DEMENTIA RESEARCH AT BAKER IDI

Dementia poses a substantial challenge to Australia’s health, aged care and social policy. Based on projections of population ageing and growth, the number of people with dementia will reach almost 400,000 by 20201.

For individuals affected by the disease, the emotional and physical toll can be debilitating. Dementia affects the way the brain functions and can adversely affect memory, speech and the ability to complete everyday tasks, resulting in lower levels of well-being, independence and loss of quality of life.

Although dementia is not an inevitable part of ageing and can affect young people, it is increasingly common with age and primarily affects older people.2 As a consequence, it is expected that the number of Australians with dementia will increase as the population ages.

One of the challenges posed by dementia from a health management perspective is that it is not a single disease. It is a term given to a collection of diseases that are characterised by cognitive impairment. Two of the more common forms of dementia are Alzheimer’s disease and Vascular Dementia.

The causes of dementia are complex and influenced by many factors acting in combination. Prevention of dementia and delay of disease onset and progression depend on an understanding of these determinants3.

Researchers at Baker IDI Heart and Diabetes Institute are committed to understanding the risk factors and tackling the underlying causes of dementia. These include diabetes and other cardiovascular risk factors such as hypertension, stroke, high cholesterol, obesity, acute and chronic ischaemic heart disease, physical inactivity and poor diet.

Diseases of the circulatory system were the most common co-existing condition amongst Australian aged care residents with dementia in 2009-10, followed closely by high blood pressure and stroke4. Together with diabetes, these conditions are closely aligned with the Institute’s research interests and ensure we are well placed to inform the diagnosis, treatment and prevention of risk-factors associated with dementia.

Dementia in Australia:

- In 2011, there were an estimated 298,000 Australians living with dementia - 23,900 of them were under the age of 65.
- The number of people with dementia is projected to triple to around 900,000 by 2050
- Dementia was the third leading cause of death in 2010, recorded as the underlying cause of 9,003 deaths - On average, 25 people died from dementia every day
- Dementia is projected to remain the fourth leading cause of burden of disease and the third leading cause of disability burden until at least 2020


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2. ibid
3. ibid
4. ibid
Investigating the Links Between Glucose Intolerance and Dementia

*Laboratory: Cellular and Molecular Metabolism*
*Laboratory head: Professor Mark Febbraio*

The prevalence of diseases associated with obesity is increasing in Australia at an alarming rate. At the same time, dementia and related diseases such as Alzheimer’s disease (AD) are on the increase. Recent data from the Australian Bureau of Statistics reveals that ischemic heart disease, cerebrovascular disease and Dementia/AD are now the three leading causes of death in Australia. It is important to note that the first two causes of death are complications of type 2 diabetes (T2D) and patients with this disease have a two-to-four fold greater risk of developing these cardiovascular diseases compared with those who do not have T2D. While T2D and AD may appear to be very different in their pathologies, evidence is emerging that links these two diseases.

There is now significant epidemiological data to suggest that T2D is a significant risk factor for all cause dementia and that impaired glucose tolerance has an important role as a risk-factor. Moreover, growing evidence at the molecular level links these diseases via the development of amyloid beta – a protein that forms a plaque between nerve cells in the brain and is thought to contribute to symptoms of Alzheimer’s disease.

Researchers in the Cellular and Molecular Metabolism Laboratory have found that cells known as adipocytes principally responsible for storing energy as fat, secrete amyloid beta in obesity. The group has demonstrated that activation of the heat shock protein, HSP72 can prevent the development of obesity-induced insulin resistance and have hypothesised that this is, in part, via the removal of amyloid beta. The CMML is currently investigating whether activation of HSP72 could be a common treatment to prevent both metabolic disease and Alzheimer’s disease.

Sedentary Behaviour and Brain Health

*Laboratory: Physical Activity*
*Laboratory head: Professor David Dunstan*

Maintaining optimal cognitive function through mid and later-life is vital for independence, quality of life and productivity. Disease-modifying pharmacological approaches for the prevention of cognitive decline currently do not exist; however, there is substantial evidence supporting the use of regular physical activity or exercise training as an effective preventive or therapeutic strategy. While a single bout of exercise can enhance several aspects of cognition in adults, it is not known whether such improvements persist in the face of prolonged sitting periods, characteristic of modern lifestyles.

With this in mind, researchers in the Physical Activity Laboratory are undertaking a study to test whether breaking up prolonged periods of sitting enhances cognition, indices of cerebrovascular function and other markers of ‘brain health’.

The research is unique in that it combines metabolic and vascular physiology and neuropsychological expertise in the first trial to investigate the impacts of interrupting prolonged sitting with moderate-intensity exercise and short, light intensity activity breaks on cognitive function in overweight adults. The study also aims to gather new evidence to inform recommendations on lifestyle changes to improve cognitive function.
**Understanding the Role of High Blood Pressure in Cognitive Decline**

*Laboratories: Human Neurotransmitters and Neurovascular Hypertension & Kidney Disease*

*Laboratory heads: Professor Gavin Lambert & Professor Markus Schlaich*

High blood pressure affects one quarter of the adult population worldwide. Evidence supporting a link between uncontrolled high blood pressure, particularly in mid-life, and subsequent cognitive decline and dementia development has emerged. The evidence shows a lowering of cognitive performance and a more rapid rate of decline in cognition is associated with hypertension. Studies have also shown as much as a five-fold increase in the risk of developing dementia for those who are hypertensive. However, the mechanisms by which hypertension may induce decline in cognitive function remain unclear, and studies at Baker IDI aim to provide greater insight. Researchers in the Institute’s Human Neurotransmitters and Neurovascular Hypertension & Kidney Disease laboratories have investigated the important role of the sympathetic nerves in the kidney as a target for the treatment of resistant-hypertension (where conventional treatment has failed). By targeting these nerves to control blood pressure, researchers have noted an improvement in cognitive performance.

Baker IDI researchers are currently undertaking studies examining the effect of blood pressure reduction on cognitive function. Given that patients with high blood pressure are at increased risk of decline in cognitive function, cognitive impairment and dementia, any treatment that can prevent such detrimental health impacts warrants careful assessment.

**Population-Based Study of the Links Between Alzheimer’s and Dementia**

*Laboratory: Diabetes and Population Health*

*Laboratory head: Dr Dianna Magliano*

While the evidence supporting an association between Alzheimer’s disease and diabetes is growing, progress has been slow because studies to-date have lacked sufficient numbers of participants to detect an effect.

Researchers in the Diabetes and Population Health laboratory at Baker IDI are hoping to address this gap in the data by analysing the National Diabetes Surveillance Scheme - one of the largest databases in the world of people with diabetes - which will be linked to the Australian Pharmaceutical Benefits Scheme. Consisting of nearly 1.2 million individual records, researchers will define those with AD according to medications treatment for AD. Using a cohort design, a group of individuals on the registry who are free of medications for AD and a control group from the PBS (who are also free from AD and diabetes) within the same period will be followed up over time to observe who develops AD.

A similar study using registry data in Finland showed that those with AD were slightly more likely to have a history of diabetes after adjustments for age and sex. Despite the lack of co-variates that is typical of registry-based studies, the contribution of this study to the literature is evident in the high impact factor journal in which it was published. Researchers at Baker IDI hope to emulate and build on this evidence, by demonstrating a statistically significant relationship between the two diseases. In turn, this may inform diabetes management and place even greater emphasis on the importance of glucose control in the treatment of diabetes.
Investigating the Role of Diet in the Prevention of Dementia

Researchers in the Epigenomic Medicine laboratory are interested in dietary interventions using antioxidants that may protect cells from the toxic effects of amyloid beta. It is believed that the accumulation of amyloid beta peptides in the brain form insoluble plaques which are responsible for Alzheimer’s disease. Amyloid beta is highly toxic, inducing progressive atrophy and death of neurons, even in the early stages of disease. Research has shown that activation of a naturally occurring set of genes called Nrf2/ARE can prevent the oxidative toxicity induced by amyloid beta and in doing so, halt the progression of disease.

Baker IDI researchers are investigating the potential of a dietary antioxidant called L-sulforaphane which is found in vegetables such as cauliflower, cabbage and broccoli and is known to be a potent activator of the Nrf2/ARE antioxidant pathway. Researchers have hypothesised that dietary antioxidants may be helpful for people with a family history of dementia or for those with some of the early signs of producing the amyloid beta peptide.

Understanding the Role of Infectious Agents in Cognitive Decline

Baker IDI researchers in the Lipoproteins and Atherosclerosis laboratory, along with collaborators at Melbourne University and Bio 21, have published a 2014 study in the Journal of Biological Chemistry on the interaction of infectious agents called ‘prions’ with cellular cholesterol metabolism. Prions are the cause of the only known transmissible neurodegenerative diseases including Creutzfeldt-Jakob Disease; they affect the structure of the brain, are untreatable and fatal. The study found that one of the key mechanisms of prion-related disease involves changing cellular cholesterol metabolism in a manner remarkably similar to the way other pathogens or infectious agents act. Consequently, it is conceivable that changes to cellular cholesterol metabolism inflicted by infection or by a metabolic disease may facilitate the onset of neurodegenerative disease.

Building on this study, the group plans to investigate how infections may increase risk or even cause neurodegenerative diseases by manipulating cholesterol metabolism at a cellular level. They will also examine whether changes in cholesterol metabolism inflicted by one disease could be a risk factor for other conditions where cholesterol metabolism is involved. The research aims to better understand whether diseases such as obesity, for example, present a risk factor for dementia or whether they have a common causality.
Identifying Cell Signalling Pathways

Laboratory: Diabetes and Dyslipidaemia
Laboratory head: Dr Brian Drew

There is significant evidence that both age-related and familial dementia including Parkinson’s Disease, Alzheimer’s Disease and Huntington’s Disease, is closely associated with a decline in the health and function of mitochondria - structures within cells responsible for producing the cell’s energy. However, the cause of this mitochondrial dysfunction - or ways in which we can prevent or reverse it - remain elusive.

In a healthy cell, mitochondria are continuously degraded and regenerated in a tightly controlled cycle that results in a constant supply of fresh and efficient mitochondria. Although there is a great deal of research about what promotes the production of mitochondria, very little is known about the mechanisms that control the removal of old and damaged mitochondria, and in particular, how this controlled removal feeds back to the cell that it needs to make replacement mitochondria.

The accumulation of damaged mitochondria observed in brain cells of patients with dementia, suggests a failure in the ability to either clear these damaged mitochondria, or a failure in the feedback pathway that promotes the generation of new healthy mitochondria – or both.

Researchers in the Diabetes and Dyslipidaemia laboratory have developed some exciting preliminary data that identifies one of the key proteins involved in the feedback mechanism necessary to regenerate new mitochondria in brain cells following controlled removal of old or damaged mitochondria. Building on this data, the group have identified a previously unidentified pathway in brain cells that may be critical to the regulation of mitochondrial health. They are now examining whether this pathway can be stimulated or repressed using various therapies to maintain the health of mitochondria in brain cells, with a view to developing an intervention that may treat or prevent familial and age related dementia.

Investigating the Role of Inflammation in Alzheimer’s Disease

Laboratory: Atherothrombosis and Vascular Biology
Laboratory head: Professor Karlheinz Peter

Inflammation is known to play an important role in the development and progression of a number of diseases which are a major burden for individuals and society. Diseases involving inflammation include hardening of the arteries, arthritis, obesity, heart attack and Alzheimer’s disease.

Inflammation is a biological response to harmful stimuli, involving a range of responses at the cellular level as the body attempts to heal and repair damaged or irritated tissue. A wide variety of proteins play a role in inflammation – some are ‘bad’ and promote inflammation while others are ‘good’ and help mitigate it.

C-reactive protein (CRP) - a protein found in blood plasma - is an indicator of inflammation, and CRP levels increase as much as 10,000-fold in response to inflammation within 24 hours. CRP tests can be used to diagnose inflammatory conditions and can be useful in distinguishing inflammatory versus non-inflammatory conditions.
Researchers in the Atherothrombosis and Vascular Biology laboratory are investigating the role of CRP as a possible cause of inflammation at the site of Alzheimer's plaques (protein deposits) in the brain.

Prior work by this group has shown that CRP interactions on the surface of ‘stressed cells’ can lead to an accumulation of a certain pro-inflammatory or ‘bad’ CRP which causes localised inflammation and blood clots. When inflammation continues in the body, it can cause chronic health problems. Researchers hope to better understand the role of CRP with a view to developing therapies that inhibit the pro-inflammatory CRP system in patients with Alzheimer’s plaques and thus halt the disease and prevent dementia.