Concept Paper Form

Provisional Paper Title: Association of early-life blood pressure exposures with mid-life brain health
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Today's Date: 10/28/2021

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

Nearly 50 million people currently live with dementia worldwide, and this figure is expected to triple by 2050(1). Despite decades of research, trials of pharmacological treatments for the condition have met with almost universal failure(2). While the reasons for these failures are still not fully understood, they may be explained by the growing appreciation that dementia represents the end result of a long preclinical phase involving multiple pathophysiological processes and overlapping disease states. Recent years have seen a growing recognition that many of these pathophysiological processes are common to another of the world's leading causes of premature mortality – cardiovascular disease (CVD) – raising the possibility that prevention strategies targeting cardiovascular health may also have a dual benefit for brain health.

In many other fields of medical science (e.g. cardiovascular disease, renal disease, hepatic disease), it has long been known that early and sustained exposure to risk factors may initiate the evolution of a long-term disease process which develops insidiously across the lifespan before culminating in clinical events in older age(3,4). Due in part to extensive research over the last 30 years by my unit at UCL, it is now accepted that the atherosclerotic CVD process starts virtually from birth, with subtle but widespread adverse changes in systemic vascular structure and function detectable even from the first decade of life(5–17). Only in recent years however, has research begun to highlight the critical role that these same factors may play in the development of cognitive impairment and dementia, culminating in a recent report by the Lancet Commission which estimated that >30% of dementias worldwide could be delayed or prevented by targeting a number of common mid-life risk factors with already well-established links to CVD(1).

Curiously, very little attention within the scientific literature has been paid to the potential effect that CVD risk factor exposures in the first 50 years of life have on brain health prior to mid-life, or the subsequent impact that these early subclinical changes may have on later dementia risk. While a limited number of studies in recent years have begun to address this question in various young adult cohorts such as the Cardiovascular Risk in Young Finns (YFS) or Coronary Artery Risk Development in Young Adults (CARDIA) studies(18–22), no study to date has been able to investigate these relationships in a longitudinal birth cohort containing both lifetime exposures to risk factors from childhood and – critically – data on early childhood cognitive function which may confound findings due to neuroselection.

Elevated blood pressure is one of the world's leading causes of CVD, has repeatedly been shown to be a robust mid-life predictor of future dementia, and has previously been demonstrated in this cohort to diverge during adolescence and track across young adulthood. This study therefore aims to investigate potential associations between cumulative exposure to blood pressure over the early decades of life and neuroimaging and cognitive outcomes in mid-life. We hypothesise that increased exposure to high blood pressure over the first 40-50 years of life will result in adverse subclinical changes in brain health which may increase risk of dementia, and that these associations will remain once the potential confounding effect of childhood cognitive function has been considered.

Data analysis methods:

All data analysis will be carried out in the Department of Psychology and Neuroscience at Duke University. Both continuous and categorical blood pressure measures will be used as potential exposures in statistical analyses. For continuous data, individual intercepts and slopes from repeated blood pressure measures will be calculated for each participant using mixed linear models, with trapezoidal integration then used to provide a continuous measure of exposure represented by the area under the curve for each participant. Trajectories of lifetime blood pressure exposure will also be tested as categorical variables using data derived from a previous publication in this cohort (Theodore et al 2015 Hypertension). Multiple linear regression will be used to test for associations between each of these exposures and a range of neuroimaging and cognitive outcomes. Firstly, a BrainAGE metric derived from previous work within this cohort will be used as a marker of overall brain health. In the event that significant associations are found with this novel biomarker, secondary analyses of more specific structural changes measured using MRI (e.g. white matter integrity, WMHs, etc) will be conducted to further explore these relationships. For cognitive outcomes, both continuous and categorical exposures will be tested against adult IQ measured at age 45. Four models will be created for each exposure: Model 1=unadjusted; Model 2=model 1 + adjustments for age and sex; Model 3=model 2 + adjustments for BMI and current blood pressure; and Model 4=model 3 + adjustments for education level and socioeconomic status. In order to test for a potential confounding effect of childhood IQ levels (i.e. neuroselection), two further approaches will be used. Firstly, additional models containing childhood IQ (average of three measures ~ age 10) will be created to assess whether the (hypothesized) independent effect of BP on mid-life outcomes remains/is attenuated/lost following statistical adjustment. Secondly, a secondary analysis employing childhood IQ as the exposure and cumulative exposure to blood pressure across early-life as outcome will be used to test for potential bidirectional relationships between these factors. Finally, if robust independent relationships are found between early-life blood pressure and mid-life outcomes, the use of

genotyping data contained within the cohort may allow the creation of polygenic risk scores for blood pressure which may provide causal inferences to be drawn from our observational findings.

Variables needed at which ages:

Exposures:

Blood pressure measures at ages 7, 11, 18, 26, 32, 38, and 45.
Blood pressure trajectories derived as part of Theodore et al 2015 Hypertension paper (DOI: 10.1161/HYPERTENSIONAHA.115.05831)
Blood pressure PRS constructed according to Vaura et al 2021 Hypertension paper (doi.org/10.1161/HYPERTENSIONAHA.120.16471).

Outcomes:

Neuroimaging (all at age 45) –

BrainAGE
Average cortical thickness, surface area, and fractional anisotropy
Parcel-wise cortical thickness and surface area
Tract-wise white matter integrity assessed via fractional anisotropy
White matter hyperintensity volumes
Subcortical grey matter volumes
Total cortical volume

Cognitive (age 45) –

Wechsler Adult Intelligence Scale - IV

Covariates:

Wechsler Intelligence Scale for Children Revised at ages 7, 9, and 11
Age, sex, BMI, blood pressure, lipids (LDL, HDL), inflammation (hsCRP), glucose at age 45
Highest education level
Socioeconomic status
Weight at birth

Significance of the Study (for theory, research methods or clinical practice):

This study proposal addresses a fundamental gap in our understanding of whether one of the major lifetime risk factors know to increase risk of CVD may also associate with the presence of subclinical brain and cognitive changes in mid-life which are believed to underlie dementia. These findings may ultimately help to shift health policies for brain health to be similar to that of heart health, in which a lifetime approach to healthy lifestyle choices is promoted as the most effective way of extending healthy years lived.

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