and the delivery of a technology-assisted CBT program for anxiety in people with MCI and dementia. The findings of this study will inform modifications to the training package for future implementation.

Exploring experiences of the routine eye examination for people living with dementia

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Background
People living with dementia are less likely to have regular eye checks. Here, we aim to explore the routine eye examination experience of people living with dementia, from the perspectives of people living with dementia and their family/carers. Understanding these experiences may help break down barriers to accessing eyecare for people living with dementia.

Methods
We conducted semi-structured interviews with 10 people living with dementia and 14 carers, using a topic guide piloted with a Dementia Advocate. Thematic analysis was undertaken on transcripts by two authors: the interviewer (JC), and an eyecare expert (MP) who was not involved in the interviews.

Results
Our preliminary analysis, which will be refined with Dementia Advocates supporting the study, reveals the following: People living with dementia enjoy many activities – often visual – day to day. Of the variety of eyecare experiences reported, experiences tended to be positive if there was an established relationship with the optometrist and a good practice environment, while negative experiences tended to arise if there were communication issues, no carer involvement opportunities, lack of patience and no adaptation of testing to accommodate dementia. The eye test was viewed as a simple process causing few issues in early stage dementia, that did not necessitate informing the optometrist of the diagnosis, but could result in anxiety and agitation in more advanced dementia, which could be helped with simple adaptations.

Discussion/Conclusion
Ability to see well matters to people living with dementia, so they can continue visual activities they enjoy, and navigate their environment with confidence. Carers want to be involved in the eye examination, so they can provide support and information. Adaptations made to the routine eye examination to accommodate different levels of dementia could improve the overall experience, such as longer appointments to allow breaks, removing distractions, and visual demonstration of tests.

Feasibility and acceptability of a tailored telehealth counselling program to support family carers of people with dementia prior to residential care placement. qualitative findings from a pilot study

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Background
Decisions surrounding residential care placement of people living with dementia can be stressful and distressing, however, providing access to information and support may help carers cope better. This pilot study aimed to test the feasibility, acceptability, and potential benefits of providing a tailored, individual counselling program developed in the United States (the Residential Care Transition Module or RCTM) to Australian family carers at an early stage in the process, i.e., following ACAT approval for residential care.

Methods
A pilot randomized controlled trial of the RCTM program (six, one hour video-call counselling sessions over 12 weeks) versus a comparison group that received a single check-in call. Both groups received help-sheets about residential care, coping with placement, and managing feelings. We report preliminary findings from semi-structured exit interviews held with participants from both groups (n=9/18 to date), analyzed using the 'framework' approach and informed by the Medical Research Council guidance for process evaluation of complex interventions.

Results
Contextual factors: Timing of the RCTM program is important. Sessions provided early in the transition process or at the time of needing respite were preferable. Mechanisms of impact: The program was perceived beneficial in terms of i) a non-judgmental, empathetic and knowledgeable person to discuss issues with, ii) support to allay feelings of guilt and validate feelings, iii) discussion of practical and emotional coping strategies and iv) preparedness for placement going forwards. Implementation: Video-call delivery of sessions was acceptable. Flexibility of sessions is valued. Help-sheets were considered 'nothing new', and often not read or remembered.

Discussion/Conclusion
Delivery of the RCTM program to carers in the pre-placement transition period following ACAT approval and via video-call is perceived to be feasible and acceptable. Participants preferred to speak to a trained counsellor and receive tailored information and advice rather than receive standard written information.

Towards better mental health of people living with dementia in residential aged care: Co-design of the mental health care indicator (MHICARE) tool

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Background
Over half of all people living within Australian residential aged care (RAC) facilities have a diagnosis of dementia. Current mental health practices for residents with dementia are often poor, with an increased risk of psychotropic prescribing for agitation and psychosis and use of antidepressants and antipsychotics. There are currently no mechanisms to monitor and promote mental health for people living with dementia in RAC. The aim of this study is to improve current practices and outcomes by co-designing a mental health care indicator performance measurement tool – the MHICare Tool.

Methods
Qualitative co-design and group concept mapping methodology will be used to develop the MHICare Tool. We are currently conducting focus groups and interviews with RAC residents living with dementia (n=6), RAC residents without dementia (n=6), RAC staff (n=6) and family members (n=6) to collect data. In the first round, we identify areas of most concern to participants and how these should be addressed. Thematic analysis will be used to derive common issues that are relevant to the development of the MHICare Tool and to generate 'discrete statements' for group concept mapping. In the second round we ask participants (where possible) to rate each statement on its importance and ease of change, resulting in a visual cluster map and Go-Zone plot utilizing specialist group concept mapping software.

Results
We will report our initial findings from the focus groups and interviews.

Discussion/Conclusion
The findings of the qualitative study will directly inform indicator development for the MHICare Tool and the items for the Delphi survey to be conducted in Stage 2 of the study. The MHICare Tool will be the first benchmarking tool developed for measuring mental health care management and outcomes for people living with dementia in Australian RAC.

Improving carers' capacity to provide behaviour support in dementia

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Background
Changed behaviours are common features of dementia. These changes significantly impact functional capacity and overall quality of life. Pharmacological interventions are often ineffective and accompanied by side-effects. Positive Behaviour Support (PBS) has been recommended as a viable non-pharmacological intervention for managing changed behaviours in dementia. We evaluated the utility of a PBS education program in supporting family carers to provide behaviour support in dementia.

Methods
Twenty-three family carers of individuals with dementia completed a five-week PBS education program via telehealth. Five 2-hour weekly sessions covered a dementia-specific PBS program (e.g., behaviour analysis, preventative strategies, crisis-aversion, etc), and carers learned generalisable behaviour support strategies. Carers completed a post-intervention feedback questionnaire immediately after the program, that comprised 22 open-ended questions relating to (1) the helpfulness of the program in developing behaviour support strategies, (2) the impact of the education program on their confidence in providing behaviour support, and (3) the telehealth format and recommendations for improvement.

Results
Nineteen out of 23 (82%) participants completed the questionnaire. Seventeen (89%) reported a positive impact of the PBS education program on how they understood and managed the changed behaviour(s). Key themes that emerged included: (i) change in carer's responses to difficult behavioural situations, (ii) increased carer confidence in managing challenging behaviours, and (iii) report of improvement in the person with dementia's behaviour (e.g., less aggressive) and mood (e.g., happier) post education.

Discussion/Conclusion
These results indicate that a 5-week dementia PBS education program results in improved family carers knowledge of and confidence in providing behaviour support. Moreover, our study demonstrates that telehealth is a viable option to administer PBS programs, increasing accessibility to carers from rural communities. Future research is needed to further evaluate the format of the education program based on participant feedback (e.g., longer PBS education programs with one-hour sessions).

Laying the foundations for an inclusive dementia-friendly community by engaging with culturally and linguistically diverse people with dementia and their carers

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Background
Dementia-friendly communities (DFCs) can reduce stigma and the gaps in health and social outcomes for people impacted by dementia. However, culturally and linguistically diverse (CALD) people have typically been excluded or underrepresented from DFC design processes, limiting impact and inclusiveness. The aim of this study was to clarify the factors that affect community engagement for CALD people impacted by dementia and ascertain their suggestions to co create a prospective DFC.

Methods
Using the multicultural city of Canterbury-Bankstown as a case study, 17 semi-structured interviews were conducted with people with dementia, their carers, and former carers from English (*n*=7), Arabic (*n*=5), and Vietnamese-speaking (*n*=5) backgrounds. Bilingual researchers facilitated in-language interviews that explored factors impacting community engagement and considerations for design and implementation of a culturally inclusive DFC. Interviews were transcribed in English, coded, and thematically analysed using an inductive approach.

Results
The most common themes that impacted community engagement for all groups were: positive and negative perceptions of dementia in the community; carers undervaluing their needs and wellbeing; level of carer advocacy, as well as environmental and transport barriers. Specific to the Arabic and Vietnamese-speaking groups, community engagement was impacted by: care provided by family; language barriers; and levels of cultural assimilation. Suggestions for a DFC included: improving transport and environmental accessibility; establishing inclusive dementia support groups and social activities; increasing the accessibility of homecare; having dementia-friendly shopping centers; and providing in-language dementia education to the community.

Discussion
Factors that impacted community engagement were aligned with the primary goals of a typical DFC intervention: reducing stigma; increasing education; creating a more accessible environment; and supporting services to be more dementia-friendly. However, there was a need for intervention strategies to be tailored to multicultural communities by offering more in-language services and accessible information, inclusive social groups that incorporate cultural awareness, and caregiver supports. Findings informed the Canterbury-Bankstown Dementia Alliance's DFC initiatives and action plan, as well as the local council's community planning efforts.

Match - music attuned technology - care via eHealth: a proof-of-concept study trialling a music-therapy informed mobile application for caregivers of people living with dementia

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Background
The therapeutic benefits of music are increasingly recognised for people living with dementia. However, music is a complex stimulus, and music-based support strategies can be challenging for carers to implement effectively. MATCH (Music Attuned Technology – Care via eHealth) is a project funded by the Medical Research Future Fund that aims to develop a mobile application that trains and assists carers to use music-based strategies to support people living with dementia. MATCH has been developed based on years of music therapy research, and in conjunction with service users. This paper presents the findings of the first trial of the MATCH-prototype app.

Methods
16 dyads (familial caregivers and people living with dementia) residing at home in Australia trialled the MATCH prototype app over an 8-week period. Caregivers completed online surveys relating to mood (NPIQ and CMAI), and assessed their understanding of music and dementia before and after the trial period. Participants also completed qualitative interviews about their experiences using the MATCH app throughout the study.

Results
Data collection is still underway. Preliminary analysis of qualitative results suggests that participants feel that using MATCH strategies has benefits including improved mood (for both caregivers and participants with dementia), reduced agitation (participants with dementia) and increased meaningful moments. Participants identified barriers that included technical challenges when using the app, and a lack of specificity of case examples.

Results will be finalised and shared in our presentation.

Discussion/Conclusion
The MATCH App prototype has been positively received by participants, and several recommendations for the future development of the app have been made to streamline the training and music elements of the app, and to enhance training content to increase accessibility and inclusivity. We will share insights relating to future uses of the app, including translation of the content for use in residential aged care.

Neuropsychological assessment of financial skills in dementia

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Background
The capacity to handle money and personal finances is crucial for living independently. Cognitive decline can lead to financial mismanagement (e.g., forgetting to pay bills, overspending) and exploitation (e.g., falling for financial scams). While greater susceptibility to financial mismanagement and exploitation is commonly reported by carers of people with dementia, objective neuropsychological measures of these financial skills are scarce. It is also unclear whether profiles of change in financial skills vary across different stages and subtypes of dementia.

Methods
A normative sample of 112 healthy controls and individuals with mild cognitive impairment (MCI; n=16), Alzheimer's disease (AD; n=7) or behavioural-variant frontotemporal dementia (bvFTD; n=18) completed a novel neuropsychological Test of Financial Skills (TOFS), which assessed performance across three key areas: everyday financial tasks, susceptibility to financial scams and financial goal planning. For all patients and controls, measures of dementia severity (Clinical Dementia Rating Scale) and general cognition (Addenbrooke's Cognitive Examination, 3rd Ed.) were also collected.

Results
Relative to controls, AD and bvFTD patients showed lower overall performance on the TOFS, whereas MCI patients did not differ significantly from controls. While AD and bvFTD patients showed similar levels of impairment on everyday financial tasks and financial goal planning, bvFTD patients performed significantly worse on the financial scams subtest. Across all participants, lower TOFS performance was associated with greater dementia severity and cognitive impairment.

Discussion/Conclusion
Our results are consistent with previous studies of carer-reported changes in financial mismanagement and exploitation in people with dementia. Notably, we found important differences in the areas of financial skills impacted by different stages and subtypes of dementia. These findings provide novel insights into the different factors that contribute to deficits in financial skills in people with dementia, highlight the importance of objective neuropsychological assessments in this area, and open avenues for targeted financial support strategies.

Palliative care services within national dementia behaviour support programs in Australia: A pilot study

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Background
Behaviours and psychological symptoms of dementia (BPSD), such as agitation, are a common experience for people living with dementia. Terminal agitation typically occurs in the last few days of life, and while this can occur for anyone with a terminal illness, the signs and symptoms can be similar, and difficult to differentiate, from BPSD.

Misattributing signs of terminal agitation as BPSD can delay or prevent the implementation of palliative care services. Dementia Support Australia (DSA), the free provider of BPSD support in Australia, has recognised the need for specialised palliative support for people referred into their programs who are suspected of experiencing terminal agitation. This study aims to describe a pilot program that focused on enhancing palliative care in the provision of DSA.

Methods
The "Palliative Care Service Enhancement" program was piloted by DSA between May 2021–May 2022. DSA referrals were eligible for the program if they were assessed as having terminal agitation as identified by a DSA medical specialist or through formal assessment (Supporting and Palliative Care Indicators Tool) and confirmed by a medical practitioner. Eligible referrals were supported by specialist palliative consultants who provided tailored support, advice, brokerage, and liaison with external specialists. Symptom severity was assessed with a modified Symptom Assessment Scale (SAS).

Results
Seventy-eight DSA referrals (M_{age} 85 years, 49% female) were found eligible for the pilot. On average, referrals were supported for 71 days. The top five contributing factors for referrals were: pain (85%), terminal illness (55%), delirium (27%), carer approach (16%) and mood disorders (14%). Overall, there was a reduction of 11 points in the total SAS score at case closure.

Discussion/Conclusion
This study demonstrates the benefits of using palliative care services within national dementia behaviour support programs. The findings flag the urgent need for such services within the context of dementia.

Physiotherapist and physiotherapy student knowledge, confidence, attitudes, and beliefs about providing care for people with dementia: A mixed-methods systematic review

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Background
Clinical care for people with dementia as a primary diagnosis, or as a co-morbidity, can be complex. Physiotherapists play a key role in the care of people living with dementia in multiple settings. The aim of this systematic review was to understand the attitudes, beliefs, knowledge and confidence of physiotherapists and physiotherapy students when working with people living with dementia.

Methods
This was a mixed-methods systematic review that included qualitative and quantitative studies. Participants were physiotherapists working in any clinical specialty (e.g. gerontology, orthopaedic, neurological), and physiotherapy students who had completed at least 5 weeks of clinical placement. The phenomena of interest were attitudes, beliefs, knowledge and confidence when working with people with dementia in any setting. Eleven databases were searched. Data synthesis followed a convergent integrated approach according to Joanna Briggs Institute methodology for mixed methods systematic reviews.

Results
Fifteen studies were included (9 quantitative and 6 qualitative studies). Seven key themes evolved. Five related to the belief that (1) working with people with dementia is complex and challenging; (2) opportunities for education in dementia care are lacking; (3) working with people with dementia is a specialized area of practice; (4) there are unsupportive systems for working with people with dementia; and (5) people with dementia deserve rehabilitation, but their potential to improve is less certain. One theme related to knowledge (lack of knowledge in some areas of dementia care), and one theme related to confidence (lack of confidence in working with people with dementia).

Discussion/Conclusion
Physiotherapists and physiotherapy students have low levels of knowledge and confidence in areas including cognition, communication and management of behavioural symptoms. Given that higher levels of knowledge and confidence may be associated with more positive attitudes and beliefs, dementia education needs of physiotherapists at all levels needs to be addressed.

Physiotherapy students are underprepared to work with people living with dementia: A qualitative study

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Background
Dementia is a major cause of disability, and physiotherapists play a vital role in the care of people with this condition. Entry-to-professional practice physiotherapy students have been found to be 'somewhat confident' in working with this population, however comprehensive data about their practice experiences, their preparedness to care for people living with dementia and any educational gaps have not been previously reported. The aims of this study were to 1) determine physiotherapy students' experiences in caring for people who have dementia. 2) determine how prepared students were to work with people who have dementia upon graduation and 3) determine if there any areas where students require further education regarding dementia, and how this would be provided.

Methods
This was a qualitative study using an interpretive description approach. Participants were 17 physiotherapy students from entry-to-professional practice education programs in three Victorian universities, in their final year of study, having completed at least 15 weeks of clinical placements. Students participated in semi-structured interviews. Thematic analysis was undertaken, with themes/subthemes derived and a qualitative thematic framework generated.

Results
The overarching theme was that students' experience of providing care for people with dementia was overwhelming. The three sub-themes were: 1) students experience significant challenges when working with people with dementia, 2) students experience a range of emotions when working with people with dementia, and 3) the quality of dementia learning experiences during entry-to-professional practice training was perceived by students as mostly inadequate. Students described the importance of supervisors during clinical placements, and suggested incorporating 'real-life' scenario classroom training to assist them to learn to manage the challenging symptoms of dementia.

Discussion/Conclusion
Physiotherapy students believe that entry-to-practice dementia education is currently insufficient. These findings have important implications for the future planning and delivery of physiotherapy dementia education.

Views of experienced physiotherapists about excellence in dementia care: A qualitative study

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Background
Physiotherapy interventions can improve mobility and prevent falls in people with dementia. However, physiotherapists have been found to have low knowledge and confidence in working with people with dementia. Excellence in dementia physiotherapy has not been described in the literature, and is important to establish given the findings from the recent Aged Care Royal Commission. It is therefore important to know more about what experienced physiotherapists view as excellence in physiotherapy dementia care. Therefore, the aims of this study were to determine 1) what is excellence in physiotherapy dementia care and 2) how can excellence be achieved.

Methods
This was a qualitative study using an interpretive description approach. Participants were 16 physiotherapists from around Australia considered to be experienced in the field of dementia care. Snowball sampling was utilised from the starting group of physiotherapists practicing in Australia, who were recognised by the National Gerontology Committee of the Australian Physiotherapy Association as experienced experts in dementia care. Physiotherapists participated in semi-structured interviews. Thematic analysis was undertaken, with themes/subthemes derived and a qualitative thematic framework generated.

Results
The four themes (and subthemes) were: 1) engaging the person with dementia (knowing the person, using knowledge to adapt the approach to successfully deliver physiotherapy interventions, optimising the physical environment), 2) collaborative care (working with care partners, working as an interdisciplinary team), 3) development of clinical skills and expertise on the job and 4) advocating for the role of physiotherapy in dementia care.

Discussion/Conclusion
Physiotherapists believe that excellence in dementia care involves being able to effectively engage the person with dementia in therapy, training and supporting care partners, and providing interdisciplinary care. Excellence in care was less about the application of evidence-based practice, but more about providing patient-centred care, achieved mainly through on-the-job learning from both physiotherapy and other health professional peers.

The effectiveness of internet-based psychoeducation programs for caregivers of people living with dementia: a systematic review and meta-analysis

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Background
Caring for people living with dementia at home is physically stressful for caregivers due to the nature of the disease which requires 24 hour supervision, assistance with activities of daily living and management of a treatment regime for chronic condition. Psychoeducation is a major category of non-pharmacological interventions and is widely used to reduce caregivers' stress. The objectives of this systematic review and meta-analysis were to identify the characteristics of internet-based psychoeducational programs for caregivers of people living with dementia and to synthesise program effectiveness.

Methods
Five English databases and four Chinese databases were searched in June 2021 with no time limit applied. A narrative summary was performed to describe the characteristics of studies reviewed. Meta-analysis was applied to synthesise the pooled effects where data were available.

Results
A total of 14352 articles were identified from the database search and 19 were included in the final review. Interventions comprised educational, psychological, and behavioural training relevant to dementia care. Program duration ranged from 3 weeks to 12 months. Meta-analysis of 13 RCTs showed that internet-based psychoeducational programs had a significant effect on reducing caregivers' depressive symptoms (SMD -0.19; 95% CI -0.03 --0.35) and stress (SMD -0.29; 95% CI -0.03 - -0.54). However, these programs did not show an effect on quality of life, anxiety, burden or self-efficacy in caregivers.

Discussion/Conclusion
Online psychoeducational programs can improve some aspects of caregivers' mental health and emotional wellbeing. The effects of programs on self-efficacy, anxiety, burden and quality of life for caregivers remain inconclusive

The impact of staff focused interventions on agitation in people with dementia living in residential aged care: A systematic review

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Background
Agitation is frequently observed in many people living with dementia in residential care. Antipsychotics can be harmful and ineffective; hence staff need to prevent and manage agitation using non-pharmacological strategy. The aim was to assess whether staff-focused interventions are effective at reducing agitation in people with dementia in residential care and to identify intervention characteristics associated with effectiveness.

Methods
We systematically searched MEDLINE, EMBASE, Scopus, Web of Science and CINAHL for papers published 2005 – Oct. 2022. Eligible studies are RCTs on the effectiveness of any intervention delivered to staff of residential care facilities to decrease agitation in people living with dementia. When available, staff outcomes were collected. Risk of bias for each study was assessed with ROB2.0. A narrative synthesis of core intervention characteristics associated with effectiveness was structured around the TIDieR characteristics.

Results
Eighteen articles relating to 17 unique studies testing 25 interventions (n = 7290 residents, 816 staff) were included. Fourteen of the 25 interventions were effective at reducing agitation in people with dementia. Effective interventions were on average shorter and slightly more likely to have an intervention protocol, guideline or manual than ineffective studies. Most interventions utilized a theory relating to resident behaviour. Few interventions were based on theories of staff behaviour change and these were more likely to be effective. Eleven of thirteen studies which collected staff outcomes found a positive effect and were more likely to be effective for residents' agitation as well. Most studies were high risk, and the rest were of some concerns.

Discussion/Conclusion
Staff focused interventions can reduce agitation in people with dementia in residential care. However, studies and results are heterogenous and inconsistent with moderate to high risk of bias. Interventionists should better describe intervention components and have a clear program logic model including context, mechanisms and outcomes.

The ripple effect: Outcomes of a volunteer dementia visiting program in residential aged care homes

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Background
Many residential aged care facility (RACF) staff would like to focus on meeting the person-centred emotional needs of their residents but time and resourcing pressures mean that they are compelled to prioritise task-focused, physical care.
In hospitals, one way of addressing the challenge of improving person-centred care (PCC) has been using volunteer support. The Volunteer Dementia and Delirium Care Program (VDDCP) trained volunteers in PCC techniques to assist older hospital patients with dementia or delirium. This project involved adapting and evaluating the program for RACFs

Methods
Mixed method, non-randomised, controlled intervention study using staff, resident, and family surveys and interviews and file audits.
Two facilities recruited and trained volunteers to provide care (n=36 residents) and two control facilities continued with care as usual (n=36 residents). Comparisons were made on loneliness, depression, food and fluid intake, hospital admissions, falls, physical restraint, psychotropic medication use, and quality of life (QOL).

Results
Preliminary outcome data on loneliness, depression, food/fluid intake, adverse incidents, medication and QOL will be presented. Qualitative data indicate that families and staff believe the program provided key 1:1 person-centred interactions for residents to improve their quality of life. Additionally, there was a ripple effect for staff who felt supported in their care and for families who felt reassured through the extra support provided. Key enablers where the clear structure of the program, including comprehensive training, role delineation, and regular volunteer support meetings. Challenges included ongoing volunteer recruitment, communication between families, volunteers, staff and residents, sustainability of volunteer support, and resident deterioration.

Discussion/Conclusion
The structured dementia volunteer program paved the way for volunteers to provide person-centred 1:1 care which enhanced quality of life for residents and positive flow-on effects to staff and families. Clear guidance on training, key enablers and challenges will assist other RACF to replicate the program.

Using past clinical trial data to guide design of a phase 2B Alzheimer's trial

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Background:
Xanamem® is a brain-penetrant inhibitor of 11β-HSD1, an enzyme highly expressed in the hippocampus which converts intracellular cortisone to cortisol. Data from 3 independent trials has demonstrated promising safety and clinical effects on cognitive and functional measures.
Methods:
The Phase 1b trials, XanaHES (n=42, 20mg) and XanaMIA-DR (n=105, 5 and 10mg), in healthy older adults assessed cognition using a computerised cognitive test battery (CTB); and the Phase 2, XanADu (n=185, 10mg) in patients with mild, probable AD prospectively analysed stored plasma samples (n=72) to explore outcomes in participants with higher (H; >6.74pg/mL) or lower (L; ≤6.74pg/mL) p-tau181. These results have been integrated with state-of-the-art cognitive assessment methods to design a Phase 2b trial in early-stage AD.
Results:
In XanaHES and XanaMIA-DR clinically significant improvements in attention and working memory were observed for Xanamem groups compared to placebo (Cohen's d up to 1.27). In XanADu, clinically significant benefit (Cohen's d of 0.41 was seen on the CDR-SB compared to placebo in the H group, but not in the L group. A positive trend was evident on the executive function component of the Neurologic Test Battery for both H and L groups (Cohen's d=0.26 to 0.34). This data supports use of a customised CTB comprising tests of attention, working memory, and executive function, and use of the CDR-SB alongside enrolment of participants with elevated plasma p-tau181.
Conclusion:
Given the acknowledged lack of success in AD drug development over the past two decades, innovative methods to increase the probability of success of future trials is much needed. Using past clinical trial data, applying contemporary rationale to select validated and treatment-sensitive endpoints, and introducing patient enrichment strategies, has led to the design of a robust Phase 2b study to demonstrate cognitive benefit and positive clinical and functional outcomes in early-stage AD.

We don’t fit: Research into the experience of navigating health and social services and support for children with dementia and their families

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Background
Childhood dementia results from progressive brain damage and is caused by over 70 rare genetic disorders. Most children die before turning 18. Previous research established that families experiencing childhood dementia had challenges interacting with health and social care services, expressing they 'do not fit’. Childhood Dementia Initiative (CDI) partnered with Nous Group to conduct targeted research in order to articulate and represent the ‘lived experience’ of families in their interactions with care and support services and identify the key challenges and opportunities for change.

Methods
A convenience sample invited participation from parents who had subscribed to the CDI Family Advocate database. Semi-structured interviews were conducted via Zoom and facilitated by representatives from Nous. Interviews were recorded with the consent of participants and transcribed using Otter. Key themes were identified using thematic analysis.

Results
Eight parents (8 mothers, n=5 caring; n=3 bereaved) consented to participate in an interview. Six themes emerged: 1. Conditions that cause childhood dementia are rare, difficult to diagnose and diverse, which results in delayed diagnosis, 2. Following diagnosis, there is no defined clinical pathway and parents find it difficult to navigate health services and supports to meet their child’s needs, 3. Parents become project managers for their child’s care, experiencing a high administrative burden, 4. Paediatric palliative care fills a necessary navigation and coordination gap but is not consistently accessed, 5. NDIS packages are an essential support for families, but are universally challenging to access and manage, 6. Following the death of their child, families need targeted, ongoing support.

Discussion/Conclusion
Families living with a child diagnosed with childhood dementia state they ‘do not fit’ in current care and support structures. This research will enable advocacy and systemic change driven by CDI to ensure appropriate, equitable and high-quality care for families affected by childhood dementia.

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