Polygenic Risk Score Effectively Predicts Risk of Depression Onset in Alzheimer's Disease

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Research

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Abstract

Introduction: Depression is a common, though heterogenous, comorbidity in late-onset Alzheimer's Disease (LOAD) patients. In addition, individuals with depression are at greater risk to develop LOAD. In previous work, we demonstrated shared genetic etiology between depression and LOAD. Collectively, this evidence suggested interactions between depression and LOAD. However, the underpinning genetic heterogeneity of depression co-occurrence with LOAD is largely unknown.

Methods: Major Depressive Disorder (MDD) genome wide association study (GWAS) summary statistics were used to create polygenic risk scores (PRS). The Religious Orders Society and Rush Memory and Aging Project (ROSMAP) and National Alzheimer's Coordinating Center (NACC) datasets were utilized to assess the PRS performance in predicting depression onset in LOAD patients.

Results: The developed PRS showed marginal results in standalone models for predicting depression onset in both ROSMAP (AUC=0.540) and NACC (AUC=0.534). Full models, with baseline age, sex, education, and *APOEε4* allele count, showed improved prediction of depression onset (ROSMAP AUC: 0.606, NACC AUC: 0.583). In time-to-event analysis, standalone PRS models showed significant effects in ROSMAP (P=0.0051), but not in NACC cohort. Full models showed significant performance in predicting depression in LOAD for both datasets (P<0.001 for all).

Discussion: This study provided new insights into the genetic factors contributing to depression onset in LOAD and advanced our knowledge of the genetics underlying the heterogeneity of depression in LOAD. The developed PRS accurately predicted LOAD patients with depressive symptoms, thus, has clinical implications including, diagnosis of LOAD patients at high-risk to develop depression for early anti-depressant treatment.

Introduction

Neuropsychiatric symptoms (NPS) are common in Late-onset Alzheimer's Disease (LOAD), characterized by heterogeneity with highly variable onset duration and severity. Amongst LOAD with comorbid NPS, depression and anxiety are the most prevalent[1–5]. Furthermore, individuals with depression are at greater risk to develop LOAD, suggesting that treating depression may delay LOAD[2, 6]. In addition, distinct trajectories of increasing risk of depression were associated with LOAD pathology such as, lower cerebrospinal fluid (CSF) $A\beta_{42}$ and higher CSF total and phosphorylated tau, highlighting the heterogeneity of depression within LOAD[5]. Interestingly, we previously identified shared genetic etiology between LOAD and major depressive disorder (MDD)[6]. Collectively, this evidence lends support for inter-relationships between LOAD and depression disorders[6].

Polygenic risk scores (PRS) offer a method to explore such relationships that may exist between LOAD and depression. The current LOAD polygenic risk scores (PRS) landscape focusses on predicting LOAD diagnosis[7–12], with a few studies applying pathway and functional analysis to the selection of SNPs for

PRS calculation[13,14]. LOAD PRS have been tested to predict mild cognitive impairment (MCI) to LOAD progression[7,12,15]. Additionally, studies have tested PRS association with LOAD phenotypes in CSF biomarkers[7,11–16] and motor-function impairment[17]. Other than associations with biomarker data, the effectiveness of PRS to predict LOAD heterogenous endophenotypes especially comorbid NPS, including depression, has yet to be thoroughly examined.

In this study we generated and tested the effectiveness of PRS to predict depression risk and onset time course in LOAD patients. We created a novel PRS based on MDD genome wide association study (GWAS) summary statistics and examined its utility in predicting the risk to develop depression symptoms in LOAD patients using two well-characterized LOAD cohorts from the Religious Orders Study and Rush Memory and Aging Project (ROSMAP)[18–20] and National Alzheimer's Coordinating Center (NACC)[21] projects.

Methods

GWAS data for PRS construction

The MDD GWAS (PGC-MDD2) conducted by Wray et al. included summary statistics of *P* values, odds ratios, standard errors, reference and alternate alleles, imputation quality score (INFO), and direction of effect in each cohort from the Psychiatric Genomics Consortium[22]. Data for 5 cohorts described by Wray et al were acquired (deCODE, Generation Scotland, GERA, iPSYCH, and UK Biobank) and used in this study. These results included genotyped and imputed data on 13,554,489 SNPs from 59,851 MDD cases and 113,154 controls. Primary manuscripts for the MDD GWAS[22] further describe details regarding genotyping procedure, quality control, and GWAS analysis. Constraining to SNPs with high quality imputation scores (INFO > 0.9) lead to 8,209,158 SNPs remaining. All genomic coordinates are based on NCBI Build 37/USCS hg19.

Study cohorts

Two cohorts were used to evaluate the performance of the PRS in predicting risk of depression onset: ROSMAP and NACC. We used only the samples that had available genetic data and information on depression phenotypes. All samples were LOAD patients. Cases were defined as LOAD with depression symptoms, and controls were LOAD individuals who did not experience depression (Fig. 1). To further control for *APOE* as a cofounding factor, we repeated the analyses using sub-cohorts stratified into *APOEε3* homozygotes (Fig. 1). Of note, the ROSMAP sample is also included in the NACC data. Table 1 summarized the descriptive statistics for the ROSMAP and NACC samples used in this study.

Table 1
Sample Demographics

	ROSMAP (n = 1708)		NACC (n = 7627)	
Sample	Full LOAD Sample	*APOEε3* Homozygote Sample	Full LOAD Sample	*APOEε3* Homozygote Sample
Subjects	n = 517	n = 284	n = 2968	n = 1092
Female %	68.0%	70.4%	52.1%	50.3%
Mean Education in years (SD)	16.2 (3.7)	16.2 (3.8)	15.6 (6.9)	15.7 (7.4)
Mean Baseline Age (SD)	81.5 (6.7)	81.8 (6.7)	76.3 (9.1)	78.0 (9.9)
Caucasian %	99.8%	100%	99.7%	100%
APOEe4 **Count**				
0	333	NA	1226	NA
1	168		1355	
2	15		376	
Depression				
Cases	187	112	1083	409
Controls	330	172	1885	683

LOAD = Late-onset Alzeihmer's Disease; ROSMAP = Relgious Orders Study and Rush Memory and Aging Project; NACC = National Alzeihmer's Coordinating Center; *APOE* = Apolipoprotein E; SD = Standard Deviation

ROSMAP

This sample was derived from two ongoing cohort studies, the Religious Orders Study (ROS) and Rush Memory and Aging Projects (MAP)[18–20]. ROS began recruiting nuns and brothers from across the United States in 1994, while MAP started recruiting individuals from northeastern Illinois in 1997. Both studies were conducted by the same team of investigators[18–20]. Thus, the studies used similar data collection procedures and shared a common set of examinations, allowing for a combined analysis. Study participants were free of known dementia at enrollment, underwent annual clinical and neuropsychological evaluations, and agreed to brain donation at the time of death. The studies were approved by the Institutional Review Board of Rush University Medical Center. Written informed consent was acquired from each participant. LOAD cases were defined using the final consensus cognitive diagnosis variable, where an Alzheimer's disease diagnosis with or without another cause of cognitive

impairment (cogdx = 4 or 5) was considered a LOAD case. LOAD cases comprised the sample for further analysis, specifically prediction of risk and onset of depression. The variable r_depres[23] indicated clinical depression diagnosis by a physician using the Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised (DSM-III-R)[24]. A diagnosis of highly probable, probable, or possible depression (r_depres = 1,2 or 3) in any study visit was deemed a depression case. Thus, one instance of depression in the study duration was considered a depression case. The classification of the cohort and number of subjects in each category (LOAD with depression and LOAD only) are described in a flowchart (Fig. 1). Other variables included were age at baseline (age_bl), sex (msex), years of education (educ), financial_need, and apoe_genotype. The educ variable represents years of education[25], and the financial_need variable estimates the total adverse events in childhood[26]. This variable is only available in the MAP data. The apoe_genotype variable specifies the subject's *APOE* genotype[27]; this variable was then converted to another variable to count the number of *APOEε4* alleles (0,1,2).

Overall, 517 LOAD cases from the ROSMAP cohort (total n = 1708) were used in our study, out of which there were 187 depression cases and 330 controls (i.e. only LOAD) (Fig. 1). The sample consisted of 68% female, with an average age at baseline of 81.5 (SD = 6.7) and years of education of 16.2 (SD = 3.7) (Table 1). 284 of the entire LOAD cases were *APOEε3* homozygote, with 112 cases (LOAD comorbid depression) and 172 controls (LOAD only) (Fig. 1). 70.4% of which were females and average baseline age of 81.8 (SD = 6.7) (Table 1).

NACC

The second sample used was obtained from the National Alzheimer's Coordinating Center (NACC)[20]. The NACC is composed of 29 Alzheimer's Disease Research Centers (ADRC) located throughout North America. The data collection and management vary between centers, with each center enrolling based on specific research interests. Some ADRCs require subjects to agree to autopsies. Written informed consent was acquired from each subject. The primary diagnosis variable (dx) was used to select LOAD cases, with dx = 050 corresponding to Alzheimer's Disease. The variable DEP was employed to select depression cases. These values result from a clinical diagnosis of depression using the Geriatric Depression Scale (GDS)[28]. Cases were defined as participants with a diagnosis for depression within the last two years (DEP = 1), while controls were those that did not have a depression diagnosis (DEP = 0). As with ROSMAP, any instance of depression throughout the study course was marked as a depression case. The classification of the cohort and number of subjects in each category (LOAD with depression and LOAD only) are described in a flowchart (Fig. 1). Other variables included were age at baseline (NACCAGEB), sex, years of education (EDUC), and *APOE* genotype.

Overall, 2,968 LOAD cases from the entire NACC data (7,627) were used in our study. Out of which were 1,083 depression cases and 1,885 controls (i.e. only LOAD) (Fig. 1). The sample consisted of 52.1% female, with an average baseline age of 76.3 (SD = 9.1) and years of education of 15.6. (SD = 6.9) (Table 1). 1092 of the NACC LOAD subjects were *APOEε*3 homozygotes, with 409 cases and 683 controls

(Fig. 1), 50.4% of which were females, and average baseline age was 78.0 (SD = 9.9) and years of education of 15.7 (SD = 7.4) (Table 1).

Genotype data for PRS construction

Genotype data from 1,708 subjects in ROSMAP and 10,256 subjects in NACC were then retrieved for the target samples used for testing the PRS. For NACC, genotype data from Alzheimer Disease Centers 1–7 were downloaded. For both datasets, imputation was performed with minimac4 on the Michigan imputation server (https://imputationserver.sph.umich.edu). For the imputation reference panel, the HRC panel (Version r1.1 2016) was used. This panel is composed of 64,940 haplotypes of mainly European ancestry. High quality SNPs were used for imputation, using the following parameters: MAF > 0.01; call rate > 95%, Hardy-Weinberg equilibrium test $P > 10^{-6}$; allele frequency difference ≤ 0.20 between the sample data and the reference panel. PLINK 1.9/2[29] was used to process the genotype data.

PRS Calculation

Two formulas were used to calculate PRS. Formula 1 describes the method of calculating PRS by multiplying beta values (β) by the number of effect alleles (X) then summing these values, which will be referenced as PRS. Formula 2 utilizes the risk allele (G), or the allele with the positive beta value, which will be referenced as risk-increasing PRS[30]. The number of risk alleles is multiplied by its respective beta value. This term is then multiplied by the total number of SNPs (T) divided by the sum of all the beta values. This term allows for the risk-increasing PRS to represent the average of risk alleles, providing an interpretable result in terms of risk allele[30].

$$\textbf{Forumla 1:} \sum \beta * X \qquad \textbf{Formula 2:} \sum \beta * G * \frac{T}{\sum \beta}$$

The *APOE* region, defined as the ± 300 Kb around the *APOE* epsilon coding SNPs (chr19:45,111,942–45,711,941), was not included in the PRS calculation. PRSice-2[31] was used to produce the PRS. SNPs were selected from the MDD GWAS data using multiple p-value thresholds (0.5, 0.4, 0.3, 0.2, 0.1, 0.05, 0.01, 0.005, 0.001, 0.0001, 10^{-5}, 10^{-6}, 10^{-7}). Then, the genotyped data of both ROSMAP and NACC was scanned to select SNPs from the MDD GWAS data at respective p-value thresholds. Missing SNPs or dosages were set to zero, with the assumption that most of the population have at least one copy of the major allele, which is best approximated with a score of zero. ROSMAP had 5,543,088 SNPs found in the MDD GWAS data. NACC contained 3,633,901 SNPs matching selected SNPs from the MDD GWAS data. Clumping was done on the resultant SNPs to account for linkage disequilibrium (LD Parameters: $R^2 > 0.1$, $P = 1.0$, window = 250kb). The total number of variants after clumping for ROSMAP and NACC were 315,079 and 243,437, respectively. **Supplementary Table 1** details the total number of SNPs used for each p-value threshold and dataset.

Statistical Analysis

Logistic regression and Receiver Operating Characteristic (ROC) curves were calculated to assess the performance of the PRS to predict depression within the LOAD only samples. These analyses were completed for all p-value thresholds to determine the optimum threshold for prediction, which then was then utilized in subsequent analyses. For ROSMAP, performance was assessed of a statistical prediction model that included the covariates *APOEε4* allele count, financial need, sex, and the 0.005 p-value SNP selection threshold PRS. For NACC, a prediction model that included covariates education, *APOEε4* allele count, sex, and 0.001 p-value SNP selection threshold PRS. Prediction models excluding PRS were constructed in both ROSMAP and NACC and compared with respective models including PRS using the DeLong test[32]. Additionally, time-to-event analysis was conducted, with left-truncated (age at entry) and right censored (age at depression onset or age at last visit) data. Statistical analysis was completed in JMP Pro 15[33] and the DeLong tests were run in the MedCalc application[34].

Results

Prediction of onset of depression in LOAD

We created 13 PRS, for each dataset, using multiple p-value thresholds (hereafter $P_{Threshold}$). For each cohort, SNPs were selected according to each p-value threshold (SNPs counts by $P_{Threshold}$ are summarized in **Supplementary Table 1**). Logistic regression plots of PRS and depression phenotype were then used to select the optimal $P_{Threshold}$; thus, the $P_{Threshold}$ with greater classification ability was selected for inclusion in the prediction models.

ROSMAP

The logistic regression analysis with a $P_{Threshold}$ of 0.005 resulted in the greatest effect (beta = 0.153, P = 0.089; **Supplementary Table 2**), with an AUC of 0.540 (Table 2). Next, we further evaluated this most significant PRS constructed based on SNPs selected for $P_{Threshold}$=0.005. We applied the full model, which, in addition to the PRS ($P_{Threshold}$=0.005), included baseline age, sex, years of education, and *APOEε4* allele count (**Supplementary Table 5**). The model resulted in an AUC of 0.606 and was improved to an AUC of 0.680 with the inclusion of childhood financial need as an additional variable (Fig. 2a, Table 2). Noteworthy, education had a significant effect in the full model (beta=-0.134, P = 0.033), while the PRS ($P_{Threshold}$=0.005) had a marginal contribution (beta = 0.249, P = 0.126) (**Supplementary Table 5**). Both models, with and without childhood financial need, were then compared to the respective model without PRS ($P_{Threshold}$=0.005) (**Supplementary Table 4**) to assess the increase in model performance attributed to the addition of PRS ($P_{Threshold}$=0.005). In both models, there was no significant increase in model performance when comparing AUCs (With, without childhood financial need: P = 0.377, P = 0.774; **Supplementary Table 6**).

Table 2
Assessing PRS ability to predict risk of depression onset

	ROSMAP		NACC	
Sample	Full LOAD Sample	*APOEε3* Homozygote Sample	Full LOAD Sample	*APOEε3* Homozygote Sample
SNP count/ p-threshold used in PRS	5915/0.005	5915/0.005	843/0.001	843/0.001
Case-Control (p-value)	0.088	0.277	0.003*	0.709
Full Model AUC	0.606[1]	0.624[2]	0.583	0.585
PRS AUC	0.540	0.535	0.534	0.509

Full Model included covariates of PRS, *APOEε4* allele count, sex, baseline age and education. Logistic regression analyses and reciever operating characteristics (ROC) curves were created to assess PRS ability to predict risk of depression onset.

[1]Improved to 0.680 with addition of financial need

[2]Improved to 0.721 with addition of financial need

*Statistical signifiance met

LOAD = Late-onset Alzeihmer's Disease; ROSMAP = Relgious Orders Study and Rush Memory and Aging Project; NACC = National Alzeihmer's Coordinating Center; *APOE* = Apolipoprotein E; SNP = Single Nucleotide Polymorphism; AUC = Area Under the Curve; PRS = Polygenic Risk Score

We repeated the analyses in the subgroup stratified for *APOEε3* homozygotes to exclude a potential confounding effect of *APOEε4* on the PRS. In this subgroup, the PRS ($P_{Threshold}$ =0.005) showed an AUC of 0.535, with an improved AUC of 0.624 in the full model, which was further improved to an AUC of 0.721 with the addition of childhood financial need (Fig. 2b, Table 2, **and Supplementary Table 8**). Baseline age (beta=-0.115, P = 0.014) and childhood financial need (beta = 0.595, P = 0.0097) had significant effects in the full model, but the PRS ($P_{Threshold}$=0.005) did not reach significance (beta = 0.349, P = 0.138) (**Supplementary Table 8**). Using the DeLong test to compare both models, with and without childhood financial need, to their respective models excluding PRS ($P_{Threshold}$=0.005) (**Supplementary Table 7**) resulted in no significant increase in the AUC, or model performance, with the addition of PRS (With, without childhood financial need: P = 0.237, P = 0.377; **Supplementary Table 9**). These results suggested that other factors have a greater contribution to prediction performance, while the PRS had a moderate contribution.

NACC

We took a similar approach in the analysis of the NACC cohort. The logistic regression analysis, for $P_{Threshold}$ values range of 0.5-0.001, demonstrated significant PRSs in case/control classification, with $P_{Threshold}$ = 0.001 deemed the optimal PRS (beta = 0.112, P = 0.0031; **Supplementary Table 3**). Thus, we pursued with further evaluations of this most significant PRS generated with SNPs selected for $P_{Threshold}$=0.001. The model that included only the PRS ($P_{Threshold}$=0.001) showed an AUC of 0.534 and the full model showed an AUC of 0.583 (Fig. 3a, Table 2, **Supplementary Table 11**). In addition, the results of the full model demonstrated significant contributions from the PRS (beta = 0.103, P = 0.0072) as well as baseline age (beta=-0.016, $P = 2e^{-4}$), and sex (beta=-0.229, $P = 4.3e^{-9}$) (**Supplementary Table 11**). However, the DeLong test comparing the full model with full model excluding PRS (**Supplementary Table 10**) demonstrated no significant gain of model performance (P = 0.194; **Supplementary Table 14**).

We also repeated the analysis using a subgroup of *APOEε3* homozygotes for the NACC cohort. The PRS ($P_{Threshold}$=0.001) alone resulted in an AUC of 0.509, and application of the full model reached an AUC of 0.585 (Fig. 3b, Table 2, **Supplementary Table 13**). In this full model analysis, baseline age (beta=-0.018, P = 0.0046) and sex (beta=-0.249, P = 1e-4) showed significant effects (Fig. 3b), but PRS ($P_{Threshold}$=0.001) did not reach statistical significance (beta = 0.015, P = 0.809; **Supplementary Table 13)**. Furthermore, the DeLong test demonstrated that the PRS ($P_{Threshold}$=0.001) did not improve the model performance when comparing to the model excluding PRS (P = 0.929; **Supplementary Table 12** and **Supplementary Table 14**).

Predicting Time to Depression Onset

Time-to-event analysis was conducted to assess the PRS ability to predict those at risk for developing depression early in their LOAD trajectory by examining the time interval between age at entry of respective study and age at depression onset (or age at last visit if no depression occurred). We tested PRS calculated by the two formulas (see Methods section): (1) PRS and, (2) risk-increasing PRS. PRS uses the standard calculation approach, while risk-increasing PRS utilizes alleles with positive betas, or risk alleles, providing an interpretable score in terms of the number of risk alleles.

ROSMAP

Models using both formulas, PRS ($P_{Threshold}$=0.005) and risk-increasing PRS ($P_{Threshold}$ =0.005), reached statistical significance (Table 3). In each of the full statistical models that included the covariates sex, baseline age, education and *APOEε4* allele count, the term for the PRS (beta = 0.146, P = 6e-4) and the risk-increasing PRS (beta = 0.006, P = 6e-4) had statistically significant effects in their respective models (**Supplementary Tables 15 and 19**).

Table 3
Assessing both PRS and risk-increasing PRS ability to predict time interval of depression in LOAD

	ROSMAP		NACC	
Sample	Full LOAD Sample	*APOEε3* Homozygote Sample	Full LOAD sample	*APOEε3* Homozygote Sample
SNP count/ p-threshold used in PRS	5915/0.005	5915/0.005	843/0.001	843/0.001
Full Model (p-value)	< 0.001*	< 0.001*	< 0.001*	< 0.001*
PRS alone (p-value)	0.005*	0.075	0.070[1]	0.101[2]
PRS: Risk-Ratio [95%CI]	1.126 [1.036, 1.222]	1.102 [0.990, 1.225]	1.013 [0.978, 1.049]	0.993 [0.939, 1.051]
Risk-increasing PRS: Risk-Ratio [95%CI]	1.005 [1.001, 1.008]	1.004 [1.000, 1.008]	0.999 [0.998, 1.000]	0.999 [0.997, 1.000]
Full Model contained covariates of PRS, *APOEε4* allele count, sex, baseline age, and education. Time-to-event analysis was performed using left-truncated (age at entry) and right censored (age at depression onset or age at last visit) data.				
[1]p-value noted with risk-PRS. With standard PRS, p-value = 0.4805				
[2]p-value noted with risk-PRS. With standard PRS, p-value = 0.8186				
*Statistical significance met				
LOAD = Late-onset Alzeihmer's Disease; ROSMAP = Relgious Orders Study and Rush Memory and Aging Project; NACC = National Alzeihmer's Coordinating Center; *APOE* = Apolipoprotein E; SNP = Single Nucleotide Polymorphism; PRS = Polygenic Risk Score				

Upon stratification for *APOEε3* homozygotes, the models using PRS and risk-increasing PRS ($P_{Threshold}$ =0.005), each alone, did not produce significant results (Table 3). Of note, the risk-increasing PRS performed comparably to its use in the full LOAD sample when comparing risk ratios. Nonetheless, the full models for both PRS formulas showed significant results (Table 3), with baseline age having a significant effect (**Supplementary Tables 16 and 20**). Furthermore, both PRS (beta = 0.139, *P* = 0.011) and risk-increasing PRS (beta = 0.006, *P* = 0.010) had significant contributions to their respective full models (**Supplementary Tables 16 and 20**, respectively).

NACC

We utilized PRS ($P_{Threshold}$ =0.001) and the risk-increasing PRS ($P_{Threshold}$ =0.001) in the time-to-event analyses. The models employing the PRS and the risk-increasing PRS, each alone, did not produce significant results; however, the risk-increasing PRS had improved performance as supported by smaller a p-value (Table 3). The full models, using each of the two PRS formulas with other covariates, showed significant results (Table 3, **Supplementary Tables 17 and 21**). The full model using the PRS had significant contributions from baseline age, sex, education, and PRS (beta = 0.041, *P* = 0.028), while the full model using risk-increasing PRS had significant contributions from baseline age, education and risk-increasing PRS (beta = 0.001, *P* = 0.034) (**Supplementary Tables 17 and 21**, respectively).

Repeating the analyses for the *APOEε3* homozygote subgroup did not show significant results for PRS and the risk-increasing PRS alone models. As in the entire LOAD NACC cohort, the risk-increasing PRS demonstrated a marginally greater performance with a smaller p-value (Table 3). The full models for both PRS and risk-increasing PRS resulted in significant results (**Supplementary Tables 18 and 22**) with major contributions from the covariates baseline age, sex, and education. However, neither the PRS nor the risk-increasing PRS had significant effects in their respective full models.

Discussion

LOAD is a heterogenous disease with various genetic etiologies[35, 36] and diverse phenotypes including: heterogeneity of biomarkers[37], coexisting pathologies[38], and clinical symptoms[38–41]. Clinical heterogeneity is manifested also by comorbid neuropsychiatric symptoms (NPS), amongst which depression is very common. However, why some LOAD patients develop depression while others do not remain elusive. Previously, we found genetic pleiotropy between MDD and LOAD[6], suggesting that genetics may contribute to the risk of depression symptom in LOAD. In this study to test this hypothesis, we performed the first genetic comparison analysis between LOAD patients with and without depression to explore the genetic heterogeneity of the risk and onset time of depression in individuals with LOAD. We derived a PRS that showed moderate effects in predicting depression onset in LOAD patients. The PRS predictive ability was improved with the inclusion of the covariates age, sex, education, *APOEε4* allele count, with the addition of childhood financial need further enhancing the predictive performance of the model.

PRS are a well-established approach for the study of the genetics of complex diseases including LOAD and the utility of PRS to predict LOAD risk has been investigated by different groups[7–17]. However, to our knowledge, this is the first study that progresses the use of PRS to predict clinical endophenotypes in LOAD, in particular depression. Our study is innovative in several ways: (1) The study was uniquely designed such that all subjects are LOAD patients whereas manifestation of depression defined the case-control status. (2) Most prior LOAD PRS studies focused on LOAD prediction employing LOAD GWAS summary statistics. Here we tested the utility of PRS based on GWAS data from a particular disorder (MDD) to predict risk for a shared phenotype (depression) in individuals with another disorder (LOAD). (3)

While previous work identified unique trajectories of depression and apathy in LOAD subjects and biomarkers associated with LOAD-specific depression progression[5], the current work focused on a genetic based prediction model of depression in LOAD. Collectively, our approach generated PRS to identify LOAD subjects with greater genetic risk of developing depression and those at risk to develop depression earlier in the time course of LOAD.

PRSs generated for the two cohorts, ROSMAP and NACC, were different, due to differing genotyped SNPs leading to a distinct number of SNPs used. However, the results of PRS in ROSMAP and NACC were applied to demonstrate the effectiveness of employing our approach in different datasets. The results obtained for the two cohorts were generally consistent. However, there are some differences. In the NACC cohort, the PRS alone was more effective in classifying depression cases as evidenced by the logistic regression analysis, and it made more significant contributions to the full prediction model than in ROSMAP. However, the overall model performance was greater in ROSMAP. A possible explanation might be that ROSMAP is more homogenous than NACC, as ROSMAP contains a reduced range of baseline ages and is disproportionately female[18–20] resulting in greater homogeneity compared to NACC. Furthermore, the study selection criteria of ROSMAP may further contribute to the homogeneity in ROSMAP, with ROS enrolling priests and MAP selecting within the northeastern Illinois region. Therefore, the covariates, such as baseline age and education, would be expected to have greater effects in ROSMAP. Thus, statistical models would be expected to show predictive ability that would appear stronger in ROSMAP. NACC's diversity and sample size led to greater classification ability, and greater contribution in the full model. In both datasets, the PRS did not add significant improvement to model performance, with the greatest statistical increase in performance attributable to PRS observed in the full LOAD NACC sample. As the PRS had promising results in two different criteria, prediction and classification, the PRS demonstrated generalizability, although with small effects. Similar results were observed for the time-to-event analysis, which tested PRS ability to distinguish individuals more at risk of developing depression earlier in their LOAD trajectory. A risk-increasing PRS was calculated to provide an interpretable score, where a unit increase in risk-increasing PRS corresponds to an additional risk allele. In ROSMAP, both PRS versions performed effectively, both as standalone models and within the full models. In NACC, both PRS types had significant contributions to their respective full statistical models, but not as PRS term only models.

The *APOEε3* homozygote sample enabled the study of the PRS without potential confounding by the *APOEε4* genotype, the strongest genetic risk factor for LOAD. *APOE* genotype may influence LOAD severity and the presence of certain endophenotypes. In terms of predicting depression onset, the PRS saw a slight decline in predictive performance relative to the analysis that included all *APOE* genotypes for the ROSMAP sample and equivalent performance in the NACC sample. The full model including financial need in ROSMAP lead to the most predictive model, with a moderate effect of the financial need variable. This result highlights that childhood struggles may translate into risk of depression later in life[26]. Unfortunately, this variable was not available in the NACC cohort for further assessments. The time-to-event analysis did not find significant results from standalone PRS models. However, in ROSMAP,

both PRS types played significant roles in the full models. The *APOEε3* homozygote study demonstrated that *APOEε4* does not have a significant role in the risk of depression onset in individuals with LOAD, with small declines in PRS performance and stable or improved full model results.

Limitations

Our study has some limitations. First, the proposed approach is the binary treatment of depression. The current method treats depression as either being present or not present throughout the individual's course in either ROSMAP or NACC. This fails to account for the possibility that depression may occur numerous times within the course of the study and might have varying degrees of severity. Further work can expand upon the number of instances of depression to enrich genetic models. Another limitation to note are the small effect sizes of the PRS and other covariates, especially for models tested in NACC. The smaller estimated effects resulting from models using NACC data, could be due to larger, genetically heterogenous data. Despite small estimates in NACC, the PRS made significant contributions. Nevertheless, this study advances the current work on PRS and further explores the performance of MDD genetic factors in predicting risk of depression development in LOAD subjects.

Conclusions

The results of this study indicate that the PRS is an effective genetic model to predict risk or onset time interval for depression in individuals with LOAD. This would facilitate greater prognostic capabilities to assess LOAD patients with potential disease trajectories predisposing depression. Furthermore, anti-depressants have had mixed results in treating depression in LOAD[42, 43]. The proposed PRS may be useful to enrich clinical trials with LOAD patients in risk to develop depression towards more precise evaluation of these drugs beneficial outcomes in LOAD with comorbid depression.

Abbreviations

LOAD=Late-onset Alzeihmer's Disease; PRS=Polygenic Risk Score; CSF=Cerebrospinal Fluid; GWAS=Genome Wide Association Studies; MDD=Major Depressive Disorder; *APOE*=Apolipoprotein E; NPS=Neuropschiatric Symptoms; MCI=Mild Cognitive Impariment; ROSMAP=Relgious Orders Study and Rush Memory and Aging Project; NACC=National Alzeihmer's Coordinating Center; SNP=Single Nucleotide Polymorphism; AUC=Area Under the Cruve; DSM-III=Diagnostic and Statistcal Manual of Mental Disorders, 3rd edition; GDS=Geriatric Dementia Scale; ADRC= Alzeihmer's Disease Research Center; MAF=Minor Allele Frequency; SD=Standard Deviation;

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

MDD GWAS summary statistics: https://www.med.unc.edu/pgc/results-anddownLOADs/mdd/

ROSMAP data can be requested at https://www.radc.rush.edu/

NACC data maybe requested using https://naccdata.org/requesting-data/submit-data-request

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

OCF and MWL contributed to conception and design of the study. SU performed the polygenic risk score creation and statistical analysis, with assistance from MWL, HL, and OCF. HL and SL provided NACC data. SU, MWL, and OCF interpreted the result. SU wrote the first draft of the manuscript. SU, MWL, SL, HL, and OCF contributed to manuscript revision, read, and approved the submitted version. OCF obtained funding.

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ROSMAP

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NACC

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Figures

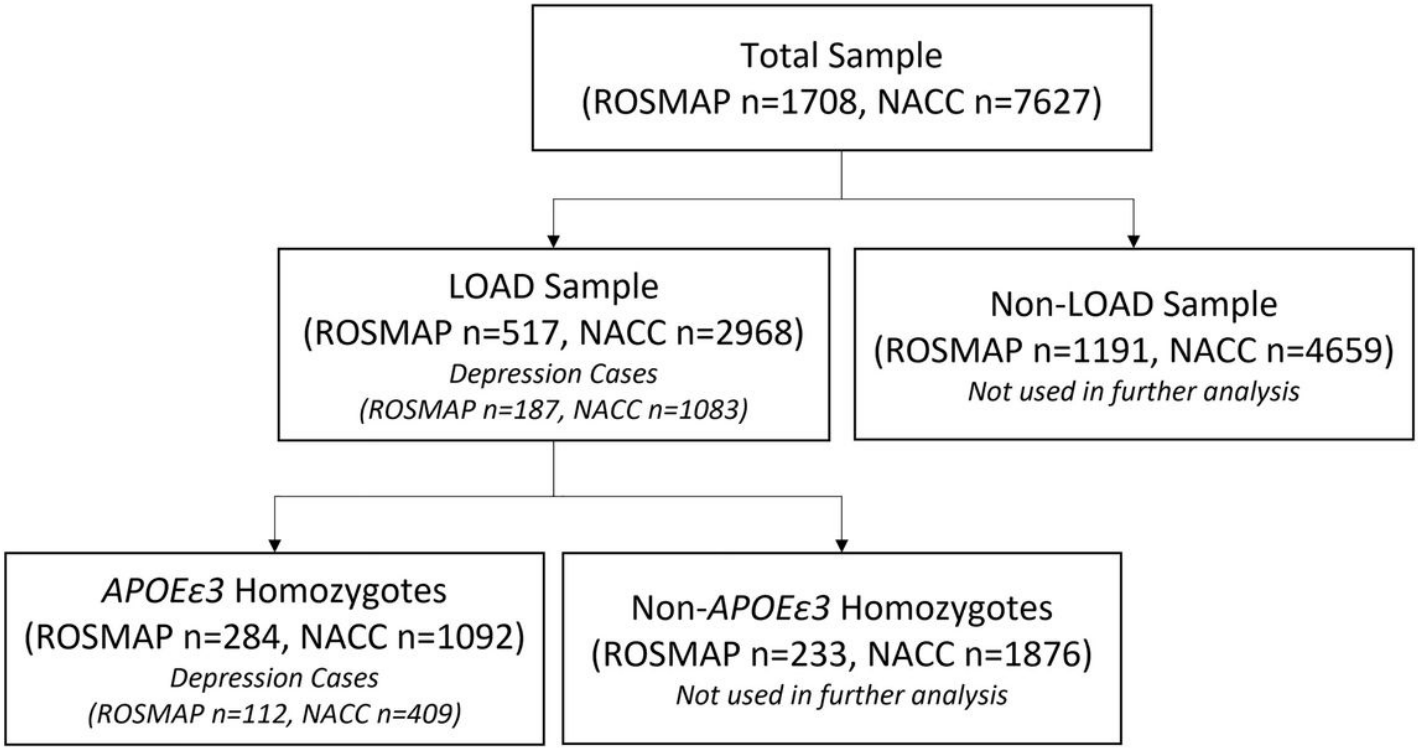

Figure 1

Sample selection flowchart. The total samples from both ROSMAP and NACC datasets were divided into LOAD and non-LOAD groups, where the non-LOAD group was not studied. Depression case and controls were identified in the LOAD sample of both datasets. APOEε3 homozygotes were then selected from the LOAD sample to account for potential confounding by the APOEε4 allele.

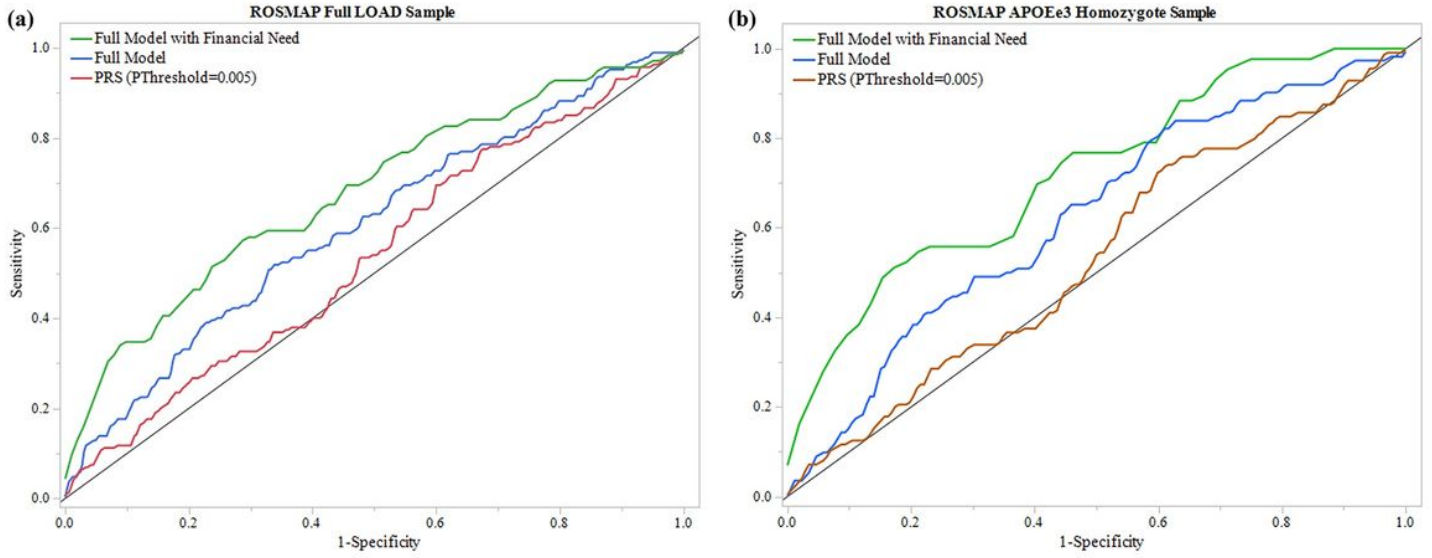

Figure 2

ROC analysis of PRS and full model in ROSMAP. Receiver operating characteristic (ROC) curves were used to assess diagnostic ability, with the Area Under the Curve (AUC) providing a quantitative measure. The models illustrated are PRS (PThreshold=0.005) alone, the full model (PRS (PThreshold=0.005), age, sex, education, and APOEε4 allele count) and the full model with financial need. (a) Models using the full LOAD ROSMAP sample. Full model including financial need had superior results (AUC=0.680) than the full model (AUC=0.606) and PRS (PThreshold=0.005) alone (AUC=0.540). (b) Similar analyses were repeated in an APOEε3 homozygote sample to assess model performance independent of APOEε4. Both full model with financial need had greater results (AUC=0.721) and full model (AUC=0.624) had greater results than in the full LOAD sample. The PRS (PThreshold=0.005) alone saw a slight decline in perfromance (AUC=0.535) compared to the full LOAD sample.

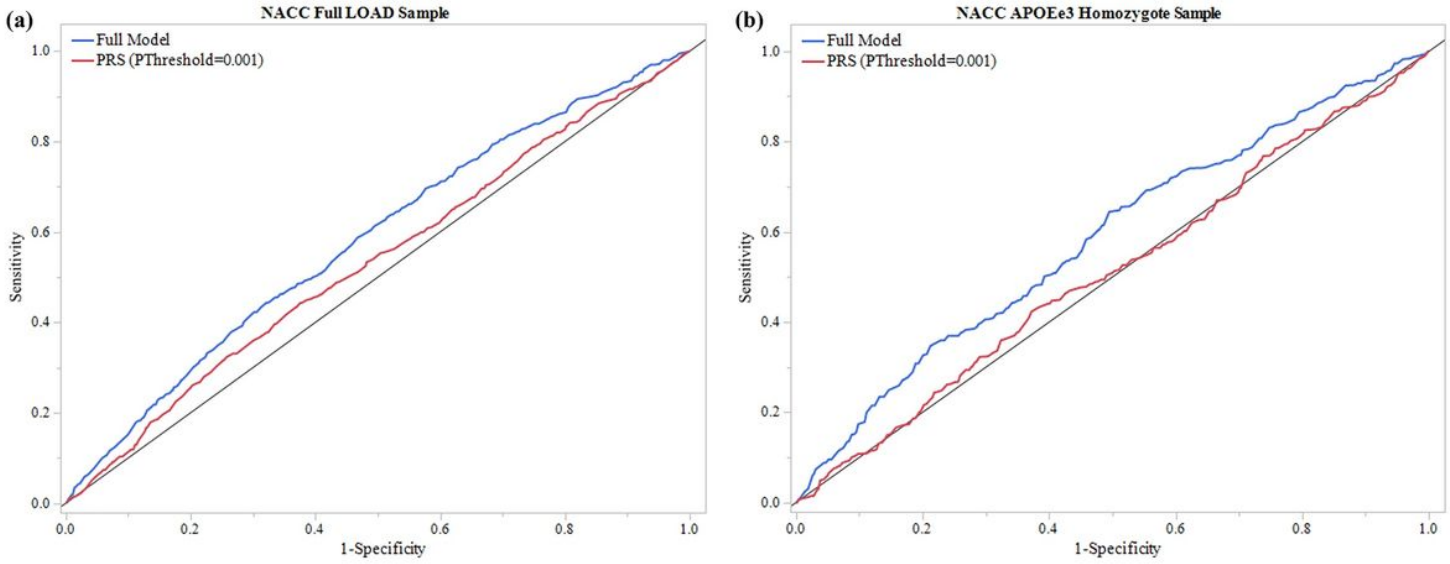

Figure 3

ROC analysis of PRS and full model in NACC. Receiver operating characteristic (ROC) curves were used to assess diagnostic ability, with the Area Under the Curve (AUC) providing a quantitative measure. The models illustrated are PRS (PThreshold=0.001) alone and the full model (PRS (PThreshold=0.001), age, sex, education, and APOEε4 allele count). (a) Models using the entire NACC LOAD sample. Full model had greater results (AUC=0.583) than PRS (PThreshold=0.001) alone (AUC=0.534). (b) Similar analysis was done in an APOEε3 homozygote sample to measure PRS effectiveness in a large dataset independent of APOEε4. Full model results were comparable to the full LOAD sample (AUC=0.585), wheras PRS alone performed worse (AUC=0.509).

Supplementary Files

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- AdditionalFile1.docx