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Relationship between Cognition and Vascular Risk Factors in Women Enrolled in the Kronos Early Estrogen Prevention Cognitive and Affective Study (KEEPS C/A) at Baseline

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Background/ Significance: Numerous vascular risk factors (VRF) have been associated with an increased risk of Alzheimer's disease (AD) leading to speculation that vascular dysfunction plays a key role in the development and progression of the disease. For instance, epidemiologic studies show that men and women with elevated serum cholesterol levels in midlife are at increased risk of developing AD decades later. Moreover, hypercholesterolemia has been linked to cognitive impairments and may promote the development of AD through a variety of mechanisms, including via its negative effects on A β metabolism and cerebrovascular dysregulation. Similarly, many studies have demonstrated that blood pressure irregularity has a negative impact on cognitive performance, is an established mid-life risk factor for AD, and has been linked to increased cognitive impairment among AD patients.

While there is a clear relationship between cognition and clinically diagnosable VRF such as hypercholesterolemia, diabetes, hypertension and hypotension, the cutoff point at which a vascular factor becomes a 'risk' for AD is less understood. Similarly, VRF can influence cognitive task performance in populations whose levels are within clinically 'normal' limits. Wharton et al. and Knecht et al. both recently reported a relationship between cognitive task performance and blood pressure, extending into the normotensive range (i.e. below 140 mm Hg). Likewise, a retrospective study showed that mildly raised total cholesterol levels at middle-age may be an early risk factor for the development of AD. Similarly, borderline diabetes, defined as a random plasma glucose level of 7.8–11.0 mmol/l, has also been associated with poor cognitive performance and an increased risk of AD. Thus, although women enrolled in the KEEPS C/A study are healthy, the sample will serve as excellent pilot data for future research exploring the relationship between vascular factors and cognitive task performance.

While participants taking lipid lowering medications and statins were excluded from the KEEPS C/A Study, participants taking blood pressure medication were permitted to participate. This presents an additional novel avenue to explore the effects of blood pressure medications on cognition. Some studies report that use of antihypertensive medication, including angiotensin converting enzyme (ACE) inhibitors, β -blockers, calcium channel blockers and diuretics, significantly reduce the rate of cognitive decline and lowered the risk of AD. Also, antihypertensive medications vary in their ability to cross the blood-brain barrier (BBB), a factor which may have implications on the ability of these drugs to modify cognitive task performance, A β PP processing and risk for AD.

The primary purpose of the current study is to investigate the relationship between VRF and cognitive task performance in the healthy, middle – aged, cohort of women enrolled in the KEEPS C/A Study. Additionally, should the dataset yield a sufficient number of participants taking antihypertensives, we intend to explore the use of these medications in regard to each



medications' specific mechanisms of action (i.e. ACE inhibitor vs. calcium channel blocker), as well as their ability to cross the BBB.

Finally, in addition to describing the relationship between baseline cognitive and vascular measures and addressing the specificity and sensitivity of the psychometric tests, this manuscript will serve to and increase awareness of the KEEPS and the KEEPS C/A Studies, as well as guide new and ongoing investigations in regard to appropriate cognitive and affective testing measurements.

Objectives:

- 1) Characterize the relationship between cognitive task performance and variables most pertinent to vascular risk including, but not limited to: Systolic and diastolic blood pressure, Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, fasting glucose and plasma estradiol.
- 2) Examine cross-sectional data from baseline visits of women enrolled in the KEEPS-CA study, in order to characterize the relationship between cognitive task performance and blood pressure medication. Depending on the number of participants taking blood pressure medication, we will examine the potential cognitive effects of different classes of medications (i.e. ACE inhibitors vs. calcium channel blockers vs. β blockers) and within each class of medications, examine the cognitive effects of those that do and do not cross the blood brain barrier (i.e. Benazepril vs. Captopril)

Hypothesis: Based on initial KEEPS C/A reports (Wharton et al.) baseline physiological and cognitive data in the KEEPS Study will likely indicate that the cohort is healthy and free of cognitive dysfunction. Although KEEPS participants are healthy, we foresee a negative relationship within participants, such that an increase in VRF will result in a cognitive deficit.

Methods/Analysis Plan: After baseline data cleaning, a basic exploratory analysis using descriptive statistics (means, variances, covariances, and correlations) will be performed. Additionally, an analysis of the distributional properties of all variables considered in this proposal will be conducted and transformations to normality will be performed as needed. Product-moment correlations will be computed among all VRF variables and cognitive test measures to explore relations among theoretically relevant variables (as discussed in the above). Correlations attaining a significance at the $p < 0.05$ level will be reported. Linear multiple regression analyses will be carried out primarily to examine the effects of baseline cholesterol and blood pressure values data on cognitive task performance using age and years of education as covariates in the models. Other relevant predictors (e.g., estradiol) that might emerge as a result of the correlational analysis will be included in the model using a hierarchical regression modeling approach. Next, if the database yields an acceptable number of participants taking antihypertensive medications, we will conduct t-tests, controlling for age and education, in order to examine potential differential cognitive effects between types of medications (ACE inhibitors vs. calcium channel blockers) and within each class of medications, the differential effects of the medications' ability to cross the BBB.

Pertinent Variables: Analyses will utilize all cognitive variables, as well as the following laboratory variables: Systolic BP, diastolic BP, Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, fasting glucose and plasma estradiol.