Rationale And Design Of The Ace RCT: Protective Mechanisms Of S-equol On Vascular Function, Cognition And White Matter

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Background: Women are more likely to develop Alzheimer's disease (AD) than men, likely due, in part, to estrogen depletion during menopause and downstream impacts on brain and vascular function. Arterial stiffness, a hallmark of vascular aging, is linked to cognitive decline and dementia, yet there are no well-established interventions to prevent its progression. Elevated arterial stiffness impairs blood flow, which affects brain health, including increased white matter lesions and reduced cognitive function. S-equol, the most biologically potent soy isoflavone metabolite, is a selective estrogen receptor modulator (SERM) with vasoactive and neuroprotective properties. This compound, particularly common in populations consuming soy-rich diets, highlights the role of natural compounds in supporting cognitive function. Epidemiological studies in East Asia, where S-equol production is prevalent (40-70% of the population), have shown an inverse relationship between soy isoflavone intake and cognitive decline, including dementia diagnosis. In contrast, only 20-30% of Western populations produce S-equol, a discrepancy attributed to dietary, gut microbiome and genetic factors influencing the body's ability to metabolize daidzein into S-equol. This trial aims to bypass these metabolic limitations by directly supplementing S-equol.

Methods: This NIA-funded, double-blind, randomized, placebo-controlled clinical trial will evaluate the potential benefit of S-equol supplementation on arterial stiffness, white matter volume, and cognitive function over two years in 400 older men and women. The trial is conducted at the University of Pittsburgh, Emory University, and Wake Forest University. Arterial stiffness is assessed using pulse wave velocity, while cognitive function is assessed using standardized neuropsychological tests. Primary MRI outcome is white matter lesion volume.

Results: To date, 344 older adults aged 65-85 without dementia have been enrolled, comprising 15% African Americans and 85% non-Hispanic white participants, and 51% women. Average age is 72 yrs, 16.8 yrs of education. Average BMI is 26.6 and BP is 129/73mmHg and 42% are hypertensive.

Conclusion: Given the growing interest in non-pharmaceutical interventions for prevention of cognitive decline and neurodegenerative disease, this trial will determine whether S-equol confers cognitive benefits in individuals with low natural production of the compound, providing a targeted approach for reducing the risk of cognitive decline through accessible dietary supplemental modification.