An Integrated Investigation of Vascular Cognitive Impairment in Population Based Studies Across Europe

UNIVERSITY OF CAMBRIDGE

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Background

- The incidence and prevalence of cognitive decline and dementia is expected to increase with population ageing.
- Ageing is associated with changes in all components of the vascular system and increased risk of cardiovascular and cerebrovascular disease.
- Vascular factors (e.g., poor diet and smoking) and conditions (e.g., stroke, hypertension and obesity) are risks for cognitive decline and dementia.
- Cognitive decline attributable to vascular factors has been termed "Vascular Cognitive Impairment" (VCI)[1].
- VCI encompasses all individuals showing cognitive decline caused by or associated with vascular factors or conditions.
- VCI ranges in severity from Vascular Cognitive Impairment No Dementia (VCIND) to dementia (Figure 1).
- Whether VCIND identifies individuals at risk of developing dementia secondary to vascular disease is not known.
- A more complete understanding of the relationship between vascular disease, cognitive decline and dementia will have important implications in identifying elderly vulnerable population subgroups for treatment and prevention.

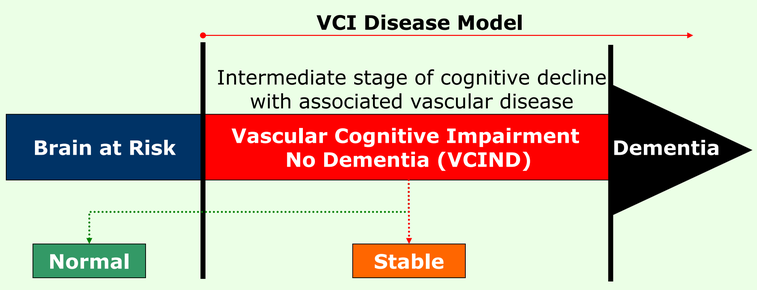

Figure 1. Model of cognitive decline and dementia risk associated with vascular ageing.

PROJECT AIMS

- **Explore the relationships between vascular factors, cognitive decline and dementia.**
- **Determine vascular markers that are sensitive and specific in identifying those individuals who are likely to progress to dementia as a consequence of co-morbid vascular disease/factors.**

Research Questions

1. Can VCIND be defined?
2. What is the population prevalence of VCIND?
3. What is the role of vascular factors and conditions in cognitive decline and its progression to dementia?
4. Do trajectories of change depend on source of information (i.e., biological, neural, molecular, nutritional, clinical), baseline severity and/or aggregation of vascular disease/factors?
5. Do demographic variables moderate the effect of vascular disease on cognitive decline and progression to dementia?
6. What are the necessary diagnostic requirements for accurate discrimination of those persons at risk of progressing to dementia secondary to vascular disease/factors?

Cross Study Collaboration

- Harmonisation of three data resources (Figure 2) including:
  - **EClipSE** Determine the prevalence and severity of neuropathological lesions across the spectrum of age associated changes (i.e., normal, VCIND, dementia).
  - **The 3C-Study** Examine tissue integrity using MRI to identify the extent of changes that render an individual susceptible to dementia in response to vascular disease/factors.
  - **EPIC-Norfolk** Investigate lifestyle/disease interactions to identify modifiable risks that initiate disease and contribute to its progression.

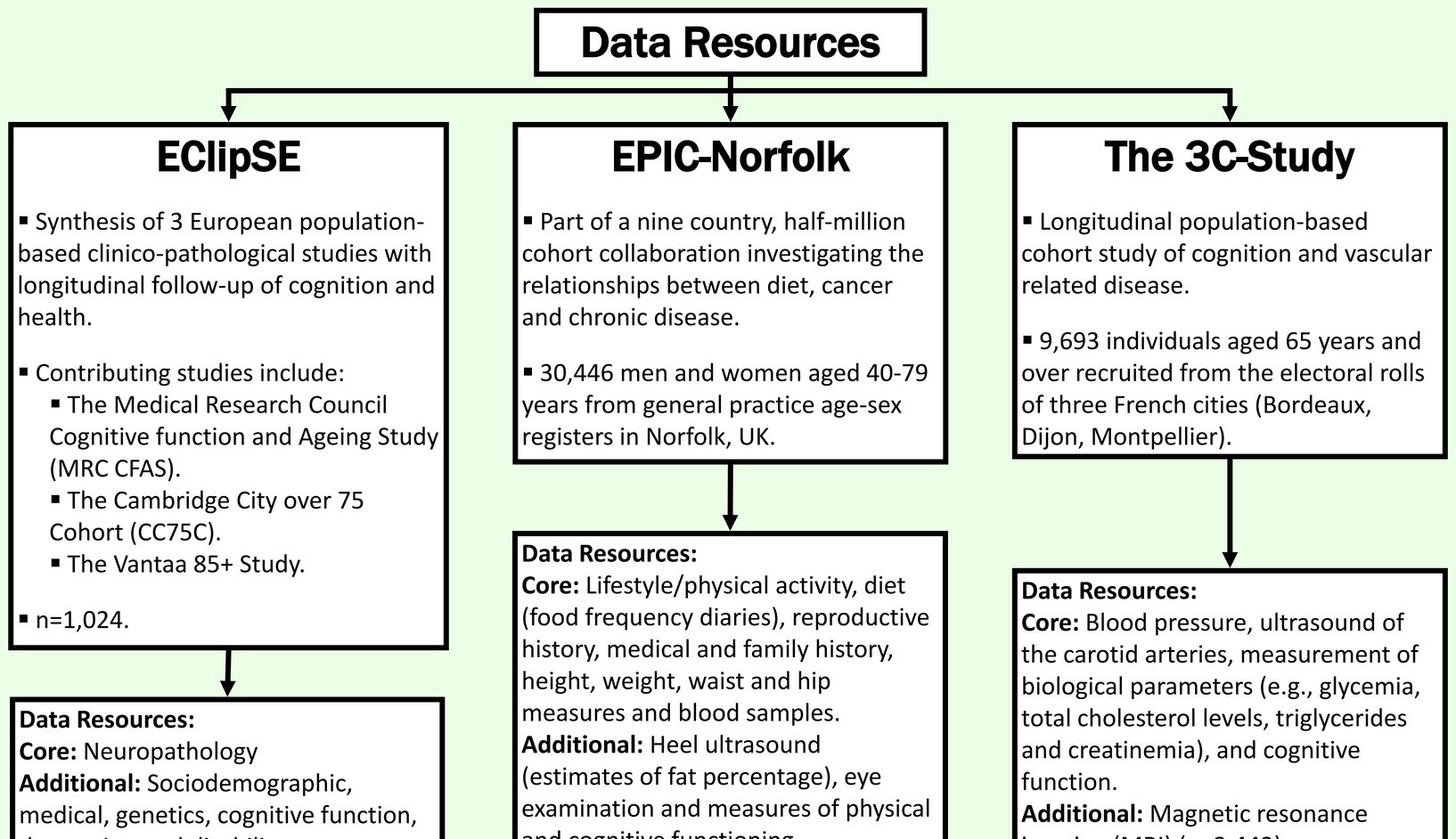

Figure 2. Data Resources.

Defining Cognitive Decline

- Cognitive decline defined using definitions of Mild Cognitive Impairment (MCI) including:
  - Age Related Cognitive Decline (ARCD)[2].
  - Mini Mental State Examination derived MCI ($MMSE_{MCI}$)[3].
  - Revised Mayo Clinic MCI (R-MCI)[4].
- Individuals will be classified into three dementia risk groups including: low, medium and high risk.
- Sub-classifications derived distinguishing impairment with (i.e., VCIND) and without (i.e., MCI) comorbid risk factors (Table 1).

Table 1. Risk Factors for Vascular Cognitive Impairment (VCI).

Demographic	**Intermediate Phenotypes (Cont.)**
Ageing	Dyslipidemia
Low Education	Head Trauma
Lifestyle	Hyperlipidemia
Alcohol Consumption	Hypertension
Cigarette Smoking	Obesity (BMI)
Exercise	**Ischemic Lesion Related Variables**
High Dietary Saturated Fat	History of Transient Ischemic Attack
Intermediate Phenotypes	Stroke
Atrial Fibrillation	**Genetic**
Coronary Heart Disease	CADASIL
Diabetes	APOE E4

Methods

- Map MCI and VCIND retrospectively in each study.
- Datasets will be harmonised to allow the different study methodologies to be evaluated.

Analysis Plan

- **Primary outcome measure:** Transition including stability, remission or progression to dementia.
- **Secondary outcome measures:** Mortality and dependency.
- Potential covariates include age, gender, genotype, site, start and follow-up date and demographic variables.
- Analysis will be completed in two main stages:
  1. Incidence and prevalence of MCI and VCIND.
  2. Longitudinal modelling of the evolution of disease and the extent to which different vascular factors influence rates of disease progression.

Preliminary Results – Prevalence of Co-morbid Risk Factors Across Dementia Risk Groups Defined Using R-MCI

- Variable prevalence of different risk factors in the non-demented groups as shown in Figure 3.
- Higher prevalence of depression, stroke, epilepsy and Parkinson's Disease in individuals with dementia (Figure 3).

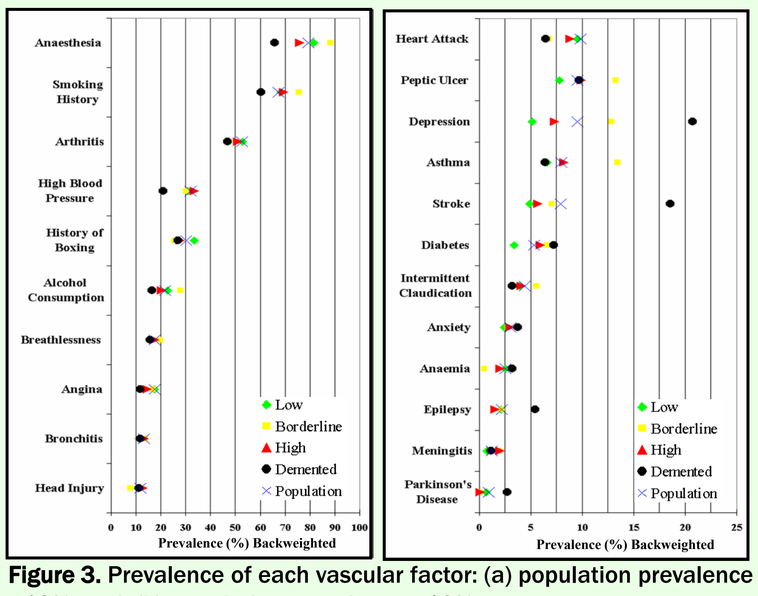

Figure 3. Prevalence of each vascular factor: (a) population prevalence >10%; and, (b) population prevalence <10%.

Preliminary Results – Dementia Risk (Multi-nominal Logistic Regression)

- For all MCI definitions, individuals with depression, diabetes, epilepsy, Parkinson's Disease and history of stroke were at an increased risk of dementia.
- All associations remained significant after covariate adjustment, with the exception of diabetes.
- Risk factor profiles varied across the different risk levels (no dementia) and were not consistent with those observed for dementia.
- Individuals with depression, asthma, history of head injury and stroke were found to be at increased risk of cognitive decline (no dementia).
- Associations depended on definition and covariate adjustment.

WHY DO THIS STUDY?

- **Cognitive impairment commonly accompanies clinical syndromes associated with vascular factors/disease.**
- **There is substantial controversy about the frequency of cognitive impairment attributable to vascular factors/disease.**
- **Risk identification offers promise for the identification and development of neuroprotective strategies.**

References

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Acknowledgements:

Thank you to all collaborating studies.

This project is supported by the Joint European Post-Doctoral Programme: The European Research Area in Ageing (ERA-AGE) Network FLARE Programme [RHAG/096]

MRC Medical Research Council

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