Genes, Alzheimer's Disease and Related Dementias (ADRD) and Economic Outcomes

Principal Investigator: Meghan M. Skira
Associate Professor of Economics
University of Georgia

Co-Investigators: Yeongmi Jeong
Ph.D. Student in Economics
University of Georgia

Nicholas W. Papageorge
Broadus Mitchell Associate Professor of Economics
Johns Hopkins University

Kevin Thom
Assistant Professor of Economics
University of Wisconsin – Milwaukee

Study Aims: Recent advances in behavioral genetics have led to the discovery of specific genetic variants that predict complex health outcomes, such as Alzheimer's disease (AD).[1,2] We aim to study associations between these variants, summarized as a linear index known as a polygenic score, and economic outcomes. Loosely, a higher polygenic score for AD (henceforth: the *AD score*) means an individual possesses more of the genetic variants associated with AD. We will also study one particular marker – APOE ε4 – separately given its substantial established links to AD. To examine relationships between genetic measures and individual outcomes, we will use data from the Health and Retirement Study (HRS), which follows a nationally representative sample of U.S. adults above age 50. The data include detailed health and economic variables for older Americans. Moreover, a large portion of the sample has been genotyped, which means the AD score and other genetic measures can be computed for thousands of individuals and paired with detailed lifecycle health and economic information. The overarching goal of the proposed research is to understand how a genetic predisposition for AD affects lifecycle behavior and outcomes; through which particular channels this occurs; how these dynamics relate to other genetic variants (e.g., those for education); and, ultimately, what policies or measures could mitigate the potential detrimental effects of a genetic predisposition for AD. Our study has four specific aims.

(a) We will estimate descriptive relationships between our genetic measures for AD, the development of Alzheimer's disease and related dementias (ADRD), and economic behavior and outcomes, including: employment, labor income, retirement age and wealth accumulation.

(b) We will explore mechanisms that explain any empirical associations between genetic variants related to AD and economic outcomes. For example, we find a negative relationship between genetic variants for AD and wealth at retirement. Additional analyses can help determine whether this relationship is due to medical expenditures, poor financial and investment decisions or other factors.

(c) We will provide initial evidence on whether policies or institutional features, such as defined benefit pension (DB) schemes or default long-term care insurance (LTCI) provision, could potentially counteract negative consequences of genetic variants related to AD.

(d) We will investigate whether (and through what mechanisms) genetic variants associated with education correlate and interact with – or counteract the effects of – genetic variants for AD.

Significance: ADRD entails massive costs to individuals and their families.[3-5] Some are direct medical expenditures.[4-7] Less direct costs include family members' time or effort to care for sick individuals, which can lead to time out of the labor market and lost income.[5,6,8,9] Other costs arise because individuals who are eventually diagnosed with ADRD experience cognitive decline earlier in life, which can lead to low productivity, early retirement, and poor financial decisions.[10,11,12] These factors can lead to low retirement wealth, which is particularly concerning because older individuals are vulnerable to costly health shocks and because it is difficult for retirees to recoup lost wealth. Thus, it is of policy interest to understand the indirect costs of ADRD.

There are several challenges to investigating these costs, however. One, some people with ADRD are never diagnosed, perhaps due to lack of access to care, early mortality or if the case is mild.[13,14] Two, it is not clear when decline begins.[i] Three, due to the discrete nature of diagnoses, it may be difficult to distinguish people with different ADRD severity in data sets, such as the HRS, even after adjusting for rich information on cognition and family structure. For example, people with the same diagnosis but vastly different outcomes may have different underlying severity of illness or the same severity, but different circumstances, e.g., support systems.

Innovation: The key innovation is the incorporation of genetic data on AD into analyses of health and economic outcomes. Literature using polygenic scores is nascent, but growing, in large part due to the discovery of genetic variants related to particular outcomes (e.g., AD) and the genotyping of large sets of individuals in nationally representative data sets. To understand this innovation, consider that genetic predispositions have heretofore been largely unobservable sources of variation across individuals.

Observing genetic variants allows us to examine people who may never be diagnosed, but who could suffer some amount of cognitive decline that is difficult to detect using available tests. We can also examine when symptoms begin to emerge regardless of whether individuals are ever diagnosed. Moreover, we can distinguish differences between people with similar diagnoses, but different AD scores.

[i] Nicholas et al. (2020) shows that difficulties making financial decisions begin as early as 6 years prior to diagnosis.

By investigating genetic predispositions for ADRD, we are also able to examine an intriguing possibility that is of policy relevance: the degree to which such a predisposition leads to precautionary measures. People with a high AD score may make poor financial decisions due to early onset of cognitive decline. On the other hand, they may be aware of their predisposition (either due to early signs of decline they or their family have noticed or due to a family history with ADRD) and thus prepare for eventual symptoms, e.g., through reliance on DB pension schemes, the purchase of LTCI, divestments, financial transfers to younger members of the family, etc. This will be helpful as we consider policies that address the full costs of ADRD, such as universal LTCI or DB pension schemes. Examining the relationship between precautionary measures and the AD score is also of policy relevance because it provides some guidance on what would happen if individuals were made aware of their genetic risk for AD. This is an ongoing debate since it is not clear if informing people of their score will lead them to prepare or to despair.[15,16; ii]

Another innovation is the ability to examine the AD score alongside other genetic variants. Of particular interest is the polygenic score for educational attainment (henceforth: the *EA score*), which earlier research has shown to predict a host of lifecycle outcomes even after controlling for completed education, including financial decisions and retirement wealth.[17] This means we can assess whether some genetic variants counteract the detrimental effects of genetic variants for AD and, if so, through what channels this occurs, which could provide guidance for the types of policies we should explore if the aim is to mitigate potential effects of a high AD score.

Approach: The four aims of this study require empirical work that is fairly standard (e.g., cross tabulations, correlations, multivariate regression analysis and non-parametric regressions). Interpretation of estimated relationships requires some care. For example, it is difficult to conclude that estimates relating genetic variants to economic outcomes are *causal*. The concern is that genes may also capture environmental factors that contribute to ADRD. Nevertheless, earlier work has shown that biases in estimated parameters tend to be small once certain key control variables are added (e.g., mother's education).[17] Moreover, for some analyses, an argument for causality can be made. To examine the impact of ADRD on spouses, we could examine the lifecycle outcomes of two individuals with similar family backgrounds, one with and one without a spouse who is a carrier of APOE ε4. The idea is that marriage to somebody with one-specific variant is arguably quasi-randomly assigned, which means we can study the causal impact of having a spouse with the APOE variant.

More broadly, the goal of the current project, embodied in our aims, is to explore basic relationships between genes and complex economic outcomes. What we learn from this work will provide an input into future work, which will build more elaborate models to be used to make more precise statements about policy.[iii] Preliminary analyses show there is much to learn. We tend to find statistically and economically significant relationships between the AD score and economic outcomes, such as retirement wealth.

Future Aims: The current project will engender future projects and grant proposals to support it. There is great interest in understanding the myriad mechanisms that generate later-life economic inequality and so there is demand for the type of work we plan to do. This proposed project will be particularly useful by providing insights that guide the development of more elaborate models. In particular, once this work is complete, we aim to develop and estimate a structural lifecycle model of retirement, savings, LTCI and later-life planning (e.g., purchasing LTCI or life insurance). We will use the estimated model to simulate a broad range of policies and interventions (e.g., lowering LTCI premiums, changing the full retirement age, universal LTCI coverage and providing individuals information about their ADRD risk), and study how they impact retirement timing and wealth, end-of-life and long-term care (LTC) planning, and actual LTC receipt. The model will also allow us to estimate whether these policies have differential effects on individuals based on their genetic risk. These differential effects may show up in behavior, outcomes or welfare measures. Such a model is computationally burdensome, so it is of critical importance to know what features need to be added and which can be safely omitted. The current proposed project embodied in the aims will provide us with necessary guidance.

[ii] No one in the HRS sample we will examine is aware of their polygenic score because they were followed at a time when genotyping was possible, but polygenic scores for complex outcomes, such as the AD score, had not yet been developed.

[iii] This progression mimics what two of the authors have done in previous work focused on the EA score.[17,18] Initial projects identified key relationships that are inputs into more elaborate models in research that is currently underway.

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