

## Discovery Award – Dr Chi-Hun Kim

### Have we overestimated the impact of vascular factors on the declining incidence of dementia?



**Dementias**  
Platform<sup>UK</sup>  
Medical Research Council

#### Objective(s):

In addressing whether we have overestimated the impact of vascular factors on the declining incidence of dementia, the award aimed to:

1. Harmonise multiple DPUK and NIA cohorts to address the hypothesis
2. Train early career researchers (ECRs) in undertaking cross-cohort harmonisation
3. Train ECRs in the statistical skills required for the project
4. Disseminate results from preliminary analysis

#### Overview Summary:

This project arose from a DPUK Discovery Award to Dr Chi-Hun Kim who was based at the University of Oxford. It aimed to investigate the impact of vascular factors on the reported declining incidence of dementia, looking specifically at whether we have overestimated the impact of vascular factors. This work will benefit not only the prioritising of preventive public health strategies but also the education of health professionals and the public for dementia prevention.

#### Executive Summary:

Dementia is a global health problem for which there is no disease modifying therapy. Recently several population-based cohort studies reported a 'declining' incidence of dementia in the UK, US and European countries ([Schrijvers et al, Neurology, 2012](#); [Matthews et al., Nature Comms., 2016](#); [Grasset et al, Alz. & Dem., 2016](#); [Satizabal et al, NEJM, 2016](#); [Ahmadi-Abhari et al, BMJ, 2017](#)). Vascular factors such as hypertension are suspected as major determinants of this trend.

However, the evidence for this is inconclusive as estimates for the impact of vascular factors on the declining incidence of dementia vary widely between studies, ranging from 'no significant modification' ([Satizabal et al, 2016](#)) to 'accounting for about 25%' ([Ahmadi-Abhari et al, 2017](#)).

Dr Kim and colleagues hypothesized that these divergent findings were due to 1) A lack of statistical power in the previous single cohort studies and 2) Survival bias: Apart from [Ahmadi-Abhari et al](#) (2017), previous studies restricted their analysis to people who remained in the study when reaching 60 years old or over (60+) or enrolled people over 60. This selection process can lead to biased estimates of mid-life exposures. For example the effect of smoking is harmful to dementia but can appear to be less harmful or even beneficial due to this selection process ([Hernán et al, Epidemiology, 2008](#)).

A harmonisation protocol for eight population-based prospective cohorts with mid-life vascular exposures and dementia cases has been undertaken (Objective 1). In the first stage, a cohort-specific analyses was undertaken estimating the impact of vascular factors on dementia by each cohort. Using conventional Cox proportional hazard models, a similar finding to previous reports was noted e.g. harmful association between mid-life BMI and dementia but inversed association between later-life BMI and dementia or null associations which may be due to lack of power. The work is being extended to investigating whether accounting for selective attrition by applying various statistical methods may remove the inversed association in later-life. In the second stage, pooled analyses will be undertaken to overcome the low statistical power of previous single cohort studies. The final results will be submitted to a peer-reviewed journal by the end of 2020.

During the project, three ECRs were trained on cross-cohort harmonisation (Objective 2) and three ECRs for advanced statistical skills for the project (Objective 3). The preliminary findings have been disseminated at domestic and international conferences (Objective 4).

#### **Summary of Outputs:** (as per Researchfish categories)

##### **Publications**

In preparation (April 2020)

**Title:** Have we overestimated the impact of vascular factors on the declining incidence of dementia?

**Summary:** *Recent population-based cohort studies have reported a declining incidence of dementia. Vascular factors are suspected as major determinants of this trend. However the evidence for this has been inconclusive. We hypothesize the estimates of the contribution of vascular factors to the reported decline in dementia may be due to specific selection biases before study enrolment in late-life cohorts and to the lack of study power in single cohort studies. In this project we aim to investigate selection bias in estimating the impact of vascular factors on dementia.*

#### **Collaborations & Partnerships**

This project facilitated a successful collaboration between the research groups led by Dr Kim and Dr Lenore Launer at NIA.

#### **Further Funding**

A separate MRC Research grant award “Using vascular factors and dementia to establish rapid data access between DPUK and NIA cohorts” was provided to Dr Kim for 12 months from 1 April 2018.

#### **Next Destinations**

Dr Kim has returned to South Korea to pursue his career there. Funds on the grant facilitated the training of ECRs Christoph Jindra, Nemanja Vaci and Catherine Calvin. All are currently involved in post-doctoral data analyses.

#### **Engagement Activities**

- Poster – Rostock Retreat on Causality, Max Planck Institute, Rostock, Germany (2-4 July 2018)
- Talk - WIN Neurodegeneration symposium, Oxford, UK (19 November 2018)
- Talk - Methods in longitudinal dementia research (MELODEM) Annual Meeting 2019, US (21-24 July 2019)

#### **Influence of policy, practice, patients & the public**

None

#### **Research Tools & Methods**

A CODEBOOK specific to the harmonisation of the data in this project is available on request.

#### **Research Databases & Models**

None

<b>Intellectual property &amp; licencing</b>
None
<b>Medical products, interventions &amp; clinical trials</b>
None
<b>Artistic &amp; creative products</b>
None
<b>Software &amp; technical products</b>
A CODEBOOK specific to the harmonisation of the data in this project is available on request.
<b>Spin outs</b>
None
<b>Awards &amp; recognition</b>
Dr Kim was awarded an MRC-NIH Partnering Award to facilitate research visits to Dr Launer's laboratory at NIA.
<b>Other outputs &amp; knowledge/future steps</b>
None
<b>Use of facilities &amp; resources</b>
None
<b>Most successful outcome and what it means for future dementia research:</b>
A cross-cohort harmonisation protocol for some UK and US dementia cohorts: One of the challenges for cross-cohort studies is different study protocols across cohorts. The harmonisation protocol will be an informative reference/example for other dementia researchers.
<b>Lessons learned:</b>
<ol style="list-style-type: none"> <li>1) Accessing multiple cohorts took longer than expected. The DPUK Data Portal substantially reduced the amount of time and effort for the UK cohorts. Personal contacts with cohort owners was used for the NIA-funded cohorts with access time varying greatly across cohorts.</li> <li>2) Harmonisation was not straightforward. All cohorts had different coding schemes and it took several months for staff to precisely identify these and develop a harmonisation protocol. In addition, some variables were impossible to harmonise, e.g. education, exercise and income levels in different countries. In those cases, multi-level ordinary or continuous variables had to be changed to simpler variables such as binary ones which lost valuable information held in the original cohorts.</li> </ol>

3) Collaboration was key to delivering all the milestones. It was essential to have both guidance from senior researchers and the hard-work from ECRs. In addition, it was critical to collaborate with cohort owners/researchers who have years of experience in their data and with statisticians who have specialty skills for longitudinal cohorts with complex data structures and related issues, e.g. non-random dropouts.

**Date of report:**

23 March 2020