DA 1

Have we overestimated the impact of vascular factors on the declining incidence of dementia? DPUK-NIA CROSS-COHORT COLLABORATION: The Dementia and Vascular disease (DemVasc) Consortium
Start date: Jul 2018 **Completion date: 31 Aug 2019**
Date of form completion: 3 Nov 2019

Team members <u>funded</u> (full or part-time) by DPUK
Chi-Hun Kim, Christoph Jindra, Catherine Calvin, Sarah Bauermeister
Team members involved with the project but <u>not</u> funded by DPUK
Lenore Launer, Graciela Muniz Terrera, Nemanja Vaci
ECR's: Chi-Hun Kim, Christoph Jindra, Catherine Calvin, Nemanja Vaci

Objectives
1. Harmonise multiple DPUK and NIA cohorts
2. Train ECRs on cross-cohort harmonisation
3. Train ECRs on statistical skills required for the project
4. Disseminate results from preliminary analysis

Dependencies to and from other work packages, networks and themes

Not applicable

Lessons Learnt (what went well, what did you have to change)

- Accessing multiple cohorts took longer than expected. But the DPUK Data Portal was a great one-stop platform for the UK cohorts from identification, access to analysis, which reduced a substantial amount of time and effort. For the NIA-funded cohorts, we followed a traditional cohort access approach, i.e. personal contacts with cohort owners, through which access time varied greatly across cohorts.
- Harmonisation comes at a price. All cohorts have different coding schemes which took a few months of time for three ECRs to precisely identify the schemes and to 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 we had to change multi-level ordinary or continuous variables to simpler variables such as binary ones which lost valuable information in the original cohorts.

Collaboration was the key to deliver all the milestones. It was essential to have both the 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.

Were all Milestones completed
Yes, all milestones have been completed.
Due to some delay in data access procedures we had to change our timelines for data access and also had to diversify our access routes, i.e. both direct collaboration and applications via public data repositories.

Deliverables	Milestones	Milestone deadline	Work package dependencies	Person(s) responsible
Objective1:				
D1. Documentation and analysis codes for cohort harmonisation will be disseminated on the DPUK Data Portal and DPUK website		M1.1 Mar 2019	None	Chi-Hun Kim
Objective2:				

D2. ECRs trained on cross-cohort harmonisation for dementia research	M2.1 Aug 2019	None	Chi-Hun Kim, Lenore Launer
Objective3:			
D3. ECRs trained on causal inference from longitudinal observational data and pooled/meta-analysis of cohorts with individual-level data	M3.1 Aug 2019	None	Chi-Hun Kim, Graciela Muniz Terrera
Objective 4:			
D4. The preliminary results from analysis will be disseminated in academic conferences	M4.1 Aug 2019	None	Chi-Hun Kim

Outcomes

Objective 1: Completed

- A harmonisation protocol and STATA/R codes have been submitted to DPUK. The protocol has been developed using information from four UK and four NIA associated cohorts. The protocol includes most commonly used variables for dementia research. By running the accompanied codes, raw cohort data is converted into a harmonised data format for cross-cohort studies. The protocol and the codes will be informative references for other dementia researchers who plan to conduct similar cross-cohort studies.

Objective 2: Completed

- Three ECRs (Drs Chi-Hun Kim, Christoph Jindra, and Catherine Calvin) were trained on cross-cohort harmonisation by regular online and in-person meetings with experienced senior researchers (Drs Lenore Launer and Graciela Muniz Terrera) and by harmonising multiple cohorts. For the latter, we directly collaborated with cohort owners/researchers when it was necessary to better understand and process the data.

Objective 3: Completed

- Three ECRs (Drs Chi-Hun Kim, Christoph Jindra, Nemanja Vaci) have been trained on statistical skills required for the project by attending training courses (causal inference, advanced regression, multilevel model and meta-analysis) and by having online and in-person meetings with statisticians with necessary skills (Drs Graciela Muniz Terrera and Osorio Meirelles, Professor Lucia Petito and many others who provided valuable advice including Professors Miguel Hernan, Eleanor Murray, Melinda Power, Vanessa Didelez, Illya Shpitser, Kate Tilling and Dr Maarten Bijlsma)

Objective 4: Completed

- Preliminary results have been disseminated at one national (Talk - WIN Neurodegeneration symposium, Oxford) and two international (Poster - Max Planck Institute, Rostock, Germany; Talk - Methods in longitudinal dementia research Annual Meeting 2019, US) conferences

Executive Summary of Project

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.

We developed a harmonisation protocol for eight population-based prospective cohorts with mid-life vascular exposures and dementia cases (Objective 1). In the first stage, we have conducted cohort-specific analyses where we estimated the impact of vascular factors on dementia by each cohort. Using conventional Cox proportional hazard models, we found similar finding to previous reports 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. We are in the process of investigating whether accounting for selective attrition by applying various statistical methods may remove the inversed association in later-life. In the second stage, we plan to conduct pooled analyses 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 as planned, which is out of the scope of this award period.

During the project, we trained three ECRs for 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). We have spent £38,842 out of £50,000 awarded and will not claim the funds remaining. As the ECRs have leveraged this award to receive other travel fellowships and some training needs were unnecessary, we have been able to save approximately £10,000 in conference, research visit and training costs.

End Report.pdf