Research Project
By Dr Marina Cavuoto

Dementia Australia™ Research Foundation

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The influence of the Aquaporin-4 gene on the relationship between poor sleep and preclinical dementia: A multi-cohort study

What is the focus of the research?

To determine whether carriers of the AQP4 minor haplotype are at greater risk of negative brain health associated with poor sleep.

How will this happen?

Stage 1: Use state-of-the art measures of early dementia detection, such as brain MRIs, cerebrospinal fluid-based markers, cognitive change measures and genetic sequencing, to examine participants from three key sleep studies who have been followed for up to 10 years.

Stage 2: Use the data to assess whether poor sleep is more strongly associated with negative brain health in people with different AQP4 variants. This will enable researchers to understand whether genetic differences may play a role in how poor sleep is associated with increased dementia risk.

Stage 3: Work with clinical collaborators across specialist clinics to develop their findings into national guidelines on the management of sleep disturbances for dementia risk reduction. They will then communicate those guidelines to the broader community.

What is AQP4?

AQP4 is a gene that plays an important role in the capacity of the brain to clear waste by "flushing out" toxic proteins through AQP4 water channels in the brain. Having too few AQP4 water channels may contribute to dysfunction in the brain's clearance system. This may lead to a build-up of toxic waste proteins that contribute to the development of Alzheimer's disease and other forms of dementia. Poor sleep is one of the things that can disrupt the brain's ability to remove toxic waste products, so understanding how that happens, and the role of AQP4, is an important step to working out how good sleep can support a healthy brain.

Why is it important?

In order to decrease the number of people developing dementia, it is not only critical to understand what risk factors exist, but also who those risk factors are strongest for. Understanding this could help doctors recognise those at highest risk, so they can start interventions early and improve the chances of preventing or delaying dementia.

We already know there is a relationship between poor sleep and increased risk of dementia. Importantly, sleep disturbance is something we can help people improve with the use of various treatments. The role a person's genes play in this increased risk remains unknown, but is an important piece to helping find those people who are in most need of early intervention.

Dr Cavuoto's study will provide critical evidence on whether AQP4 genetic variants contribute to differences in the relationship between sleep and preclinical dementia. It will be the first study to comprehensively examine the effect of the AQP4 gene on the relationship between sleep and both cognitive decline and early markers of dementia. It will help identify those people at greatest risk of developing dementia and inform who would benefit most from interventions designed to prevent dementia.

What will this mean for people with dementia?

If we show that different AQP4 variants are associated with a greater risk of negative brain health in the face of poor sleep, there may be:

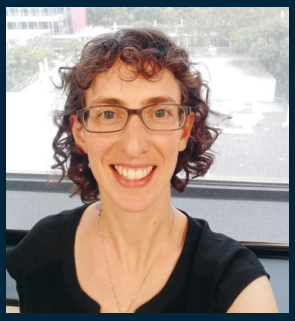
- Greater chance of people being identified if they are high-risk.
- The potential to develop personalised sleep interventions that reduce dementia risk.

What will this mean for the future?

- Access to clinicians who can help people analyse their risk and understand what is happening or what could eventually happen. A greater understanding of how modifiable (e.g. sleep) and non-modifiable (e.g. genetic) risk factors interrelate to influence risk of preclinical dementia.
- An understanding of whether genetic testing can be clinically useful for identifying individuals at greatest risk of cognitive decline and dementia in the context of sleep disturbances.
- Important pilot data to inform future research.
- The potential to significantly improve risk reduction strategies for many causes of dementia.

There are so many types of dementia, how can this study be useful to them all?

There are some risk factors that are common to many forms of dementia. By using brain MRI, cerebrospinal fluid, and cognitive function to detect pre-clinical markers of dementia, researchers can make inferences about different causes of dementia. For example, cerebrospinal fluid can provide information about several neurodegenerative diseases (including Alzheimer's disease) that cause dementia; brain MRI will allow the assessment of vascular contributions to cognitive impairment and dementia; and cognitive assessment will allow the examination of cognitive profile changes that are typical of different kinds of dementia, including Alzheimer's disease, vascular dementia, frontotemporal dementia and others.



Who's undertaking the research?

Dr Marina Cavuoto, Monash University

Dr Marina Cavuoto is a clinical neuropsychologist with expertise in cognitive ageing and dementia. She completed her PhD on the association between sleep and memory function in preclinical Alzheimer's disease and healthy ageing. She is a post-doctoral research fellow at the Epidemiology of Dementia Group at the Turner Institute of Brain and Mental Health. Dr Cavuoto's primary research interests are on understanding risk factors for cognitive decline and dementia, with a focus on sleep disturbances, gene-sleep interactions, and social determinants of health. She also coordinates the Sleep and Dementia Consortium, which aims to investigate the relationship between sleep disturbances and cognitive, dementia and brain MRI outcomes. Dr Cavuoto and Dementia Australia Research Foundation would like to acknowledge the support of Lucas' Papaw Remedies in making this research possible.