Development of a New Measure for Genetic Risk of Alzheimer's Disease for Use in Economic and Social Science Research

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Proposal Abstract

Alzheimer's disease (AD) is one of our society's most pressing public health concerns. Every 65 seconds, someone in the United States develops Alzheimer's disease and the estimated cost for caring for Americans with AD is $277 billion[1]. Epidemiological studies suggest that most cases of Alzheimer's disease stem from a combination of genetic and environmental risk factors. However, work exploring interplay between genetic and social influences (e.g. gene x environment studies) in etiology of Alzheimer's disease has been hampered by the relative lack of a highly penetrant genetic predictor. In contrast, research on other major medical conditions such as cardiovascular disease are being advanced rapidly cite based on the development of predictive polygenic risk scores (PRS). A polygenic risk score is a measure of aggregate genetic risk for an individual that is calculated from Genome-Wide Association Study (GWAS)[2]. Their use is become increasingly popular in economics[3] and other social sciences and has been used in studies of wealth[4], educational attainment[5], and disease[6], among others.

The most well-established polygenic risk score is based on a large case-control GWAS of Alzheimer's disease[7], but has very poor predictive power in population-based studies of cognition such as the Health and Retirement Study (HRS) and Wisconsin Longitudinal Study (WLS). This may be in part because of the case/control nature of the GWAS; the very environmental influences we are trying to identify have already exhibited their lifecourse influence by the time individuals in the GWAS study are classified as cases or controls. Recent developments in the creation of polygenic scores have introduced methods for the joint analysis of summary statistics from GWAS of different traits[8] (e.g. MTAG, Genomic SEM) resulting in potentially much more powerful and informative polygenic risk scores.

We propose to (1) use these newly-developed method of joint analysis of summary statistics (specifically Genomic SEM) to create a new polygenic risk score for Alzheimer's disease and (2)

to evaluate performance of this score in population-based studies of health and aging such as the HRS. We do so through the joint analysis of 5 recent GWAS from AD phenotypes from imaging[9] and autopsies[10], phenotypes that are more proximate measures of disease and less confounded by environmental factors. Our work plan will take the following steps: First, we will utilize Genomic SEM methods to recreate a new polygenic risk score from the 5 AD GWAS results. Secondly, we will test the predictive power of this score in HRS relative to the existing polygenic risk score in use. Thirdly, we will validate these results in the WLS. We already have access to the AD summary statistics to be used as inputs as well as the genetic data for both HRS and WLS. Successful findings from this pilot grant could unlock a large number of research possibilities examining the social and economic influences and consequences of Alzheimer's disease and are consistent with current NIH/NIA funding priorities.

References

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