Final Project Report Discovery Award DA1

The development of an Alzheimer's disease clinical trial simulator, parameter estimation from international patient cohorts and standardizing epidemiological measurement platform for cohort studies.

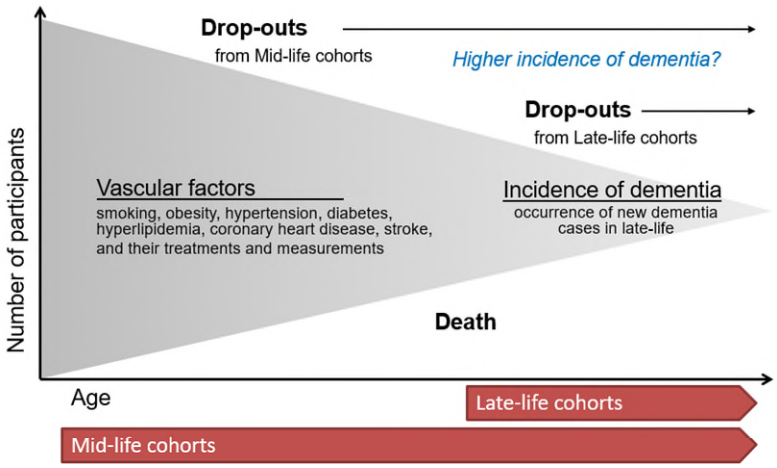
- **Introduction**

Dementia is a global health problem for which there is no disease modifying therapy (Prince et al, 2015). Encouragingly, several population-based cohort studies have 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). Filling this knowledge gap is critical to the development of public health based dementia prevention strategies.

We hypothesize that the divergent findings were due to

1) 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 by 60 years old or over (60+) or enrolled people who survived by 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).



- **Section I**

To address these design issues, we propose

1) To identify all DUPK and NIA cohorts with mid-life (40+ years) vascular exposures and to conduct a pooled analysis. Preliminary scoping has identified 4 DPUK Portal cohorts and 4 NIA cohorts, over 80,000 participants that can be accessed through the DPUK-NIA partnership. Dr Kim has been awarded an MRC-NIH partnering award (research visit costs only) to conduct this joint DPUK-NIA project with Dr Lenore Launer at NIA. As far as we are aware this is one of the largest population-based mid-life cohort consortia relevant to our research question.

2) To harmonise data across the cohorts: Dr Launer has developed cross-cohort harmonisation procedures for the NIA cohorts. These will be adopted and applied to the DPUK cohorts. The developed harmonisation procedures will be made available to other researchers.

3) To develop longitudinal causal models: Causal inference from longitudinal observational data is challenging but critical to address our question. Formal causal models will be developed to account for non-random dropouts and death (e.g. joint models for longitudinal and survival data) and time-varying exposures (e.g. causal graphical models).

- **Section II**

*Cohorts

Selection criteria are population-based mid-life cohorts that include 1) participants aged between 40 and 60 years at baseline, 2) clinical dementia diagnosis or relevant cognitive and/or functional impairment tests to derive algorithmic dementia diagnosis and 3) mid-life vascular factors.

Exclusion criteria are 1) late-life cohorts – all participants are older than 60 years old at baseline or 2) too young cohorts – age of the last data collection is younger than 60 years old in all participants.

Suitable cohorts are

-Four DPUK Portal cohorts: Caerphilly Prospective Study (CaPS; Fish et al, Neuroepidemiol, 2008), English Longitudinal Study of Ageing (ELSA; Ahmadi-Abhari et al, BMJ, 2017), National Study of Health and Development (NSHD; Kuh et al, Int J Epidemiol, 2011), Stress and Health Study (WH II; Wadsworth et al, Int J Epidemiol, 2006)

-Four NIA cohorts: Honolulu-Asia Aging Study (HAAS; White et al, JAMA, 2015), AGES-Reykjavik Study (AGES; Harris et al, Am J Epidemiol, 2007), Framingham Heart Study (FHS; Satizabal et al, NEJM, 2016) and Atherosclerosis Risk in Communities study (ARIC; Gottesman et al, JAMA Neurol, 2017)

A brief summary of the eights cohorts is as below. For details please find the Table 1 in the attached file in the 'Additional Information' Section.

Name(N):	Age at baseline	Data period	Vascular factors	Dementia diagnosis	Comments
CaPS(2959):	42-61	1979-2004	Yes	C, S	Male only
ELSA(17906):	50+	2002-2017	Yes	A	
NSHD(5362):	Birth	1946-2015	Yes	D	
WH II(10308):	35-55	1985-2016	Yes	D	Civil servants
HAAS(8006):	45-68	1965-2011	Yes	C, S	Male only
AGES(30795):	32-60	1967-2011	Yes	C, S	
FHS(15338):	5-85	1948-2015	Yes	C, S	
ARIC(15792):	44-66	1987-2013	Yes	C	

[Abbreviations - C: clinical diagnosis, S: dementia subtype diagnosis available, A: algorithmic diagnosis published, D: we will develop algorithmic diagnoses using available cognitive and functional tests]

- **Section III**

*Variables (we are aware that not all variables are available from each cohort)

-Exposures: diagnosis of hypertension, diabetes, hyperlipidemia, cardiovascular disease and stroke; smoking, obesity (body mass index, waist and hip circumferences), relevant treatments (e.g. antihypertensives, antidiabetics, statins, antiplatelets) and clinical measurements (e.g. blood pressure, blood glucose/HbA1c, cholesterol)

-Outcomes: all-cause dementia diagnosis. If available, Alzheimer's dementia and vascular dementia diagnosis (If a cohort does not have clinical dementia diagnosis, we will follow published procedures to derive algorithmic dementia diagnoses from each cohort as was done in the ELSA study (Ahmadi-Abhari et al, 2017). In addition as part of cohort harmonisation, we will develop procedures for algorithmic dementia diagnoses across the cohorts. This will be based on standardised scores (e.g. age-specific z scores) from both cognitive and functional impairment tests.

-Covariates: age, sex, education, socioeconomic status, alcohol, physical activity, APOE genotype and race

-Others: cognitive tests (e.g. memory, executive/processing, global), functional impairment tests (e.g. IADL), cohort administrative data (e.g. dates for event start and end, reasons for dropout), date and reason for death, family history of dementia and vascular factors, other brain disorders, medications and surgeries that may affect cognitive function (e.g. depression, Parkinson's disease, brain tumour)

- **Section IV**

*Analysis Plan

This project is a cross-cohort study with the eight population-based prospective cohorts. When necessary, variables (e.g. life style covariates) across the eight cohorts will be harmonized by developing ranked scores within each cohort following similar procedures developed for the NIA cohorts (Meirelles et al, unpublished). Dr Kim will visit Dr Launer's group at NIA to learn these procedures. Drs Kim and Muniz Terrera will support Drs Bauermeister and Calvin to develop their skills in DPUK cohort harmonisation in addition to their strong psychological background.

Cox proportional hazards regression models will be used to calculate dementia incidence across calendar years. The impact of vascular factors will be estimated using each as an exposure in regression models after adjusting for covariates. Stratification and interaction analyses will be performed using the covariates defined above. In addition we will further develop longitudinal causal models to account for non-random dropouts and death (e.g. illness-death models (Leffondré et al, Int J Epidemiol, 2013) and joint models for longitudinal and survival data (Rizopoulos, 2012)) and time-varying exposures and confounders (e.g. g-methods and causal graphical models (Robins et al, Am J Epidemiol, 2007)). Drs Muniz Terrera and Launer will provide advice given their expertise on these analyses. Drs Kim, Jindra and Vaci will attend training course to strengthen their analytical skills.

Before pooling the eight cohorts, we will use the same analytical methods across the cohorts. We will assess heterogeneity between estimates from each cohort by visual inspection of forest plots and by Chi-squared tests and I^2 statistics. If the statistical heterogeneity is within reasonable limits (e.g. I^2 less than 60%), we will conduct a pooled analysis using either random or fixed effect models.

To evaluate sources of potential heterogeneous results between cohorts, we will conduct subgroup analyses based on age group, calendar year, sex, education and country.

Potential survival bias in the previous studies may have caused biased estimates by using only the individuals who remained in the study 60+ years (see Figure 1 in the attached file in the 'Additional Information' Section). For example people who are susceptible to mid-life exposure to smoking will be depleted by 60 years old as they may die early or become too ill to participate in late-life cohort studies. To estimate the magnitude of this bias, we will conduct secondary analyses restricting to the people who remained in the cohorts 60+ years. By comparing these results and those from our full-cohort analyses, we may demonstrate the magnitude of survival bias in cohorts with only 60+ participants. Specifically we will visualise this using a forest plot with coefficients and confidence intervals (CIs). In the forest plot, eight individual cohorts and the single pooled data will be represented with two CI lines for each: one with full-cohort estimates and the other with restricted-cohort estimates.

- **Conclusion**

All four objectives have been completed and the remaining unspent budget will not be claimed. The preliminary findings showed promising results replicating previous reports. The ongoing final data analysis will be completed and submitted to a peer-reviewed journal as originally planned.

- **Recommendations**

Researchers are encouraged to use the DPUK Data Portal to conduct cross-cohort studies. We have also demonstrated this capacity can be leveraged for ECRs with great ideas to receive research grants and to gain access to comparable cohorts in other countries. However, the researchers should not underestimate the time and effort for data access and harmonisation and should seek advice from the experienced DPUK researchers to make realistic plans.

- **Bibliography**

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