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Pathway-specific polygenic risk scores as predictors of β-amyloid deposition and cognitive function in a sample at increased risk for Alzheimer's disease

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Abstract

Polygenic risk scores (PRSs) have been used to combine the effects of variants with small effects identified by genome-wide association studies. We explore the potential for using pathway-specific PRSs as predictors of early changes in Alzheimer's disease (AD)-related biomarkers and cognitive function. Participants were from the Wisconsin Registry for Alzheimer's Prevention, a

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longitudinal study of adults who were cognitively asymptomatic at enrollment and enriched for a parental history of AD. Using genes associated with AD in the International Genomics of Alzheimer's Project's meta-analysis, we identified clusters of genes that grouped into pathways involved in β-amyloid (Aβ) deposition and neurodegeneration: Aβ clearance, cholesterol metabolism, and immune response. Weighted pathway-specific and overall PRSs were developed and compared to *APOE* alone. Mixed models were used to assess whether each PRS was associated with cognition in 1,200 individuals, cerebral Aβ deposition measured using amyloid ligand (Pittsburgh compound B) positron emission imaging (PET) in 168 individuals, and cerebrospinal fluid (CSF) Aβ deposition, neurodegeneration, and tau pathology in 111 individuals, with replication performed in an independent sample. We found that PRSs including *APOE* appeared to be driven by the inclusion of *APOE*, suggesting that the pathway-specific PRSs used here were not more predictive than an overall PRS or *APOE* alone. However, pathway-specific PRSs could prove to be useful as more knowledge is gained on the genetic variants involved in specific biological pathways of AD.

Keywords

Alzheimer's disease; Genetics; Polygenic risk scores; Genetic risk scores; Cognitive function; Beta-amyloid; Cerebral spinal fluid; Pittsburgh compound B; WRAP; *APOE*

INTRODUCTION

Alzheimer's disease (AD) is clinically characterized by a progressive decline in cognition and functional status. However, β-amyloid (Aβ) deposits as plaques, and hyperphosphorylation and aggregation of tau into tangles, may accumulate in the brain of an AD patient long before cognitive decline is evident[1]. This accumulation blocks neural signaling and nutrient transport and is thought to lead to the characteristic neurodegeneration of AD. The amyloid hypothesis proposes that AD is caused by an imbalance between Aβ production and Aβ clearance that leads to Aβ accumulation[2]. Aβ clearance rates have been shown to be reduced in late onset AD patients whereas Aβ production rates appear to be normal, suggesting that impaired Aβ clearance may be the primary mechanism for Aβ accumulation[3]. Altered cholesterol metabolism is another characteristic of AD that may be closely linked to Aβ production and Aβ clearance[4]. Further, immune response may contribute to neurodegeneration and tau pathology in AD; blocking a pro-inflammatory cytokine Interleukin 1, which is elevated in the plasma, brain, and cerebral spinal fluid (CSF) of individuals with AD or mild cognitive impairment, has been shown to regulate brain inflammatory responses and attenuate neuronal tau pathology, while also improving cognition[5]. The involvement of these latter two pathways is further supported by a recent pathway analysis performed by the International Genomics of Alzheimer's Project (IGAP) [6]. Variations in genes involved in these metabolic pathways may elucidate heritable mechanisms that contribute to the onset and clinical spectrum of AD.

In a meta-analysis of genome-wide association studies (GWAS) that included over 74,000 individuals with and without late onset AD, 11 novel susceptibility single nucleotide polymorphisms (SNPs) were identified, as well as 8 that were previously reported to be

associated with AD[7]. While this study confirmed that many genetic factors contribute to the risk of AD, each of these variants had a fairly small effect size. Polygenic risk scores (PRSs) utilize allele-counting methods to combine the effects of many individual SNPs and have been found to serve as good predictors[8, 9]. While an overall PRS that combines the effects of all AD-associated SNPs may be more powerful for predicting cognitive function and decline due to a constellation of pathways contributing to AD pathology, a pathway-specific PRS[10] may be a more powerful predictor of specific biomarkers contributing to a component of the underlying AD pathology, such as levels of Aβ deposition.

Using longitudinal data from a sample of cognitively healthy adults enriched for a parental history of AD from the Wisconsin Registry for Alzheimer's Prevention (WRAP), we explored the potential of pathway-specific PRSs in predicting changes in cognitive function and AD-related biomarkers. In particular, we developed weighted PRSs for Aβ Clearance, Cholesterol Metabolism, and Immune Response, in addition to an Overall PRS, using the single most significant variant from each gene associated with late onset AD in the International Genomics of Alzheimer's Project's (IGAP) meta-analysis. These PRSs were tested for associations with cognitive function and biomarkers of Aβ deposition ([C-11]Pittsburgh compound B (PiB) positron emission tomography (PET) and CSF $A\beta_{42}$ and $A\beta_{42}/A\beta_{40}$), neurodegeneration (CSF total tau (T-tau)), and tau pathology (CSF phosphorylated tau (P-tau)). Replication analyses were performed using an independent sample of cognitively healthy adult participants from the Wisconsin Alzheimer's Disease Research Center (W-ADRC).

MATERIALS AND METHODS

Participants

Study participants were from WRAP, a longitudinal study of middle-aged adults who were cognitively asymptomatic at enrollment and enriched for a parental history of AD. A positive parental history was defined as having one or both parents with either autopsy-confirmed or probable AD as defined by NINCDS-ADRDA research criteria[11]. Baseline recruitment began in 2001 with initial follow up after 4 years and subsequent ongoing follow up every 2 years. Enrollment of one or more siblings of WRAP participants was allowed. Further details of the study design and methods used have been previously described[12–14].

The present analyses were limited to self-reported non-Hispanic Caucasian participants due to sample size limitations of other racial or ethnic groups. Participants were excluded if they reported having diseases or comorbidities that might be expected to influence cognitive test performance (e.g., multiple sclerosis, Parkinson's disease, stroke, epilepsy/seizures, or meningitis) or developed AD on or before the second visit.

This study was conducted with the approval of the University of Wisconsin Institutional Review Board and all subjects provided signed informed consent before participation.

Neuropsychometric Assessments

The WRAP cognitive test battery consists of standardized widely used clinical neuropsychological tests, which were selected to provide a comprehensive estimate of cognitive abilities with an emphasis on abilities most likely to be affected in early-stage AD. Factor analysis was conducted to reduce the number of outcome measures to a smaller number of reliable cognitive factors and obtain weights used to combine the measures within each factor[15]. The following six cognitive factor scores were used in the present analysis: Immediate Memory, Verbal Learning and Memory, Visual Learning and Memory, Story Recall, Working Memory, and Speed and Flexibility. Tests comprising each of these factors are described elsewhere[16]. The resulting weighted factor scores were then standardized (~N [0,1]) into z-scores, using means and standard deviations obtained from the whole baseline sample.

PiB PET Imaging

[C-11]PiB PET imaging studies began in 2010 for a subset of WRAP participants and were scheduled as close to cognitive assessment as possible[17]. [C-11]PiB PET images were collected on a Siemens HR+ scanner in 3D mode. Radiochemical synthesis, acquisition parameters and generation of distribution volume ratio (DVR) maps were detailed previously[17]. Briefly, after a 70 minute dynamic [C-11]PiB PET acquisition, PET data were reconstructed using a filtered back-projection algorithm (DIFT). Data were corrected for random events, attenuation of annihilation radiation, deadtime, scanner normalization, and scatter radiation. The data were then realigned and coregistered in SPM12 and transformed into DVR maps of [C-11]PiB binding using the time activity curve in the gray matter of the cerebellum as the reference region. To reduce the number of statistical tests, a summary measure of amyloid burden was calculated by averaging the means of amyloid binding within 8 bilateral regions of interest (angular gyrus, anterior cingulate gyrus, posterior cingulate gyrus, frontal medial orbital gyrus, precuneus, supramarginal gyrus, middle temporal gyrus, and superior temporal gyrus), as previously described[18].

CSF Measures and Quantification

CSF studies also began in 2010 on the same protocol as the [C-11]PiB PET imaging studies. CSF measurements in the present analyses included $A\beta_{42}$, T-tau, P-tau, and the $A\beta_{42}/A\beta_{40}$ ratio. Previous literature has demonstrated that $A\beta_{42}/A\beta_{40}$ is decreased in AD [19, 20] and that it normalizes the $A\beta_{42}$ concentration to a measure of overall amyloidogenic processing by amyloid precursor protein, making it possible to detect low $A\beta_{42}$ in high Aβ producers and vice versa [21].

CSF was collected via lumbar puncture (LP) in the morning after a 12-hour fast using a Sprotte 25- or 24-gauge spinal needle at the L3/4 or L4/5 interspace using gentle extraction into polypropylene syringes. CSF (22 mL) was then gently mixed, and centrifuged at 2000g for 10 minutes. Supernatants were frozen in 0.5 mL aliquots in polypropylene tubes and stored at −80°C.

CSF $A\beta_{42}$, T-tau, and P-tau were quantified with sandwich ELISAs (INNOTEST β-amyloid1–42, hTAU-Ag, and Phospho-Tau[181P], respectively; Fujirebio Europe, Ghent,

Belgium). For the $A\beta_{42}/A\beta_{40}$ ratio, CSF levels of $A\beta_{42}$ and $A\beta_{40}$ (a less amyloidogenic Aβ fragment as compared to $A\beta_{42}$) were quantified by electrochemiluminescence (ECL) using an Aβ triplex assay (MSD Human Aβ peptide Ultra-Sensitive Kit, Meso Scale Discovery, Gaithersburg, MD). All measurements were performed in one round of analyses using one batch of reagents by board-certified laboratory technicians who were blind to the clinical characteristics of participants. Intra-assay coefficients of variation were below 10%.

DNA Collection, Genotyping, and Quality Control

DNA was extracted from whole blood samples using the PUREGENE® DNA Isolation Kit (Gentra Systems, Inc., Minneapolis, MN). DNA concentrations were quantified using UV spectrophotometry (DU® 530 Spectrophotometer, Beckman Coulter, Fullerton, CA). The 21 SNPs used in this analysis (19 IGAP SNPs in Supplementary Table 1 and 2 *APOE* SNPs in Table 1) were genotyped in 1,448 individuals using competitive allele-specific PCR based KASP™ genotyping assays (LGC Genomics, Beverly, MA). Duplicate quality control (QC) samples from 102 individuals were placed randomly throughout each of the 96-well plates. The genotype concordance rate was 99.89%. All discordant genotypes were set to missing. To assess the potential for sample mislabeling, concordance was also assessed with previous genotyping that included three overlapping variants (rs7412 and rs429358 in apolipoprotein E (*APOE*), and rs6656401 in *CR1*) in 1,152 individuals. Six genotypes were discordant in six different individuals, who were removed from further analyses.

Further QC was conducted using PLINK v1.07[22]. Twenty-seven individuals were excluded due to high missingness of alleles (>10%). No SNPs were excluded due to low call rates (<95%). Hardy-Weinberg equilibrium (HWE) was assessed among a subset of 1,120 unrelated individuals using a Bonferroni adjusted p-value threshold. One SNP failed HWE but was retained due to the negligible difference from the p-value threshold (rs28834970 in *PTK2B*). Remaining sample call rates ranged from 91.2% to 100.0% and SNP call rates ranged from 97.8% to 100.0%. A total of 1,415 individuals and 21 SNPs remained after the completion of all QC procedures. For PRS analyses, variants were coded additively according to the number of risk alleles based on IGAP, whereas for individual SNP analyses, variants were coded additively according to the number of minor alleles. *APOE* was coded by the ε2/ε3/ε4 genotype formed by rs7412 and rs429358.

Polygenic Risk Scores

Gene Ontology (GO)[23] was primarily used to map SNPs to pathway-specific PRSs for Aβ Clearance, Cholesterol Metabolism, and Immune Response, which were formed by combinations of the 21 SNPs from IGAP and *APOE*; however, the first two pathways were identical in GO. Therefore, a literature search was conducted to better identify which SNPs mapped to each of these pathways. This suggested that genes involved in Aβ Clearance included *PICALM*, *CLU*, *CR1*, and *APOE*[24, 25], while those involved in Cholesterol Metabolism included *ABCA7*, *CLU*, and *APOE*[4, 6, 26], the latter of which was consistent with GO. GO identified the *INPP5D, CLU, CR1, HLA-DRB1, MEF2C,* and *PTK2B* genes as being in the Immune Response pathway, which is also largely consistent with the IGAP pathway analysis[6]. An Overall PRS (including all of the IGAP genes, as listed in

Supplementary Table 1, plus *APOE*) and a risk score for *APOE* alone were also created for comparison.

PRSs were calculated for each participant using the following equation:

$PRS_i = \sum_{n=l}^{k} \ln(OR_n) * C_n$, where *i* represents the individual whose score is calculated by summing over all SNPs *n* in the pathway ranging from the first SNP *l* to the last SNP *k; OR* is the odds ratio of the risk allele for SNP *n*; and *C* is the individual's count of risk alleles (not minor alleles) for SNP *n*. A higher PRS corresponds with having more risk alleles and thus, a higher amount of genetic risk for the outcome. With the exception of *APOE*, SNP ORs used in the present analysis were provided from the IGAP meta-analysis, as indicated in Supplemental Table 1. Risk due to *APOE* status was not calculated additively, but instead according to the OR of the ε2/ε3/ε4 genotype, as indicated in the meta-analysis of *APOE* genotype frequencies in studies reported in AlzGene[27]. These ORs were based on studies of Caucasian individuals to be consistent with our data and were calculated using the ε2/ε2 genotype as the reference (ε2/ε2 OR=1) as follows: ε2/ε3 OR=1.38, ε3/ε3 OR=2.00, ε2/ε4 OR=4.45, ε3/ε4 OR=6.78, ε4/ε4 OR=25.84. Since *APOE* is known to have a large effect size, PRSs were also calculated excluding *APOE* to determine the effect of the PRS beyond that of *APOE* alone.

Statistical Analyses

Genetic associations with cognitive function or AD-related biomarkers were tested using linear mixed effects regression models implemented in the SAS MIXED procedure to account for the within-family and within-subject (due to repeated measures) correlations while allowing for missing data[28]. Each mixed effects model included random intercepts for both family and participant. Unconditional models were used to compare covariance structures (unstructured, compound symmetry, and variance components) for each outcome. The structure providing the best model fit, determined by the Akaike Information Criterion (AIC), was used for the corresponding outcome. A random effect for time (age centered) was included when its inclusion led to a better model fit. After selecting the best model for each outcome, individual PRSs were added to the models (each model only included one PRS), as well as fixed effects for gender and age, which was centered for ease of interpretation. The performance of each PRS was compared using the partial likelihood ratio test r^2 (r^2_{LR}) [29, 30], with further comparisons of model fit made by assessing differences in AIC values when r^2 values were fairly dissimilar (an AIC difference of 4 is considered to be meaningful, suggesting the model with the lower AIC is a better fit[31]). Individual SNPs were similarly assessed (each model only included one SNP), with fixed effects for gender and age. No corrections for multiple comparisons were performed.

Replication Study

CSF-related findings were replicated in an independent sample of cognitively normal unrelated individuals from the Wisconsin Alzheimer's Disease Research Center (W-ADRC), which began enrolling participants in 2009. Replication analyses were limited to CSF-related findings because the W-ADRC uses a different neuropsychological testing battery to assess cognitive function, which would make comparisons difficult, and does not collect

PiB. The W-ADRC sample was limited to non-Hispanic Caucasian participants with CSF and genotypes for the 19 IGAP SNPs and 2 *APOE* SNPs.

CSF samples were collected at baseline (only one time point) using identical collection and processing methods as those used with the WRAP samples. DNA was extracted from whole blood samples using the 5 Prime PerfectPure™ DNA Blood Kit (Fisher Scientific Company, LLC, Pittsburgh, PA). DNA concentrations were quantified using UV spectrophotometry (Synergy™ 2 Multi-Mode Microplate Reader, BioTek Instruments, Inc., Winooski, VT). The 21 SNPs used in this analysis were genotyped in 620 unrelated individuals by LGC Genomics (Beverly, MA), as were WRAP samples. Duplicate QC samples from 12 individuals were placed randomly throughout each of the 96 well plates. No genotypes were discordant. Additional QC was conducted using the PLINK software v1.07[22]. Two individuals were excluded due to high missingness of alleles (>10%). No SNPs were removed due to low call rates (<95%). There were no deviations from Hardy-Weinberg equilibrium at a Bonferroni adjusted p-value threshold. Remaining sample call rates ranged from 92.9% to 100.0% and SNP call rates ranged from 98.7% to 100.0%.

Genetic associations with CSF biomarkers were tested using linear regression models implemented in SAS. Gender and age, which was centered for ease of interpretation, were included as covariates. The performance of each PRS was compared using the partial r-squared (r_p^2) statistic, with further comparisons of model fit (AIC) when r_p^2 appeared to differ.

RESULTS

Participants

A total of 1,200 WRAP participants met the inclusion criteria and had cognitive data available for up to five visits. A subset of 111 and 168 of these participants had CSF and PiB data, respectively, for up to two visits. There were 100 participants who were in both the CSF and PiB subsets. Participant characteristics are described in detail in Table 1. At baseline, the full set of participants were 53.6 years of age with 16.3 years of education on average, were predominantly female (68.9%), and most had a parental history of AD (70.2%). As expected, this sample had a higher frequency of the *APOE* ε4 allele and lower frequency of the ε2 allele than the general population. These characteristics were fairly consistent within the CSF and PiB subsets of participants, with the exception of the mean age being 7 years older in both subsets when compared to the full set of participants. The distribution of each PRS and the *APOE* risk score is described for the full sample in Supplementary Table 2. As expected, mean PRSs were lower when *APOE* was excluded.

Cognitive Outcomes

Associations between single SNPs and cognitive outcomes were largely non-significant and would not withstand corrections for multiple testing (Supplementary Table 3). This was also true for associations between the PRSs and cognitive outcomes (Table 2 and Supplementary Table 4). A reduced set of participants who had complete data (i.e. had all PRSs) was used to compare the amount of variation in the cognitive factor score that was explained by each

PRS, indicated by r^2_{LR} (Table 3). The largest r^2_{LR} was .2%, which indicates that the PRSs explained essentially none of the model variances.

AD-Related Biomarker Outcomes

Associations between single SNPs and AD-related biomarkers were largely non- significant and would not withstand corrections for multiple testing (Supplementary Table 5). Associations between the PRSs and AD-related biomarkers suggest that a higher Aβ Clearance PRS, Cholesterol PRS, and Overall PRS were significantly associated with lower levels of $A\beta_{42}$, a smaller $A\beta_{42}/A\beta_{40}$ ratio, and higher PiB (Table 4). Upon removing *APOE* from the Aβ Clearance, Cholesterol, and Overall PRSs, these associations became non-significant with the exception of the association between the Cholesterol PRS and $A\beta_{42}/A\beta_{40}$ (p=.02); however, this would not withstand corrections for multiple testing (Supplementary Table 6). A higher Immune Response PRS was associated with higher T-tau (p=.01), indicating higher risk for AD; however, this also would not withstand corrections for multiple testing. A reduced set of participants who had complete data was used to compare the amount of variation in the AD-related biomarker that was explained by each PRS, indicated with r^2_{LR} (Table 3). The Cholesterol, Aβ Clearance, and Overall PRSs explained a similar amount of variance as the *APOE* risk score for the $A\beta_{42}/A\beta_{40}$ ratio (14%), PiB (3%), T-tau (2%), and P-tau (0%). Variance explained was also similar for $A\beta_{42}$, (all 10% except the Overall PRS, 8%), but the Cholesterol PRS and *APOE* risk score had better model fits than the Overall PRS (Overall PRS AIC was 4.7 higher than the Cholesterol PRS and 4.0 higher than the *APOE* risk score). The Immune Response PRS explained a much smaller amount of variance for each outcome, with the exception of T-tau, for which it explained 5% and had a better model fit than the *APOE* risk score (AIC was 4.6 higher for the *APOE* risk score).

Replication Study

For the replication analyses, a total of 131 W-ADRC participants met the inclusion criteria and had CSF data available for one visit. Participant characteristics are described in detail in Table 1. Participants were 61.2 years of age with 16.2 years of education on average, were predominantly female (69.5%), and most had a parental history of AD (74.8%). These characteristics were very similar to the subset of WRAP participants with CSF. The distribution of each PRS is described in Supplementary Table 2 and is almost identical to those of the WRAP sample.

Results using the W-ADRC sample were consistent with those found in the WRAP sample, suggesting that a higher Aβ Clearance PRS, Cholesterol PRS, and Overall PRS were significantly associated with lower levels of $A\beta_{42}$ and a smaller $A\beta_{42}/A\beta_{40}$ ratio (Table 5). However, the association between the Immune Response PRS and T-tau was not replicated in the W-ADRC sample. Upon removing *APOE* from the Aβ Clearance, Cholesterol, and Overall PRSs, the associations were no longer statistically significant (Supplementary Table 7). A reduced set of participants who had complete data was used to compare the amount of variation explained by each PRS, indicated by r^2_p (Table 6). The Immune Response PRS explained the least amount of variance for each outcome. In general, the remaining PRSs

explained a similar amount of variance as the *APOE* risk score for $A\beta_{42}$ (14%), $A\beta_{42}/A\beta_{40}$ ratio (17%), T-tau (0.1%), and P-tau (0.2%). However, the Cholesterol PRS explained slightly more variance than the Overall PRS for the $A\beta_{42}/A\beta_{40}$ ratio (19% versus 15%, respectively), and the Cholesterol PRS had a better model fit (AIC was 6.2 higher for the Overall PRS).

DISCUSSION

We assessed the potential for pathway-specific PRSs to predict AD-related outcomes, including cognitive function and biomarkers of Aβ deposition (amyloid PET and CSF $A\beta_{42}$ and $A\beta_{42}/A\beta_{40}$), neurodegeneration (CSF T-tau), and tau pathology (CSF P-tau). Present findings suggest that the risk scores assessed here were poor predictors of cognitive function. While the risk scores were better predictors for the CSF and PiB outcomes, much of the strength of the pathway-specific PRSs, Aβ Clearance and Cholesterol, and the Overall PRS appeared to be driven by the inclusion of *APOE*. These results suggest that these additional variants did not add much predictive power over *APOE* alone.

While the Immune Response PRS typically performed poorly, it was the only risk score found to be nominally associated with T-tau in the WRAP cohort. These findings are in agreement with previous reports suggesting that immune response contributes to neurodegeneration in AD[5], which T-tau is a biomarker of, and thus, with the concept of pathway-specific PRSs being more predictive than PRSs including all known disease variants. Although this association would not withstand corrections for multiple testing and did not hold in the replication study, it may warrant further investigation as the function of these genetic variants becomes better understood.

The minimal amount of statistically significant findings observed when assessing cognitive function is similar to the findings of two studies that concluded that a PRS based on all significant IGAP genes one including and one excluding *APOE*, was not associated with cognitive function in older non-demented individuals[34, 35]. Two other studies did find associations between cognitive function and an overall PRS using a subset of IGAP genes in general populations; however, removing *APOE* from the PRS eliminated the statistical significance[36, 37]. In our analyses, the Overall PRS including *APOE* was not statistically associated with any cognitive outcomes. Because our sample had a younger mean age than these studies, it is possible that our sample may not have experienced sufficient cognitive decline to detect the effect of *APOE* or a PRS on cognition. It is notable that our most significant findings were in Working Memory, as we recently found that Working Memory is the most heritable cognitive factor score of those assessed here [16]. PRS analyses have been reported to have better power to detect associations when the traits have high heritability[38], which could account for our observations. A much larger sample size may be needed to detect associations in cognitive traits with lower heritability.

The nominal association between the Overall PRS and CSF $A\beta_{42}$ has been found in other studies investigating the IGAP variants[32, 33]. Similar to our study, Sleegers, et al. found that upon removing *APOE* from the Overall PRS, this association was no longer significant. However, Martiskainen et al. found that significance held upon removing *APOE*. This

discrepancy could be due to the different SNPs included in the Martiskainen, et al. PRS, which included only 12 of the IGAP meta-analysis variants and the top 10 variants from AlzGene, whereas our Overall PRS and that of Sleegers, et al. included all of the IGAP variants. Given that our study is based on a preclinical sample of participants, the minimal associations with T-tau and P-tau is consistent with other findings suggesting that these are later markers of AD, whereas Aβ deposition is an earlier marker[39].

Associations were stronger for Aβ deposition than for cognition, which is consistent with the AD pathological cascade, suggesting that Aβ biomarkers become abnormal long before cognitive decline during the development of AD[1]. The current diagnostic criteria for AD primarily concerns impairments in cognition despite mounting evidence suggesting that measurements of Aβ deposition could be used to detect AD at a much earlier stage than is possible with cognitive function[39–41]. This is likely because measuring Aβ deposition can be expensive and requires either access to a PET facility (amyloid PET) or experience in performing lumbar puncture, which is regarded as an invasive procedure (CSF Aβ). Further, proxy measures of Aβ based on peripheral blood proteins, which would be less costly and invasive, are not yet able to definitively identify abnormal Aβ levels[42]. A pathway-specific PRS could be used to identify patients with a higher genetic risk of having elevated Aβ deposits who may be candidates for Aβ accumulation screening. The ability to identify these individuals will be of particular importance if effective treatments for AD become available.

Due to the limited sample sizes of participants with measures of Aβ deposition in WRAP and the W-ADRC sample used for replication, it is possible that the present investigation did not have sufficient power to detect all associations, which could also explain the inability to replicate the association between the Immune Response PRS and T-tau. The accuracy of our results is, in part, limited by knowledge regarding the biological function of genes at the time of genotyping, which guided the development of the pathway-specific PRSs used in this study. Since the time that genotyping was performed for this study, a pathway analysis performed by the IGAP investigators identified several pathways that may contribute to AD[6]; however, we were unable to incorporate most of these pathways since our genotyping dataset only included the IGAP SNPs and *APOE*. It will be crucial to modify these pathway-specific PRSs to reflect new findings in order to improve their predictive ability. One recent successful approach used a large number of the top IGAP SNPs (~16,000) to develop an overall PRS, potentially utilizing many other relevant genetic variants that did not meet statistical significance, and found that it was associated with cognitive function, Aβ deposition, hippocampal volume, and clinical progression[35]. A possible interesting expansion of this approach could be to develop pathway-specific PRSs using this large panel of SNPs and the pathways outlined by the IGAP pathway analysis[6].

Although the majority of our findings did not suggest that pathway-specific PRSs are more predictive than PRSs including all known disease variants, their predictive potential should not be ruled out. As recently indicated by the IGAP pathway analysis, there are numerous distinct biological pathways that contribute to AD[6]; as such, the biological function of genes should be taken into consideration when designing a PRS that will be tested for associations with heterogeneous risk factors of AD (e.g. beta-amyloid and tau), which are influenced by different genetic variants. As more knowledge is gained on the genetic

variants involved in specific biological pathways of AD and as therapies to target particular pathways become available, pathway-specific PRSs may be useful in identifying individuals at increased genetic risk for AD pathology before the onset of clinical symptoms and could facilitate preventative, diagnostic, and treatment decisions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010; 9:119–128. [PubMed: 20083042]
2. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002; 297:353–356. [PubMed: 12130773]
3. Mawuenyega KG, Sigurdson W, Ovod V, Munsell L, Kasten T, Morris JC, Yarasheski KE, Bateman RJ. Decreased clearance of CNS beta-amyloid in Alzheimer's disease. Science. 2010; 330:1774. [PubMed: 21148344]
4. Martins IJ, Berger T, Sharman MJ, Verdile G, Fuller SJ, Martins RN. Cholesterol metabolism and transport in the pathogenesis of Alzheimer's disease. J Neurochem. 2009; 111:1275–1308. [PubMed: 20050287]
5. Kitazawa M, Cheng D, Tsukamoto MR, Koike MA, Wes PD, Vasilevko V, Cribbs DH, LaFerla FM. Blocking IL-1 signaling rescues cognition, attenuates tau pathology, and restores neuronal beta-catenin pathway function in an Alzheimer's disease model. J Immunol. 2011; 187:6539–6549. [PubMed: 22095718]
6. International Genomics of Alzheimer's Disease C. Convergent genetic and expression data implicate immunity in Alzheimer's disease. Alzheimers Dement. 2015; 11:658–671. [PubMed: 25533204]
7. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, Jun G, Destefano AL, Bis JC, Beecham GW, Grenier-Boley B, Russo G, Thornton-Wells TA, Jones N, Smith AV, Chouraki V, Thomas C, Ikram MA, Zelenika D, Vardarajan BN, Kamatani Y, Lin CF, Gerrish A, Schmidt H, Kunkle B, Dunstan ML, Ruiz A, Bihoreau MT, Choi SH, Reitz C, Pasquier F, Hollingworth P, Ramirez A, Hanon O, Fitzpatrick AL, Buxbaum JD, Campion D, Crane PK, Baldwin C, Becker T, Gudnason V, Cruchaga C, Craig D, Amin N, Berr C, Lopez OL, De Jager PL, Deramecourt V, Johnston JA, Evans D, Lovestone S, Letenneur L, Moron FJ, Rubinsztein DC, Eiriksdottir G, Sleegers K, Goate AM, Fievet N, Huentelman MJ, Gill M, Brown K, Kamboh MI, Keller L, Barberger-Gateau P, McGuinness B, Larson EB, Green R, Myers AJ, Dufouil C, Todd S, Wallon D, Love S, Rogaeva E, Gallacher J, St George-Hyslop P, Clarimon J, Lleo A, Bayer A, Tsuang DW, Yu L, Tsolaki M, Bossu P, Spalletta G, Proitsi P, Collinge J, Sorbi S, Sanchez-Garcia F, Fox NC, Hardy J, Naranjo MC, Bosco P, Clarke R, Brayne C, Galimberti D, Mancuso M, Matthews

F, Moebus S, Mecocci P, Del Zompo M, Maier W, Hampel H, Pilotto A, Bullido M, Panza F, Caffarra P, Nacmias B, Gilbert JR, Mayhaus M, Lannfelt L, Hakonarson H, Pichler S, Carrasquillo MM, Ingelsson M, Beekly D, Alvarez V, Zou F, Valladares O, Younkin SG, Coto E, Hamilton-Nelson KL, Gu W, Razquin C, Pastor P, Mateo I, Owen MJ, Faber KM, Jonsson PV, Combarros O, O'Donovan MC, Cantwell LB, Soininen H, Blacker D, Mead S, Mosley TH Jr, Bennett DA, Harris TB, Fratiglioni L, Holmes C, de Bruijn RF, Passmore P, Montine TJ, Bettens K, Rotter JI, Brice A, Morgan K, Foroud TM, Kukull WA, Hannequin D, Powell JF, Nalls MA, Ritchie K, Lunetta KL, Kauwe JS, Boerwinkle E, Riemenschneider M, Boada M, Hiltunen M, Martin ER, Schmidt R, Rujescu D, Wang LS, Dartigues JF, Mayeux R, Tzourio C, Hofman A, Nothen MM, Graff C, Psaty BM, Jones L, Haines JL, Holmans PA, Lathrop M, Pericak-Vance MA, Launer LJ, Farrer LA, van Duijn CM, Van Broeckhoven C, Moskvina V, Seshadri S, Williams J, Schellenberg GD, Amouyel P. European Alzheimer's Disease I, Genetic, Environmental Risk in Alzheimer's D, Alzheimer's Disease Genetic C, Cohorts for H, Aging Research in Genomic E. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet. 2013

8. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P. International Schizophrenia C. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 2009; 460:748–752. [PubMed: 19571811]
9. Wineinger NE, Harper A, Libiger O, Srinivasan SR, Chen W, Berenson GS, Schork NJ. Genomic risk models improve prediction of longitudinal lipid levels in children and young adults. Front Genet. 2013; 4:86. [PubMed: 23734161]
10. Klimentidis YC, Wineinger NE, Vazquez AI, de Los Campos G. Multiple metabolic genetic risk scores and type 2 diabetes risk in three racial/ethnic groups. J Clin Endocrinol Metab. 2014; 99:E1814–1818. [PubMed: 24905067]
11. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984; 34:939–944. [PubMed: 6610841]
12. Sager MA, Hermann B, La Rue A. Middle-aged children of persons with Alzheimer's disease: APOE genotypes and cognitive function in the Wisconsin Registry for Alzheimer's Prevention. J Geriatr Psychiatry Neurol. 2005; 18:245–249. [PubMed: 16306248]
13. La Rue A, Hermann B, Jones JE, Johnson S, Asthana S, Sager MA. Effect of parental family history of Alzheimer's disease on serial position profiles. Alzheimers Dement. 2008; 4:285–290. [PubMed: 18631980]
14. Engelman CD, Koscik RL, Jonaitis EM, Okonkwo OC, Hermann BP, La Rue A, Sager MA. Interaction between two cholesterol metabolism genes influences memory: findings from the Wisconsin Registry for Alzheimer's Prevention. J Alzheimers Dis. 2013; 36:749–757. [PubMed: 23669301]
15. Dowling NM, Hermann B, La Rue A, Sager MA. Latent structure and factorial invariance of a neuropsychological test battery for the study of preclinical Alzheimer's disease. Neuropsychology. 2010; 24:742–756. [PubMed: 21038965]
16. Darst BF, Koscik RL, Hermann BP, La Rue A, Sager MA, Johnson SC, Engelman CD. Heritability of Cognitive Traits Among Siblings with a Parental History of Alzheimer's Disease. J Alzheimers Dis. 2015
17. Johnson SC, Christian BT, Okonkwo OC, Oh JM, Harding S, Xu G, Hillmer AT, Wooten DW, Murali D, Barnhart TE, Hall LT, Racine AM, Klunk WE, Mathis CA, Bendlin BB, Gallagher CL, Carlsson CM, Rowley HA, Hermann BP, Dowling NM, Asthana S, Sager MA. Amyloid burden and neural function in people at risk for Alzheimer's Disease. Neurobiol Aging. 2014; 35:576–584. [PubMed: 24269021]
18. Sprecher KE, Bendlin BB, Racine AM, Okonkwo OC, Christian BT, Koscik RL, Sager MA, Asthana S, Johnson SC, Benca RM. Amyloid burden is associated with self-reported sleep in nondemented late middle-aged adults. Neurobiol Aging. 2015
19. Skoog I, Davidsson P, Aevarsson O, Vanderstichele H, Vanmechelen E, Blennow K. Cerebrospinal fluid beta-amyloid 42 is reduced before the onset of sporadic dementia: a population-based study in 85-year-olds. Dementia and geriatric cognitive disorders. 2003; 15:169–176. [PubMed: 12584433]

20. Blennow K. Cerebrospinal fluid protein biomarkers for Alzheimer's disease. NeuroRx. 2004; 1:213–225. [PubMed: 15717022]
21. Lewczuk P, Lelental N, Spitzer P, Maler JM, Kornhuber J. Amyloid-beta 42/40 cerebrospinal fluid concentration ratio in the diagnostics of Alzheimer's disease: validation of two novel assays. Journal of Alzheimer's disease : JAD. 2015; 43:183–191. [PubMed: 25079805]
22. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, Sham PC. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007; 81:559–575. [PubMed: 17701901]
23. Ashburner M, Ball CA, Blake JA, Botstein D, Butler H, Cherry JM, Davis AP, Dolinski K, Dwight SS, Eppig JT, Harris MA, Hill DP, Issel-Tarver L, Kasarskis A, Lewis S, Matese JC, Richardson JE, Ringwald M, Rubin GM, Sherlock G. Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. Nat Genet. 2000; 25:25–29. [PubMed: 10802651]
24. Xu W, Tan L, Yu JT. The Role of PICALM in Alzheimer's Disease. Mol Neurobiol. 2015; 52:399–413. [PubMed: 25186232]
25. Carter C. Alzheimer's Disease: APP, Gamma Secretase, APOE, CLU, CR1, PICALM, ABCA7, BIN1, CD2AP, CD33, EPHA1, and MS4A2, and Their Relationships with Herpes Simplex, C. Pneumoniae, Other Suspect Pathogens, and the Immune System. Int J Alzheimers Dis. 2011; 2011:501862. [PubMed: 22254144]
26. Guerreiro RJ, Hardy J. Alzheimer's disease genetics: lessons to improve disease modelling. Biochem Soc Trans. 2011; 39:910–916. [PubMed: 21787322]
27. AlzGene. [Accessed July 15, 2015] alzgene.org
28. Singer JD. Using SAS PROC MIXED to fit multilevel models, hierarchical models, and individual growth models. Journal of Educational and Behavioral Statistics. 1998; 23:323–355.
29. Magee L. R 2 Measures Based on Wald and Likelihood Ratio Joint Significance Tests. The American Statistician. 1990; 44:250–253.
30. Kramer, M. 2005 Proceedings of the Conference on Applied Statistics in Agriculture; Manhattan, KS. 2005. p. 148-160.
31. Burnham, KP., Anderson, DR. Model Selection and Multimodel Inference. Springer-Verlag; New York: 2002. Information and Likelihoood Theory: A Basis for Model Selection and Inference; p. 49-97.
32. Sleegers K, Bettens K, De Roeck A, Van Cauwenberghe C, Cuyvers E, Verheijen J, Struyfs H, Van Dongen J, Vermeulen S, Engelborghs S, Vandenbulcke M, Vandenberghe R, De Deyn PP, Van Broeckhoven C. consortium B. A 22-single nucleotide polymorphism Alzheimer risk score correlates with family history, onset age, and cerebrospinal fluid Abeta. Alzheimers Dement. 2015
33. Martiskainen H, Helisalmi S, Viswanathan J, Kurki M, Hall A, Herukka SK, Sarajarvi T, Natunen T, Kurkinen KM, Huovinen J, Makinen P, Laitinen M, Koivisto AM, Mattila KM, Lehtimaki T, Remes AM, Leinonen V, Haapasalo A, Soininen H, Hiltunen M. Effects of Alzheimer's disease-associated risk loci on cerebrospinal fluid biomarkers and disease progression: a polygenic risk score approach. J Alzheimers Dis. 2015; 43:565–573. [PubMed: 25096612]
34. Harris SE, Davies G, Luciano M, Payton A, Fox HC, Haggarty P, Ollier W, Horan M, Porteous DJ, Starr JM, Whalley LJ, Pendleton N, Deary IJ. Polygenic risk for Alzheimer's disease is not associated with cognitive ability or cognitive aging in non-demented older people. J Alzheimers Dis. 2014; 39:565–574. [PubMed: 24246418]
35. Mormino EC, Sperling RA, Holmes AJ, Buckner RL, De Jager PL, Smoller JW, Sabuncu MR. Alzheimer's Disease Neuroimaging I. Polygenic risk of Alzheimer disease is associated with early- and late-life processes. Neurology. 2016
36. Verhaaren BF, Vernooij MW, Koudstaal PJ, Uitterlinden AG, van Duijn CM, Hofman A, Breteler MM, Ikram MA. Alzheimer's disease genes and cognition in the nondemented general population. Biol Psychiatry. 2013; 73:429–434. [PubMed: 22592056]
37. Vivot A, Glymour MM, Tzourio C, Amouyel P, Chene G, Dufouil C. Association of Alzheimer's related genotypes with cognitive decline in multiple domains: results from the Three-City Dijon study. Mol Psychiatry. 2015
38. Dudbridge F. Power and predictive accuracy of polygenic risk scores. PLoS Genet. 2013; 9:e1003348. [PubMed: 23555274]

39. Buchhave P, Minthon L, Zetterberg H, Wallin AK, Blennow K, Hansson O. Cerebrospinal fluid levels of beta-amyloid 1–42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia. Arch Gen Psychiatry. 2012; 69:98–106. [PubMed: 22213792]

40. Blennow K, Dubois B, Fagan AM, Lewczuk P, de Leon MJ, Hampel H. Clinical utility of cerebrospinal fluid biomarkers in the diagnosis of early Alzheimer's disease. Alzheimers Dement. 2015; 11:58–69. [PubMed: 24795085]

41. Cohen AD, Klunk WE. Early detection of Alzheimer's disease using PiB and FDG PET. Neurobiol Dis. 2014; 72(Pt A):117–122. [PubMed: 24825318]

42. Apostolova LG, Hwang KS, Avila D, Elashoff D, Kohannim O, Teng E, Sokolow S, Jack CR, Jagust WJ, Shaw L, Trojanowski JQ, Weiner MW, Thompson PM. Alzheimer's Disease Neuroimaging I. Brain amyloidosis ascertainment from cognitive, imaging, and peripheral blood protein measures. Neurology. 2015; 84:729–737. [PubMed: 25609767]

Table 1
Participant Characteristics at Baseline

Mean (SD) or N (%).

	WRAP			W-ADRC
Characteristic	**Full Sample (N=1,200)**	**Sample with CSF (n=111)**	**Sample with PiB (n=168)**	**Replication with CSF (N=131)**
Age (years)	53.6 (6.6)	60.8 (6.5)	60.9 (5.8)	61.2 (8.8)
Gender (female)	827 (68.9)	73 (65.8)	114 (67.9)	91 (69.5)
Years of Education	16.3 (2.8)	16.6 (2.4)	16.6 (2.9)	16.2 (2.5)
Parental History of AD	842 (70.2)	84 (75.7)	121 (72.0)	98 (74.8)
Enrolled Siblings/Family	1.2 (.7)	1.1 (.5)	1.1 (.4)	--
Max Number of Visits				
1	94 (7.8)	86 (77.5)	40 (23.8)	131 (100.0)
2	174 (14.5)	25 (22.5)	128 (76.2)	--
3	366 (30.5)	--	--	--
4	539 (44.9)	--	--	--
5	27 (2.3)	--	--	--
APOE Genotype				
ε2/ε2	4 (.3)	0	0	0
ε2/ε3	99 (8.3)	10 (9.0)	17 (10.1)	11 (8.4)
ε2/ε4	38 (3.2)	3 (2.7)	6 (3.6)	5 (3.8)
ε3/ε3	623 (51.9)	57 (51.4)	84 (50.0)	69 (52.7)
ε3/ε4	383 (31.9)	38 (34.3)	58 (34.5)	39 (29.8)
ε4/ε4	53 (4.4)	3 (2.7)	3 (1.8)	7 (5.3)
CSF $A\beta_{42}$ (pg/ml)	--	754.5 (223.9)	--	738.7 (199.9)
CSF $A\beta_{42}/A\beta_{40}$		.10 (.02)		.10 (.02)
CSF T-tau (pg/ml)	--	312.5 (115.9)	--	310.6 (156.5)
CSF P-tau (pg/ml)	--	42.7 (15.0)	--	42.2 (16.0)
PiB	--	--	1.27 (.2)	--

WRAP: Wisconsin Registry for Alzheimer's Prevention; W-ADRC: Wisconsin Alzheimer's Disease Research Center; SD: Standard deviation; CSF: Cerebrospinal fluid; PiB: Pittsburgh compound B; AD: Alzheimer's disease; Aβ: β-amyloid; T-tau: Total tau; P-tau: Phosphorylated tau; pg/ml: Picrograms per milliliter.

Table 2

Risk Score Associations with Cognitive Factors in WRAP (N=1,200).

	Risk Scores									
	Immune		**Aβ Clearance**		**Cholesterol**		**Overall**		***APOE***	
Cognitive Factor	***β (SE)***	***P***	***β (SE)***	***P***	***β (SE)***	***P***	***β (SE)***	***P***	***β (SE)***	***P***
Memory Domain										
Immediate Memory	.03(.13)	.85	−.04(.03)	.20	−.05(.03)	.11	−.03(.03)	.44	−.05 (.03)	.11
Verbal Learning & Memory	−.05(.15)	.74	−.03(.03)	.38	−.05(.04)	.19	−.01(.03)	.69	−.05 (.03)	.13
Visual Learning & Memory	.08(.14)	.58	−.02(.04)	.55	−.04(.04)	.30	−.003(.04)	.94	−.03 (.04)	.47
Story Recall	−.05(.15)	.75	−.05(.04)	.22	−.07(.04)	.08	−.02(.04)	.58	−.07 (.04)	.07
Executive Function Domain										
Working Memory	−.14(.15)	.36	−.08(.04)	.03	−.08(.04)	.03	−.07(.04)	.06	−.08 (.04)	.04
Speed & Flexibility	.06(.14)	.66	−.01(.03)	.77	−.02(.03)	.58	.02(.03)	.60	−.02 (.03)	.58

WRAP: Wisconsin Registry for Alzheimer's Prevention; Aβ: β-amyloid; β: Estimate; SE: Standard error

Immune Response Pathway: INPP5D, CLU, CR1, HLA-DRB1, MEF2C, PTK2B

Aβ Clearance Pathway: *APOE, CLU, CR1, PICALM.*

Cholesterol Pathway: *APOE, ABCA7, CLU.*

Overall: All IGAP SNPs plus *APOE.*

Bolded values are statistically significant at an α <.05 level.

All models are adjusted for age and gender.

J Alzheimers Dis. Author manuscript; available in PMC 2016 November 25.

Table 3

r^2_{LR} **Values for each Model in WRAP.** Based on a reduced subset of WRAP participants who had all PRSs (Cognitive factor outcomes N=1,059, CSF outcomes N=98, and PiB N=148).

	Risk Scores				
Outcome	**Immune**	**Aβ Clearance**	**Cholesterol**	**Overall**	***APOE***
Immediate Memory	0	**.001**	**.001**	.0002	**.001**
Verbal Learning & Memory	.0001	.0003	**.0004**	.00003	**.0004**
Visual Learning & Memory	0	.00047	**.001**	0	.0003
Story Recall	0	**.001**	**.001**	.0001	**.001**
Working Memory	.0001	**.002**	**.002**	.001	**.002**
Speed & Flexibility	0	.00003	**.0001**	**.0001**	.00003
CSF $A\beta_{42}$	.001	**.10**	**.10**	.08	**.10**
CSF $A\beta_{42}/A\beta_{40}$	.03	.15	**.16**	**.16**	.14
CSF T-tau	**.05**	--	.02	.03	.02
CSF P-tau	**.003**	--	0	0	0
PiB	.0004	**.04**	.03	.03	.03

r^2_{LR}: Partial likelihood ratio r-squared; WRAP: Wisconsin Registry for Alzheimer's Prevention; PRS: Polygenic risk score; CSF: Cerebrospinal fluid; PiB: Pittsburgh compound B; Aβ: β-amyloid; T-tau: Total tau; P-tau: Phosphorylated tau.

Immune Response Pathway: INPP5D, CLU, CR1, HLA-DRB1, MEF2C, PTK2B

Aβ Clearance Pathway: *APOE, CLU, CR1, PICALM.*

Cholesterol Pathway: *APOE, ABCA7, CLU.*

Overall: All IGAP SNPs plus *APOE.*

Bolded values explain the largest percentage of variance for the outcome.

-- Association not tested because the pathway specific PRS was not hypothesized to be associated with the outcome.

Table 4

Risk Score Associations with CSF (n=111) and PiB (n=168) Outcomes in WRAP.

	Risk Scores									
	Immune		**Aβ Clearance**		**Cholesterol**		**Overall**		***APOE***	
Biomarker	***β (SE)***	***P***	***β (SE)***	***P***	***β (SE)***	***P***	***β (SE)***	***P***	***β (SE)***	***P***
CSF $A\beta_{42}$	40.2(105.3)	.70	−114.7(26.7)	**<.0001**	−113.2(26.5)	**<.0001**	−96.6(28.7)	**.001**	−113.9(27.4)	**<.0001**
CSF $A\beta_{42}/A\beta_{40}$	−.02(.01)	.05	−.01(.002)	**<.0001**	−.01(.002)	**<.0001**	−.01(.002)	**<.0001**	−.01(.002)	**<.0001**
CSF T-tau	139.1(54.7)	**.01**	--	**--**	26.5(15.0)	.1	29.3(15.0)	.05	24.7(15.5)	.11
CSF P-tau	3.6(6.8)	.60	--	**--**	.7(1.8)	.7	.3(1.8)	.88	.9(1.8)	.63
PiB	.02(.06)	.73	.05(.01)	**.002**	.05(.01)	**.002**	.05(.01)	**.002**	.04(.01)	**.004**

CSF: Cerebrospinal fluid; PiB: Pittsburgh compound B; WRAP: Wisconsin Registry for Alzheimer's Prevention; Aβ: β-amyloid; β: Estimate; SE: Standard error; T-tau: Total tau; P-tau: Phosphorylated tau.

Immune Response Pathway: INPP5D, CLU, CR1, HLA-DRB1, MEF2C, PTK2B

Aβ Clearance Pathway: *APOE, CLU, CR1, PICALM.*

Cholesterol Pathway: *APOE, ABCA7, CLU.*

Overall: All IGAP SNPs plus *APOE.*

Bolded values are statistically significant at an α <.05 level.

All models are adjusted for age and gender.

-- Association not tested because the pathway specific PRS was not hypothesized to be associated with the outcome.

J Alzheimers Dis. Author manuscript; available in PMC 2016 November 25.

Table 5

Risk Score Associations with CSF (n=131) Outcomes in W-ADRC.

	Risk Scores									
	Immune Response		**Aβ Clearance**		**Cholesterol**		**Overall**		***APOE***	
Biomarker	***β (SE)***	***P***	***β (SE)***	***P***	***β (SE)***	***P***	***β (SE)***	***P***	***β (SE)***	***P***
CSF $A\beta_{42}$	89.9 (98.2)	.36	-99.3 (22.4)	**<.0001**	-101.4 (22.0)	**<.0001**	-92.3 (22.5)	**<.0001**	-100.4 (21.8)	**<.0001**
CSF $A\beta_{42}/A\beta_{40}$	.01 (.01)	.50	-.01 (.002)	**<.0001**	-.01 (.002)	**<.0001**	-.01 (.002)	**<.0001**	-.01 (.002)	**<.0001**
CSF T-tau	22.6 (76.1)	.77	--	--	17.2 (17.7)	.33	1.7 (18.8)	.93	13.1 (17.3)	.45
CSF P-tau	4.2 (7.9)	.60	--	--	1.6 (1.8)	.38	1.0 (1.9)	.60	1.2 (1.8)	.49

CSF: Cerebrospinal fluid; W-ADRC: Wisconsin Alzheimer's Disease Research Center; Aβ: β-amyloid; β: Estimate; SE: Standard error; T-tau: Total tau; P-tau: Phosphorylated tau.

Immune Response Pathway: INPP5D, CLU, CR1, HLA-DRB1, MEF2C, PTK2B

Aβ Clearance Pathway: APOE, CLU, CR1, PICALM.

Cholesterol Pathway: *APOE, ABCA7, CLU.*

Overall: All IGAP SNPs plus *APOE.*

Bolded values are statistically significant at an α <.05 level.

All models are adjusted for age and gender.

-- Association not tested because the pathway specific PRS was not hypothesized to be associated with the outcome.

J Alzheimers Dis. Author manuscript; available in PMC 2016 November 25.

Table 6

r_p^2 **Values for each Model in the W-ADRC.** Based on a reduced subset of W-ADRC participants who had all PRSs (n=115).

	Risk Scores				
Biomarker	**Immune Aβ**	**Clearance**	**Cholesterol**	**Overall**	***APOE***
CSF $A\beta_{42}$	.01	.14	**.14**	.12	.14
CSF $A\beta_{42}/A\beta_{40}$	.01	.17	**.19**	.15	.17
CSF T-tau	.0001	--	**.002**	.0001	.001
CSF P-tau	.001	--	**.004**	.002	.002

r_p^2: Partial r-squared; W-ADRC: Wisconsin Alzheimer's Disease Research Center; PRS: Polygenic risk score; CSF: Cerebrospinal fluid; Aβ: β-amyloid; T-tau: Total tau; P-tau: Phosphorylated tau.

Immune Response Pathway: INPP5D, CLU, CR1, HLA-DRB1, MEF2C, PTK2B

Aβ Clearance Pathway: *APOE, CLU, CR1, PICALM.*

Cholesterol Pathway: *APOE, ABCA7, CLU.*

Overall: All IGAP SNPs plus *APOE.*

Bolded values explain the largest percentage of variance for the outcome.

-- Association not tested because the pathway specific PRS was not hypothesized to be associated with the outcome.