Alzheimer's disease genetic risk variants beyond APOE ε4 predict mortality

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Genetics

Alzheimer’s disease genetic risk variants beyond \textit{APOE} $\epsilon 4$ predict mortality

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Abstract

**Introduction:** We hypothesized that, like apolipoprotein E (\textit{APOE}), other late-onset Alzheimer’s disease (LOAD) genetic susceptibility loci predict mortality.

**Methods:** We used a weighted genetic risk score (GRS) from 21 non-\textit{APOE} LOAD risk variants to predict survival in the Adult Changes in Thought and the Health and Retirement Studies. We meta-analyzed hazard ratios and examined models adjusted for cognitive performance or limited to participants with dementia. For replication, we assessed the GRS-longevity association in the Cohorts for Heart and Aging Research in Genomic Epidemiology, comparing cases surviving to age $\geq 90$ years with controls who died between ages 55 and 80 years.

**Results:** Higher GRS predicted mortality (hazard ratio = 1.05; 95% confidence interval: 1.00–1.10, $P = .04$). After adjusting for cognitive performance or restricting to participants with dementia, the relationship was attenuated and no longer significant. In case-control analysis, the GRS was associated with reduced longevity (odds ratio = 0.64; 95% confidence interval: 0.41–1.00, $P = .05$).

**Discussion:** Non-\textit{APOE} LOAD susceptibility loci confer risk for mortality, likely through effects on dementia incidence.

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Keywords: Alzheimer’s disease; Longevity; Mortality; Survival analysis; Genetic risk score; Selection bias; Collider stratification bias; Survivor bias; Genome-wide association study (GWAS); \textit{APOE}; Adult Changes in Thought (ACT); Health and Retirement Study (HRS); Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)

1. Introduction

Risk variants from 22 genes have been identified for late-onset Alzheimer’s disease (LOAD) incidence. Of these, apolipoprotein E $\epsilon 4$ (\textit{APOE} $\epsilon 4$) has the largest effect [1].
Genome-wide association studies (GWASs) of longevity in older adults have identified APOE e4 as a risk factor for mortality [2–4]. This risk may be partially mediated through dementia incidence [5,6], as dementia is a leading cause of mortality in older adults [7]. Given the association of both APOE e4 and dementia with mortality, we hypothesized that other genetic variants associated with LOAD incidence would also be associated with mortality in older adults. We anticipated that cognitive function and dementia incidence would mediate the relationship with mortality. In other words, we expected that LOAD genetic risk variants would increase risk for cognitive decline and LOAD dementia, which would in turn increase risk for death (Fig. 1, solid arrows).

Quantifying and explaining the link between LOAD genetic risk and mortality is critical for genetic research on determinants of LOAD incidence: severe survivor bias could make it difficult to identify genetic variants that increase disease incidence or could falsely implicate genetic variants that are not actually associated with disease incidence [8]. For example, LOAD cases who are APOE e4 carriers may be omitted from research because they declined faster and died before study enrollment or disease ascertainment [9]. APOE has also been implicated in risk for other disease processes including cardiovascular disease [10], so it may influence mortality via mechanism(s) other than dementia, thereby introducing potential survivor bias in its relationship with LOAD. By assessing whether non-APOE genes associated with LOAD are also associated with increased mortality, we can provide reassurance that the effect estimates of these loci are not actually associated with disease incidence [8].

Here, we attempt to replicate the previously reported link between APOE e4 and mortality and, in novel analyses, assess whether non-APOE loci, previously found to be associated with LOAD incidence, are also associated with mortality. Because the effect size for each non-APOE variant is small, we estimate the combined genetic risk that each subject had for developing LOAD by calculating a genetic risk score (GRS). In primary analyses in two longitudinal population-based prospective cohort studies, the Adult Changes in Thought (ACT) study and the Health and Retirement Study (HRS), we assessed the GRS relationship with time to death using survival analysis. In subsequent models, we tested whether cognition or dementia mediated or moderated the relationship between the GRS and mortality. We conducted a follow-up, confirmatory case-control analysis in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), comparing the GRS among longevity cases age ≥90 years versus controls who died between ages 55 and 80 years. Our findings could suggest new genetic risk loci for longevity, add insight into how LOAD risk loci affect dementia incidence and disease course, and provide reassurance that the effect estimates of these loci on LOAD incidence do not suffer from selection bias.

2. Methods

2.1. Study populations

2.1.1. Adult Changes in Thought

The ACT cohort draws from a population base defined by the Group Health membership; the Group Health is an integrated healthcare delivery system in King County, WA. The ACT study enrolled 3392 cognitively normal community-dwelling adults 65 years or older in two enrollment phases (n = 2581 in 1994–1996 and n = 881 in 2001–2003) and initiated ongoing enrollments in 2004. After obtaining informed consent, in-person biennial interviews assessed participants’ demographic, medical history, and functional status. ACT stopped assessing participants diagnosed with dementia but still obtained mortality information. For the current analyses, from 4131 individuals with ACT visits, we excluded participants who self-reported to be Hispanic or nonwhite (to avoid confounding from population stratification; n = 383) or who were not genotyped (n = 1418). This left an analytic sample of 2330 individuals.

2.1.2. Health and Retirement Study

The HRS is a nationally representative cohort study initiated in 1992 with enrollments in 1992, 1993, 1998, 2004, and 2010. The target population is all noninstitutionalized adults in the contiguous United States aged 50+ years. Biennial interviews (or proxy interviews for decedent or severely impaired participants) are available through 2012 [12]. Our analyses used a subsample with genetic data collected in 2006 or 2008. From 20,662 individuals alive in 2006 with HRS visits, we excluded participants who were not genotyped (n = 8580), who self-reported to be Hispanic or nonwhite (to avoid confounding from population stratification; n = 2894), or who were under age 65 years (to mimic ACT; n = 3224). This left an analytic sample of 5964 individuals.

2.1.3. Cohorts for Heart and Aging Research in Genomic Epidemiology

The CHARGE consortium includes participants from the following studies: Rotterdam Study, Study of Osteoporotic Fractures, Cardiovascular Health Study, Osteoporotic Fractures in Men Study, Framingham Heart Study, Health and Retirement Study, Age, Gene/Environment Susceptibility—Reykjavik Study, Religious Orders Study, Rush Memory and Aging Project, Invecchiare nel Chianti, Baltimore Longitudinal
Study of Aging, New England Centenarians Study, Long Life Family Study, and European Union Longevity Consortium. The current analysis includes the same participants as a case-control GWAS of longevity reported previously [13]. Only the participants of European ancestry were included. There were 6036 cases, defined as participants who reached age ≥90 years, and 3757 controls, defined as participants who died between the ages of 55 and 80 years.

All individuals were recruited under the protocols approved by the appropriate Institutional Review Boards.

2.2. Measures

2.2.1. GRS for LOAD

Genotyping, imputation, and derivation of principal components to control for population substructure are described in the Supplementary Methods, and further details have been described previously for ACT [14], HRS [15], and CHARGE [13].

In ACT and HRS, we generated a weighted GRS for LOAD based on the effect size of single-nucleotide polymorphisms (SNPs) that achieved genome-wide significance. Twenty-one genetic loci, other than APOE, have been confirmed as genome-wide significant predictors of LOAD, with meta-analyzed odds ratios (ORs) reported most recently in the Lambert et al. meta-analysis [1]. Because some of the reported SNPs from Lambert et al. could not be confidently imputed, we used proxy SNPs (two in ACT; four in HRS) reported most recently in the Lambert et al. meta-analysis [1].

2.2.2. Mortality

In ACT, we used mortality information obtained via death certificates, state death registry data, annual telephone contact with family members of study participants with dementia, quarterly mailings to participants, and thorough review of local obituaries. In HRS, we used mortality information obtained via National Death Index linkage from 2008 to 2012. Information from proxy interviews was used for individuals without National Death Index information.

2.2.3. Cognitive performance

In ACT, cognitive performance was assessed using the Cognitive Abilities Screening Instrument (CASI) [17]. Raw scores range from 0 to 100, with higher scores indicating better performance. Because of concerns about nonlinear scaling, we used CASI scores that were previously derived using the item response theory [18]. In HRS, we used a previously developed memory composite score combining direct and proxy memory assessments for longitudinal analyses. All HRS participants who were interviewed directly were asked to complete an immediate and delayed recall test based on a 10-word list. For individuals too impaired to directly participate in memory assessments, the informants, typically spouses, assessed the participants’ memory on a 5-item Likert scale and completed a 16-item version of the Informant Questionnaire for Cognitive Decline (IQCODE). We used an algorithm to integrate direct and proxy assessments to retain severely impaired individuals in longitudinal studies of cognitive function. The composite score was derived in an 856-subject subsample who participated in a comprehensive neuropsychological battery as part of the Aging, Demographics, and Memory Study and then uses regression models to calibrate the direct and proxy reports from the prior HRS core interview to predict the Aging, Demographics, and Memory Study outcomes. We then apply these prediction rules to estimate memory in the entire HRS sample [19]. We standardized the memory score by dividing each score by the 1995 standard deviation so that every unit change in memory score corresponded to one standard deviation in the population before baseline.

2.2.4. Dementia diagnosis in ACT

At baseline and every 2 years, ACT participants were administered the CASI. Those with raw scores below 86 received a diagnostic evaluation that included physical and neurological examinations, neuropsychological testing, and laboratory studies, if not already available. A consensus panel, which included study physicians, a neuropsychologist and a research nurse, determined whether these participants met criteria for dementia based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria [20]. Participants remained in the cohort until they were diagnosed with dementia or, if not demented, were censored as a result of death or discontinuation of participation in the study.

2.2.5. Covariates

All models that included ACT and HRS participants were adjusted for time constant covariates: sex, intake age, intake age², wave of genetic data collection, and the first three (in ACT) or six (in HRS) principal components used to adjust for population substructure in genetic analyses.

2.3. Analytic plan

In ACT, we used Cox proportional hazards models to estimate the association between the GRS and APOE e4 with dementia onset date. We did not evaluate this relationship in HRS because we recently published these analyses for HRS separately, reporting that the GRS and APOE e4 both...
predicted dementia probability and memory score [21].
Next, in ACT and HRS, we used Cox models to estimate
the independent effects of the GRS and APOE e4 on time
to death. We used time from study baseline as the timescale
in the Cox models. In subsequent models in both ACT and
HRS, we adjusted for cognitive performance using either
time-dependent CASI-item response theory in ACT or
time-dependent memory score in HRS. To further explore
the role of dementia in explaining the link between the
GRS and mortality, we stratified follow-up time for ACT
participants by dementia diagnosis. We defined the
dementia-free group as anyone who had not been diagnosed
with dementia by the current visit, even if they were diag-
nosed at a later date. Our dementia-diagnosed group was
defined as anyone with a dementia diagnosis at the current
or previous visit, and in these analyses, follow-up time for
the Cox models began at diagnosis instead of study baseline.
Therefore, some people contributed person-time to both cat-
egories, that is, before and after diagnosis. If dementia inci-
dence was the primary mechanism linking the GRS to
mortality, we would not expect the GRS to have a large effect
on mortality in either the dementia-free or the dementia-
diagnosed groups, assuming no misclassification.

We meta-analyzed the estimated effect of the GRS on time
to death in ACT and HRS from both the unadjusted model and
the model adjusting for time-dependent cognitive performance,
using a fixed effects model with inverse variance weights, as
implemented in the metan package in Stata 11.2 [22].

In CHARGE, because individual-level data were not
available, we reanalyzed the published summary statistics
for the GRS as a linear predictor of longevity as follows:

\[ \hat{a} = \frac{\sum_{i=1}^{m} W_i \hat{\beta}_i S_i^2}{\sum_{i=1}^{m} W_i S_i^2} \]

with a standard error estimate of

\[ se(\hat{a}) = \sqrt{ \frac{1}{\sum_{i=1}^{m} W_i S_i^2} } \]

where i indexes the SNPs in the GRS, \( W_i \) is the parameter es-
timate of SNP i on the log odds of LOAD status, \( \hat{\beta}_i \) is the
parameter estimate of SNP i on the log odds of longevity sta-
tus, and \( s_i \) is the standard error of \( \hat{\beta}_i \) [23,24].

3. Results

Characteristics from the first wave in which each individ-
ual contributed an observation are shown for the 2330 ACT
sample members and 5964 HRS sample members used in
our models (Table 1). Average follow-up time was 8.6 years
(up to 18 years) in ACT and 4.6 years (up to 6 years) in HRS.
In ACT, 1267 (54.4%) participants died during the study,
whereas 705 (11.8%) died in HRS. When we limited the
follow-up time in ACT to match HRS (i.e., 6 years), 561
(23.7%) participants died. Characteristics of each cohort
from the CHARGE consortium have been described
previously [13].

In ACT, both the GRS (hazard ratio [HR] = 1.27; 95%
confidence interval [CI]: 1.14–1.41) and APOE e4
(HR = 1.98; 95% CI: 1.62–2.43) predicted time to dementia
onset. Using Cox models, we found a significant association
between higher GRS and time to death, but not between
APOE e4 and time to death (Table 2). In models adjusted
for time-dependent CASI score, the association between
the GRS and time to death was attenuated by more than
half and was no longer significant. In addition, we found
no evidence that the GRS predicted time to death when re-
stricting analyses to either individuals with or individuals
without a dementia diagnosis.

In HRS, the association between the GRS and time to
death was not statistically significant, although the 95% CI
included the point estimate from the ACT model. The point
estimate in HRS was attenuated by about half when the time-
dependent memory score was included in the model,
although the absolute change was small from a point esti-
mate of 1.02 to 1.01 (Table 3). We found no evidence of
an association between APOE e4 and time to death.

In the meta-analysis of the ACT and HRS results from the
models unadjusted for cognitive performance, there was a
significant association between the GRS and time to death
(Table 4). In the meta-analysis of the models adjusted for
time-dependent cognitive performance, we found that the
point estimate was attenuated by about 60% and was no
longer statistically significant. Using GWAS summary sta-
tistics for longevity from the CHARGE [13] and for
LOAD from the Lambert et al. meta-analysis [1], we found
an OR of 0.64 (95% CI: 0.41–1.00), suggesting the GRS
reduced chances of living past age 90 years.

4. Discussion

In the ACT study, we found that a GRS based on 21 non-
APOE loci that achieved genome-wide significance in a
large meta-analysis of LOAD incidence [1] predicted reduced time to death, and this association was largely explained by cognitive function or dementia incidence. Although the GRS was nonsignificantly associated with higher mortality in the HRS sample, adjusting for cognitive performance attenuated the association to a similar magnitude, as in ACT, albeit the absolute change was quite small. In addition, the meta-analysis of ACT and HRS supported an association between the GRS and time to death and an attenuation of that association with adjustment for time-dependent cognitive performance. As confirmation of the unadjusted result, we found that the GRS predicted reduced odds of surviving to age ≥90 years (compared to dying between the ages of 55 and 80 years) in participants in the CHARGE Consortium.

We investigated whether the GRS was related to mortality because APOE e4, the largest risk allele for LOAD, has consistently been identified as a risk factor for death in the GWAS of longevity [2–4]. The heritability of longevity has been estimated to be approximately 20% to 30%; however, with many complex traits, genetic risk factors for longevity identified through GWAS only account for a small portion of the predicted heritability, suggesting other loci also contribute [25]. Our findings suggest that LOAD risk loci other than APOE e4 may contribute to the heritability of longevity, most likely via their influence on dementia incidence.

Although most genetic studies of longevity have used a case-control design, comparing long-lived “cases” with younger “controls”, a few studies have used survival analysis in a community-based cohort. These survival studies have allowed for investigation of whether dementia status mediates the effect of APOE e4 on longevity, but results have been inconsistent. Two smaller studies showed that dementia mediates the relationship [5,6], whereas a larger meta-analysis of several cohorts did not show evidence of mediation [26]. APOE e4 has also been implicated in risk for other disease processes including cardiovascular disease [10], so it may influence longevity via mechanism(s) other than dementia. In our study, we found an estimated effect of the GRS on mortality, but we did not find statistically significant associations between APOE e4 and mortality in either ACT or HRS. The lack of association with APOE e4 may reflect the older age of the ACT and HRS samples considered here, as carriers may not have been included because they were already impaired by age 65 years. Of note, the HRS begins enrollment at age 50 years, and when we included all genotyped participants (rather than just those age >65 to mimic ACT), APOE e4 still was not significantly associated with mortality. Another possibility is that we were simply underpowered to detect an association. Although CIs describing the association between APOE e4 and mortality in ACT (0.91, 1.17) and in HRS (0.91, 1.27) were consistent with increases in mortality, the previous longevity studies reported point estimates larger than the upper bounds of these CIs. A third possibility is true heterogeneity of effects of APOE e4 across populations, for reasons that remain to be discovered.

The estimated effect of the GRS on mortality was attenuated by adjusting for cognition, providing evidence that the GRS influences mortality primarily through cognition (Fig. 1, arrows 1–3, 5). Collider stratification bias, a type of survival bias that can occur when stratifying on a variable in a causal system that is a shared effect of more than one

Table 2
Hazard ratios and 95% confidence intervals for GRS and APOE e4 status on time to death in the ACT study

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Pooled analyses (N = 2330)</th>
<th>Stratified analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>AD-GRS</td>
<td>1.07 (1.01–1.14)</td>
<td>.03</td>
</tr>
<tr>
<td>APOE e4 (yes/no any e4 alleles)</td>
<td>1.03 (0.91–1.17)</td>
<td>.64</td>
</tr>
<tr>
<td>CASI score</td>
<td>0.59 (0.55–0.62)</td>
<td>.07</td>
</tr>
</tbody>
</table>

Abbreviations: ACT, Adult Changes in Thought; AD-GRS, Alzheimer’s disease genetic risk score; CASI, Cognitive Abilities Screening Instrument; CI, confidence interval; HR, hazard ratio; SD, standard deviation.

NOTE. All models were adjusted for sex, intake age and age2, wave of genetic data collection, and the first three principal components of population substructure. Models include pooled analyses with and without adjustment for time-dependent CASI score and dementia-stratified analyses.
cause [27], is recognized as an important potential bias in genetic studies of LOAD but has rarely been formally assessed. Because genes can influence mortality through more than one mechanism (pleiotropy), genetic studies of late-life health outcomes, which by default stratify on survival (i.e., only those who have survived can be studied), may suffer from collider stratification bias [8]. This study provides evidence that collider stratification bias is less likely to be a large concern in genetic studies of LOAD. Because most of the effect of the GRS on mortality was through cognition (Fig. 1, arrows 1–3, 5) and not an alternative pathway (Fig. 1, of the effect of the GRS on mortality was through cognition [29]. Here, it allowed us to investigate the mechanism by which the GRS affects mortality.

Important limitations of this study include the possibility that people with prodromal LOAD were at higher mortality risk before diagnosis, as suggested by the nonsignificant but slightly elevated mortality risk associated with the GRS among people without a dementia diagnosis in ACT. This is partially mitigated by the ACT study practice of decreasing the time between visits from 2 years to 1 year for participants with impaired CASI scores who do not meet criteria for dementia, so that they can be followed more closely. Another limitation is that we did not replicate in HRS the association of the GRS with mortality that we observed in ACT. However, the HRS genetic cohort had accumulated a relatively small number of deaths at the time of this analysis, leading to wide CIs; the HRS and ACT results were consistent based on the CIs. In addition, the CHARGE case-control analysis provided confirmation (if not true replication) of the ACT finding. The CHARGE consortium longevity case-control analysis included 785 HRS participants (out of 9793 total participants), many of whom were likely included in our HRS survival analysis. Unfortunately, it was not possible to conduct CHARGE analyses without these individuals. A further limitation is that we could only examine genetic variants that have been shown to predict LOAD; to the extent that survivor bias is severely affecting LOAD GWAS, some important genetic risk factors for LOAD may not yet have been identified. There is no straightforward solution to this problem, but it suggests the potential value of evaluating sensitivity to survival bias in the primary GWAS. Finally, we note that the lack of evidence for a pathway from the GRS to mortality that does not go through cognitive decline is not necessarily evidence for the absence of the pathway. Rather, we may not have power to detect a small effect.

Table 4
GRS survival meta-analysis and longevity case/control analysis

<table>
<thead>
<tr>
<th>Studies</th>
<th>N</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Effect size* (95% CI)</td>
<td>Effect size* (95% CI)</td>
</tr>
<tr>
<td>Survival meta-analysis (ACT and HRS)</td>
<td>7294</td>
<td>1.05 (1.00–1.10)</td>
<td>1.02 (0.97–1.07)</td>
</tr>
<tr>
<td>Longevity case/control (CHARGE)</td>
<td>9793</td>
<td>0.64 (0.41–1.00)</td>
<td>.47</td>
</tr>
</tbody>
</table>

Abbreviations: ACT, Adult Changes in Thought; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; CI, confidence interval; GRS, genetic risk score; HR, hazard ratio; HRS, Health and Retirement Study; OR, odds ratio.

*HRs for survival models and OR for case/control model. Note HRs and ORs are not on the same scale and cannot be directly compared.

**Controls (died between the ages of 55 and 80 years) are the reference group.
In conclusion, we found that a non-APOE LOAD GRS is associated with mortality and that this relationship may be mediated by cognitive changes before dementia diagnosis. Our study identifies new genetic risk factors for longevity and provides insight into the mechanism by which they may act. It also provides evidence that collider stratification bias is unlikely to be a large concern in genetic studies of LOAD. Future studies that are better powered should investigate the role of LOAD genetic risk factors on mortality among nondemented older individuals.

Acknowledgments

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.dadm.2017.07.002.

RESEARCH IN CONTEXT

1. Systematic review: We searched PubMed to identify relevant publications. References that contextualize the hypothesis, methodology, and findings are cited. To our knowledge, no previous study has analyzed the relationship between the cumulative effect of non-APOE late-onset Alzheimer’s disease (LOAD) genetic risk variants and mortality.

2. Interpretation: Our findings suggest new genetic risk loci for longevity, add insight into how LOAD risk loci affect dementia incidence and disease course, and provide reassurance that the effect estimates of these loci on LOAD incidence do not suffer from selection bias.

3. Future directions: We find that a fraction of the mortality risk from LOAD risk variants is related to cognitive deterioration before the diagnosis of dementia, but larger data sets are necessary to more precisely quantify this effect in dementia-free individuals.

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