WHI Investigator Investigator Meeting
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SUBCLINICAL DISEASE AS PREDICTORS OF VASCULAR DISEASE, AGING, COGNITION, AND DISABILITY

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Morbidity and Mortality

1. Morbidity and mortality at older ages is determined primarily by the extent of clinical and subclinical disease rather than levels of "traditional risk factors".

2. Most of the determinants of subclinical disease were present for many years (long incubation period). Therefore, current measures of the independent variables are inadequate.

3. Populations of older healthy individuals can be subdivided into those without major subclinical disease and with subclinical disease but who have successfully avoided conversion from subclinical to clinical diseases. These are 2 distinct populations likely differ in genomics, metabolomics, proteomics, etc.

Need For Better Phenotypes

4.	The determinants of these 2 subpopulations above are related to genomics, metabolomics, proteomics, epigenetic factors, etc., almost certainly differ from each other, and therefore separation of these subpopulations, e.g. the phenotype, is critical for etiological (epidemiological) research as well as genomics, etc. and probably for clinical trials, especially in older individuals.

5.	Research in the elderly, therefore, requires measures of subclinical disease as the independent variable and "diseases" such as Alzheimer's disease, dementia, heart failure, stroke, disability, as the dependent variable.

Types of Questions for WHI and Aging Research

1. Question – Why do some older women, perhaps 10-15% above age 80-85, have 0 CAC? Such women have substantial longevity and very low risk of dementia and disability.

2. Question – Is the apparent benefit of walking on subsequent risk of disability, dementia determined by increased brain blood flow, especially to the frontal lobes, improve executive function, including gait speed, decreased depression, socialization and better ADLs?

3. Is brain aging and peripheral (outside brain) aging determined by similar variables, e.g. can markers of peripheral aging predict brain aging and dementia?

4. Would "aggressive approaches" to prevention of atherosclerosis and arteriosclerosis among older women with low atherosclerotic burden decrease dementia and disability and increase longevity?

Types of Questions for WHI and Aging Research

5. Survival to older ages is determined primarily by 2 variables: the extent of CVD, especially subclinical disease, and fitness.

6. Practically all older women have extensive CAD as well as vascular disease in other "beds," especially the brain.

7. Fitness is, in part, determined by the extent of CVD but does not determine the extent of atherosclerosis or vascular disease.

8. Determinants of fitness include cardiac and pulmonary function, Hb (oxygenation of blood), muscle function, mitochondrial activity, and in part, determined by both physical activity and genomics.